NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Caplacizumab for treating adults experiencing an episode of acquired thrombotic thrombocytopenic purpura [ID1185]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from Sanofi

2. **Clarification questions and company responses**

3. **Patient group, professional group and NHS organisation submission** from:
   a. TTP Network (written by patient expert Jo McIntyre)
   b. Royal College of Pathologists (written by clinical expert Prof Marie Scully)

4. **Expert personal perspectives** from:
   a. Dr Will Lester – clinical expert, nominated by Sanofi
   b. Fiona Marley – NHSE commissioning expert, nominated by NHS England
   c. Jamie Blackshaw - patient expert, nominated by TTP Network

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engagement prepared by Peninsula Technology Assessment Group (PenTAG)

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Caplacizumab for treating acute acquired thrombotic thrombocytopenic purpura [ID1185]

Document B

Company evidence submission

October 2019

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ID1185_081019_DocumentB_AIC_CIC	Final	Yes	8 October 2019

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Tables and figures

Executive summary

Thrombotic thrombocytopenic purpura (TTP) is an ultra-rare, life-threatening disease that represents an urgent, medical emergency. It is a blood disorder caused by deficiency of ADAMTS13 enzyme activity, leading to persistence of ultra large von Willebrand factor (UL-vWF) that spontaneously capture platelets, resulting in widespread formation of microvascular thrombi.[1] These microvascular thrombi cause tissue ischaemia and organ damage (particularly in the heart, brain and kidney) that can have devastating consequences both in the short and long-term.[1] TTP can either be congenital (due to an inherited deficiency of ADAMTS13) or acquired (due to an autoantibody directed deficiency of ADAMTS13). The focus of this submission is on acquired TTP (aTTP).

aTTP is an acute-onset disease characterised by episodes of sudden and severe onset of symptoms which can lead to long-term complications or death, and carries a lifetime risk of relapse (for those who survive the acute episode).[1] Patients are typically young adults (median age 43 years), more often female than male (73% vs 27%), and disproportionately of Afro-Caribbean heritage (22% vs 3.4% general population norm[2]).[3] Early signs of an acute episode can be seemingly mild and non-specific but quickly progress to much more severe symptoms such as stroke and coma.[1, 4] In England, there are an estimated 100-150 patients presenting with an acute episode of aTTP each year[5], with patients typically presenting to emergency care units where rapid diagnosis and referral for specialist care is critical. Failure to achieve rapid control of acute episodes of aTTP can be fatal with mortality rates exceeding 90% if untreated.[1] Acute mortality has improved with specialist care but is still documented to be as high as 50% in patients presenting to non-specialist centres.[5]

Patients who survive the episode rarely recover in full due to long-term complications. These can include physical disability (e.g. loss of function from stroke) and psychological disability (e.g. permanent cognitive impairment from cerebral damage, post-traumatic stress disorder [PTSD], anxiety and depression), along with an increased risk of cardiac and renal failure and premature death.[6-12] The impact of these complications, and the unpredictable risk of relapse have a substantial impact on patient quality of life, and on the lives of the patients' family, friends and carers.[4, 6,

[8, 13-15] Cerebral damage and resulting cognitive impairment is shown to be particularly detrimental to patient's wellbeing and quality of life.[6, 8, 15]

Specialist care for the treatment of an acute episode of aTTP currently consists of plasma exchange therapy (PEX) and immunosuppression. These treatments aim to restore ADAMTS13 activity by replenishing the enzyme itself (PEX) and by controlling the underlying autoimmune disease (immunosuppression). However, it can take several days for treatment to have an effect, during which time, platelet aggregation and microvascular thrombosis is ongoing and patients remain at risk of suffering organ damage and death.[10, 16, 17]

Even with current care, permanent cognitive impairment is observed in over half of all patients, severe or moderate depression is observed in approximately 40% of patients and premature death rates are reported to be as high as 21%.[6, 8-10] In a proportion of patients (~35%), acute symptoms (e.g. thrombocytopenia and microangiopathic haemolytic anaemia [MAHA]) recur despite initial platelet count normalisation, requiring reinitiation of PEX.[1, 16, 18] There is also a proportion of patients (~10%) who fail to respond to PEX and immunosuppression and have limited or no change in platelet counts resulting in refractory disease and a poor prognosis.[19] It is not possible to predict which patients will not respond to PEX, and there is no different care pathway for these patients.

To improve patient outcomes in aTTP, there is an urgent clinical need for a new intervention to complement current standard of care (SoC) and reduce the time patients spend in the occluded state during an acute episode, and the risk of recurrence and refractory disease.[10] Caplacizumab (Cablivi®) provides the first licensed treatment specific to aTTP and the first advancement in acute phase therapeutics for 30 years. Caplacizumab is a first-in-class humanised nanobody with a novel mode of action that directly targets vWF binding to platelets to prohibit the vWF-mediated platelet aggregation that is characteristic of the disease, and thus complements existing care. It is administered prior to, and then post-daily PEX and for 30 days after PEX cessation. With the exception of the first dose (which is administered via intravenous infusion), caplacizumab is administered by subcutaneous injection, and can be self-administered with training.

The efficacy and safety of caplacizumab in conjunction with PEX and immunosuppression (n=72) has been compared to PEX and immunosuppression only (without caplacizumab) (n=73) in the Phase III double-blind, randomised placebo-controlled trial, HERCULES, that enrolled adult patients with a clinical diagnosis of aTTP. HERCULES is the largest trial conducted to date in the aTTP population and provides pivotal Phase III data that informed the marketing authorisation of caplacizumab in Europe. The addition of caplacizumab to PEX and immunosuppression significantly reduced the median time to platelet count response (2.69 vs 2.88 days, p=0.01) and patients receiving caplacizumab were 1.55 times more likely to achieve normalisation of platelet count at any given time point.[16] These data demonstrate faster resolution of the aTTP episode in terms of microvascular thrombosis control and were considered of particular clinical relevance by the European Medicines Agency (EMA) as they represent reduced time at the highest risk for morbidity for patients.[17]

The proportion of patients with a composite endpoint event of TTP-related death, recurrence of TTP, or a major thromboembolic event was 74% lower when caplacizumab was administered in addition to PEX and immunosuppression (12% vs 49%, p<0.001).[16] The proportion of patients with a recurrence of aTTP at any time during the trial was 67% lower with caplacizumab (12% vs 38%, p<0.001) and no patient treated with caplacizumab demonstrated refractory disease (compared to three patients who received PEX and immunosuppression without caplacizumab).[16] Patients who received caplacizumab also had lower healthcare resource utilisation with: a 38% reduction in duration of PEX treatment (5.8 vs 9.4 days); a 41% reduction in the volume of plasma exchanged (21.3 vs 35.9 litres); a 31% reduction in duration of hospitalisation (9.9 vs 14.4 days); and a 65% reduction in duration of intensive care unit (ICU) stay (3.4 vs 9.7 days).[16] ICU care has previously been associated with significant symptoms of anxiety, depression or PTSD[11] such that any reduction in ICU care would be expected to reduce the risk of such symptoms, as well as reducing the high costs associated with such care to the NHS. Phase II data from the TITAN trial support the outcomes of HERCULES with similar observations of clinical benefit.[20]

Across the clinical trial programme, caplacizumab was generally well tolerated and no patient enrolled to TITAN or HERCULES died while receiving treatment with caplacizumab, which also supports an acute mortality benefit.[16, 20] The safety profile of caplacizumab was consistent across both trials and characterised by an increased risk of bleeding related to its mode of action. In the Phase III HERCULES trial, bleeding-related adverse events were reported in 65% of patients receiving caplacizumab (compared to 48% of patients in the placebo group) but were mostly of mild to moderate severity and resolved without intervention.[16] The most common bleeding-related adverse events with an increased risk in the caplacizumab group were epistaxis/nose bleeds (32% vs 3%) and gingival/gum bleeds (18% vs 1%).[16] Although relatively uncommon, some patients (11%) did experience a serious bleeding event (most commonly epistaxis) related to caplacizumab treatment.[16] Recommendations for management of such events are available and clinical opinion is that they are easily resolved in practice.[21, 22] Only one serious bleeding event of epistaxis required medical intervention in HERCULES.[16] Considering favourable and unfavourable effects of treatment, the EMA concluded the benefits outweigh the risks and the overall benefit:risk ratio of caplacizumab is positive.[17]

There are some uncertainties regarding the longer-term benefits and potential harms of treatment as HERCULES only provides data up to 28 days after the end of study drug treatment, however, an ongoing Post-HERCULES study is intended to address this. In the interim, a modified-Delphi process was conducted to explore the potential longer-term benefits of caplacizumab treatment.[10] During this process, ten UK clinical experts agreed that it is biologically plausible that caplacizumab plus PEX and immunosuppression would reduce the risk of long-term consequences associated with acute organ damage, such as neurocognitive complications, and that adding caplacizumab to the NHS formulary would offer several benefits to both the patient and the healthcare system.

Quality of life data are not available from the caplacizumab clinical trial programme at this time and it is extremely difficult to capture robust health-related quality of life (HRQL) data relating to the treatment of an acute episode of aTTP. In the real-world setting, we would expect a treatment that results in rapid control of microvascular thrombi and thus limits tissue ischaemia and organ damage and the long-term

consequences of such damage to positively impact patient and carer wellbeing. Not only is the value of a treatment that can quickly control the disease physical, but it provides hope and reassurance to patients' and their loved ones, and confidence to healthcare professionals, that cannot be adequately captured in a clinical trial setting or quality-adjusted life year (QALY) measurement.

No other clinical studies are planned for caplacizumab in this indication, but ongoing data collection to provide further demographic, clinical and healthcare resource use information on aTTP include:

- Analysis of the UK aTTP registry based at University College London (UCL)
- Analysis of linked Clinical Practice Research Datalink (CPRD)-Hospital Episode Statistics (HES)-Office of National Statistics (ONS) datasets in England only
- A UK-based non-interventional cross-sectional study collecting data on the quality of life (QoL) of people with aTTP and carers via an online survey

A *de novo* economic model aligned to model conceptualisation guidance provided by NICE, and the NICE reference case, has been developed to explore the cost-effectiveness of caplacizumab for the treatment of aTTP.[23] The model was constructed based on consultation with UK clinicians and reflects the NICE decision problem, the disease and the potential consequences of disease.[14] The model includes a short-term and long-term assessment of the benefits and costs associated with an acute episode of aTTP and follow-up care, although it should be noted that the long-term complications of aTTP could only be captured in part, due to a paucity of evidence in this ultra-rare indication. While incremental costs of £[redacted] are observed with caplacizumab addition to PEX and immunosuppression, these are outweighed by incremental gains of 5.48 life years (LYs) and [redacted] quality-adjusted life years (QALYs) over a patients' lifetime. With a resulting base case incremental cost-effectiveness ratio (ICER) of £37,986 per QALY, caplacizumab is considered a good use of NHS resource within the context of an acute, ultra-rare, life-threatening disease requiring highly specialised life-saving care where the willingness-to-pay (WTP) threshold should arguably be higher compared to standard thresholds. The introduction of caplacizumab would also be financially manageable with an estimated budget impact not exceeding £20 million in any of the first three years following launch.

In conclusion, aTTP is a disease where the suddenness and severity of symptoms can result in otherwise healthy people being admitted to ICU within days. For those who survive this, there is a high chance they will have to learn to live with long-term complications, while in constant fear of relapse; patient and carer interviews highlight their struggles coming to terms with the life-changing nature of this condition.[12.] Caplacizumab offers a truly innovative, clinically effective and cost-effective treatment option and offers a step-change in the management of this ultra-rare, life-threatening disease with high unmet clinical need. Withholding caplacizumab leaves patients at risk of tissue ischemia, organ damage and death in the early stages of an acute episode, and thus at risk of the potentially devastating consequences resulting from such damage.

There is strong clinical support for the addition of caplacizumab to routine care for an acute episode of aTTP. Since May 2018, caplacizumab has been supplied free of charge to specialist centres in the UK to fulfil unsolicited requests from clinicians, and in recognition of the urgent clinical need caplacizumab addresses. Clinician feedback from this compassionate use programme has been extremely positive with several comments relating to the remarkability of outcomes with caplacizumab. With a highly specialised aTTP service in development, this is a timely appraisal that, if resulting in positive recommendation for caplacizumab, could allow patients in England access to an innovative intervention for their condition as part of this new nationalised service.[5]

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1. Decision problem

The submission covers the technology's full marketing authorisation for this indication, as detailed in Table 1.

The company submission is consistent with the NICE reference case, however, differs from the final NICE scope in that a subgroup analysis of people with severe refractory aTTP was not considered, as this does not represent a group of patients that are clinically identifiable at presentation, and no clinical evidence is therefore available specific to such a group. Refractory disease is defined by International Consensus as "lack of a sustained platelet count increment or platelet counts $<50\times10^9$/L and persistently raised LDH (>1.5x upper limit of normal [ULN]) despite 5 plasma exchanges and steroid treatment"[1] and therefore cannot be identified before treatment initiation. Refractory disease is therefore captured as an outcome measure in the caplacizumab trial programme and data on patients with refractory disease is presented in Section B.2.6. Severe disease can be indicated by neurological or cardiac pathology but patients presenting with such pathology do not necessarily develop refractory aTTP, and no other baseline characteristics are known to predict refractory disease.

Table 1: The decision problem

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults experiencing an episode of acquired thrombotic thrombocytopenic purpura	As per scope	N/A
Intervention	Caplacizumab in addition to plasma exchange and immunosuppression	As per scope	N/A
Comparator(s)	• Plasma exchange therapy (with or without spun apheresis, steroids or rituximab), without caplacizumab. For people with severe refractory acquired TTP, a combination of one or more of: • Plasma exchange therapy (with or without spun apheresis, steroids, rituximab, splenectomy, vincristine or immunosuppression e.g. cyclophosphamide) without caplacizumab.	• Plasma exchange therapy (with or without spun apheresis, steroids or rituximab), without caplacizumab.	Refractory disease cannot be identified before treatment initiation and severe disease does not correlate to refractory disease. People with "severe refractory acquired TTP" does not therefore represent a group of patients that are clinically identifiable at presentation, and no clinical evidence is available specific to such a group. Additional treatments listed as comparators for people with severe refractory acquired TTP (splenectomy, vincristine, cyclophosphamide) are not advised (due to a lack of prospective data) and are rarely used, as reported in the literature and confirmed by current clinical expert opinion.[1, 24] As such, "Plasma exchange therapy (with or without spun apheresis, steroids or rituximab), without caplacizumab" is the only relevant comparator for all adults experiencing an episode of acquired TTP.

Outcomes	The outcome measures to be considered include: • change in cognitive function • mortality • major thromboembolic events • recurrence of disease • reduction of time-to-recovery • time to platelet count response • TTP-related events • neuro-psychological impact (including depressive symptoms, anxiety and PTSD) following an episode • length of hospital stay • volume and frequency of plasma exchange • adverse effects of treatment • health-related quality of life	Outcomes considered in the submission include: • change in cognitive function • mortality • major thromboembolic events • recurrence of disease • reduction of time-to-recovery • time to platelet count response • TTP-related events • neuro-psychological impact (including depressive symptoms, anxiety and PTSD) following an episode • length of hospital stay • volume and frequency of plasma exchange • adverse effects of treatment • health-related quality of life	N/A
Subgroups to be considered	If evidence allows, subgroup analysis of people with severe refractory acquired TTP will be considered.	Subgroup analysis of people with ADAMTS13 activity <10% is considered.	Evidence does not allow subgroup analysis of people with severe refractory acquired TTP, and this is not a clinically relevant population. ADAMTS13 activity <10% aligns with the modern UK diagnostic criteria for aTTP; this subgroup comprises 85% of patients enrolled to HERCULES.

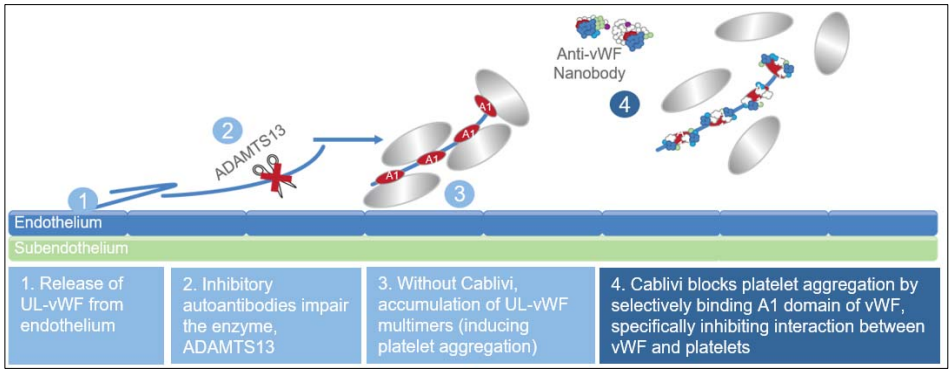
Key: aTTP, acquired thrombotic thrombocytopenic purpura; EQ-5D, EuroQol-5 Dimension; HRQL, health-related quality of life; HST, highly specialised technology; N/A, not applicable; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, Personal Social Services; PTSD, post-traumatic stress disorder; QALY, quality-adjusted life year; SF-36, Short Form-36.

B.1.2. Description of the technology being appraised

The summary of product characteristics (SmPC) and the European public assessment report (EPAR) are provided in Appendix C.

Table 2 provides a summary of the technology being appraised.

Table 2: Technology being appraised

UK approved name **Brand name**	Caplacizumab Cablivi®
Mechanism of action	Caplacizumab is a humanised bivalent nanobody that consists of two identical building blocks (PMP12A2hum1), genetically linked by a three-alanine linker, targeting the A1-domain of vWF and inhibiting the interaction between vWF and platelets. As such, caplacizumab prevents the UL-vWF-mediated platelet adhesion characteristic of aTTP and which is observed with reduced ADAMTS13 activity. It also affects the disposition of vWF, leading to transient reductions of total vWF antigen levels and to concomitant reduction of factor VIII:C levels during treatment. This mode of action is depicted in the figure below. 
Marketing authorisation	European Commission Marketing authorisation for the indication detailed in this submission was granted on 30th August 2018.
Indications and any restriction(s)	Cablivi is indicated for the treatment of adults experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in conjunction with plasma exchange and immunosuppression.
Method of administration and dosage	First dose – intravenous (IV) injection of 10 mg of caplacizumab prior to plasma exchange (PEX). Subsequent doses – daily subcutaneous (SC) injection of 10 mg of caplacizumab after completion of each PEX for the duration of daily PEX treatment, followed by daily SC injection of 10 mg of caplacizumab for 30 days after stopping daily PEX. Patients or caregivers may inject caplacizumab after proper training in the SC injection technique. If at the end of this period there is evidence of unresolved immunological disease, it is recommended to optimise the immunosuppression regimen and continue daily SC administration of 10 mg of caplacizumab until the signs of underlying immunological disease are resolved (e.g. sustained normalisation of ADAMTS13 activity level).

Additional tests or investigations	No additional tests or investigations are needed to those required for the diagnosis and monitoring of an episode of aTTP.
List price and average cost of a course of treatment	List price: £4,143 per 10mg vial Average cost of treatment: £[redacted] per episode* based on list price; £[redacted] per episode with price discount
Patient access scheme	A patient access scheme is agreed with the Department of Health as a simple discount of [redacted]% from the list price.
Key: aTTP, acute thrombotic thrombocytopenic purpura; IV, intravenous; PEX, plasma exchange; SC, subcutaneous; UL-vWF, ultra large von Willebrand factor; vWF, von Willebrand factor. **Source:** Cablivi SmPC.[21] *****Based on [redacted] days caplacizumab treatment duration	

B.1.3. Health condition and position of the technology in the treatment pathway

B.1.3.1. Disease overview

Thrombotic thrombocytopenic purpura (TTP) is an ultra-rare, life-threatening disease that represents an urgent, medical emergency. It is a blood disorder, caused by deficiency of ADAMTS13 enzyme activity, leading to persistence of ultra-large von Willebrand factor (UL-vWF); UL-vWF spontaneously captures platelets, resulting in widespread formation of microvascular thrombi.[1] TTP can either be congenital (due to an inherited deficiency of ADAMTS13 enzyme) or acquired (due to an autoantibody that clears the enzyme from circulation and inhibits its activity).

Congenital TTP makes up only about 5% of TTP cases.[1] The diagnosis of congenital TTP is confirmed by ADAMTS13 activity of less than 5%, absence of antibody and confirmation of homozygous or compound heterozygous defects of the ADAMTS13 gene (1A). Current guidelines recommend plasma infusion or intermediate purity Factor VIII for management of congenital TTP.[1]

In contrast, severe deficiency of ADAMTS13 along with the presence of an inhibitor or IgG antibodies, confirms diagnosis of acquired TTP (aTTP). This submission is for aTTP only. aTTP is an acute-onset disease characterised by episodes of sudden and severe onset of symptoms which can lead to long-term complications or death, and carries a lifetime risk of relapse.[1] Patients are typically young adults (median age

43 years) and more often female than male (73% vs 27%), and disproportionately of Afro-Caribbean heritage (22% vs 3.4% general population norm[2]). [3] From January 2009 to December 2018, there were 602 patients with clinically suspected TTP in the UK and 475 patients enrolled to the UK TTP registry.[3] Across the aTTP cohort registered (n=399), there were 564 recorded episodes, of which 475 were acute presentations (first diagnosis or relapse).[3] These data suggest an annual incidence of 53 acute episodes of identified aTTP in the UK, which is lower than NHS England (NHSE) estimates of 100-150 patients with aTTP need acute admission per year.[5] There is some uncertainty around incidence of annual aTTP episodes given the difficulty in diagnosis and potential for the patient to die before TTP is suspected and diagnosed.[5]

B.1.3.2. Burden of disease

The widespread formation of microvascular thrombi resulting from an acute episode of aTTP can have devastating outcomes including tissue ischaemia leading to organ damage (and thus dysfunction) commonly observed in the heart, kidney and brain as well as death.[1] Acute mortality rates exceed 90% when episodes are left untreated, and while advancements in aTTP therapeutics have markedly improved acute mortality rates, they are still as high as 50% dependent on treatment centre and response.[1, 25, 26]

Early signs of an acute episode can include fatigue, headache, and bruising but quickly progress to much more severe symptoms e.g. confusion, stroke and coma.[1, 4] Patients therefore typically present to emergency care units where rapid diagnosis and referral for specialist care is critical (see Clinical pathway of care). For patients who survive, long-term complications are commonly observed with many patients feeling like they never completely recover from an acute episode of aTTP in current practice, particularly when cerebral damage, and resulting cognitive impairment, has occurred.

Registry data is available for TTP in the UK and the US. However, due to the rarity of the condition, the number of patients recruited into either registry is small and datasets are therefore limited. In the US, the Oklahoma Thrombocytopenic Purpura-Hemolytic Uremic Syndrome (TTP-HUS) Registry is an established registry of patients with TTP (with over 30 years of follow-up from January 1989).[27] Although

the UK registry now plans to collect data on neurocognitive impact on aTTP on surviving patients, there is no existing UK data.

In a cohort of patients enrolled to the Oklahoma Registry with confirmed aTTP (ADAMTS13 activity <10%) who had recovered from an acute episode and returned to their normal work and daily activities (n=24), significant defects in cognitive function were observed on evaluation.[8] Eighteen (75%) patients performed below expectation on one or more of 4 cognitive domains: complex attention and sequencing, manual dexterity, rapid language generation, and list learning, placing them at or below the 16th percentile of the US population norm. Five patients (21%) had moderate or severe impairment on one or more of these 4 domains, placing them at or below the 2nd percentile of the US population norm.

In a separate evaluation of neurologic injury in 'normal functioning' patients with a history of aTTP across the US and the UK (n=27), cognitive impairment was observed in 63% of patients (according to neurocognitive testing) and magnetic resonance imaging (MRI) abnormality was observed in 39% of patients.[6] Health-related quality of life (HRQL) scores were also significantly lower than age- and gender-matched US norms for both the mental component score (MCS) and the physical component score (PCS) of the SF-36 quality of life questionnaire (v2). The PCS was more closely aligned to patients with anaemia, depression or cancer. The MCS was significantly lower than in patients with anaemia and cancer, and on par with patients with depression.

Significantly higher prevalence rates of stroke and headache are reported in aTTP survivors compared to population norms.[12, 13, 28] In a recently published US cohort study, of 137 patients surviving an acute episode of aTTP, 13.1% subsequently had a stroke, reported as higher than the expected prevalence of 2.6% based on age- and sex-matched controls. Persistent ADAMTS13 deficiency is also associated with a significantly increased risk of stroke in survivors. In this same US cohort study, out of 52 patients with measured ADAMTS13 activity, stroke following recovery from an acute aTTP episode occurred in 0% of patients with normal remission ADAMTS13 activity (>70%) in contrast to 27.6% of patients with low ADAMTS13 activity (≤ 70%).[12] Median time from first TTP diagnosis to stroke for these patients was 2.8 years (range: 0.8-10 years). Stroke experienced during the acute episode of aTTP or

after the episode can have marked physical and mental effects with a third of people who have a stroke left with long-term disability (data not aTTP-specific).[29]

Depression is also commonly observed following an acute episode of aTTP, with significantly higher prevalence rates of depression in aTTP survivors compared to population norms or controls reported across several studies.[13, 15, 30-32] Severe or moderate depression has been observed in 44% of Oklahoma Registry patients[9] and symptoms of at least mild depression were reported in 81% of TTP survivors in a cross-sectional study in the US (n=236), with 37% showing symptoms of severe depression.[13] Cognitive impairment and depression may be related with an observational cohort study of aTTP survivors (n=104) reporting a positive correlation between impairment of mental performance and severity of depression (r_s = 0.779).[15] However, whereas cognitive impairment tends to be permanent, depression in aTTP survivors may be more transient in nature.[22]

These longer-term complications of an acute episode of aTTP, in addition to other potential long-term complications (e.g. chronic kidney disease or hypertension), can impact the life expectancy of aTTP survivors. Premature death rates have been reported to be as high as 21%, which considering this disease typically affects young adults is significantly higher than population norms.[9] While acute mortality rates have improved over time, there are limited data suggesting any improvement in long-term mortality over the last two decades.[33]

Such morbidity can have a substantial impact on patients daily living and quality of life, and on the lives of their family, friends and carers. Patients are normally in critical care for several days following onset of an acute episode (which is sudden and often severe), and survivors can suffer from post-traumatic stress disorder (PTSD), similar to brain injury patients but with the added fear of relapse given the nature of their diagnosis.[4, 13, 14] Formal assessment of HRQL in Oklahoma Registry patients reported that in people who had survived an acute episode of aTTP, significantly worse functioning and well-being was observed than expected based on US population norms ($p<0.05$).[34]

While not formally investigated to our knowledge, the long-term complications suffered by patients along with the lifetime risk of relapse and premature death is

also likely to negatively impact the quality of life of their family, friends and carers. This is expected to be particularly pertinent for the family, friends and carers of patients who suffer cerebral damage, resulting in permanent cognitive impairment. In two separate studies in Australia, caregivers of patients with mild cognitive impairment (MCI) reported clinically significant levels of burden. In a 3-year observational study of 185 people with MCI and their caregivers, between 21-30% of caregivers reported clinically significant burden with severity of neuropsychiatric symptoms, functional impairment and employment status of caregivers predictive of burden.[35] In a cross-sectional study of 64 people with MCI versus 36 controls and their caregivers, 36% of caregivers reported clinically significant burden with behavioural problems contributing the most to this burden, followed by patient depression and cognition.[36] For family and friends, the emotional impact of watching their loved ones suffer and change may add further burden. In the initial acute episode, the patient is often unaware of what is happening whereas their family, friends are watching events unfold; health care professionals also feel the pressure of dealing with an urgent, medical emergency.[4]

B.1.3.3. Clinical pathway of care

Diagnosis and treatment aims for an acute episode of aTTP are to rapidly control the formation of microvascular thrombi and thus limit tissue ischaemia and organ damage, and to resolve the underlying immunological disease to prevent recurrence of disease. In clinical practice, this is demonstrated by complete platelet normalisation, and recovery of ADAMTS13 activity, respectively.

The British Committee for Standards in Haematology (BCSH, 2012) make the following key recommendations for the diagnosis and treatment of an acute episode of aTTP[1]:

- The diagnosis of TTP should be treated as a medical emergency
- Suspected TTP can be diagnosed on presentation of microangiopathic haemolytic anaemia (MAHA) and thrombocytopenia in the absence of any other identifiable clinical cause
- Diagnosis of aTTP should be confirmed through ADAMTS13 activity levels and anti-ADAMTS13 antibody detection

  - Subsequent International Consensus Guidelines specify ADAMTS13 activity levels of <10% are diagnostic for TTP[37]
- Treatment with PEX (that removes plasma from the patient's blood and replaces it with fresh plasma) should be initiated as soon as possible following a diagnosis of suspected TTP, preferably within 4-8 hours
- Immediately after PEX, start administering steroids (either intravenous [IV] methylprednisolone or oral prednisolone with an oral proton pump inhibitor) and oral folic acid
- Consider administering rituximab in patients presenting with neurological/cardiac pathology in conjunction with PEX and steroids
- When platelet count >50 x 10^9L, start low molecular weight heparin thromboprophylaxis and aspirin
- Continue daily PEX for a minimum of two days after platelet count has normalised (>150 x 10^9/L) then stop
- If symptoms progress or there are signs or refractory disease or early relapse, increase PEX and offer rituximab, ciclosporin A can also be considered to prevent acute relapse

Treatment patterns recently reported from the UK TTP registry show alignment to the BCSH guidelines and general trends of a reduced number of PEX treatments to remission, and an increase in elective rituximab use over the years (2009-2018).[3] Rituximab is a monoclonal antibody that depletes circulating B-cells and reduces the formation of inhibitory autoantibodies to ADAMTS13 and is increasingly used in addition to traditional immunosuppressive agents (steroids) to address the underlying autoimmune process.[17] In 2017-2018, the median number of PEX treatments to remission was 8 (range: 3-65), rituximab was used to treat 78% of acute episodes and elective rituximab was used to treat 29% of subacute relapse cases (26/89).[3]

Patients must be referred to an specialist centre as soon as aTTP diagnosis is suspected and transferred to a treating centre urgently as delayed treatment can impact mortality. All patients should be initiated on PEX between 4-8 hours of referral to the specialist TTP centre. Currently, there are two highly specialist centres in England with clinical expertise that provide discrete services for aTTP patients and

where the survival rate is as high as 80% (these are referred to as expert centres within the submission). There are also a number of further specialist centres with clinical expertise in aTTP (referred to as specialist centres). However, in areas of the country that are physically distant from expert or specialist centres, patients typically present to emergency care units that may not be linked to specialist centres, and a formal referral process is not currently established. This can result in geographic variation in quality of care where the mortality rate in non-specialist centres is as high as 50% (see Section B.1.4).[25]

As the current pathway of care is disjointed, a highly specialised service for TTP patients commissioned by NHSE, has been proposed in order to establish expert centres and clear pathways to improve outcomes[5]. Importantly, this proposed specialist service covers ongoing care and monitoring following the initial diagnosis of aTTP which is critical to the prevention of disease recurrence given it is not possible to predict which patients will relapse or when. In current practice, patients formally referred to specialist centres receive follow-up care in line with BCSH guidance such that true relapse rates are low (estimated to occur in ~1% of patients annually[22]). This may not be the case for patients not formally referred to expert or specialist centres, and relapse has historically been reported in up to 40% of patients.[26]

Caplacizumab is indicated in conjunction with PEX and immunosuppression and therefore would become part of the NHSE highly specialised service for patients with TTP if made available. Once diagnosis of aTTP is confirmed, the loading dose of 10mg caplacizumab would be administered by IV injection prior to the next PEX session.[21, 38] Following that PEX session, a subcutaneous (SC) dose of 10mg caplacizumab would be administered (so patients would receive two doses of caplacizumab on the day of initiation). Subsequently, daily SC administration of 10mg caplacizumab would continue after every PEX for the duration of daily PEX and for up to 30 days after the last daily PEX. Patients and carers can be given training to self-administer caplacizumab (after the last daily PEX).

If at the end of this period there is evidence of unresolved immunological disease, it would be recommended to optimise the immunosuppression regimen and continue

daily caplacizumab until the signs of underlying immunological disease are resolved (e.g. sustained normalisation of ADAMTS13 activity).[21]

B.1.3.4. Unmet clinical need

Current specialist care aims to restore ADAMTS13 activity by replenishing the enzyme itself (PEX) and by controlling the underlying autoimmune disease (immunosuppression), but it can take several days for treatment to have an effect. For example, at least 3-7 days of rituximab treatment is needed to achieve B-cell depletion and an even longer treatment period is needed to restore ADAMTS13 activity levels.[17] During this time, platelet aggregation and microvascular thrombosis is ongoing and patients remain at risk of suffering organ damage and death, and thus increasing risk of long-term complications, including permanent cognitive impairment, depression and premature death. 'Rapid control of microvascular thrombosis' is a recognised unmet need in current practice and with current care, surviving patients rarely return to previous functional capability.[10]

In a proportion of patients, acute symptoms (e.g. thrombocytopenia and MAHA) recur despite initial platelet count normalisation requiring reinitiation of PEX. There is also a proportion of patients whose condition fails to respond to PEX and immunosuppression and have limited or no change in platelet counts (refractory disease) which is associated with a poor prognosis. In a French Thrombotic Microangiopathies Reference Center, 17% of patients had refractory disease and the acute mortality rate was 42% in this cohort, compared to 25% in the total cohort.[19] In the HERCULES trial (see Section B.2), 7% of patients treated with PEX and immunosuppression demonstrated refractory disease and the acute mortality rate was [redacted] in this cohort (data on file), compared to 4% in the total cohort.[16, 39] PEX is also commonly associated with complications such as fever, urticaria and hypocalcaemic symptoms.[40] In HERCULES, none of the patients on caplacizumab developed refractory disease.[16]

To improve patient outcomes in aTTP, there is an urgent clinical need for a new intervention to complement current standard of care (SoC) and reduce the time patients spend in the state of microvascular occlusion during an acute episode, and the risk of recurrence and refractory disease.

B.1.3.5. Introduction to caplacizumab

Caplacizumab is a first-in-class humanised nanobody with a novel mode of action that directly targets vWF binding to platelets (see Section B.1.2) to inhibit the vWF-mediated platelet aggregation that is characteristic of the disease. Caplacizumab is the first treatment specifically licensed for aTTP and complements current SoC to offer a step-change in the management of this ultra-rare life-threatening disease. The clinical evidence presented in Section B.2 shows how caplacizumab treatment results in rapid control of microvascular thrombosis, reduces tissue ischemia and organ damage, and reduces disease recurrence and the incidence of refractory disease. This is expected to result in an associated reduction in long-term complications, including permanent cognitive impairment, neuro-psychological impairment and premature death. In a modified-Delphi process, ten UK clinical experts agreed that it is biologically plausible that caplacizumab would reduce the risk of long-term consequences associated with acute organ damage, such as neurocognitive complications.[10] This is further discussed in Section B.2.13.

B.1.4. Equality considerations

Treatment for an episode of aTTP is provided in centres with the facilities to do so or patients are transferred to one of the a few expert or specialist centres with clinical expertise in the disease and round-the-clock access to PEX facilities. Patients that present to non-specialist centres have delayed access to specialist care and may have less favourable outcomes at initial point of contact and follow-up. This results in variable geographic mortality risk for patients.[25]

There are advanced commissioning plans for highly specialised haematology services that would cover the care needs of aTTP in NHS England[5]; when these are operationalised (anticipated to be [redacted][41]), the current inequality in care would be addressed.

Prevalence of aTTP is higher in people of Afro-Caribbean descent and in people with HIV which in conjunction with unequal service provision, could lead to inequalities in care and levels of risk.

B.2. Clinical effectiveness

B.2.1. Identification and selection of relevant studies

See Appendix D for full details of the systematic literature review (SLR) used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2. List of relevant clinical effectiveness evidence

Two core studies, HERCULES (Phase III) and TITAN (Phase II), provide clinical effectiveness evidence of caplacizumab for the treatment of aTTP.

HERCULES and TITAN provide evidence of direct relevance to the decision problem in that they compare the efficacy and safety of caplacizumab in conjunction with PEX and immunosuppression to the efficacy and safety of SoC for the treatment of an acute episode of aTTP.

Although both studies were submitted as part of the application for European Union (EU) marketing authorisation, only HERCULES data were used to inform product information due to some concerns the EMA had with the quality of TITAN data that are discussed in Section B.2.5. Only HERCULES were therefore used to inform the economic modelling presented in Section B.3.

An ongoing follow-up study to HERCULES, Post-HERCULES (Phase IIIb), will provide additional clinical effectiveness evidence of caplacizumab for the treatment of aTTP, including health-related quality of life (HRQL) and longer-term mortality data but is not expected to complete before October 2020, with data available in early 2021 (see Section B.2.11).

Table 3 provides an overview of the clinical effectiveness evidence.

Table 3: Clinical effectiveness evidence

Study	**HERCULES (NCT02553317)**	**TITAN (NCT01151423)**
Study design	Phase III, double-blind, placebo-controlled, randomised study	Phase II, single-blind, placebo-controlled, randomised study
Population	Adults with clinical diagnosis of aTTP and who have received one PEX treatment for that episode	Adults with a clinical diagnosis of aTTP and experiencing an episode necessitating PEX therapy

Study	HERCULES (NCT02553317)					TITAN (NCT01151423)				
Intervention	Caplacizumab 10 mg in conjunction with PEX and immunosuppression					Caplacizumab 10 mg plus standard of care				
Comparator	Placebo in conjunction with PEX and immunosuppression					Standard of care without caplacizumab				
Indicate if trial supports application for marketing authorisation	Yes	✓	**Indicate if trial used in the economic model**	Yes	✓	Yes		**Indicate if trial used in the economic model**	Yes	
	No			No		No	✓		No	✓
Rationale for use/non-use in the model	Pivotal trial supporting the use of caplacizumab in the target population					Supportive trial for the use of caplacizumab in the target population – not considered in regulatory application (B.2.4)				
Reported outcomes specified in the decision problem	• **mortality** • **recurrence of disease** • **length of hospital stay** • **volume and frequency of plasma exchange** • **adverse effects of treatment** • change in cognitive function • major thromboembolic events • reduction of time-to-recovery • time to platelet count response • TTP-related events					• mortality • recurrence of disease • volume and frequency of plasma exchange • major thromboembolic events • change in cognitive function • reduction of time-to-recovery • time to platelet count response • TTP-related events • adverse effects of treatment				
All other reported outcomes	• **refractory disease** • platelet count responders • PK and PD profile • disease-related markers					• PK and PD profile • RBC transfusion • blood line placement and replacement for PEX • concomitant medication				

Key: aTTP, acquired thrombotic thrombocytopenic purpura; PD, pharmacodynamic; PEX, plasma exchange; PK, pharmacokinetic; RBC, red blood cell.
Notes: outcomes in bold used in the base case model.

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

Table 4 outlines the methodology used by HERCULES and TITAN; trial schematics for HERCULES and TITAN are provided in Figure 1 and Figure 2. Important differences and points to note are discussed in text. Details of the methodology of Post-HERCULES are summarised in text and the statistical analysis plan is provided in the reference pack.[42]

B.2.3.1. Trial design

HERCULES was a Phase III double-blind placebo-controlled trial and TITAN was a Phase II single-blind placebo-controlled trial design. HERCULES allowed switching to open-label caplacizumab in the event of disease recurrence in a subject randomised to placebo (recurrence is a new decrease in platelet count that necessitated reinitiation of PEX) during the treatment period, however, the initial treatment allocation remained concealed and data from the double-blind treatment period are used for primary analyses.

Both primary studies consisted of a study drug treatment period that covered the PEX treatment period (duration defined by the treating clinician) and the 30-day post-daily PEX treatment period of study drug administration. During the study drug treatment period patients enrolled to HERCULES also received corticosteroids (and other immunosuppressants) in line with study protocol; patients enrolled to TITAN could receive immunosuppression or other adjunctive treatment according to site guidelines for treatment of TTP. Based on learnings from TITAN, HERCULES also included a treatment extension period that allowed further study drug treatment for a maximum of 28 days beyond the 30-day post-daily PEX treatment period. This was guided by risk factors for disease recurrence such as persistent ADAMTS13 deficiency and accompanied by optimisation of immunosuppressive therapy as needed to restore normal ADAMTS13 activity. In TITAN, study drug administration continued in case of re-initiation of PEX for an exacerbation of TTP with a maximum total treatment duration limited to 90 days after first administration of study drug.

The follow-up period was 28 days after the end of study drug treatment in HERCULES and TITAN was two-step at 30 days after the end of study drug treatment for primary and secondary endpoints, and up to 1 year for relapses and other longer-term endpoints (although the study was terminated early such that not all patients completed the 1-year follow-up visit - see Section B.2.4).

B.2.3.2. Patient eligibility

HERCULES enrolled patients with a clinical diagnosis of aTTP and TITAN enrolled patients with a clinical diagnosis of TTP not known to be congenital TTP. Although paediatric and/or adolescent inclusion was allowed post-protocol amendment in both studies, no patients <18 years of age were enrolled. Patients were enrolled to

HERCULES following receipt of one PEX treatment, this was also the case for some patients in TITAN following a protocol amendment but initially patients were enrolled prior to initiation of PEX treatment.

B.2.3.3. Trial endpoints

The primary outcome in HERCULES and TITAN was time to platelet count response but the definition of platelet count response differed across trials (Table 4). Normalisation of platelet count is a clinically important and relevant study endpoint as it is a measure of control of further microvascular thrombosis (see Section B.2.13). Definitions of recurrence of TTP aligned to International Consensus definitions and classed a recurrence within 30 days after PEX treatment cessation as an exacerbation, and a recurrence more than 30 days after PEX treatment cessation as a relapse.[37] Please see Sections B.2.13.3 and B.3.3.1 (Exacerbations) for further detail on definition of recurrence as applied in the economic model. Refractory disease was a pre-specified endpoint in in HERCULES and was measured against two definitions, one of which similarly aligned to the International Consensus definition. The occurrence of refractory TTP was a post-hoc analysis conducted in TITAN.[18] Applicability of trial endpoints is discussed further in Section B.2.13.

B.2.3.4. Subgroups

The most relevant subgroup analyses to the decision problem is that based on ADAMTS13 activity at baseline (<10% / ≥10%) as this allows patients meeting the modern UK diagnostic criteria for aTTP to be considered. Please note, that trial eligibility was assessed on clinical criteria alone, and an ADAMTS13 assay result was not a requirement for inclusion in either study.[16, 18] This is further discussed in Section B.2.13.

Table 4: Summary of trial methodology

	HERCULES	TITAN
Location	55 study centres in 15 countries: Australia (3 centres), Austria (1 centre), Belgium (4 centres), Canada (4 centres), Czech Republic (2 centres), France (6 centres), Hungary (2 centres), Israel (4 centres), Italy (5 centres), The Netherlands (1 centre), Spain (6 centres), Switzerland (1 centre), Turkey (3 centres), United Kingdom (3 centres) and the US(10 centres)	32 centres in 11 countries: Australia (1 site), Austria (1 site), Belgium (4 sites), France (1 site), Germany (5 sites), Israel (2 sites), Italy (4 sites), Spain (3 sites), Switzerland (2 sites), United Kingdom (1 site) and the US (8 sites)
Trial design	Phase III, double-blind, placebo-controlled, parallel group randomised study evaluating the efficacy and safety of caplacizumab in more rapidly restoring normal platelet counts as compared to standard treatment; normalisation of platelet count is a measure of control of further microvascular thrombosis. Randomisation was conducted through IWRS/IVRS with stratification for severity of neurological involvement (GCS ≤12 vs GCS 13-15).	Phase II, single-blind, placebo-controlled, parallel-group randomised study determining whether caplacizumab is safe and effective as adjunctive treatment to PEX and immunosuppression in patients with aTTP. Randomisation was conducted through IWRS.
Trial periods	The study consisted of the following periods: 1. the study drug treatment period covering: a. the daily PEX treatment period b. the 30-day post-daily PEX treatment period 2. the treatment extension period - 7-day treatment extensions up to 28 days 3. the follow-up period - 28 days after the end of study drug treatment	The study consisted of the following periods: 1. the study drug treatment period covering: a. the daily PEX treatment period b. the 30-day post-daily PEX treatment period 2. the follow-up period covering: a. 30 days after the end of study drug treatment for primary and secondary endpoints b. up to 1 year for relapses and other longer-term endpoints[a]
Eligibility criteria: - **inclusion**	• Male or female ≥18 years of age (adults)[b]	• Male or female ≥18 years of age (adults)[a]

	HERCULES	TITAN
	• Clinical diagnosis of acquired TTP • Required initiation of PEX therapy and had received one PEX treatment prior to randomisation within 24 hours of study PEX • Patient, or legally acceptable representative or independent physician where the patient was unconscious or unable to give consent, to provide informed consent and assent • Negative pregnancy test and willing to accept an acceptable contraceptive regimen	• Clinical diagnosis of TTP • Required initiation of PEX therapy - one single PEX treatment prior to randomisation was allowed following a protocol amendment • Accessible to follow-up and able to provide signed and dated informed consent and assent • Willing to accept an acceptable contraceptive regimen
- exclusion	• Platelet count ≥100,000/uL • Serum creatinine level >200 umol/L in case platelet count was >30 x 10^9/L (to exclude possible cases of aHUS) • Known other causes of thrombocytopenia, including (but not limited to): – Clinical evidence of enteric infection with E.coli 0157 or related organism – Atypical aHUS – Haematopoietic stem cell or bone marrow transplantation-associated thrombotic microangiopathy – Known or suspected sepsis – Diagnosis of disseminated intravascular coagulation • Known congenital TTP • Clinically significant active bleeding or high risk of bleeding (excluding thrombocytopenia)	• Platelet count ≥100,000/uL • Known other causes of thrombocytopenia: – Severe active infection indicated by sepsis – Clinical evidence of enteric infection with E.coli 0157 or related organism – Anti-phospholipid syndrome – Diagnosis of disseminated intravascular coagulation – Haematopoietic stem cell or bone marrow transplantation-associated thrombotic microangiopathy • Known congenital TTP • Active bleeding or high risk of bleeding • Uncontrolled arterial hypertension • Known chronic treatment with anticoagulant treatment that could not be stopped safely • Severe or life-threatening clinical condition other than TTP that would impair participation in the study

	HERCULES	TITAN
	• Known chronic treatment with anticoagulant treatment that could not be stopped safely • Malignant arterial hypertension • Clinical condition other than that associated with TTP with life expectancy <6 months • Known hypersensitivity to the active substance or excipients of the study drug • Enrolled in a clinical study with another investigational drug or device currently or <28 days prior to enrolment in this study • Considered by the investigator to be an unsuitable candidate for the study • Previously enrolled in a clinical study with caplacizumab and received caplacizumab or for whom the assigned treatment arm was unknown • Pregnancy or breastfeeding	• Malignancies resulting in a life expectation of less than 3 months • Known or suspected bone marrow carcinosis • Severe liver or renal impairment • Known hypersensitivity to the active substance or excipients of the study drug • Unable to comply with study protocol requirements and procedures • Pregnancy or breastfeeding
Settings and locations where the data were collected	Patients were treated in hospital/secondary care settings. Samples for platelet counts, creatinine, pregnancy and safety parameters were assessed by the local laboratory. All other samples were analysed centrally. Determination of ADAMTS13 was conducted at 1 of 3 selected diagnostic laboratories. A DSMB consisting of an independent group of clinical experts not participating in the study were appointed to review unblinded safety data and mortality information. MMs also provided medical oversight to ensure careful monitoring of patients' safety and welfare.	Patients were treated in hospital/secondary care settings. Samples for platelet counts, cardiac markers, BNP and safety parameters were assessed by the local laboratory. All other samples including those for ADAMTS13 activity were analysed centrally. A DSMB consisting of an independent group of clinical experts not participating in the study were appointed to review unblinded safety data and mortality information. MMs also provided medical oversight to ensure careful monitoring of patients' safety and welfare.

	HERCULES	TITAN
Intervention (n)	Caplacizumab (n=72) • Loading dose of 10 mg IV from 6 hours to 15 minutes prior to the first PEX post-randomisation. • Subsequent daily dose of 10 mg SC after daily PEX treatment and beyond for a period of 30 days post-daily PEX treatment and additional 7-day periods up to a maximum of 28 days as clinically indicated (considering underlying disease activity as indicated by weekly assessment of ADAMTS13 activity) PEX: as per comparator Immunosuppression: as per comparator	Caplacizumab (n=36) • Loading dose of 10 mg IV from 6 hours to 15 minutes prior to the first PEX post-randomisation • Subsequent daily dose of 10 mg SC after daily PEX treatment and beyond for a period of 30 days post-daily PEX treatment. • If PEX treatment was reinitiated for an exacerbation of TTP, daily dose of 10 mg SC after daily PEX treatment could continue with a maximum total treatment duration limited to 90 days. PEX: as per comparator Additional treatment: as per comparator
Comparator (n)	Placebo (n=73) Placebo: as per caplacizumab but without the active ingredient PEX: plasma at 1 to 1.5 x estimate plasma volume daily as of randomisation. Once platelet count ≥150 x 10^9/L, daily PEX continued for at least 2 days. Tapering of PEX was strongly discouraged and if considered, had to be discussed with the MM. Immunosuppression: corticosteroid treatment initiated/continued with a (methyl)prednisolone or (methyl)prednisone regimen of at least 1 mg/kg/day IV or PO during the daily PEX period and continued for 1-week post-daily PEX treatment. Afterwards, corticosteroids were 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 (including consideration of ADAMTS13 activity).	Placebo (n=39) Placebo: as per caplacizumab but without the active ingredient PEX: as per local practice and judged appropriate by the Investigator. Discontinuation depended on normalisation of platelet count, neurological status and other clinical and laboratory parameters. Tapering of PEX was at the discretion of the Investigator but was not recommended. Additional treatment: as per local practice and judged appropriate by the Investigator – could include one or more of the following: • Immunosuppressive treatment (including corticosteroids and rituximab) • Antiplatelet agents (e.g. aspirin) • Supportive therapy with red cell transfusion or folate supplementation

	HERCULES	TITAN
	Other immunosuppressive treatment: the use of other immunosuppressive treatment e.g. rituximab was permitted per standard site practice but was to be considered in light of protocol required corticosteroid treatment.	• Treatment with vincristine or cyclosporin in case of refractory TTP
Treatment switching	Treatment switching to open-label caplacizumab was permitted in the event of disease recurrence in a subject randomised to placebo, defined as a new decrease in platelet count that necessitated reinitiation of PEX, during the treatment period.	No treatment switching.
Permitted and disallowed concomitant medication	The use of other immunosuppressive treatments, including rituximab, was permitted per local practice but had to be considered in light of protocol required corticosteroid treatment. Additional concomitant medication needed as supportive care was permitted with the exception of desmopressin that is not indicated in TTP.	After platelet counts had partially recovered, LMWH could be used prophylactically in subjects at high risk of venous thromboembolism. Additional concomitant medication needed as supportive care was permitted with the exception of desmopressin that is not indicated in TTP.
Primary outcome	Time to platelet count response defined as recovery of platelets ≥150,000/uL with subsequent stop of daily PEX treatment within 5 days (i.e. initial recovery of platelet count).	Time to platelet count response defined as recovery of platelets ≥150,000/uL confirmed at 48 hours by a de novo measure of platelets ≥150,000/uL and LDH ≤2 x ULN (i.e. confirmed platelet response).
Other outcomes used in the economic model/specified in the scope	Mortality/recurrence of disease/major thromboembolic events: • Proportion of patients with TTP-related death, recurrence of TTP or at least one treatment-emergent major thromboembolic event from randomisation to the end of study drug treatment (key secondary endpoint) Recurrence of disease (key secondary endpoint):	Recurrence of disease: • Proportion of patients with complete remission, defined as platelet count response and absence of exacerbation from randomisation to 30 days after the end of study drug treatment (secondary endpoint) • Proportion of patients with exacerbations of TTP defined as recurrent thrombocytopenia following platelet count response requiring a re-initiation of daily PEX therapy within 30 days after the last

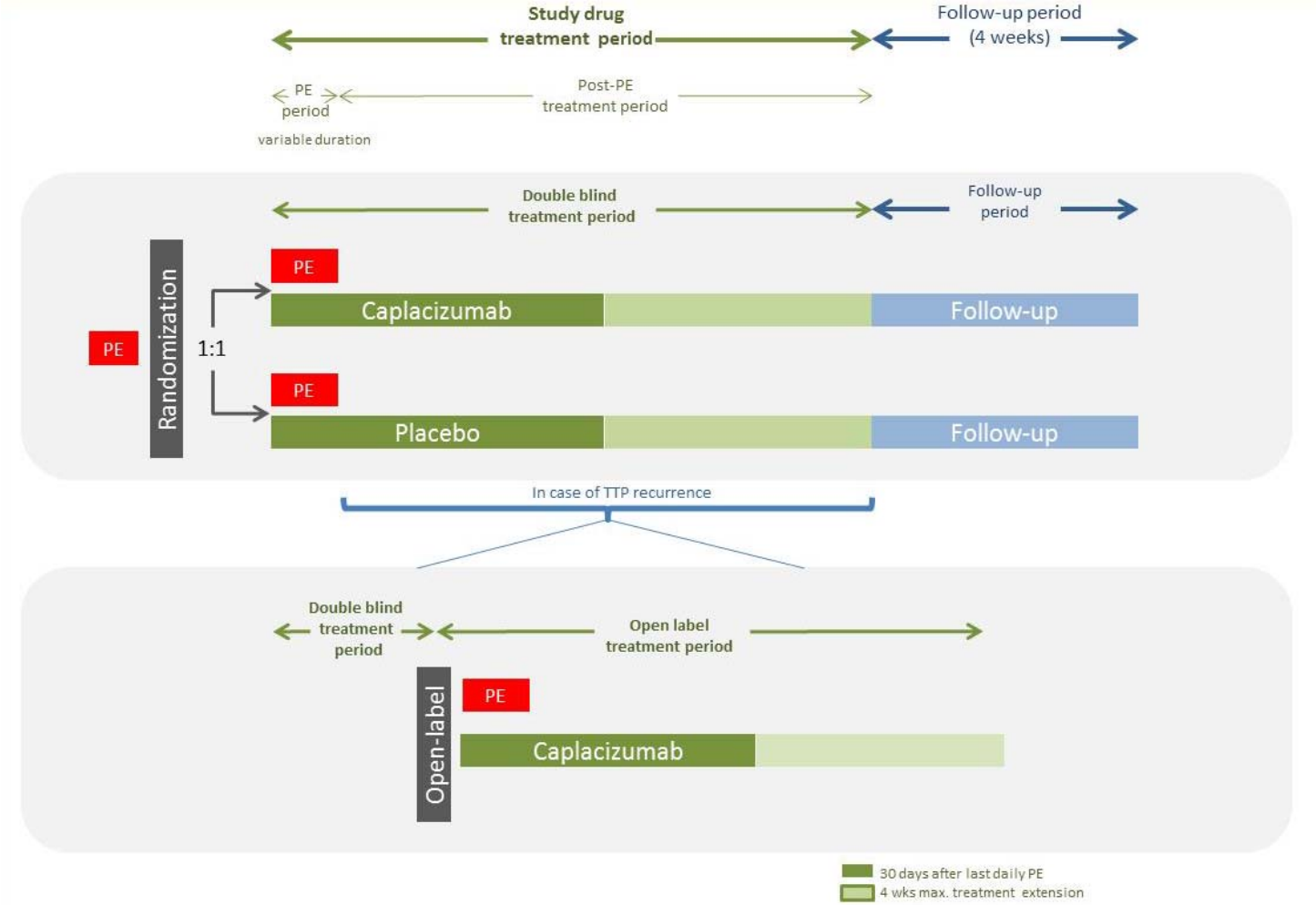
	HERCULES	TITAN
	• Proportion of patients with exacerbations of TTP defined as recurrent thrombocytopenia following platelet count response requiring a re-initiation of daily PEX therapy within 30 days after the last daily PEX treatment • Proportion of patients with relapsing of TTP defined as a de novo episode requiring re-initiation of daily PEX therapy that occurs more than 30 days after the last daily PEX treatment Refractory disease: • Proportion of patients with refractory TTP, defined as absence of platelet count doubling after 4 days of standard treatment and LDH >ULN (key secondary endpoint) • Proportion of patients with a lack of sustained platelet count increment or platelet counts <50 x 10^9/L and persistently raised LDH (>1.5 x ULN) despite 5 PEX treatments and steroid treatment (secondary endpoint) Reduction of time to recovery: • Total volume of plasma administered and number of days of daily PEX treatment from randomisation to 30 days after the end of study drug treatment (secondary endpoint) • Number of days in ICU and in hospital within (i) the PEX treatment period (ii) the overall treatment period (iii) the follow-up period (4 weeks after the end of study drug treatment) (iv) the overall study period (secondary endpoint)	daily PEX treatment, and time to exacerbation of TTP (secondary endpoint) • Proportion of patients with relapsing of TTP defined as a de novo episode requiring re-initiation of daily PEX that occurs more than 30 days after the last daily PEX treatment, and time to first relapse of TTP (secondary endpoint) • Proportion of patients with relapsing of TTP within 1 year after the last daily PEX and time to first relapse of TTP (longer-term tertiary endpoint) Reduction of time to recovery: • Number of daily PEX sessions, total volume of plasma administered and number of days of daily PEX treatment from randomisation to 30 days after the end of study drug treatment (secondary endpoint) TTP-related events: • Resolution or improvement of TTP-related signs and symptoms as captured on physical examination and as AEs, at complete remission and at the end of the study drug treatment period (secondary endpoint) Mortality within (i) the PEX treatment period (ii) the subsequent study drug treatment period (secondary endpoint)

	HERCULES	TITAN
	TTP-related events: • Proportion of patients with treatment-emergent clinically significant TTP-related events, and the number of such events (secondary endpoint) Mortality within (i) the PEX treatment period (ii) the subsequent study drug treatment period (iii) the follow-up period (iv) the overall study period (secondary endpoint) Change in cognitive function: • Proportion of patients with neurological symptoms based on neurological assessment on Days 1-5 and Weeks 1 and 5 of the study drug treatment period, and the first and final follow-up (secondary endpoint) • Cognitive mental status as measured by the SMMSE on Days 1-5 and Weeks 1 and 5 of the study drug treatment period, and the first and final follow-up (secondary endpoint) Adverse effects of treatment: • Incidence of AEs, SAEs, laboratory data, vital signs, ECG and physical examinations • Bleeding events	Change in cognitive function as measured by a neurocognitive test battery (CNTB) - descriptive statistics summary[c] Adverse effects of treatment: • Incidence of PEX treatment-related AEs • Incidence of caplacizumab treatment-emergent AEs and relationship to study drug – including major thromboembolic events • Development of ADAs ≤30 days post-last study drug treatment and >30 days post-last study drug treatment (longer-term tertiary endpoint) • Bleeding events
Subgroup analyses	Pre-planned subgroups: • Severity of disease at baseline • Nature of aTTP episode – initial/recurrent	Pre-planned subgroups: • ADAMTS13 activity at baseline - <5% / ≥5% • vWF:Ag level at baseline

	HERCULES	TITAN
	• ADAMTS13 activity at baseline - <10% / ≥10% • Treatment extension for safety – yes/no • Antithrombotic agent for bleeding events – yes/no	• Nature of aTTP episode – initial/recurrent • RICO suppression of <20% throughout treatment period – yes/no • PEX prior to randomisation – yes/no Post-hoc subgroups: • ADAMTS13 activity at baseline - <10% / ≥10%

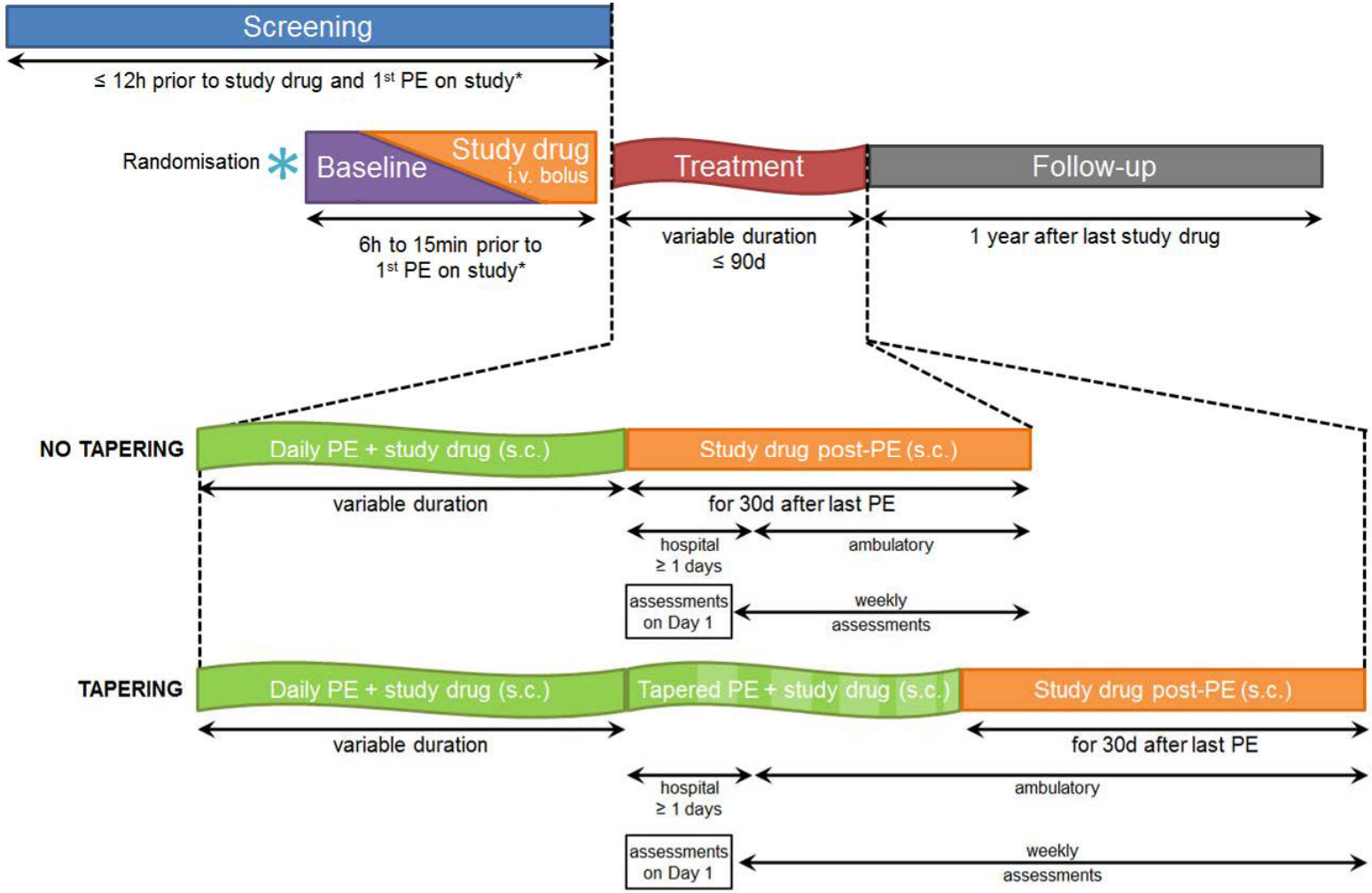
Key: ADA, anti-drug antibody; AE, adverse event; Ag, silver; aHUS, atypical haemolytic uremic syndrome; aTTP, acquired thrombotic thrombocytopenic purpura; BNP, brain natriuretic peptide; CNTB, Computerised Neuropsychological Test Battery; DSMB, data and safety monitoring board; ECG, electrocardiogram; GCS, Glasgow coma score; ICU, intensive care unit; IV, intravenous; LDH, lactate dehydrogenase; LMWH, low molecular weight heparin; MM, Medical Monitor; PEX, plasma exchange; PO, oral; RICO, ristocetin cofactor activity; SAE, serious adverse event; SC, subcutaneous; SMMSE, standardised mini mental state examination; TTP, thrombotic thrombocytopenic purpura; ULN, upper limit of normal; vWF, von Willebrand factor.
Notes: [a], due to early trial termination, not all patients completed the 1 year follow-up period; [b], in a protocol amendment paediatric patients aged ≥2 to <18 years were allowed in certain centres but no patients <18 years were enrolled; [c], originally defined as a secondary endpoint but due to homogenous baseline assessment timepoints (often after start of treatment), change from baseline analyses were not considered meaningful.
Source: HERCULES CSR[43]; TITAN CSR.[44]

Figure 1: Study schematic for HERCULES



Key: PE, plasma exchange; wks, weeks; max, maximum.
Source: Scully et al. 2019.[16]

Figure 2: Study schematic for TITAN



Key: h, hour; i.v.; intravenous; PE, plasma exchange; s.c., subcutaneous.
Source: TITAN CSR.[44]

B.2.3.5. Baseline characteristics and concomitant treatment

Demographic and disease characteristics of participants in HERCULES and TITAN, and concomitant treatment use are detailed in Table 5.

Within trials, baseline characteristics and concomitant treatment use were generally well balanced with the exceptions discussed below. Across trials, differences are observed in the proportion of Caucasian participants, platelet counts at baseline, LDH levels at baseline and immunosuppressive therapy use.

In HERCULES, an imbalance is observed in the nature of aTTP episode where a higher proportion of patients in the caplacizumab arm were having an initial TTP episode (rather than a recurrent episode). This imbalance potentially represents a worse prognosis at baseline in the caplacizumab arm as initial episodes tend to be more serious at presentation due to slower diagnosis of early signs of aTTP.

In TITAN, an imbalance is observed in cardiac marker levels (cardiac troponin I [cTnI] and brain natriuretic peptide [BNP]) which are higher in the placebo arm, and in platelet counts which are higher in the caplacizumab arm. It is difficult to say if these imbalances represent a worse prognosis at baseline in either group.

ADAMTS13 activity at baseline was below 10% in the majority of patients enrolled to both studies which confirmed the clinical diagnosis of aTTP (85% in HERCULES and 77% in TITAN). Of patients who had ADAMTS13 activity at or above 10% at baseline in HERCULES, 13 out of 20 patients had an aTTP diagnosis confirmed on the basis of a history of TTP or of ADAMTS13 activity below 10% at other time points during the trial. For the remaining 7 patients, the diagnosis of aTTP with severe ADAMTS13 deficiency could not be confirmed.

Immunosuppressive therapy use was higher in HERCULES than TITAN which is likely protocol-led, nonetheless, the majority of patients in both trials received adjunctive immunosuppressive treatment with glucocorticoids. The rate of rituximab use differed both within and across trials with more patients in the placebo arm of both trials receiving rituximab at some point during the overall study periods. This suggests patients in the placebo groups may have been better protected from disease recurrence than patients in the caplacizumab groups.

Section B.2.13 includes a discussion of the trial populations compared to the UK patients.

Table 5: Baseline characteristics of participants in caplacizumab trials

	HERCULES		TITAN	
	CAPLA (n=72)	**PBO (n=73)**	**CAPLA (n=36)**	**PBO (n=39)**
Mean age, years (range)	45 (18-77)	47 (21-79)	41 (19-72)	43 (21-67)
Gender, female n (%)	49 (68)	51 (70)	24 (67)	20 (51)
Race, n (%)				
White	47 (65)	50 (68)	32 (89)	34 (87)
Black	15 (21)	13 (18)	4 (11)	5 (13)
Asian	4 (6)	0	0	0
BMI, mean (range)	30 (18-53)	30 (19-59)	29 (16-51)	29 (19-46)
Median platelet count, per mm^3 (range)	24,000 (3,000-119,000)	25,000 (9,000-133,000)	[redacted]	[redacted]
TTP episode, n (%)				
Initial	48 (67)	34 (47)	24 (67)	27 (69)
Recurrent	24 (33)	39 (53)	12 (33)	12 (31)
Number of previous TTP episodes, n (%)				
0	[redacted]	[redacted]	NR	NR
1				
2				
>2				
ADAMTS13 activity, n (%)				
<10%	58 (81)	65 (89)	28 (78)	30 (77)
≥10%	13 (18)	7 (10)	2 (6)	6 (15)
Missing	1 (<1)	1 (<1)	6 (17)	3 (8)
PEX prior to randomisation, n (%)	NA	NA	2 (5.6)	4 (10.3)
Median cTnI, ug/L (range)	0.09 (0.01-75.96)	0.07 (0.01-7.28)	[redacted]	[redacted]
Median LDH, U/L (range)	449 (120-2,525)	403 (151-3,343)	[redacted]	[redacted]
Median serum creatinine, umol/L (range)	77 (35-717)	82 (52-482)	NR	NR
Mean BNP, pg/mL (SD)	NR	NR	[redacted]	[redacted]

	HERCULES		TITAN	
	CAPLA (n=72)	PBO (n=73)	CAPLA (n=36)	PBO (n=39)
Mean NSE, ng/mL (SD)	NR	NR	[redacted]	[redacted]
GCS score, n (%)			NR	NR
≤12	6 (8)	5 (7)		
13-15	65 (90)	67 (92)		
Missing	1 (<1)	1 (<1)		
SMMSE total score			NR	NR
N	[redacted]	[redacted]		
Median (range)	[redacted]	[redacted]		
Immunosuppressive therapy, n (%)				
Glucocorticoids	69 (96)	71 (97)	32 (89)	36 (92)
Rituximab	28 (39)	35 (48)	[redacted]	[redacted]
Frontline (up to day 3)	9 (12)	16 (22)	2 (6)[a]	9 (23)[a]
During PEX (after day 3)	3 (4)	7 (10)	NR	NR
After PEX	11 (15)	6 (8)	NR	NR
During PEX for EXCB	0	1 (1)	NR	NR
After PEX for EXCB	0	2 (3)	NR	NR
During follow-up	5 (7)	3 (4)	NR	NR
Mycophenolate mofetil	6 (8)	0	NR	NR
Hydroxychloroquine	2 (3)	1 (1)	NR	NR
Bortezomib	2 (3)	0	NR	NR
Cyclophosphamide	1 (1)	1 (1)	NR	NR
Cyclosporin	1 (1)	1 (1)	NR	NR
Other treatments for TTP, n (%)				
Splenectomy			NR	NR
Before the trial	0	5 (7)		
During the trial	2 (3)	1 (1)		
IGC infusion	4 (6)	0	NR	NR
Immunoadsorption	1 (1)	0	NR	NR

Key: BMI, body mass index; BNP, brain natriuretic peptide; CAPLA, caplacizumab; cTnI, cardiac troponin I; EXCB, exacerbation; IGC, immune globulin concentrate; LDH, lactate dehydrogenase; NA, not applicable; NR, not reported; NSE, neuron-specific enolase; PBO, placebo; PEX, plasma exchange; SMMSE, standardised mini mental state examination; TTP, thrombotic thrombocytopenic purpura.
Notes: [a], rituximab use during daily PEX.
Source: HERCULES CSR[43]; Peyvandi et al. 2016[18]; Scully et al. 2019[16]; TITAN CSR.[44]

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

Table 6 summarises the statistical analysis plans for HERCULES and TITAN.

B.2.4.1. Analysis sets

Primary efficacy analyses were conducted in the intention-to-treat (ITT) population which included all patients assigned to treatment arms ‘as randomised’.

Safety analyses were conducted in the safety population which included all patients who received at least one dose of caplacizumab or placebo assigned to treatment arms ‘as treated’.

Secondary efficacy analyses were conducted in the per protocol (PP) population which included all patients assigned to treatment arms ‘as randomised’ who had no major protocol violations.

For the HERCULES trial where switching to open-label caplacizumab was permitted in subjects randomised to placebo, the ITT population was based on treatment assignment for the double-blind period. After switch to open-label caplacizumab an all-treated analysis was conducted in a separate pooled open-label caplacizumab group for efficacy and safety outcomes.

B.2.4.2. Statistical analysis

Statistical analysis planning was based on the primary outcome of time to platelet count response for both trials. In addition, HERCULES applied a fixed-sequence approach for analyses of key secondary outcomes that were hierarchically ordered on the basis of clinical relevance as follows:

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

2. Proportion of patients with a recurrence of TTP in the overall study period (including the 4-week follow-up period)

3. Proportion of patients with refractory TTP, defined as an absence of platelet count doubling after 4 days of standard treatment and LDH >ULN

4. Time to normalisation of all three of the following organ damage marker levels: LDH ≤1 x ULN, cTnI ≤ ULN and serum creatinine ≤1 x ULN

Formal analysis was to be conducted once all data for the 1-month follow-up was clean and locked for both trials. There was to be a second formal analysis at the end of the planned 1-year follow-up for TITAN, however, on 13th January 2014, a decision was made to stop patient recruitment due to a low recruitment rate. At that time, it was communicated that the conduct of the study would be stopped when the last patient randomised reached the 1-month follow-up visit. TITAN data reported in this submission therefore includes data up to 1-month follow-up for all patients and the available data up to 1-year follow-up for patients who remained in the study after 1-month follow-up.

Protocol amendments and study conduct

The original HERCULES protocol was amended twice during the study: Version 2.0 reordered and reworded secondary endpoints and added an exclusion criterion to exclude patients who may have received prior caplacizumab (among other more minor changes); Version 3.0 increased the planned sample size to account for drop-outs and increase the statistical power of the key secondary endpoint analysis and removed IMP kit from the schedule of assessments. In addition, a local amendment was submitted to selected sites to allow enrolment of paediatric patients.

The original TITAN protocol was amended 12 times during the study. Major changes included: Version 3.0 updated the primary endpoint from reduction of time to recovery to time to platelet count response; Version 8.0 addressed issues related to the case report form (CRF), changed dosing rules of study treatments, changed duration of hospitalisation rules, deleted the pharmacokinetic/pharmacodynamic sub study, and provided several other necessary clarifications; Version 10.0 defined exacerbation and relapse and provided further clarifications deemed necessary; Version 10.0 opened the study to adolescents; Version 12.0 allowed the recruitment of patients who have received one prior PEX treatment.

In addition to the issues related to the CRF addressed through protocol amendment Version 8.0, the following issues related to central laboratory and local laboratory use were identified:

- Laboratory specifications were not synchronised with the CRF/database such that an unknown volume of data were unassignable and therefore not usable
- The sampling schedule was driven by PEX or hospital stay and the laboratory did not know what samples to expect when
- Changes in the sampling schedule were not updated in time/provided to sites in time such that samples were taken out of protocol scope or missing
- Certain samples were not taken per protocol such that some data could not be assigned to a specific study visit and had to be mapped to unscheduled visits
- Not all local laboratory ranges were timely available – ranges were documented in a Note to File
- Local laboratory ranges were only available very late in the study so serious outliers were not flagged through a programmed check and were included as original recorded in the data for analysis
- Some units were updated via 'deduction' as the result was not plausible according to the unit (e.g. factor 1000 above upper limit)

B.2.4.3. Patient disposition

A total of 145 patients were randomised in HERCULES, 72 into the caplacizumab group and 73 into the placebo group. All but one patient in the caplacizumab group received study drug and were included in the safety population. A total of 20 patients in the caplacizumab group and 5 patients in the placebo group had at least one week of double-blind treatment extension. Three-quarters of the randomised patients completed the study (up to 1-month follow-up) with the main reason for patients discontinuing prematurely being an adverse event.

Open-label caplacizumab was received by 28 patients in HERCULES, 2 from the double-blind caplacizumab group and 26 from the double-blind placebo group. Of these, 71% completed the study with the main reason for patients discontinuing prematurely being withdrawal of consent or physician choice.

A total of 75 patients were randomised in TITAN, 36 into the caplacizumab group and 39 into the placebo group. All but three patients (one in the caplacizumab group and two in the placebo group) received study drug and were included in the safety population. Approximately half of the randomised patients completed the study (up to

1-year follow-up) with the main reason for patients discontinuing prematurely being the termination of the study by the Sponsor. A total of 32 patients in the caplacizumab group and 31 patients in the placebo group attended the 1-month follow-up visit.

Patient disposition data for both studies are provided in further detail in Appendix D.

Table 6: Summary of statistical analysis plans in caplacizumab trials

	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
HERCULES	The hypothesis tested was the superiority of caplacizumab to placebo with respect to the time to platelet count response (initial platelet count ≥150 × 10^9/L with subsequent stop of daily PEX within 5 days).	Time to platelet count response was compared between groups with the use of a two-sided stratified log-rank test on the basis of a KM analysis; the stratification factor was the severity of neurological involvement at baseline (GCS score of ≤12 vs >13). The rate ratio for time to platelet count response was also estimated with a Cox proportional-hazards regression model with outcome as a dependent variable, and treatment group and GCS category as independent variables. Of the key secondary outcomes, the first three in the hierarchy were analysed with the use of a CMH test adjusting for GCS category. The fourth outcome was analysed with the use of a stratified log-rank test that was based on a KM analysis, with	It was estimated that with a sample of 132 patients, the trial would have 80% power to detect a median time to platelet count response that was 40% shorter with caplacizumab than with placebo, using a log-rank test at a 5% significance level and assuming a 10% dropout rate. This sample size would also provide 83% power to detect a rate of the first key secondary outcome (composite endpoint) that was 20% lower in the caplacizumab group, using a chi-square test with a large sample approximation and a 5% significance level.	In time to platelet count response KM analysis, an observation was censored if the defined time interval of 45 days after first administration of study drug was not met due to any cause (e.g. endpoint not reached within this time point or patient lost to follow-up). In key secondary endpoints 1 and 2, any event that occurred prior to a switch to open-label caplacizumab was included. In key secondary endpoint 3, patients who discontinued the study before Day 5 were excluded from the analysis. Missing values were imputed using multiple imputation (MCMC) by averaged simulated parameter values. In key secondary endpoint 4, patients who switched to caplacizumab before having reached the

	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		adjustment for GCS category and baseline LDH.		endpoint were censored at time of switch.
TITAN	The hypothesis tested was the superiority of caplacizumab to placebo with respect to the time to platelet count response (recovery of platelets ≥150 × 10^9/L confirmed at 48 hours by a de novo measure of platelets ≥150 × 10^9/L and LDH ≤2 x ULN).	Time to platelet count response was compared between groups with the use of a one-sided stratified log-rank test on the basis of a KM analysis; the stratification factor was the absence/presence of one PEX session prior to randomisation. The rate ratio for time to platelet count response was also estimated with a Cox proportional-hazards regression model with one PEX session prior to randomisation (yes/no) as a covariate.	It was estimated that with a sample of 110 patients, the trial would have 80% power to detect a median time to platelet count response that was 44% shorter with caplacizumab than with placebo, using a log-rank test at a 2.5% significance level and assuming a 15% dropout rate. Only 75 patients were enrolled to the trial, resulting in its premature termination.	In time to platelet count response KM analysis, an observation was censored if the defined time interval of 30 days after first administration of study drug was not met due to any cause (e.g. endpoint not reached within this time point or patient lost to follow-up). The primary, secondary and longer-term endpoint analyses were based on available data.

Key: CMH, Cochran–Mantel–Haenszel; GCS, Glasgow Coma Scale; KM, Kaplan–Meier; LDH, lactate dehydrogenase; MCMC, Markov Chain Monte Carlo; PEX, plasma exchange; ULN, upper limit of normal.
Source: HERCULES CSR[43]; Peyvandi et al. 2016[18]; Scully et al. 2019[16]; TITAN CSR.[44]

B.2.5. Quality assessment of the relevant clinical effectiveness evidence

Details of the quality assessment conducted for HERCULES and TITAN are provided in Appendix D.

HERCULES had an overall low risk of bias. The study was performed in compliance with the principles of Good Clinical Practice (GCP) and Good Laboratory Practice (GLP) and considered to address most of the uncertainties associated with the earlier TITAN study. While uncertainties remain regarding long-term effects of caplacizumab and caplacizumab re-treatment, the ongoing Post-HERCULES study is designed to address these uncertainties.

There were several deviations to protocol in HERCULES that should be acknowledged with 44.1% of patients having a major protocol deviation. The most commonly reported deviations were 'treatment non-compliance', reported in 15 patients in the caplacizumab group (21%) and 21 patients in the placebo group (29%), and 'selection criteria not met', reported in 11 patients in the caplacizumab group (15%) and 10 patients in the placebo group (14%). The specific nature of these deviations were similar between study groups and are not thought to materially impact the outcomes of the study, a conclusion supported by the EMA.[17] This is demonstrated in the results of the PP analysis that support the ITT analysis (see Appendix L).

TITAN had an overall high risk of bias. Although TITAN was planned under the rules of GCP, several issues relating to its conduct were observed: the premature termination, the number of major protocol amendments, central and local laboratory issues, missing data (with the extent often not clear to the assessor), a need to conduct several analyses mandated by the FDA post-hoc, and a relatively large volume of protocol deviations (see below). As a result, the EMA did not consider data from TITAN adequate to be reflected in the product information.[17]

A total of 48 patients (64.0%) in TITAN had a major protocol deviation. The most commonly reported deviation was 'treatment non-compliance', reported in 19 patients in the caplacizumab group (52.8%) and 19 patients in the placebo group

(48.7%). While the PP analysis supports the ITT analysis as observed in HERCULES, the PP population was very small in TITAN given the low recruitment.

B.2.6. Clinical effectiveness results of the relevant trials

B.2.6.1. Time to platelet count response (primary outcome)

Caplacizumab treatment resulted in a statistically significant reduction in time to confirmed platelet count response, as summarised in Table 7.

Patients treated with caplacizumab in HERCULES were 1.55 times more likely to achieve platelet count normalisation at any given time point than patients treated with PEX and immunosuppression alone (p=0.01), and the median time to response was reduced by 0.19 days.

Similarly positive outcomes were observed in TITAN (HR for time to platelet count response: 2.20) (Table 7). Data suggest the median time to response was slightly longer in patients who did not receive PEX treatment within 24 hours prior to randomisation, which we would expect as platelet counts may have started to improve on receipt of PEX in the one prior session group.

Table 7: Time to platelet count response in caplacizumab trials (ITT)

	HERCULES		**TITAN**	
	CAPLA (n=72)	**PBO (n=73)**	**CAPLA (n=36)**	**PBO (n=39)**
Patients with event, n	66	66	31 (86.1)	28 (71.8)
Median days to response (95% CI)	2.69 (1.89, 2.83)	2.88 (2.68, 3.56)	2.97 (2.74, 3.65)	4.79 (3.51, 5.94)
HR for time to platelet count response (95% CI)	1.55 (1.09, 2.19)		2.20 (1.28, 3.78)	
p-value	0.01		0.005	
One PEX session prior to randomisation	NA	NA	2.44 (1.92, 2.97)	4.31 (2.91, 5.68)
No PEX session prior to randomisation	NA	NA	3.00 (2.74, 3.88)	4.92 (3.21, 6.59)

Key: CAPLA, caplacizumab; CI, confidence interval; ITT, intention-to-treat; NA, not applicable; PBO, placebo; PEX, plasma exchange; RR, rate ratio; ULN, upper limit of normal.
Notes: platelet count response defined as ≥150,000/uL with subsequent stop of daily PEX treatment within 5 days in the HERCULES trial, and recovery of platelets ≥150,000/uL confirmed at 48 hours by a de novo measure of platelets ≥150,000/uL and LDH ≤2 x ULN in the TITAN trial.

Source: Cablivi EPAR[17]; Peyvandi et al. 2016[18]; Scully et al. 2019.[16]

Results obtained from various sensitivity analyses of the primary endpoint in both trials confirmed the results of the primary efficacy analysis in the ITT population. Data for all sensitivity analyses are provided in Appendix L.

B.2.6.2. Composite of TTP-related death, recurrence or major thromboembolic event (secondary outcome)

Caplacizumab demonstrated a statistically significant lower incidence (74%; p<0.001) of a component of the composite outcome of TTP-related death, recurrence of TTP or a major thromboembolic event during the treatment period, as summarised in Table 8.

Table 8: Composite of TTP-related death, recurrence or major thromboembolic event in HERCULES (ITT – study drug treatment period)

	CAPLA (n=72)	PBO (n=73)	p-value
Composite outcome, n (%)	9 (12)	36 (49)	<0.001
TTP-related death, n (%)	0	3 (4)	NR
Recurrence of TTP[a], n (%)	3 (4)	28 (38)	NR
Major thromboembolic event, n (%)	6 (8)	6 (8)	NR

Key: CAPLA, caplacizumab; ITT, intention-to-treat; NR, not reported; PBO, placebo; TTP, thrombotic thrombocytopenic purpura.
Notes: [a], based on exacerbation of TTP episode.
Source: Scully et al. 2019.[16]

B.2.6.3. Recurrence of disease (secondary outcome)

Recurrence of disease data for HERCULES and TITAN are summarised in Table 9.

Caplacizumab demonstrated a 67% lower incidence in recurrence of disease in HERCULES over the entire study period (up to 1-month follow-up). All recurrences in the placebo arm occurred within 30 days of the last daily PEX treatment, which met the formal definition of exacerbation. Of the nine patients experiencing disease recurrence in the caplacizumab arm, two had an exacerbation that was possibly triggered by concurrent infection and one had an exacerbation that was related to non-adherence to caplacizumab while having low ADAMTS13 activity levels. The

other six patients had a recurrence that occurred during the follow-up period and thus were considered to have had a relapse, according to International Consensus definitions. In each of these patients, the ADAMTS13 activity level was still below 10% when caplacizumab was stopped, which indicated unresolved underlying autoimmune disease.

No differences were observed in recurrence of disease rates between treatment arms in TITAN over the entire study period (up to 12 months follow-up), although there was a reduced risk of exacerbation with caplacizumab and a higher rate of complete remission (confirmed platelet count response and absence of exacerbation). Of the 11 patients experiencing relapse in the caplacizumab arm, seven patients still had an ADAMTS13 activity level below 10% when caplacizumab was stopped and relapsed within 4-10 days of stopping caplacizumab treatment. The other four patients were considered 'de novo relapse events' as they had restored ADAMTS13 activity ≥10% at the end of the study treatment period. Relapses in these patients occurred within 30-127 days of stopping caplacizumab treatment.

Differences observed in relapse rates between trials (22% in TITAN and 8% in HERCULES) reflect the extended caplacizumab treatment period in HERCULES for patients with persistent severe ADAMTS13 deficiency that was born from the TITAN learnings that such patients were relapsing early post treatment discontinuation. These outcomes further support the use of ADAMTS13 monitoring in guiding treatment duration decisions including caplacizumab as well as immunosuppressive treatment.

Table 9: Recurrence of disease in caplacizumab trials (ITT)

	HERCULES		**TITAN**	
	CAPLA (n=72)	**PBO (n=73)**	**CAPLA (n=36)**	**PBO (n=39)**
Patients with recurrence of disease, n (%)	9 (12)	28 (38)	13 (36.1)	13 (33.3)
p-value	<0.001		NR	
Patients with exacerbation, n (%)	3 (4)	28 (38)	3 (8)	11 (28)
Patients with relapse, n (%)	6 (8)	0	11 (31)	3 (8)

	HERCULES		TITAN	
	CAPLA (n=72)	PBO (n=73)	CAPLA (n=36)	PBO (n=39)
Patients with complete remission, n (%)	NR	NR	29 (81)	18 (46)

Key: CAPLA, caplacizumab; ITT, intention-to-treat; NR, not reported; PBO, placebo.
Notes: exacerbation defined as recurrent thrombocytopenia following platelet count response requiring a re-initiation of daily PEX therapy within 30 days after the last daily PEX treatment; relapse defined as a de novo episode requiring re-initiation of daily PEX therapy that occurs more than 30 days after the last daily PEX treatment; complete remission defined as platelet count response and absence of exacerbation from randomisation to 30 days after the end of study drug. Data up to the 12-month follow-up reported for TITAN.
Source: Cablivi EPAR.[17]; Peyvandi et al. 2016[18]; Scully et al. 2019.[16]

B.2.6.4. Refractory disease (secondary outcome)

No patient in the caplacizumab group of HERCULES had refractory disease compared to three patients in the placebo group (4%) according to the key secondary endpoint criterion for this outcome (absence of platelet count doubling accompanied by LDH >ULN).[16] This difference did not reach statistical significance due to the overall low number of patients meeting this strict definition of refractory disease.

According to the International Consensus definition for refractory disease (lack of sustained platelet count increment or platelet counts <50 x 10^9/L and persistently raised LDH [>1.5 x ULN] despite 5 PEX treatments and steroid treatment[1]), which is the more recently published definition (2017), and more common criteria used to define refractory disease in clinical practice, no patient in the caplacizumab group had refractory disease compared to [redacted] patients ([redacted]%) in the placebo group.[43]

B.2.6.5. Time to normalisation of organ damage marker levels (secondary outcome)

The median time to normalisation of organ damage markers in HERCULES was 2.86 days (95% CI: 1.93, 3.86) in the caplacizumab group versus 3.36 days (95% CI: 1.88, 7.71) in the placebo group, demonstrating a trend towards faster time to organ damage marker normalisation with caplacizumab treatment.[16]

B.2.6.6. Reduction of time to recovery, including length of hospital stay and volume and frequency of plasma exchange (secondary outcome)

As can be seen from the data summarised in Table 10, caplacizumab treatment reduced the number of days of PEX therapy total volume of plasma administered and hospitalisation needs.

In HERCULES there was a 38% shorter duration of PEX therapy in the caplacizumab group compared to the placebo group and a 41% lower volume of plasma exchanged.[16] Moreover, there was a 65% shorter duration of care in an intensive care unit (ICU) and a 31% shorter duration of hospitalisation.

Table 10: Reduction of time to recovery data in caplacizumab trials (ITT)

	HERCULES		TITAN	
	CAPLA (n=72)	**PBO (n=73)**	**CAPLA (n=36)**	**PBO (n=39)**
Days of PEX therapy Mean (95% CI) [SD] Median (range) [min-max]	 5.8 (4.8, 6.8) 5.0 (1.0-35.0)	 9.4 (7.8, 11.0) 7.0 (3.0-46.0)	 5.9 [2.4] [3-15]	 7.9 [6.4] [2-35]
Volume of plasma - L Mean (95% CI) [SD] Median (range) [min-max]	 21.3 (18.1, 24.6) 18.1 (5.3-102.2)	 35.9 (27.6, 44.2) 26.9 (4.0-254.0)	 19.9 [8.2] [5.0-44.8]	 28.3 [21.4] [7.1-103.8]
Hospitalisation days Mean (95% CI) Median (range)	 9.9 (8.5, 11.3) 9.0 (2.0-37.0)	 14.4 (12.0, 16.9) 12.0 (4.0-53.0)	NR	NR
Patients admitted to ICU, n (%)	28 (39)	27 (37)	NR	NR
ICU days Mean (95% CI) Median (range)	 3.4 (2.6, 4.2) 3.0 (1.0-10.0)	 9.7 (5.3, 14.1) 5.0 (1.0-47.0)	NR	NR

Key: CAPLA, caplacizumab; CI, confidence interval; ICU, intensive care unit; ITT, intention-to-treat; L – litre; NR, not reported; PBO, placebo; PEX, plasma exchange; SD, standard deviation.
Source: Peyvandi et al. 2016[18]; Scully et al. 2019.[16]

B.2.6.7. TTP-related events (secondary outcome)

Treatment-emergent clinically significant TTP-related events reported in HERCULES are summarised in Table 11. These data demonstrate fewer patients experienced

TTP-related events when treated with caplacizumab compared to placebo but are mainly driven by the difference in disease recurrence rates reported in Table 9.

In TITAN, TTP-related signs or symptoms had resolved or improved in [redacted]% of patients in the caplacizumab group compared to [redacted]% of patients in the placebo group at the 1-month follow-up visit. A total of [redacted] patients in the placebo group and [redacted] patients in the caplacizumab group lost resolution or improvement in TTP-related signs and symptoms at 1-month follow-up compared with the end of study drug treatment period; [redacted] patients in the caplacizumab group and no patients in the placebo group gained resolution or improvement in TTP-related signs and symptoms at 1-month follow-up compared with the end of study drug treatment period.

Table 11: Treatment-emergent clinically significant TTP-related events in HERCULES (ITT)

n (%)	Study drug treatment period		Overall study period	
	CAPLA (n=71)	PBO (n=73)	CAPLA (n=72)	PBO (n=73)
At least one TTP-related event	[redacted]	[redacted]	[redacted]	[redacted]
Cardiovascular event	[redacted]	[redacted]	[redacted]	[redacted]
Neurological event	[redacted]	[redacted]	[redacted]	[redacted]
TTP-related death	[redacted]	[redacted]	[redacted]	[redacted]
TTP	3 (4.2)	28 (38.4)	9 (12.5)	28 (38.4)
Other	[redacted]	[redacted]	[redacted]	[redacted]

Key: CAPLA, caplacizumab; CI, confidence interval; ITT, intention-to-treat; TTP, thrombotic thrombocytopenic purpura.
Source: HERCULES CSR.[43]; Scully et al. 2019.[16]

B.2.6.8. Mortality (secondary outcome)

None of the patients in the caplacizumab group of HERCULES died during the study drug treatment period compared to three patients in the placebo group.[16] Each of these deaths were assessed as TTP-related by the adjudication committee. The cause of death was (i) worsening massive ischemic attack with haemorrhagic transformation (ii) worsening TTP with coma and (iii) hypoxia with bleeding in the lung. During follow-up, one patient in the caplacizumab group died: this death was

assessed as TTP-related; the cause of death was cerebral ischemia and subsequent investigation found that there was a recurrence of TTP in this individual.

Post-hoc analyses showed that of the three patients who died during the study drug treatment period, [redacted] had refractory disease according to the International Consensus definition (data on file).

In TITAN, no patients in the caplacizumab group died up to and including 1-month follow-up.[18] Two patients in the placebo group died and both deaths were considered to be TTP-related. The cause of death was (i) severe refractory TTP (ii) cerebral haemorrhage. Neither patient had achieved a platelet count response and therefore were considered to have died from the acute episode.

B.2.6.9. Change in cognitive function (secondary outcome / descriptive summary)

At baseline, [redacted] patients in the caplacizumab group and [redacted] patients in the placebo group of HERCULES had neurological symptoms, including disorientation, agitation, and dysarthria.[43] The number of patients with neurological symptoms decreased during the daily PEX treatment period in both groups to [redacted] patients in the caplacizumab group and [redacted] patients in the placebo group. At the end of the 30-day post-daily PEX treatment period, this had further decreased to [redacted] patients in each group and at the end of the 1-month follow-up only [redacted] patient in the caplacizumab group and [redacted] patients in the placebo group had neurological symptoms.

Cognitive mental status as assessed using the SMMSE was [redacted] at baseline in both groups of HERCULES and [redacted] in both groups during the study.[43]

B.2.7. Subgroup analysis

A clear treatment benefit was observed in all patients treated with caplacizumab in HERCULES, irrespective of severity of the episode, nature of episode or ADAMTS13 activity level. These data are presented in full in Appendix E.

In patients with ADAMTS13 activity <10% at baseline who would meet the current UK diagnostic criteria for aTTP, the relative treatment effect of caplacizumab versus

placebo was higher in magnitude to the ITT population and the subgroup of patients with ADAMTS13 activity ≥10%, as summarised in Table 12.

In post-hoc analysis of TITAN data, less conclusive outcomes are observed with a higher magnitude of effect observed in the subgroup of patients with ADAMTS13 activity ≥10%, as summarised in Table 12. However, these data are based on small patient numbers with only two patients in the caplacizumab group included in the ADAMTS13 activity ≥10%, and therefore should be interpreted with caution.

Table 12: Time to platelet count response based on ADAMTS13 activity

HR (95% CI) Caplacizumab vs placebo	**HERCULES**	**TITAN**
ITT population	1.55 (1.09, 2.19)	2.20 (1.28, 3.78)
ADAMTS13 <10%	1.70 (1.16, 2.49)	1.63 (0.92, 2.92)
ADAMTS13 ≥10%	1.52 (0.47, 4.92)	[redacted]
Key: CI, confidence interval; HR, hazard ratio. **Source:** Cablivi EPAR[17]; Peyvandi et al. 2016[18]; TITAN CSR.[44]		

B.2.8. Meta-analysis

An integrated summary of efficacy was developed as part of the Biologics License Application for caplacizumab: this document is provided in the reference pack.[45]

In brief, all patients across HERCULES and TITAN were integrated and included in the analysis population. The primary efficacy endpoint for the integrated analysis was time to platelet count response, and platelet count response definitions, censoring and event plans remained as per the original study. Key secondary endpoints were aligned to the HERCULES trial with the exception that time to normalisation of organ damage marker levels was replaced with the proportion of patients with at least one treatment-emergent major thromboembolic event.

As can be seen in Table 13, outcomes of the HERCULES trial were supported in the integrated analysis with patients [redacted] times more likely to achieve platelet count response when treated with caplacizumab compared to placebo. Treatment with caplacizumab also resulted in a [redacted]% lower incidence of a component of the composite outcome of TTP-related death ([redacted]), recurrence of TTP or a major thromboembolic event, an [redacted]% reduction in disease recurrence ([redacted]), and a [redacted]% ([redacted]) reduction in treatment-emergent major thromboembolic events ([redacted]).

Table 13: Primary and secondary outcomes in an integrated analysis across HERCULES and TITAN (ITT)

	CAPLA (n=108)	PBO (n=112)	p-value
Primary outcome			
Median days to response (95% CI)	[redacted]	[redacted]	[redacted]
HR for time to platelet count response (95% CI)	[redacted]		
Key secondary outcomes			
Composite of TTP-related death, recurrence of TTP or an MTE, n (%)	[redacted]	[redacted]	[redacted]
Patients with recurrence of disease, n (%)	[redacted]	[redacted]	[redacted]
Patients with refractory disease, n (%)	[redacted]	[redacted]	[redacted]
Patients with at least one MTE, n (%)	[redacted]	[redacted]	[redacted]
Other secondary outcomes			
Mortality rate during treatment period, n (%)	[redacted]	[redacted]	[redacted]
Mortality rate during overall study period, n (%)	[redacted]	[redacted]	[redacted]
Patients with refractory disease - ICD, n (%)	[redacted]	[redacted]	[redacted]
Number of PEX days Mean (SD) Median (range)	[redacted]	[redacted]	[redacted]

Key: MTE, major thromboembolic event; NR, not reported; PEX, plasma exchange.
Notes: Platelet count response defined as ≥150,000/uL with subsequent stop of daily PEX treatment within 5 days in the HERCULES trial and recovery of platelets ≥150,000/uL confirmed at 48 hours by a de novo measure of platelets ≥150,000/uL and LDH ≤2 x ULN in the TITAN trial.
Source: Integrated summary of efficacy.[45]

B.2.9. Indirect and mixed treatment comparisons

An indirect treatment comparison is not required as head-to-head data vs. SoC are available for comparison of relevance to the decision problem.

B.2.10. Adverse reactions

Caplacizumab was generally well tolerated across HERCULES and TITAN trials, as summarised in the following sections. An integrated summary of safety was

developed as part of the Biologics License Application that included seven clinical trials investigating caplacizumab across aTTP and percutaneous coronary intervention indications: this document is provided in the reference pack.[46]

B.2.10.1. Extent of exposure

The median duration of exposure to caplacizumab was 35.0 days in the double-blind treatment period of HERCULES.[16] Twenty patients had at least one week of double-blind treatment extension with nine patients receiving four additional weeks of caplacizumab treatment after the 30-day post-daily PEX treatment period.[43] Of patients switching to open-label caplacizumab on disease recurrence, the median duration of exposure was 36.5 days in those originally treated with placebo (n=26) and 34.5 days in those originally treated with caplacizumab (n=2).[43] The median duration of exposure to caplacizumab was similar in TITAN at 36.0 days across the study period (6.0 days during daily PEX treatment period and 30.0 days post-daily PEX treatment).[17]

B.2.10.2. Adverse events

Most patients in both treatment arms of HERCULES and TITAN experienced at least one treatment emergent adverse event (TEAE) but most were medically manageable with a low rate of TEAEs leading to withdrawal, and no patient dying while receiving treatment with caplacizumab.

Summary safety data for the overall study period of both trials are provided in Table 14; safety data for the open-label caplacizumab group and total caplacizumab group of HERCULES are provided in Appendix F.

Table 14: Summary table of adverse events in caplacizumab trials (safety)

n (%)	HERCULES		TITAN	
	CAPLA (n=71)	PBO (n=73)	CAPLA (n=35)	PBO (n=37)
TEAE	69 (97.2)	71 (97.3)	34 (97.1)	37 (100)
SAE	28 (39.4)	39 (53.4)	20 (57.1)	19 (51.4)
TEAE leading to death	1 (1.4) [a]	3 (4.1)	0	2 (5.4)
TEAE leading to withdrawal	5 (7.0)	9 (12.3)	4 (11.4)	2 (5.4)

n (%)	HERCULES		TITAN	
	CAPLA (n=71)	PBO (n=73)	CAPLA (n=35)	PBO (n=37)
TEAE leading to interruption	NR	NR	3 (8.6)	4 (10.8)
TEAE possibly treatment-related	41 (57.7)	32 (43.8)	20 (57.1)	5 (13.5)
SAE possibly treatment-related	10 (14.1)	4 (5.5)	7 (20.0)	0
Bleeding event – SMQ 'haemorrhage'	49 (69.0)	49 (67.1)	NR	NR
Bleeding event – CRF	47 (66.2)	36 (49.3)	NR	NR

Key: CRF, case report form; NR, not reported; SAE, serious adverse event; SMQ, Standardised MedDRA Query; TEAE, treatment emergent adverse event.
Notes: [a], the event occurred during the Follow-up Period, off active treatment, and was assessed by the investigator as not related to study drug treatment.
Source: Cablivi EPAR.[17]

Common adverse events

Common adverse events (reported in at least 5% of patients in either treatment group for HERCULES or in at least 5 patients in either treatment group for TITAN) are summarised in Table 15.

The most frequently affected system organ classes were general disorders and administrative site conditions, gastrointestinal disorders and nervous system disorders in both treatment arms of both trials.

The most frequently reported events were epistaxis and headache in the caplacizumab arm of both studies (Table 15). TTP as a TEAE was reported in a similar number of patients across treatment arms in TITAN but in a reduced number of patients treated with caplacizumab in HERCULES (12.7% vs 39.7%).[17]

A higher proportion of patients in the placebo arm of HERCULES experienced hypokalaemia that could be related to a longer duration of PEX but such a trend was not observed in TITAN (Table 15). Post-hoc analysis of PEX complications in HERCULES showed that [redacted]% of patients in the placebo arm experienced a PEX complication in the double-blind treatment period compared to [redacted]% of patients in the

caplacizumab arm; in the overall study period these rates were [redacted]% versus [redacted]%, respectively (data on file).[39]

The most frequently reported events deemed related to study drug treatment in the caplacizumab arm of HERCULES were epistaxis (24% vs 1%), gingival bleeding (11% vs 0%) and contusion (7% vs 4%). The most frequently reported event deemed related to study drug treatment in the caplacizumab arm of TITAN was injection site haemorrhage, reported in two patients. Details of treatment-related TEAEs are provided in Appendix F.

Table 15: Common adverse events in caplacizumab trials (safety)

n (%)	HERCULES		TITAN	
	CAPLA (n=71)	PBO (n=73)	CAPLA (n=35)	PBO (n=37)
General disorders and administrative site conditions	37 (52.1)	36 (49.3)	21 (60.0)	22 (59.5)
Catheter site haemorrhage	5 (7.0)	5 (6.8)	-	-
Fatigue	10 (14.1)	6 (8.2)	6 (17.1)	5 (13.5)
Pyrexia	10 (14.1)	6 (8.2)	6 (17.1)	6 (16.2)
Oedema peripheral	4 (5.6)	7 (9.6)	-	-
Asthenia	3 (4.2)	4 (5.5)	1 (2.9)	6 (16.2)
Chest pain	1 (1.4)	5 (6.8)	-	-
Catheter site pain	1 (1.4)	5 (6.8)	-	-
Injection site pain	1 (1.4)	4 (5.5)	-	-
Pain	4 (5.6)	1 (1.4)	-	-
Gastrointestinal disorders	36 (50.7)	27 (37.0)	22 (62.9)	25 (67.6)
Nausea	10 (14.1)	7 (9.6)	10 (28.6)	11 (29.7)
Gingival bleeding	13 (18.3)	1 (1.4)	5 (14.3)	2 (5.4)
Constipation	7 (9.9)	5 (6.8)	7 (20.0)	10 (27.0)
Diarrhoea	7 (9.9)	5 (6.8)	6 (17.1)	3 (8.1)
Abdominal pain	5 (7.0)	4 (5.5)	2 (5.7)	5 (13.5)
Vomiting	3 (4.2)	4 (5.5)	7 (20.0)	8 (21.6)
Nervous system disorders	32 (45.1)	27 (37.0)	21 (60.0)	23 (62.2)
Headache	16 (22.5)	6 (8.2)	12 (34.3)	10 (27.0)
Dizziness	7 (9.9)	8 (11.0)	8 (22.9)	3 (8.1)
Paraesthesia	8 (11.3)	6 (8.2)	8 (22.9)	8 (21.6)
Respiratory, thoracic and mediastinal disorders	32 (45.1)	14 (19.2)	18 (51.4)	15 (40.5)
Epistaxis	23 (32.4)	2 (2.7)	11 (31.4)	4 (10.8)
Dyspnoea	7 (9.9)	2 (2.7)	5 (14.3)	4 (10.8)
Cough	-	-	5 (14.3)	2 (5.4)

n (%)	HERCULES		TITAN	
	CAPLA (n=71)	PBO (n=73)	CAPLA (n=35)	PBO (n=37)
Infections and infestations	25 (35.2)	16 (21.9)	16 (45.7)	13 (35.1)
Urinary tract infection	4 (5.6)	4 (5.5)	5 (14.3)	0
VURT infection	4 (5.6)	0	-	-
Skin and subcutaneous tissue disorders	23 (32.4)	28 (38.4)	15 (42.9)	9 (24.3)
Urticaria	12 (16.9)	5 (6.8)	-	-
Rash	5 (7.0)	9 (12.3)	-	-
Pruritus	5 (7.0)	6 (8.2)	-	-
Petechiae	4 (5.6)	5 (6.8)	-	-
Ecchymosis	2 (2.8)	4 (5.5)	-	-
Musculoskeletal and connective tissue disorders	20 (28.2)	20 (27.4)	17 (48.6)	16 (43.2)
Pain in extremity	4 (5.6)	6 (8.2)	5 (14.3)	8 (21.6)
Myalgia	-	-	7 (20.0)	1 (2.7)
Arthralgia	4 (5.6)	3 (4.1)	3 (8.6)	8 (21.6)
Back pain	5 (7.0)	3 (4.1)	-	-
Muscle spasms	-	-	4 (11.4)	5 (13.5)
Muscular weakness	4 (5.6)	2 (2.7)	-	-
Cardiac disorders	16 (22.5)	14 (19.2)	9 (25.7)	8 (21.6)
Sinus tachycardia	4 (5.6)	3 (4.1)	-	-
Tachycardia	2 (2.8)	4 (5.5)	-	-
Psychiatric disorders	16 (22.5)	22 (30.1)	14 (40.0)	17 (45.9)
Insomnia	6 (8.5)	8 (11.0)	5 (14.3)	5 (13.5)
Anxiety	4 (5.6)	6 (8.2)	4 (11.4)	5 (13.5)
Agitation	5 (7.0)	4 (5.5)	3 (8.6)	5 (13.5)
Blood and lymphatic system disorders[a]	6 (8.5)	8 (11.0)	7 (20.0)	12 (32.4)
Anaemia	4 (5.6)	6 (8.2)	3 (8.6)	8 (21.6)
Metabolism and nutrition disorders	15 (21.1)	26 (35.6)	15 (42.9)	16 (43.2)
Hypokalaemia	6 (8.5)	14 (19.2)	9 (25.7)	8 (21.6)
Hyperglycaemia	4 (5.6)	4 (5.5)	2 (5.7)	5 (13.5)
Hypocalcaemia	1 (1.4)	5 (6.8)	-	-
Vascular disorders	15 (21.1)	14 (19.2)	13 (37.1)	15 (40.5)
Hypertension	4 (5.6)	8 (11.0)	5 (14.3)	6 (16.2)
Hypotension	4 (5.6)	2 (2.7)	-	-
Reproductive system and breast disorders	12 (16.9)	4 (5.5)	5 (14.3)	3 (8.1)
Vaginal haemorrhage	4 (5.6)	2 (2.7)	-	-

n (%)	HERCULES		TITAN	
	CAPLA (n=71)	PBO (n=73)	CAPLA (n=35)	PBO (n=37)
Injury, poisoning and procedural complications	11 (15.5)	18 (24.7)	7 (20.0)	7 (18.9)
Contusion	5 (7.0)	10 (13.7)	-	-
Investigations	10 (14.1)	12 (16.4)	11 (31.4)	14 (37.8)
Renal and urinary disorders	8 (11.3)	11 (15.1)	-	-
Haematuria	5 (7.0)	2 (2.7)	-	-
Eye disorders	8 (11.3)	7 (9.6)	7 (20.0)	5 (13.5)
Blurred vision	5 (6.8)	5 (7.0)	-	-

Key: TEAE, treatment emergent adverse event; TTP; Thrombotic thrombocytopenic purpura; VURT, Viral upper respiratory tract infection.
Notes: [a], relapse and exacerbation of TTP were not included as adverse events under this system organ class, but were reported as secondary efficacy outcomes.
Common adverse events defined as reported in at least 5% of patients in either treatment group for HERCULES or in at least 5 patients in either treatment group for TITAN. Dashes represent events for which these criteria are not met.
Source: Cablivi EPAR[17]; Peyvandi et al. 2016[18]; Scully et al. 2019[16].

Bleeding-related adverse events

Severe bleeding-related adverse events were reported in three patients treated with caplacizumab (epistaxis, gingival bleeding, upper gastrointestinal haemorrhage) in HERCULES and one patient treated with placebo (haemorrhagic transformation stroke).[16] Serious adverse events of bleeding were reported in 8 patients treated with caplacizumab in HERCULES (11%) and one patient in the placebo arm. The most commonly reported serious adverse event of bleeding was epistaxis, which occurred in four patients in the caplacizumab group. One patient received von Willebrand factor concentrate as the only treatment for resolution of a severe, serious adverse event of epistaxis. No temporal relationship between the occurrence of bleeding and the duration of exposure to caplacizumab was observed.

In TITAN, clinically relevant bleeding that occurred during the first week of daily PEX treatment did not require intervention, with the exception of one patient in the caplacizumab arm who required medical intervention for metrorrhagia on Days 5 and 6 and one patient in the placebo group who required intervention for vomiting blood on Day 18.[17] During the 30-day post daily PEX period, clinically relevant bleeding was reported in 5 patients treated with caplacizumab and 2 patients in the placebo

arm. Two patients required intervention for bleeding events of epistaxis (caplacizumab arm) and haematuria (placebo arm).

Deaths, serious adverse events and other significant adverse events

Four patients died during HERCULES: three patients during the study drug treatment period, all of whom were in the placebo arm and one patient during the treatment-free follow-up period who was randomised to caplacizumab.[16] Two patients died during TITAN, both of whom were in the placebo arm and died during the 1-month follow-up period.[18] All six deaths were TTP-related.

Serious adverse events (SAE) were reported in fewer patients treated with caplacizumab in HERCULES, but SAE rates in TITAN were similar across treatment arms (Table 14). SAEs occurring in more than one patient treated with caplacizumab in individual studies were epistaxis (reported in four patients in HERCULES), headache (reported in [redacted] patients in HERCULES) and dizziness (reported in two patients in TITAN). Other SAEs occurring in more than one patient in the placebo arms of individual studies were anaphylactic transfusion reaction (reported in [redacted] patients in HERCULES), which is a risk associated with PEX, and septic shock (reported in [redacted] patients in HERCULES).

Table 16: Serious adverse events in caplacizumab trials (safety)

n (%)	HERCULES		TITAN	
	CAPLA (n=71)	PBO (n=73)	CAPLA (n=36)	PBO (n=39)
Blood and lymphatic system disorders[a]	0	1 (1.4)	1 (3)	1 (3)
TTP	0	0	0	1 (3)
Thrombotic microangiopathy	0	1 (1.4)	0	0
Anaemia	0	0	1 (3)	0
Gastrointestinal disorders	5 (7.0)	1 (1.4)	0	3 (8)
Gingival bleeding	1 (1.4)	0	0	0
Upper GI haemorrhage	1 (1.4)	0	0	0
Colitis	1 (1.4)	0	0	0
Gastric ulcer haemorrhage	1 (1.4)	0	0	0
GI necrosis	0	1 (1.4)	0	0
Haematemesis	1 (1.4)	0	0	0
Intestinal ischaemia	0	1 (1.4)	0	0
Intestinal perforation	0	1 (1.4)	0	0
Small intestinal obstruction	0	1 (1.4)	0	0
Abdominal pain general	0	0	0	1 (3)
Abdominal pain upper	0	0	0	1 (3)
Dysphagia	0	0	0	1 (3)
Nausea	0	0	0	1 (3)
Vomiting	0	0	0	1 (3)
Respiratory, thoracic and mediastinal disorders	5 (7.0)	2 (2.7)	2 (6)	1 (3)
Epistaxis	4 (5.6)	0	0	0
Hypoxia	0	1 (1.4)	0	0
Respiratory failure	0	1 (1.4)	0	0
Pulmonary embolism	1 (1.4)	0	1 (3)	1 (3)
Dyspnoea	0	0	1 (3)	0
Cardiac Disorders	4 (5.6)	1 (1.4)	0	1 (3)
Myocardial infarction	1 (1.4)	1 (1.4)	0	0
Arteriospasm coronary	1 (1.4)	0	0	0
Cardiac tamponade	1 (1.4)	0	0	0
Cardiogenic shock	1 (1.4)	0	0	0
Ventricular fibrillation	1 (1.4)	0	0	0
Atrial fibrillation	0	0	0	1 (3)
Atrial flutter	0	0	0	1 (3)

n (%)	HERCULES		TITAN	
	CAPLA (n=71)	PBO (n=73)	CAPLA (n=36)	PBO (n=39)
Nervous system disorders	4 (5.6)	2 (2.7)	5 (14)	3 (8)
Headache	2 (2.8)	0	1 (3)	1 (3)
Cerebral ischaemia	1 (1.4)	0	0	0
Encephalopathy	1 (1.4)	0	0	0
HTS	0	1 (1.4)	0	0
Hemiparesis	0	1 (1.4)	0	0
Dizziness	0	0	2 (6)	0
Transient ischaemic attack	0	0	1 (3)	1 (3)
Dysarthria	0	0	1 (3)	0
Paraesthesia	0	0	1 (3)	0
Subarachnoid haemorrhage	0	0	1 (3)	0
Cerebral haemorrhage	0	0	0	1 (3)
Facial paresis	0	0	0	1 (3)
Infections and infestations	3 (4.2)	2 (2.7)	3 (9)	1 (3)
Septic shock	0	2 (2.7)	0	0
Bacteraemia	1 (1.4)	0	0	0
Device related sepsis	1 (1.4)	0	0	1 (3)
Diverticulitis	1 (1.4)	0	0	0
Bacterial infection	0	0	1 (3)	0
Sepsis	0	0	1 (3)	0
Muscle abscess	0	0	1 (3)	0
Urinary tract infection	0	0	1 (3)	0
Musculoskeletal and connective tissue disorders	2 (2.8)	0	1 (3)	1 (3)
Pain in extremity	1 (1.4)	0	0	1 (3)
Arthropathy	1 (1.4)	0	0	0
Muscle spasms	0	0	1 (3)	0
Reproductive system and breast disorders	2 (2.8)	0	1 (3)	1 (3)
Menorrhagia	1 (1.4)	0	0	0
Haemorrhagic ovarian cyst	1 (1.4)	0	0	0
Metrorrhagia	0	0	1 (3)	0
Prostatitis	0	0	0	1 (3)
Injury, poisoning and procedural complications	1 (1.4)	3 (4.1)	0	1 (3)
Anaphylactic transfusion reaction	0	3 (4.1)	0	0
Subarachnoid haemorrhage	1 (1.4)	0	0	0
Traumatic fracture	0	0	0	1 (3)

n (%)	HERCULES		TITAN	
	CAPLA (n=71)	PBO (n=73)	CAPLA (n=36)	PBO (n=39)
Investigations	1 (1.4)	1 (1.4)	3 (9)	1 (3)
GGT increase	0	1 (1.4)	0	0
Platelet count decrease	1 (1.4)	0	0	0
Autoantibody test	0	0	1 (3)	0
Aminotransferases increased	0	0	2 (6)	0
Liver function test abnormal	0	0	0	1 (3)
General disorders and administration site conditions	1 (1.4)	1 (1.4)	0	0
Asthenia	1 (1.4)	0	0	0
SIRS	0	1 (1.4)	0	0
Hepatobiliary disorders	1 (1.4)	1 (1.4)	1 (3)	0
Bile duct stone	1 (1.4)	0	0	0
Cholecystitis	0	1 (1.4)	0	0
Gallbladder necrosis	0	1 (1.4)	0	0
Elevated liver enzymes	0	0	1 (3)	0
Immune system disorders	1 (1.4)	0	0	0
Serum sickness	1 (1.4)	0	0	0
Vascular disorders	0	2 (2.8)	0	1 (3)
Deep vein thrombosis	0	1 (1.4)	0	1 (3)
Jugular vein thrombosis	0	1 (1.4)	0	0
Skin and subcutaneous tissue disorders	0	0	2 (6)	0
Allergic dermatitis	0	0	1 (3)	0
Hyperhidrosis	0	0	1 (3)	0
Eye disorders	0	0	1 (3)	0
Retinal haemorrhage	0	0	1 (3)	0
Renal and urinary disorders	0	0	0	1 (3)
Haematuria	0	0	0	1 (3)
Psychiatric disorders	0	0	2 (6)	0
Mental status changes	0	0	1 (3)	0
Substance-induced psychotic disorder	0	0	1 (3)	0

Key: ALT, Alanine aminotransferase; AST, Aspartate transaminase; GGT, Gamma-glutamyltransferase increase; GI, gastrointestinal; HTS, Haemorrhagic transformation stroke; PBO, placebo; SIRS, Systemic inflammatory response syndrome; TTP; Thrombotic thrombocytopenic purpura.
Notes: [a], relapse and exacerbation of TTP were not included as adverse events under this system organ class, but were reported as secondary efficacy outcomes.
Source: Peyvandi et al. 2016[18]; Scully et al. 2019.[16]

B.2.10.3. Safety overview

Across the clinical trial programme, caplacizumab demonstrated a predictable and manageable safety profile and was generally well tolerated. Across HERCULES and TITAN, low rates of discontinuation due to TEAEs were observed and no patient died while receiving treatment with caplacizumab. All deaths that were observed were TTP-related, and these were higher in the placebo arms.

The safety profile of caplacizumab was consistent across trials and characterised by an increased risk of mucocutaneous bleeding related to its mode of action. Most bleeding events reported were of mild to moderate severity and resolved without intervention. Epistaxis was the only serious bleeding event to occur in more than one patient in individual studies (reported in four patients in HERCULES), and only one of these events required medical intervention.

A risk management plan is in place that makes recommendations for early identification and management of clinically relevant bleeding, and there is a precaution of use noted in the caplacizumab SmPC where in case of active, clinically significant bleeding, treatment should be interrupted.[21] Clinical expert consensus is that the bleeding risk associated with caplacizumab is usually minor and generally manageable.[22] There may also be a reduction in PEX-related adverse events with a reduction in PEX treatment duration in clinical practice, as suggested in post-hoc analyses of HERCULES data.

When considering favourable and unfavourable effects of treatment, the EMA concluded that the data are sufficiently robust to support a benefit:risk estimation, and that the benefits outweigh the risks such that the overall benefit:risk ratio of caplacizumab is positive.[17]

B.2.11. Ongoing studies

Post-HERCULES is an ongoing non-interventional follow-up study for adult patients who completed HERCULES to further evaluate longer-term safety and efficacy of caplacizumab. Patients are assessed every 6 months for 3 years with the baseline visit scheduled to take place within one month of the final follow-up visit in HERCULES.

Planned assessments include clinical measures of patient health and adverse events, disease-related markers including ADAMTS13 activity and patient reported outcome measures. Upon recurrence of TTP, patients are treated with open-label caplacizumab as per the treatment rules of HERCULES and visit schedules are increased to monitor outcomes of caplacizumab treatment for relapsed disease. The expected completion date for Post-HERCULES is October 2020, with data available in early 2021.

No other clinical studies are planned for caplacizumab in this indication, but ongoing data collection to provide further demographic, clinical and healthcare resource use information on aTTP include:

- **Analysis of the UK aTTP registry based at University College London (UCL):** The key objective of this study is to investigate patient outcomes in aTTP including, proportion of patients experiencing exacerbation/relapse, estimated mortality, long-term complications, and healthcare resource use. This will exclude patients in the registry who have been treated with caplacizumab on a compassionate use scheme which are being analysed independently
- **Analysis of linked Clinical Practice Research Datalink (CPRD)-Hospital Episode Statistics (HES)-Office of National Statistics (ONS) datasets in England only**: The objective of this study will be to record the demographic profile, clinical outcomes and healthcare resource use of adult patients with TTP in England. Anticipated outputs include incidence/prevalence of TTP, mortality, cognitive impairment, anxiety/depression, relapse/recurrence, GP appointments, prescriptions, inpatient/outpatient appointments, A&E visits, number of plasma exchange.
- **A UK-based non-interventional cross-sectional study collecting data on the quality of life (QoL) of people with aTTP and carers via an online survey**: The key objective of this study is to describe QoL (including cognitive function, anxiety and depression) of patients and carers of patients with aTTP and carers of patients with aTTP.

B.2.12. Innovation

Caplacizumab is a truly innovative treatment, representing the first nanobody developed from camelid heavy-chain-only antibodies to be approved in any indication. Caplacizumab is the first licensed treatment specific to aTTP and has a unique mode of action that directly targets the pathologic mechanism of this disease. The approval of caplacizumab is the first advancement in acute phase therapeutics for 30 years and offers a step-change in the management of this ultra-rare, life-threatening disease. The innovative nature of caplacizumab is recognised by the clinical community and there is strong support for it to be made available.[10, 22] Since May 2018, caplacizumab has been supplied free of charge to specialist centres in the UK to fulfil unsolicited requests from clinicians, and in recognition of the urgent clinical need caplacizumab addresses. Clinician feedback from this compassionate use programme has been extremely positive with several comments relating to the remarkability of outcomes with caplacizumab. The UK is at the forefront of innovation and advancement of management of aTTP and has been a high recruiter of patients in the global early access programme. In addition, more patients from the UK were recruited into HERCULES than from any other participating country. While every attempt has been made to capture the impact of caplacizumab on quality of life in the economic analyses, its full potential cannot be fully assessed due to a paucity of evidence in this ultra-rare indication, and the difficulty in assessing HRQL in this setting (see Section B.2.13). aTTP is a disease where the suddenness and severity of symptoms can result in otherwise healthy people being admitted to ICU within a matter of days. For those who survive this, there is a high chance they will have to learn to live with long-term complications including permanent cognitive impairment and neuro-psychological impairment, while in constant fear of relapse. Patient and carer interviews highlight the struggle patients have coming to terms with the life-changing nature of their condition with patients feeling snappy, angry, sad and frustrated that they cannot do things for themselves and are suffering with short-term memory problems.[4] Some patients report feeling very isolated and fearful but the psychological impact extends to the people close to them, and to healthcare professionals who are under pressure to save these patients lives.[4] The value of a treatment that can quickly control the disease is therefore not only physical but provides hope and reassurance to patients and their loved ones, and confidence to

healthcare professionals, that cannot be adequately captured in a clinical trial setting or QALY measurement.

There are also some potential economic losses to society relating to a reduced ability to work in patients suffering from long-term morbidity and/or premature mortality that have not been formally considered in the economic evaluation.

B.2.13. Interpretation of clinical effectiveness and safety evidence

B.2.13.1. Principal findings

Caplacizumab addition to PEX and immunosuppression significantly reduced the time to platelet count response for patients experiencing an acute episode of aTTP[16, 47], representing faster resolution of the aTTP episode compared to SoC in terms of microvascular thrombosis control. This benefit was observed irrespective of whether the patient was experiencing an initial or recurrent episode of aTTP. Caplacizumab addition to PEX and immunosuppression also resulted in lower rates in composite outcomes of TTP-related death, recurrence or major thromboembolic event and TTP-related events, reduced the time to normalisation of organ damage markers, and reduced the volume and frequency of plasma exchange, length of hospital and ICU stay. ICU care has previously been associated with significant symptoms of anxiety, depression or PTSD[11] such that reduced ICU care would be expected to reduce the risk of such symptoms.

Disease recurrence was significantly reduced with caplacizumab addition to PEX and immunosuppression, and relapses that were observed in the caplacizumab arm were associated with unresolved underlying autoimmune disease (ADAMTS13 activity <10%), likely resulting from premature immunosuppression discontinuation.[16, 47] No patient treated with caplacizumab demonstrated refractory disease: a disease state associated with poor prognosis that cannot be identified before treatment initiation. Furthermore, no patient died while receiving caplacizumab treatment and acute mortality was significantly reduced in the caplacizumab arm in integrated analyses.[45]

Cognitive function data from the clinical trial programme are limited and as would be expected from a clinical trial of short duration within the acute setting, no clear

differences were observed in these outcomes across treatment groups that would be expected as a result of the duration of time the patient spends in the most acute phase of the disease. In the real-world setting, it would be expected that a treatment that results in rapid control of microvascular thrombi and thus limits tissue ischaemia and organ damage (which would include cerebral damage) to have a positive impact on cognitive function; indeed, evidence has demonstrated the detrimental effect of aTTP acute episodes upon individual's functioning so it can be assumed that improved treatment would reduce this negative impact. Similarly, it would be expected that such a treatment to have a positive impact on patients' wellbeing, both in terms of their physical and mental health but HRQL data are not available from the caplacizumab clinical trial programme at this time. It is extremely challenging to capture robust HRQL data relating to the treatment of an acute episode of aTTP. Patients are otherwise fit and well prior to the initial episode such that baseline HRQL data cannot be collected, and during the acute phase of their disease, patients are receiving urgent life-saving care and it would be inappropriate to ask them to self-assess their current quality of life. Post-HERCULES is capturing HRQL data following the acute episode and therefore will help to fill this evidence gap in part, but the potential lifelong nature of complications and lifetime risk of relapse mean the data from this trial will still be limited when considering lifetime impact. A patient-reported outcome study investigating the quality of life of patients living with aTTP in current practice is also ongoing.

In recognition of the absence of robust data investigating longer-term benefits from the caplacizumab clinical trial programme at this time, a modified-Delphi process was conducted to explore the potential longer-term benefits of caplacizumab treatment.[10] Consensus statements from this process, included:

- Time to platelet count normalisation is directly related to the acute outcomes and it is biologically plausible that a difference in time to platelet normalisation would be directly related to a difference in long-term complications
- Based on its mode of action, caplacizumab plus PEX and immunosuppression would substantially reduce the relative risk (compared to PEX and immunosuppression alone) of:
  - Mortality

  - Organ damage
  - Myocardial ischaemia
  - Cerebral ischaemia
  - Length of ICU / hospital stay
  - PEX and plasma exchange
  - Exacerbations
- Based on its mode of action alone, it is biologically plausible that caplacizumab plus PEX and immunosuppression would reduce the risk of long-term consequences associated with acute organ damage, such as neurocognitive complications which are prevalent in this population (compared to PEX and immunosuppression alone)
- Caplacizumab plus PEX and immunosuppression would improve the management of an aTTP episode, reducing the burden on the healthcare system (length of stay, ICU days, use of PEX, early readmission)
- The bleeding risk associated with caplacizumab is usually minor and generally manageable, however drug costs and the need for national guidelines/a centralised system are potential barriers for adding caplacizumab to the formulary
- The UK is well-positioned to use caplacizumab effectively, due to the national network of expert and specialist aTTP treatment centres

Overall, this supports a clinical conclusion that to withhold treatment with Cablivi leaves patients with aTTP at risk of death, thrombotic complications and long-term complications associated with ischaemic tissue damage.

Importantly, caplacizumab offers a predictable and manageable safety profile alongside its beneficial efficacy profile. Across the clinical trial programme, the safety profile of caplacizumab was consistent, characterised by an increased risk of bleeding related to its mode of action.[16, 47] Most bleeding events reported were of mild to moderate severity and resolved without intervention. Epistaxis was the only serious bleeding event to occur in more than one patient in individual studies (reported in four patients in HERCULES), and one of these events required medical intervention. Recommendations for management of such events are available and clinical opinion is that they are easily resolved in practice.[21, 22] Considering

favourable and unfavourable effects of treatment, the EMA concluded the benefits outweigh the risks and the overall benefit:risk ratio of caplacizumab is positive.[17]

B.2.13.2. Internal validity

There are some quality concerns with the TITAN data such that the EMA did not consider the data adequate to reflect in the product information. Learnings from this trial were taken through to the design of HERCULES which is the largest trial conducted to date in the aTTP population and provides pivotal Phase III data that informed the marketing authorisation of caplacizumab in Europe. This trial (HERCULES) informs the cost-effectiveness analyses presented in Section B.3.

B.2.13.3. External validity

The overarching design of the caplacizumab clinical trials generally reflected clinical practice. Patients had to have started PEX treatment prior to randomisation which would probably happen in practice while diagnosis is being confirmed, although caplacizumab would preferably be administered as early as possible. Any bias resulting from this delay would likely be against rather than in favour of caplacizumab but there may have been some patients experiencing a severe episode who would have died prior to potential randomisation. Along with the fact that severe patients are often in a comatose state on presentation and therefore would have been unable to provide consent to participate in the trial, and the use of open-label caplacizumab to treat disease exacerbations in HERCULES, the acute mortality rates from the clinical trial programme are thought to be lower than would be expected in practice. Estimates from real-world datasets are also thought to underestimate acute mortality due to patients dying before PEX can be initiated in clinical practice or prior to consent for inclusion in registry (and physicians tend not to ask their families for consent).

Dosing of caplacizumab in HERCULES is reflected in the product information and all patients in this trial received concomitant immunosuppression. There were some differences observed in care patterns in that rituximab use in UK clinical practice is reported to be higher (78%[3]) than was seen in HERCULES (43%). Although a higher use of rituximab may have improved the observed relapse rates, the use of rituximab was lower in the caplacizumab arm than the placebo arm such that any within trial bias would have been against caplacizumab.

With regard to patient populations, again the trials generally reflected clinical practice. Four UK sites were involved in TITAN and HERCULES with 7 and 21 UK patients enrolled to each study, respectively. There were some differences observed in fitness as patients had to be 'stably unwell' to be enrolled. This is a common issue in clinical trial design but could further explain the lower mortality rates, and the lower rates of refractory disease observed in the control arm, with refractory disease rates reported at 17% in French practice[19] compared to the 7% observed in HERCULES. There were also some patients enrolled to TITAN and HERCULES who did not meet the modern UK diagnostic criteria for ADAMTS13 activity (<10%). Subgroup analyses confirm that the clinical benefit observed in the ITT group was consistent in the ADAMTS13 activity <10% subgroup (see Section B.2.7) such that this is not thought to impact the applicability of data to UK patients.

The breadth of endpoints assessed across TITAN and HERCULES investigate outcomes of clinical relevance to patients, families and carers, and of resource relevance to healthcare systems. The primary endpoint, time to platelet count response, demonstrate improved control of microvascular thrombosis that is a clinically recognised area of unmet need with current SoC[10], and this endpoint was considered of clinical relevance by the EMA as it represents reduced time at the highest risk for morbidity for patients.[17] The substantial reduction in the risk of aTTP recurrence was also deemed an important clinical outcome by the EMA.[17] Medical resource outcomes not only represent a more rapid recovery time for patients but will reduce the costs associated with PEX use and length of hospitalisations and ICU stay. It should also be noted that patients or caregivers may inject caplacizumab after proper training in the SC injection technique such that the incremental administration burden of introducing this treatment to the NHS is low.

One nuance that should be acknowledged is that the trials use the International Consensus definition for relapse such that a reduction in platelets requiring re-initiation of daily PEX therapy that occurs more than 30 days after the last daily PEX treatment is classed as a relapse. Given the trials only provide a short follow-up, clinical opinion is that relapses captured in the trial were late exacerbations rather than true relapses when the latter is considered a disease recurrence following a

prolonged period of disease stabilisation.[14, 22] This has been considered in the design of the cost-effectiveness model presented in Section B.3.

In consideration of this short follow-up in the HERCULES trial (and the early termination of the TITAN trial), there is some uncertainty around the longer-term benefit of caplacizumab treatment. However, there is consensus across the clinical community that the clinical benefits shown in the caplacizumab data would translate to longer-term benefits based on biological rationale (see Principal findings). There is also strong clinical support for the addition of caplacizumab to routine care for an acute episode of aTTP. Caplacizumab is currently being supplied free of charge to specialist centres in the UK to fulfil unsolicited requests from clinicians, and in recognition of the urgent clinical need caplacizumab addresses. Clinician feedback from this compassionate use programme has been extremely positive with several comments highlighting improved outcomes in patient who received caplacizumab.

Given that a highly specialised aTTP service is in development by NHS England, this is a timely appraisal that, if resulting in positive recommendation for caplacizumab, could allow patients access to an innovative intervention for their condition as part of this new nationalised service.

B.2.13.4. End-of-life criteria

An acute episode of aTTP is considered an urgent, medical emergency during which patients may die or experience irreversible neurological and vascular damage before there is an opportunity to respond to SoC treatment. Although caplacizumab does not strictly meet the traditional end-of-life criterion on life expectancy set by NICE, it does meet the additional survival and small population criteria. Therefore, it could be considered in the context of an acute, ultra-rare, life-threatening disease requiring highly specialised life-saving care where the willingness-to-pay (WTP) thresholds could be increased compared to standard thresholds. This is further discussed in Section B.3.

B.3. Cost effectiveness

B.3.1. Published cost-effectiveness studies

An SLR did not identify any previous cost-effectiveness studies for caplacizumab for the treatment of aTTP. Full details of the search are provided in Appendix G. Furthermore, searches of the NICE website confirmed that no previous NICE appraisals have been conducted in this disease area, therefore a *de novo* model was required.

B.3.2. Economic analysis

A *de novo* cost-effectiveness model was developed to capture both acute and long-term aspects of aTTP. As discussed in Section B.1.2, aTTP is an ultra-rare, life threatening disease that represents an urgent, medical emergency. It is a blood disorder caused by deficiency of ADAMTS13 enzyme activity leading to persistence of UL-vWF multimers that spontaneously capture platelets, resulting in widespread formation of microvascular thrombi that can cause tissue ischaemia and organ damage, particularly in the heart, kidney and brain and death.[1] When left untreated, mortality associated with an acute aTTP episode has been reported to be as high as 90%.[1] Administration of PEX can significantly reduce acute mortality, however, patients surviving an initial acute episode, often suffer from a wide variety of long-term complications including irreversible neurological damage. Patients also remain at risk of suffering from subsequent aTTP episodes.[16]

Caplacizumab prevents the UL-vWF-mediated formation of microvascular thrombi and thus limits tissue ischaemia in an acute episode of aTTP. The Phase III HERCULES study demonstrated that caplacizumab, in addition to PEX and immunosuppression, significantly reduced the time to platelet count response and the proportion of patients with disease recurrence, when compared with SoC treatment alone.[16] Furthermore, no patients on caplacizumab developed refractory disease. Caplacizumab was also associated with shorter hospital and ICU stays and a 41% reduction in PEX volume, not only leading to a reduction in medical resource use costs for caplacizumab-treated patients but also lessening the traumatic experience of unexpected hospitalisation which is expected to lead to a reduction in long-term disease burden.[22] Finally, aTTP-related mortality was also reduced for

patients on caplacizumab; no patient died while receiving caplacizumab treatment in HERCULES.

Due to the severity of the condition at presentation, collection of HRQL data during the acute episode is not appropriate. Therefore, quantifying the short-term QALY benefit to patients treated with caplacizumab is challenging. In terms of the long-term health gains for caplacizumab patients, a large body of literature has shown that patients suffer a range of long-term complications as a result of the acute microvascular damage (see Section B.1.3). It is biologically plausible and strongly supported by clinical experts that caplacizumab would reduce the risk of long-term complications.[10] However, due to the rarity of aTTP and the short-term nature of the available evidence, uncertainty exists in the quantification of caplacizumab's long-term benefit. Extensive clinical input supplemented by a targeted literature review (TLR) (Section B.3.3, Appendix R) were used to address this area of uncertainty.

B.3.2.1. Patient population

The patient population considered in the cost-effectiveness model is consistent with the ITT population of the pivotal Phase III trial HERCULES; the EMA marketing authorisation for caplacizumab, granted on 31 August 2018[17]; and the final NICE decision problem scope.[48] As explained in Section B.2.2, due to concerns with the conduct of the Phase II TITAN trial, HERCULES was the key clinical trial used to inform the regulatory submission to the EMA and therefore the economic analysis reported here.

Patients in HERCULES were adults aged ≥18 years, diagnosed with TTP on the basis of clinical presentation (the presence of both thrombocytopenia and microangiopathic haemolytic anaemia with schistocytes seen on blood smear). Patients had a mean age of 46 years, and 69% of patients were female.

A subgroup analysis was also investigated based on patients with ADAMTS13 activity <10% at baseline. Confirmed ADAMTS13 activity <10% was not an eligibility criterion of HERCULES (as testing is not standard practice in many countries from which patients were enrolled) but aligns to the modern diagnostic criteria for TTP.[37] An ADAMTS13 activity of <10% was reported for 81% of patients in the caplacizumab arm and 89% in the SoC arm. Scenario analyses for the ADAMTS13

<10% subgroup are presented in Section B.3.9. Results were consistent between the ITT population and the ADAMTS13 <10% subgroup.

Age and sex patient characteristics for the HERCULES ITT population and the HERCULES population with ADAMTS13 activity <10% are presented in Table 17.

Table 17: Patient characteristics in HERCULES, ITT population and subgroup with ADAMTS13 activity <10%

Characteristic	HERCULES, ITT			HERCULES, ADAMTS13 activity <10%		
	Capla (N=72)	Placebo (N=73)	Total (N=145)	Capla (N=58)	Placebo (N=65)	Total (N=123)
Mean age (SD) – years	45 (18–77)	47 (21–79)	46 (18–79)	[redacted]	[redacted]	[redacted]
Female sex – N (%)	49 (68)	51 (70)	100 (69)	[redacted]	[redacted]	[redacted]

Key: Capla, caplacizumab; ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs 13; ITT, intention-to-treat; N, number.
Source: HERCULES CSR Post-hoc analyses[39]; Scully et al. 2019.[16]

B.3.2.2. Model structure

The *de novo* cost-effectiveness model includes a decision tree to model the acute aTTP episode (Figure 3), followed by a Markov model to model patients in remission and following relapse (Figure 4). Extensive clinical input was sought throughout model development, initially at a clinical advisory board attended by seven clinicians and one pharmacist, then after model construction was completed during individual clinical expert validation meetings.

Various potential model structures were considered to capture the long-term consequences of aTTP. Whilst trial data is available for the acute phase, modelling of the likely impact of caplacizumab on long-term consequences is more difficult. Options considered for this included:

- Direct surrogacy relationship based on an outcome such as TTPN/time spent with microangiopathy – dismissed as no quantitative evidence was found to inform this (see TLR Appendix R and White Paper[49])

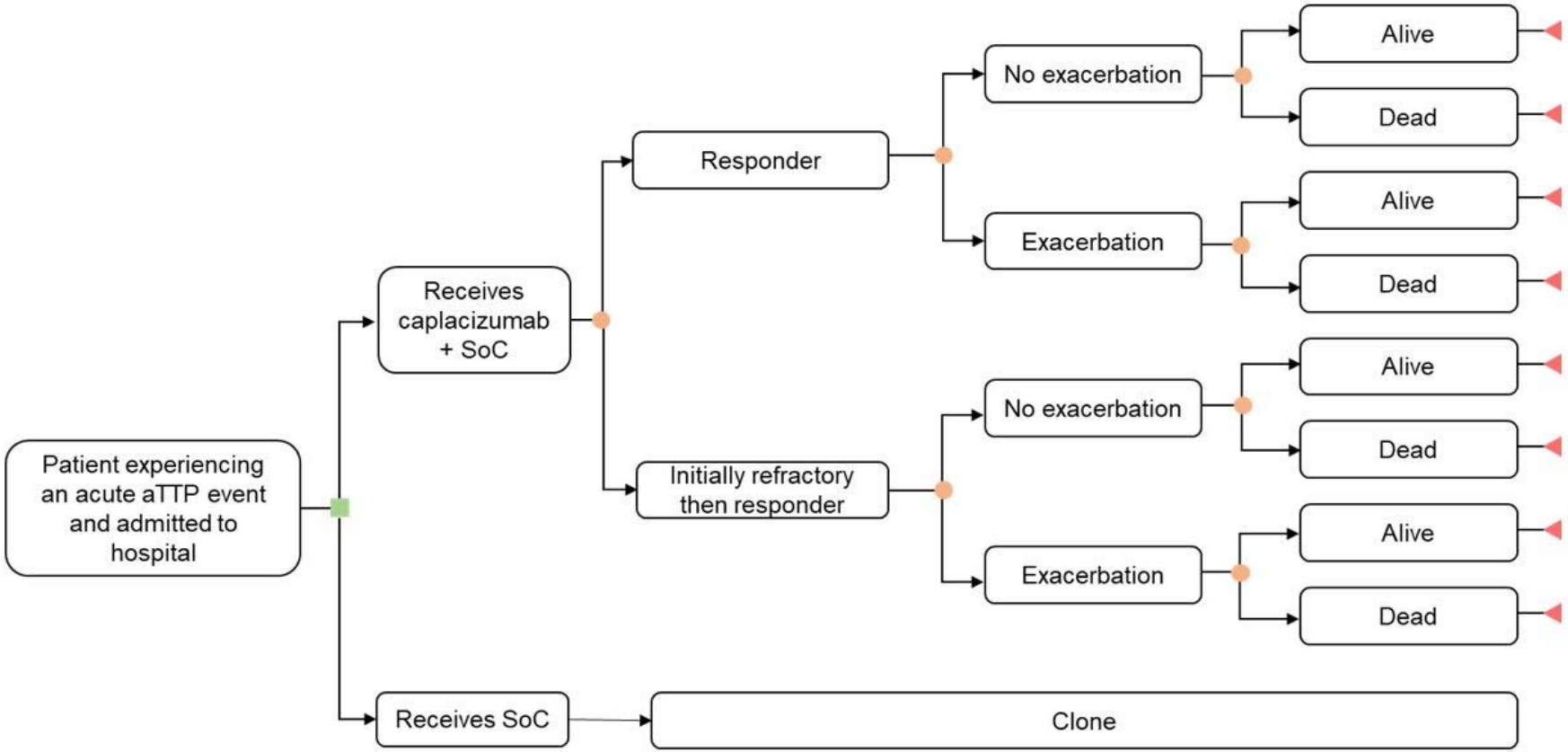
- Treatment effect based upon expert opinion on the translatability of a wide range of proxy measures of the reduction of the time patients are at risk – final option chosen

Decision tree model

A decision tree structure has been selected to model the acute aTTP episode as this structure is well suited to modelling acute illness. It is appropriate for evaluating a limited number of outcomes at a small number of discrete time points and is considered by clinicians to simply yet adequately reflect patient pathways and outcomes during an acute aTTP episode.[22]

The decision tree model (Figure 3) captures possible patient pathways and short-term outcomes over the acute aTTP episode. Patients start the model experiencing an acute episode of aTTP and are admitted to hospital. From there, they can either receive caplacizumab plus SoC or SoC alone. Subsequently, patients can either respond to treatment or suffer from refractory disease. Further details of how refractory disease is defined are provided in Section B.3.3.1. It is important to note that patients who are initially refractory do not remain refractory and either respond eventually or die. Following initial response, patients may or may not experience an exacerbation. Further details of how exacerbation is defined are provided in Section B.3.3.1. The probability of exacerbation is assumed to be independent of whether the patient is initially a responder or refractory. The decision tree model assumes that patients are only able to experience a single exacerbation. This is a simplifying and conservative assumption, as experiencing multiple exacerbations is clinically plausible and caplacizumab greatly reduces the exacerbation rate (see Section B.3.3). Acute mortality is also captured within the decision tree model.

Figure 3: Decision tree model, acute aTTP episode



Key: aTTP, acquired thrombotic thrombocytopenic purpura; SoC, standard of care.

Markov model

A cohort level Markov model structure was chosen to capture patient outcomes following the acute aTTP episode. Markov models divide the time horizon into fixed time periods known as cycles. At the end of each cycle patients may either remain in, or transition to one of a finite number of mutually exclusive health states. Markov models are frequently used in economic evaluations to support health technology appraisals (HTAs) and are considered appropriate when patients remain at risk of certain events over a long period of time, when the timing of events is important and when a given event may occur more than once.[50] These features were considered appropriate to reflect the clinical pathway of aTTP patients from the time entering remission following the initial acute aTTP episode until death.

Patients who survive the acute aTTP episode (are alive at the end of the decision tree model) transition into the Markov model. The Markov model tracks patients following an acute episode of aTTP for their remaining lifetime. It is split into three main health states, corresponding to remission, relapse and death. Relapse in the Markov model is referred to as 'true relapse' so as not to confuse the model definition with relapse as per HERCULES. Further explanation of the definitions used in the trial and economic model are provided in Section B.3.3. Patients in remission are all patients surviving the acute aTTP episode and not currently experiencing a true relapse. No patients enter the true relapse state immediately following the acute aTTP episode. It is assumed that patients may only relapse following a period of remission, consistent with the clinical definition of relapse.

There is a wealth of data suggesting that patients with aTTP in remission experience long-term detrimental effects.[51] Long-term effects discussed in the literature include cognitive impairment, depression, anxiety, PTSD, premature mortality, cardiac failure, renal failure, arterial hypertension and stroke.[12, 51] The most robust data demonstrate long-term detrimental effects with respect to cognitive impairment and depression/anxiety/PTSD, collectively termed neuro-psychological impairment.[6, 8, 15, 31, 32] There is also clinical consensus that these conditions have long-term consequences for patients.[10, 14] These conditions are therefore included in the Markov model. There are little data to support the explicit inclusion of other long-term complications such as cardiac and renal failure and stroke; however, clinical experts

explained that these conditions may lead to reduced life expectancy for patients with aTTP. Due to the paucity of data, however, these conditions are conservatively not explicitly modelled.[22]

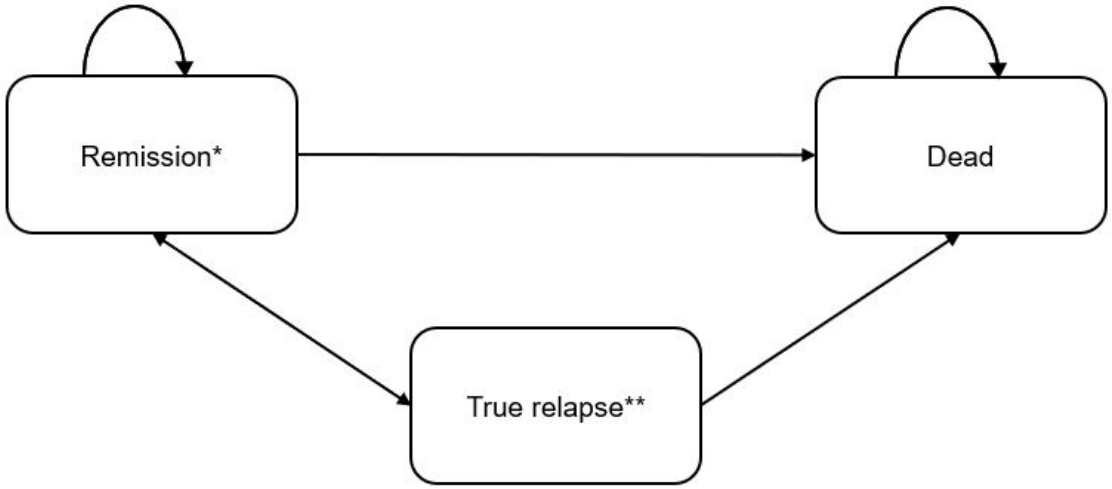
Therefore, the remission health state is further split into sub-states for:

- Cognitive impairment
- Neuro-psychological impairment
- Both cognitive impairment and neuro-psychological impairment combined
- No chronic conditions

As no increased risk of mortality is assumed for cognitive impairment or neuro-psychological impairment the sub-states are not modelled explicitly, instead, the main health state of remission instead combines all long-term complications. The costs and QALYs accrued by patients in remission are dependent on the sub-state in which they reside.

In the Markov model, patients can transition from remission to dead or from remission to true relapse. Patients who do not die or relapse remain in the remission health state.

Figure 4: Markov model, aTTP in remission



Key: aTTP, acquired thrombotic thrombocytopenic purpura.
Notes: *The remission state includes patients with no chronic conditions, patients with cognitive impairment, patients with neuro-psychological impairment, and patients with both cognitive and neuro-

psychological impairment; **Treatment costs for the acute episode also apply to the true relapse state.

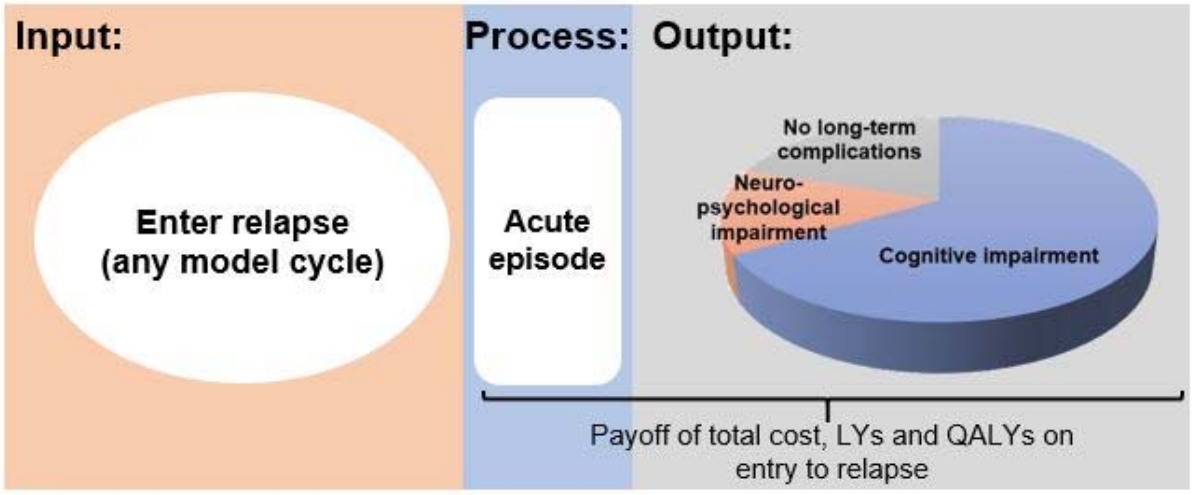
The lifetime costs and QALYs for patients relapsing are calculated using the payoff approach, as described in detail in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 19.[52] All costs and outcomes from the time of relapse until death are applied as a one-off lump sum upon entry to the true relapse state. This approach incorporates time-dependent transition rates from intermediate health states while preserving a simple model structure, thus removing the need to use complex and computationally intensive tunnel state calculations to track the time since relapse to account for the duration of long-term complications. Transitions from true relapse back to remission are not explicitly included in the Markov trace, rather included as part of the payoff for relapsed patients.

A representation of the flow of patients following a relapse is provided in Figure 5. Intermediate states comprising both the acute episode of the relapse and also the various sub-states within remission were included. The payoff approach works by calculating the remaining life years at each cycle for patients experiencing a true relapse and then dividing it by the time spent in each of the intermediate states. Technical implementation of the payoff approach is described in detail in the NICE DSU TSD 19 and also reported below in Appendix N.

Costs and disutilities associated with sub-states are the same whether experienced by patients in the remission state or following relapse in the payoff approach.

Conservatively, only a single relapse is modelled using the payoff approach, as the additional complexity required to model multiple relapses, was not considered to have a substantial impact on the results given the low annual probability of true relapse. Similarly, the payoff only includes cognitive impairment and neuro-psychological impairment as long-term complications for simplicity, conservatively patients with combined cognitive and neuro-psychological impairment are not modelled in the payoff. The impact of this is expected to be minimal as only a small proportion of patients experience a true relapse and an even smaller proportion experience both long-term complications as a result.

Figure 5: Model structure following true relapse



The Markov model combined with the payoff approach includes several simplifying assumptions but was considered to be broadly reflective of the clinical pathway by clinicians attending the advisory board and subsequent clinical expert validation meetings. Further details are provided in Section B.3.10.

The Markov model uses an annual discount rate of 3.5% for both costs and QALYs in the base-case, as specified in the NICE reference case.[53] For simplicity, discounting is only applied in the Markov model due to the short (3 month) time horizon of the short-term model as discussed below. As caplacizumab is a treatment with high upfront costs for the acute episode but long-term benefits through reduced acute mortality, the use of a 3.5% discount rate biases against caplacizumab as benefits are heavily discounted but not costs. Results using alternative discount rates, including a 1.5% discount rate for both costs and outcomes, are presented as scenarios in Section B.3.8.3.

Key features of the economic model including both decision-tree and Markov model components are summarised in Table 18. As no previous NICE appraisals were identified in aTTP, Table 18 summarises the model features for the current appraisal only.

Table 18: Features of the economic analysis

Factor	Chosen values	Justification
Time horizon	Decision tree model: 3 months	Time horizon reflects the duration appropriate to fully capture short-term outcomes associated with an acute aTTP episode.
	Markov model: Lifetime (55 years)	Long enough to reflect all important differences in costs or outcomes between the technologies being compared as recommended by the NICE reference case.[53] Time horizon set to 55 years in the model, by which time the cohort is 100 years of age and all patients are assumed to have died.
Treatment waning effect	Decision tree model: Not applied	Treatment waning effect not relevant for caplacizumab as treatment is only given for the acute episode. Efficacy estimates taken directly from HERCULES, no extrapolation of trial efficacy data is required.
	Markov model: Not applied	
Source of utilities	Decision tree model: Data from published sources associated with proxy conditions such as hospitalisation were included	Patient reported HRQL data for an acute aTTP episode are not available. Collection of HRQL data during an acute aTTP episode is considered unethical due to the severity of the condition and significant risk of imminent death. Clinical expert opinion informed the choice of proxy conditions to use as an alternative.
	Literature sources used	EQ-5D utilities for patients with aTTP in remission and for proxy conditions suggested during clinical consultation were obtained through literature searches.[14]
Source of costs	Drug costs – BNF and eMIT;[54] [55] resource use costs – NHS reference costs and PSSRU [56, 57]	Standard cost sources used, consistent with NHS and PSS perspective.[53]
Key: BNF, British National Formulary; HRQL, health-related quality of life; NHS, National Health Service; PSS, Personal Social Services; PSSRU, Personal and Social Services Research Unit.		

As stated in Table 18, the Markov model adopts a lifetime horizon, while a time horizon of 3 months is adopted for the decision tree model. This is considered long enough to capture outcomes for the acute aTTP episode; very few acute episodes extend beyond this duration.

The cycle length used in the Markov model is 3 months, equal to the time horizon of the short-term model. This cycle length was considered appropriate, as, following the acute episode, patients remain in a relatively stable condition and transitions between health states occur infrequently. Therefore 3 months was considered to be appropriate. Further reducing the cycle length was deemed not to provide any additional accuracy, whilst increasing the computational burden.

Half-cycle correction is also applied in the Markov model by averaging the proportion of patients at the start and end of each cycle. This was considered to increase accuracy as in reality, transitions can occur at any time throughout the model cycle.

Utility data are derived from published sources, and costs are included based on standard cost sources, in line with the NICE reference case.[53] Drug costs are based on the British National Formulary (BNF) or the Electronic Market Information Tool [54, 55], and resource use costs are based on NHS reference costs or the Unit Costs of Health and Social Care published by the Personal and Social Services Research Unit (PSSRU).[56, 57]

B.3.2.3. Intervention technology and comparator

In line with the final scope, the model compares caplacizumab in combination with PEX and immunosuppression (including steroids and rituximab) versus PEX and immunosuppression alone (referred to as SoC throughout this submission).

Intervention technology

Caplacizumab is included within the model in accordance with the product licence (discussed in Section B.1.2), and the regimen used in the HERCULES trial.[16, 21] The product licence (SmPC) states that caplacizumab is indicated for the treatment of adults experiencing an episode of aTTP in conjunction with PEX and immunosuppression, and that treatment with caplacizumab should be initiated and supervised by physicians experienced in the management of patients with thrombotic

microangiopathies.[21] One minor difference between the SmPC and the HERCULES trial was that in HERCULES, patients were required to have received one PEX prior to randomisation, this is not a requirement in the product licence and may potentially bias against caplacizumab as starting treatment early is expected to reduce mortality and morbidity; however, it is likely that patients will be initiated on PEX prior to diagnosis, and the extent of bias cannot be ascertained.

The first dose of caplacizumab is administered as an initial IV injection at a dose of 10 mg prior to that day's PEX. This is followed by daily SC administration of 10 mg of caplacizumab after completion of each daily PEX for the duration of daily PEX treatment, followed by daily SC injection of 10 mg of caplacizumab for 30 days after stopping daily PEX treatment. Patients or caregivers may inject caplacizumab after proper training in the SC injection technique.[21]

If at the end of this period there is evidence of unresolved immunological disease, the SmPC recommends optimising the immunosuppression regimen and continuing daily SC administration of 10 mg of caplacizumab until the signs of underlying immunological disease are resolved (i.e. sustained normalisation of ADAMTS13 activity level).

Comparator

The comparator defined within the final NICE decision problem scope is PEX therapy (with or without spun apheresis, steroids or rituximab), without caplacizumab. This is aligned with the SoC regimen used for patients on the placebo arm of HERCULES and implemented in the model. Additional treatments listed as comparators in the final NICE scope for people with severe refractory acquired TTP (splenectomy, vincristine, cyclophosphamide) are not advised (due to a lack of prospective data) and are rarely used, as reported in the literature and confirmed by current clinical expert opinion.[1, 24]

As such, "Plasma exchange therapy (with or without spun apheresis, steroids or rituximab), without caplacizumab" is the only relevant comparator for all adults experiencing an episode of acquired TTP.

All patients in the HERCULES trial were given PEX, and glucocorticoids (steroids) and rituximab were the immunosuppressants of choice given to patients, provided

there were no contraindications. This is also aligned with UK guidelines, although clinicians at the advisory board explained that rituximab use in UK practice is likely to be more extensive than in HERCULES.[14, 58] Other immunosuppressant regimens used in HERCULES were mycophenolate mofetil, hydroxychloroquine, bortezomib, cyclophosphamide and ciclosporin. For simplicity, these were not included in the model, as the proportions of patients receiving these were low (<5% across both treatment arms), and use is not aligned with UK clinical practice.

B.3.3. Clinical parameters and variables

This section is split into clinical parameters and variables used in the decision tree model (acute aTTP episode) and those used in the Markov model (aTTP in remission). Where possible, data is presented for both the ITT population of HERCULES, and the population with confirmed aTTP via ADAMTS13 activity <10%. This subgroup was included in the model as patients in clinical practice are expected to receive caplacizumab only after diagnosis confirmed by an ADAMTS13 activity <10%. However the ITT population was selected to inform the model base case as 1) this makes use of all available data; 2) patients with ADAMTS13 activity >10% comprise a small minority (14%) of the total HERCULES population; 3) ADAMTS13 activity was not a stratification factor in HERCULES, therefore randomisation is broken and 4) outcomes are consistent across the ITT and ADAMTS13 activity <10% populations.

Clinical data to inform the model were taken from a wide range of sources and are summarised in Table 19.

Table 19: Summary of data sources informing the economic model

Data source	Description
HERCULES	Decision tree model parameters are based primarily on the ITT population of HERCULES in line with the EMA's assessment and reflective of the product licence.[17, 21]
Clinical input	Throughout model development, clinical input was sought on the efficacy inputs and assumptions used to ensure that the model aligns with UK expert option. Details of clinical validation are provided in Section B.3.10 and included an initial advisory board followed by expert validation teleconferences (TCs) and follow-up resource use survey
SLRs/TLRs	Where data were not collected within HERCULES, data identified in the SLRs (presented in Appendices G, H, I) and TLRs (presented in Appendix H) are used. An additional burden of disease SLR and meta-

Data source	Description
	analysis was used to identify inputs where trial data were deemed not appropriate or available, such as for acute mortality or the proportions of patients with long-term complications following an acute aTTP episode. Any data identified through literature searches were subsequently validated by clinicians.[51]
Key: aTTP, acquired thrombotic thrombocytopenic purpura, EMA, European Medicines Agency; ITT, intention-to-treat; SLR, systematic literature review; TCs, teleconferences; TLR, targeted literature review.	

B.3.3.1. Decision tree model

Refractory disease

Caplacizumab in combination with PEX and immunosuppression is associated with a reduced risk of refractory disease compared with PEX and immunosuppression alone, improving patient prognosis. In HERCULES, no patient on the caplacizumab arm experienced refractory disease.

The model base case uses data from HERCULES for the proportion of patients with refractory disease. As explained in Section B.2.6, the definition of refractory disease are used and reported within the HERCULES trial was based on Benhamou et al. (2015) which describes refractory disease as "the absence of platelet count doubling after four full days of standard intensive treatment with persistently elevated LDH levels."[19]

Subsequent to the HERCULES trial, a more recent definition of refractory disease was published by Scully et al. (2017) describing refractory disease as "persistent thrombocytopenia, lack of a sustained platelet count increment or platelet counts of $<50 \times 10^9$ L^{-1} and a persistently raised lactate dehydrogenase (LDH) level (>1.5 upper limit of normal [ULN]) despite five plasma exchanges and steroid treatment."[37]

The Scully et al. (2017) (International Consensus) definition is used in the model base case as clinical experts confirmed the definition is currently used within UK clinical practice, with a scenario applying the alternative definition presented in Section B.3.8.3.

Clinical experts also suggested that the proportion of patients on SoC with refractory disease in HERCULES is lower than would be anticipated in clinical practice

therefore the base case is conservative. Alternative published estimates of 17% for SoC thought to better reflect UK clinical practice were investigated in the scenario analysis in Section B.3.8.3.[19] Inputs for refractory disease are also available for the HERCULES subgroup with ADAMTS13 activity<10%, however the ITT population is used in the base case. Table 20 summarises the proportions of refractory patients, by definition and data source.

While HERCULES clearly demonstrated that caplacizumab reduced the proportion of patients developing refractory disease, this was considered an outcome of the clinical trial, rather than a prospective subgroup which should be considered separately. For this reason and as summarised previously (see Section B.1.1), refractory patients are not considered as a separate subgroup within the economic model.

Table 20: Refractory disease per data source and definition

Data source	Definition of refractory disease					
	Scully (2017)[37]			Benhamou (2015)[19]		
	Caplacizumab	SoC	Source	Caplacizumab	SoC	Source
HERCULES (ITT)	[redacted]	[redacted]	HERCULES CSR Table 14.2.1.2.4 - DB treatment period[43]	0.00%	4.11%	HERCULES CSR, Table 14.2.1.2.3 - DB treatment period[43]
HERCULES (aTTP only)	[redacted]	[redacted]	HERCULES post-hoc analysis - page 59	[redacted]	[redacted]	HERCULES CSR, Table 28[43]
Clinical expert opinion	17%*					Sanofi clinical advisory board (2019)[14]

Key: aTTP, acquired thrombotic thrombocytopenic purpura; CSR, clinical study report; DB, double blind; ITT, intention-to-treat; NR, not reported; SoC, standard of care.
Notes: *Estimate applies to patients on SoC, clinicians did not give a corresponding percentage for patients on caplacizumab.[14]

Exacerbations

As discussed in Section B.2.6, patients on the caplacizumab arm in HERCULES had a greatly reduced risk of recurrence at any time during the trial compared to patients on SoC (12.7% versus 38.4%, respectively), therefore reducing the time in which patients are experiencing microvascular damage.

Section B2.6 details the definitions of exacerbation and relapse used in the HERCULES trial. Based on HERCULES, an exacerbation is defined as a recurrence occurring *during* the first 30-day post-daily PEX period. A relapse is defined as a recurrence occurring *after* the 30-day post-daily PEX period.

Based on clinical expert opinion, exacerbations during the first 30-day post-PEX period (termed early exacerbations) and after the first 30-day post-PEX period (termed late exacerbations) are combined. Please note, the term 'late exacerbations' was applied in this economic model to represent relapses as defined in the HERCULES trial. Further details of clinical input on are presented in Section B.3.10. As late exacerbations only occurred for patients on the caplacizumab arm (likely due to ongoing suppression of ADAMTS13 activity) pooling increases the proportion with exacerbations on caplacizumab, while the exacerbation proportion on SoC remains the same (i.e. the standard HERCULES definitions of exacerbation and relapse could still be considered to apply), therefore adopting this alternative definition is considered conservative. A scenario is presented where only early exacerbations, within 30 days of stopping PEX, as per HERCULES, are included. This is presented in Section B.3.8.3.

As with refractory disease, exacerbation inputs are also available for the subgroup with ADAMTS13 activity <10% only. Clinical opinion is not presented for this parameter as clinicians agreed that the exacerbation rate observed in HERCULES was reflective of UK clinical practice.[14]

Table 21 summarises the proportions of patients experiencing an exacerbation, when considering early exacerbations and considering pooled early and late exacerbations, based on the HERCULES ITT population and the subgroup with ADAMTS13 activity <10%. The base-case analysis uses the ITT population and pools exacerbations, as described above.

Table 21: Exacerbations per data source and categorisation

Data source	Categorisation of exacerbations					
	Early exacerbations			Pooled early and late exacerbations		
	Caplacizumab	SoC	Source	Caplacizumab	SoC	Source
HERCULES (ITT)	4.17%	38.36%	HERCULES CSR Table 19 - DB treatment period[43]	12.68% (base case)	38.36% (base case)	Calculation: Exacerbations in the DB/SB drug treatment period plus exacerbations in the follow-up period. Follow up period: HERCULES CSR p130[43]
HERCULES (ADAMTS13 <10%)	[redacted]	[redacted]	HERCULES CSR Table 28, DB treatment period[43]	[redacted]	[redacted]	Calculation: Exacerbations in the DB/SB drug treatment period plus exacerbations in the follow-up period. Follow-up period: HERCULES CSR Table 28[43]

Key: aTTP, acquired thrombotic thrombocytopenic purpura; CSR, clinical study report; DB, double-blind; ITT, intention-to-treat; NR, not reported; SB, single-blind; SoC, standard of care.

Acute mortality

Patients treated with caplacizumab have a lower mortality rate during the acute episode than patients on SoC. As described in Section B.2.6, no patient died while on treatment with caplacizumab in HERCULES, and three patients died in the SoC arm (4.2%).

Clinical expert opinion suggested that mortality in HERCULES was much lower than expected in UK clinical practice (further details presented in Section B.3.10). Clinicians stated that a mortality of 13.2% based on a meta-analysis of literature sources[14, 51] was a more realistic estimate. This is also validated by alternative estimates taken from sources authored by expert clinicians stating an acute mortality on SoC of between 13-15%.[25, 26]

Clinicians at the advisory board also discussed how mortality was unlikely to be 0% for caplacizumab patients, as observed in HERCULES. Furthermore, clinicians explained that the difference in mortality between arms was also expected to be larger than that observed in HERCULES (i.e. applying the same absolute difference as in HERCULES was considered inappropriate).

Due to the lack of reliable mortality data from both arms of HERCULES from which to estimate a treatment effect, alternative sources were sought. Mortality data for caplacizumab-treated patients are available from the compassionate use programme.[59] As of 30 September 2019, 187 patients have been treated with caplacizumab globally, and there have been 8 deaths, equating to a mortality of 4.28% (data on file).[59] In this programme, treatment with caplacizumab is started later than it would be if it was made available through routine funding (as requests are individual and caplacizumab is not available on site). Mortality data based on this programme should therefore be considered as the maximum mortality expected with caplacizumab.

For the reasons detailed above, the model base case assumes 13.2% mortality rate for patients on SoC, with a 4.28% mortality rate assumed for caplacizumab, resulting in an acute mortality RR of 0.32 for caplacizumab treated patients. As the model is sensitive to the acute mortality assumptions used, this RR was tested extensively in the threshold analysis in Section B.3.8.3, with mortality data based on HERCULES

presented as a scenario also in Section B.3.8.3. In HERCULES, there was one death in the treatment-free follow up period in the caplacizumab arm. A scenario analysis including this death is therefore also presented in B.3.8.3.

Acute mortality sources are summarised in Table 22.

The average time to death, based on HERCULES data for SoC patients ([redacted]), is used in the decision tree model to adjust QALYs and LYs for patients who die, rather than assuming that patients who die do so at the end of the decision tree model, which would result in overestimated benefits.

Table 22: Mortality sources included in the model

Data source – Base Case	Treatment		Source
Clinical opinion, acute episode - SoC	13.20%		Clinical expert opinion (2019)[14] SLR and meta-analysis on the clinical burden of disease (2018)[51]
Early access programme, acute episode - caplacizumab	4.28%		Early Access Programme (2019)[59]
RR caplacizumab	0.32		Calculation
Data source - Scenario	**Caplacizumab**	**SoC**	**Source**
HERCULES ITT, responder, double blind period, acute event	0.00%	3.03%	HERCULES post-hoc TLF, Table 6.1.2
HERCULES ITT, refractory, double-blind period, acute event	NA	20.00%	HERCULES post-hoc TLF, Table 6.1.2

Key: ITT, intention-to-treat; SoC, standard of care; NA, not applicable – no refractory patients; TLF, tables lists and figures.

B.3.3.2. Markov model

Treatment effect: caplacizumab

A wealth of literature sources report multiple long-term complications following an acute episode of aTTP. These conditions include cognitive impairment[6, 8, 15, 31], neuro-psychological impairment [13, 15, 31, 32], headache[28], hypertension[13, 32], chronic kidney disease[60], stroke[12] and an increased risk of premature death.[32, 61] In addition, ICU stay in the UK has been associated with significant symptoms of anxiety, depression or PTSD.[11] These sources underscore the major impact of aTTP on patient HRQL and mortality. A summary of published sources detailing the long-term impact of acute aTTP is available.[51]

Evidence suggests that clinical outcomes in aTTP are driven by the consequences of platelet aggregation that result in microvascular thrombosis.[49] While PEX and immunosuppression, the SoC therapy for aTTP, *gradually* normalises platelet aggregation, the addition of caplacizumab to SoC therapy specifically and rapidly targets platelet aggregation through binding to UL-vWF. This reduces the time patients are at risk of suffering microvascular damage.[49] In addition, patients on caplacizumab have a reduced risk of exacerbation or refractory disease, further reducing the total time in which patients are at risk.

Due to the reduced time spent in the occluded state, there is extensive clinical support for a long-term treatment benefit of caplacizumab,[10, 14, 49] however, directly quantifying the expected treatment benefit is challenging, as the HERCULES trial considered the acute episode only and as caplacizumab is a relatively new treatment, there is currently a lack of evidence demonstrating its long-term benefit. In light of the paucity of trial data on the long-term treatment effect of caplacizumab, a TLR to establish surrogacy relationships between HERCULES outcomes and long-term complications, specifically cognitive impairment, was performed (for full details see Appendix R), and extensive clinical expert input was sought (Section B.3.10).

Surrogacy TLR

The TLR concluded that there is a dearth of evidence in the literature linking outcomes from the acute aTTP episode to cognitive impairment. Among the 1,372 papers that were initially identified from the PubMed, Embase and Cochrane library

searches, only two were deemed relevant for extraction, Han et al. (2015),[31] and Falter et al. (2017).[15] These studies focussed on the TTP population and measured the link between cognitive impairment and recurrence/relapse, with both concluding that there was no association between the outcomes.

Most importantly, no data were identified on the relationship between the time spent at risk of microvascular thrombosis (measured by TTPN, hospitalisation/ICU/PEX days) and long-term cognitive impairment, therefore the TLR concluded that further long-term data collection following an acute aTTP episode will be important to quantify this relationship.

Long-term outcomes for patients experiencing an acute aTTP episode are expected to be available in UK aTTP registry data in the future. However, clinical opinion was considered the most appropriate current source to inform the model in the absence of information from alternative sources.

- An overview of the results from the Han et al. (2015) and Falter et al. (2017) studies are summarised below:In Han et al. (2015), no statistical difference was found in cognitive impairment measured by Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) overall score between patients with or without relapsed disease from the first aTTP episode over a maximum of 10 years ($p = 0.978$)
- In Falter et al. (2017), no statistical difference in cognitive impairment measured by the Questionnaire for Complaints of Cognitive Disturbances (German: FLei) overall score was found across patients with one vs two vs three or more acute TTP episodes ($p = 0.078$)
- In Falter et al. (2017), no positive correlation was found between the FLei scores and the number of acute TTP episodes ($r = 0.115$; second survey, $r = 0.092$)
- In Falter et al. (2017), there was no statistical difference in the FLei overall score between patients with or without neurologic symptoms during any acute TTP episode, assessed over a maximum of one and two years (for the first and second surveys, respectively) for patients diagnosed prior to the start of the study and a maximum of two years (for first cognitive assessment) for patients diagnosed after the start of the study.

Clinical input

Throughout the development of the model, clinicians were consulted on the expected improvement in long-term outcomes for patients taking caplacizumab. At the clinical advisory board, clinicians explained that reducing the time with active disease will benefit patients and improve long-term cognitive and neuro-psychological impairment.[14] Clinicians at the expert validation TCs discussed their experiences of the long-term impact of aTTP. One clinician explained that with SoC, patients rarely survived without long-term impacts from an acute aTTP episode.[22] In addition, one clinician attending expert validation TCs, with experience treating patients with caplacizumab, explained that patients do not appear to suffer any long-term consequences in contrast to patients treated with SoC.[22]

As a starting point for discussions with clinicians regarding how to quantify the expected long-term improvement, proxy RRs and HRs were calculated based on HERCULES trial outcomes, as shown in Table 23. As can be seen from Table 23, all calculated results are in alignment and patients on caplacizumab perform better than patients on SoC.

Table 23: Estimates of RRs/HRs for long-term complications based on HERCULES trial data

Parameter	Caplacizumab	SoC	HR* / Proxy RR**	Source
Exacerbations (early and late)	12.68%	38.36%	0.33**	Economic model; Efficacy G81
Time to platelet count response, initial (days); HR: SoC versus caplacizumab	1.55		0.65*	HERCULES CSR table 18
Time to platelet count response, initial and exacerbation	N/A	N/A	0.57**	Calculation*
Number of days PEX (mean) – overall treatment period	5.8	9.4	0.62**	HERCULES CSR, Table 14.2.1.5.2
Volume of PEX (litres) – overall treatment period	21.3	35.9	0.59**	HERCULES CSR, Table 14.2.1.5.3
Number of days hospitalisation (mean) – overall treatment period	9.9	14.4	0.69**	HERCULES CSR, Table 14.2.1.6.3
Number of days in ICU for those admitted (mean) – overall treatment period	3.4	9.7	0.35**	HERCULES CSR, Table 14.2.1.6.4
Number of days PEX (mean) – all phases, per modelled resource use	[redacted]	[redacted]	0.62**	Economic model; Costs Q150
Volume of PEX (litres) – all phases, per modelled resource use	[redacted]	[redacted]	0.60**	Economic model; Costs Q150
Number of days hospitalisation (mean) – all phases, per modelled resource use	[redacted]	[redacted]	0.79**	Economic model; Costs Q148
Number of days in ICU for those admitted (mean) – all phases, per modelled resource use	[redacted]	[redacted]	0.35**	Economic model; Costs Q149

Key: HR, hazard ratio; ICU, intensive care unit; PEX, plasma exchange; RR, relative risk; SoC, standard of care.
Notes: *Formula: *HR time to platelet count response*(1-RR exacerbations) + HR time to platelet count response^2 * RR exacerbations*

When presented with the proxy RRs/HRs in Table 23, clinicians again emphasised the uncertainty, however stated that the ratio of hospitalisation/ICU days during the overall treatment period was a reasonable proxy for the RR of long-term cognitive impairment and neuro-psychological impairment (Section B.3.10). This was based

on the rationale that quicker time to resolution of disease and a reduced overall time spent in the occluded state leads to lessening of the microthrombi burden, which leads to a reduction in acute organ damage with long-term consequences and on the rationale that this was consistent with outcomes for other proxies such as TTPN and PEX days. In addition, more subtle links exist between the reduction in time in hospital and long-term outcomes, as reducing a lengthy and stressful hospital stay should result in a reduced risk of developing long-term complications. The RR was calculated as follows:

$$RR\ for\ long\ term\ complications = \frac{p(hospitalisation\ cap) * hospitalisation\ days\ cap + p(ICU\ cap) * ICU\ days\ cap}{p(hospitalisation\ SoC) * hospitalisation\ days\ SoC + p(ICU\ SoC) * ICU\ days\ SoC}$$

While the RR associated with hospitalisation stay is applied in the base case model, it should be highlighted that the quantitative relationship between short-term outcomes and long-term complications ultimately remains largely unknown and highly uncertain. Therefore, alternative assumptions are tested extensively in the threshold analysis in Section B.3.8.3.

The long-term complications that are considered in the model for which the proxy RR applies are cognitive impairment, neuro-psychological impairment, which is a conservative approach excluding other potential long term complications. The same risk of relapse across both treatment arms is assumed, based on the clinical rationale that as caplacizumab is only given for the acute episode and no effect on relapse is expected. Finally, the proxy RR is applied to mortality in remission to account for the clinical expectation of a reduction in mortality expected through reduced acute organ damage.[22] Again, as caplacizumab was only studied in the acute episode, downstream effects often occurring years into the future are highly uncertain. Therefore again, the assumed reduction in long-term mortality is tested extensively using threshold analysis (see Section B.3.8.3.).

True relapse

As explained in Section B.3.3.1, the HERCULES trial defined a relapse as a recurrence after initial recovery of platelet count, requiring re-initiation of daily PEX, occurring *after* the 30-day post-daily PEX period. However, clinicians at the advisory

board explained that the relapses observed in HERCULES, which occurred in caplacizumab patients only, were late exacerbations due to stopping treatment while the patient still had unresolved disease activity (i.e. ADAMTS13 activity <10%). Therefore, the 'relapses', as defined in HERCULES, are categorised as exacerbations in the decision tree model, and 'true relapse' in the model occurs only after initial resolution of disease and full normalisation of ADAMTS13 activity.

As the HERCULES trial only followed patients experiencing an acute aTTP episode, alternative sources were sought to inform the relapse rate applied in the model. While various relapse rates are reported in published literature sources, literature on this parameter lacks generalisability to current clinical practice, as treatment and monitoring of patients has improved greatly in recent years and clinical monitoring of ADAMTS13 activity and pre-emptive rituximab use in patients at risk of relapse have now become the norm in specialist centres. An annual relapse rate of 1% is applied in the model, informed by clinical expert opinion, which suggested that of 100 patients attending clinics for monitoring, approximately one patient would relapse per year.[22] Alternative annual relapse rates are investigated in the scenario analysis in Section B.3.8.3. It is assumed that, as caplacizumab is given as an acute treatment only, there is no differential effect on relapse rates between treatments.

Cognitive impairment

Proportion of patients

A universally recognised consequence of an acute aTTP episode is long-term cognitive impairment. Clinicians at the advisory board explained that patients often cannot return to the same jobs they had prior to the acute episode as they have reduced higher cognitive functioning.[14] Similarly, patient and carer interviews conducted highlight a period of struggle, with patients feeling snappy, angry, sad and frustrated that they cannot do things for themselves, and struggle with short-term memory problems.[4]

In December 2018, the UK TTP registry began collecting data on long-term impact following an acute aTTP episode. Over the coming years, the registry may provide a rich source of data on long-term outcomes for UK patients.

A number of studies identified in an SLR on the clinical burden of disease[51] also indicate the presence of persistent cognitive impairment in remission[6, 8, 9, 15, 31], with abnormalities found upon magnetic resonance imaging (MRI) scans.[6] Various instruments were used to measure the cognitive impairment experienced by patients in these studies, including the FLei,[15] Montreal Cognitive Assessment (MCoA) and RBANS,[31] and the Groton Maze Learning Test.[6]. In addition, testing in Kennedy et al. was comprehensive, with 23 individual tests used to assess 11 domains of cognitive function.[8]

Kennedy et al. reported the proportion of patients experiencing mild impairment (54.2%) and moderate to severe impairment (20.8%). Given that patients were separated by severity of impairment, Kennedy et al. was initially selected to inform the proportion of patients in the SoC arm with cognitive impairment in the base-case analysis. Alternative proportions based on Cataland et al. were tested in the scenario analysis in Section B.3.8.3.

During clinical expert consultation, clinicians explained that the figures presented in Kennedy et al. were “in the right ballpark”, and even added that patients rarely survived without long-term complications from an acute aTTP episode.[22] In light of this, a scenario assuming all patients have long-term impairment was explored (Section B.3.8.3). It could be inferred from these insights, that the measures used by Kennedy and Cataland may still not be sensitive enough to capture the full extent of cognitive impairment for some aTTP patients. Therefore, the base case analysis using the proportions from Kennedy et al. is considered conservative.

In addition, clinicians suggested that cognitive impairment is cumulative for patients who experience more than one episode.[22] However, owing to the lack of data regarding the extent of this impact, the model adopts a simplified, conservative approach and does not capture this cumulative impact.

Duration

The likely duration of cognitive impairment was also discussed with clinicians. Han et al. investigated cognitive impairment over a period of 8 years and found that time since the initial TTP episode had no bearing on McoA and RBANS test scores.[31]

Similarly, Kennedy et al. suggested that abnormalities related to cognitive function were not related to time since most recent aTTP episode.

Finally, Cataland et al. describe how, in the nine patients with abnormal MRIs, there was no significant difference in the presence of MRI abnormalities between the subjects studied within one year of their last acute episode of TTP and those greater than one year since their last acute episode. However, there was a significantly lower rate of cognitive impairment in the latter group.[6]

Expert input into the likely duration of cognitive impairment was sought. Clinicians at the expert validation meeting explained that neurocognitive issues are unlikely to improve, and regeneration is rare as neuro-cerebral pathways are affected. Clinicians explained that memory issues are likely to persist over the patient's remaining lifetime.[22] Therefore, a lifetime duration is assumed in the model for cognitive impairment, with alternative scenarios investigated in Section B.3.8.3.

Neuro-psychological impairment

Proportion of patients

Other long-term consequences of an acute episode of aTTP are depression, anxiety and PTSD.[13, 15, 31, 32] These conditions are collectively termed neuro-psychological impairment, in alignment with the NICE final scope.[48] In the UK, ICU stay alone has been associated with significant symptoms of anxiety, depression and PTSD.[11]

As the HERCULES trial did not investigate neuro-psychological impairment after the acute episode of aTTP, alternative sources for the proportion of patients with, and the duration of neuro-psychological impairment were sought in addition to the likely improvement with caplacizumab. Alternative sources included clinical opinion and published literature sources.

Clinicians at the advisory board explained that an acute episode of aTTP is a catastrophic, unexpected experience, particularly since most patients experiencing an episode are young and previously in full health. Patients find the process of treatment frightening, in particular the long stay in ICU and the unfamiliar, unsettling PEX procedure[14], and this can lead to severe mental health problems in the long-term.[22] During patient and carer interviews, patients explained how they struggle to

come to terms with the life-changing nature of the condition and some feel very isolated and fearful; the psychological impact also extends to the people close to the patient and carers.[4] The burden of neuro-psychological impairment is reflected in the recent national aTTP service specification, highlighting the need for specialist centres to have access to a dedicated clinical psychologist.[5]

Published literature sources also discuss psychological issues as a significant long-term burden of acute aTTP.[9, 13, 15, 31, 32] Chaturvedi et al. reported rates of depression and PTSD in survivors of TTP of 36.8% and 35.1%, respectively, using two validated self-administered questionnaires: the PTSD checklist for the Diagnostic and Statistical Manual of Mental Disorders-5 (PCL-5) and the Beck Depression impairment Inventory-II (BDI-II). The correlation between depression and PTSD in Chaturvedi et al. is high (Spearman's R =0.822, p<0.001). Other studies report rates of depression between 19% and 59%, with variation likely due to the different measures used. The proportion of patients in Chaturvedi et al. with depression represents a mid-range estimate and was considered to appropriately reflect the prevalence of depression in aTTP survivors by UK clinicians.[22] Alternative scenarios are presented in Section B.3.8.3, using higher and lower proportions of neuro-psychological impairment.[22]

Duration

Clinicians at the expert validation TCs, stated that they expect that psychological issues will gradually improve over time. However, they could not estimate an average duration over which symptoms persist.[22] Therefore, a targeted search of evidence supporting NICE technology appraisals and clinical guidelines for depression was conducted.

The search identified NICE Clinical Guideline 90 (CG90) – Depression in adults: recognition and management, and Clinical Guideline 91 (CG91) – Depression in adults with a chronic physical health problem: recognition and management.[62, 63] An appraisal of vortioxetine for the treatment of major depressive episodes (MDEs), was also identified (TA367).[64] CG91 was considered to be of greater relevance to aTTP patients suffering from depression due to lifelong risk of acute episodes.

CG91 reported that while depression is considered to be a time-limited disorder, relapse and recurrence are common. The guideline suggested that antidepressant therapy, if beneficial, should be continued for at least 6 months in order to reduce the risk of relapse. TA367 was consistent with CG91, as the accompanying economic model assumed patients remain on treatment for depression for 6 months. The Evidence Review Group (ERG) for this appraisal, cited a key publication by the World Health Organization (WHO) reporting that an untreated episode lasts on average between 5 and 6 months[65], while up to 50% of patients diagnosed with depression impairment suffered episodes lasting in excess of 1 year.[66] The ERG acknowledged that treatment may even continue for up to 2 years for high-risk patients.

These guidelines suggest that the duration of depression is heterogeneous. A duration of 6 months represents a conservative estimate as the duration of treatment prior to benefit is not included in this estimate and, in addition, the population of patients who benefit from treatment is only a subset of the population with depression as a whole. Therefore, a duration of 12 months for neuro-psychological impairment was used in the base-case model as a mid-range estimate and in light of the fact that the model does not account for recurrent episodes of impairment. Scenarios assuming durations of 6 months and 2 years are presented in Section B.3.8.3.

It is unclear if the duration of neuropsychological impairment in patients with aTTP is the same as in the general population due to a lack of data in the aTTP population. However, due to the correlation of neuro-psychological and cognitive impairment, this is likely to be a conservative assumption (see next section).

Table 24 summarises the proportions of patients with cognitive impairment and neuro-psychological impairment on SoC and the RRs associated with caplacizumab applied in the model.

Table 24: Proportion of patients with long-term complications and RR for caplacizumab

Long-term sequela	Proportion of patients, SoC	RR caplacizumab	Proportion of patients, caplacizumab	Source
Mild cognitive impairment	54.17%	0.62	33.85%	Kennedy (2009)[8], RR for caplacizumab Clinical expert opinion[22]
Moderate/severe cognitive impairment	20.83%	0.62	13.02%	Kennedy (2009)[8], RR for caplacizumab Clinical expert opinion [22]
Neuro-psychological impairment (severe depressive symptoms)	36.84%	0.62	23.02%	Chaturvedi (2015)[13], RR for caplacizumab clinical expert opinion[22]
Key: RR, relative risk; SoC, standard of care.				

Combined cognitive impairment and neuro-psychological impairment

The model also includes a heath state for the proportion of patients with combined cognitive and neuro-psychological impairment.

Neuro-psychological impairment and cognitive impairment are closely linked. Cognitive impairment due to ischaemic damage leads to problems with memory and higher cognitive functioning. Many patients cannot return to work or find that cognitive impairment impacts upon their daily lives, which has wider consequences on patients' mental health and wellbeing.[14]

No data were identified on the proportion of patients with cognitive impairment who also suffer from neuro-psychological impairment and vice versa. Therefore, the probabilities of each are assumed to be independent (i.e. the prevalence of neuro-psychological impairment is the same in patients with and without cognitive impairment, and, similarly, the prevalence of cognitive impairment is the same in those with and without neuro-psychological impairment). Calculations are presented in Appendix M.

The resulting proportions of patients in each health state are summarised in Table 25.

Table 25: Distribution across health states at the start of the Markov model

Condition	Proportion of patients, SoC	Proportion of patients, caplacizumab
Proportion with cognitive impairment and neuro-psychological impairment	27.63%	10.62%
Proportion with cognitive impairment only	47.37%	35.88%
Proportion with neuro-psychological impairment only	9.21%	12.22%
Proportion with neither	15.79%	41.28%
Total:	**100.00%**	**100.00%**
Key: SoC, standard of care.		

Due to the additional complexity required to capture the impact of patients with combined cognitive and neuro-psychological impairment within the payoff approach, this sub-state was excluded from the payoff. To account for this, the method used to calculate the proportion of patients with cognitive impairment only, or neuro-psychological impairment only was adjusted accordingly. This involved simply assuming all of those with both complications would have only cognitive impairment. The impact of this is anticipated to be minimal as few patients relapse and for even fewer relapse results in both complications.

Table 26: Distribution across health states at the start of payoff for relapse

Condition	Proportion of patients, SoC	Proportion of patients, caplacizumab
Proportion with cognitive impairment only	75.00%	46.50%
Proportion with neuro-psychological impairment only	9.21%	12.22%
Proportion with neither	15.79%	41.28%
Total:	100.00%	100.00%
Key: SoC, standard of care.		

The durations for which each condition are applied in both the main Markov model and payoff are presented in Table 27.

Table 27: Durations of long-term complications applied in the Markov model

Condition	Duration (years)	Source
Cognitive impairment	55	Clinical expert opinion, lifetime effect[22]
Neuro-psychological impairment	1	NICE TA367 - ERG report[64]
Key: ERG, Evidence Review Group; MDD, major depressive disorder; NICE, National Institute for Health and Care Excellence.		

Mortality in remission

Clinicians attending the expert validation TCs stated that they would expect an increase in mortality for patients with aTTP due to downstream effects of organ damage leading to cardiac and renal failure and reduced life expectancy compared to the general population[22]. Similarly, literature sources report reduced life expectancy in aTTP patients compared to general population.[9, 12, 32] Clinicians at the expert validation TC also discussed that caplacizumab may reduce the risk of long-term cardiac and renal failure through quicker resolution of the acute episode and reduced time at risk of microvascular damage.

To capture the increase in mortality for patients with aTTP, two sources were used. Deford et al. (2013), n=70, compares mortality based on Oklahoma registry data with matched general population mortality. Kaplan-Meier (KM) curves were digitised and the Guyot algorithm performed to recreate individual patient-level data.[67] Following this, a Cox proportional-hazards analysis was conducted in the statistical software package *R*, resulting in a standardised mortality ratio (SMR) of 7.8.

The other source, Upreti et al. (2019), n=170, did not report KM data. However, an SMR was estimated based on age matched general population mortality versus mortality reported in the publication. This resulted in an SMR of 8.3.

Both SMRs are similar, however the SMR based on Upreti et al. was selected for the model base case as Upreti is a more up to date source.

For the relative improvement in mortality for patients on caplacizumab, the same RR was applied as for the risk of long-term complications, in the absence of any other long-term estimates for patients on caplacizumab. Application of this RR resulted in an SMR for caplacizumab (when using the Upreti et al. source) of 5.2. Due to the

uncertainty surrounding these parameters, they were tested extensively in scenario and threshold analyses in Section B.3.8.3.

Resulting SMRs were applied to general population mortality based on the latest (2015–2017) Office for National Statistics (ONS) Life Tables for England and Wales.[68]

B.3.4. Measurement and valuation of health effects

B.3.4.1. Health-related quality-of-life data from clinical trials

HRQL data were not collected in either the Phase II TITAN trial or the Phase III HERCULES trial.[43, 44] Acute aTTP episodes are severely disabling and present a significant risk of imminent death if the disease cannot be controlled.[1, 32] Thus, it would be considered unethical to collect such data from patients, which is reflected in the design of the trials. In addition, severe patients present in a coma, meaning that patient-reported data collection is not possible. In addition, there is a current lack of long-term HRQL data for patients surviving the acute aTTP due to the rarity of the disease. However, the ongoing Post-HERCULES trial may provide long-term follow-up HRQL data for the first time in a clinical trial setting.

B.3.4.2. Mapping

No *de novo* mapping analyses were performed for this submission.

B.3.4.3. Health-related quality-of-life studies

Overview

An SLR was conducted in July 2018 and updated in May 2019 to identify any published HRQL studies or utility data for patients with aTTP. The study selection methods and results of the SLR are presented in Appendix H.

The SLR identified five studies reporting HRQL data for patients with aTTP in remission. Of these five studies, two investigated the HRQL of patients using the SF-36 [6, 34], and three used disease-specific instruments relating to neuro-psychological and cognitive impairment.[13, 15, 31] The studies that used the SF-36 reported significantly lower HRQL scores than age- and gender-matched US norms in both the mental and physical components. The studies reporting on disease-specific

measures all reported high proportions of cognitive impairment and neuro-psychological impairment relative to the general population.

The SLR did not formally include conference abstracts and posters, however, presented these for information purposes. One such conference poster, Burns et al., describes a mapping analysis of SF-36 scores from patients with aTTP in remission, to EQ-5D utility values.[69] Although conducted on US patients in the Oklahoma registry, this was considered the most appropriate source of utility for patients in remission.

Acute aTTP episode

The acute episode is an extremely traumatic experience for both patients and carers; the onset is unexpected, and the treatment is unpleasant, particularly PEX. The more severe patients present in a comatose state, with patients who are more lucid well aware that they are experiencing a life-threatening emergency. Often this is communicated to the patient and the family early on causing significant distress.[4] Given the paucity of HRQL data for the acute episode, clinical experts at the advisory board were asked to suggest proxy conditions for which HRQL may be representative of an acute aTTP episode.[14]

Suggestions included:

- Severe brain injury
- Cerebral vein thrombosis
- Sepsis (young patients without comorbidities)
- Guillain–Barré syndrome
- Meningitis
- Patients in critical care or intensive care (ICU)

To investigate the available evidence base for the listed proxy conditions, a TLR was conducted. The study selection methods and results of the TLR are presented in Appendix H. Based on this TLR, a number of useful sources reporting EQ-5D utility scores for patients with the associated proxy conditions were identified and are discussed below.

Ultimately, the identified studies demonstrated a high degree of variation in the reported utility values. Of the seven studies considered to be highly relevant to the acute aTTP episode, three did not report the quality-of-life instrument used, and one only collected data in remission. These studies were therefore not considered appropriate to inform the acute episode. Of the remaining studies, a study by Pappas et al. investigating QALY loss in intracranial haemorrhage and ischemic stroke, (which employed a method similar to Chit et al. 2015 and using data gathered by McPhail and colleagues from hospitalised participants who were admitted to a tertiary hospital in Australia), was chosen as the most relevant study in the absence of any more appropriate UK data sources.[70-72]

This source had several advantages. First, baseline utilities were reported, allowing calculation of a multiplier that could be applied to baseline utility derived using HERCULES data. Second, the study reported utility values collected at time points thought to capture the immediate impact on quality of life and subsequent improvement during hospitalisation that were comparable to an acute aTTP episode (Table 28), and finally, utility estimates from this study demonstrate face validity in that patient quality of life is low on admission, then improved at discharge, but does not exceed quality of life estimates for remission.

It is important to note that utility estimates for the acute episode are not key drivers of cost-effectiveness results as they are applied in the model for a relatively short time.

The utility for the entire hospital stay was estimated by averaging the utilities at admission and discharge and adjusting for baseline utility in the study to obtain a utility multiplier value of 0.64. The utility following discharge was also adjusted for baseline utility before applying in the model resulting in a utility multiplier of 0.82 post discharge. Utilities in Table 28 are only applied in the decision tree as they reflect the acute episode.

Table 28: EQ-5D utility for hospitalised patients and age-matched general population

Health state	Utility	Utility Multiplier	Description
Pappas et al baseline utility (before episode)	0.80	--	Age matched general population utility [70, 73]
Utility following admission	0.37	--	Utility within 72 hours of admission.[70-72]
Utility following discharge	0.66	--	Utility at discharge from hospital.[70-72]
HERCULES baseline utility (before episode)	0.87	--	Calculated using age/sex PLD from HERCULES and estimating patient utility based on Ara and Brazier[74]
Utility multiplier, aTTP event – hospitalisation	--	0.64	Utility multiplier calculated based on average utility between hospital admission (0.37) and discharge (0.66) divided by baseline utility (0.80)
Utility multiplier, aTTP event - after discharge	--	0.82	Utility multiplier calculated based on utility at hospital discharge (0.66) divided by baseline utility (0.80)
Key: aTTP, acquired thrombotic thrombocytopenic purpura; PLD, patient level data.			

aTTP in remission

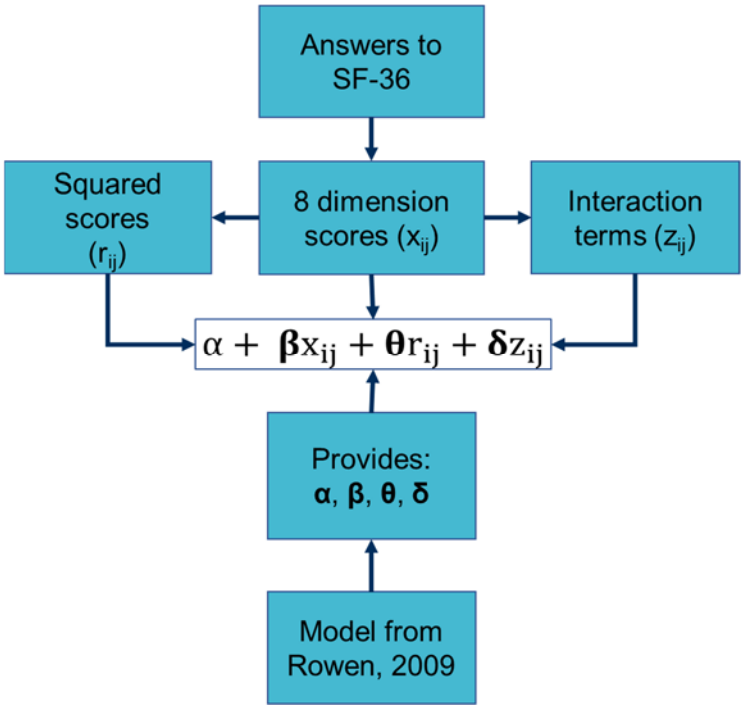
Following the acute episode, patient HRQL is not expected to return to the same level as prior to the episode. During patient and carer interviews, patients described obsession with their blood values, memory and concentration loss, and fatigue. These problems have an impact on patients' and carers' day-to-day lives. Patients explained how they were embarrassed and self-conscious due to cognitive issues and for one patient, it even caused a dangerous accident in the home.[4] Clinicians attending the expert validation TCs described how some patients are worried about sleeping alone in fear that they may not wake up.[22]

This impact on quality of life is reflected in the literature sources identified in the utilities SLR in B.3.4.1.

The Burns et al. conference poster which maps SF-36 scores from patients with aTTP in remission, to EQ-5D utility values was used to inform utility in remission.[69] Although conducted on US aTTP patients in the Oklahoma registry, this was considered the most appropriate source of utility for patients in remission.

Burns et al. used the mapping algorithm published by Rowen et al. to convert SF-36 observations to EQ-5D-3L utilities.[75] Figure 6 illustrates the process of estimating EQ-5D utilities using SF-36 response data and the approach described by Rowen et al. Initially, individual answers from the SF-36 instrument are used to calculate eight dimension scores (x_{ij}), as described above. Interactions (z_{ij}) and squared scores (r_{ij}) are then calculated. Following this, the coefficient estimates from the models presented by Rowen et al. (β, θ and δ) are multiplied by their respective values. The results are summed along with the constant term (α) to provide an estimate of a corresponding EQ-5D utility.

Figure 6: Mapping algorithm proposed by Rowen et al. (2009)



Source: Rowen et al., 2009.[75]

This algorithm has been used in several successful NICE submissions, and the level and has a high level of precision at high utility values. Below this threshold, the algorithm is known to produce overestimations of utility. This should be kept in mind when interpreting the following estimates.

Of 380 patients within the Oklahoma registry, 72 patients were identified as having aTTP. Although the registry states that only aTTP patients were included, it is not

clear what criteria were used for selection. Of the 72 aTTP patients, 371 complete SF-36 observations from a total of 55 patients were used in the main analysis, while baseline demographics and comorbidities data were available for 295 observations from 54 patients. Several characteristics of the study population are of importance for interpretation of results below. First, there was a higher proportion of female patients in the Oklahoma registry (74.5%) than in the HERCULES trial (69%). Second, patients were also younger (39.75 years) when compared to the HERCULES ITT population (46.1 years). Finally, the mean time since end of treatment for their first aTTP episode was 5.72 years, and observations were collected both before and after the introduction of rituximab to standard clinical practice in the US.

Linear mixed-effects regression models were fitted to the mapped EQ-5D utilities. For the main analysis a utility of 0.707 was predicted. For the analysis including baseline demographics and comorbidities, an unadjusted model predicted a utility of 0.736. Stepwise model selection identified neurological symptoms as the only statistically significant predictor of utility and resulted in the final model (Table 29).

Table 29: Burns et al. final comorbidities model

Model	Coefficient	SE
Constant	0.736	0.031
Neurological symptoms	-0.054	0.020
Observations	295	
LL	145.1	
AIC	-282.2	

Key: AIC, Akaike information criterion; aTTP, acquired thrombotic thrombocytopenic purpura; LL, log-likelihood; SE, standard error; HSUV, health state utility value; GLS, generalised least squares.
Notes: As the regression includes no covariates, the constant covariate of 0.707 is the estimated HSUV of aTTP remission.
Source: Burns et al. 2018.[69]

Long-term complications

In the Markov model, utility in remission is also dependent on whether long-term complications following the acute episode were experienced (i.e. utility multipliers for long-term complications are applied based on the health state in which patients reside).

Burns et al. provided utility estimates for baseline utility in remission for aTTP patients as well as a utility decrement for neurological symptoms (Table 29). However, the study only included patients with mild cognitive impairment, and alternative sources were therefore required to inform moderate to severe cognitive impairment, as well as neuro-psychological impairment. Therefore, a TLR was performed (Appendix H).

Clinicians at the expert validation TCs explained that stroke was a reasonable proxy for patients suffering from the more severe forms of cognitive impairment. Therefore, a published source reporting utility for mild, moderate and major stroke, Gage et al., was used, weighted by the proportions of patients suffering from each severity stroke based on Freeman et al.[76, 77] An alternative source of utility data for stroke patients was identified, Sorenson et al., however this was not used in the base case as the utility values reported could not be traced back to their original source.[78] For depression, a well-known source of UK EQ-5D utilities, Sullivan et al., was used.[79]

It is important to note that in Sullivan et al., utility is reported for 'depressive disorder' so therefore should be considered conservative as the impact of anxiety/PTSD are not captured. All utilities for long-term complications identified in the literature were converted to multipliers by adjusting for baseline utility before being applied to the corresponding health state in the Markov model.

A summary of the disease-related utility values, baseline utility values and calculated multipliers is presented in Table 30.

Table 30: Utility multipliers for aTTP patients in remission

Health state in model	Condition in source for which utility value is reported	Disease-related utility value/decrement in source	Baseline utility value in source	Utility multiplier applied in model	Source
Mild cognitive impairment (base case)	Neurological symptoms	-0.054	0.736	0.93	Burns et al.[69]
Moderate/severe cognitive impairment (base case)	Stroke – (clinically validated proxy) weighted according to severity based on proportions with each severity in Freeman et al.[76]	Mild, 0.76; Moderate, 0.48; Major, 0.13.	0.82	0.61	Gage et al.[77]
Neuro-psychological impairment (base case)	Depressive disorder	0.64	0.83	0.77	Sullivan et al.[79]
Key: aTTP, acquired thrombotic thrombocytopenic purpura.					

Carer HRQL

It was also important to consider the impact on the HRQL of carers as recommended in the NICE methods guide.[53] After the aTTP episode, a period of struggle ensues, with patients feeling snappy, angry, sad and frustrated that they cannot do things for themselves. Patients often have to rely on support at home, and many patients were forced to change their working hours, careers, take more sick days and reduce their social life.[4]

A targeted search of the literature was performed to identify carer disutilities/HRQL in relevant proxy conditions. A systematic review was identified, in which one of the studies reported utility for informal caregivers of patients with stroke (considered to be a good proxy for the worst forms of cognitive impairment by clinicians).[22] The source reported an EQ-5D utility value for substantially burdened caregivers of 0.67 versus population norms of 0.81. This was converted to a multiplier (0.83) then applied to the moderate to severe cognitive impairment utility assuming an average of one caregiver per patient. Conservatively, caregiver utility loss was not applied to any of the other health states as no relevant source could be found.

B.3.4.4. Adverse reactions

As described in Section B.2.10, caplacizumab and SoC have comparable safety profiles, with the only noticeable difference being an increased risk of bleeding events (such as epistaxis and gingival bleeding) for patients treated with caplacizumab.

SAEs occurring in > 5% of patients in either treatment of arm of the HERCULES trial, by system organ class, during the overall study period, are included in the model as per Table 16. Adverse events (AEs) were grouped by system organ class, due to small patient numbers experiencing individual AEs.

The overall study period includes both the double-blind treatment period, open-label treatment period and follow-up period. However, for patients on SoC who switched to open-label caplacizumab for an exacerbation, AEs were not included from the point of switch (i.e. the 28 subjects on SoC who experienced an exacerbation do not contribute to the placebo group from the time of the exacerbation onwards).

Therefore, the inclusion of AEs is conservative as the treatment exposure for patients on SoC who exacerbated was truncated.

During clinical validation AEs were discussed. Clinicians agreed that epistaxis was important to include however stated that, although serious, this was easily managed. Epistaxis is captured within the 'respiratory, thoracic and mediastinal disorders' system organ class. Similarly, gingival bleeding is captured within the 'gastrointestinal disorders' system organ class. Clinicians also explained that PEX complications were important to include; reducing the time spent receiving PEX and reducing the PEX volume with caplacizumab will likely reduce PEX-related AEs such as deep vein thrombosis and line infections.[22] Therefore, the list was expanded to include serious PEX complications such as DVT and line infections, included in the vascular disorders and infections/infestations system/organ classes, of Table 16, respectively, despite these AEs having an incidence of <5%.

Clinicians at the advisory board emphasised the importance of capturing acute renal events, however discussed that these are likely to be quickly resolved. There were no serious renal events (system organ class: renal and urinary disorders) occurring during HERCULES, therefore renal and urinary disorders were included irrespective of seriousness.[14]

In the model, it is assumed that patients only experience AEs while receiving treatment for an acute episode or relapse of aTTP. AEs included in the model are presented in Table 31.

Table 31: AEs included in the model

Treatment-emergent SAE	Caplacizumab	SoC	Source
Gastrointestinal Disorders	[redacted]	[redacted]	HERCULES CSR, Table 44/Table 14.3.1.4
Respiratory, Thoracic and Mediastinal Disorders	[redacted]	[redacted]	
Cardiac Disorders	[redacted]	[redacted]	
Nervous System Disorders	[redacted]	[redacted]	
Vascular disorders*	[redacted]	[redacted]	
Infections and infestations*	[redacted]	[redacted]	
Renal and urinary disorders**	[redacted]	[redacted]	*HERCULES CSR, Table 40*

Key: AEs, adverse events; CSR, clinical study report; SAE, serious adverse event; SoC, standard of care.

Notes: AE incidence based on Number of events in HERCULES trial overall study period; *Included based on clinical consultation despite incidence <5% in HERCULES: **No serious renal and urinary disorders in HERCULES, renal and urinary disorders included irrespective of seriousness

In the model base case, AE disutilities are included in order to reflect the reduced quality of life for the proportion of patients experiencing AEs. As the SLR identified no studies reporting AE disutilities in aTTP, AE disutilities were sourced from searches of previous NICE appraisals and standard literature sources.[79] Disutilities are assumed based on the most common AE within the system organ class. AE disutilities applied in the model and associated assumptions are summarised in Table 32.

Table 32: AE disutilities applied in the model

Treatment-emergent serious AE*	Mean disutility	Source
Gastrointestinal disorders	0.13	Assumed major bleeding event (MBE): NICE TA327 (2014), Company submission, Table 113 (MBE)
Respiratory, thoracic and mediastinal disorders	0.13	Assumed major bleeding event (MBE): NICE TA327 (2014), Company submission, Table 113 (MBE)
Cardiac disorders	0.06	Assumed acute myocardial infarction: NICE TA420; Sullivan et al. 2011, ICD 410
Nervous system disorders	0.15	Assumed other and unspecified disorders of the nervous system: Sullivan et al. 2011, ICD 349
Vascular disorders	0.25	Assumed DVT: NICE TA327 (2014), Company submission, Table 113 (MBE)
Infections and infestations	0.37	Assumed sepsis; Wu 2018; Baseline utility (0.96) minus sepsis in hospital ward (0.59)
Renal and urinary disorders	0.13	Assumed major bleeding event: NICE TA327 (2014), Company submission, Table 113 (MBE)

Key: AE, adverse event; ICD, International Classification of Diseases; MBE, major bleeding event; NICE, National Institute for Health and Care Excellence; TA, technology appraisal.

To enable calculation of QALY decrements for AEs, information on the duration over which the AE persists is required. A duration of 28 days and 7 days is assumed in the model for serious and non-serious AEs, respectively. Varying the duration over which the disutility is applied has minimal impact on cost-effectiveness results, no

AE is anticipated to have long-term consequences. AE durations and associated QALY decrements are presented in Table 33.

Table 33: AE durations and QALY decrements applied in the model

Treatment-emergent SAE	Duration (days)	QALY decrement per SAE	QALY decrement accounting for incidence		Source
			Caplacizumab	SoC	
Gastrointestinal Disorders	28	0.00997	0.000702	0.000546	Assumptions
Respiratory, Thoracic and Mediastinal Disorders	28	0.00997	0.000702	0.000273	
Cardiac Disorders	28	0.00480	0.000270	0.000066	
Nervous System Disorders	28	0.01146	0.000646	0.000314	
Vascular disorders	28	0.01916	0.000000	0.000314	
Infections and infestations	28	0.02836	0.000484	0.000314	
Renal and urinary disorders	7	0.00249	0.000281	0.000375	
Total QALY decrement:			**0.003085**	**0.002202**	Calculation

B.3.4.5. Health-related quality-of-life data used in the cost-effectiveness analysis

A summary of utility values used in the base-case cost-effectiveness analysis is provided in Table 34. For the acute aTTP episode, baseline utility is calculated using UK age- and gender-matched utility values based on HERCULES patient-level data.[74]

The utility in remission was taken from Burns et al. and adjusted according for age, gender and proportion with neuro-psychological impairment before applying in the model.

Utility multipliers for the acute episode are estimated based on the TLR source identified for hospitalisation as described in Section B.3.4.3. These are used to apply treatment-specific utilities dependent on the proportion of time patients spent

hospitalised during the acute aTTP episode. Utility is conservatively assumed to be the same irrespective of whether patients are in the ICU or the general hospital ward. Utility estimates for patients experiencing a true relapse are also assumed to be the same as the acute aTTP episode. This was considered a reasonable assumption as Burns et al. shows no impact on HRQL based on number of previous episodes.[69]

Utility multipliers for long-term complications were identified through the TLR as described in Section B.3.4.3. The Burns et al. analysis provided the utility decrement for neurological symptoms, which was applied to patients with mild cognitive impairment in the model. Utility multipliers for moderate/severe cognitive impairment were taken from sources reporting utility values in stroke, as stroke was considered by clinicians to be a reasonable proxy for the worst patients.

The utility for neuro-psychological impairment was taken from the catalogue of EQ-5D scores for the UK based on the International Classification of Diseases (ICD) code for depressive disorder (ICD311).[79]

Multipliers for mild cognitive impairment and moderate/severe cognitive impairment were weighted by the proportions of patients experiencing each to obtain a single weighted multiplier to apply to patients with cognitive impairment in the model. In the event that patients have both cognitive impairment and neuro-psychological impairment, estimates are applied multiplicatively as recommended in NICE DSU TSD 12.[80] All utility estimates within remission are adjusted for age and gender based on a published and widely used regression analysis.[74]

Further details, including the approach taken to adjust utility values for age and gender and the method used to calculate an average multiplier for cognitive impairment, are provided in Appendix O.

Table 34: Summary of utility values/multipliers applied in base case cost-effectiveness analysis

State	Utility value: mean (standard error)	Reference in submission (section and page number)	Justification
Acute aTTP episode			
Baseline utility – prior to acute episode	0.87	B.3.4.3	Age-matched general population utility derived using HERCULES data for patient age
Acute episode – hospitalised (multiplier)	0.64	B.3.4.3	Average of utility at admission and discharge, divided by age-matched general population utility in study.[70-72]
Acute episode – post discharge (multiplier)	0.82	B.3.4.3	Utility at discharge divided by age-matched general population utility in study.[70-72]
QALY decrement for AEs, caplacizumab	0.003085	B.3.4.4	Disutilities based on a targeted searches of previous NICE submissions and standard utility sources were identified for AEs, durations based on assumptions
QALY decrement for AEs, SoC	0.002202	B.3.4.4	Disutilities based on a targeted searches of previous NICE submissions and standard utility sources were identified for AEs, durations based on assumptions

State	Utility value: mean (standard error)	Reference in submission (section and page number)	Justification
Remission			
Baseline utility	0.77	B.3.4.3	Oklahoma registry analysis of mapped SF-36 data to EQ-5D utilities 0.736,[69] adjusted for age, gender and proportion with neuro-psychological impairment.
Mild cognitive impairment (multiplier)	0.93	B.3.4.3	Decrement of -0.054 reported for neurological symptoms vs baseline of 0.736 for aTTP patients.[69] Average multiplier for combined impairment severity applied as described in Appendix O.
Moderate /severe cognitive impairment (multiplier)	0.61	B.3.4.3	No aTTP specific utility data available. Stroke utility per severity taken weighted according to stroke severity proportions.[76, 77] Average multiplier for combined impairment severity applied as described in Appendix O.
Neuro-psychological impairment (multiplier)	0.73	B.3.4.3	No aTTP specific utility data available. Assumed comparable to depressive disorder.[79]
Carer disutility for moderate /severe cognitive impairment (multiplier)	0.83	B.3.4.3	Important to capture the impact on HRQL for caregivers of patients with moderate to severe cognitive impairment. Stroke carer HRQL used as stroke considered a good proxy for the worst forms of cognitive impairment [22, 53, 81, 82]

Key: AE, adverse event**;** aTTP, acquired thrombotic thrombocytopenic purpura; EQ-5D, EuroQol-5 Dimension; HRQL, health-related quality of life; NA, not applicable; SF-36, Short Form-36.

B.3.5. Cost and healthcare resource use identification, measurement and valuation

Addition of caplacizumab to SoC generates cost savings in resource use versus SoC alone, due to faster disease control resulting in reduced utilisation of PEX (5.8 vs 9.4 days), a 41% reduced plasma volume, reduced length of ICU stay (3.4 vs 9.7 days) and a reduced overall length of hospital stay (9.9 vs 14.4 days), based on HERCULES data from the overall treatment period.

The shorter durations of hospitalisation and ICU stays are of particular importance, as clinicians at the validation meeting explained how reducing a lengthy and traumatic hospital stay is likely to reduce the risk of experiencing long-term complications.

The SLR used to identify published HRQL studies and utility data also included searches for published resource use data for aTTP/TTP (see Appendix I for further details). Cost and resource use estimates used to inform the economic model were taken primarily from data collected from the HERCULES trial and UK treatment guidelines identified in the resource use SLR. These data were supplemented by estimates provided by UK clinical experts in response to a healthcare resource use survey.[58]

B.3.5.1. Intervention and comparators' costs and resource use

Caplacizumab

The list price of caplacizumab submitted to the Department of Health is £4143 per pack containing one 10 mg caplacizumab powder vial for injection. With the confidential commercial patient access scheme (PAS) discount of [redacted] applied, this results in a net price per pack of [redacted]. Caplacizumab is given in combination with current SoC, which is described below.

Comparator

The comparator included within the economic model is SoC. SoC consists of daily PEX until at least 2 days after platelet count normalisation, in addition to immunosuppressant therapy. Immunosuppressants include steroids and rituximab, and are included in the model in accordance with their licensed doses and UK

treatment guidelines.[1] In addition to steroids and rituximab, a number of other immunosuppressants were given during HERCULES, such as mycophenolate mofetil, hydroxychloroquine, bortezomib, cyclophosphamide and ciclosporin, however these were not included in the modelling as are not expected to be used in clinical practice and the number of patients on these treatments was small (<5% across both treatment arms). Splenectomy was also given to three patients in HERCULES, however this, again, is not standard practice in the UK. Costs for SoC are discussed in more detail in Section B.3.5.2.

Administration costs

For patients on both treatments, no additional administration costs are assumed to apply. During hospitalisation, costs for treatment administration are assumed to be covered by the hospitalisation costs discussed in Section B.3.5.2. There is assumed to be no additional cost for administration of SC caplacizumab after discharge as this is self-administered/administered by the patient's carer. These assumptions were clinically validated in the resource use survey.[58]

B.3.5.2. Health-state unit costs and resource use

The types of resources required and associated frequencies in the treatment of the acute episode were based on data collected from the HERCULES trial, to obtain estimate of comparative resource use, and UK clinical guidelines identified in the resource use SLR.[1] For resource use in remission, we relied heavily on clinical opinion, as no data were identified on this in the SLR.[58]

This section is separated for resource use applied in the decision tree model for patients experiencing an acute episode (and patients experiencing true relapse) and resource use in the Markov model for patients in remission.

Decision tree, resource use

<u>Treatment duration and drug costs</u>

The dosing regimen used for caplacizumab for the treatment of the acute episode in the model is in line with the product licence and HERCULES trial.[16, 21] A single 10 mg IV loading dose is given once initially, followed by daily SC administration of 10 mg

caplacizumab after completion of each PEX for the duration of PEX treatment and for 30 days after PEX treatment has ended.[21]

In order to calculate the total costs for acute treatment per patient, both estimates of treatment duration and compliance were required.

Treatment duration (days) was calculated based on the double-blind period of HERCULES (all patients) with the open-label period also being taken into account for patients who exacerbated. Compliance based on the double-blind period and open-label period was then applied.

To translate days into doses, the additional loading dose was added to the number of days (i.e. all patients had one dose per day, however on the first day an additional IV loading dose was given).

A summary of the treatment duration and compliance applied in the acute model is presented in Table 35.

Table 35: Treatment duration and compliance

Compliance	Mean	SE	Source
Compliance, caplacizumab double blind treatment period	[redacted]	[redacted]	HERCULES CSR: Exposure to study medication: descriptive statistics - Table 14.1.2.9
Compliance, caplacizumab open label treatment period	[redacted]	[redacted]	HERCULES CSR: Exposure to study medication: descriptive statistics - Table 14.1.2.10
Compliance, caplacizumab, weighted average	[redacted]		Calculation; Economic model Costs E24
Treatment duration	**Mean**	**SE**	**Source**
Treatment duration (days), caplacizumab, double blind period	[redacted]	[redacted]	HERCULES CSR: Exposure to study medication: descriptive statistics - Table 14.1.2.9
Treatment duration (days), caplacizumab, open label period	[redacted]	[redacted]	HERCULES CSR: Exposure to study medication: descriptive statistics - Table 14.1.2.10
Treatment duration (days), double blind + open label	[redacted]		Calculation; Economic model Costs E28
Number of loading doses	1		HERCULES CSR
Total number of doses taking into account compliance and loading	[redacted]		Calculation; Economic model Costs E30
Key: CSR, clinical study report; SE, standard error.			

Total drug costs for caplacizumab applied in the acute episode are presented in Table 36.

Table 36: Total caplacizumab drug costs for acute episode

Number of doses, all patients	Treatment duration (days)	Total treatment cost per episode	Total treatment cost per episode (PAS discount applied)
All patients	[redacted]	[redacted]	[redacted]
Key: PAS, patient access scheme.			

Healthcare resource use costs: acute episode (decision tree only)

Healthcare resources used in the acute episode include hospitalisation/ICU days, PEX procedures and volume of PEX required, steroids, rituximab, outpatient visits and ADAMTS13 tests.

Resource use costs used in the model were taken from NHS reference costs 2017–2018.[56] Drug costs were sourced from the electronic Market Information Tool (eMIT) where possible. The British National Formulary (BNF) was used for drug costs not listed in eMIT.[54, 55]

The cost of a hospital stay was based on the non-elective long stay cost for a cerebrovascular accident, nervous system infection or encephalopathy, with complication and comorbidity (CC) Score 14+. This was selected based on feedback from clinicians at the advisory board who agreed that cerebral vein thrombosis and adult meningitis are considered good proxies for aTTP in the acute setting.[14] The cost was divided by the average length of stay (14 days) as reported in NHS reference costs to derive a daily cost for hospitalisation. ICU costs were taken from critical care costs reported in NHS reference costs. The cost for the PEX procedure was assumed not to include the cost of plasma itself so this was costed separately, based on NHS Blood and Transplant (NHSBT) data.[83]

Other costs include the cost for ADAMTS13 tests and immunosuppressants. Experts attending the validation meeting explained that the ADAMTS13 test is not a standard test covered by direct access pathology services (DAPS). Clinicians estimated that the ADAMTS13 activity test cost is currently in the region of £200 but is expected to reduce over time.[58] Costs for immunosuppressant drugs were obtained from eMIT or the BNF, as detailed in Table 37.

Table 37: Resource use unit costs – acute episode (decision tree only)

Resource	Cost	Source
Hospitalisation cost, general ward (per stay)	£6,543.53	NHS reference costs 2017-2018, Non-elective long stay, currency code AA22C: Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 14+ - based on clinical proxies of cerebral vein thrombosis and adult meningitis
Average length of stay (days)	14	NHS reference costs 2017-2018, Non-elective long stay, currency code AA22C. Average length of stay. Used to calculate cost per days hospitalisation.
Hospitalisation cost, general ward (cost per day)	£467.40	Calculation based on the hospitalisation cost per stay divided by the average length of stay
ICU cost (per day)	£1,466.60	NHS reference costs 2017-2018, Critical care, weighted average (based on activity) of currency codes XC01Z-XC07Z: Non-specific, general adult critical care patients predominate - assumed that this is cost for one day only
PEX procedure cost	£602.34	NHS reference costs 2017-2018, Non-elective long stay, currency code SA44A: Single PEX or Other Intravenous Blood Transfusion, 19 years and over
PEX cost per unit	£28.46	NHSBT (2018), a unit of plasma is assumed to be 250mls – Levy (2007)[83, 84]
Outpatient visit (haematology specialist)	£250.00	Clinical expert opinion – healthcare resource use survey[58]
ADAMTS13 activity test	£200.00	Clinical expert opinion – healthcare resource use survey[58]
Methylprednisolone (IV) (cost per 1g dose)	£6.42	electronic Market Information Tool (2019); Methylprednisolone sodium succinate 1g powder and solvent for solution for injection vials / Packsize 1[55]

Resource	Cost	Source
Rituximab (cost per dose with wastage – dose variable per BSA)	£1,205.24	BNF (2019), rituximab – assumed Rixathon® or Truxima® brands used as these are cheaper than MabThera®
Key: ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; BNF, British National Formulary; BSA, body surface area; CC, complication and comorbidity; ICU, intensive care unit; IV, intravenous; NHS, National Health Service; PEX; plasma exchange.		

Healthcare resource use frequencies: acute episode (decision tree only)

Resource use frequencies in the decision tree model are based on HERCULES trial data, and UK clinical guidelines identified in the SLR[1]. The latter source, Scully et al., provides valuable, UK-specific information on the treatment of an acute aTTP episode and was used to fill data gaps after incorporation of resource use estimates from HERCULES.[1]

The immunosuppressant regimens used in the model are in line with their licenced doses and the UK treatment guidelines. Methylprednisolone included at a dose of 1 g/d for three consecutive days and rituximab included at a dose of 375 mg/m^2 weekly for 4 weeks.

As rituximab is variably dosed by patient body surface area (BSA) there is the potential for wastage, as leftover drug remaining in the vial after administration is discarded. Clinicians completing the resource use survey explained that there would be wastage associated with rituximab use as preparation is on an individual basis,[58] rather than for populations where vials can be shared between pre-prepared rituximab infusion bags. Further detail on the calculations used to estimate rituximab drug costs are provided in Appendix P.

Resource use reported in the overall treatment period of HERCULES is likely to underestimate resource use for patients on the SoC arm, as patients who exacerbated were switched to caplacizumab, therefore incurring less resource use than they would in UK clinical practice had they not switched. For this reason, it was important to analyse the data per subgroup. Resource use for patients exacerbating on SoC was assumed the same as resource use for non-exacerbators (i.e. patients were expected to incur the same resource use costs again if they exacerbated). This

assumption was validated by clinicians.[22] Resource use frequencies per subgroup and per trial period based on HERCULES data are presented in Appendix S.

Resource use estimates not available from the trial were taken from UK treatment guidelines or were based on assumptions. UK treatment guidelines state that patients on rituximab require four, once weekly 375mg/m^2 doses and patients on steroids require three 1g doses of methylprednisolone. Assumptions were made for the number of outpatient visits and ADAMTS13 activity tests as no data were identified for these parameters. All patients were assumed to require two outpatient visits and four ADAMTS13 activity tests per acute episode.

Resource use unit costs were multiplied by resource use frequencies to estimate resource use costs per treatment arm for the acute episode of aTTP. In total, resource use in the acute episode is much lower for caplacizumab patients than for SoC patients, demonstrating resource use cost savings for patients on the caplacizumab arm.

A summary of the final resource use frequencies and costs applied in the model is presented in Table 38.

Table 38: Final resource use frequencies and costs applied in the model

	SoC				Caplacizumab			
	Responders	**Responders who exacerbate**	**Refractory**	**Refractory who exacerbate**	**Responders**	**Responders who exacerbate**	**Refractory**	**Refractory who exacerbate**
Frequencies (weighted by proportions)								
Total hospitalisation days (excluding ICU)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total ICU days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEX days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEX volume (L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Outpatient visit (haematology specialist)	2.0	2.0	2.0	2.0	2.0	2.0	0.0	0.0
ADAMTS13 activity test	4.0	4.0	4.0	4.0	4.0	4.0	0.0	0.0
Total number of Methylprednisolone (IV) doses	3.0	3.0	3.0	3.0	3.0	3.0	0.0	0.0
Total number of rituxumab doses	1.9	1.9	1.9	1.9	1.6	1.6	0.0	0.0
Resource use costs								

	SoC				Caplacizumab			
	Responders	**Responders who exacerbate**	**Refractory**	**Refractory who exacerbate**	**Responders**	**Responders who exacerbate**	**Refractory**	**Refractory who exacerbate**
Total hospitalisation days (excluding ICU)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total ICU days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEX days	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PEX volume (L)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Outpatient visit (haematology specialist)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADAMTS13 activity test	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of Methylprednisolone (IV) doses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of rituxumab doses	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total resource use cost per subgroup	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; ICU, intensive care unit; IV, intravenous; PEX, plasma exchange; SoC, standard of care.

Markov model, resource use

Resource use in remission is dependent on the extent of long-term complications arising from the acute aTTP episode. For all patients irrespective of long-term complications, resource use in remission consists of frequent disease monitoring using ADAMTS13 tests and outpatient visits, with approximately 10% of patients receiving rituximab to reduce the risk of relapse.[22] Resource use in remission irrespective of long-term conditions is presented in Table 39.

Table 39: Resource use in remission

Resource	Frequency per year	Source
ADAMTS13 activity test	4	Clinical validation[22]
Outpatient visit (haematology specialist)	4	Assumption
Rituximab (doses)	4	Scully et al.[1]
Proportion of patients receiving rituximab	10%	Clinical validation[22]
Key: ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13.		

Resource use frequencies and costs for long-term complications are presented in the tables below. Estimates are based on clinical expert opinion as no other sources of long-term resource use in aTTP were identified in the SLR. However, the NHS England service specification highlights the need for specialist care in remission.[5]

Resource use frequencies for mild cognitive impairment, moderate to severe cognitive impairment and neuro-psychological impairment are presented in Table 40.

Table 40: Resource use costs for long-term complications in remission

Resource	Proportion of patients	Annual frequency	Reference
Mild cognitive impairment			
Stroke/neurology services	50%	4	Proportions, Clinician's resource use survey;[58] frequencies, assumptions
Further cerebral imaging	40%	4	
Moderate to severe cognitive impairment			
Stroke/neurology services	50%	4	Proportions, Clinician's resource use survey;[58] frequencies, assumptions
Further cerebral imaging	20%	4	
Physiotherapy/social services	20%	4	
Neuro-psychological impairment			
Psychology/counselling/mental health services	33%	4	Proportions, Clinician's resource use survey;[58]frequencies, assumptions
Antidepressants	20%	12	
Clinic time	50%	4	Proportions, Clinician's resource use survey;[58]frequencies, assumptions

Resource use costs for patients with long-term complications are presented in Table 41.

Table 41: Resource use costs for long-term complications in remission

Resource	Cost	Reference
Stroke/neurology services	£570.00	NHS reference costs 2017-2018; Outpatient procedures; Code AA33C; Conventional EEG, EMG or Nerve Conduction Studies, 19 years and over[56]
Cerebral imaging	£90.00	NHS reference costs 2017-2018; Code IMAGOP RD20A; Computerised Tomography Scan of One Area, without Contrast, 19 years and over[56]
Physiotherapy/social services	£55.00	NHS reference costs 2017-2018; Total Outpatient Attendances; Code 650; Physiotherapy[56]
Psychology/counselling/mental health services	£170.00	NHS reference costs 2017-2018; Total Outpatient Attendances; Code 656; Clinical Psychology[56]
Antidepressants (pack)	£0.51	electronic Market Information Tool (2019); citalopram 20mg tablets (28) [55]

Clinic time	£37.00	PSSRU Unit costs of health and social care (2018); GP visit; Per surgery consultation lasting 9.22 minutes, including direct care staff costs, with qualification costs[57]
Key: EEG, electroencephalogram; EMG electromyogram; GP, general practitioner; PSSRU, Personal and Social Services Research Unit.		

Total resource use costs for long-term complications in remission are presented in Table 42. It is assumed for patients with combined cognitive impairment and neuro-psychological impairment that resource use is additive, as the resources used do not overlap.

Table 42: Total resource use costs for long-term complications in remission

Long term condition	Annual cost	Cost per model cycle
Cognitive impairment (mild)	£1,284.00	£321.00
Cognitive impairment (moderate/severe)	£1,256.00	£314.00
Neuro-psychological impairment	£301.89	£75.47

Total resource use costs in remission per health state are presented in Table 43.

Table 43: Resource use in remission per health state

Health state	Both treatments – cost per model cycle
No chronic conditions	[redacted]
Cognitive impairment only (weighted average cost by severity)	[redacted]
Neuro-psychological impairment only	[redacted]
Cognitive impairment and neuro-psychological impairment	[redacted]

Summary

A summary of resource use by health state in both the decision tree and Markov models is provided in Table 44.

Table 44: Resource use per health state

	Caplacizumab	SoC

Decision tree model		
Health state	**Total resource use**	
Responders	[redacted]	[redacted]
Responders who exacerbate	[redacted]	[redacted]
Refractory	[redacted]	[redacted]
Refractory who exacerbate	[redacted]	[redacted]
Markov model		
Health state	**Total resource use – per model cycle**	
No chronic conditions	[redacted]	
Cognitive impairment only (weighted average cost by severity)	[redacted]	
Neuro-psychological impairment only	[redacted]	
Cognitive impairment and neuro-psychological impairment	[redacted]	
Key: SoC, standard of care		

B.3.5.3. Adverse reaction unit costs and resource use

AE management costs are not included in the base case analysis as it is assumed that the cost for treating AEs would already be included in the hospitalisation costs. An alternative scenario including costs for treating AEs is presented in Section B.3.8.3.

For this scenario, AE costs are taken from NHS reference costs 2017–2018, assuming a non-elective long-stay setting (Table 45).[56]

Table 45: AE unit costs

Treatment-emergent serious AE*	Cost of treatment	Source
Gastrointestinal disorders	£1,493.94	NHS reference costs 2017-2018, Non-elective long stay, FD03H, Gastrointestinal Bleed without Interventions, with CC Score 0-4[56]
Respiratory, thoracic and mediastinal disorders	£1,324.90	NHS reference costs 2017-2018, Non-elective long stay, CA12Z, Major Treatment of Epistaxis[56]
Cardiac disorders	£1,617.18	NHS reference costs 2017-2018, Non-elective long stay, EB10E, Actual or Suspected Myocardial Infarction, with CC Score 0-3[56]
Nervous system disorders	£2,364.26	NHS reference costs 2017-2018, Non-elective long stay, AA22G, Cerebrovascular Accident, Nervous System Infections or Encephalopathy, with CC Score 0-4[56]
Vascular disorders	£837.60	NHS reference costs 2017-2018, Non-elective long stay, YQ51E, Deep Vein Thrombosis with CC Score 0-2[56]
Infections and infestations	£1,947.55	NHS reference costs 2017-2018, Non-elective long stay, WJ06J, Sepsis without Interventions, with CC Score 0-4[56]
Renal and urinary disorders	£470.05	NHS reference costs 2017-2018, Non-elective short stay, LA07P, Acute Kidney Injury without Interventions, with CC Score 0-3[56]
Key: AE, adverse event; CC, complication and comorbidity; NHS, National Health Service. **Notes:** *Plasma exchange complications and renal/urinary disorders included irrespective of severity.		

Total costs per treatment arm for AEs are presented in Table 46.

Table 46: Total AE costs per treatment arm

Treatment-emergent serious AE	Caplacizumab	SoC
Gastrointestinal Disorders	[redacted]	[redacted]
Respiratory, Thoracic and Mediastinal Disorders	[redacted]	[redacted]
Cardiac Disorders	[redacted]	[redacted]
Nervous System Disorders	[redacted]	[redacted]
Vascular disorders	[redacted]	[redacted]
Infections and infestations	[redacted]	[redacted]
Renal and urinary disorders	[redacted]	[redacted]
Total cost	[redacted]	[redacted]
Key: AE, adverse events; SoC, standard of care.		

B.3.5.4. Miscellaneous unit costs and resource use

No other costs are included that have not been summarised in the above sections.

B.3.6. Summary of base case analysis inputs and assumptions

B.3.6.1. Summary of base case analysis inputs

All inputs used in the cost-effectiveness model and their associated distributions are presented in Appendix Q.

Uncertainty information such as SEs and 95% CIs were obtained from the input source where available. Where uncertainty information was not reported, an SE of 10% was assumed. A normal distribution is used for costs, resource use frequencies, and durations as per the central limit theorem. A beta distribution is used for probabilities, proportions and utilities, as these inputs are non-negative and do not exceed 1. A log-normal distribution was used for RRs and SMRs acknowledging that these cannot be negative and are skewed to the right. Parameters not associated with parameter uncertainty, such as the time horizon, discount rates and alternative modelling assumptions; are investigated in the scenario analysis.

B.3.6.2. Assumptions

The assumptions of the economic analysis and their justifications are detailed in Table 47.

The approach to modelling was designed to make the best use of the available data to inform the decision problem, in line with the NICE reference case and guidance on methods of appraisal. In the absence of key data, given the ultra-rare nature of the population, assumptions were necessary. To minimise potential bias in the analysis, conservative assumptions are made, and presented in the table below is the likely direction of bias from the assumptions made and where this can be identified.

Table 47: Key model assumptions

Assumption	Likely direction of bias	Justification / source	Section
Decision tree model			
Patients in the model can have a maximum of one exacerbation during the acute episode.	Against caplacizumab	This is a simplifying and conservative assumption, as experiencing multiple exacerbations is clinically plausible and caplacizumab greatly reduces the exacerbation rate.	Section B.3.3
There is no additional mortality associated with an aTTP exacerbation.	Against caplacizumab	This conservative assumption is based on feedback from experts who stated that the mortality as a result of the acute episode is primarily during the acute event. Mortality data is not available post exacerbation for SoC as all patients received open-label caplacizumab after exacerbation.	Section B.3.3
The probability of exacerbations is the same for patients with refractory disease (i.e. patients with a delayed response measured by platelet count and lactate dehydrogenase [LDH] levels) and responders, and is 12.7% for patients on caplacizumab and 38.4% for patients on SoC	None expected	There is a lack of available data, given the small proportion of patients who develop refractory aTTP. It may be that patients who develop refractory disease are in poorer health and at greater risk of exacerbation.	Section B.3.3
At the end of the short-term model no patients enter the true relapse state immediately following the acute aTTP episode. It is assumed that patients may only relapse following a period of remission.	None expected	This is consistent with the definition of true relapse as a disease recurrence following a period of disease stabilisation.	Section B.3.3
No discounting is applied in the decision tree model	None expected	This is a simplifying assumption as the decision tree considers outcomes over a short (3-month) time horizon.	Section B.3.2

Assumption	Likely direction of bias	Justification / source	Section
Utility for patients experiencing an acute episode is based on utility for hospitalisation[70]	None expected	Acute episodes of aTTP are associated with significant morbidity. Collection of HRQL data during the acute episode is therefore not ethically justifiable, clinically validated proxy treatment areas were sought to identify appropriate utility values to use. Acute utility has little impact on overall cost-effectiveness results due to the short duration of the episode.	Section B.3.4
Markov model			
Long-term complications other than cognitive impairment and neuro-psychological impairment are not included	Against caplacizumab	A range of other long-term complications have been identified in the published literature such as arterial hypertension, cardiac and renal failure. The risk of these may be reduced with caplacizumab due to the shorter time spent in the occluded state. However, due to the paucity of data on these conditions these were not included within the cost-effectiveness analysis. Excluding these additional conditions is inherently conservative as the benefit of caplacizumab may not be fully captured.	Section B.3.3
The risk of cognitive impairment and neuro-psychological impairment are considered independent.	Unknown but unlikely to be a major ICER influencer	No data were identified on the proportion of patients with cognitive impairment who also suffer from neuro-psychological impairment and vice versa.	Section B.3.3
A lifetime duration for cognitive impairment is assumed in the model, this is equivalent to the model time horizon of 55 years	For caplacizumab	Clinicians at the expert validation meeting agreed that cognitive issues are unlikely to improve as regeneration of brain cells is rare. Memory issues are therefore likely to persist over the patient's remaining lifetime.	Section B.3.3
Duration of neuro-psychological impairment following acute episode informed by published literature and is assumed to be 1 year	Against caplacizumab	Data specific to aTTP was not available, therefore published sources were sought for the duration of neuro-psychological impairment. This is likely to be conservative as the correlation between cognitive impairment and neuropsychological impairment in aTTP patients is not accounted for in the model	Section B.3.3
Moderate/severe cognitive impairment was assumed to be consistent with the HRQL of	None expected	Clinical opinion was that stroke would not be an unreasonable HRQL proxy for the worst patients[22]	Section B.3.4

Assumption	Likely direction of bias	Justification / source	Section
patients with stroke.[77] The utility value of patients with stroke calculated from this publication is 0.61.			
The treatment effect for caplacizumab has the same benefit for mild, moderate and severe cognitive impairment, neuro-psychological impairment and mortality in remission, and is based on the ratio of days spent in hospital/ICU between treatments. This results in a RR of 0.62 applied for patients on caplacizumab.	Direction of bias unknown	There is a lack of data to support alternative assumptions, therefore treatment effect assumed the same. Hospitalisation/ICU days used as a proxy for the RR of long-term complications. Clinicians considered this a reasonable proxy to use in the absence of alternative data as the ratio of hospitalisation/ICU days captures both the improved effectiveness of treatment and more rapid normalisation and is consistent with other outcomes such as TTPN.	Section B.3.3
Both decision tree and Markov models			
Patient body surface area (BSA) estimated using the Du Bois formula from HERCULES height and weight data is comparable to patient BSA in clinical practice	None expected	Patient population in HERCULES trial assumed to be generalisable to UK clinical practice	Section B.3.5
Relating to true relapse			
The risk of true relapse is independent of long-term conditions resulting from the acute episode. For example, patients with cognitive impairment are no more likely to relapse than patients with no chronic conditions.	Against caplacizumab	No data were identified to suggest long-term complications associated with increased risk of aTTP relapse, this is a conservative assumption as the prevalence of long-term complications is greater in SoC patients	Section B.3.3

Assumption	Likely direction of bias	Justification / source	Section
True relapse rate is constant over time, assumed relapse rate is 1% annually	None expected	Published data suggest that relapse rates have declined over time, this may be due to improvements in clinical practice through proactive monitoring and pre-emptive rituximab use. Clinical estimates are used based on current UK experience.	Section B.3.3
The probability of true relapse is not dependent on treatment given for the acute episode.	None expected	Caplacizumab is used to treat the acute episode only. Clinicians did not anticipate differential effects between treatments for true relapse rates.	Section B.3.3
Patients who experience a true relapse are treated with the same treatment, for the same duration as in the acute episode.	None expected	If caplacizumab is available, it is expected that this would be used every time a patient has an acute episode	N/A
For patients who experience a true relapse, it is assumed that mortality is the same as the initial episode	Direction of bias unknown	Simplifying assumption made due to limited available data. Alternative assumptions investigated in the scenario analysis.	Section B.3.3
It is assumed that there is no cumulative impact of true relapse on chronic conditions	Against caplacizumab	Simplifying assumption made due to the low probability of true relapse and additional complexity of modelling cumulative impact of relapse.	Section B.3.3
Utility estimates for patients experiencing a true relapse were assumed to be the same as the initial acute aTTP episode.	None expected	No evidence of a relationship between episode number and utility in a published regression analysis[69]	Section B.3.4

Key: aTTP, acquired thrombotic thrombocytopenic purpura; BSA, body surface area; HRQL, health-related quality of life; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; RR, relative risk; SMR, standardised mortality ratio; SoC, standard of care.

B.3.7. Base case results

B.3.7.1. Base case incremental cost-effectiveness analysis results

Table 48 shows the discounted cost-effectiveness results for caplacizumab. All results are presented inclusive of the proposed simple commercial discount of [redacted].

Caplacizumab is associated with 5.48 incremental life years, [redacted] incremental QALYs and incremental costs of [redacted] per patient, compared with SoC. The incremental cost-effectiveness ratio (ICER) is £37,986 per additional QALY gained. Assuming dosing and treatment duration in line with HERCULES and the SmPC,[21] and inclusive of the submitted commercial discount, the NHS England acquisition cost for treatment of an acute episode of aTTP is [redacted]

Although higher than the NICE standard cost-effectiveness threshold of £20,000-£30,000 applied in single technology appraisals,[53] caplacizumab is a life-saving treatment that also improves quality of life in the long-term for patients and carers through reducing the risk of long-term cognitive and neuro-psychological impairment. Caplacizumab is the only licensed treatment specific to aTTP and addresses an urgent clinical need for new interventions that can complement current SoC in this ultra-rare serious and debilitating disease. There is evidence to suggest that higher value should be placed on life-saving treatments for acute and serious diseases under the principle of the “rule of rescue”.[85] ICERs are well below the range generally considered cost-effective for treatments of this nature. [86]

Undiscounted results are reported in Table 49 and disaggregated cost-effectiveness results are presented in Appendix J.

Table 48: Discounted base case results, with PAS discount applied for caplacizumab

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER incremental (£/QALY)
SoC	[redacted]	15.85	[redacted]				
Caplacizumab	[redacted]	21.33	[redacted]	[redacted]	5.48	[redacted]	£37,986
Key: ICER, incremental cost-effectiveness ratio; LY, life years; PAS, patient access scheme; QALY, quality-adjusted life year.							

Table 49: Undiscounted base case results, with PAS discount applied for caplacizumab

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER incremental (£/QALY)
SoC	[redacted]	15.85	[redacted]				
Caplacizumab	[redacted]	21.33	[redacted]	[redacted]	5.48	[redacted]	£24,851
Key: ICER, incremental cost-effectiveness ratio; LY, life years; PAS, patient access scheme; QALY, quality-adjusted life year.							

B.3.8. Sensitivity analyses

B.3.8.1. Probabilistic sensitivity analysis

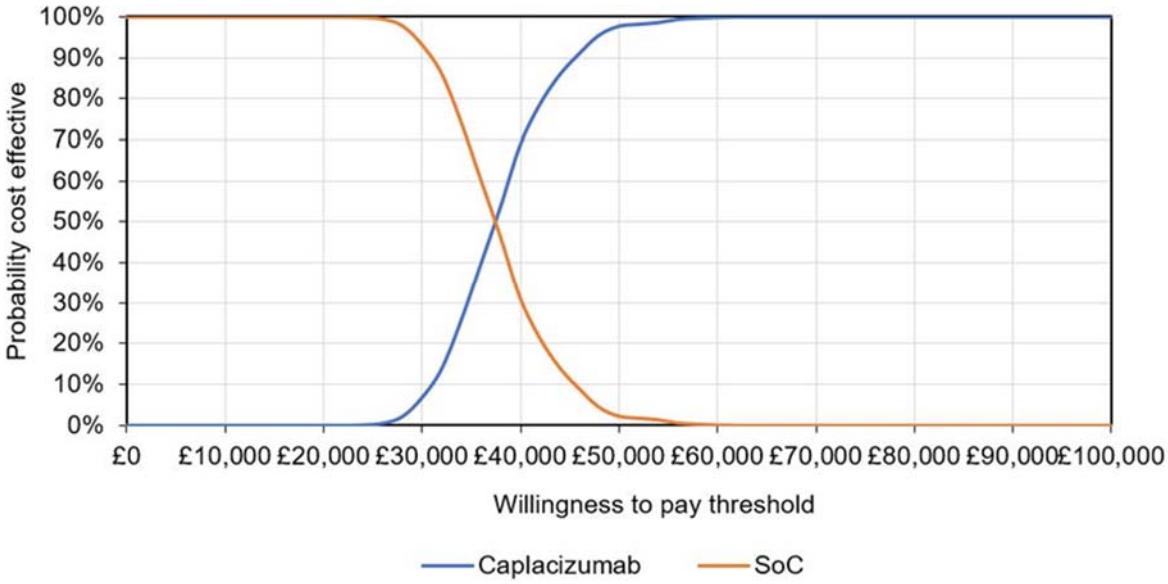
Probabilistic sensitivity analysis (PSA) was carried out to explore the sensitivity in the deterministic base case model results when all model parameters were varied simultaneously. Each parameter was varied according to its associated distribution 1,000 times, and mean model results were recorded. The mean model results were then used to inform a PSA scatter plot and a cost-effectiveness acceptability curve (CEAC); these are presented in Figure 7 and Figure 8, respectively. The probabilistic ICER was £37,370, which is congruent with the deterministic ICER of £37,986.

There is a reasonably high level of uncertainty in the ICER due to the ultra-rare nature of the condition and the fact that much of the uncertainty cannot be reflected within the PSA itself and is instead explored via alternative modelling scenarios. Additionally, there is more uncertainty around the QALYs than the costs. The treatment costs for caplacizumab can be predicted with a high level of certainty as treatment is only given during the acute episode.

Figure 7: PSA scatterplot, PAS discount applied for caplacizumab

Key: PAS, patient access scheme; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; WTP, willingness-to-pay.

Figure 8: Cost-effectiveness acceptability curve, PAS discount applied for caplacizumab



Key: PAS, patient access scheme; SoC, standard of care.

Table 50: Mean PSA results

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER incremental (£/QALY) [95% CI]
SoC	[redacted]	15.85	[redacted]				
Caplacizumab	[redacted]	21.50	[redacted]	[redacted]	5.54	[redacted]	£37,370 [£28,183 -£49,578]

Key: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year; PSA, probabilistic sensitivity analysis.

B.3.8.2. Deterministic sensitivity analysis

One-way sensitivity analysis (OWSA) was conducted to explore the sensitivity in the deterministic base case model results when one parameter is varied at a time. Each parameter was set to the lower and upper bound of its 95% confidence interval (CI), and the deterministic model results were recorded. The top 20 most influential parameters on the ICER are presented as a tornado diagram in Figure 9.

As shown in the tornado diagram, the most influential parameters on the model results were mortality in remission, treatment duration, relapse rates and the RR of experiencing long-term mild cognitive impairment.

Figure 9: One-way sensitivity analysis: Tornado diagram

Key: ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; RR, relative risk; SoC, standard of care; SMR, standardised mortality ratio.

B.3.8.3. Scenario and threshold analysis

As described throughout this submission, a full range of scenario analyses were investigated in order to assess the impact of alternative modelling assumptions. The scenario analyses investigated are summarised in Table 51. In addition, threshold analyses were conducted for key parameters such as acute and long-term mortality and the RR of long-term complications. Results of these analyses for mortality and long-term complications are presented in Table 52 and Table 53, respectively.

ICERs from the scenario analyses ranged between £22,304 and £49,756. As expected, based on the threshold analyses, the ICERs were sensitive to both acute and long-term mortality and the RR long-term complications.

As described in Section B.3.3.2, an RR for long-term complications and mortality of 0.62 is assumed based on proxy trial data and clinical opinion. Despite there being a wealth of qualitative evidence to show that quicker resolution of the acute episode can be linked to a reduced long-term risk of conditions and mortality, there is a lack of data demonstrating the quantitative relationship. Therefore, it was important to investigate a range of scenarios assuming various RRs for both of these important parameters.

As explained in Section B.3.2.2, alternative discount rates were also important to explore. Caplacizumab is a treatment with high upfront costs for the acute episode but long-term benefits through reduced acute mortality, the use of a 3.5% discount rate biases against caplacizumab as benefits are heavily discounted but not costs. Results assuming alternative discount rates are presented in Table 51. Importantly, considering a discount rate of 1.5% for both costs and QALYs reduces the ICER to £29,970.

A final key scenario using a higher QALY weight is included based on a NICE Citizens Council report that discusses how society should place a higher value on life-saving interventions in situations of urgent need.[85] Using a QALY modifier of 1.7, equivalent to the end-of-life criteria allowing for a £50,000 threshold to be considered for life-saving treatments at the end of life[53], resulted in an ICER of £22,304.

Table 51: Scenario analysis results

Scenario	Base case	Incremental costs	Incremental QALYs	ICER	Change from base-case ICER
Base case ICER	**-**	[redacted]	[redacted]	**£37,986**	**-**
General settings					
Time horizon: 40 years	Lifetime	[redacted]	[redacted]	£38,017	£31
Time horizon: 20 years	Lifetime	[redacted]	[redacted]	£47,416	£9,430
Discount rate, both costs and QALYs: 1.5%	3.5%	[redacted]	[redacted]	£29,970	-£8,016
Discount rate, both costs and QALYs: 6%	3.5%	[redacted]	[redacted]	£49,756	£11,771
Efficacy					
Definition of refractory: Benhamou et al.	Scully et al.	[redacted]	[redacted]	£38,064	£78
Refractory %: User inputs; 17% SoC, RR 0.2 caplacizumab	HERCULES ITT	[redacted]	[redacted]	£37,323	-£662
Exacerbations: Early only (<30 days after PEX cessation)	Combined early and late	[redacted]	[redacted]	£37,672	-£314
Annual probability of true relapse, 0% per annum	1%	[redacted]	[redacted]	£34,125	-£3,861
Annual probability of true relapse, 2% per annum	1%	[redacted]	[redacted]	£40,884	£2,898
Source for baseline cognitive impairment % SoC: Cataland (2011)	Kennedy (2009)	[redacted]	[redacted]	£38,750	£764
Source for baseline neuro-psychological impairment % SoC: (Deford 2013)	Chaturvedi (2015)	[redacted]	[redacted]	£38,073	£87
Duration of mild, moderate and severe cognitive impairment: 20 years	Lifetime	[redacted]	[redacted]	£37,710	-£276
Duration of neuro-psychological impairment: 0.5 years	1 year	[redacted]	[redacted]	£38,080	£94

Duration of neuro-psychological impairment: 2 years	1 year	[redacted]	[redacted]	£37,810	-£176
Assume that all patients experience some form of chronic conditions	As per literature sources	[redacted]	[redacted]	£34,283	-£3,702
Mortality					
Acute mortality RR caplacizumab 0.0	0.32	[redacted]	[redacted]	£32,875	-£5,111
Acute mortality based on HERCULES ITT data	0.32	[redacted]	[redacted]	£42,853	£4,867
Apply different survival rate for relapse compared to acute aTTP episode (Capla 95%, SoC 90%)	Same mortality assumed for relapse	[redacted]	[redacted]	£38,287	£301
Mortality source in remission: Deford (2013)	Upreti (2019)	[redacted]	[redacted]	£37,824	-£162
Utility					
Include decline in utility with increasing age?: No	Age adjustment applied	[redacted]	[redacted]	£35,490	-£2,496
Include QALY decrements for AEs?: No	QALY decrements for AEs applied	[redacted]	[redacted]	£37,969	-£16
QALY modifier: 1.7	No QALY weighing applied	[redacted]	[redacted]	£22,304	-£15,682
Include caregiver QoL?: No	Yes	[redacted]	[redacted]	£38,573	£587
Costs					
Include wastage when costing rituximab? No	Yes	[redacted]	[redacted]	£37,961	-£25
Include costs for treating AEs?: Yes	No	[redacted]	[redacted]	£38,085	£99

Key: AE, adverse event; aTTP, acquired thrombotic thrombocytopenic purpura; FU, follow-up; ICER, incremental cost-effectiveness analysis; ITT, intention-to-treat; QALY, quality-adjusted life year; SMR, standardised mortality ratio.

Table 52: Threshold analysis showing impact on ICER when varying RR of acute mortality and mortality in remission for caplacizumab

		RR mortality in remission									
		0.1	**0.2**	**0.3**	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**	**1**
RR acute mortality	**0.1**	£18,694	£21,313	£23,953	£26,787	£29,929	£33,497	£37,630	£42,509	£48,396	£55,671
	0.2	£19,121	£21,881	£24,682	£27,710	£31,095	£34,973	£39,510	£44,933	£51,571	£59,924
	0.3	£19,575	£22,490	£25,470	£28,715	£32,375	£36,609	£41,621	£47,692	£55,248	£64,956
	0.4	£20,059	£23,144	£26,323	£29,814	£33,788	£38,436	£44,007	£50,861	£59,557	£71,005
	0.5	£20,577	£23,850	£27,250	£31,020	£35,355	£40,486	£46,726	£54,539	£64,674	£78,413
	0.6	£21,133	£24,613	£28,263	£32,349	£37,103	£42,805	£49,853	£58,859	£70,853	£87,697
	0.7	£21,729	£25,441	£29,372	£33,822	£39,065	£45,449	£53,488	£64,006	£78,460	£99,670
	0.8	£22,372	£26,342	£30,593	£35,464	£41,283	£48,492	£57,766	£70,243	£88,057	£115,703
	0.9	£23,067	£27,327	£31,943	£37,303	£43,811	£52,030	£62,872	£77,956	£100,541	£138,278
	1	£23,820	£28,407	£33,443	£39,380	£46,718	£56,197	£69,075	£87,739	£117,447	£172,429

Key: ICER, incremental cost-effectiveness ratio; RR, relative risk; SMR, standard mortality rate; SoC, standard of care.

Table 53: Threshold analysis showing impact on ICER when varying RR of long-term cognitive and neuro-psychological impairment with caplacizumab

		RR mild, moderate and severe cognitive impairment, caplacizumab									
		0.1	**0.2**	**0.3**	**0.4**	**0.5**	**0.6**	**0.7**	**0.8**	**0.9**	**1**
RR neuro-psychological impairment, caplacizumab	**0.1**	£26,301	£28,019	£29,914	£32,015	£34,356	£36,983	£39,950	£43,329	£47,211	£51,717
	0.2	£26,351	£28,074	£29,974	£32,081	£34,430	£37,065	£40,042	£43,432	£47,328	£51,851
	0.3	£26,402	£28,130	£30,035	£32,148	£34,504	£37,147	£40,134	£43,536	£47,445	£51,987
	0.4	£26,454	£28,186	£30,096	£32,215	£34,578	£37,229	£40,226	£43,639	£47,564	£52,122
	0.5	£26,505	£28,242	£30,158	£32,283	£34,652	£37,312	£40,319	£43,744	£47,683	£52,259
	0.6	£26,557	£28,298	£30,219	£32,350	£34,727	£37,395	£40,412	£43,849	£47,802	£52,396
	0.7	£26,609	£28,354	£30,281	£32,418	£34,802	£37,479	£40,505	£43,954	£47,922	£52,534
	0.8	£26,660	£28,411	£30,343	£32,486	£34,878	£37,563	£40,599	£44,060	£48,042	£52,673
	0.9	£26,713	£28,468	£30,405	£32,555	£34,953	£37,647	£40,693	£44,167	£48,164	£52,812
	1	£26,765	£28,525	£30,468	£32,624	£35,029	£37,731	£40,788	£44,273	£48,285	£52,952

Key: ICER, incremental cost-effectiveness ratio; RR, relative risk.

B.3.9. Subgroup analysis

Subgroup analysis for the subgroup of patients with aTTP confirmed by ADAMTS13 activity <10% at baseline was conducted. Results for this subgroup are presented in Table 54. The difference in results versus the ITT analysis was minimal suggesting that the treatment benefit of caplacizumab is equal across groups.

Table 54: Discounted base case results, with PAS discount applied for caplacizumab, subgroup with ADAMTS13 activity <10% at baseline

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER incremental (£/QALY)
SoC	[redacted]	15.94	[redacted]				
Caplacizumab	[redacted]	21.44	[redacted]	[redacted]	5.50	[redacted]	£37,493
Key: ICER, incremental cost-effectiveness ratio; LY, life years; PAS, patient access scheme; QALY, quality-adjusted life year.							

B.3.10. Validation

B.3.10.1. Overview

Throughout the model conceptualisation and development process, extensive clinical input was sought. Clinical expert opinion was considered particularly important due to the rarity of aTTP.

An HTA advisory board and Delphi expert elicitation panel was conducted on 6 March 2019. These were attended by seven clinical expert haematologists and one pharmacist, all with extensive experience in treating aTTP patients. At the advisory board, insight was gained into the proposed model structure, modelling inputs and assumptions. The Delphi expert elicitation panel involved presenting evidence on the important long-term consequences of acute aTTP to experts with the aim of gaining consensus on which to include in the modelling. Following model construction, three further expert validation TCs were held on 11 and 13 June 2019, to validate modelling inputs and assumptions in detail. In addition to expert input and validation, the model also underwent thorough quality control checks at key points during development by senior staff not involved in the model development. A summary of the model verification/validation is presented in Table 55.

Table 55: Summary of model verification/validation

Aspect of validation/verification	Date	Purpose
Clinical expert advisory board	6 March 2019	To gain clinical expert insight into the conceptual modelling and long-term complications to include in the economic model.
Delphi expert elicitation	6 March 2019	To reach consensus on the unmet need for patients experiencing an aTTP episode and the need for and potential benefits of a rapid intervention such as caplacizumab.
Clinical expert validation TCs	11 and 13 June 2019	To validate the cost-effectiveness model structure, inputs and assumptions
Model QC	May-Sept 2019	To verify that all model calculations are correct and that the model presented in a clear and transparent manner, appropriate for review by NICE and the ERG.

Key: aTTP, acquired thrombotic thrombocytopenic purpura; ERG, Evidence Review Group; NA, not applicable; NICE, National Institute for Health and Care Excellence; QC, quality control; TCs, teleconferences.

B.3.10.2. Clinical validation by topic

HERCULES trial generalisability

Clinicians at the advisory board discussed how some of the HERCULES data may lack generalisability to patients in UK clinical practice.[14] Clinicians discussed how mortality in HERCULES was low compared to the UK average as fitter patients were enrolled and recruited from specialist centres with better outcomes overall. Clinicians also commented that the same number of thromboembolic events between treatment arms was unexpected. The frequency of thromboembolic events was expected to decrease for patients taking caplacizumab based on the increased time to platelet count response, reduced risk of refractory disease and reduced exacerbation risk. This finding was likely due to the small sample size of HERCULES and low numbers of events.

Clinicians also commented on how the proportion of patients with refractory disease in the HERCULES trial was low compared to UK clinical practice and stated that the 17% refractory rate as reported in real-world evidence is more appropriate.[19]

Furthermore, not all patients had TTP as confirmed by ADAMTS13 activity <10%. Clinicians also suggested that treatment practices are continuing to evolve, especially with respect to the use of rituximab. It was thought that the use of rituximab in HERCULES does not match current UK clinical expectation as this varied by standard site practice and was not given to patients with unresolved disease to reduce the risk of recurrence.

All of the limitations above may bias against caplacizumab, by reducing the relative efficacy (i.e. mortality, thromboembolic events, refractoriness and eligibility) or the relative costs (i.e. rituximab use) compared to SoC, as discussed in Section B.2.13.

Model structure and long-term complications

The structure of the Markov model was informed by discussions with clinicians at the initial advisory board[14] and validated by clinicians during expert TCs.[22] Clinicians at the advisory board explained how patients are often left with lifelong disabling effects following an acute episode of aTTP, particularly in terms of neurocognitive aspects; many patients experience problems with functioning to the same level as before the episode, and neuropsychological aspects; many patients experience severe depression, anxiety and PTSD following the unexpected and life-threatening acute episode.

Experts at the clinical validation meeting reiterated that caplacizumab shortens the time in which brain cells are being destroyed, and that it was intuitive that quicker time to resolution of disease leads to lessening of the microthrombi burden. [22] Clinicians explained that reducing a lengthy and stressful hospital or ICU stay should also result in a reduced risk of developing long-term complications.

In an earlier version of the model, a health state was included for patients who survived a myocardial infarction or stroke during the acute episode. However, during the advisory board, clinicians explained that cardiac events in aTTP patients in the acute stagfe are not comparable to classic myocardial infarction and are usually fatal.[14] In addition, while chronic neurology is a major issue around stroke, aTTP patients were said not to experience a classic stroke but instead experience paraesthesia. Patients typically present in a coma and this resolves with treatment and long-term consequences are not observed. Therefore, this health state was not

included in the model as mortality was already captured separately. During the expert validation meeting, clinicians explained that there may be damage to the kidneys and heart due to microthrombotic processes, which may only manifest later in life. However, neither of these long-term complications were explicitly modelled due to limited long-term evidence.[22] Other long-term complications of aTTP discussed in the literature include arterial hypertension, digestive issues and non-specific weakness. These were also conservatively excluded from the model due to limited evidence or lack of consensus among clinicians.[10]

Relapse

Clinicians at the advisory board explained that true relapse is rare in current UK clinical practice. One clinician discussed how, out of approximately 100 patients currently being monitored in the hospital in which she practices, approximately one relapse would occur per year.[22] This is due to proactive monitoring and pre-emptive treatment with rituximab if ADAMTS13 activity falls below acceptable levels. Clinicians explained how the disease recurrences observed in HERCULES after 30 days of stopping plasma exchange (for patients on caplacizumab due to lack of ADAMTS13 suppression) were likely due to untreated disease rather than true relapses. However, relapse is included as a health state in the model to increase clinical credibility and to allow for scenario testing as while relapse is rare in current UK clinical practice, it does still occur.

Clinicians at the advisory board explained that, while these are the conventional definitions used historically for SoC[37], the relapses observed in HERCULES (which only occurred for patients on the caplacizumab arm) were deferred, or late exacerbations, which could be avoided in clinical practice with proactive monitoring and pre-emptive treatment with rituximab. Indeed, all six patients experiencing disease recurrence during the HERCULES follow-up period had low ADAMTS13 activity (<10%) at the end of their 30-day post-daily PEX treatment, and the majority did not receive optimisation of the immunosuppressive regimen.

Clinicians attending the expert validation meetings explained that using ADAMTS13 levels to determine if recurrences are exacerbations or relapses may be more valuable than defining relapse/exacerbation in terms of time after cessation of PEX.[22] Hence, the pre-/post-30-day definition of relapse is deemed by clinicians to be less

meaningful in the context of treatment with caplacizumab and thus may need to be revisited.[22]

Acute mortality

Clinicians at the advisory board explained that mortality observed in HERCULES was much lower than that observed in clinical practice.[14] Clinicians explained that this was likely due to the selection criteria in HERCULES; patients had to be 'stably unwell' to be eligible for inclusion in the trial, and therefore patients with the most severe disease were excluded. In addition, patients in a comatose state with severe disease are not able to provide consent. HERCULES was also conducted in specialist centres with better outcomes than UK clinical practice overall. Furthermore, the HERCULES protocol stated that patients were required to have one PEX prior to randomisation. This is not a requirement in clinical practice, caplacizumab is licenced for treatment prior to first PEX, athough most patients will be initiated on PEX prior to diagnosis. This could contribute to the low mortality observed in HERCULES as patients may have died prior to randomisation.

Overall mortality for the acute episode is expected to be approximately 13.2%, as reported in a meta-analysis of studies identified in the literature.[51] Clinicians expected mortality for patients on caplacizumab to be much lower than this, but agreed that assuming 0% mortality from HERCULES for caplacizumab patients was unrealistic. Furthermore, clinicians explained that the difference in mortality between arms was also expected to be larger than that observed in HERCULES (i.e. applying an absolute difference of 3% was considered inappropriate).

While future insights into the UK aTTP registry data may allow mortality to be determined for a large sample of UK patients, these data are also likely to be biased, as patients again had to consent to being included in the registry. In addition, missing deaths from non-specialised centres included in the registry lead to a reduction in reported mortality.

Long-term mortality

There is a lack of long-term data in the literature on life expectancy following an acute episode of aTTP, and there is a lack of consensus among clinicians on this topic.[10] Experts at the clinical validation meeting explained that it is clinically

plausible that the ischaemic damage in the acute episode caused by prolonged microvascular thrombosis would lead to early cardiac and renal failure later in life, resulting in a reduced life expectancy for aTTP patients.[22] In addition, patients on caplacizumab might be expected to have a reduced risk of organ failure in the long term based on the quicker resolution of the acute episode. See Section B.2.13 for a summary of consensus statements reached in the modified-Delphi process previously described.

Resource use

Resource use data from HERCULES may not be reflective of clinical practice in the UK for a number of reasons. Firstly, the HERCULES trial was conducted globally, and resource use estimates are not UK specific – there may be geographical differences in treatment practices/guidelines. Secondly, there is a lack of long-term information on resource use as HERCULES only considered patients experiencing an acute episode. Lastly, in HERCULES, all patients received open-label caplacizumab on exacerbation. Therefore, there is not an accurate estimate of resource use for SoC in clinical practice (without caplacizumab treatment on exacerbation). Clinicians did agree with compliance based on HERCULES and stated that compliance is likely to be high in clinical practice, reflecting the importance of treatment for this life-threatening disease.[22]

Due to the above issues, a resource use survey was developed and sent to UK clinicians to estimate resource use in the UK setting in the model and fill any data gaps left by HERCULES.[58]

B.3.11. Interpretation and conclusions of economic evidence

Caplacizumab addresses an urgent clinical need for a new intervention that reduces the time in which patients remain exposed to the consequences of microvascular thrombosis (time in the occluded state).[10, 17] Withholding caplacizumab leaves patients at continued risk of suffering organ damage and death in the early stages of an acute episode, and thus at risk of the potentially devasting life-long consequences resulting from such damage.

In the clinical trial programme, caplacizumab as a complement to SoC demonstrated a clear benefit over PEX and immunosuppression alone in multiple outcomes of

clinical relevance to patients, carers and health services. This included significantly reduced time to platelet count response, demonstrating fast resolution of the aTTP episode in terms of microvascular control, and significantly reduced lengths of ICU stay for patients requiring such care.

The true impact of caplacizumab on the lives of patients' and their loved ones is unlikely to be captured in the economic analysis. In part due to a current lack of data assessing the longer-term benefit of caplacizumab on patients physical and mental well-being, but also due to the difficulty of capturing the full value of true innovation for an ultra-rare disease in a clinical trial setting or QALY measurement. Despite this, with a base case ICER of £37,986 per QALY, caplacizumab is considered a good use of NHS resource within the context of an acute, ultra-rare, life-threatening disease requiring highly specialised life-saving care in an urgent, medical emergency setting.

In conclusion, caplacizumab offers a truly innovative, clinically effective and cost-effective treatment option and offers a step-change in the management of aTTP. With a highly specialised TTP service on the horizon, this is a timely appraisal that, if resulting in positive recommendation for caplacizumab, could allow patients in NHS England access to an innovative intervention as part of this nationalised service.

B.4. References

1. Scully M, Hunt B, Benjamin S, et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. *Br J Haematol*. 2012; 158:323-35.
2. GOV.UK. Population of England and Wales. 2018. Available at: https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/national-and-regional-populations/population-of-england-and-wales/latest#by-ethnicity Accessed: 28 August 2019.
3. Shin JS, Alwan F, Austin S, et al. Thrombotic thrombocytopenic purpura: demographic analysis of the UK TTP registry from 2009 to 2018. British Society for Haematology 59th Annual Scientific Meeting Glasgow, Scotland. 1-3 April 2019. BSH19-OR-032.
4. Sanofi. aTTP Patient Journey. March 2019. Data on file.
5. NHS England. Service specification 1668: Schedule 2 - The Services. Draft for consultation. Available at: https://www.engage.england.nhs.uk/consultation/thrombocytopenic-purpura/user_uploads/thrombotic-thrombocytopenic-purpura-service-specification.pdf. Accessed: 28 March 2019.
6. Cataland SR, Scully MA, Paskavitz J, et al. Evidence of persistent neurologic injury following thrombotic thrombocytopenic purpura. *Am J Hematol*. 2011; 86(1):87-9.
7. Chaturvedi S, Abbas H and McCrae KR. Increased morbidity during long-term follow-up of survivors of thrombotic thrombocytopenic purpura. *Am J Hematol*. 2015; 90(10):E208.
8. Kennedy AS, Lewis QF, Scott JG, et al. Cognitive deficits after recovery from thrombotic thrombocytopenic purpura. *Transfusion*. 2009; 49(6):1092-101.
9. George JN. TTP: long-term outcomes following recovery. *Hematology Am Soc Hematol Educ Program*. 2018; 2018(1):548-52.
10. Sanofi. Expert consensus to support the use of caplacizumab in aTTP. (SA8248A Version 2.0) 18 April 2019. Data on file.
11. Hatch R, Young D, Barber V, et al. Anxiety, Depression and Post Traumatic Stress Disorder after critical illness: a UK-wide prospective cohort study. *Critical Care*. 2018; 22(1):310.
12. Upreti H, Kasmani J, Dane K, et al. Reduced ADAMTS13 activity during TTP remission is associated with stroke in TTP survivors. *Blood*. 2019:blood.2019001056.
13. Chaturvedi S, Oluwole O, Cataland S and McCrae KR. Post-traumatic stress disorder and depression in survivors of thrombotic thrombocytopenic purpura. *Thromb Res*. 2017; 151:51-6.
14. Sanofi. HTA advisory board 06 March 2019. Data on file.
15. Falter T, Schmitt V, Herold S, et al. Depression and cognitive deficits as long-term consequences of thrombotic thrombocytopenic purpura. *Transfusion*. 2017; 57(5):1152-62.
16. Scully M, Cataland SR, Peyvandi F, et al. Caplacizumab Treatment for Acquired Thrombotic Thrombocytopenic Purpura. *N Engl J Med*. 2019; 380(4):335-46.
17. European Medicines Agency (EMA). Cablivi: Assessment report. 2018. Available at: https://www.ema.europa.eu/en/documents/assessment-report/cablivi-epar-public-assessment-report_en.pdf. Accessed: 25 June 2019.

18. Peyvandi F, Scully M, Kremer Hovinga JA, et al. Caplacizumab for acquired thrombotic thrombocytopenic purpura. *N Engl J Med*. 2016; 374(6):511-22.
19. Benhamou Y, Boelle PY, Baudin B, et al. Cardiac troponin-I on diagnosis predicts early death and refractoriness in acquired thrombotic thrombocytopenic purpura. Experience of the French Thrombotic Microangiopathies Reference Center. *J Thromb Haemost*. 2015; 13(2):293-302.
20. Peyvandi F, Scully M, Kremer Hovinga JA, et al. Caplacizumab reduces the frequency of major thromboembolic events, exacerbations and death in patients with acquired thrombotic thrombocytopenic purpura. *J Thromb Haemost*. 2017; 15(7):1448-52.
21. Ablynx NV. Summary of Product Characteristics (SPC),. Cablivi 10mg powder and solvent for solution for injection. 2018. Available at: https://www.ema.europa.eu/documents/product-information/cablivi-epar-product-information_en.pdf. Accessed: 31 January 2019.
22. Sanofi. HTA model review and clinical validation June 2019. Data on file.
23. Kaltenthaler E, Tappenden P, Paisley S and Squires H. NICE DSU Technical Support Document 13: Identifying and Reviewing Evidence to Inform the Conceptualisation and Population of Cost-Effectiveness Models. 2011. Available at: http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD-13-model-parameters.pdf. Accessed: 3 July 2019.
24. Barbour T, Johnson S, Cohney S and Hughes P. Thrombotic microangiopathy and associated renal disorders. *Nephrol Dial Transplant*. 2012; 27(7):2673-85.
25. Lester W, Begaj I, Ray D and Pagano D. Trends in diagnosis and mortality from thrombotic thrombocytopenic purpura in England from 2003 to 2013: are we improving outcomes? 55th Annual Scientific Meeting of the British Society for Haematology. Edinburgh, UK. 20-22 April 2015. 100.
26. Orpha.net. Acquired thrombotic thrombocytopenic purpura. 2015. Available at: http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=93585. Accessed: 07 March
27. George JN, Terrell DR, Swisher KK and Vesely SK. Lessons learned from the Oklahoma thrombotic thrombocytopenic purpura-hemolytic uremic syndrome registry. *J Clin Apher*. 2008; 23(4):129-37.
28. Saultz JN, Wu HM and Cataland S. Headache prevalence following recovery from TTP and aHUS. *Ann Hematol*. 2015; 94(9):1473-6.
29. Department of Health. National Stroke Strategy. 2007. Available at: https://webarchive.nationalarchives.gov.uk/20130104224925/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_081059.pdf. Accessed: 29 July 2019.
30. Falter T, Alber KJ and Scharrer I. Long term outcome and sequelae in patients after acute thrombotic thrombocytopenic purpura episodes. *Hamostaseologie*. 2013; 33(2):113-20.
31. Han B, Page EE, Stewart LM, et al. Depression and cognitive impairment following recovery from thrombotic thrombocytopenic purpura. *Am J Hematol*. 2015; 90(8):709-14.
32. Deford CC, Reese JA, Schwartz LH, et al. Multiple major morbidities and increased mortality during long-term follow-up after recovery from thrombotic thrombocytopenic purpura. *Blood*. 2013; 122(12):2023-9; quiz 142.

33. Kremer Hovinga J. *Platelets in thrombotic and non-thrombotic disorders: Pathophysiology, pharmacology, and therapeutics*. Springer International Publishing, 2017.
34. Lewis QF, Lanneau MS, Mathias SD, et al. Long-term deficits in health-related quality of life after recovery from thrombotic thrombocytopenic purpura. *Transfusion*. 2009; 49(1):118-24.
35. Connors MH, Seeher K, Teixeira-Pinto A, et al. Mild Cognitive Impairment and Caregiver Burden: A 3-Year-Longitudinal Study. *Am J Geriatr Psychiatry*. 2019.
36. Paradise M, McCade D, Hickie IB, et al. Caregiver burden in mild cognitive impairment. *Aging Ment Health*. 2015; 19(1):72-8.
37. Scully M, Cataland S, Coppo P, et al. Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies. *J Thromb Haemost*. 2017; 15(2):312-22.
38. TTP Registry. Use of caplacizumab in the UK: Consensus statement. March 2019. Data on file.
39. Ablynx NV. HERCULES CSR: Post-hoc data analysis. 2017. Data on file.
40. Shemin D, Briggs D and Greenan M. Complications of therapeutic plasma exchange: a prospective study of 1,727 procedures. *J Clin Apher*. 2007; 22(5):270-6.
41. TTP Registry. UK TTP Forum Annual Meeting - 7th March 2019 MINUTES. March 2019. Data on file.
42. Ablynx NV. Post-HERCULES Clinical Study Protocol: Prospective Follow-up Study for Patients who Completed Study ALX0681-C301 (HERCULES) to Evaluate Long-term Safety and Efficacy of Caplacizumab. (Clinical Study Protocol) 2016. Data on file.
43. Ablynx NV. HERCULES CSR: a phase III double-blind, randomized, parallel group, multicenter placebo-controlled trial to study the efficacy and safety of caplacizumab in patients with acquired thrombotic thrombocytopenic purpura (Clinical Study Report: ALX0681-C301) 2017.
44. Ablynx NV. TITAN CSR: a phase II, single-blind, randomised, placebo-controlled trial to study the efficacy and safety of anti-von willebrand factor nanobody administered as adjunctive treatment to patients with acquired thrombotic thrombocytopenic purpura. (Clinical Study Report: ALX-0681-2.1/10) 2015.
45. Ablynx NV. Integrated Summary of Efficacy. Caplacizumab. 2018. Data on file.
46. Ablynx NV. Integrated Summary of Safety. Caplacizumab. 2018. Data on file.
47. Peyvandi F, Scully M, Kremer Hovinga JA, et al. Impact of caplacizumab treatment on mortality and major thromboembolic events in acquired TTP: phase II titan study results. *Haematologica*. 2016; 101:144.
48. National Institute for Health and Care Excellence (NICE). Caplacizumab for treating adults experiencing an episode of acquired thrombotic thrombocytopenic purpura [ID1185] - Final scope. 2019. (Updated: 09 August 2019) Available at: http://nicedsu.org.uk/wp-content/uploads/2017/06/Partitioned-Survival-Analysis-final-report.pdf. Accessed: 21 August 2019.
49. Sanofi. White Paper: Time to platelet count normalisation as indicator of clinical outcome and long-term morbidity in acute acquired thrombotic thrombocytopenic purpura (aTTP). 14 February 2019 2019. Data on file.
50. Sonnenberg FA and Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making*. 1993; 13(4):322-38.

51. Ablynx. Systematic review on the clinical burden of disease in thrombotic thrombocytopenic purpura. 2018. Data on file.
52. National Institute for Health and Care Excellence (NICE). NICE DSU Technical Support Document 19: Partitioned Survival Analysis for Decision Modelling in Health Care: A critical Review. 2017. Available at: http://nicedsu.org.uk/wp-content/uploads/2017/06/Partitioned-Survival-Analysis-final-report.pdf. Accessed: 25 June 2019.
53. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal. 2013. Available at: https://www.nice.org.uk/process/pmg9/chapter/foreword. Accessed: 14 February 2018.
54. British National Formulary (BNF). Drug costs. 2019. Available at: https://bnf.nice.org.uk/. Accessed: 04 July 2019.
55. Department of Health. Drugs and pharmaceutical electronic market information tool (eMIT). 2019. Available at: https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. Accessed: 13 September 2019.
56. Department of Health. National Schedule of Reference Costs. 2018. Available at: https://improvement.nhs.uk/resources/reference-costs/. Accessed: 16 April 2019.
57. Personal and Social Services Research Unit (PSSRU). Unit Costs of Health and Social Care. 2018. Available at: https://www.pssru.ac.uk/project-pages/unit-costs/. Accessed: 13 September 2019.
58. Sanofi. Estimating Resource Use for Acquired Thrombocytopenic Purpura Patients Experiencing an Acute Episode and in Remission: Questionnaire. 2019. Data on file.
59. Sanofi. Early access program: UPDATE. September 2019 2019.
60. Zafrani L, Mariotte E, Darmon M, et al. Acute renal failure is prevalent in patients with thrombotic thrombocytopenic purpura associated with low plasma ADAMTS13 activity. *J Thromb Haemost*. 2015; 13(3):380-9.
61. Lara PN, Jr., Coe TL, Zhou H, et al. Improved survival with plasma exchange in patients with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. *Am J Med*. 1999; 107(6):573-9.
62. National institute for Health and Care Excellence (NICE). CG90: Depression in adults: recognition and management. 2018. Available at: https://www.nice.org.uk/guidance/cg90. Accessed: 15 July 2019.
63. National institute for Health and Care Excellence (NICE). CG91: Depression in adults with a chronic physical health problem: recognition and management. 2009. Available at: https://www.nice.org.uk/guidance/cg91. Accessed: 15 July 2019.
64. National institute for Health and Care Excellence (NICE). TA367: Vortioxetine for treating major depressive episodes. 2015. Available at: https://www.nice.org.uk/guidance/ta367. Accessed: 15 July 2019.
65. Simon GE, Goldberg DP, Von Korff M and Ustun TB. Understanding cross-national differences in depression prevalence. *Psychol Med*. 2002; 32(4):585-94.
66. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *Jama*. 2003; 289(23):3095-105.
67. Guyot P, Ades AE, Ouwens MJ and Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol*. 2012; 12:9.

68. Office for National Statistics (ONS). National life tables: England and Wales. 2019. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandandwalesreferencetables. Accessed: 12 April 2019.
69. Burns D, Lee D, Vesely S, et al. Patient health-related quality of life associated with remission of aTTP. A regression analysis using non-randomised observational data from the Oklahoma TTP registry. ISPOR. Barcelona, Spain. 10-14 November 2018 2018. PSY192.
70. Chit A, Becker DL, DiazGranados CA, et al. Cost-effectiveness of high-dose versus standard-dose inactivated influenza vaccine in adults aged 65 years and older: an economic evaluation of data from a randomised controlled trial. *Lancet Infect Dis*. 2015; 15(12):1459-66.
71. McPhail S and Haines T. Response shift, recall bias and their effect on measuring change in health-related quality of life amongst older hospital patients. *Health Qual Life Outcomes*. 2010; 8:65.
72. Pappas MA, Vijan S, Rothberg MB and Singer DE. Reducing age bias in decision analyses of anticoagulation for patients with nonvalvular atrial fibrillation - A microsimulation study. *PLoS One*. 2018; 13(7):e0199593.
73. Clemens S, Begum N, Harper C, et al. A comparison of EQ-5D-3L population norms in Queensland, Australia, estimated using utility value sets from Australia, the UK and USA. *Qual Life Res*. 2014; 23(8):2375-81.
74. Ara R and Brazier JE. Populating an economic model with health state utility values: moving toward better practice. *Value Health*. 2010; 13(5):509-18.
75. Rowen D, Brazier J and Roberts J. Mapping SF-36 onto the EQ-5D index: how reliable is the relationship? *Health Qual Life Outcomes*. 2009; 7:27.
76. Freeman JV, Zhu RP, Owens DK, et al. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. *Ann Intern Med*. 2011; 154(1):1-11.
77. Gage BF, Cardinalli AB and Owens DK. The effect of stroke and stroke prophylaxis with aspirin or warfarin on quality of life. *Arch Intern Med*. 1996; 156(16):1829-36.
78. Sorensen SV, Kansal AR, Connolly S, et al. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: a Canadian payer perspective. *Thromb Haemost*. 2011; 105(5):908-19.
79. Sullivan PW, Slejko JF, Sculpher MJ and Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. *Med Decis Making*. 2011; 31(6):800-4.
80. Ara R and Wailoo A. NICE DSU technical support document 12: The use of health state utility values in decision models. 2011. Available at: http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD12-Utilities-in-modelling-FINAL.pdf. Accessed: 07 May 2019.
81. van Exel NJ, Koopmanschap MA, van den Berg B, et al. Burden of informal caregiving for stroke patients. Identification of caregivers at risk of adverse health effects. *Cerebrovasc Dis*. 2005; 19(1):11-7.
82. Wittenberg E and Prosser LA. Disutility of illness for caregivers and families: a systematic review of the literature. *PharmacoEconomics*. 2013; 31(6):489-500.
83. NHSBT. NHSBT Pricing Proposals for 2017-18. 2016. Available at: https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/2188/16-80.pdf. Accessed: 20 September 2019.

84. Levy JH, McKee A, Sidebotham A and Gillham M. *Cardiothroracic Critical Care*. 2007.
85. National Institute for Health and Care Excellence. Report on NICE Citizens Council meeting, departing from the threshold. 2007. Available at: https://www.nice.org.uk/Media/Default/Get-involved/Citizens-Council/Reports/CCReport11DepartingThreshold.pdf. Accessed: 29 April 2019.
86. National Institute for Health and Care Excellence (NICE). TA588: Nusinersen for treating spinal muscular atrophy. 2019. Available at: https://www.nice.org.uk/guidance/ta588.

B.5. Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life and resource use studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Additional clinical trial data

Appendix M: Calculations for the proportion of patients with long-term outcomes

Appendix N: Payoff approach

Appendix O: Utilities to inform the economic model – additional information

Appendix P: Rituximab dosing

Appendix Q: Summary of variables applied in the economic model

Appendix R: Cognitive impairment TLR

Appendix S: Resource use frequencies and proportions

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Caplacizumab for treating adults experiencing an episode of acquired thrombotic thrombocytopenic purpura [ID1185]

Clarification questions

October 2019

File name	Version	Contains confidential information	Date
ID1185-22112019_ Caplacizumab_Clarification Request_Sanofi Responses_Updated FINAL_redacted	1	**Yes**	22 November 2019

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Section A: Clarification on effectiveness data

Literature searches, systematic review methods

A1. Priority question. Please supply a copy of the full (line by line) clinical effectiveness search strategies used, with the different versions for each database searched.

Please see details of all strategies used for clinical effectiveness and cost-effectiveness searches across databases in Appendix A.

A2. DARE, HTA and NHS EED have not been available in Wiley Cochrane Library since August 2018. Please provide information about which platform was used to search for all the update searches (clinical effectiveness, cost effectiveness, health-related quality of life, utilities).

Please see details of all platforms used for clinical effectiveness and cost-effectiveness searches in Appendix A. DARE, HTA and NHS EED were all searched using the CRD interface, as detailed in this appendix.

HERCULES

A3. Do all patients in HERCULES receive only one plasma exchange (PEX) treatment prior to receiving caplacizumab?

Per protocol, all subjects recruited to HERCULES were to receive one PEX prior to randomisation. Protocol deviations were reported in both groups:

- *5 subjects (4 caplacizumab, 1 placebo) did not receive PEX prior to randomisation;*
- *1 subject (caplacizumab) received more than one PEX prior to randomisation;*
- *5 subjects (3 caplacizumab, 2 placebo) had the pre-study PEX more than 24 hours prior to randomisation [p106, HERCULES CSR[1]]*

A4. Please can you provide details of ranges of biomarkers used to define people presenting with severe TTP in HERCULES (e.g. troponin) and reference any publications or guidelines that define accepted ranges for severity.

In HERCULES, very severe TTP was defined as:

- *A French severity score of ≥3 or*
- *Severe neurological involvement (coma, seizure, focal deficit) or*
- *Cardiac involvement (troponin >2.5x upper limit of normal – >0.25mcg/l)*

The French severity score is a score from 0-4, involving the following 3 parameters:

- *Cerebral involvement: yes=1; no=0*
- *Lactate dehydrogenase: >10x ULN=1; <10x ULN=0*
- *Age: >60 y=2; >40 and <60=1; <40=0*

This scoring system was developed and published in 2012 by Benhamou et al.[2]

[redacted]

[redacted]

There are limited data on cardiac damage in TTP. A brief literature search combining the terms TTP and troponin returns a total of 8 results.

The French group have published an analysis of cardiac troponin at presentation and its association with mortality and the development of refractory TTP. In this analysis, a cardiac troponin I of >0.25mcg/l was the sole independent predictor of mortality and the development of refractory TTP.[4]

The UK guideline for the management of TTP highlights the point that a significant proportion of patients have raised troponin at presentation - it describes this as a sinister finding as coronary artery occlusion is a common mode of early death.[5]

An earlier analysis of a cohort of patients treated in London between 2004 and 2007 examined the association of troponin levels with clinical symptoms of cardiac involvement in acute TTP.[6] This identified raised troponin as a better indicator of cardiac involvement than clinical symptoms alone. Mortality and acute morbidity were associated with higher troponin on admission.

It is important to note that severity of disease at presentation does not change clinical management strategies, or choice of treatments. TTP is a very severe condition and all presentations are potentially life-threatening regardless of sub-types of severity analysed in the trial and used in clinical practice, which is why acute TTP is considered a medical emergency.[5]

A5. Is elevated cardiac troponin level (e.g. above 0.4 mcg/l) indicative of patients with more severe disease? Was any subgroup analysis of HERCULES conducted by troponin level? *[[Linked also to Clarification B16]]*

As noted above in the answer to question A4, elevated troponin is only one component of the definition of severe disease and is relevant as coronary artery occlusion is a common mode of early death in patients with TTP. No subgroup analysis has been conducted by troponin level alone in HERCULES.

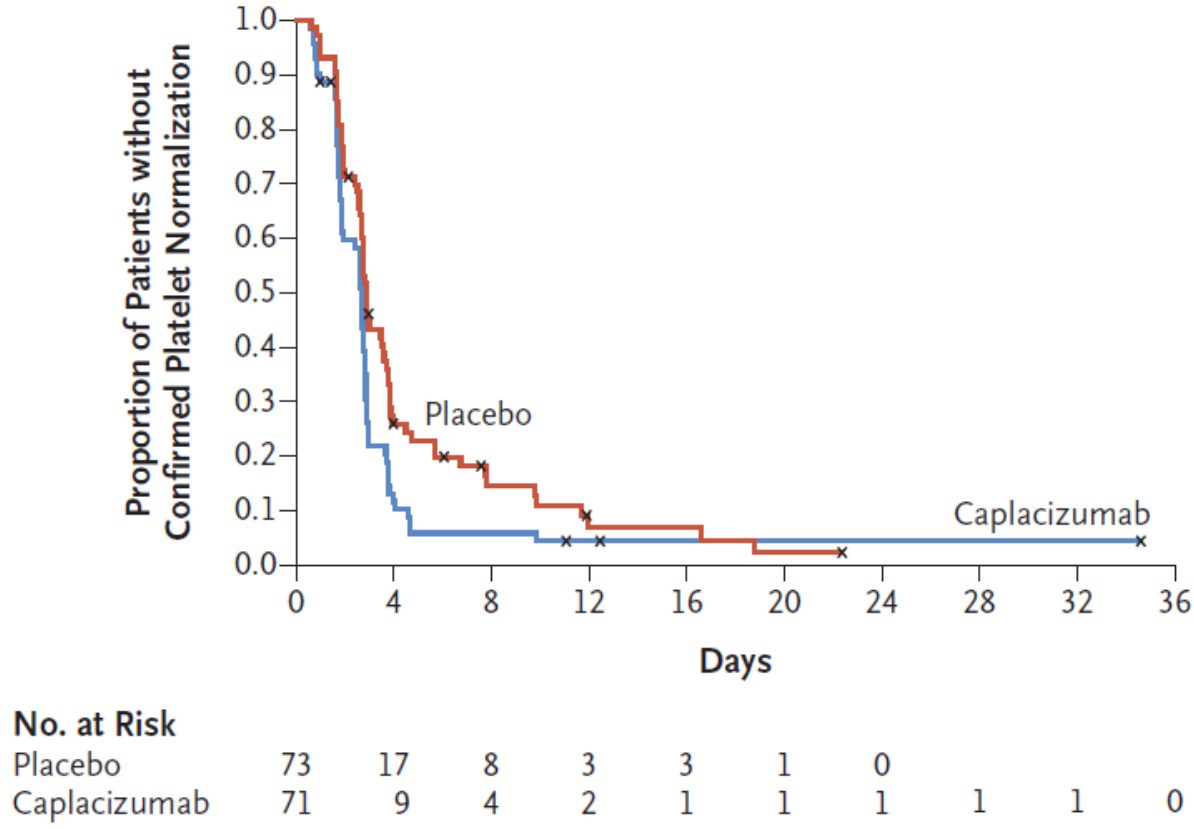
A6. Is the number of hospitalisation days reported in Table 2 of the HERCULES NEJM paper (and Clinical Study Report [CSR], Table 14.2.1.6.3) inclusive or exclusive of intensive care unit (ICU) days?

The number of hospitalisation days reported are inclusive of intensive care unit days.

A7. Please provide Kaplan-Meier curves for all clinical outcomes where time to event methods were used.

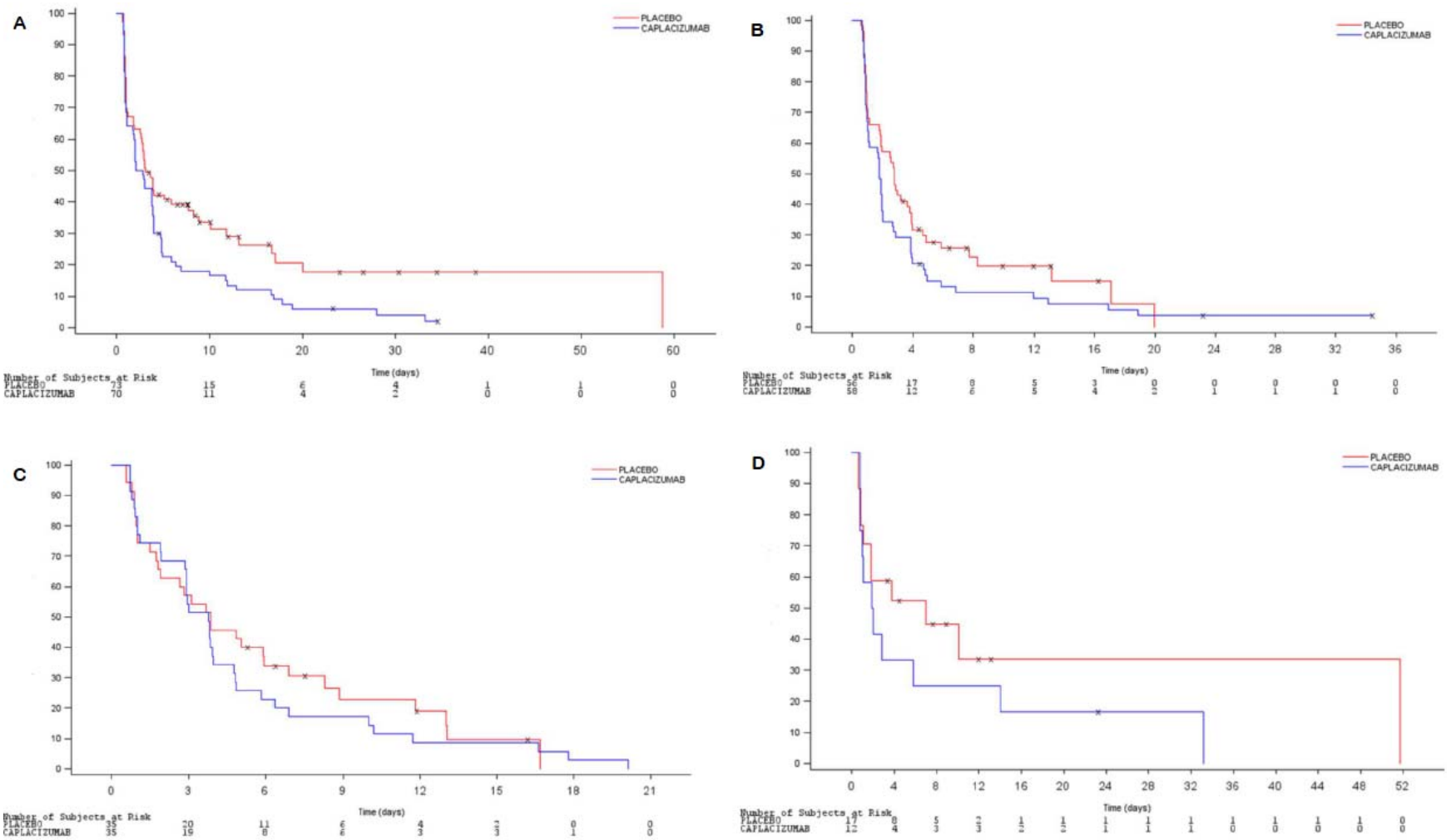
Kaplan-Meier curves for time to platelet count response and time to normalisation of organ damage markers are provided in Figure 1 and Figure 2.

Figure 1: Kaplan-Meier curve for time to platelet count response



Source: *Scully et al. 2019.*[7]

Figure 2: Kaplan-Meier curve for time to normalisation of organ damage markers: lactate dehydrogenase, cardiac Troponin I, creatinine (A), lactate dehydrogenase (B), cardiac Troponin I (C), and creatinine (D)



Source: *Scully et al. 2019.*[7]

A8. The Evidence Review Group (ERG) have concerns that assumptions of proportional hazards would not hold for clinical outcomes in this population, including the primary outcome of HERCULES. Please provide the results of a test of proportional hazards for any and all outcomes where time to event methods were used, and provide a rationale for why you believe proportional hazards would be valid in each case.

In May 2018 a letter to the editor of the New England Journal of Medicine in response to the HERCULES publication challenged this assumption. The response to this confirms that the adequacy of the assumption was tested by two different methods.[8] Both analyses showed that the proportional-hazards assumption was met.

A9. There is a discrepancy in the rates of recurrence reported between Table 9 (CS, Document B) and Table 13 (CS, Document B; also presented as Table 4 in CS, Document A) with the number of patients exhibiting recurrence higher in HERCULES than is reported in the integrated analysis. Please explain the reason for this discrepancy.

The rates of recurrence reported for the individual studies in Table 9 are for the overall study period so include disease recurrence that occurred during the treatment period and during follow-up. The rates of recurrence reported for the integrated analyses in Table 13 are for the blinded treatment period only, hence the discrepancy. Disease recurrence rates from the integrated analyses for the overall study period (that align to those reported for the individual studies) are provided in Table 1.

Table 1: Recurrence of disease in an integrated analysis across HERCULES and TITAN for the overall study period (ITT)

	CAPLA (n=108)	***PBO (n=112)***	***p-value***
Patients with recurrence of disease, n (%)	[redacted]	[redacted]	[redacted]

Key: *CAPLA, caplacizumab; ITT, intention-to-treat; PBO, placebo.*
Source: *Integrated summary of efficacy.[9]*

A10. In the HERCULES trial, please clarify whether follow-up periods are variable depending on treatment course and response. If this is the case, does this mean that follow-up period is variable for each patient? Please provide the mean (standard

deviation [SD]) / median (interquartile range [IQR]) / range of follow-up for each of the trial arms.

In HERCULES the follow-up period was standard for all subjects: 7 and 28 days after the end of the study drug treatment period. It is correct that treatment course and response are variable between patients. Full details of treatment duration can be found in table 14.1.2.9 in the HERCULES clinical study report.

A11.PRIORITY: Please provide estimates of treatment effect for each outcome presented from HERCULES without 'censoring' after switching to open-label caplacizumab. Relatedly, please describe how many patients and events were not counted as instances of each outcome as a result of censoring because of switching.

Table 2 below provides an overview of number of patients, number of events and treatment effect for each outcome (requested by the ERG in email dated 11/11/19) without 'censoring' for switching to open-label caplacizumab. Please note, the primary endpoint (time to normalisation of platelet count) can only be analysed during daily plasma exchange (PEX). In clinical practice, PEX is stopped when the patient has a sustained platelet count. Therefore, in order to experience a recurrence, the patient must have a platelet count response first. We can confirm that time to normalisation of platelet count is thus not impacted by the switch to the open-label period for patients experiencing a recurrence. In response to the specific queries raised by the ERG regarding question A11 (from email dated 12/11/2019), please see responses below:

1. *The ERG understands that, in the analysis of HERCULES, events occurring subsequent to the switch from placebo to open-label caplacizumab were excluded for all outcomes. Please could the company confirm that this is the case.*

   No, this is not the case. Events occurring subsequent to switch to open-label were not excluded for all outcomes in HERCULES. Analysis of resource use and safety endpoints from HERCULES did include data from the open-label treatment

period. However, efficacy endpoints from HERCULES did not include events from the open-label treatment period.

2. *It would satisfy the ERG if the company could confirm that estimates of the HERCULES primary outcome ('time to normalization of platelet count') are unaffected by these exclusions (if so, no need for new analysis).*

   Yes, we can confirm this is the case. As noted above, time to normalisation of platelet count is analysed during the daily PEX period and a recurrence can only occur following sustained platelet count and after PEX is stopped. Therefore, we can confirm that time to normalisation of platelet count is not impacted by the switch to the open-label for patients having a recurrence. As such, no 'uncensored' analysis (including open-label treatment period) were performed for the time to platelet count normalisation endpoint. Please see results in Table 2 below for time to normalisation of platelet count (from original analysis).

   Please note, the censored events for time to normalisation of platelet count listed in the table below ([redacted] for caplacizumab, and [redacted] for placebo) refers to censoring in the Kaplan Meier (KM) analysis (not 'censoring' as a result of switch to the open-label period).

3. *The ERG is interested to know the counts of subjects and events in the HERCULES trial when events are *not* excluded (i.e. uncensored), for the secondary outcomes in this table:*

   Please see Table 2 below for the re-analysed counts of subjects and events in HERCULES when events from the open-label treatment period were not excluded from the analysis.

Table 2: Summary of results for requested efficacy outcomes for overall study period (double blind + open-label + follow-up)

Efficacy outcome:	*Caplacizumab*		*Placebo*		*Treatment effect (risk/rate ratio)*
	# subjects	*# events*	*# subjects*	*# events*	
*Time to normalisation of platelet count**	*72***	[redacted]	*73***	[redacted]	*HR (95%CI): 1.55 (1.095; 2.195)*
TTP-related death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence of TTP as exacerbation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence of TTP as relapse	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Major thromboembolic event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: *HR: Hazard ratio; KM: Kaplan Meier; TTP: thrombotic thrombocytopenic purpura*
Notes*: *Time to normalisation of platelet count is not impacted by the switch to open-label treatment period, therefore the results presented here are from original analysis (not including open-label period)*
***Please note, as time to normalisation of platelet count is a time-to-event outcome, the # subjects in Table 2 for this outcome represent the total number of patients in each trial arm.*

A12. The footnote to Table 2 in HERCULES NEJM publication states that admission to ICU for PEX "is standard practice at some centres". Was this standard practice at the UK centres? The ERG believes this could have inflated (absolute) ICU stay. Percentages of patients admitted directly to ICU were similar across arms (caplacizumab 39%, placebo 37%). *[[Linked also to Clarification B11]]*

We have asked the principal investigators at the three UK sites to confirm their practice in respect of ICU admission. In two (Bristol, Liverpool) the policy is to admit all acute TTP cases to ICU. In London, TTP cases are admitted to ICU where clinically necessary. Upon further enquiry they confirmed that their ICU admission rate is between 40-50% of admissions. On this basis we believe the ICU admission figure in HERCULES is representative of UK practice.

HERCULES AND TITAN

A13. Please provide further details of the composition of the 'treatment non-compliance' protocol deviation summarised in B2.5 for HERCULES (36 patients) and

TITAN (38 patients). Please explain any discrepancies with the tables in the CS (Document B, Reference17 [EMA 2018 Cablivi: Assessment Report - pages 45 [for TITAN] and 59 [HERCULES]).

Further details of the composition of the 'treatment non-compliance' protocol deviations are summarised in Table 3. We do not believe there are any discrepancies with the information provided in the CS and further detailed here, and information captured in the European Public Assessment Report. The tables referenced in this question (pages 45 and 59) provide patient disposition data as opposed to protocol violation data. Study discontinuations are reported in these tables. Several are relating to patients who discontinued prematurely because of a protocol violation but not all patients with a protocol violation discontinued prematurely.

Table 3: Composition of treatment non-compliance protocol deviations - HERCULES and TITAN

	HERCULES		***TITAN***	
	CAPLA (n=72)	***PBO (n=73)***	***CAPLA (n=36)***	***PBO (n=39)***
Patients with a treatment non-compliance protocol deviation, n	*15*	*21*	*19*	*19*
Missed daily PEX (HERCULES) and/or had an excursion of dosing time window (TITAN), n	[redacted]	[redacted]	[redacted]	[redacted]
Daily PEX not continued for at least 2 days after platelet count normalisation, n	[redacted]	[redacted]	[redacted]	[redacted]
Study drug administration interrupted, n	[redacted]	[redacted]	[redacted]	[redacted]
Incorrect storage conditions for study drug, n	[redacted]	[redacted]	[redacted]	[redacted]
Administration of the wrong study drug dose, n	[redacted]	[redacted]	[redacted]	[redacted]
Use of the wrong route of administration, n	[redacted]	[redacted]	[redacted]	[redacted]
Administration of the wrong study drug, n	[redacted]	[redacted]	[redacted]	[redacted]
Received two doses of study drug in error, n	[redacted]	[redacted]	[redacted]	[redacted]

Key: *CAPLA, caplacizumab; PBO, placebo; PEX, plasma exchange.*
Note: *some patients had more than one treatment non-compliance violation, hence the total composition may add up to more than the total number of patients with a violation.*
Source: *HERCULES CSR[1]; TITAN CSR.[10]*

Compassionate Use Scheme

A14. [redacted] (refer to CS, Section B.3.3.1). Please confirm whether these deaths

were observed in the acute period. Please also provide the baseline characteristics for these patients to compare with HERCULES.

As discussed during the clarification call on 07/11/19, the compassionate use programme is in place to respond to unsolicited requests for access to caplacizumab. It is not a clinical study. [redacted]

A15. Please clarify the follow-up period for outcomes measured from the compassionate use scheme. Please also provide data for any other clinical outcomes from this dataset that have been measured, in addition to mortality.

As discussed during the clarification call on 07/11/19, [redacted] *We have provided all the data that is currently available within our submission.* [redacted]

Section B: Clarification on cost-effectiveness data

Literature searches, systematic review methods

B1. Priority question. Please supply a copy of the full (line by line) cost-effectiveness search strategies used, with the different versions for each database searched.

Please see details of all strategies used for clinical effectiveness and cost-effectiveness searches across databases in Appendix A.

B2. Please confirm which database the utilities search strategy, Table 20, p57, Appendix H, was carried out in.

The search was conducted in MEDLINE In-Process® (via PubMed) for full-text journal articles and abstracts of suitable material. The search was performed on 16 April 2019.

B3. For the targeted literature review of utility estimates, the citations used to identify studies as high, medium, and low relevance (CS, Document B, Appendix, p.56) do not match those reported in the associated tables (Table 21 [CS, Document B Appendix, p. 59]; and Table 22 [CS, Document B Appendix, p. 63 – 69]). It's therefore not possible to evaluate the reasons for why studies were allocated to each category. Please clarify which studies were of high, medium and low relevance for *the cost effectiveness model.*

There are two discrepancies between the text in CS, Document B, Appendix, p.56 and Table 22 (CS, Document B Appendix, p. 63 – 69). The first is that the study by Sznajder et al. is discussed in the text as being highly relevant, when it is classified incorrectly as low relevance in Table 22. This study is considered highly relevant as it reports utility values for patients after an ICU stay – a clinically validated proxy for aTTP, therefore should be labelled as highly relevant in Table 22.

The second discrepancy is that the study by Shankar et al. is incorrectly categorised as highly relevant in Table 22. This study should be categorised as low relevance as, although the study reports quality of life data for patients with meningitis (another clinically validated proxy), utility values are not reported meaning that the study is of little use for the cost-effectiveness model.

To summarise, please refer to the citations in the text to identify highly relevant studies, rather than the categorisations in Table 22. Clarification of those studies considered highly relevant vs of medium relevance vs of low relevance is provided in Appendix B.

B4. Which criteria were used to determine the relevance of utility studies identified in the targeted literature review? Please also clarify who determined the relevance or criteria for relevance (e.g. clinical opinion, advisory board, literature review).

Formal criteria were not used to assess the relevance of studies identified in the targeted literature review for the cost-effectiveness model. Instead, the assessment was conducted pragmatically by the reviewer and was based on a number of factors such as:

- *Relevance of source to patient population defined in NICE decision problem scope (i.e. adults experiencing an episode of acquired thrombotic thrombocytopenic purpura)[11]*
- *Relevance to proxy conditions for aTTP suggested in the clinical advisory board meeting (brain injury, cerebral brain thrombosis, Guillain–Barré syndrome, adult meningitis, patients receiving plasma exchange, and patients receiving critical care on an intensive care unit [ICU])[12]*
- *Whether the source reported utility values and the instrument/tariff used (EQ-5D-3L scores valued using the UK tariff is NICE's preferred method) [13]*
- *Whether sources demonstrated face validity in the context of each other*
- *Whether the source reported baseline utility enabling calculation of a utility multiplier*
- *Whether the source reported utility values that aligned with the model health states*

Out of all seven of the studies categorised as 'high' relevance, their relevance in modelling utility in acute aTTP was determined. Three studies did not report the quality-of-life instrument used,[14-16] and one study only collected data in remission.[17] These studies were therefore not considered appropriate to inform the acute episode. Subsequently, three studies remained.[18-20]. During clinical validation, these sources were presented to clinicians who agreed that the sources seemed reasonable in the context of acute aTTP.[21].

The study by Pappas et al. 2018[20] (primary references Chit et al. 2015 and McPhail et al. 2010[22, 23]) investigating QALY loss in hospitalisation, was chosen for the model base case for the acute episode as the study reported utility values collected at time points thought to capture the immediate impact on quality of life and subsequent improvement during hospitalisation that were comparable to an acute aTTP episode (i.e. utility values for patients before admission to hospital and after discharge were reported allowing for calculation of utility for the entire aTTP episode). Furthermore, baseline utilities were reported, allowing calculation of a multiplier that could be applied to baseline utility derived using HERCULES data. Finally, utility estimates from this study demonstrate face validity in that patient quality of life is low on admission, then improved at discharge, but does not exceed quality of life estimates at baseline.

It is important to note that utility estimates for the acute episode are not key drivers of cost-effectiveness results as they are applied in the model for a relatively short time.

For patients in remission, only one source was identified which reported EQ-5D utilities for aTTP patients.[17] Therefore this source was selected for use in the model. This source had the advantage that it also provided a utility decrement for neurological symptoms (i.e. mild cognitive impairment) that could be converted to a multiplier and applied to patients with mild cognitive impairment in the model. Clinicians validated this utility decrement for mild cognitive impairment as the Oklahoma registry data this was based on excluded patients who are disabled as a result of stroke so probably underestimates the impact of cognitive impairment.

Utility values were also required for moderate to severe cognitive impairment and depression. Based on the clinical validation TCs, clinicians suggested that stroke would not be an unreasonable proxy for the worst forms of cognitive impairment (i.e. an upper limit).[21] In light of this, utilities based on a publication by Gage et al. in stroke were used for the utility of patients with moderate to severe cognitive impairment.[24] This publication was the primary source of utility values reported in Freeman et al. (2011), the latter initially classified as low relevance prior to clinical input on long-term proxy conditions. For neuropsychological impairment, Sullivan et

al. a standard source reporting UK EQ-5D utilities for a range of conditions was used.[25]

Economic model

B5. For clarity, please provide a table explaining the definition of each of the following outcomes: relapse ("true relapse"), remission, recurrence, exacerbation, and refractory. Please state where these definitions are used in the submission, and how they were derived. Please use a separate row for each definition. Please indicate where definitions (i.e. rows) overlap.

Definitions for each outcome across the trials and cost-effectiveness model are provided in Table 4. In our model, the definitions of these outcomes do not overlap. Key differences are outlined below.

Exacerbations as defined in HERCULES are defined as early exacerbations in the model, and relapses as defined in HERCULES are defined as late exacerbations in the model. These two outcomes were pooled based on feedback from clinicians at the advisory board who suggested that the exacerbations occurring >30 days after stopping plasma exchange (PEX) in HERCULES (occurring solely for patients on the caplacizumab arm) were late exacerbations and would not be expected in clinical practice due to closer monitoring of ADAMTS13 activity levels and pre-emptive rituximab use. A scenario is presented in Table 51, CS, Document B, Section 3.8.3 including early exacerbations only (Sheet 'Control', G45 in original submitted model). In this scenario, the ICER, with PAS discount applied, reduces from £37,986 to £37,672,

Furthermore, the key secondary endpoint definition of refractory disease in HERCULES was as per Benhamou et al. (2015),[4] however the secondary endpoint definition of refractory disease in HERCULES as per the International Consensus definition was used in the model,[26] based on feedback from clinicians attending the UK advisory board.[12] A scenario is presented in Table 51, CS, Document B, Section3.8.3 using the Benhamou et al. definition of refractory disease (Sheet

‘Control’, G41 in originally submitted model) . In this scenario, the ICER, with PAS discount applied, increases from £37,986 to £38,064.

Table 4: Definitions of outcomes used in the caplacizumab trials and cost-effectiveness model

	TITAN[10]	***HERCULES[1]***	***Decision-tree***	***Markov***
Exacerbation	*Recurrent thrombocytopenia following platelet count response requiring a re-initiation of daily PEX therapy within 30 days after the last daily PEX treatment*	*Recurrent thrombocytopenia following platelet count response requiring a re-initiation of daily PEX therapy within 30 days after the last daily PEX treatment*	*Early exacerbation – Recurrent thrombocytopenia following platelet count response requiring a re-initiation of daily PEX therapy within 30 days after the last daily PEX treatment (as per definition of exacerbation in the trials)* *Late exacerbation – A de novo TTP episode requiring re-initiation of daily PEX therapy that occurs more than 30 days after the last daily PEX treatment (as per definition of exacerbation in the trials), still within trial period* *Early and late exacerbations were combined (pooled) based on clinical feedback at clinical advisory board [12] (CS Section B.3.3.1)*	*Same as decision tree for patients who experience true relapse*
Relapse	*A de novo TTP episode requiring re-initiation of daily PEX that occurs more than 30 days after the last daily PEX treatment*	*A de novo TTP episode requiring re-initiation of daily PEX therapy that occurs more than 30 days after the last daily PEX treatment*	*Definition not used in the model, so as not to confuse with trial definitions of relapse (See CS, Document B, Section B.3.2.2, B.3.3.2)*	*Definition not used in the model, so as not to confuse with trial definitions of relapse (See CS, Document B, Section B.3.2.2, B.3.3.2)*
Recurrence	*Umbrella term encompassing both exacerbation and relapse (as defined in the trial)*	*Umbrella term encompassing both exacerbation and relapse (as defined in the trial)*	*Equivalent to combined early and late exacerbations*	*Definition not used in Markov model, recurrences in Markov model are termed 'true relapse'*
'True' relapse	*Definition not used as trials consider the acute phase only*	*Definition not used as trials consider the acute phase only*	*Definition not used in decision tree as relapse is only an outcome in Markov model*	*A de novo acute episode occurring in the Markov model – outside of trial period and only after initial resolution of disease and full normalisation of ADAMTS13 activity*

Remission	*Complete remission after the initial course of daily plasma exchange (i.e. plasma exchange given for the presenting acquired TTP episode) is defined as confirmed normalisation of the platelet count and absence of exacerbation[27]*	*Not an outcome in HERCULES*	*Definition not used in decision tree, it is assumed that all surviving patients enter Markov model in remission*	*Any patient surviving the acute episode (i.e. alive at the end of the decision tree enters the Markov model in remission). Decision tree time horizon of 3 months assumed long enough to capture the acute period of illness* *In the Markov model, all patients who are alive and not currently experiencing true relapse are assumed to be in remission*
Refractory	*Not an outcome in TITAN*	*Key secondary endpoint definition:* *Proportion of patients with refractory TTP, defined as absence of platelet count doubling after 4 days of standard treatment and LDH >ULN (as per Benhamou, et al. 2015[4])*	*Lack of sustained platelet count increment or platelet counts <50×109/L and persistently* *raised LDH (>1.5x ULN) despite 5 plasma exchanges and steroid treatment (International Consensus Definition)[26]* *International consensus definition used for model base case as considered less arbitrary by clinicians attending advisory board[12] (CS, Document B, Section B.3.3.1)*	*Same as decision tree for patients who experience true relapse*
***Key:** CS, company submission; CSR, clinical study report; LDH, lactate dehydrogenase; TTP, thrombotic thrombocytopenic purpura; ULN, upper limit of normal.*				

B6. Please provide the full calculation (including the numbers which were used in the formula below) for the proxy relative risk (RR) of 0.62 used for the reduction in long-terms complications with caplacizumab.

$$RR\ for\ long\ term\ complications = \frac{p(hospitalisation\ cap) * hospitalisation\ days\ cap + p(ICU\ cap) * ICU\ days\ cap}{p(hospitalisation\ SoC) * hospitalisation\ days\ SoC + p(ICU\ SoC) * ICU\ days\ SoC}$$

Data from the overall treatment period of HERCULES were used in this calculation as presented in Table 5 below:

Table 5: Hospitalisation/ICU days and proportions, HERCULES overall treatment period

	Caplacizumab	**SoC**	**Reference**
Hospitalisation days	[redacted]	[redacted]	*HERCULES CSR, Table 14.2.1.6.3: Safety related parameters - number of days in hospital (Overall treatment)*
ICU days	[redacted]	[redacted]	*HERCULES CSR, Table 14.2.1.6.4: Safety related parameters - number of days in ICU (Overall treatment)*
Probability of hospitalisation (%) - overall treatment period	[redacted]	[redacted]	*HERCULES CSR, Table 14.2.1.6.3: Safety related parameters - number of days in hospital (Overall treatment)*
Probability of intensive care unit stay (%) - overall treatment period	[redacted]	[redacted]	*HERCULES CSR, Table 14.2.1.6.4: Safety related parameters - number of days in ICU (Overall treatment)*
***Key:** CSR, clinical study report; ICU, intensive care unit; SoC, standard of care.*			

The calculation presented with the numbers used from the table above to calculate the proxy relative risk of 0.62 is as follows:

[redacted]

At the point of conducting clinical expert validation TCs (June 2019), the above data/clarifications were not available (as it was Ablynx rather than Sanofi who ran the clinical trial programme). Please refer to the top 7 rows of CS, Document B, Table 23

for the proxy hazard ratios [HRs]/relative risks [RRs] presented to clinicians. The clinicians consulted suggested that the ratio of hospitalisation/ICU days could be considered a reasonable proxy based on the range of values presented[21] – this reduces reliance on this datapoint alone.

The following data clarifications were awaited at this timepoint:

- *Resource use data per subgroup according to the model structure (to allow correction to be made for switching to caplacizumab on exacerbation as resource use for SoC patients is likely to be greater in clinical practice where caplacizumab treatment is not available)*
- *Clarification of whether Table 14.2.1.6.3 of the HERCULES CSR included or excluded ICU days*

Data per subgroup were received in September 2019 and included within the economic model at this point.

To account for treatment switching on exacerbation, assumptions were required for SoC patients who exacerbated and therefore received open-label caplacizumab. Rather than using the open-label resource use data, it was assumed that for the exacerbation, resource use would be the same as the initial event (i.e. double-blind period resource use is applied again for these patients) this assumption was supported by clinicians during the clinical validation TC.[21] Clarification was received that Table 14.2.1.6.3 of the HERCULES CSR included ICU days (whereas the previous working assumption had been that these were excluded); see response to question A6.

Following the data update, updated HRs/RRs were calculated as presented in the Sheet 'Costs'; Cells P148:P151 of the economic model and in the bottom 4 rows of CS, Document B, Table 23). The recalculated RR for all hospitalisation days (general ward and ICU) was calculated as 0.79 (Cell P148) and for ICU days only, 0.35 (Cell

P149). The original RR of 0.62 applied in the model still falls in the middle of the range of RRs presented as was the case at the clinical validation in June 2019.

Scenarios using these RRs are presented in Table 6 and Table 7 (Sheet 'Controls', G112 in the updated 'ERG model' submitted along with this response). For reference, the submitted base case ICER with PAS discount applied was £37,986.

Table 6: Discounted base case results, with PAS discount applied for caplacizumab, RR long-term complications and mortality 0.79, proxy RR calculated based on all hospitalisation days (general ward and ICU)

Technologies	*Total costs (£)*	*Total LYs*	*Total QALYs*	*Incremental costs (£)*	*Incremental LYs*	*Incremental QALYs*	*ICER incremental (£/QALY)*
SoC	[redacted]	*15.85*	[redacted]				
Caplacizumab	[redacted]	*19.44*	[redacted]	[redacted]	*3.58*	[redacted]	*£56,216*
Key: *ICER, incremental cost-effectiveness ratio; LY, life years; PAS, patient access scheme; QALY, quality-adjusted life year.*							

Table 7: Discounted base case results, with PAS discount applied for caplacizumab, RR long-term complications and mortality 0.35, proxy RR calculated based on only ICU days

Technologies	*Total costs (£)*	*Total LYs*	*Total QALYs*	*Incremental costs (£)*	*Incremental LYs*	*Incremental QALYs*	*ICER incremental (£/QALY)*
SoC	[redacted]	*15.85*	[redacted]				
Caplacizumab	[redacted]	*25.95*	[redacted]	[redacted]	*10.09*	[redacted]	*£23,158*
Key: *ICER, incremental cost-effectiveness ratio; LY, life years; PAS, patient access scheme; QALY, quality-adjusted life year.*							

Due to the rarity of the disease and lack of long-term follow-up data for patients treated with caplacizumab, estimates of long-term benefit are uncertain. Throughout the submission, we have attempted to address this uncertainty in multiple ways, through:

- *Conducting a targeted literature review exploring the links between short- and long-term outcomes – see CS, Document B, Section B.3.3.2*
- *Seeking extensive input through clinical consultation – see CS, Document B, Section B.3.3.2*
- *Assessing uncertainty through testing of a wide range of alternative inputs in the threshold analysis, to determine the scenarios in which the ICER exceeds thresholds considered cost-effective by NICE – see CS, Document B, Section B.3.8.3, Table 52 and Table 53*

B7. Mortality estimates used in the acute phase of the model relied on a monitoring programme for caplacizumab and a meta-analysis of mortality in acquired thrombotic thrombocytopenic purpura (aTTP) generally. Was similarity between the sources in terms of key risk factors for mortality and poor prognosis in aTTP assessed? If so, please provide the conclusions of this assessment.

The monitoring programme for caplacizumab was a compassionate use programme rather than a data collection programme. As such, the only information available includes where the patient was from, whether caplacizumab was received and whether the patient died, as explained on the clarification call on 07/11/2019 and in our response to question A14. Therefore, an assessment of the similarity between mortality sources using patient characteristics could not be conducted. However, clinicians agreed that treatment with caplacizumab is started later in the compassionate use programme that it would be if it was made available through routine funding (as requests are individual and caplacizumab is not available on site). Mortality data based on this programme should therefore be considered as the maximum mortality expected with caplacizumab.

The report titled 'Ablynx. Systematic review on the clinical burden of disease in thrombotic thrombocytopenic purpura. 2018'[28], submitted to NICE on 28/10/2019, provides further details on the meta-analysis of sources for SoC mortality.

The report explains that only studies using plasma exchange as first line treatment were included. This is aligned with the NICE final scope.[11] It also explains that 129 studies were included in the analysis and the average mortality of the included studies is 13.2% (95% CI; 11.9-14.5%) which includes mortality during the first acute phase and relapsing episodes of TTP. Due to the large number of studies included it is not feasible to present key risk factors for mortality and poor prognosis in aTTP for all studies, however due to the large sample size it is likely that the combined outcomes will be a good representation of averages.

B8. PRIORITY: Please fully explain how total hospitalisations and total ICU data in Table 38 (CS Document B) and Table 40 (CS, Appendix S) were calculated. Please provide the source of these data, because it is not clear in the tables nor the economic model. Also

- **How do these data relate to the ICU/hospitalisation summaries from HERCULES (Table 10, CS Document B)?**
- **Are any assumptions used in the calculations?**
- **Please explain how to alter these parameters in the economic model**

Much of the information in our response to this question relates to our response to question B6, however it has been re-stated here for clarity.

Resource use data from the overall treatment period of HERCULES (as per CS, Document B, Table 10) were initially considered for use in the economic model. However, due to the structure of the decision tree and the need to correct for caplacizumab used in exacerbators post SoC, data were required for the following subgroups for both treatments:

- *Non refractory, non-exacerbators*
- *Non refractory, exacerbators*
- *Refractory, non-exacerbators*
- *Refractory, exacerbators*

Therefore, post-hoc subgroup analyses of HERCULES resource use data were required. These data are presented in Table 40, CS Appendix S.

The key issue with using the overall treatment period data (as per CS, Document B, Table 10) is that resource use for patients on SoC who switched to caplacizumab on exacerbation is likely to be underestimated. Resource use for SoC patients is likely to be greater in clinical practice where caplacizumab treatment is not available.

The data in Table 40, CS Appendix S were used to calculate the final resource use frequencies and costs presented in Table 38 (CS Document B), with the exception of outpatient visits, ADAMTS13 activity tests and the number of methylprednisolone and rituximab doses, which were based on clinical opinion and published sources due to a lack of data in HERCULES.[5, 21]

Calculations are presented in Sheet 'Costs' Cells E148:L151 of the originally submitted economic model.

- *To calculate total resource use for patients on both treatment arms who respond (i.e. non-refractory) without exacerbation, resource use in the double-blind period is added to resource use in the follow-up period (open-label resource use is not used as data only apply to patients who exacerbated).*
- *To calculate total resource use for patients on caplacizumab who respond (i.e. non-refractory) then exacerbate, resource use for the double-blind period was added to resource use from the open label period and the follow-up period.*
- *To calculate total resource use for patients on SoC who respond (i.e. non-refractory) then exacerbate, assumptions were required. Rather than using biased open-label resource use data, it was assumed that SoC patients who*

exacerbated would have the same resource use as per the initial event (i.e. double-blind period resource use is applied again for these patients) this assumption was supported by clinicians during the clinical validation TC.[21]

Resource use for refractory patients was calculated in the same manner.

Total resource use frequencies were multiplied by resource use costs to obtain total resource use costs per each branch of the decision tree. In the decision tree, resource use costs are then weighted according to the proportion of patients in each branch.

To alter resource use parameters in the economic model, alternative values can be input into the table in Sheet 'Costs' Cells F76:M135 of the originally submitted model. Although a simpler approach would be to overtype final resource use estimates in Sheet 'Costs' Cells E148:L151, or final resource use costs in Sheet 'Costs' Cells E165:L165 in the originally submitted model.

B9. Table 28 of the CS reports the acute phase utilities. Please explain why the utility multipliers are based on the Pappas et al. baseline utility rather than HERCULES (which is the base case used in the model).

Utility multipliers are calculated based on the utility reported in the source relative to baseline utility in the source (rather than the baseline utility for patients in the model). This is because the utility multiplier should represent the impact of the comorbidity relative to a patient without the comorbidity from the original source. The assumption here is that the impact of the comorbidity is the same irrespective of age, gender and other patient characteristics. Subsequently the multipliers are applied to model health states – which already consider age-adjusted baseline utility. This method is aligned with NICE Decision Support Unit (DSU), Technical Support Document (TSD) 12.[29]

B10. PRIORITY: There appears to be a disconnect between the economic model and the CS (Document B) with respect to utilities for long-term complications. The utility values (baseline and multipliers) and sources in Table 34 (CS, Document B) do not match those in the economic model ("Utility" worksheet cells E79-I84). For example, Table 34 reports the utility

multiplier for neuropsychological impairment as 0.73 whilst the model (Cell E81) reports it as 0. 93. Please clarify the utility values and multipliers used for each long-term complication and their sources.

For clarity, a summary of the utility values used in the economic model, along with their Sheet/Cell reference and source is provided in Table 8. There is a single discrepancy between the utility values reported in CS, Table 34 and the economic model. The utility multiplier for neuro-psychological impairment should be reported as 0.77 as per the economic model rather than 0.73 as per CS Table 34. This value was updated in the model following QC feedback that the baseline utility source used was incorrect. The utility value of 0.93 (Sheet 'Utilities', E81) is the multiplier for mild cognitive impairment (see Table 8 below). Utilities for hospitalisation in the acute episode are based on a publication by Chit et al. (2015).[22] This publication was identified in the TLR. The secondary source Pappas et al. (2018) was categorised as high relevance (see response to question B3).[20]

Table 8: Summary of utility values/multipliers applied in base case cost-effectiveness analysis

State	Utility value	Sheet/Cell reference in economic model	Source
Decision tree model			
Baseline utility – prior to acute episode	*0.87*	*Utilities, E16*	*Age-matched general population utility derived using HERCULES data for patient age [30]*
Acute episode – hospitalised (multiplier)	*0.64*	*Utilities, E17*	*Utility based on supplementary webappendix in Chit et al (2015)* – [22] *Utility multiplier calculated based on average utility between hospital admission (0.368) and discharge (0.656) divided by baseline utility in source (0.7952).*
Acute episode – post discharge (multiplier)	*0.82*	*Utilities, E18*	*Utility based on supplementary webappendix in Chit et al (2015)[22]* *Utility multiplier calculated based on average utility at hospital discharge (0.656) divided by baseline utility in source (0.7952).*
QALY decrement for AEs, caplacizumab	*0.003085*	*Decision tree, T50*	*Calculation based on AE incidence in HERCULES, disutilities reported in previous submissions to NICE and assumed AE durations*
QALY decrement for AEs, SoC	*0.002202*	*Decision tree, T65*	*Calculation based on AE incidence in HERCULES, disutilities reported in previous submissions to NICE and assumed AE durations*
Markov model			
Baseline utility	*0.77*	*Utilities, E104*	*Based on Burns et al. (2018)[17] adjusted for age, gender and proportion of patients with depression (neuro-psychological impairment) – See CS, Appendix O*
Mild cognitive impairment (multiplier)	*0.93*	*Utilities, E90*	*Based on Burns et al (2018)[17] multiplier calculated from reported decrement of 0.054 versus baseline of 0.736.*
Moderate /severe cognitive impairment (multiplier)	*0.61*	*Utilities, E83*	*Multiplier calculated for stroke based on utilities for mild, moderate and severe stroke reported in Gage et al. (1996) [31], weighted by proportions with each stroke severity based on Freeman et al.[32] – See CS, Appendix O*
Neuro-psychological impairment (multiplier)	*0.73*	*Typo in submission dossier, should be 0.77 as in Utilities, E126*	*Based on Sullivan et al. ICD311 depressive disorder utility (0.63722304) versus general population utility (0.82831802).*
Carer disutility for moderate /severe cognitive impairment (multiplier)	*0.83*	*Utilities, E116*	*Van Exel (2005)[33] – Utility of 0.67 versus baseline of 0.81*
Key: *AE, adverse event; CS, company submission; ICD, International Classification of Diseases; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year; SoC, standard of care.*			

B11. In the “Costs” worksheet (cell D137) it is noted that for hospitalisation days excluding ICU some subjects have a value of 0, which means they did not have general ward stay days, only ICU days. Discharge directly from ICU is unlikely unless there is a fatal event; although we note that in the HERCULES trial (as reported in the NEJM article), some patients were admitted to ICU as per local protocol, rather than due to clinical need. Please provide a scenario where ICU days are reduced in both arms; for example, where ICU days are reduced by 20%.

As outlined in response to question A12, we have asked the principal investigators at the three UK sites to confirm their practice in respect of ICU admission. In two (Bristol, Liverpool) the policy is to admit all acute TTP cases to ICU. In London, TTP cases are admitted to ICU where clinically necessary. Upon further enquiry they confirmed that their ICU admission rate is between 40-50% of admissions. On this basis we believe the ICU admission figure in HERCULES is representative of UK practice.

A scenario where ICU days are reduced by 20% on each arm is provided below in Table 9 (Sheet ‘Controls’ G123 in updated ‘ERG model’ submitted along with this response). For reference, the submitted base case ICER with PAS discount applied was £37,986.

Table 9: Discounted base case results, with PAS discount applied for caplacizumab, ICU days reduced by 20% for both treatment arms

Technologies	*Total costs (£)*	*Total LYs*	*Total QALYs*	*Incremental costs (£)*	*Incremental LYs*	*Incremental QALYs*	*ICER incremental (£/QALY)*
SoC	[redacted]	*15.85*	[redacted]				
Caplacizumab	[redacted]	*21.33*	[redacted]	[redacted]	*5.48*	[redacted]	*£39,012*
Key: *ICER, incremental cost-effectiveness ratio; LY, life years; PAS, patient access scheme; QALY, quality-adjusted life year.*							

B12. Please provide the rationale for using a normal (rather than the gamma) distribution for costs.

The Gamma distribution is considered an appropriate choice of parameterisation of uncertainty in PSA regarding costs if the costs themselves apply to an individual. However, the costs considered in the model apply for the cohort, and therefore the use of a Gamma distribution would be inappropriate. This is due to the Central Limit Theorem which states that the sampling distribution, that is, the distribution of means from each sample taken (cohort-level information) is normally distributed if a sufficient sample size exists irrespective of the underlying distribution of the (individual-level) data themselves.[34] Therefore, as the costs included in the model for administration and medical resource use are cohort-level mean costs and from NHS reference costs (i.e. have a large sample size), they are assumed to be normally distributed, although the individual-level costs may follow a Gamma distribution. Further information regarding the Central Limit Theorem and its applicability to cost-effectiveness analysis may be found in Briggs (2005).[35]

B13. The distributions for the PSA in Table 39 (Appendix Q) appear to be wrongly parameterised using the upper and lower 95% CIs rather than e.g. the mean and SE for the Normal, and α and β for the beta. Furthermore, in the model "parameters" worksheet, "Refractory, Scully HERCULES (aTTP only), caplacizumab" and "Refractory, Scully HERCULES (aTTP only), SOC" are missing the β parameter (cells J23 & J27) and "Compliance caplacizumab, open-label period" is missing a standard error (cell G117). Please provide a corrected model or explain the reasons for this.

Table 39 in Appendix Q presents the deterministic values for each parameter and associated 95% confidence intervals and is labelled as such. The SE for the Normal distribution and α and β for the Beta distribution are not presented in this table but are used in the model to determine the uncertainty around each parameter.

An updated table with information on SE, α and β parameters added is presented below (Table 10). The minor omissions flagged by the ERG (cells J23, J27 and G117) have now been fixed in the 'ERG model' submitted with this response, with no notable impact on neither the PSA nor the OWSA results.

Table 10: Summary of variables applied in the economic model

Variable	Value	SE	α	β	Measurement of uncertainty and distribution (95% CI)	Reference
Efficacy – refractory						
Refractory, Scully, HERCULES (ITT), caplacizumab	[redacted]	-	[redacted]	[redacted]	Beta [redacted]	Section B3.3
Refractory, Scully, HERCULES (ITT), SoC	[redacted]	-	[redacted]	[redacted]	Beta [redacted]	
Efficacy – exacerbations						
Exacerbations, combined early and late, HERCULES (ITT), caplacizumab	12.68%	-	9	62	Beta (0.06,0.21)	Section B.3.3
Exacerbations, combined early and late, HERCULES (ITT), SoC	38.36%	-	28	45	Beta (0.28,0.5)	
Efficacy – true relapse						
True relapse, annual probability	1.00%	-	1	99	Beta (0,0.04)	Section B.3.3
Efficacy – time to death						
Time to death (days) for patients who die from the acute episode	[redacted]	[redacted]	-	-	Normal [redacted]	Section B.3.3
Efficacy – long-term conditions						
Proportion with neuro-psychological impairment, Chaturvedi	36.84%	-	77	132	Beta (0.3,0.43)	Section B.3.3
Proportion with mild cognitive impairment, Kennedy	54.17%	-	13	11	Beta (0.34,0.73)	
Proportion with moderate to severe cognitive impairment, Kennedy	20.83%	-	5	19	Beta (0.07,0.39)	
RR mild cognitive impairment, caplacizumab	0.62	0.06	-	-	Log-normal (0.51,0.75)	
RR moderate/severe cognitive impairment, caplacizumab	0.62	0.06	-	-	Log-normal (0.51,0.75)	
RR neuro-psychological impairment, caplacizumab	0.62	0.06	-	-	Log-normal (0.51,0.75)	
Duration of cognitive impairment (years)	55.00	5.50	-	-	Normal (44.22,65.78)	
Duration of neuro-psychological impairment (years)	1.00	0.10	-	-	Normal (0.8,1.2)	
Adverse events						
Adverse events, GI disorders, caplacizumab	[redacted]	-	[redacted]	[redacted]	Beta [redacted]	Section B.3.4
Adverse events, respiratory, thoracic and mediastinal disorders, caplacizumab	[redacted]	-	[redacted]	[redacted]	Beta [redacted]	
Adverse events, cardiac disorders, caplacizumab	[redacted]	-	[redacted]	[redacted]	Beta [redacted]	

Variable	Value	SE	α	β	Measurement of uncertainty and distribution (95% CI)	Reference
Adverse events, nervous system disorders, caplacizumab	[redacted]	-	[redacted]	[redacted]	Beta [redacted]	
Adverse events, vascular disorders, caplacizumab	[redacted]	-	[redacted]	[redacted]	Beta [redacted]	
Adverse events, infections and infestations, caplacizumab	[redacted]	-	[redacted]	[redacted]	Beta [redacted]	
Adverse events, renal, caplacizumab	[redacted]	-	[redacted]	[redacted]	Beta [redacted]	
Adverse events, GI disorders, SoC	[redacted]	-	[redacted]	[redacted]	Beta [redacted]	
Adverse events, respiratory, thoracic and mediastinal disorders, SoC	[redacted]	-	[redacted]	[redacted]	Beta [redacted]	
Adverse events, cardiac disorders, SoC	[redacted]	-	[redacted]	[redacted]	Beta [redacted]	
Adverse events, nervous system disorders, SoC	[redacted]	-	[redacted]	[redacted]	Beta [redacted]	
Adverse events, vascular disorders, SoC	[redacted]	-	[redacted]	[redacted]	Beta [redacted]	
Adverse events, infections and infestations, SoC	[redacted]	-	[redacted]	[redacted]	Beta [redacted]	
Adverse events, renal, SoC	[redacted]	-	[redacted]	[redacted]	Beta [redacted]	
Mortality						
Mortality, UK expected, all patients, SoC	*13.20%*	*0.01*	*87*	*570*	*Beta (0.11,0.16)*	*Section B.3.3*
Mortality, acute RR UK expected, caplacizumab	[redacted]	[redacted]	*-*	*-*	*Log-normal* [redacted]	
Mortality in remission, SMR, Upreti	*8.31*	*0.83*	*-*	*-*	*Log-normal (6.8,10.05)*	
Mortality in remission, RR caplacizumab	*0.62*	*0.06*	*-*	*-*	*Log-normal (0.51,0.75)*	
Utility						
Utility at baseline - acute aTTP episode	*0.87*	*0.09*	*12*	*2*	*Beta (0.66,0.99)*	*Section B3.4*
Utility multiplier, aTTP event - hospitalisation	*0.64*	*0.06*	*35*	*19*	*Beta (0.51,0.76)*	
Utility multiplier, aTTP event - after discharge	*0.82*	*0.08*	*17*	*4*	*Beta (0.64,0.95)*	
Baseline utility in remission: Burns et al.	*0.74*	*0.03*	*148*	*53*	*Beta (0.67,0.79)*	
Utility multiplier for chronic conditions: Burns et al. - neurological symptoms	*0.93*	*0.06*	*39*	*25*	*Beta (0.66,1)*	
Utility multiplier for chronic conditions: Gage et al. - stroke	*0.61*	*0.08*	*22*	*7*	*Beta (0.49,0.72)*	
Utility multiplier for chronic conditions: Sullivan et al. - depression	*0.77*	*0.10*	*-1*	*0*	*Beta (0.6,0.9)*	
Utility multiplier, caregiver, baseline, SoC	*1.00*	*0.10*	*-1*	*0*	*Beta (1,1)*	
Utility multiplier, caregiver, baseline, caplacizumab	*1.00*	*0.10*	*-1*	*0*	*Beta (1,1)*	

Variable	Value	SE	α	β	Measurement of uncertainty and distribution (95% CI)	Reference
Utility multiplier, caregiver, mild cognitive impairment	*1.00*	*0.08*	*16*	*3*	*Beta (1,1)*	
Utility multiplier, caregiver, moderate/severe cognitive impairment	*0.83*	*0.10*	*-1*	*0*	*Beta (0.64,0.95)*	
Utility multiplier, caregiver, neuro-psychological impairment	*1.00*	*0.01*	*90*	*604*	*Beta (1,1)*	
Disutility, Gastrointestinal Disorders	*0.13*	*0.01*	*90*	*604*	*Beta (0.11,0.16)*	
Disutility, Respiratory, Thoracic and Mediastinal Disorders	*0.13*	*0.01*	*21*	*316*	*Beta (0.11,0.16)*	
Disutility, Cardiac Disorders	*0.06*	*0.06*	*6*	*32*	*Beta (0.04,0.09)*	
Disutility, Nervous System Disorders	*0.15*	*0.03*	*75*	*224*	*Beta (0.06,0.28)*	
Disutility, Vascular disorders	*0.25*	*0.04*	*63*	*107*	*Beta (0.24,0.26)*	
Disutility, Infections and Infestations	*0.37*	*0.01*	*90*	*604*	*Beta (0.3,0.44)*	
Disutility, Renal and urinary disorders	*0.13*	*2.80*	*-*	*-*	*Beta (0.11,0.16)*	
Disutility duration (days), Gastrointestinal Disorders	*28.00*	*2.80*	*-*	*-*	*Normal (22.51,33.49)*	
Disutility duration (days), Respiratory, Thoracic and Mediastinal Disorders	*28.00*	*2.80*	*-*	*-*	*Normal (22.51,33.49)*	
Disutility duration (days), Cardiac Disorders	*28.00*	*2.80*	*-*	*-*	*Normal (22.51,33.49)*	
Disutility duration (days), Nervous System Disorders	*28.00*	*2.80*	*-*	*-*	*Normal (22.51,33.49)*	
Disutility duration (days), Vascular disorders	*28.00*	*2.80*	*-*	*-*	*Normal (22.51,33.49)*	
Disutility duration (days), Infections and infestations	*28.00*	*0.70*	*-*	*-*	*Normal (22.51,33.49)*	
Disutility duration (days), Renal and urinary disorders	*7.00*	*0.06*	*39*	*25*	*Normal (5.63,8.37)*	
Costs and resource use						
Compliance, caplacizumab double blind treatment period	[redacted]	[redacted]	*-*	*-*	*Normal* [redacted]	*Section B3.5*
Compliance, caplacizumab open label treatment period	[redacted]	[redacted]	*-*	*-*	*Normal* [redacted]	
Treatment duration (days), caplacizumab patients double blind period	[redacted]	[redacted]	*-*	*-*	*Normal* [redacted]	
Treatment duration (days), caplacizumab patients open label period	[redacted]	[redacted]	*-*	*-*	*Normal* [redacted]	
Administration cost, caplacizumab	*£0.00*	*0.00*	*-*	*-*	*Normal* [redacted]	
Administration cost, SoC	*£0.00*	*0.00*	*-*	*-*	*Normal* [redacted]	
Proportion with mild cognitive impairment requiring stroke/neurology services	*50.00%*	*0.05*	*50*	*50*	*Beta (0.4,0.6)*	

Variable	Value	SE	α	β	Measurement of uncertainty and distribution (95% CI)	Reference
Proportion with mild cognitive impairment requiring cerebral imaging	40.00%	0.04	60	89	Beta (0.32,0.48)	
Proportion with moderate/severe cognitive impairment requiring stroke/neurology services	50.00%	0.05	50	50	Beta (0.4,0.6)	
Proportion with moderate/severe cognitive impairment requiring cerebral imaging	20.00%	0.02	80	319	Beta (0.16,0.24)	
Proportion with moderate/severe cognitive impairment requiring physiotherapy	20.00%	0.02	80	319	Beta (0.16,0.24)	
Proportion with neuro-psychological impairment requiring psychology/counselling	33.33%	0.03	66	133	Beta (0.27,0.4)	
Proportion with neuro-psychological impairment requiring antidepressants	20.00%	0.02	80	319	Beta (0.16,0.24)	
Proportion with neuro-psychological impairment requiring clinic time	50.00%	0.05	50	50	Beta (0.4,0.6)	
Mild cognitive impairment, stroke/neurology services, annual frequency	4.00	0.40	-	-	Normal (3.22,4.78)	
Mild cognitive impairment, cerebral imaging annual frequency	4.00	0.40	-	-	Normal (3.22,4.78)	
Moderate/severe cognitive stroke/neurology services annual frequency	4.00	0.40	-	-	Normal (3.22,4.78)	
Moderate/severe cognitive impairment, cerebral imaging annual frequency	4.00	0.40	-	-	Normal (3.22,4.78)	
Moderate/severe cognitive impairment, physiotherapy annual frequency	4.00	0.40	-	-	Normal (3.22,4.78)	
Neuro-psychological impairment psychology/counselling, annual frequency	4.00	0.40	-	-	Normal (3.22,4.78)	
Neuro-psychological impairment antidepressants annual frequency	12.00	1.20	-	-	Normal (9.65,14.35)	
Neuro-psychological impairment clinic time annual frequency	4.00	0.40	-	-	Normal (3.22,4.78)	
Hospitalisation cost, general ward, per stay	£6,543.53	654.35	-	-	Normal (5261.02,7826.04)	
Hospitalisation cost, ICU, per day	£1,466.60	146.66	-	-	Normal (1179.15,1754.05)	
PEX procedure cost (excluding plasma itself)	£602.34	60.23	-	-	Normal (484.28,720.4)	
Plasma cost per unit	£28.46	2.85	-	-	Normal (22.88,34.04)	
Millilitres per unit of plasma	250.00	25.00	-	-	Normal (201,299)	
Outpatient haematology specialist visit cost	£250.00	25.00	-	-	Normal (201,299)	

Variable	Value	SE	α	β	Measurement of uncertainty and distribution (95% CI)	Reference
ADAMTS13 activity test cost	*£200.00*	*20.00*	*-*	*-*	*Normal (160.8,239.2)*	
Methylprednisolone, cost per dose	*£6.42*	*0.64*	*-*	*-*	*Normal (5.16,7.68)*	
Rituximab, cost per dose	*£1,205.24*	*120.52*	*-*	*-*	*Normal (969.02,1441.46)*	
Stroke/neurology services cost	*£570.00*	*57.00*	*-*	*-*	*Normal (458.28,681.72)*	
Cerebral imaging cost	*£90.00*	*9.00*	*-*	*-*	*Normal (72.36,107.64)*	
Physiotherapy/social services cost	*£55.00*	*5.50*	*-*	*-*	*Normal (44.22,65.78)*	
Psychology/counselling/mental health services cost	*£170.00*	*17.00*	*-*	*-*	*Normal (136.68,203.32)*	
Antidepressants (pack) cost	*£0.51*	*0.05*	*-*	*-*	*Normal (0.41,0.61)*	
Clinic time cost	*£37.00*	*3.70*	*-*	*-*	*Normal (29.75,44.25)*	
Adverse event cost, gastrointestinal disorders	*£1,493.94*	*149.39*	*-*	*-*	*Normal (1201.13,1786.74)*	
Adverse event cost, respiratory, thoracic and mediastinal disorders	*£1,324.90*	*132.49*	*-*	*-*	*Normal (1065.22,1584.57)*	
Adverse event cost, cardiac disorders	*£1,617.18*	*161.72*	*-*	*-*	*Normal (1300.22,1934.15)*	
Adverse event cost, nervous system disorders	*£2,364.26*	*236.43*	*-*	*-*	*Normal (1900.87,2827.65)*	
Adverse event cost, vascular disorders	*£837.60*	*83.76*	*-*	*-*	*Normal (673.44,1001.77)*	
Adverse event cost, infections and infestations	*£1,947.55*	*194.75*	*-*	*-*	*Normal (1565.84,2329.26)*	
Adverse event cost, renal and urinary disorders	*£470.05*	*47.00*	*-*	*-*	*Normal (377.92,562.18)*	
Number of ADAMTS13 tests in remission (per year)	*4.00*	*0.40*	*-*	*-*	*Normal (3.22,4.78)*	
Number of outpatient haematology visits in remission (per year)	*4.00*	*0.40*	*-*	*-*	*Normal (3.22,4.78)*	
Number of rituximab doses in remission (per year)	*4.00*	*0.40*	*-*	*-*	*Normal (3.22,4.78)*	
Proportion receiving rituximab in remission at any one time	*10.00%*	*0.01*	*-*	*-*	*Normal (0.08,0.12)*	

Key: *ADAMTS13, a disintegrin and metalloprotease with thrombospondin type 1 repeats, member 13; aTTP, acquired thrombotic thrombocytopenic purpura; CI, confidence interval; GI, gastrointestinal; ICU, intensive care unit; ITT, intention-to-treat; PEX, plasma exchange; RR, relative risk; SMR, standardised mortality ratio; SoC, standard of care.*

B14. PRIORITY: Please run a scenario in the economic model assuming the RR for long-term complications with caplacizumab is informed by only differences in ICU stay rather than ICU and hospitalisation combined.

Results for this scenario for the subgroup analysis of HERCULES data are presented in Table 6. The resulting ICER is £23,158, a £14,828 (39%) reduction from the base case ICER of £37,986. The RR based on the overall treatment period data is the same as that of the subgroup analysis, resulting in the same ICER as data based on the subgroup analysis.

B15. Please conduct a subgroup analysis in the economic model for the both the very severe and less severe subgroups as defined in the clinical study report (CSR) (very severe disease at baseline was defined as French severity score ≥ 3 or severe neurological involvement or cardiac involvement (cTnI > 2.5 x ULN)).

Data for the less severe and very severe subgroups have now been added into the updated 'ERG model' (attached with our responses), on the "Subgroup analysis" sheet. The subgroup analysis was conducted for the key outcomes in HERCULES which were applied in the economic modelling:

- *Refractory disease, Benhamou et al. (2015) definition[4]*
- *Refractory disease, International Consensus definition[26]*
- *Recurrence within 30 days of stopping PEX (termed exacerbation in HERCULES, termed early exacerbation in model)*
- *Recurrence after 30 days of stopping PEX (termed relapse in HERCULES, termed late exacerbation in model)*

Data are presented in Table 11. There is a clear treatment benefit observed in subjects treated with caplacizumab, irrespective of disease severity at baseline. Data for the ITT population and a calculation of percentage change from the ITT population for each subgroup are presented in Table 12.

Table 11: Outcomes for less severe/very severe subgroups in HERCULES

Outcome	Less severe						Very severe						Source
	Caplacizumab (Total N =42)			Placebo (Total N = 48)			Caplacizumab (Total N = 30)			Placebo (Total N = 25)			
	n	N	%	n	N	%	n	N	%	n	N	%	
Refractory disease (as per Benhamou et al. definition)	[redacted]												*HERCULES CSR, Table 26*
Refractory disease (as per International Consensus definition)	[redacted]												*HERCULES post-hoc analysis, Table 2.1: Baseline disease characteristics: tabulation and descriptive statistics - refractory patients (Scully et al. 2017)*
Recurrence within 30 days of stopping PEX (termed exacerbation in HERCULES, termed early exacerbation in model)	[redacted]												*HERCULES CSR, Table 26*
Recurrence after 30 days of stopping PEX (termed relapse in HERCULES, termed late exacerbation in model)	[redacted]												*HERCULES CSR, Table 26*

Key: *CSR, clinical study report; PEX, plasma exchange.*

Table 12: Outcomes for the ITT population, and comparison to less severe and very severe subgroups

Outcome	ITT population						Less severe (% change from ITT)		Very severe (% change from ITT)		Source
	Caplacizumab (Total N =72)			Placebo (Total N = 73)							
	n	N	%	n	N	%	Caplacizumab	Placebo	Caplacizumab	Placebo	
Refractory disease (as per Benhamou et al. definition)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*0.0%*	*-49.3%*	*0.0%*	*94.7%*	*HERCULES CSR, Table 14.2.1.2.3 - DB treatment period*
Refractory disease (as per International Consensus definition)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*0.0%*	*-8.7%*	*0.0%*	*16.8%*	*HERCULES CSR Table 14.2.1.2.4 - DB treatment period*
Recurrence within 30 days of stopping PEX (termed exacerbation in HERCULES, termed early exacerbation in model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*-100.0%*	*8.6%*	*136.7%*	*-16.6%*	*HERCULES CSR Table 19 - DB treatment period*
Recurrence after 30 days of stopping PEX (termed relapse in HERCULES, termed late exacerbation in model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*37.5%*	*0.0%*	*-57.7%*	*0.0%*	*HERCULES CSR p130, follow up period*

Key: *CSR, clinical study report; DB, double blind; ITT, intention to treat; PEX, plasma exchange.*

The option to select the less severe/very severe subgroups has now been added into the model "Controls" sheet Cell G27 of the 'ERG model'.

The subgroup data for % refractory, using both the Benhamou et al. (2015) and the International Consensus definition have been added to the "Efficacy" sheet in the 'ERG model' in Rows 28 and 29, and Rows 36 and 37; respectively.

The final option selected in Sheet 'Efficacy', Cells E50:F0 is dependent on the definition of refractory used and subgroup selected.

Similarly, the subgroup data for exacerbations, the subgroup data have been added to the "Efficacy" sheet of the 'ERG model' in Rows 66 and 67 for early exacerbations (termed exacerbations in HERCULES) and in Rows 73 and 74 for late exacerbations (termed relapses in HERCULES). Similarly, to the ITT data, the total combined early and late exacerbations has been calculated for the subgroups in Rows 80 and 81.

The final option selected in Sheet 'Efficacy', Cells E94:F94 is dependent on the definition of exacerbation used and subgroup selected.

Results for the less severe and very severe subgroups are presented in Table 13 and Table 14, respectively. For reference, the submitted base case ICER with PAS discount applied was £37,986.

Please note, the patient numbers for this subgroup analysis are very low (as shown in Table 11 above) and therefore results of the model analysis should be treated with caution.

Table 13: Discounted base case results, with PAS discount applied for caplacizumab, less severe subgroup

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER incremental (£/QALY)
SoC	[redacted]	15.85	[redacted]				
Caplacizumab	[redacted]	21.33	[redacted]	[redacted]	5.48	[redacted]	£37,585

Key: ICER, incremental cost-effectiveness ratio; LY, life years; PAS, patient access scheme; QALY, quality-adjusted life year.

Table 14: Discounted base case results, with PAS discount applied for caplacizumab, very severe subgroup

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER incremental (£/QALY)
SoC	[redacted]	15.85	[redacted]				
Caplacizumab	[redacted]	21.33	[redacted]	[redacted]	5.48	[redacted]	£38,756

Key: ICER, incremental cost-effectiveness ratio; LY, life years; PAS, patient access scheme; QALY, quality-adjusted life year.

As discussed in response to question A4, it is important to note that severity of disease at presentation does not change clinical management strategies, or choice of treatments. TTP is a very severe condition and all presentations are potentially life-threatening regardless of sub-types of severity analysed in the trial and used in clinical practice, which is why acute TTP is considered a medical emergency.[5]

B16. If data are available for subgroup analysis by troponin level (i.e. assuming troponin level is a proxy for severity), please conduct a scenario analysis for the economic model by troponin level i.e. those patients with normal and those with elevated troponin. *[[Linked to Clarification Question A5]]*

Not applicable as discussed during the clarification call on 07/11/19.

Section C: Textual clarification and additional points

C1. Please provide Appendix 16.2.7 from the HERCULES CSR.

Appendix 16.2.7 is provided as an accompanying document to this response.

C2. Please supply the listing of adverse event leading to death (listing 16.2.7.4 in HERCULES CSR).

Listing 16.2.7.4 is part of Appendix 16.2.7 provided as an accompanying document.

Appendix A

A.1: **Source:** Ovid MEDLINE(R) ALL
Interface / URL: Ovid
Database coverage dates: 1946 to May 10, 2019
Search date: 13/05/2019
Retrieved records: 43
Search strategy:

1 (caplacizumab$ or alx-0081 or "alx 0681" or "alx 81" or alx0081 or alx0681 or alx81 or 2r27ab6766 or 915810-67-2).ti,ab,kf,nm,rn. 45
2 Cablivi$.ti,ab,kf,nm,rn. 2
3 1 or 2 45
4 exp Animals/ not Humans/ 4578616
5 3 not 4 43

A.2: **Source:** Embase
Interface / URL: Ovid
Database coverage dates: 1974 to May 10 2019
Search date: 13/05/2019
Retrieved records: 183
Search strategy:

1 (caplacizumab$ or alx-0081 or "alx 0681" or "alx 81" or alx0081 or alx0681 or alx81 or 2r27ab6766 or 915810-67-2).ti,ab,kw,dj,rn,tn,dy. 186
2 Cablivi$.ti,ab,kw,dj,rn,tn,dy. 4
3 caplacizumab/ 131
4 1 or 2 or 3 186
5 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ 5732950
6 4 not 5 183

A.3: **Source:** CDSR and CENTRAL
Interface / URL: The Cochrane library
Database coverage dates: Issue 5 of 12, May 2019
Search date: 14/05/2019
Retrieved records: 34
Search strategy:

(caplacizumab* or "alx-0081" or "alx 0681" or "alx 81" or alx0081 or alx0681 or alx81 or 2r27ab6766 or "915810-67-2" or Cablivi*)

A.4: **Source:** PubMed
Interface / URL: https://www.ncbi.nlm.nih.gov/pubmed
Database coverage dates: Information not found

Search date: 14/05/2019
Retrieved records: 13
Search strategy:

#1 Search "caplacizumab"[mesh] 0
#2 Search (((caplacizumab*[tiab] OR caplacizumab*[nm] OR caplacizumab*[rn]) OR ("alx-0081"[tiab] OR "alx-0081"[nm] OR "alx-0081"[rn]) OR ("alx 0681"[tiab] OR "alx 0681"[nm] OR "alx 0681"[rn]) OR ("alx 81"[tiab] OR "alx 81"[nm] OR "alx 81"[rn]) OR ("alx0081"[tiab] OR "alx0081"[nm] OR "alx0081"[rn]) OR ("alx0681"[tiab] OR "alx0681"[nm] OR "alx0681"[rn]) OR ("alx81"[tiab] OR "alx81"[nm] OR "alx81"[rn]) OR ("2r27ab6766"[tiab] OR "2r27ab6766"[nm] OR "2r27ab6766"[rn]) OR ("915810-67-2"[tiab] OR "915810-67-2"[nm] OR "915810-67-2"[rn]))) 43
#3 Search ((Cablivi*[tiab] OR Cablivi*[nm] OR Cablivi*[rn])) 3
#4 Search (#1 OR #2 OR #3) 43
#5 Search (animals [mh] NOT humans[mh:noexp]) 4580171
#6 Search (#4 not #5) 41
#7 Search medline[sb] 25821634
#8 Search (#6 not #7) 13

A.5: **Source:** DARE/HTA/NHS EED
Interface / URL: CRD
Database coverage dates: Information not found. The last updates to DARE were published in the April 2015 issue of the Cochrane Library (published 30 April 2015). The April 2015 updates contain bibliographic records from database searches until the end of 2014.
Search date: 14/05/2019
Retrieved records: 1 (HTA)
Search strategy:

(caplacizumab* or "alx-0081" or "alx 0681" or "alx 81" or alx0081 or alx0681 or alx81 or 2r27ab6766 or "915810-67-2" or Cablivi*)

A.6: **Source:** Science Citation Index Expanded (SCI-EXPANDED)
Conference Proceedings Citation Index- Science (CPCI-S)
Interface / URL: Web of science
Database coverage dates: 1900 to present
Search date: 14/05/2019
Retrieved records: 66
Search strategy:

TS=(caplacizumab* or "alx-0081" or "alx 0681" or "alx 81" or alx0081 or alx0681 or alx81 or 2r27ab6766 or "915810-67-2" or Cablivi*)

A.7: **Source:** Clinical Trials
Interface / URL: clinicaltrials.gov
Database coverage dates: Information not found
Search date: 14/05/2019

Retrieved records: 6
Search strategy:

We ran the following search in Expert Search.

caplacizumab OR "alx-0081" OR "alx 0681" OR "alx 81" OR alx0081 OR alx0681 OR alx81 OR 2r27ab6766 OR "915810-67-2" OR Cablivi

A.8: Source: ICTRP
Interface / URL: http://apps.who.int/trialsearch/
Database coverage dates: Information not found
Search date: 14/05/2019
Retrieved records: 32 records for 8 trials
Search strategy:

We ran the search in the default search box

caplacizumab OR alx-0081 OR alx 0681 OR alx 81 OR alx0081 OR alx0681 OR alx81 OR 2r27ab6766 OR 915810-67-2 OR Cablivi

A.9: Source: CEA registry
Interface / URL: https://cevr.tuftsmedicalcenter.org/databases/cea-registry
Database coverage dates: Information not found
Search date: 14/05/2019
Retrieved records: 0
Search strategy:

We ran the following search terms in the ‘full search contents’ search box.

caplacizumab
alx-0081
alx 0681
alx 81
alx0081
alx0681
alx81
2r27ab6766
915810-67-2
Cablivi

A.10: Source: FDA
Interface / URL: https://www.accessdata.fda.gov/scripts/cder/daf/
Database coverage dates: Information not found
Search date: 14/05/2019
Retrieved records: 1 result 3 PDFs

Search strategy:

We searched Drugs@FDA: FDA Approved Drug Products for the following search terms.

caplacizumab

A.11: Source: EMA
Interface / URL: https://www.ema.europa.eu/en
Database coverage dates: Information not found
Search date: 14/05/2019
Retrieved records: 1 result 4 PDFs
Search strategy:

We sought European Public Assessment Reports. Searches were conducted from the 'Search Medicines' search interface at: https://www.ema.europa.eu/en/medicines

cablivi

A.12: Source: CADTH
Interface / URL: https://www.cadth.ca/
Database coverage dates: Information not found
Search date: 14/05/2019
Retrieved records: 0
Search strategy:

We searched using the default search box for the following search terms individually:

caplacizumab
alx-0081
alx 0681
alx 81
alx0081
alx0681
alx81
2r27ab6766
915810-67-2
Cablivi

A.13: Source: NICE
Interface / URL: nice.org.uk
Database coverage dates: Information not found
Search date: 14/05/2019
Retrieved records: 0
Search strategy:

We searched using the default search box for the following search terms:

caplacizumab
alx-0081
alx 0681
alx 81
alx0081
alx0681
alx81
2r27ab6766
915810-67-2
Cablivi

A.14: Source: EU clinical trials register
Interface / URL: https://www.clinicaltrialsregister.eu/ctr-search/search
Database coverage dates: Information not found
Search date: 14/05/2019
Retrieved records: 4
Search strategy:

We searched using the default search box for the following terms:

Caplacizumab
alx-0081
alx 0681
alx 81
alx0081
alx0681
alx81
2r27ab6766
915810-67-2
Cablivi

A.15: Source: Klinische Prüfungen (Clinical Trials) database
Interface / URL: https://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.html
Database coverage dates: Information not found
Search date: 14/05/2019
Retrieved records: 3
Search strategy:

We searched using the clinical exams investigation page: https://portal.dimdi.de/clinical-trials/servlet/FlowController/AcceptDisclaimer#__DEFANCHOR__. We searched using the following search terms.

Caplacizumab
alx-0081
alx 0681

alx 81
alx0081
alx0681
alx81
2r27ab6766
915810-67-2
Cablivi

A.16: Source: Econlit
Interface / URL: Ovid
Database coverage dates: 1886 to May 02, 2019
Search date: 14/05/2019
Retrieved records: 0
Search strategy:

1 (caplacizumab$ or alx-0081 or "alx 0681" or "alx 81" or alx0081 or alx0681 or alx81 or 2r27ab6766 or 915810-67-2).ti,ab,kw. 0
2 Cablivi$.ti,ab,kw. 0
3 1 or 2 0

A.17: Source: Annual meeting of the American Society of Hematology (ASH)
Interface / URL: http://www.bloodjournal.org/content/132/suppl_1?sso-checked=true
Database coverage dates: N/A
Search date: 15/05/2019
Retrieved records: No results
Search strategy:

We searched abstracts for the last 3 years using Control and Find on each of the following webpages containing that year's abstracts.

2018 - http://www.bloodjournal.org/content/132/suppl_1?sso-checked=true – no results
2017 - http://www.bloodjournal.org/content/130/suppl_1 - no results
2016 - http://www.bloodjournal.org/content/128/22 - no results

The following search terms were used for this search:

Caplacizumab
alx
2r27ab6766
915810-67-2
Cablivi

A.18: Source: Annual meeting of the International Society of Thrombosis and Haemostasis (ISTH)
Interface / URL: https://www.hematology.org/Annual-Meeting/Archive.aspx
Database coverage dates: N/A

Search date: 15/05/2019
Retrieved records: 3
Search strategy:

We searched abstracts for the last 3 years using Control and Find on each of the following webpages containing that year's abstracts.

2018 - https://onlinelibrary.wiley.com/doi/10.1002/rth2.12125– 3
2017 - https://onlinelibrary.wiley.com/doi/epdf/10.1002/rth2.12012- - no results
2016 - https://onlinelibrary.wiley.com/doi/epdf/10.1111/jth.13325- no results

The following search terms were used for this search:

Caplacizumab
alx
2r27ab6766
915810-67-2
Cablivi

A.19: Source: Annual scientific meeting of the British Society for Haematology (BHS)
Interface / URL: http://www.b-s-h.org.uk/
Database coverage dates: N/A
Search date: 15/05/2019
Retrieved records: 1
Search strategy:

We searched abstracts for 2019 and the three previous years by using Control and Find to search within the PDF containing that year's abstracts.

2019 - https://onlinelibrary.wiley.com/doi/epdf/10.1111/bjh.15854 - no results
2018 - https://onlinelibrary.wiley.com/doi/epdf/10.1111/bjh.15226– 1
2017 - https://onlinelibrary.wiley.com/doi/epdf/10.1111/bjh.14613- no results
2016 - https://onlinelibrary.wiley.com/doi/epdf/10.1111/jth.13325- no results

The following search terms were used for this search:

Caplacizumab
alx
2r27ab6766
915810-67-2
Cablivi

Appendix B

The following seven studies were considered highly relevant:

- *11. Davies A, Ridley S, Hutton J, et al. Cost effectiveness of drotrecogin alfa (activated) for the treatment of severe sepsis in the United Kingdom. Anaesthesia. 2005; 60(2):155-62.*
- *12. Ersson A, Beckman A, Jarl J and Borell J. Effects of a multifaceted intervention QI program to improve ICU performance. BMC Health Serv Res. 2018; 18(1):838.*
- *13. Hernandez RA, Jenkinson D, Vale L and Cuthbertson BH. Economic evaluation of nurse-led intensive care follow-up programmes compared with standard care: the PRaCTICaL trial. Eur J Health Econ. 2014; 15(3):243-52.*
- *14. Sznajder M, Aegerter P, Launois R, et al. A cost-effectiveness analysis of stays in intensive care units. Intensive Care Med. 2001; 27(1):146-53.*
- *15. Pappas MA, Vijan S, Rothberg MB and Singer DE. Reducing age bias in decision analyses of anticoagulation for patients with nonvalvular atrial fibrillation - A microsimulation study. PLoS One. 2018; 13(7):e0199593.*
- *16. Kim AS, Nguyen-Huynh M and Johnston SC. A cost–utility analysis of mechanical thrombectomy as an adjunct to intravenous tissue-type plasminogen activator for acute large-vessel ischemic stroke. Stroke. 2011; 42(7):2013-8.e*
- *24. Burns D, Lee D, Vesely S, et al. Patient health-related quality of life associated with remission of aTTP. A regression analysis using non-randomised observational data from the Oklahoma TTP registry. ISPOR. Barcelona, Spain. 10-14 November 2018 2018. PSY192.*

The following six studies were considered of medium relevance:

- *17. Soliman IW, de Lange DW, Peelen LM, et al. Single-center large-cohort study into quality of life in Dutch intensive care unit subgroups, 1 year after admission, using EuroQoL EQ-6D-3L. J Crit Care. 2015; 30(1):181-6.*

- *18. Rozenbaum MH, van Hoek AJ, Fleming D, et al. Vaccination of risk groups in England using the 13 valent pneumococcal conjugate vaccine: economic analysis. BMJ. 2012; 345:e6879.*

- *19. Oostenbrink R, HA AM and Essink-Bot ML. The EQ-5D and the Health Utilities Index for permanent sequelae after meningitis: a head-to-head comparison. J Clin Epidemiol. 2002; 55(8):791-9.*

- *20. Linko R, Suojaranta-Ylinen R, Karlsson S, et al. One-year mortality, quality of life and predicted life-time cost-utility in critically ill patients with acute respiratory failure. Critical Care. 2010; 14:R60.*

- *21. Golicki D, Niewada M, Buczek J, et al. Validity of EQ-5D-5L in stroke. Qual Life Res. 2015; 24(4):845-50.*

- *22. Pages A, Iriart X, Molinier L, et al. Cost Effectiveness of Candida Polymerase Chain Reaction Detection and Empirical Antifungal Treatment among Patients with Suspected Fungal Peritonitis in the Intensive Care Unit. Value Health. 2017; 20(10):1319-28.*

The following 20 studies were considered of low relevance:

- *23. Ament JD, Yang Z, Khatchadourian V, et al. Cost-Effectiveness of Endoscopic Versus Microscopic Transsphenoidal Surgery for Pituitary Adenoma. World Neurosurg. 2018; 110:e496-e503.*

- *25. Cadilhac DA, Dewey HM, Vos T, et al. The health loss from ischemic stroke and intracerebral hemorrhage: evidence from the North East Melbourne Stroke Incidence Study (NEMESIS). Health Qual Life Outcomes. 2010; 8:49.*

- *26. Capuzzo M, Bertacchini S, Davanzo E, et al. Health-related quality of life before planned admission to intensive care: memory over three and six months. Health Qual Life Outcomes. 2010; 8:103.*

- *27. Castiglia P, Pradelli L, Castagna S, et al. Overall effectiveness of pneumococcal conjugate vaccines: An economic analysis of PHiD-CV and PCV-13 in the immunization of infants in Italy. Hum Vaccin Immunother. 2017; 13(10):2307-15.*

- *28. Cho BH, Clark TA, Messonnier NE, et al. MCV vaccination in the presence of vaccine-associated Guillain-Barre Syndrome risk: a decision analysis approach. Vaccine. 2010; 28(3):817-22.*

- *29. Christensen MC, Mayer S and Ferran JM. Quality of life after intracerebral hemorrhage: results of the Factor Seven for Acute Hemorrhagic Stroke (FAST) trial. Stroke. 2009; 40(5):1677-82.*

- *30. Cohen YC, Djulbegovic B, Shamai-Lubovitz O and Mozes B. The bleeding risk and natural history of idiopathic thrombocytopenic purpura in patients with persistent low platelet counts. Arch Intern Med. 2000; 160(11):1630-8.*

- *31. Cuthbertson BH, Roughton S, Jenkinson D, et al. Quality of life in the five years after intensive care: a cohort study. Crit Care. 2010; 14(1):R6.*

- *32. Cuthbertson BH, Rattray J, Campbell MK, et al. The PRaCTICaL study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomised controlled trial. BMJ. 2009; 339:b3723.*

- *33. Fletcher JJ, Kotagal V, Mammoser A, et al. Cost-effectiveness of transfers to centers with neurological intensive care units after intracerebral hemorrhage. Stroke. 2015; 46(1):58-64.*

- *34. Freeman JV, Zhu RP, Owens DK, et al. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. Ann Intern Med. 2011; 154(1):1-11.*

- *35. Graf J, Muhlhoff C, Doig GS, et al. Health care costs, long-term survival, and quality of life following intensive care unit admission after cardiac arrest. Crit Care. 2008; 12(4):R92.*

- *36. Graf J, Wagner J, Graf C, et al. Five-year survival, quality of life, and individual costs of 303 consecutive medical intensive care patients--a cost-utility analysis. Crit Care Med. 2005; 33(3):547-55.*

- *37. Jiang Y, Gauthier A, Annemans L, et al. Cost-effectiveness of vaccinating adults with the 23-valent pneumococcal polysaccharide vaccine (PPV23) in Germany. Expert Rev Pharmacoecon Outcomes Res. 2012; 12(5):645-60.*

- *38. Kabrhel C, Ali A, Choi JG and Hur C. Systemic Thrombolysis, Catheter-Directed Thrombolysis, and Anticoagulation for Intermediate-risk Pulmonary Embolism: A Simulation Modeling Analysis. Acad Emerg Med. 2017; 24(10):1235*

- *40. Malhotra AK, Goldberg SR, McLay L, et al. DVT surveillance program in the ICU: analysis of cost-effectiveness. PLoS One. 2014; 9(9):e106793.*

- *41. Shankar MB, Staples JE, Meltzer MI and Fischer M. Cost effectiveness of a targeted age-based West Nile virus vaccination program. Vaccine. 2017; 35(23):3143-51.*

- *42. Sorensen SV, Kansal AR, Connolly S, et al. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: a Canadian payer perspective. Thromb Haemost. 2011; 105(5):908-19.*

- *43. van der Schaaf IC, Wermer MJ, Velthuis BK, et al. Psychosocial impact of finding small aneurysms that are left untreated in patients previously operated on for ruptured aneurysms. J Neurol Neurosurg Psychiatry. 2006; 77(6):748-52.*

- *55. King JT, Jr., Glick HA, Mason TJ and Flamm ES. Elective surgery for asymptomatic, unruptured, intracranial aneurysms: a cost-effectiveness analysis. J Neurosurg. 1995; 83(3):403-12.*

References

1. Ablynx NV. HERCULES CSR: a phase III double-blind, randomized, parallel group, multicenter placebo-controlled trial to study the efficacy and safety of caplacizumab in patients with acquired thrombotic thrombocytopenic purpura (Clinical Study Report: ALX0681-C301) 2017.
2. Benhamou Y, Assié C, Boelle P-Y, et al. Development and validation of a predictive model for death in acquired severe ADAMTS13 deficiency-associated idiopathic thrombotic thrombocytopenic purpura: the French TMA Reference Center experience. Haematologica. 2012; 97(8):1181-6.
3. [redacted]
4. Benhamou Y, Boelle PY, Baudin B, et al. Cardiac troponin-I on diagnosis predicts early death and refractoriness in acquired thrombotic thrombocytopenic purpura. Experience of the French Thrombotic Microangiopathies Reference Center. J Thromb Haemost. 2015; 13(2):293-302.
5. Scully M, Hunt B, Benjamin S, et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol. 2012; 158:323-35.
6. Hughes C, McEwan JR, Longair I, et al. Cardiac involvement in acute thrombotic thrombocytopenic purpura: association with troponin T and IgG antibodies to ADAMTS 13. J Thromb Haemost. 2009; 7(4):529-36.
7. Scully M, Cataland SR, Peyvandi F, et al. Caplacizumab Treatment for Acquired Thrombotic Thrombocytopenic Purpura. N Engl J Med. 2019; 380(4):335-46.
8. Scully M, Minkue Mi Edou J and Callewaert F. Caplacizumab Treatment for Acquired Thrombotic Thrombocytopenic Purpura: Response to Yang letter to the editor. N Engl J Med. 2019; 380(18):e32(1-2).
9. Ablynx NV. Integrated Summary of Efficacy. Caplacizumab. 2018. Data on file.
10. Ablynx NV. TITAN CSR: a phase II, single-blind, randomised, placebo-controlled trial to study the efficacy and safety of anti-von willebrand factor nanobody administered as adjunctive treatment to patients with acquired thrombotic thrombocytopenic purpura. (Clinical Study Report: ALX-0681-2.1/10) 2015.
11. National Institute for Health and Care Excellence (NICE). Caplacizumab for treating adults experiencing an episode of acquired thrombotic thrombocytopenic purpura [ID1185] - Final scope. 2019. (Updated: 09 August 2019). Accessed: 21 August 2019.
12. Sanofi. HTA advisory board 06 March 2019. Data on file.
13. National Institute for Health and Care Excellence (NICE). Position statement on use of the EQ-5D-5L value set for England (updated October 2019). 2019. Available at: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l. Accessed: 6 November 2019.
14. Ersson A, Beckman A, Jarl J and Borell J. Effects of a multifaceted intervention QI program to improve ICU performance. BMC Health Serv Res. 2018; 18(1):838.
15. Kim AS, Nguyen-Huynh M and Johnston SC. A cost–utility analysis of mechanical thrombectomy as an adjunct to intravenous tissue-type plasminogen activator for acute large-vessel ischemic stroke. Stroke. 2011; 42(7):2013-8.

16. Shankar MB, Staples JE, Meltzer MI and Fischer M. Cost effectiveness of a targeted age-based West Nile virus vaccination program. Vaccine. 2017; 35(23):3143-51.
17. Burns D, Lee D, Vesely S, et al. Patient health-related quality of life associated with remission of aTTP. A regression analysis using non-randomised observational data from the Oklahoma TTP registry. ISPOR. Barcelona, Spain. 10-14 November 2018 2018. PSY192.
18. Davies A, Ridley S, Hutton J, et al. Cost effectiveness of drotrecogin alfa (activated) for the treatment of severe sepsis in the United Kingdom. Anaesthesia. 2005; 60(2):155-62.
19. Hernandez RA, Jenkinson D, Vale L and Cuthbertson BH. Economic evaluation of nurse-led intensive care follow-up programmes compared with standard care: the PRaCTICaL trial. Eur J Health Econ. 2014; 15(3):243-52.
20. Pappas MA, Vijan S, Rothberg MB and Singer DE. Reducing age bias in decision analyses of anticoagulation for patients with nonvalvular atrial fibrillation - A microsimulation study. PLoS One. 2018; 13(7):e0199593.
21. Sanofi. HTA model review and clinical validation June 2019. Data on file.
22. Chit A, Becker DL, DiazGranados CA, et al. Cost-effectiveness of high-dose versus standard-dose inactivated influenza vaccine in adults aged 65 years and older: an economic evaluation of data from a randomised controlled trial. Lancet Infect Dis. 2015; 15(12):1459-66.
23. McPhail S and Haines T. Response shift, recall bias and their effect on measuring change in health-related quality of life amongst older hospital patients. Health Qual Life Outcomes. 2010; 8:65.
24. Gage BF, Cardinalli AB, Albers GW and Owens DK. Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation. Jama. 1995; 274(23):1839-45.
25. Sullivan PW, Slejko JF, Sculpher MJ and Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. Med Decis Making. 2011; 31(6):800-4.
26. Scully M, Cataland S, Coppo P, et al. Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies. J Thromb Haemost. 2017; 15(2):312-22.
27. Peyvandi F, Scully M, Kremer Hovinga JA, et al. Caplacizumab for acquired thrombotic thrombocytopenic purpura. N Engl J Med. 2016; 374(6):511-22.
28. Ablynx. Systematic review on the clinical burden of disease in thrombotic thrombocytopenic purpura. 2018. Data on file.
29. Ara R and Wailoo A. NICE DSU technical support document 12: The use of health state utility values in decision models. 2011. Available at: http://nicedsu.org.uk/wp-content/uploads/2016/03/TSD12-Utilities-in-modelling-FINAL.pdf. Accessed: 07 May 2019.
30. Ablynx NV. HERCULES Individual Patient Level Data. 2017. Data on file.
31. Gage BF, Cardinalli AB and Owens DK. The effect of stroke and stroke prophylaxis with aspirin or warfarin on quality of life. Arch Intern Med. 1996; 156(16):1829-36.
32. Freeman JV, Zhu RP, Owens DK, et al. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. Ann Intern Med. 2011; 154(1):1-11.
33. van Exel NJ, Koopmanschap MA, van den Berg B, et al. Burden of informal caregiving for stroke patients. Identification of caregivers at risk of adverse health effects. Cerebrovasc Dis. 2005; 19(1):11-7.

34. Hale O and Lee D. How central limit theorem relates to the selection of distributions for probabilistic sensitivity analysis. ISPOR EU Copenhagen, Denmark. 2-6 November 2019. PNC217.
35. Briggs AH, Weinstein MC, Fenwick EA, et al. Model parameter estimation and uncertainty analysis: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group-6. Med Decis Making. 2012; 32(5):722-32.

NICE National Institute for Health and Care Excellence

Patient organisation submission

Caplacizumab for treating adults experiencing an episode of acquired thrombotic thrombocytopenic purpura [ID1185]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	TTPNetwork
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	TTPNetwork is a patient support group for patients and family members and medical professionals. We are primarily concerned with the very rare blood condition Thrombotic Thrombocytopenic Purpura. We established in 1998. We have a patient following of over 550 people. We are known worldwide, but we focus on care and treatments and information in the UK domain. Our website build and maintenance is paid for by the UCL Charity – TTP Education & Research Fund. We run a small 'shop' via our website and this has recently funded a reprint of leaflets. In the past: leaflets and saleable items have been funded by the UCL Charity – TTP Education & Research Fund, and also the National Blood & Transfusion Service.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	The organisation has not received any funding from the manufacturers of the technology. The organisation has in the past liaised with Ablynx and have received hospitality from them in the form of hotel and transport costs when speaking at a staff conference to give scientists an understanding of living with the condition. The organisation has engaged with staff at Sanofi following the take over from Ablynx and representatives from TTPNetwork have spoken at Sanofi staff events about TTP and to staff about living with TTP and the work of TTPNetwork patient support group.

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	We do not have any links with or funding from the Tobacco industry.
5. How did you gather information about the experiences of patients and carers to include in your submission?	We canvassed patients via our closed Facebook group and we invited them to complete a short, on line questionnaire. We also carried out a Facebook 'poll'. We emailed patients whose details we have and asked them to complete the on line questionnaire. We have lots more comments, examples and statements than we have room to write on this form and we would be happy to share them with you.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	It doesn't define who I am thankfully - as I am in remission I tend to forget about this condition as much as possible and carry on as normal. I feel safe in the knowledge that if I didn't feel well then I have a wonderful support system (Drs at [redacted] that I can call upon to be checked out *Scary! Always tired, and every time you get a bruise panic. Waiting for the relapse, that always seems to appear.* Two respondents simply said: "Scary"

	My mum is living with TTP I worry about her every day shes being monitored every 2 weeks,but currently her white blood cells are dangerously low & is having to check her temperature every day & if it gets to 38 she needs to get to hospital it's very worrying *Difficult and worrying* Stressful and draining. It affects all aspects of life including work and personal as it causes fatigue. It is always there in the background and any infection causes anxiety of a relapse. *Very debilitating. Every day is exhausting I go to bed tired and I wake up tired. I have on going memory issues and I feel very low at times simply because I have no energy. I wish I could be back to my old self. I also pick up colds, flu, infections much quicker since diagnosed so I become unwell quickly and it lasts longer. My energy and stamina are affected and I can't do what I should be able to do at my age. - I have not been the same since I was diagnosed. Every part of me aches constantly* Sometimes it can be very difficult, it's every time at the back of your mind, you never know when you can have a relapse. When there's a health problem your first thought is am I heading for a relapse. It affects your family as well, especially children. I still have problems with my daughter anxiety issues and it's been three years. But with time you somehow manage to learn to live with it. *Exhausting* Always on edge wondering if and when the next attack might happen *Difficult, I'm surprised how much it has affected my life. The symptoms of relapse quite ambiguous, therefore, it is always just at the back of your mind. The thought of a relapse, and having to stop your life for weeks on end while you receive treatment, is always hanging over you. I'm not the same person, I'm often exhausted, my memory is causing me severe problems at home and at work.* For 25 years I have lived with a constant worry of relapsing. I am hyper vigilant and live with anxiety about my health. I have a daily battle with my memory and Aphasia. I have low energy levels and must balance my work/life in favour of taking regular rest. I tire very quickly and feel extreme tiredness. My whole body aches at times. My family, particularly parents, remain constantly worried about my health despite me being nearly 50. *Carers are also scared watching the symptoms, having to do everything for the person due to extreme fatigue*

	Constant worry *Carers are in a constant state of worry in case the enzyme or platelet levels level drops.* Extremely tired, confused, headachy, sickly like I want to be sick, forgetful, scared but won't show it. Body feels like a ton weight and on (the treatment)machine like I have a tap on fast forward pouring fluid into my body - very fast feeling which makes me feel sickly and heart pound. I had three strokes on initial diagnoses, so I get worried I will have more. Family / carers have always felt scared and a bit isolated. Anxious and stressed. *My partner suffers from impaired mobility, memory, and cognitive awareness, for starters!* Tiredness, difficulty concentrating, aches and pains.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	I feel very fortunate to be under the team at [redacted] and have only had very positive experiences with my care and treatment *I find it difficult to be treated in a regional unit, as it is about 2 hours from home for me. The first time I was ill, had no idea what was happening, felt really poorly and scared to death, and then moved to hospital 2 hrs from home. which made it even scarier.* Most amazing doctors who know about the disease, never heard of it until diagnosis. *I think the treatment & care my mum is receiving is the best [redacted] have really looked after my mum & shes having the best treatment* The care at specialist treatment centres is very good but elsewhere medical professionals are often not aware of the condition or its treatment. *I am aware that there is a difference in treatments and care across England. Some patients are regularly monitored and receive prophylaxis treatment, whilst others are left with no long term follow up and they relapse.* Plasmapheresis seems archaic now and very long winded however the care and attention has been excellent.

	I'm with [redacted] so I'm lucky. I can't be more grateful to [redacted] [redacted] and Team. The care and support they provide is incredible. Not only when you're in the hospital but after care as well. Unfortunately, from what I've heard from other patients it's not the case throughout the UK. Not readily available *First class* When first diagnosed I was shocked by the amount of plasma transfusions I needed, 4 hours a day, Rituximab caused allergic reactions for me which weren't very pleasant. Just lengthy and time consuming. *Plasma for me was the worse ever 4hours twice a day for god knows how long , made me feel sick , got mad tingles so then had to have calcium drip, omg every time they came in to my ward with the trolley I cried* I had an allergic reaction to ffp. I don't know what triggered it and have never had a reaction to any food or drinks so it is a worry that there is something that will do that to me! I do feel guilty for using so much ffp during an episode of ttp too, it takes such a huge volume of donations to recover, and sometimes if the plasma exchange doesn't go well it can actually be wasted which is terrible considering people have taken the time to donate! I do find it a worry that with the overuse of antibiotics if something was to slip through the net during testing of the donated plasma, it may be very dangerous. *I have mixed emotion about plasma exchange but needs to be done.*
8. Is there an unmet need for patients with this condition?	Fortunately, as I live in [redacted] I have very easy access to [redacted] and the team there *There is not much knowledge about it, and quite a lot of ignorance about problems such as tiredness. I was once asked by a Haematology registrar why I was tired, and she implied it was because I was lazy!* More info about long term, what happens when you leave hospital. Do GP's get involved once in remission *Yes* Haven't come across any at the moment *Yes*

	The quick treatment of TTP ensures less time in hospital and other drugs that could potentially cause side effects. *Ongoing support, help in the workplace, ongoing issues with benefits if your unable to work. Help in attending appointments if needed. More updates on new ideas* Having a access to a psychologist not only for the patients but for their families as well. I feel that I benefited very much from meeting with a psychologist. *Psychological* Cant think of any *Access to any medication that would reduce the length of relapses, the length of hospital stays.*
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	I absolutely believe that along with other treatment it can speed up a patient's recovery *Worked well for me, kept my platelets up, once stopped platelets dropped. Given to use for one month at home. Believe this helped me leave hospital earlier and kept me well* Saves lives *This enabled our mum to come home* These include faster recovery of platelets so there is less chance of death! The quicker treatment and recovery means less time in hospital with all the disruptions that causes. There is also less chance of relapse. *Looks promising and a new way forward* I was on the trial. The doctors believed that I was on the real drug as I had a side effect, excessive bleeding. I blacked out because of that but it was my fault partially as I didn't want to take the medication for stopping my period. Now that the doctors know the side effects it's much easier to manage it. It shortened the time to recovery, took me only a few days. The quicker the recovery the less the damage to

	your body. Even with the side effect I had I wouldn't change it. *From everything that I have read, quicker recovery time, which would lead to less time in hospital/having treatment. This would really help with wellbeing and mental recovery.*
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Possible side affects as with any medication *None for me, perhaps a bit of bruising* Possible other complications *Possibly the costs.* Possibly the side affects and frequency of doses *I haven't read about any disadvantages, so can't add to this.* Minimal disadvantages, - some possible side effects
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Not sure, although anyone with TTP (acquired in my case) would surely benefit *Chronic relapsers like myself who have to spend long periods in hospital on relapse* I think it's important for everyone. In TTP case every minute is important for survival. *All TTP patients.....those with small children can be back up to speed quicker, those who have full time jobs can be back to normal quicker...* Patients who are treated a long way from home will have reduced stays in hospital and can return to their support network among family and friends – something which can be lacking when those people would need to travel long distances to visit during visiting hours.

	I would not have needed to take 4 months off work, resulting in reduced salary and debts.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Not sure *Not in my experience* Should be readily available *None that I can think of* I'm not sure what this means *TTP disproportionately affects Black afro Caribbean people and of women generally. There is some research to suggest that Black Caribbean communities suffer an inequality of health and some of this can be attributed to poor take-up of health care*
Other issues	
13. Are there any other issues that you would like the committee to consider?	If a medication has the ability to aid a patient's recovery from a life-threatening disease then surely it should be available to anyone that may potentially benefit from it *Any treatments should be made available, I have just had 4 doses of Ritux, and even though it is over 2 months since my last dose I am still suffering with nausea. When I need this drug in the future which I no doubt will, I am going to be reluctant to have it due to this side effect.* Really felt this drug helped me so much, and reduced my hospital stay. It helped me maintain the platelets at 150 so I was able to leave intensive care quicker *I would like the committee to look into the long standing affects of TTP not only physically but emotionally too. More support and help is needed for patients after each relapse. The condition is such that it affects every single part of your day to day life and you have to prepare and plan even a day out due to tiredness and lethargy.*

	My daughter has always been treated extremely well so can't think of anything
14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] if there are none delete highlighted rows and renumber below	

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Patients who have had an acute TTP episode experience long term conditions/side effects as a result
- Patients fear relapse and have concerns about the use of plasma exchange
- Family and carers worry about their loved one relapsing.
- There is an inequality of treatment across the country.
- Patients who believe they were treated with the technology speak positively about its use.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Caplacizumab for treating adults experiencing an episode of acquired thrombotic thrombocytopenic purpura [ID1185]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	**RCPath**

3. Job title or position	[redacted] [redacted]
4. Are you (please tick all that apply):	☐ **x** an employee or representative of a healthcare professional organisation that represents clinicians? ☐ **x** a specialist in the treatment of people with this condition? ☐ **x** a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	The main aim of treatment is to achieve a complete remission, achieved initially by prompt normalisation of platelet count, which prevents ongoing microvascular thrombi formation and reduce significant morbidity of the condition related to end organ damage.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Prompt and sustained platelet count increment and reduced morbidity. Ultimately, complete remission

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Definitely. The period of increased mortality and morbidity is within 24-48 hours from diagnosis. Intensive therapy is still often associated with exacerbations or refractory disease, in 10-20% of patients. The use of capla both within the trials and in the real world is associated with a prompt increase in plt counts, no exacerbations while therapy is continued and refractoriness is now very rare.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Currently by plasma exchange and immunosuppressive therapies, usually high dose steroids and eg rituximab. This needs to continue as it treats replacement of the missing enzyme, ADAMTS 13 and removes antibodies to ADAMTS 13
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	BSCH
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	No the initial pathway is well defined across the UK and the treaters of this rare condition work together. In refractory cases, further immunosuppressive therapy may be required, discussed on a case by case basis

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	As stated above, the time to normalisation of plt count is significantly quicker with capla. This will reduce organ morbidity, which has significant clinical impact in the longer term. There is now rarely exacerbations, associated with having to increase treatment protocols and patients are discharged from the hospital much quicker, with reduced plasma exchange episodes and a significant reduction in plasma requirements.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes it will be added to the current treatment pathways already established.
• How does healthcare resource use differ between the technology and current care?	Addition of capla will reduce the amount of high dose steroid therapy (given the plt count will normalise quicker), which is significant from a side effect profile. It will also reduce the time in hospital, PEX procedures and plasma useage
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Capla should be used in all patients where a diagnosis of TTP is confirmed, associated with severe deficiency of ADAMTS 13 activity.
• What investment is needed to introduce the technology? (For	Availability of the therapy within specialist treatment centre, real time availability of ADAMTS 13 assays and dedicated clinics to follow up the patients.

example, for facilities, equipment, or training.)	
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Most definitely, as seen within the compassionate use programme in the UK (reflecting the clinical trial findings), in respect to time in hospital, morbidity and mortality outcomes
• Do you expect the technology to increase length of life more than current care?	Yes and reduce the impact of end organ damage, certainly acutely and long term under investigation
• Do you expect the technology to increase health-related quality of life more than current care?	Yes because of the above
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with TTP

The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	There are no issues for use with health care professionals as it is subcutaneous and patients similarly are taught to give at home daily.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Yes, starting only if ADAMTS 13 levels are severely reduced in keeping with a diagnosis of TTP. Stopping will be dictated by the ADAMTS 13 level. From the studies, at least 30 days after finishing PEX. Continuation after that will be assessed weekly based on ADAMTS 13 activity levels. Once activity levels are normal x 2 values, or > 30iu/dl and increasing, capla can be stopped. There will be a spread re the exact time point, dependant on the level and potency of Anti ADAMTS 13 antibody.

15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Unable to answer
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Most definitely-as answered above
• Is the technology a 'step-change' in the management of the condition?	Definitely, a very positive change in the treatment pathway
• Does the use of the technology address any	Yes as per above answer re acute mortality, morbidity, exacerbations and refractory disease

particular unmet need of the patient population?	
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The bleeding risk appears to be surface /epithelial only and is manageable. The effect of capla can theoretically be reversed with a factor concentrate, but this would only be required under life threatening situations
Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Time to normalisation of plt counts, time in hospital, no exacerbations, significant reduction in refractory disease, reduced PEX and plasma-all highlighted in the clinical trials
• If surrogate outcome measures were used, do they adequately predict	Long term data needs to be collected

long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to date
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TAXXX]? [delete if there is no NICE guidance for the comparator(s) and renumber subsequent sections]	

21. How do data on real-world experience compare with the trial data?	Exactly the same-a major advancement in the treatment of patients with acute TTP
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	NO
22b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
23 [To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains	

uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Significant improvement in time to platelet count normalisation
- Reduced morbidity and mortlaity
- Reduction in exacerbation rates and refractory disease
- Reduction in time in hospital
- Reduction in number of plasma exchanges and plasma usage

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Caplacizumab for treating adults experiencing an episode of acquired thrombotic thrombocytopenic purpura [ID1185]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Will Lester**
2. Name of organisation	**University Hospitals NHS Trust**

3. Job title or position	**Haematology consultant**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? **x** a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it x other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To interrupt the immediate down stream disease process – the occlusion of the microvasculature with platelets bound to VWF. This results in a more rapid remission and may reduce long term disability
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	Any reduction in mortality Any reduction in refractoriness to standard therapy in the intial treatment phase Any reduction in early exaccerbations Any statistically significant reduction in the number of ITU bed days Any statistically significant reduction in the number of plasma exchange procedures required
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Outside of the trial and registry setting, mortality remains up to 30% (and in some regions has been as high as 50%). Even with maximal therapy the mortality rates can be 10-20%. There is a need for adjuvant treatments to reduce early death The period of active treatment for acute TTP can be quite prolonged - in some individuals this can be many weeks, even months. During that time, the disease process (microvascular thrombosis and ischaemia) remains active. Current standard of care is immune suppression to remove autoantibodies and plasma exchange to try and overcome the inhibition of the ADAMTS13 enzyme. This requires intensive therapy, often in an ICU setting, with central venous catheters which become thrombosed or infected and exposure

	to large amounts of human plasma. There has been an unmet need because of a lack of immediate therapy to block the microthrombotic process which results from uncorrected ADAMTS13 depletion For those who survive, TTP is a condition with long term morbidity, particularly neuropsychiatric. It is plausible that the longer a patient takes to respond to treatment, the greater the burden of morbidity due to the duration of ongoing microvascular ischaemia
What is the expected place of the technology in current practice?	
10. How is the condition currently treated in the NHS?	Plasma exchange, High dose steroids and Rituximab have been the cornerstones of therapy.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Guidelines from the British Society of Haematology which are currently due update Scully, M., Hunt, B.J., Benjamin, S., Liesner, R., Rose, P., Peyvandi, F., Cheung, B., Machin, S.J. and (2012), Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol, 158: 323-335. doi:10.1111/j.1365-2141.2012.09167.x
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is defined – however there is some variation in access to highly specialist care and immediate access to plasma exchange
• What impact would the technology have on the current pathway of care?	It would be used within the current pathway. The current move to highly specialist care in designated centres in England would complement the introduction of this technology in terms of appropriate usage

11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	It has been available in the UK as part of an early access scheme. Larger more experienced centres have adopted the technology rapidly as the new standard of care however other centres with less experienced or engaged clinicians have not done so, or have done so after considerable delay.
• How does healthcare resource use differ between the technology and current care?	With this technology, there is a reduction in the duration of ICU care, inpatient bed days and numbers of plasma exchanges required and we aren't seeing early exacerbations and readmissions
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Initiated in secondary care with follow up in specialist clinics after discharge
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None. The administration is simple with one IV bolus and then subcut injections which patients can generally be taught to do themselves. There is already intensive medical and nursing input for these patients and this falls well within existing capacity
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	We have seen the same impact as the trials with shorter durations of intensive standard therapy required. It's worth noting that the process for accessing the drug on an early access scheme for named patients (until recently) required a degree of internal bureaucracy which could delay introduction of the drug by a day or so. I expect to see even better patient outcomes as 1. The technology and turnaround for ADAMTS13 testing becomes quicker and 2. The drug is available immediately without delay

• Do you expect the technology to increase length of life more than current care?	It will save some patients from early death and reduce morbidity from stroke which could be life shortening
• Do you expect the technology to increase health-related quality of life more than current care?	It is certainly plausible that the extent of chronic neuropsychiatric morbidity reflects the extent of microvascular thrombosis in the brain and so the longer the duration of active disease at presentation, the more extensive the ischaemic damage and the greater the long term morbidity. Any treatment which speeds up remission should reduce that long term morbidity and improve quality of life
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	To my knowledge, subgroups likely to benefit more (or less) haven't been identified from the trials or early post trial access to date.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	It is straightforward to use. Centres familiar in the care of TTP have been early adopters of the patient access scheme as noted above. There has been some concern about access to von Willebrand Factor Concentrate for patients who bleed while using the technology. My experience reflects that of the trials with minor bleeding which doesn't need

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	VWF therapy. Access to VWF concentrate is generally OK in the UK and the tertiary centres that manage most TTP patients will have stocks
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	We haven't yet had a reason to stop treatment prematurely other than a few doses in one patient with haemorrhagic transformation of ischaemic stroke. There might occasionally be a futility argument however therapy is rarely withdrawn as patients can be salvaged after prolonged durations of disease. Currently we are using recovery of ADAMTS13 levels as a stop rule and setting the cut off could give some flexibility in being able to stop treatment earlier than in the phase 3 trials
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	As noted previously, I have a similar opinion to many TTP treaters in the UK; in addition to the early benefits described in the trials, there is likely to be a greater mortality benefit in standard practice and the long term morbidity, particularly neuropsychiatric, could be reduced by truncating the ischaemic damage during the initial TTP presentation

17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	The technology is innovate and complements current therapy.
• Is the technology a 'step-change' in the management of the condition?	It is a stepchange due to the mechanism of action being a novel complement to existing therapy. We have seen the same benefits as the trial in the early access scheme
• Does the use of the technology address any particular unmet need of the patient population?	Certainly for those patients previously at risk of refractory disease and early exacerbations which are distressing for patients and families. We have seen less venous catheter infections due to the shorter duration of plasma exchange required. We have seen patients survive who historically would have been expected to die on ICU
18. How do any side effects or adverse effects of the technology affect the	There is an increased risk of mucocutaneous bleeding – often epistaxis – although this usually settles without intensive therapy

management of the condition and the patient's quality of life?	
Sources of evidence	
19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – however as noted previously, the local bureaucracy required for a named patient early access scheme has slightly delayed the first dose historically
• If not, how could the results be extrapolated to the UK setting?	NA
• What, in your view, are the most important outcomes, and were they measured in the trials?	The important early outcomes were measured in the trial however the longer term impact hasn't been to date
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	It is plausible that reduced time on ICU and time to remission and reduced exacerbations will be reflected in improved quality of life and function (able to return to work etc)
• Are there any adverse effects that were not apparent in clinical trials	Not noted to date

but have come to light subsequently?	
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	The UK TTP forum is a group of clinicians with an interest in TTP and they have been collecting outcome data from patients in the early access scheme. We have contributed our local data and I have seen the preliminary national data which is encouraging, however the issue has been a suitable control group for comparison. The TTP registry in the UK is now collecting longer term quality of life data which may also become informative over time
21. How do data on real-world experience compare with the trial data?	Very similar
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Black African and Caribbean people appear to be at increased risk of TTP and it is more common in younger women than in men
22b. Consider whether these issues are different from issues with current care and why.	Not that has become apparent to date

Key messages
23. In up to 5 bullet points, please summarise the key messages of your statement. • That the experience from the early access scheme reflects the trials with improved patient outcomes • That this technology represents a step change in the management of acute TTP • That it's biologically plausible that a reduced duration of acute disease will improve long term outcomes • That the UK TTP forum and registry is collecting real world data •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……

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NICE National Institute for Health and Care Excellence

NHS commissioning expert statement

Caplacizumab for treating adults experiencing an episode of acquired thrombotic thrombocytopenic purpura [ID1185]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. Your response should not be longer than 10 pages.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1. Your name	**Fiona Marley**
2. Name of organisation	**NHS England**

3. Job title or position	**Head of Highly Specialised Commissioning**
4. Are you (please tick all that apply):	☒ commissioning services for a CCG or NHS England in general? ☒ commissioning services for a CCG or NHS England for the condition for which NICE is considering this technology? ☐ responsible for quality of service delivery in a CCG (for example, medical director, public health director, director of nursing)? ☐ an expert in treating the condition for which NICE is considering this technology? ☐ an expert in the clinical evidence base supporting the technology (for example, an investigator in clinical trials for the technology)? ☐ other (please specify):
Current treatment of the condition in the NHS	
5. Are any clinical guidelines used in the treatment of the condition, and if so, which?	Services for patients with TTP are currently commissioned by CCGs. NHS England will become the responsible commissioner for services for patients with TTP during 2020/21. Once a nationally commissioned service has been established, NHS England would work with the designated providers to develop guidelines for any drugs that have been recommended for treatment.
6. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your	The general pathway of care for patients with TTP is set out in a service specification that has been developed by a working group facilitated by NHS England: https://www.engage.england.nhs.uk/consultation/thrombocytopenic-purpura/ [The final version has not yet been published because of priority having been given to COVID-19 documents]

experience is from outside England.)	
7. What impact would the technology have on the current pathway of care?	Evidence suggests that the drug reduces: clot formation; lengths of stay in ITU; and the length of time needed for plasma exchange by a faster resolution of an acquired TTP (aTTP) episode with a significantly shorter time to platelet count response. This leads to a reduction in aTTP-related relapses and deaths.
The use of the technology	
8. To what extent and in which population(s) is the technology being used in your local health economy?	The only patients in receipt of this treatment would be those who were on a clinical trial or who have received the drug through an early access programme.
9. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The treatment would be used in designated centres, of which there are likely to be eight or nine, or under the supervision of designated centres if the patient could not travel to one of the designated centres within an optimal period of time.
• How does healthcare resource use differ between the technology and current care?	There may be a reduction in the length of plasma exchange and ITU stays by a faster resolution of an aTTP episode with a significantly shorter time to platelet count response. This leads to a reduction in aTTP-related relapses and deaths.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The drug would be initiated in designated centres.
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional facilities or equipment would be required.
• If there are any rules (informal or formal) for starting and stopping treatment with the technology, does this include any additional testing?	No additional testing is required.
10. What is the outcome of any evaluations or audits of the use of the technology?	To date, there has been a review of the use of the technology by Liverpool University Hospitals NHS Foundation Trust, which has been shared with the UK TTP registry but not yet published. The outcome of the review was supportive of the technology.
Equality	

11a. Are there any potential equality issues that should be taken into account when considering this treatment?	TTP can, to a small degree, disproportionately affect patients from Afro-Caribbean communities and pregnant women. There are some risks of bleeding associated with the drug so these would have to be taken into account by the prescribing clinician if it was to be considered in pregnancy.
11b. Consider whether these issues are different from issues with current care and why.	Not different.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

NICE National Institute for Health and Care Excellence

Patient expert statement

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Jamie Blackshaw**
2. Are you (please tick all that apply):	√ a patient with the condition? ☐ a carer of a patient with the condition? √ a patient organisation employee or volunteer?

	☐ other (please specify):
3. Name of your nominating organisation	TTP Network
4. Did your nominating organisation submit a submission?	√ yes, they did ☐ no, they didn't ☐ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	√ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	√ I have personal experience of the condition √ I have personal experience of the technology being appraised I have other relevant personal experience. Please specify what other experience: √ I am drawing on others' experiences. Please specify how this information was gathered: Through a survey with other patients and people living with TTP, which was led by the TTP Network.
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	I suffered an acute episode of life threatening TTP in 2016, the onset of which was sudden. The symptoms became progressively worse (purpura, breathlessness, headache and a jaundice appearance) though at first did not necessarily indicate, to me, the seriousness of what was going on. The acute nature of TTP and the way in which it manifested itself was frightening and it was only on presenting to A&E that the full picture of my blood counts i.e. very low platelets and low red blood cell count became evident. I consider myself lucky in that at the age of 44 years, I was relatively healthy, and that I acted and sought care prior to suffering any serious damage to my organs and/or suffering any serious cardiovascular conditions.

	Pre-diagnosis was an overwhelmingly anxious time and being diagnosed was a relief, in part, as it meant that the doctors could treat me. Early in the treatment, I experienced nausea and vomiting during the plasma exchanges and whilst the exchanges led to exhaustion, with each cycle of exchange hope of getting better flowed through me. The steroids dampened down my immune system though disrupted my sleep, which in turn didn't help with my levels of anxiety, which was at an increased level. I signed up to the Hercules trial as that point it seemed sensible and logical to use every possible treatment option to get better. The rituximab and the explanation provided to me in terms of what it would do in terms of suppressing my immune system, over the longer term, made complete sense to me. During those 3 or so weeks of treatment in hospital I got better, and my blood counts improved. I lost weight (despite retaining my appetite), felt fatigued and got my anxiety levels under control, though was completely obsessed with platelet counts. Coming off the exchanges and then leaving hospital was both fantastic though equally worrying in terms of what might happen. My family and I had been apart for weeks and I knew that this had been a distressing and worrying time for them. The care regime post episode and my role in the trial meant (which meant self-administering the trial injections) that I felt confident that if relapse did happen that the care and support was there. I was off work for 6 weeks after discharge and was supported in a phased return – this support meant that I could fully recuperate and begin to get used to living with the aftermath of aTTP. For me, the challenge of moving on with my life was facilitated by my family & friends; the tremendous care and support of the team at UCLH; and my caring employer. I also found solace in engaging with the TTP Network and other TTP patients. The ongoing 6 monthly check ups (and the follow ups with the research) have I believe been instrumental in helping me get on with my life and not become caught up in the what ifs and what might happen. This should not be taken as though I just shrugged it off, as that is not the case – weeks, months and years on from the episode I am still overly interested in my platelet and enzyme levels and I, like many other TTP patients, monitor bruises and rashes to make sure they do not progress into something more sinister.

I know that other surviving TTP patients and their families (and carers) experience ongoing impacts in their life:

- an episode can **cause shock to the patient and family**
- **distress, worry, stress and anxiety** for all involved with the patient, which does prolong
- some patients do **suffer relapse**, which can resurface/exacerbate anxiety
- some report a possible **relapse playing on their minds**
- some report TTP **affected their livelihood**, including access to benefits and challenges in getting on with their life
- living with TTP makes it **difficult and expensive to access life and health insurance**, which can cause worry and stress.

I consider myself very fortunate and especially so given that I know if TTP remains untreated up to 95% of cases end in death. With TTP there is a risk of stroke, neurological damage and damage to the kidneys – treatment and rehabilitation can help though if suffered then these complications will worsen and compound the life changing impact of TTP.

I can fully empathise with and understand how suffering from TTP can exacerbate feelings of anxiety and heighten the risk of common mental health conditions, such as anxiety, panic attacks and emotional distress. In some patients the trauma of the acute episode can trigger serious conditions, including PTSD.

For me suffering from TTP has been life changing and it opened my eyes to how fragile life, my life, is. It also reinforced how amazing our NHS is and how brilliant and innovative it is at treating such very rare diseases and exploring new treatments, such as through the Hercules trial. This and other factors are why I volunteered to support the TTP Network and felt obliged to provide this personal statement.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	I benefited from an exemplary level of care at UCLH. My experience of the combination of TTP treatments and procedures extended to: - **The vascular catheters** – insertion and removal was invasive; I suffered a fair bit of bleeding; and removal of them was uncomfortable and led to heightened anxiety. - **Plasma exchange** – I was sick during the first cycle and nauseous for the first few exchanges; the exchanges were many and lengthy though essential. - **Steroids** – were a necessity in the first week or so and dosage did seem to play havoc with my sleep and anxiety levels which were already quite elevated. - **Rituximab** – I did not suffer any negative effects of the dosage or any that I am aware of. I know that other patients do sometimes suffer allergic reactions. - **Hercules trial and Caplacizumab** – I opted to participate in the study and I fully complied with the self-administration of the trial drug. I did experience a nose bleed and excessive bleeding (from incision due to catheter) during early administration, though as it was a double-blind approach I cannot vouch as to whether I received the drug or placebo. What is clear though is that the treatment I received got me better and the combination of these procedures and treatments prevented the TTP getting worse; me suffering organ damage; stroke etc and gradually replenished my plasma and increased my platelet; red blood cell; and enzyme counts. The after care, immediately following the episode, which consisted of weekly check-ups was both necessary and reassuring – this made me slightly obsessive about platelets, red blood cell and enzyme counts though gave me confidence to get on with my life. I must add that the care at Darenth Valley hospital where I was admitted via A&E was also exceptional. The consultant haematologist was sighted on the signs of TTP, I believe in part to the work of Dr Scully in

	reaching out to this broader network of NHS clinicians. The way I was expedited from there to UCLH for further investigation was at the time scary though ultimately life-saving. I know that other patients under the care of the team at UCLH share similar sentiments to myself in terms of the quality of care. I do know however, that there is variation in care although I believe that there is now a specialist specification in place for the treatment of TTP, which should help to reduce any variation and ensure consistency of practice across Centres.
10. Is there an unmet need for patients with this condition?	It does seem from TTP patients in the UK that there is some variation in care and treatment. From what I am aware of some of the past unmet needs of patients have been met in part through the pursuit of clinicians treating TTP with care and deploying relevant and new treatments, such as Rituximab. Exploring new technologies and curative approaches to treat patients presenting with aTTP, such as through the Hercules trial enables patients to benefit without perhaps knowing that this was an unmet need. From my experience suffering from aTTP, whether I had an unmet need or not was a moot issue – the combination of treatment I received including either placebo or Caplacizumab alongside other care helped me to recover and get my health back. If I did receive an active drug in Caplacizumab (and indications were that I may have) then to me this establishes an un-met need that perhaps for me was met. The Hercules trial findings suggest that the intervention group did benefit from Caplacizumab and as such, given that not all TTP patients receive it as part of care this does represent an un-met need. Some patients state that extending standard care to include psychological support would satisfy an un-met need – this is I believe something which the NHS is acting upon and putting measures in place.

Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	Patients who receive Caplacizumab perceive that it enabled their platelet count to increase more rapidly; reduce the time or need for plasma exchange; mitigate any severe symptoms; and reduce time spent in hospital. Effective treatment of what is a very rare disease using this innovative technology, as part of a multi-treatment approach, according to the evidence, has a direct effect on a patient's physiological process and the pathogenesis of the disease. Perhaps just as important is the benefit this may have on patients; their families and carers well-being and psychological disposition. I suffered aTTP in 2016 and so think myself fortunate to have presented with disease at a time when the combination of treatments I received were standard operating practice at UCLH. I did not know any different though it is evident since I was diagnosed with TTP that progression of treatments for TTP had not changed since rituximab was introduced. From a patient perspective therefore, the possibility of a beneficial treatment which could form part of treatment for an acute episode or relapse of TTP is to be welcomed. It also brings potential benefits to the NHS in terms of mitigating risk of more severe symptoms; a reduced need perhaps for plasma exchange; plasma; and which could plausibly lead to these technologies being freed up for other clinical use.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	From my perspective as a patient, and my experience (admitting that I cannot be sure of being an active recipient of Caplacizumab) I do not necessarily perceive any disadvantages of the technology being appraised. Yes, I did suffer a nose bleed and bleeding from insertion of a vascular catheter. I recognise that there may be other identified or unidentified adverse events in response to the treatment. Other patients, like myself, recognise that such treatments may have side effects.

Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	If variation of treatment for TTP exists across the UK, then this could mean that there are groups of TTP patients who could benefit more from this technology being part of standard care for TTP. Given that Hercules trial and practice indicates benefits for the patient it seems logical that if absent from care then introducing it would mean an increase in benefit.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	The TTP network in its submission did indicate inequalities in that aTTP does seem to disproportionately impact on women, which could have impacts in terms of caring duties if those women are typically the primary care giver. I know that studies have identified a risk associated with people from certain ethnicities.
Other issues	
15. Are there any other issues that you would like the committee to consider?	The evidence provided in the Hercules trial suggests a faster recovery for TTP patients treated with caplacizumab- the cumulative effect of this maybe worth considering in terms of: • reducing the demand of other therapeutics • freeing up the apheresis machines for other utilisation • potential reduction in bed use

	• potentially reduction in complications. I have mentioned earlier in my statement about the psychological impact that suffering from TTP has on people (the patient and families/carers). Whether this is in part caused by any physical damage to the brain and/or the trauma of the episode (or for some episodes) it can and does impact on the quality of a person(s) life; their well-being; are they are active in the labour market; and it may cause or contribute towards poor mental health, which could mean people use the NHS and/or other public services for support, therapy and/or treatment. Information like this is, I know, not always to straightforward to collect and utilise though these are the sort of impacts that disease like TTP have on people and need to be factored in when considering how to care and treat. Whilst recognising the Committee can only consider what is currently available there maybe unpublished findings from follow up that indicate other yet unreported benefits to patients in the longer term.
Topic-specific questions	
16. [To be added by technical team if required, after receiving the company submission. For example, if the company has deviated from the scope (particularly with respect to comparators) – check whether	

this is appropriate. Ask specific, targeted questions such as “Is comparator X [excluded from company submission] considered to be established clinical practice in the NHS for treating [condition Y]?”] **if not delete highlighted rows and renumber below**	

Key messages

17. In up to 5 bullet points, please summarise the key messages of your statement:

- Acquired TTP is a very rare life-threatening disease, which can manifest itself very subtly and lead rapidly to severe symptoms, including death (95% of cases will result in death if untreated?)
- TTP can have lasting physical and psychological impacts and living with TTP requires regular check-ups, which whilst reassuring can also trigger worry, anxiety and unease in patients and their families/carers
- Patients will/do benefit from a combination of treatment through blood/plasma infusion; plasma exchange; steroids; rituximab and caplacizumab (in an appropriate specialised centre)
- Patients suffering TTP need to know that the NHS has the relevant treatments, its clinicians believe in and evidence demonstrate is effective, at their disposal to prevent serious symptoms of the disease; mitigate organ damage; and facilitate recovery

- Patients recovering from and living with TTP could benefit from advances in treatment through speedier recovery, less time in hospital; and fewer plasma exchanges – these factors also have other potential benefits to the health and social care system

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

Caplacizumab for treating adults experiencing an episode of acquired thrombotic thrombocytopenic purpura [ID1185]

A Single Technology Appraisal

Produced by

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Author Contributions:	
Caroline Farmer	Project lead, critical appraisal of the company submission, writing and editorial input
David A. Scott	Critical appraisal of the economic evidence, checked and re-analysed the economic model, and carried out further scenario analyses
Justin Matthews	Critical appraisal of the statistical/clinical evidence
Linda Long	Critical appraisal of the clinical background (disease and treatment pathway) and clinical evidence
Sophie Robinson	Critical appraisal of the literature search strategies and developing and running additional ERG literature searches
Michael Desmond Creagh	Clinical advice and review of draft report
Sarah Allford	Clinical advice and review of draft report
Amanda Clark	Clinical advice and review of draft report
Louise Crathorne	Critical appraisal of the company submission, writing and editorial input, and co-supervised the final report
G.J. Melendez-Torres	Critical appraisal of the company submission, writing and editorial input, and co-supervised the final report. Guarantor of the report.

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Abbreviations

AE	adverse event
ADA	anti-drug antibody
ADAMTS13	a Disintegrin with Metalloproteinase with Thrombospondin Type 1 motif, member 13
AE	adverse event
Ag	silver
aHUS	atypical haemolytic uremic syndrome
AMI	acute myocardial infarction
aTTP	acquired thrombotic thrombocytopenic purpura
BDI	beck depression inventory
BNP	brain natriuertic peptide
CAPLA	caplacizumab
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CNTB	Computerised Neuropsychological Test Battery
CPT-3	continuous performance test
CS	company submission
CT	computed tomography
DAT	direct antiglobulin test
DB	double-blind
DSMB	data and safety monitoring board
DVT	deep vein thrombosis
ECG	electrocardiogram
EMA	European Medicines Agency
EQ-5D	EuroQol five dimension
ERG	Evidence Review Group
FBC	full blood count
FLei 5	Fragebogen zur subjektiven Einschatzung der geistigen Leistungsfahigkeit German questionnaire for complaints of cognitive disturbance
FU	follow up
GCS	Glasgow coma score
GI	gastrointestinal
GP	general practitioner
HIT	headache impact test
HIV	human immunodeficiency virus

HR	hazard ratio
HRQoL	health-related quality of life
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IDS-SR	inventory of depressive symptomatology (self-report)
ITT	Intention-to-treat
IV	intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
KM	Kaplan-Meier
L	litre
LDH	lactate dehydrogenase
LFTs	liver function tests
LMWH	Low molecular weight heparin
LY	life years
MAHA	microangiopathic haemolytic anaemia
MCMC	Markov Chain Monte Carlo
MM	medical monitor
MoCA	Montreal cognitive assessment
NA	not applicable
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	network meta-analysis
NR	not reported
OD	once daily
OWSA	one-way sensitivity analysis
PAS	patient access scheme
PE	pulmonary embolism
PEX	plasma exchange
PO	oral
PSA	probabilistic sensitivity analysis
PTSD	post traumatic stress disorder
QA	quality assessment
QALY	quality adjusted life year

RBANS	Repeatable battery for the assessment of neuropsychological states
RCT	randomised controlled trial
RICO	ristocetin cofactor activity
RR	relative risk
RTX	Rituximab
S/D FFP	solvent/detergent-treated fresh frozen plasma
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SF-36	36-item short-form
SG	standard gamble
SIRS	systemic inflammatory response syndrome
SLR	systematic literature review
SMMSE	standardised mini mental state examination
SMQ	standardised MedDRA queries
SoC	standard of care
TA	Technology Appraisal
TEAE	treatment emergent adverse event
TFT	thyroid function test
TIA	transient ischaemic attack
TTO	time trade off
TTP	thrombotic thrombocytopenic purpura
U+E	urea and electrolytes test
ULN	upper limit of normal
vs	versus
vWF	von-Willebrand factor
WTP	willingness to pay

1. EXECUTIVE SUMMARY

1.1. Critique of the decision problem in the company's submission

The decision problem presented by the company matched substantially the decision problem in the NICE scope. Evidence presented related to adults experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), and compared caplacizumab in addition to standard of care (SoC), which was considered to be plasma exchange (PEX) and immunosuppression, against SoC alone. Immunosuppression included steroids and, as prescribed, rituximab. Outcomes presented in the company's decision problem matched those in the NICE scope, though evidence relating to health-related quality of life and neuro-psychological outcomes were not included in the relevant trial evidence and were thus not presented. Scoped outcomes included change in cognitive function, mortality, major thromboembolic events, disease recurrence, reduction in time to recovery, time to platelet count response, other TTP-related events, length of hospital stay, volume and frequency of PEX and adverse events of treatment. The population, intervention and comparator matched the EMA licence granted for caplacizumab.

Additional comparators were scoped for a subgroup of patients with 'severe refractory acquired TTP', but this subgroup was not included in the company's submission. This was because the company asserted that the subgroup was not clinically identifiable at presentation and there was a lack of evidence.

Other relevant factors discussed by the company and relevant to the decision problem include innovation, end-of-life criteria and equality. The company asserted that caplacizumab is innovative and that while it does not formally meet end-of-life criteria, its use is believed to extend life in the context of a life-threatening disease. The ERG noted that this statement, while plausible, was not supported by specific evidence. Equality issues relate to the difference in care between specialist and non-specialist centres, and the disproportionate disease burden carried by people of Afro-Caribbean descent and by people living with HIV.

1.2. Summary of clinical effectiveness evidence submitted by the company

The clinical effectiveness evidence submitted by the company included a systematic literature review and the two trials that were located through this review: HERCULES and TITAN. Both trials tested the effectiveness of caplacizumab against SoC, to include PEX, immunosuppression and where indicated, rituximab.

The company noted that due to issues with the conduct of TITAN, it was not used for EMA decision-making; the ERG's own assessment of quality coincided and thus TITAN was not presented in depth. An integrated data analysis incorporating TITAN and HERCULES was presented. The ERG did not regard that this integrated data analysis was probative given the inclusion of TITAN in these estimates and ERG concerns relating to inconsistencies in the methods and data sources underlying the integrated data analysis.

Follow-up in HERCULES ran for 28 days after an initial treatment period conicident with PEX and an additional 30 days of study drug. This meant that follow-up was variable between patients and between treatment arms, as total time under follow-up was related to total days receiving daily PEX. Statistical methods used in analysis of real outcomes were broadly appropriate, though a number of ambiguities and analytic decisions, including in respect of censoring, taken by the company raise questions about the trustworthiness of the results.

On the whole, the ERG regarded that HERCULES yielded reasonable evidence that as compared to SoC, caplacizumab is effective at reducing time to normalisation of platelet count, the trial's primary outcome (HR=1.55, 95% CI [1.09, 2.19]), reduced the volume and frequency of plasma exchange (days of PEX therapy MD=-3.60, 95% CI [-5.49, -1.71]), and reduced the length of days spent in ICU (MD=-6.3, 95%CI [-10.77, -1.83]).

However, evidence for other outcomes presented, including major thromboembolic events (8% in both arms) and cognitive function (no difference between arms), was less convincing. Overall risk of recurrence was lower in caplacizumab than in SoC, though the estimate of difference between arms varied by specfic definition of recurrence used. Mortality was sparse, with only four deaths recorded; the only death in the caplacizumab arm occurred during follow-up.

Subgroup analyses for selected outcomes stratified by ADAMTS13 at baseline, previous episode and severity of disease did not yield convincing evidence of effect modification.

1.3. Summary of the ERG's critique of clinical effectiveness evidence submitted

Methods for the SLR were reasonable and the ERG agreed that it was unlikely any further studies would have been found.

While the ERG agreed with the company's assessment of TITAN and thus did not present this trial in depth, the ERG's quality assessment of HERCULES also noted several important issues with the trial, including a high number of protocol deviations, though the cumulative impact and

direction of that impact on effectiveness estimates remains uncertain. In addition, while the ERG agreed that trial analysis methods were reasonable, the ERG highlighted a number of ambiguities and inconsistencies in trial analysis methods, including the use of censoring to account for treatment switching, that while individually may not have had a major impact on counts of events (e.g. censoring only affected a small number of events across outcomes), might collectively alter the reliability of presented analyses. Moreover, inconsistencies in outcome data between different sources of evidence presented to the ERG led to more general concerns about the trustworthiness of effect estimates. In particular, definitions of recurrence of disease, which included exacerbation as an 'earlier' recurrence than relapse, meant that a comparison of all recurrences between arms might obscure meaningful differences between arms in types of recurrence.

Finally, the ERG noted that follow-up in HERCULES was short term, which the ERG regarded as a salient issue for decision-making given the potential long-term impacts of caplacizumab and the possibility for late relapse. In addition, the size of the trials meant that estimation of some key outcomes, including mortality, was highly uncertain and was hampered by sparse data. The lack of data on health-related quality of life and neuro-psychological impacts, while understandable in the acute phase of the trial where obtaining these data would have been challenging, was of concern given that collecting these data in the follow-up period was likely more feasible. Collectively, the impact of these limitations is that key outcomes from HERCULES were not used to inform economic modelling.

1.4. Summary of cost effectiveness evidence submitted by the company

The company presented SLRs for previous cost-effectiveness analyses, measurement and evaluation of health effects and healthcare resource use and costs. A large-scale targeted literature review relating to the clinical burden of disease was included, and reported on the findings of 141 studies, from which data either from meta-analyses or specific studies were used to inform model parameters; an additional targeted literature review addressed surrogacy between outcomes reported in HERCULES and long-term model parameters. Across most reviews, criteria of relevance were applied to distinguish between different data sources, though these criteria were not explicitly stated. In addition, the proxy conditions considered across different reviews varied both in their nature and in the extent to which evidence from proxy conditions was considered relevant and usable.

Economic modelling by the company was presented as a *de novo* economic model. The ERG noted that this largely matched the reference case, though health-related quality of life data were not drawn from HERCULES and long-term benefits were derived using numerous assumptions. The economic model included a decision tree component and a long-term Markov model component. The decision tree component included the acute phase of illness. Patients either responded or were initially refractory before responding. They then have disease exacerbation or no exacerbation and patients alive at the end of the decision tree process progress to the lifetime Markov model. The long-term Markov component includes states for remission, where all patients start; relapse; and death. Remission included substates for cognitive impairment, neuropsychological impairment, both of these, and none of these. The decision tree model was informed by HERCULES in defining patients with disease recurrence, described as exacerbation. However, acute mortality estimates were drawn from the targeted literature reviews and comparison with a compassionate use scheme; that is, HERCULES did not inform this model parameter. The Markov component was informed by estimates from the literature alone, as follow-up in HERCULES did not permit the trial to inform long-term impacts of caplacizumab.

The company's base case estimate yielded an ICER of £37,986, which was closely matched by estimates from probabilistic sensitivity analysis. One-way sensitivity analyses suggested that key parameters impacting cost-effectiveness were relative risk for mortality in remission, annual probability of relapse, caplacizumab treatment duration, relative risk of experiencing long-term mild cognitive impairment, and the utility multiplier for neurological symptoms (part of the remission health state). Scenario analyses also suggested that ICERs were sensitive to acute mortality.

1.5. Summary of the ERG's critique of cost effectiveness evidence submitted

In appraising the literature reviews submitted by the company, the ERG accepted that evidence was sparse and that the parameter estimates selected by the company from the literature were generally the best available, even if the data sources themselves were of poor quality. However, the use of seemingly arbitrary relevance criteria and inconsistency in application of proxy conditions cast doubt on the transparency of the procedures used.

The ERG identified several minor errors in procedure costs, and in uncertainty applied in the probabilistic sensitivity analyses. The probabilistic sensitivity analyses applied arbitrary and limited uncertainty around many parameters.

Because of the sparseness of data to inform model parameters and, indeed, the limited ability of HERCULES to inform the model even in the acute decision tree component, the base case is highly uncertain. Indeed, because the HERCULES data were in many respects deemed atypical of a UK population, economic modelling relied on literature-sourced estimates. This is most notable for acute mortality; the sparseness of data from HERCULES for mortality meant that a non-randomised comparison drawing from two different data sources—a meta-analysis and data opportunistically gathered as part of a compassionate use scheme—were crudely divided to estimate mortality. The ERG additionally identified issues with the use of ICU days as a surrogate for long-term complications, and re-calculated these estimates to provide more robust relative risks.

1.6. ERG commentary on the robustness of evidence submitted by the company

While acknowledging the challenges of generating and locating evidence for a rare disease, the limitations of HERCULES—and the limited use of HERCULES in the economic modelling—generate multiple areas of uncertainty.

1.6.1. Strengths

The ERG acknowledged that aTTP is a relatively rare condition, and thus the presentation of a randomised trial in this area was a strength. In addition, the structure of the economic model had good face validity, as acknowledged through clinical advice to the ERG.

1.6.2. Weaknesses and areas of uncertainty

Of the two trials presented, only one was considered probative for decision-making. This trial, HERCULES, had a number of inconsistencies and ambiguities in methods and presentation of results. However, the ERG was unable to conclude what the total impact of these issues would be on effect estimation.

In addition, the trial population did not match the expected UK population in several respects. First, the mismatch between high-quality care in a ‘controlled’ trial environment may not match the UK’s current service arrangement, nor might the narrow application of caplacizumab to the ‘stably unwell’, as was done in HERCULES, match its potentially broader use in the UK for a wider range of acuity of aTTP on presentation. Finally, the use of rituximab in HERCULES was lower than would be expected in the UK context, which may affect the actual benefit gained from caplacizumab in clinical practice.

As noted above, the company's economic model was highly uncertain. This was due to the relatively poor quality of available data to parameterise the model, as well as the limited contribution of HERCULES to informing model parameters. In several cases, model parameters were derived from the literature or from surrogate relationships in HERCULES, but the ERG could not reconstruct the chain of inference or had to generate corrected estimates. The ERG regarded that this uncertainty was not appropriately carried through in probabilistic sensitivity analyses.

1.7. Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG implemented corrections and validated the model. The ERG also developed its preferred base case. This base case included a higher rate of refractory disease in the SoC arm, based on clinical advice; a higher rate of rituximab use across both arms, based on UK registry data; separate relative risks for long-term complications and long-term mortality; higher resource use estimates for long-term complications; and higher resource use and resource costs for several parameters in the long-term phase of the model. This generated an ICER of £39,630 per QALY. The ERG also explored scenarios relating to clinical, cost and resource use and structural parameters.

2. BACKGROUND

Within Section B.1 of the company submission (CS, Document B), the company provides an overview of:

- caplacizumab, including its mode of action, dose and method of administration (CS, Document B, Section B.1.2);
- acquired thrombotic thrombocytopenia purpura (aTTP) including disease overview, burden of disease, clinical pathway of care, unmet clinical need (CS, Document B, Section B.1.3).

2.1. Critique of the company's description of underlying health problems

Thrombotic thrombocytopenic purpura (TTP) is a rare blood disorder characterised by the formation of platelet aggregates in small blood vessels resulting in red cell fragmentation and thrombocytopenia (thrombotic microangiopathy). It has an acute clinical onset with a classical pentad of symptoms and signs, although not all are always present – neurological changes, pyrexia, renal dysfunction, thrombocytopenia, and anaemia with fragmented red cells. Major bleeding problems are rare but petechiae are common. Neurological symptoms can include headache, confusion, altered consciousness, coma, seizures, hemiparesis and visual disturbances. TTP is a thrombotic microangiopathy caused by a deficiency of ADAMTS13 enzyme activity leading to persistence of ultra-large von Willebrand factor (UL-vWF) multimers that spontaneously capture platelets, resulting in microvascular thrombi. Patients remain at risk of tissue ischemia, organ damage and death.[1] The commonest cause of early death is due to the formation of platelet aggregation in the coronary circulation leading to arrhythmia, infarction and cardiac arrest.

TTP can either be congenital (due to an inherited deficiency of ADAMTS13) or acquired (due to an autoantibody directed deficiency of ADAMTS13). Acquired TTP (aTTP) may be associated with pregnancy, human immunodeficiency virus (HIV), and other autoimmune conditions such as systemic lupus erythematosus (SLE). Other forms of TMA that can mimic can also occur in malignancy or after bone marrow transplants (usually a different mechanism of disease with normal ADAMTS 13 or slight reduction). aTTP is an acute-onset disease of an episodic nature, carrying a lifetime risk of relapse.[1]

The company report estimates of 100–150 patients in England presenting with an acute episode of aTTP each year.[2] The upper end (n=150) of this is assumed by the company in its budget

impact analysis and the company noted that this is likely to be overestimated as this number will include patients with congenital TTP (5–10% of all TTP cases[2]) and children (2–5 children presenting per year[2]) (company Budget Impact Analysis, Section 3, p.6). UK registry data (Scully, 2008) estimated an incidence of six per million per year suggesting higher annual incidence, and the protocol for the UK TTP registry quoted 100 cases per year. The ERG noted that the estimate cited by the company falls between these two estimates but is at the lower end. Patients typically present to emergency care where rapid diagnosis and referral for specialist care is critical for survival. Failure to achieve rapid control of acute aTTP episodes can be fatal with mortality rates exceeding 90% if untreated.[1] Acute mortality improves with specialist care but can be as high as 50% in patients presenting to non-specialist centres.[2]

The company asserts that patients who survive the episode rarely recover in full due to long-term complications. These can include physical disability (e.g. loss of function from stroke) and psychological disability (e.g. permanent cognitive impairment from cerebral damage, post-traumatic stress disorder [PTSD], anxiety and depression), along with an increased risk of cardiac and renal failure and premature death. The company assert that the impact of these complications, and the unpredictable risk of relapse have a substantial impact on patient quality of life and on the lives of the patients' family, friends and carers. While not formally investigated to the ERG's knowledge, clinical advisors to the ERG concur with this assertion. Clinical advisors to the ERG highlight that the long-term psychological impact of surviving aTTP may not be accurately reflected in the trial data because of the absence of psychologists involved in relevant trial design /execution. The company asserted that cerebral damage and resulting cognitive impairment are shown to be particularly detrimental to patient's wellbeing and quality of life, and clinical advisors to the ERG are in agreement with this assertion.

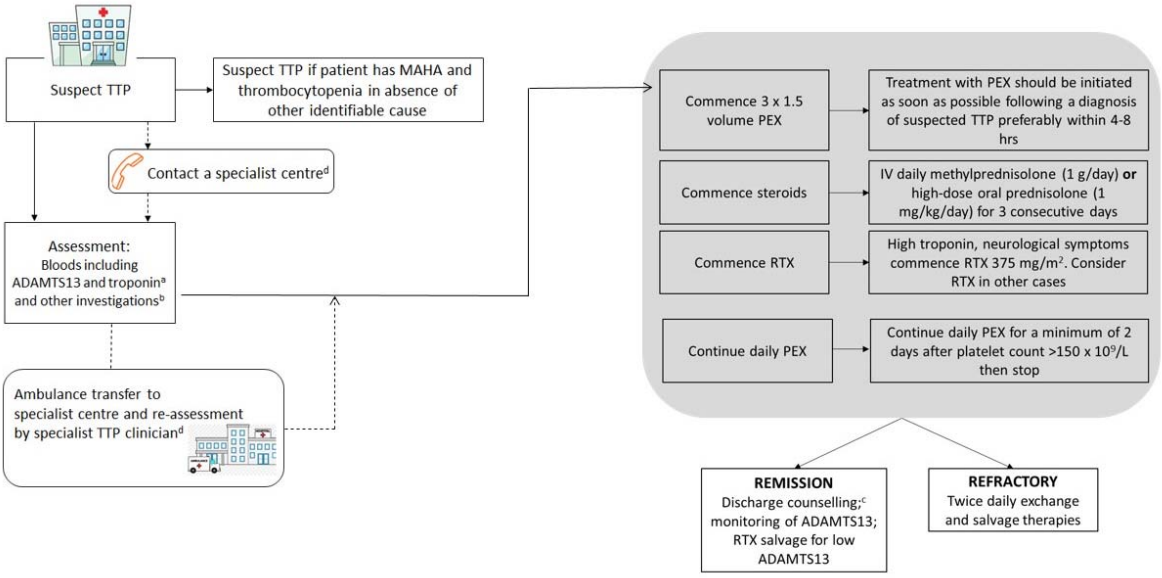
The ERG considered the CS to present an accurate overview of TTP that was relevant to the decision problem.

2.2. Critique of company's overview of current service provision

According to the British Committee for Standards in Haematology (BCSH) guidelines, diagnosis of aTTP should be confirmed through ADAMTS13 activity levels and anti-ADAMTS13 antibody detection.[1] Subsequent International Consensus Guidelines specify ADAMTS13 activity levels of <10% are diagnostic for TTP.[3] However, clinical advice to the ERG is that ADAMTS13 10-20% is a "grey area" over whether patients can be diagnosed with aTTP.

Current treatment guidelines from the BCSH provide guidance on the management of TTP and related thrombotic microangiopathies, defined by thrombocytopenia, microangiopathic haemolytic anaemia (MAHA) and small vessel thrombosis (Figure 1).[1] Clinical advisors to the ERG were not aware of other guidelines but highlighted that the 2012 guidelines are outdated as they don't refer to rituximab as part of emergency treatment which would now be regarded as part of standard care (SoC). The ERG's clinical advisors noted that the International Society of Thrombosis and Haemostasis (ISTH) guidelines are soon to be published, but noted that UK clinicians would currently follow the British Society of Haematology (BSH) guidelines (previously BCSH when the TTP guideline was written).

Figure 1: Summary treatment pathway for aTTP



Key: ADAMTS13, a Distntegrin and Metalloproteinase with a Thrombospondin Type 1 motif, member 13; CT, computed tomography; DAT, direct antiglobulin test; FBC, full blood count; HIV, human immunodeficiency virus; IV, intravenous; LDH, lactate dehydrogenase; LFTs, liver function tests; MAHA, microangiopathic haemolytic anaemia; PEX, plasma exchange, RTX, rituximab; S/D FFP, solvent/detergent-treated fresh frozen plasma; OD, once daily; RTX, rituximab; TFT, thyroid function test; TTP, thrombotic thrombocytopenia purpura;

Notes: a Take blood before starting PEX: FBC, blood film reticulocytes, clotting, fibrinogen, urea and electrolytes, troponin I/troponin T, LFTs, amylase, TFTs, calcium, LDH, pregnancy test, DAT, blood pressure, DAT, blood group with antibody screen, ADAMTS13, hepatitis A/B/C, HIV serology and autoantibody screen; b Other investigations should be performed promptly but can be delayed until after starting PEX: urinanalysis, stool culture (if diarrhoea), echocardiogram, CT brain (if neurological signs), and CT chest/abdomen/pelvis to check for underlying malignancy (if indicated); c Patients should be counselled about symptoms, signs and risk of relapse before discharge with verbal and written information; d If patient has not presented at a specialist centre

Source: Adapted from: Figure 1 in Scully et al., 2012[1]; Figure 1 NHS England Service Specification Thrombotic thrombocytopenic purpura (all ages)[2]; and input from the ERG's clinical advisors

Guidelines recommend that PEX should be started with three 1.5 plasma volume (PV) exchanges using solvent/detergent-treated plasma.[1] The volume of exchange can be reduced to 1.0 PV when the clinical and laboratory test results have stabilised.[1] Intensification in frequency and or volume of PEX procedures should be considered in life-threatening cases.[1] Daily PEX should continue for a minimum of two days after platelet count has been >150 x 10^9/l and then stopped.[1]

Steroids are widely used in combination with PEX in the initial treatment of aTTP. Guidelines recommend the use of intravenous (IV) daily methylprednisone (1 g/day for three consecutive days) or high-dose oral prednisolone (1 mg/kg/day for three consecutive days) in combination with PEX as an initial treatment.[4]

The ERG note that the company highlight that guidelines[1] recommend starting RTX if there is neurological or cardiac involvement. The ERG's clinical advisors noted that what constitutes neurological or cardiac involvement is not specifically defined, and highlighted that raised troponin has been associated with worse outcomes and that neurological involvement can vary from headache to coma with a full spectrum of symptoms in between. For patients with refractory or relapsing aTTP, rituximab (RTX) (unlicensed for this indication) may also be offered at a recommended dose of 375 mg/m^2 weekly for four weeks. Patients should be counselled about symptoms, signs and risk of relapse before discharge with verbal and written information.

The company reference an abstract reporting data from the UK TTP registry[5], and emphasise alignment with the BCSH guidelines. They also highlight trends of a reduced number of PEX treatments to remission and an increase in elective RTX use (2009 to 2018). In 2017-2018, the median number of PEX treatments to remission was eight (range: 3-65), RTX was used to treat 78% of acute episodes and elective RTX was used to treat 29% of sub-acute relapse cases (26/89).

On suspicion of a clinical diagnosis of aTTP (i.e. MAHA and thrombocytopenia in the absence of other identifiable cause), patients must be transferred to a treating centre urgently as delayed treatment can impact mortality. All patients should be initiated on PEX between four and eight hours of referral to a treating centre. In the UK, the company note that there are two highly specialist centres and a number of specialist centres with clinical expertise in aTTP. In areas of the country that are geographically distant from the specialist centres, patients typically present to emergency care units that may not be linked to a specialist centre. The company highlight

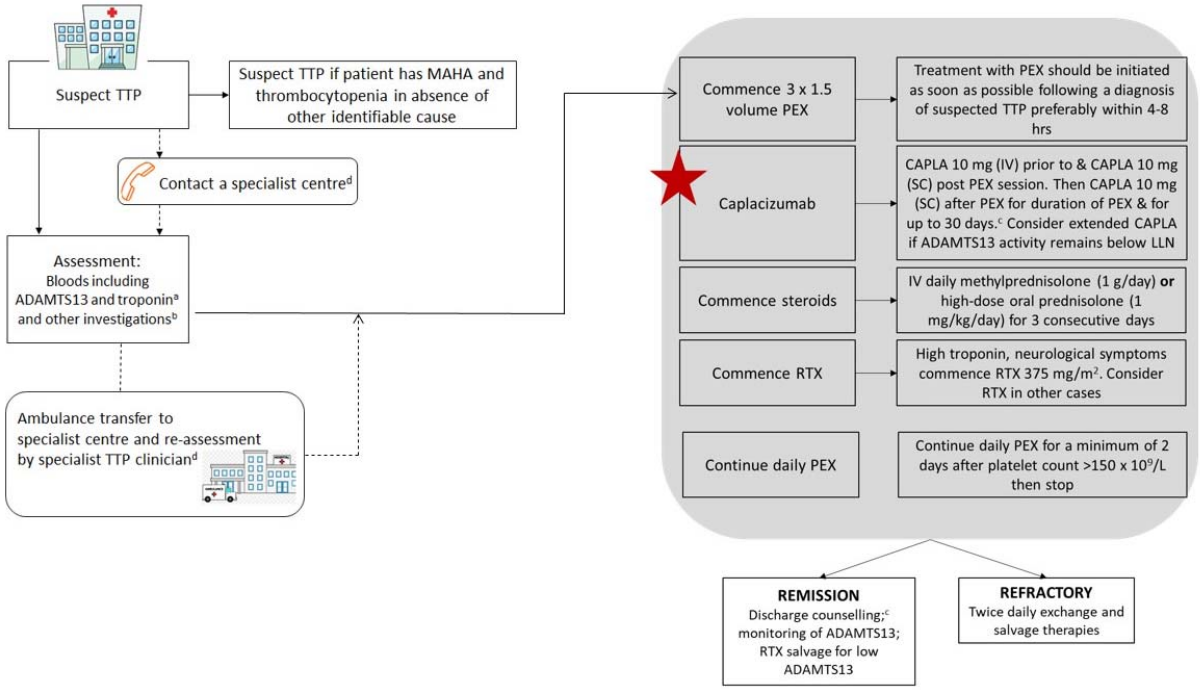
that NHSE are commissioning a highly specialised service for TTP patients to establish expert centres and clear pathways to improve outcomes. The company note that the proposed service will cover: “ongoing care and monitoring following the initial diagnosis of aTTP which is critical to the prevention of disease recurrence given it is not possible to predict which patients will relapse or when”. In current practice, patients formally referred to specialist centres receive follow-up care in line with BCSH guidance.[1]

Based on advice from its clinical experts, the ERG considers the CS to provide an accurate description of the current treatment algorithm for the management of people with aTTP, as depicted in Figure 1.

The company presents the positioning of caplacizumab as an adjunct to current standard of care (SoC) (PEX and immunosuppression) for adults experiencing an episode of aTTP (CS, Document B, p.21) (see also ERG’s representation of the proposed positioning in context of the current pathway in Figure 2). On confirmed diagnosis (ADAMTS13 <10%), a loading dose of 10 mg caplacizumab would be administered by IV injection prior to the next PEX session. Following that PEX session, a subcutaneous (SC) dose of 10 mg caplacizumab would be administered (so patients will receive two doses of caplacizumab on the day of initiation). Daily SC administration of 10 mg caplacizumab would continue after PEX for the duration of daily PEX and for a minimum of 30 days after the last daily PEX. The company note that if there is evidence of unresolved immunological disease, it is recommended to optimise the immunosuppression regimen and continue daily caplacizumab until the signs of underlying immunological disease are resolved (e.g. sustained normalisation of ADAMTS13 activity).

The ERG considered the company’s description of current service provision to be appropriate and relevant to the appraisal. The treatment pathway described in the CS was considered to be representative of clinical practice in the UK. However, clinical advice received by the ERG highlighted that rituximab is used as part of emergency treatment and is now regarded as part of standard care (SoC), and noted that published treatment guidelines (2012) do not reflect this. The ERG’s clinical advisors noted that current UK agreed guidance for caplacizumab usage (from the UK TTP Forum) fits with the company’s proposed positioning. However, clinical advice also acknowledged that in some cases, caplacizumab may be administered before confirmed diagnosis on the basis of clinician preference and clinical diagnosis before laboratory confirmation, in an effort to arrest further deterioration in patient condition.

Figure 2: Company positioning of caplacizumab



Key: ADAMTS13, a Distntegrin and Metalloproteinase with a Thrombospondin Type 1 motif, member 13; CAPLA, caplacizumab; CT, computed tomography; DAT, direct antiglobulin test; FBC, full blood count; HIV, human immunodeficiency virus; IV, intravenous; LDH, lactate dehydrogenase; LFTs, liver function tests; LLN, lower limit of normal; MAHA, microangiopathic haemolytic anaemia; PEX, plasma exchange, RTX, rituximab; S/D FFP, solvent/detergent-treated fresh frozen plasma; OD, once daily; RTX, rituximab; TFT, thyroid function test; TTP, thrombotic thrombocytopenia purpura; U + E, urea and electrolytes test; d If patient has not presented at a specialist centre

Notes: a Take blood before starting PEX: FBC, blood film reticulocytes, clotting, fibrinogen, U+R, troponin I/troponin T, LFTs, amylase, TFTs, calcium, LDH, pregnancy test, DAT, blood pressure, DAT, blood group with antibody screen, ADAMTS13, hepatitis A/B/C, HIV serology and autoantibody screen; b Other investigations should be performed promptly but can be delayed until after starting PEX: urinanalysis, stool culture (if diarrhea), echocardiogram, CT brain (if neurological signs), and CT chest/abdomen/pelvis to check for underlying malignancy (if indicated); c To continue after PEX for the duration of daily PEX and for up to 30 days after the last daily PEX. The company note that if there is evidence of unresolved immunological disease, it is recommended to optimise the immunosuppression regimen and continue daily caplacizumab until the signs of underlying immunological disease are resolved (e.g. sustained normalisation of ADAMTS13 activity); d Patients should be counselled about symptoms, signs and risk of relapse before discharge with verbal and written information

Source: Adapted from: Figure 1 in Scully et al., 2012[1]; Figure 1 NHS England Service Specification Thrombotic thrombocytopenic purpura (all ages)[2]; and input from the ERG's clinical advisors

2.3. Critique of Company's definition of decision problem

A critique of the company's definition of the decision problem is set out in Table 1 and subsequent sub-sections (Section 2.3.1to Section 2.3.5).

Table 1: Critique of company's decision problem

	Final scope	CS and company rationale if different from scope	ERG Comment
Population	Adults experiencing an episode of acquired thrombotic thrombocytopenic purpura	As per scope	As per scope; appropriate. See Section 2.3.1
Intervention	Caplacizumab in addition to PEX and immunosuppression	As per scope	As per scope; appropriate. See Section 2.3.2
Comparators	PEX therapy (with or without spun apheresis, steroids or RTX), without caplacizumab. For people with severe refractory acquired TTP, a combination of one or more of: PEX therapy (with or without spun apheresis, steroids, RTX, splenectomy, vincristine or immunosuppression e.g. cyclophosphamide) without caplacizumab.	PEX therapy (with or without spun apheresis, steroids or RTX), without caplacizumab **Rationale:** Refractory disease cannot be identified before treatment initiation and severe disease does not correlate to refractory disease. People with "severe refractory acquired TTP" does not therefore represent a group of patients that are clinically identifiable at presentation, and no clinical evidence is available specific to such a group.	The ERG regarded that this omission was justified on the basis of the evidence presented. The ERG clinical advisors noted that splenectomy, vincristine and cyclophosphamide are rarely used in routine practice in this population See Section 2.3.3
Outcomes	Change in cognitive function Mortality Major thromboembolic events Recurrence of disease Reduction of time-to-recovery Time to platelet count response TTP-related events Neuro-psychological impact (including depressive symptoms, anxiety and PTSD) following an episode Length of hospital stay Volume and frequency of PEX	As per scope	The following outcomes were not covered in the CS due to a lack of clinical trial data: HRQoL Neuro-psychological impact (including depressive symptoms, anxiety and PTSD) following an episode The company used a proxy approach in its model for both of these outcomes. Measures relating to reduction of time-to-recovery were considered to include principally reduction in days of PEX and volume of plasma used, though the outcome days of ICU was also considered informative.

	Final scope	CS and company rationale if different from scope	ERG Comment
	AEs of treatment HRQoL		Only the main outcome of the included trials, time to platelet response, was presented as time to event outcome. See Section 2.3.4
Subgroups	If evidence allows, subgroup analysis of people with severe refractory acquired TTP will be considered.	If evidence allows, subgroup analysis of people with severe refractory acquired TTP will be considered. **Rationale:** Evidence does not allow subgroup analysis of people with severe refractory acquired TTP, and this is not a clinically relevant population. ADAMTS13 activity <10% aligns with the modern UK diagnostic criteria for aTTP; this subgroup comprises 85% of patients enrolled to HERCULES.	As described above, the ERG regarded that the omission of patients with severe refractory disease was justified on the basis of the evidence presented, however the company did provide subgroup analysis based on disease severity, as based on a commonly used prognostic tool. Subgroup analysis based on ADAMTS threshold was considered to be informative. See Section 2.3.1

Key: CS, company submission; ERG, Evidence Review Group; PEX, plasma exchange; PTSD, post traumatic stress disorder; RTX, rituximab; TTP, thrombotic thrombocytopenia purpura

Source: Adapted from CS, Document B, Section B.1.1., Table 1

2.3.1. Population

The population defined in the NICE final scope is: “Adults experiencing an episode of acquired thrombotic thrombocytopenic purpura”.[6] The population defined in the final scope is consistent with the European Medicines Agency (EMA) marketing authorisation application (MAA) indication for caplacizumab: “Cablivi® (caplacizumab) is indicated for the treatment of adults experiencing an episode of aTTP”.[7]

The CS was consistent with the NICE final scope and the EMA licence. The evidence presented in the CS comprises the population in the pivotal trial (HERCULES); i.e. adults experiencing an episode of aTTP.

A subgroup of patients considered to have ‘severe refractory aTTP’ was specified in the NICE scope as a group of patients who may need special consideration, as they may receive more

intensive care (additional immunosuppressive therapy). Evidence for this subgroup was not presented as the company noted that this would be impossible to determine at presentation. The ERG agreed this was justified. However, the company presented a subgroup analysis of data from HERCULES for patients with less and more severe disease at baseline, according to the French severity score (defined as a score </≥3). Clinical advisors to the ERG noted that aTTP is a heterogenous disease, with variation in patient outcomes that are difficult to predict. Prognostic risk markers or tools, including the French severity score, intended to identify those patients at risk of complications may be crude and result in unreliable estimates; however, they are currently the best method for identifying these patients in clinical practice. Clinical advisors suggested that evidence of the effectiveness of caplacizumab according to baseline risk could be a useful means of informing the potential efficacy and use of caplacizumab in clinical practice. For example, it would be useful to understand if caplacizumab may be more cost-effective for use in only those patients considered to be of high risk.

At clarification, the ERG requested that the company provide a further scenario analysis in the economic model for the severe and less severe subgroups.

Following the response to clarification, the ERG considered the evidence provided by the company to sufficiently address the NICE scope.

The population considered in the trial evidence and the company's economic model is discussed further in Section 3.2.1.3 and Section 4.2.2, respectively.

2.3.2. Intervention

The intervention evaluated in the CS is caplacizumab (Cablvi®, Sanofi) delivered in addition to standard care, in line with its licensed indication. The dose and administration of caplacizumab was consistent with the way that it would be expected to be used in UK clinical practice.

Standard care consists of plasma exchange therapy (PEX), and the administration of immunosuppressive therapy as required. The administration of standard care and additional background care will be delivered alongside caplacizumab at the discretion of treating clinicians, and will vary according to patient need. Standard care is likely to be more intensive for those patients who are more severe, such as those patients who experience a delay in receiving treatment. Clinical advisors to the ERG advised that the availability of equipment for diagnosing aTTP and delivering PEX is limited to a few specialist centres in the UK, which may delay treatment for those patients who do present to other centres. A new NHS England (NHSE)

initiative to expand the number and coverage of specialist centres, aims to speed up diagnosis (education of relevant healthcare providers and provision of ring-fenced beds i.e. automatic admission to centres where the correct treatment can be delivered). While it is argued that specialist centres may provide better outcomes as has been observed for myocardial infarction and stroke specialist centres,[8] clinical advisors to the ERG commented that it may not eradicate delays in treating patients with aTTP in some areas of the UK, due to continuing delays in diagnosis and in access to specialist equipment. Patients treated in the company's pivotal trial (HERCULES) were primarily identified and treated in specialist centres (CS, Document B, Section B.3.10.2, p.159), and exhibited improved outcomes than those representative of UK clinical practice (see Section 3.2.1.3), potentially due to having received treatment sooner. It is therefore likely that the evidence presented in the CS does not represent the delivery of standard care that would be delivered alongside caplacizumab (for more discussion of this issue, see Section 3.2.1.4).

2.3.3. Comparators

The comparator described in the NICE scope is standard care, to include PEX and immunosuppressive therapy as required. While this comparator matched the clinical evidence presented, the ERG noted more general contextual concerns about the relevance of the evidence presented in the CS regarding standard care are described above (Section 2.3.2).

2.3.4. Outcomes

The company presented evidence for the majority of outcomes specified in the NICE scope. However, no evidence was presented for HRQoL or neuro-psychological impact (including depressive symptoms, anxiety and post-traumatic stress disorder [PTSD]).

The company stated that it was not possible to collect HRQoL at the time of the acute episode due to ethical concerns. Clinical advisors to the ERG agreed with the company that eliciting reliable HRQoL data from patients during the acute stage would not be ethical or possible. However, the ERG considered that HRQoL data measured at timepoints following the acute episode would have been both ethical and possible, and would have contributed meaningfully to this submission. As such, the ERG considered that the CS does not provide sufficient evidence for understanding the potential effect of caplacizumab on patients' HRQoL. Further, the company did not present evidence for the neuropsychological effects of aTTP, despite these outcomes being considered in the company's economic model (see Section 4.2.5). The ERG considered that the follow-up used in the HERCULES trial (28-days following the end of

treatment) may have been too short to capture the impact of aTTP on these outcomes. Clinical advisors to the ERG noted that experiencing an episode of aTTP, and coming to terms with the condition in the aftermath, may have a significant impact on patients' neuropsycological wellbeing. However, it is unclear to what extent treatment may impact on long-term neuropsychological impact; for example, treatment that reduces time in hospital may not eradicate the distressing impact of the admission and the diagnosis. The ERG therefore considered this to be a noteworthy gap in the evidence presented in this submission.

The ERG regarded, based on clinical advice, that evidence for reduction in time to recovery drew principally from reduction in days of PEX and volume of FFP, though additional outcomes presented, such as days in ICU, were informative for this outcome as well. The ERG considered that more time-to-event data would have been useful to address this outcome. The company provided time-to-event data for the trials' primary outcome (time to platelet count response); however, the ERG considered that time to event data for other measures of recovery (e.g. time to relapse, time to exacerbation) would have aided understanding of the efficacy of caplacizumab.

2.3.5. Other relevant factors

The company claims that caplacizumab is innovative in that is it the: "first licensed treatment specific to aTTP and has a unique mode of action that directly targets the pathologic mechanism of this disease." (CS, Document B, p.68). Since May 2018, caplacizumab has been supplied free of charge to specialist centres in the UK. The company noted in the CS that this has been in response to clinical demand (CS, Document B, p.68).

The company has submitted a patient access scheme (PAS) for a simple discount to the Department of Health. The proposed PAS price is equal to a discount of [redacted] from the list price (CS, Document B, p.15).

End-of-life criteria are not applicable for this appraisal. However, the company assert that "… caplacizumab meets additional survival and small population criteria" and should therefore "…be considered in the context of an acute, ultra-rare, life-threatening disease requiring highly specialised life-saving care where the willingness-to-pay (WTP) thresholds should arguably be increased compared to standard thresholds." The ERG regarded that this was a plausible assertion, but noted that the company did not systematically present evidence to support this.

The company claims there are several equality issues that need to be taken into account including:

- patients who present to non-specialist centres have delayed access to specialist care and may have less favourable outcomes at initial point of contact follow-up resulting in variable geoographic mortality risk. The company noted in the CS that this equality would be addressed by the proposed commissionning on a highly specialised haematology service (anticipated [redacted]) (CS, Document B, p.23).
- prevalence of aTTP is higher in people of Afro-Caribbean descent and in people with HIV which in conjunction with unequal service provision the company consider could lead to inequalities in care and levels of risk.

3. CLINICAL EFFECTIVENESS

3.1. Critique of the methods of review

3.1.1. Searches

The company presented a Medline search strategy for the clinical and cost effectiveness searches in response to a request from the ERG. This was a keyword search for the drug name caplacizumab with synonyms only. The results for this were very small but a filter (to exclude animal studies) was nevertheless applied.

In clarification the company presented search strategies for a variety of databases including Embase, Cochrane and Web of Science. Clinical trials registries and conference websites were also searched. These sources were searched until May 2019 and any more recent material would not have been identified.

3.1.2. Inclusion and exclusion criteria

The inclusion and exclusion criteria applied in the selection of evidence for the clinical effectiveness review, are detailed in the CS (refer to Table 2 below). To be included in the final evidence base, studies had to meet all of the inclusion criteria and none of the exclusion criteria.

Table 2: Eligibility criteria applied to identify efficacy and safety evidence

	Inclusion criteria	Exclusion criteria
Population	Patients of any age with a diagnosis of aTTP Where possible data was collected separately for the following subgroups of patients: • Adults (over the age of 18) and children • Use of rituximab (yes, no) • Prior aTTP episodes (yes, no) • Severity of ADAMTS13 activity (<10% vs ≥10%) • Patients with serious aTTP (defined by clinical score) • Refractory patients	Patients with a diagnosis of congenital or inherited TTP Patients with known causes of thrombocytopenia Patients with clinical evidence of enteric infection with E. coli 0157 or related organism Patients with a diagnosis of aHUS Patients with hematopoietic stem cell, bone marrow or organ transplantation-associated thrombotic microangiopathy Patients with known or suspected sepsis Patients with a diagnosis of disseminated intravascular coagulation
Intervention	Caplacizumab (of any length of treatment) alone or in combination with any other	-

	Inclusion criteria	Exclusion criteria
	therapy or standard of care.	
Comparators	Any other intervention or combination of interventions for the treatment of aTTP	-
Outcomes	Time to platelet count response Reduction of time-to-recovery, including: PEX days and frequency of PEX hospitalisation days ICU days Incidence of aTTP-related events, including: • Cardiac signs (e.g. arterial hypertension) • Renal impairment • Digestive issues (e.g. nausea, vomiting, diarrhoea, abdominal pain) • Non-specific weakness • Bleeding (e.g. menorrhagia, purpura, ecchymosis) • Fever • Neurological abnormalities • Change in ADAMTS13 activity • Recurrence/relapse • Exacerbation • Refractory TTP Time to normalisation of the following organ damage marker levels: • Time to LDH ≤ 1 x ULN • cTnI ≤ 1 x ULN • Serum creatinine ≤ 1 x ULN • Brain biomarker (S100β or NSE) Adverse events including: • Bleeding events • Treatment-emergent major thromboembolic event (e.g. stroke, transient ischaemic attack, myocardial infarction, cerebrovascular accident, pulmonary embolism or deep venous thrombosis) • Mortality (all cause and aTTP-related)	-

	Inclusion criteria	Exclusion criteria
	HRQL, including: • RBANS • HIT • MoCA • CPT-3 • Beck anxiety inventory • Beck depression inventory Long-term outcomes, including: • Headaches • Neurocognitive impairment • Depression • Arterial hypertension	
Study design	• Randomised controlled trials • Non-randomised comparative studies • Single arm studies for safety data • Systematic literature reviews	• Case reports • Case studies • News reports • Commentary • Editorials • Letters
Restrictions	• No date restriction • No language restriction	-

Key: aHUS, atypical haemolytic uremic syndrome; aTTP, acquired thrombotic thrombocytopenic purpura; CPT-3, continuous performance test; HIT, headache impact test; HRQL, health-related quality of life; ICU, intensive care unit; LDH, lactate dehydrogenase; MoCA, Montreal cognitive assessment; PEX, plasma exchange; RBANS, Repeatable battery for the assessment of neuropsychological status; ULN, upper limit of normal

Source: CS, Appendix D, Table 2, p.5

The specified eligibility criteria were considered broadly appropriate for the clinical literature.

Searches for efficacy and safety were conducted alongside searches for cost-effectiveness evidence. In total, 367 citations were identified through database searching and four citations were identified through other sources. Following de-duplication, 233 citations remained. At initial screening (based on title and abstract review), 188 citations were excluded as they clearly did not meet the eligibility criteria outlined in Table 2. Of the 45 citations accessed in full for further review, 41 met the eligibility criteria and made up the final evidence base (see CS, Appendix D, Table 3, p.9).

The company did not provide a table of excluded studies in the CS and so it is not possible for the ERG to review whether the reasons for excluding studies were justifiable. The ERG therefore cannot rule out the possibility that relevant data may have been excluded. However, given the small size of the evidence base in this patient group, this was judged by the ERG to be unlikely.

3.1.3. Critique of the screening process and data extraction

3.1.3.1. Screening

Details of screening are provided in Appendix D of the CS (p. 7-8). No details are given in the CS on how initial title and abstract screening and full text screening were conducted. Specifically, it was not stated by the company if more than one reviewer undertook screening for either screening stage or if a third reviewer was available to adjudicate in the event of disagreements. The ERG hence believe there is potential for screening to have been poorly conducted with the consequence that potentially relevant studies may have been missed.

The study selection process is summarised as a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram in Appendix D (p.8) of the company submission. In the CS, numbers of studies excluded by reason were provided, however a list of excluded studies was not provided as part of the CS.

The ERG judged that the process on study selection may not have followed appropriate methodological practice. A table of excluded studies was not provided by the company, so decreasing confidence in the appropriateness of decisions taken. The study selection process is summarised adequately however, and with no apparent discrepancies, as a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram (refer to CS, Appendix D).

3.1.3.2. Data extraction

Details of data extraction are provided in the CS (Appendix D).

The company provided details for data extraction which were in accord with accepted best practice as set out by CRD, University of York[9] (CS Appendix D, p. 5). Data from included studies were extracted by one reviewer and checked by a second independent reviewer, with reconciliation of any differences carried out by a third independent reviewer.

The ERG judged that the procedure for data extraction described in the CS (CS Appendix D, p.12) fulfilled accepted methodological practice, with specific details of data extraction criteria provided by the company which further increased confidence in the process.

3.1.4. Quality assessment

The quality assessment strategy for both HERCULES and TITAN used an appraisal tool based on the Centre for Reviews and Dissemination guidance for undertaking reviews in healthcare (CS, Appendix D.3, Table 5) as provided in NICE's template for company submission of evidence to the Single Technology Appraisal (STA) process.[10] The number of reviewers involved and whether judgments were checked or undertaken in duplicate was not stated. The ERG independently validated the company's assessment which, together with accompanying comments from the ERG is presented in Section 3.2.2.

The ERG considered that the CS included an appropriate quality assessment tool and provided judgements to support ratings. However, lack of detail on how the appraisal was carried out decreased confidence in the quality assessment strategy used.

3.1.5. Evidence synthesis

On p. 55 of CS Document B, the company note that an 'integrated summary of efficacy' was prepared. The methods for this are not stated in the CS. However, in the Integrated Summary of Efficacy[11] the company note that integrated data were analysed using primarily stratified Cochrane Mantel-Haenszel tests, with trial as the key stratification factor. A pooled hazard ratio for normalisation of platelet count was generated using a Cox proportional hazards model with a random effect, though for only two studies. The ERG regarded that the choice of these methods was reasonable, though as discussed in Section **Error! Reference source not found.**, their implementation remained opaque.

3.2. Critique of trials of the technology of interest, their analysis and interpretation

Two trials were presented by the company: HERCULES and TITAN. Because of major issues with the conduct and interpretation of TITAN (discussed in Sections 3.2.1.2 and 3.2.2 below), our critique and presentation of results focuses on HERCULES.

3.2.1. Methodology of included studies

3.2.1.1. Study design

The study designs for the studies included in the company's SLR of clinical effectiveness of evidence are summarised in Table 4 of CS Document B (p. 28). Key details are provided below in Table 3.

In summary, both HERCULES (Phase 3) and TITAN (Phase 2) were multicentre randomised controlled trials following similar study design – two-arm, 1:1 allocation, placebo-controlled trials where caplacizumab was administered with standard of care, to include PEX, corticosteroids and were indicated rituximab. Both trials assessed time to platelet count normalisation as the primary outcome. Randomisation in HERCULES was stratified according to severity of neurological involvement at baseline (GCS ≤12 vs. GCS 13-15); no stratification was used in TITAN.

The ERG noted that the designs of the two trials differ in relation to switching and as a consequence they represent different treatment pathways in the control arm. These designs differed in part because HERCULES built on learning from TITAN. In TITAN, the comparator is a pathway where patients are never offered caplacizumab, whereas the HERCULES comparator is a pathway where patients are offered caplacizumab should they experience a recurrence (a platelet decline requiring reinitiation of PEX). In HERCULES, initial treatment was double-blind, but caplacizumab was administered open-label when provided following recurrence. Open-label Caplacizumab was received by 28/145 (19.3%) patients in HERCULES; 2/72 from the Caplacizumab arm and 26/73 from the SoC arm. Data from the double-blind treatment period are presented for efficacy analyses in HERCULES; at clarification (Clarification Question A11) the company reported that resource use and safety endpoints included data from the open-label period (further information reported in Section 3.2.4).

Table 3: Summary of trial methodology

	HERCULES	TITAN
Trial periods	The study consisted of the following periods: 1. the study drug treatment period covering: a. the daily PEX treatment period b. the 30-day post-daily PEX treatment period	The study consisted of the following periods: 1. the study drug treatment period covering: a. the daily PEX treatment period b. the 30-day post-daily PEX treatment period

	HERCULES	TITAN
	2. the treatment extension period - 7-day treatment extensions up to 28 days 3. the follow-up period - 28 days after the end of study drug treatment	2. the follow-up period covering: a. 30 days after the end of study drug treatment for primary and secondary endpoints b. up to 1 year for relapses and other longer-term endpoints[a]
Intervention (n)	Caplacizumab (n=72) PEX Immunosuppression	Caplacizumab (n=36) PEX Additional treatment
Comparator (n)	SoC (n=73) SoC: as per caplacizumab but without the active ingredient PEX Immunosuppression Other immunosuppressive treatment: the use of other immunosuppressive treatment e.g. RTX was permitted per standard site practice	SoC (n=39) SoC: as per caplacizumab but without the active ingredient PEX Additional treatment: as per local practice and judged appropriate by the Investigator
Primary outcome	Time to platelet count response defined as recovery of platelets ≥150,000/uL with subsequent stop of daily PEX treatment within 5 days (i.e. initial recovery of platelet count).	Time to platelet count response defined as recovery of platelets ≥150,000/uL confirmed at 48 hours by a de novo measure of platelets ≥150,000/uL and LDH ≤2 x ULN (i.e. confirmed platelet response).

Key: LDH, lactate dehydrogenase; PEX, plasma exchange; RTX, rituximab; SoC, standard care; ULN, upper limit of normal

Source: CS, Document B, Table 4, p.28

3.2.1.2. Trial conduct

The ERG noted several key issues with trial conduct, the collective impact of which is to suggest that both HERCULES and TITAN have an elevated risk of bias, though the direction of this bias is unclear based on the information presented. Risk of bias is discussed further in Section 3.2.2. These issues related to: a) study-level protocol amendments, b) patient and study-level protocol deviations in both trials, and c) early stopping in TITAN.

Both HERCULES and TITAN had several protocol amendments. As noted by the company (CS, Document B, p.42), HERCULES protocol amendments included changes to the sequence of secondary endpoints; exclusion of patients with prior use of caplacizumab; changes to the

sample size and removal of an assessment from the schedule. The company did not discuss the other 'minor changes' implemented. The impact of these protocol changes on HERCULES risk of bias is unclear. However, TITAN included 12 protocol amendments, including switching the primary outcome, dosing and hospitalisation rules, and redefined exacerbation and relapse (CS, Document B, p.42).

In addition, HERCULES had an unusually high rate of protocol deviations at the patient level, affecting 44.1% of patients in the trial. The company claimed that these protocol deviations 'are not thought to materially impact the outcomes of the study', but this opinion was not substantiated; indeed, the inclusion of 21 patients who did not meet the selection criteria. In TITAN, 64.0% of patients had a major protocol deviation, including treatment non-compliance, affecting 38 patients in this trial.

At clarification, the ERG requested additional information on what constituted treatment non-compliance (Table 4). The majority of treatment non-compliance protocol deviations related to an 'excursion of dosing time window' in TITAN.

Table 4: Treatment non-compliance protocol deviations in HERCULES and TITAN

	HERCULES		TITAN	
	CAPLA (n=72)	**SoC (n=73)**	**CAPLA (n=36)**	**SoC (n=39)**
Patients with a treatment non-compliance protocol deviation, n	15	21	19	19
Missed daily PEX (HERCULES) and/or had an excursion of dosing time window (TITAN), n	[redacted]	[redacted]	[redacted]	[redacted]
Daily PEX not continued for at least 2 days after platelet count normalisation, n	[redacted]	[redacted]	[redacted]	[redacted]
Study drug administration interrupted, n	[redacted]	[redacted]	[redacted]	[redacted]
Incorrect storage conditions for study drug, n	[redacted]	[redacted]	[redacted]	[redacted]
Administration of the wrong study drug dose, n	[redacted]	[redacted]	[redacted]	[redacted]
Use of the wrong route of administration, n	[redacted]	[redacted]	[redacted]	[redacted]
Administration of the wrong study drug, n	[redacted]	[redacted]	[redacted]	[redacted]
Received two doses of study drug in error, n	[redacted]	[redacted]	[redacted]	[redacted]

Key: CAPLA< caplacizumab; PEX, plasma Exchange; SoC, standard care

Source: Clarification Response A13, Table 3.

In addition, the company noted several major study-level issues with protocol deviations in TITAN (CS, Document B, p.43). These primarily related to unreliable laboratory practice both centrally and locally (at study sites), and would thus be expected to impact key study outcomes such as time to platelet response. The impact of these issues is plausibly to bias the estimate of treatment effect but the direction is unclear.

Finally, TITAN was stopped early due to low recruitment rate. This means that the planned sample size was not reached (CS, Document B, p.47). Again, the impact of these issues is plausibly to bias the estimate of treatment effect but the direction is unclear.

3.2.1.3. Population characteristics and generalisability to the UK context

Overall, eligibility criteria for the two included trials were consistent with the NICE scope and the intended patient population for caplacizumab. Full inclusion and exclusion criteria are described in Table 4 of CS Document B (p.28).

The ERG noted, however, that several eligibility criteria that may affect the generalisability of the trial populations to the UK. Firstly, the company noted that those patients included in the trials were at lower risk at baseline than the UK aTTP population, due to eligibility criteria for patients to be the “stably unwell” (CS, Document B, p.73). Criteria therefore excluded those patients who were at imminent and/or high risk of death on admission. Due to requirements for consent to participate in the trial, patients who were in a coma or were unconscious (and, in the case of HERCULES, could not provide consent by proxy) may have also been omitted from the trial. The disparity between the trial populations and the UK population is evident in the outcomes of the trial, where mortality and response rates varied widely from UK population data, and the expectation of clinical advisors to the company and the ERG. As discussed in Section 3.2.1.3, the disparity between the trial populations and the UK population may also be explained by the role of specialist centres in the recruitment and treatment of patients (CS, Document B, p.159). As there is no other evidence evaluating caplacizumab in a broader population of patients with aTTP, it is unclear how the evidence from the included trials can be generalised to the UK population; however, it is likely that the inclusion of patients at higher risk at baseline would increase rates of mortality and adverse events. It is unclear whether caplacizumab is likely to be more or less effective in patients excluded from the trials. Clinical advice to the ERG was conflicting as to whether the mechanism of action of Caplacizumab would vary in sicker patients, and the ERG was not aware of any empirical evidence investigating this. While there remains considerable uncertainty about this, without evidence to the contrary, the ERG opted to

calculate relative treatment effect estimates for each of the clinical outcomes. In its assessment, the ERG preferred to use the calculated relative treatment effect estimate over the absolute treatment effect estimates provided by the company.

A further discrepancy between the trial and inclusion criteria was the diagnostic criteria used, which varied with UK clinical practice. In the UK, aTTP is diagnosed when ADAMTS13 is below 10%, whereas this criterion was not used universally in the participating centres. This would allow for the inclusion of patients with an improved prognosis in the trials, and who would not be eligible for caplacizumab in the UK. There were 13/72 (18.1%) patients in the caplacizumab arm and 7/73 (9.6%) of patients in the SoC arm with ADAMTS13 ≥10% at baseline, which may be a sufficient number of patients to affect generalisability of the treatment effect if treatment with caplacizumab was thought to work differently in these patients. A subgroup analysis provided by the company (discussed in Section 3.2.5.12) shows some variation in treatment effect between the groups. However, this analysis was inconclusive, and based on clinical advice, the ERG was not concerned that this factor alone would bias effect estimation.

All patients included in HERCULES were required to have received one PEX treatment prior to randomisation; the ERG requested information at clarification about the number of PEX treatments received prior to randomisation in HERCULES. This inclusion criterion was adopted in TITAN after a protocol amendment (CS, Document B, p.29), although Table 5 in the CS (Document B, p.39) reports that only 8% (6/75) of patients in TITAN received PEX prior to randomisation. The company note (CS, Document B, p. 62) that patients who receive PEX prior to randomisation are likely to have improved outcomes, as the most unwell patients may have died before randomisation.

Finally, the ERG noted that that the trial population may be healthier in several respects as compared to a ‘standard’ patient population. Evidence from registry data cited in the CS (Document B, p.22) noted that in a French cohort of patients with aTTP, 17% experienced refractory disease; this was [redacted] in HERCULES PBO and 0% in the caplacizumab arm. The reasons for this are manifold, including protocol-led treatment in a trial context. While the company claims that introduction of a specialist centre will remedy any difference in outcomes between trial and UK practice, clinical advice received by the ERG suggested both that remediation of the difference is unlikely based on differences between a trial context and clinical practice. Clinical advice also observed that specialist provision is largely in place currently and thus unlikely to change practice for many patients. Caplacizumab may also be used in a wider

range of patient profiles in clinical practice (i.e. beyond the “stably unwell”) and thus outcomes in practice may appear different than what is presented in the trial.

3.2.1.4. Intervention characteristics

The intervention characteristics used in the trials evaluating caplacizumab, as detailed in the CS (Document B, Table 4, p.31), are summarised below.

Intervention

The active intervention was caplacizumab. This was administered with a loading dose of 10 mg IV between six hours and 15 min before the first PEX after randomisation. Subsequent daily 10 mg doses of caplacizumab were administered SC after daily PEX treatment. This dosing schedule continued for 30 days after the conclusion of daily PEX treatment, but could be extended for 7-day periods up to 28 days when clinically indicated (i.e. based on disease activity). Caplacizumab was administered alongside standard of care, described below.

Comparator

Standard of care (SoC) consisted of daily PEX until at least two days after platelet count normalisation, in addition to immunosuppressant therapy. Immunosuppressants include steroids and RTX. In addition to steroids and RTX, a number of other immunosuppressants were given during HERCULES, such as mycophenolate mofetil, hydroxychloroquine, bortezomib, cyclophosphamide and ciclosporin; however, these are not expected to be used in clinical practice and the number of patients on these treatments was small (<5% across both treatment arms). Three patients in HERCULES received splenectomies; however this, again, is not standard practice in the UK.

The ERG considered that the dose and administration of caplacizumab used in HERCULES and TITAN is consistent with its licensed indications and how the treatment may be used in UK clinical practice.

The company did not plan or conduct analyses to investigate how RTX may moderate the effectiveness of caplacizumab on measured trial outcomes. RTX use is lower in the HERCULES trial population (43% in the trial population) compared to what would be expected in clinical practice in the UK.[5] Therefore, assuming RTX improves outcomes, the ERG believe that potentially outcomes will be different in the trial population than would be seen in UK. It is of note that the company claim that higher RTX use in the comparator arm compared to the

intervention arm in HERCULES would disadvantage caplacizumab; however, this was not clearly evidenced (CS, Document B, p.72).

3.2.1.5. Outcome assessment

Clinical advisors to the ERG advised that the outcomes evaluated by the two included trials generally encompassed all of the key outcomes for evaluating the efficacy of caplacizumab. Additional outcomes considered by advisors to be important to evaluating the effectiveness of treatment in this population included HRQoL, patient-reported and carer-reported outcomes. In particular, the ERG noted that measures of neuro-psychological impact (specified in the NICE scope and including PTSD, depression and anxiety), which are all potential consequences of an acute aTTP episode, were missing. The ERG noted that the acute episode of aTTP may have a significant impact on carers, who may also be expected to administer treatment with caplacizumab following discharge; yet these outcome data, if they exist, were not made available to the ERG.

Generally, the ERG were concerned that the length of follow-up used in both trials as submitted by the company would be insufficient for evaluating the efficacy of caplacizumab. HERCULES follow-up was 28 days following the end of treatment, while TITAN follow-up was one year (although due to trial termination, limited data was available at the one-year timepoint). The International Consensus definition of relapse requires a follow-up period of greater than 30 days after stopping treatment with PEX[3], and was only evaluated at the one-year follow-up for TITAN. Further, as described in Section 3.2.1.2, due to the early termination of TITAN, relapse data at one year are incomplete for half of patients (CS, Document B, Section B.1.4.3). Another key issue relating to outcome assessment and follow-up is the use of variable follow-up times in HERCULES. Because the follow-up times are linked to duration of study drug treatment (as noted in the company's response to clarification Question A10; seven and 28 days after conclusion of study drug), study outcomes that are not linked to time-to-event thus conceivably have structurally different follow-up times between arms. Indeed, in Table 14.1.2.9 of the HERCULES CSR (p.430), total treatment duration appears different between arms in the double-blind period [redacted]. This suggests that different arms experienced different 'potential time' for events to accrue.

In conclusion, the ERG considered that the included trials were able to capture the principal outcomes required to evaluate caplacizumab in the acute stage (up to four weeks), but that the

evidence does not provide reliable evidence of the potential effect of caplacizumab after this time.

Outcome definitions

Definitions for the outcomes measured in the included trials were reported in the CS (Document B, Table 4, p32-34). However, the ERG found the definitions for outcomes related to disease recurrence were not well documented in the CS, specifically that they lacked clarity. Due to overlap between these outcomes, and some change in terminology used to define the outcomes for the company's economic model, the ERG considered greater clarity to be useful, and so at clarfication the ERG requested that the company provide further detail about the way outcomes were defined in the included trials. This information is incorporated in Table 5.

Aside from concerns about the short length of follow-up used in the trials, as mentioned above, the ERG generally considered outcome definitions used by the company to be acceptable. In the economic model, "relapse" was re-defined as "late exacerbation", to account for the short follow-up (Section 4.2.5.1). Methods for determining whether adverse events were 'treatment-emergent' were not described in the CS. Finally, at clarification, the company clarified that length of hospitalisation, as measured in the HERCULES trial, included days spent in ICU.

Table 5: Outcome definitions used in the included trials

Outcome		HERCULES	TITAN
Change in cognitive function		Proportion of patients with neurological symptoms based on neurological assessment (assessment unclear) Cognitive mental status as measured by the SMMSE	Change in cognitive function as measured by a change in GCS and scores on the neurocognitive battery (CNTB)
Mortality		All-cause mortality TTP-related mortality	All-cause mortality
Major thromboembolic events		Incidence of treatment-emergent thromboembolic event (assessment unclear)	Incidence of major thromboembolic events
Recurrence of disease	Exacerbation	Recurrent thrombocytopenia following platelet count response requiring a re-initiation of daily PEX therapy within 30 days after the last daily PEX treatment	Recurrent thrombocytopenia following platelet count response requiring a re-initiation of daily PEX therapy within 30 days after the last daily PEX treatment
	Relapse	A de novo TTP episode requiring re-initiation of daily PEX therapy that occurs more than 30 days after the last daily PEX treatment	A de novo TTP episode requiring re-initiation of daily PEX that occurs more than 30 days after the last daily PEX treatment
	Recurrence	Umbrella term encompassing both exacerbation and relapse (as defined in the trial)	Umbrella term encompassing both exacerbation and relapse (as defined in the trial)
	'True' relapse	Definition not used as trials consider the acute phase only	Definition not used as trials consider the acute phase only
	Remission	NA	Complete remission after the initial course of daily plasma exchange (i.e. plasma exchange given for the presenting acquired TTP episode) is defined as confirmed normalization of the platelet count and absence of exacerbation[12]
	Refractory	Trial definition: An absence of platelet count doubling after 4 days of standard treatment and LDH >ULN (as per Benhamou et al. 2015[13]) International definition:	NA

Outcome		HERCULES	TITAN
		Lack of sustained platelet count increment or platelet counts <50 x 10^9/L (as per Scully et al 2017[3])	
Time to platelet count response		Time to platelet count response (recovery of platelets ≥150,000/uL with subsequent stop of daily PEX treatment within 5 days [i.e. initial recovery of platelet count])	Time to platelet count response (recovery of platelets ≥150,000/uL confirmed at 48 hours by a de novo measure of platelets ≥150,000/uL and LDH ≤2 x ULN [i.e. confirmed platelet response])
TTP-related events		Proportion of patients with treatment-emergent clinically significant TTP-related events Proportion of treatment-emergent clinically significant TTP-related events	Resolution of improvement of TTP-related signs and symptoms, as measured by physical examination and as AEs
Length of hospital stay		Number of days in ICU Number of days in hospital (including ICU stay)	NA
Volume and frequency of plasma exchange		Total volume of plasma administered from randomisation Number of days of daily PEX treatment from randomisation	Number of daily PEX sessions Number of days of daily PEX treatment from randomisation Total volume of plasma administered
AEs of treatment		Incidence of AEs, SAEs, laboratory data, vital signs, ECG, and physical examinations Bleeding events	Incidence of PEX treatment-related AEs Incidence of caplacizumab treatment-emergent AEs and relationship to study drug Bleeding events

Key: AEs, adverse events; CNTB, Computerised Neuropsychological Test Battery; ECG, electrocardiogram; ICU, intensive care unit; LDH, lactate dehydrogenase; NA, not applicable; PEX, plasma exchange; SAEs, serious adverse events; SMMSE, standardised mini-mental state examination; TTP, thrombotic thrombocytopenic purpura; ULN, upper limit of normal

Source: Clarification Response B5; TITAN CSR p. 60[14]; CS p. 33-34

3.2.2. Quality assessment

The ERG had regard to the quality assessment for both HERCULES and TITAN. While the company suggested that only TITAN was at high risk of bias, the ERG regarded that numerous items in the HERCULES trial suggest that risk of bias is higher than suggested by the company. The ERG agreed with the company that TITAN was at high risk of bias.

Presentation of quality assessment for HERCULES is in Table 6. While the ERG agreed that the randomisation was done to an appropriate standard, it remained unconvinced that the risk of bias from baseline imbalance in prognostic factors was against caplacizumab, as suggested by the company. This is partly due to the lack of an extensive epidemiological understanding of prognosis in aTTP, but also because of the presence of other baseline imbalances in ADAMTS13 activity between arms, with SoC having a higher proportion of patients with low activity. Because of an open-label phase of treatment, it is possible that uncensored data would have a high risk of bias from provider unblinding. Finally, the use of censoring to account for treatment switching is arguably inconsistent with an intention to treat approach.

An issue that is central to the risk of bias in HERCULES is the role of protocol deviations. The company notes that 44.1% of patients experienced a major protocol deviation (CS, Document B, p 47). While some evidence is presented by the company that these protocol violations do not affect study results, this conclusion is based on a per protocol analysis which unto itself may be susceptible to other sources of bias.

Table 6: Quality assessment of HERCULES

Risk of bias item	Company judgment	ERG judgment
Was randomisation carried out appropriately?	Yes	Yes
	Randomisation was assigned using a computerised randomisation schedule with stratification for severity of neurological involvement (GCS ≤12 vs GCS 13-15).	As noted by the company
Risk of bias	Low	Low
Was the concealment of treatment allocation adequate?	Yes	Yes
	Randomisation implemented via a centralised IVRS/IWRS	As noted by the company
Risk of bias	Low	Low
Were the groups similar at the outset of the study in terms of prognostic	No	No
	An imbalance is observed in the	As noted by the company

Risk of bias item	Company judgment	ERG judgment
factors?	nature of aTTP episode – more patients in the caplacizumab arm were having an initial aTTP episode.	There is also a potential imbalance in baseline ADAMTS13 activity, with a higher proportion in SoC having <10% [4]. The impact of these biases is unclear, though the ERG regards that risk of bias arising collectively from these imbalances is high.
Risk of bias	Against caplacizumab	High,
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	No
	Patients and investigators remained blinded to treatment allocation during the double-blind and open-label periods.	Care providers would not have been blind to treatment allocation during the open-label phase of treatment.
Risk of bias	Low	High, depending on outcome
Were there any unexpected imbalances in drop-outs between groups?	No	No
	Early discontinuation rates generally similar between groups. More patients in the SoC arm received open-label caplacizumab due to disease recurrence in the study treatment period – this was not unexpected.	As noted by the company
Risk of bias	Low	Low
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	As noted by the company
Risk of bias	Low	Low
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Unclear
	Primary efficacy analyses followed the ITT principal and included all patients assigned to treatment arms 'as treated'. Censoring methods were used to account for lack of event data in KM analyses. Missing data were only imputed for the endpoint of patients with refractory TTP.	The use of censoring as a statistical method to account for treatment switching may be a source of bias in this trial. While ITT was used to the extent that people were analysed in the arm to which they were randomised, the lack of more appropriate adjustment for treatment switching may form a source of bias. The ERG noted that the trial primary outcome, time to normalisation of platelet count, was unaffected by censoring.
Risk of bias	Low	Unclear
Are there any other	No	Yes

Risk of bias item	Company judgment	ERG judgment
potential concerns relating to quality?	-	As noted by the company, 44.1% of patients in HERCULES had a major protocol deviation (CS, Document B, p 47). These protocol deviations include enrolment of patients not meeting the selection criteria. While the company notes that the specific protocol violations were not considered by the EMA 'to materially impact the outcomes of the study' and present a per protocol analysis to support this, the impact of deviations remains unclear in its direction.
Risk of bias	Low	High

Key: ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aTTP, acquired thrombotic thrombocytopenic purpura; EMA, European Medicines Agency; ERG, Evidence Review Group; GCS, Glasgow Coma Scale; ITT, intention to treat; IVRS, interactive voice response system; IWRS, interactive web response system; KM, Kaplan-Meier; SoC, standard care; TTP, thrombotic thrombocytopenic purpura

Source: CS Table 5, Appendix D

Presentation of the quality assessment for TITAN is in Table 7. The ERG disagreed with the company that objective measurement of outcomes necessarily suggests a low risk of bias in terms of blinding to treatment allocation, as unblinding of allocation may influence other treatment decisions leading to a biased estimate of effect. The ERG agreed with the company that the numerous issues with protocol deviations suggest a high risk of bias in this trial. As a result, the ERG regard that TITAN is not suitable for decision-making in this context. Indeed, the EMA did not include TITAN in the summary of product characteristics for this reason, as acknowledged by the company (CS, Document B, p 47).

Table 7: Quality assessment of TITAN

Risk of bias item	Company judgment	ERG judgment
Was randomisation carried out appropriately?	Yes	Yes
	Randomisation was assigned using a computerised randomisation schedule.	As noted by the company
Risk of bias	Low	Low
Was the concealment of treatment allocation adequate?	Yes	Yes
	Randomisation implemented via a centralised IWRS.	As noted by the company

Risk of bias item	Company judgment	ERG judgment
Risk of bias	Low	Low
Were the groups similar at the outset of the study in terms of prognostic factors?	Unclear	No
	An imbalance is observed in cardiac marker levels and BNP – these are higher in the SoC arm.	As stated by the company Additionally, the caplacizumab group had a greater proportion of women than the SoC group.
Risk of bias	Unclear	Unclear
Were the care providers, participants and outcome assessors blind to treatment allocation?	No	No
	Only patients were blinded to treatment allocation, but outcomes were objectively measured.	As noted by the company Even if outcomes were objectively measured, unblinding of treatment allocation may influence other treatment decisions, biasing estimation of the treatment effect
Risk of bias	Low	High
Were there any unexpected imbalances in drop-outs between groups?	No	No
	Early discontinuation rates similar between groups.	As noted by the company
Risk of bias	Low	Low
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No
		No discussion was provided by the company, but there do not appear to be more outcomes measured than reported.
Risk of bias	Low	Low
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes
	Primary efficacy analyses followed the ITT principal and included all patients assigned to treatment arms 'as treated'. Censoring methods were used to account for lack of event data in KM analyses. Missing data were not imputed.	As noted by the company Unlike HERCULES, there was no evidence of treatment switching in this trial; in this case, censoring is a standard part of time-to-event analysis
Risk of bias	Low	Low

Risk of bias item	Company judgment	ERG judgment
Are there any other potential concerns relating to quality?	Yes	Yes
	Several issues relating to conduct were observed: The trial was terminated prematurely due to low enrolment There were 12 protocol amendments, including some major amendments There were issues with central and local laboratories There was a lot of missing data with the extent often not clear to the assessor Several important analyses were conducted post-hoc There was a high number of protocol deviations	As noted by the company In total, 64% of patients had a major protocol deviation in this trial (CS, Document B, p 47).
Risk of bias	High	High

Key: BNP, B-type natriuretic peptide; CS, company submission; ERG, Evidence review Group; ITT, intention to treat; KM, Kaplan-Meier; SoC, standard care

Source: CS Table 5, Appendix D

3.2.3. Baseline characteristics

3.2.3.1. Participant characteristics in the included trials

Patients included in the HERCULES criteria were aged between 18-79 years (mean 45 and 47 years for caplacizumab and SoC arms, respectively), were more likely to be female (100/145, 69.0%), and with a significant minority of patients of Black ethnicity (28/145, 19.3%). This is consistent with epidemiological data for the general aTTP population, where patients have a median age of patients of 43 years, are more likely to be female, and are disproportionately of Afro-Caribbean heritage (CS, p. 15-16, [5]).

Both of the included trials recruited patients worldwide, although three centres in the UK participated in the HERCULES trial (21/145, 14.5%) and one centre participated in TITAN (7/75, 9.3%).

[redacted] The company argues that this could lead to imbalance in

prognosis due to an increased delay in diagnosis for initial episodes (CS, Document B, p. 38). A total of [redacted] of patients had experienced one previous episode, [redacted] had experienced two previous episodes, and [redacted] had experienced more than two previous episodes. In TITAN, slightly more patients were experiencing their first TTP episode (68.0%; 51/75), with no detail provided on the breakdown of recurrent episodes.

Median platelet count of patients in HERCULES was 24k (range 3k – 133k), which was higher than reported for patients in TITAN [redacted]. Clinical advice to the ERG suggested that the reported platelet range was greater than would be typical for acute TTP but may represent the fact that [redacted] of participants in HERCULES and TITAN, respectively were relapses, thus facilitating earlier diagnosis. Clinical advisors to the ERG advised that levels of cardiac troponin (cTnI), lactate dehydrogenase (LDH), serum creatinine, brain natriuretic (BNP), and neuron-specific enolase (NSE) were consistent with expected levels for this population, and did not represent any risk to generalisability.

In HERCULES, 7.6% (11/145) of patients had moderate or severe brain injury (Glasgow Coma Score [GCS] ≤12) at baseline. This relatively low proportion likely reflects the trial's focus on the "stably unwell", to the exclusion of those unconscious or unstable on arrival. Those patients who were able to complete the standardised mini mental state examination (SMMSE) reported a median score consistent with normal cognition [redacted], although patient scores ranged the full length of the scale (range 0-30), indicating that at least one patient in each arm was found to have severe limitations in cognition at baseline. No GCS or SMMSE data were reported for patients in TITAN.

Clinical advice to the ERG reflected that rituximab use in HERCULES was lower than would be expected in clinical practice; 43.4% (63/145) of patients had received rituximab at baseline (CS, Document B, p.40), compared to an estimate of approximately 78% indicated in UK Registry data.[5] RTX is considered to be associated with improved outcomes in aTTP patients. The ERG's clinical advisors noted that, in the UK, rituximab would typically be added if raised troponin or neurological dysfunction were detected; however, this varies between clinicians (e.g. neurological dysfunction varies from headache to coma) and local protocol, ranging from use only in refractory patients to use in all aTTP patients. Other factors influencing rituximab use typically include severity or clinician preference. The ERG's clinical advisors commented that while historically there has been varied access to rituximab due to budget constraints, practice to use rituximab is becoming more widespread.

Other therapies received by patients throughout the trial were considered to be consistent with UK practice, with the exception of splenectomy, which was received by 7% of patients in the SoC arm of HERCULES (5/73) and has not been used to treat TTP in the UK since 1970.[15] No patients in the caplacizumab arm had received spenectomy at baseline.

3.2.3.2. Comparability between treatment arms at baseline and in concomitant treatments

Baseline characteristics in the included trials were generally comparable across reported characteristics, with several notable exceptions. In HERCULES, it was noted by the company that a higher proportion of patients in the caplacizumab arm were experiencing their first acute TTP episode. Clinical advisors to the ERG agree with the company that the imbalance in patients experiencing their first or subsequent episode of aTTP may indicate that patients in the caplacizumab arm may be at a higher risk of poorer outcomes. However they were unsure to what extent this would affect trial outcomes, and subgroup analysis of data from HERCULES reported in the trial CSR[16] did not show a difference in time to platelet count response or recurrence rate between patients experiencing their first or recurrent episode.

It was also noted that more patients in the caplacizumab arm (13/72, 18.1%) than the SoC arm (7/73, 9.6%) had ADAMTS13 ≥10% at baseline. Subgroup analysis reported in the CS appears to show that time to platelet count was faster in patients with ADAMTS13 ≥10%; however as the number of patients with ADAMTS13 ≥10% was small (n=20 across both trial arms) the ERG were uncertain as to how much this would affect overall treatment outcomes.

Imbalances in SoC use of concomitant treatments were also noted, with a higher proportion of patients in the SoC arm having received RTX as a concomitant therapy (48% vs. 39%), and a higher proportion of patients in the caplacizumab arm having received mycophenolate mofetil. As above, because the ERG's advisors also noted that RTX is associated with improved outcomes, this suggests a possible bias against caplacizumab. Moreover, as noted in Section 3.2.3.1, 7% of patients in the SoC arm had received a splenectomy compared to 0% in the caplacizumab arm. Overall, while the ERG noted these imbalances between treatment arms in HERCULES, it did not consider there to be evidence of a significant or consistent bias towards any trial arm. Clinical advisors to the ERG did not consider other imbalances to have significant impact on the trial results.

3.2.4. Description and critique of statistical approach used

The methods used by the company to analyse the data for primary and secondary outcomes in the included trials is described below. In the ERG's opinion, the statistical methods used were broadly appropriate, though a number of ambiguities and analytic decisions taken by the company raise questions about the trustworthiness of the results (summarised in Sections 3.2.4.1 - 3.2.4.3).

Primary outcomes

In HERCULES, the primary endpoint (time to normalisation of platelet count with discontinuation of PEX within five days thereafter) was compared with a two-sided log-rank test, stratified by severity of neurologic involvement (Glasgow Coma Scale score of ≤12 vs ≥13). A further comparison was made using Cox regression (proportional hazards).

In TITAN, the primary endpoint (time to confirmed normalisation of platelet count) used KM analysis stratified for "absence or presence of one plasma-exchange session before randomisation, with a one-sided log-rank test …".

Secondary outcomes

In HERCULES, four 'key' secondary outcomes were defined and compared statistically. The first three (composite outcome, recurrence of TTP and refractory TTP) were analysed with Cochrane Mantel-Haenszel and the fourth (normalisation of organ-damage markers) with a stratified log rank test (p-value not reported in the CS [Document B, Section B.2.6.5]).

Secondary outcomes in TITAN and 'other' (not key) secondary outcomes in HERCULES were presented but not compared statistically.

In TITAN a subset of outcomes had lengthy (one-year) follow-up, however this trial was subject to considerable attrition (see Section 3.2.1.2).

In HERCULES, key secondary outcomes underwent censoring after switching, further detailed in 3.2.4.2. The ERG finds this contrary to the description of the analysis as ITT.

3.2.4.1. Proportional hazards assumption

The Cox model used for analysis of the primary outcome makes an assumption of proportional hazards. The KM curves presented for HERCULES cross, which indicates a potential violation

of the proportional hazards assumption, but could have occurred as a stochastic result through sampling. The ERG raised this as a potential problem in clarification (Clarification Question A8), and the company state "… the adequacy of the assumption was tested by two different methods. Both analyses showed that the proportional-hazards assumption was met" (Clarification Response A8).

The company drew attention to a letter and response in the New England Journal of Medicine (response to Scully et al. 2019[4]). Alternative analysis by a critic using reconstructed data at 20 days gives a difference in mean survival times of 1.33 days (95% CI -0.31 to 2.97) and the authors' response using the same approach with real data gives 1.45 (95% CI 0.05 to 1.45). Both alternative analyses have similar interpretations favouring caplacizumab though only the latter is formally significant. The ERG notes that regardless of this, the hazard ratio estimates are not used in the economic model.

3.2.4.2. Censoring

The approach to censoring in the HERCULES trial is summarised in Table 8 (refer also to the CS, Document B, Table 6, p.45).

Table 8: Excerpt showing censoring / data exclusions from HERCULES statistical analysis plan

Outcomes	Company description
Time to platelet count response	In the time to platelet count response KM analysis, an observation was censored if the defined time interval of 45 days after first administration of study drug was not met due to any cause (e.g. endpoint not reached within this time point or patient lost to follow-up).
Key secondary outcome 1: Composite of TTP-related death, exacerbation of TTP, major thromboembolic event Key secondary outcome 2 : Recurrences of TTP at any time during the trial (exacerbations and relapses)	In key secondary endpoints 1 and 2, any event that occurred prior to a switch to open-label caplacizumab was included.
Key secondary outcome 3 : Refractory TTP (number of patients)	In key secondary endpoint 3, patients who discontinued the study before Day 5 were excluded from the analysis. Missing values were imputed using multiple imputation (MCMC) by averaged simulated parameter values.

Outcomes	Company description
Key secondary outcome 4: median time to normalisation of organ-damage markers	In key secondary endpoint 4, patients who switched to caplacizumab before having reached the endpoint were censored at time of switch.

Key: KM, Kaplan-Meier; MCMC, Markov Chain Monte Carlo; TTP, thrombotic thrombocytopenic purpura

Source: CS, Document B, Table 6

Censoring is properly accounted for in the survival analysis for platelet normalisation (primary outcome) and organ damage markers (key secondary outcome 4). However the CS implies that key secondary outcomes 1-2 (composite outcome and recurrences) (Table 8) are addressed by excluding events after a treatment switch, which could lead to exclusion of later major events (death, major thromboses) from the data presented or distortion of recurrence information. The ERG requested further information from the company to establish the composition of the exclusions.

It is anticipated that the time to platelet count response would be unaffected by treatment-switching exclusions because they are only made after first event (first platelet count response); the company confirmed that this was the case in response to Clarification Question A11.

The company provided information for efficacy outcomes without censoring after switching, (see Clarification Response A11, Table 2). This response confirmed that only small numbers of exacerbations, relapses and major thromboembolic events were excluded by censoring for treatment-switching.

With respect to key secondary outcome 3 (refractory patients), patients who withdrew early (before day 5) might have proceeded to a refractory state that is missing from the data in either trial arm. The ERG was unable to find any further information within the CS relating to the imputation process that is mentioned in Table 8, and the CSR cites details in an appendix not available to the ERG.

3.2.4.3. Recurrence information

Recurrence, relapse and exacerbation information is available in the CS (Document B, Table 9 and Table 13), and the clarification response to A11 on uncensored results. Information is also available from the published trial results (HERCULES: Scully et al. 2019[4], Figure 2 and Table 2; TITAN: Peyvandi et al. 2016[12], Figure 2 and Table 2). As highlighted in the ERG's discussion of the clinical effectiveness results (Section 3.2.5.4), interpretation of the analysis of these

outcomes was complicated by ambiguities and inconsistencies between different evidence sources in the company's submission.

3.2.5. Clinical effectiveness results

Most of the outcomes specified in the NICE scope were reported in the CS: change in cognitive function; mortality; major thromboembolic events; recurrence of disease; time to platelet count response; TTP-related events; length of hospital stay; volume and frequency of plasma exchange; and adverse effects of treatment. No data were presented for neuropsychological impact of an acute episode of aTTP, or health-related quality of life (HRQoL). The company stated that it was not possible to evaluate HRQoL due to ethical considerations of evaluating HRQoL while patients are extremely sick or dying; this justification has been validated by the FDA, and was considered by the ERG to be appropriate for HRQoL as well as for other patient-reported outcomes (PROs). However, no measures of HRQoL, neuropsychological impact, or PROs were evaluated at timepoints following the acute episode. Finally, based on clinical advice, the ERG regarded that outcomes for reduction in time to recovery, a scoped outcome, were principally informed by reduction in days of PEX and volume of FFP, though additional outcomes such as days in ICU were also informative.

The primary outcome in HERCULES was time to normalisation of platelet count. The company stated that analyses were conducted in both intention to treat (ITT) and per protocol (PP) datasets, however the majority of data presented in the CS was for the ITT population. Data for the PP data set were presented in the appendix for the primary outcome of both trials.

Data were primarily reported in their absolute form (e.g. counts and proportions of participants exhibiting a particular outcome); with a relative effect estimate only provided for the primary outcome of the two trials (HR for time to platelet response). As the population in the HERCULES trial is healthier than those that would be seen in clinical practice (as discussed in Section 3.2.1.3), the ERG judged that absolute data would be less generalisable to understanding the potential impact of caplacizumab for patients in the UK. As clinical advisors to the ERG advised that they did not know of any reason why caplacizumab would work differently in those patients who were excluded from the HERCULES trial, the ERG considered relative effect estimates to be more useful for interpreting the effect of caplacizumab relative to standard care. The ERG chose to calculate relative effect estimates for each of the clinical outcomes, where possible. Relative effect estimates were primarily used to inform conclusions about clinical effectiveness.

3.2.5.1. Change in cognitive function

In HERCULES, cognitive function was evaluated using the presence of neurological symptoms, the SMMSE, and the Glasgow Coma Scale (GCS). However, GCS was only reported at baseline, and follow-up data for SMMSE were not reported in the CS (but was identified by the ERG in the CSR p. 561-570). The data are reported in Table 9 below. A relative treatment effect has been calculated by the ERG.

The results indicated that participants in both arms of the trial showed an overall improvement in cognitive abilities from baseline, as assessed using the SMMSE. Change in cognitive function was similar between arms, with no discernible difference in mean scores on the SMMSE between trial arms. According to an assessment of the presence of neurological symptoms, the data indicated that fewer patients in the caplacizumab trial arm exhibiting neurological symptoms at the end of daily PEX therapy, but this effect was not seen at subsequent follow-up. Event rates for the presence of neurological symptoms were low in both arms. Overall, the ERG did not consider there to be evidence that treatment with caplacizumab was associated with overall improvement in cognitive function, though these outcomes were short-term and may not reflect longer-term development, or resolution, of cognitive impairment.

Table 9: Change in cognitive function in HERCULES

	Timepoint	**CAPLA (n=71) N(%)**	**SoC (n=73) N(%)**	**Treatment effect[a]**
Presence of neurological symptoms (e.g. disorientation, agitation, dysarthria)	Baseline	[redacted]	[redacted]	[redacted]
	End of daily PEX	[redacted]	[redacted]	[redacted]
	30-day post-PEX	[redacted]	[redacted]	[redacted]
	Final 28 day follow-up	[redacted]	[redacted]	[redacted]
SMMSE mean (SE) Scores range between 0-30, higher is better. Scores 26-30 = general population; 20-25 = mild cognitive impairment; 10-20 = moderate cognitive impairment; 0-9 = severe cognitive impairment	Baseline	[redacted]	[redacted]	[redacted]
	Day 5	[redacted]	[redacted]	[redacted]
	30-day post-PEX	[redacted]	[redacted]	[redacted]
	Final 28-day follow-up	[redacted]	[redacted]	[redacted]

	Timepoint	CAPLA (n=71) N(%)	SoC (n=73) N(%)	Treatment effect[a]
GCS	Baseline	[redacted]	[redacted]	[redacted]
	Follow-up	NR	NR	NA

Key: CAPLA, caplacizumab; NR, not reported; SoC,standard care

Note: [a] Calculated by ERG

Source: CS, Document B, p. 54; HERCULES CSR p. 561-570

3.2.5.2. Mortality

In HERCULES, one participant died in the caplacizumab arm, compared to three participants in the SoC arm (RR 0.34, 95% CI 0.04, 3.22; calculated by the ERG). The death in the caplacizumab arm occurred during follow-up; i.e. not during the study drug period (CS, document B, p.53). However, in response to Clarification Question A11, the company states that no TTP-related deaths occurred in the caplacizumab arm, even through follow-up. The ERG were unable to determine the reason for this discrepancy. All deaths were determined to be TTP-related. The ERG considered it possible that mortality may be lower following treatment with caplacizumab compared to standard care, although given the very low numbers and the sample size, the ERG was unable to conclude any effect of caplacizumab on mortality.

Mortality estimates from HERCULES were not used in the company's economic model because the company were unable to establish external validity for these. The generalisability of the HERCULES population is discussed in Section 3.2.1.3; mortality rates used in the company's economic model are presented in Section 4.2.5.

3.2.5.3. Major thromboembolic events

An equal number of major thromboembolic events occurred in both arms of the HERCULES trial (six events (8%) in both arms; CS, Document B, p.49).

From these data, the ERG did not consider there to be evidence of a difference in the risk of major thromboembolic events following treatment with caplacizumab.

3.2.5.4. Recurrence of disease

The company reported several outcomes to measure recurrence of disease in HERCULES: relapse (a de novo TTP episode), exacerbation (recurrent TTP episode occurring within 30-days of the end of treatment), recurrence (exacerbation or relapse; see Section 3.2.1.5 for full

outcome definitions), and refractory disease absence of platelet count doubling accompanied by LDH>ULN). The data are reported in Table 10 below.

When considering the rate of relapse and exacerbation together (i.e. 'recurrence'), the rate of recurrence at 28 days in HERCULES was significantly lower amongst participants receiving caplacizumab than those receiving SoC. This reduction was equivalent to a 67% lower incidence in the recurrence of the disease (CS, Document B, p.49). Breaking this up, the effect was comprised of a statistically *lower* risk of exacerbation for participants receiving caplacizumab, but a statistically *higher* risk of relapse (though the effect was smaller). There was a statistically significant lower risk of refractory disease in the caplacizumab arm compared to SoC: [redacted] patients in the caplacizumab arm were assessed as having refractory disease at follow-up, compared to [redacted] in the SoC arm (according to the international consensus definition; 4.2% (3/72) according to the original trial criteria) .

Overall, the ERG considered the evidence to indicate that treatment with caplacizumab may reduce the overall recurrence of TTP, as evaluated up to 28-days after treatment. However, the ERG considered it possible that a higher risk of relapse shown for patients in the caplacizumab arm may be due to caplacizumab delaying an exacerbation of aTTP. Clinical advice to the ERG is that this is plausible, and is consistent with the perceived benefit of caplacizumab in this population. Due to the short-follow-up of the HERCULES trial, it is not possible to determine whether the risk of relapse continues to be higher in the caplacizumab arm, and therefore what proportion of exacerbations avoided at the 28-day timepoint appear as relapses later. The ongoing impact on caplacizumab on recurrence of the disease is therefore unclear. Clinical advisors to the ERG considered that because caplacizumab has a near-immediate action when given intravenously, it is possible that the drug would not have a long-term effect after discontinuation of treatment. Thus, long-term relapse rates may be expected to become equal between arms. The ERG regarded that the lack of relapses observed at 28 days in the SoC arm could represent either a true effect exaggerated by short follow-up, or baseline imbalance in prognosis. In response to Clarification Question A11, the company noted that one relapse occurred in the SoC arm during the open label phase. The ERG considered the evidence to indicate that caplacizumab may reduce the risk of refractory disease during the follow-up period (28 days following the end of treatment). However, clinical advisors to the company regarded the overall rate of refractory disease reported in HERCULES to be considerably lower than would be expected in clinical practice; they estimated a refractory rate of 17% to be more representative of practice in the UK. The rates reported in HERCULES are therefore considered

to be conservative, and may be reflective of the healthier population included in the HERCULES trial. However, one of the ERG experts suggested that there are unlikely to be refractory patients after using caplacizumab in the full target population, which may mean that the treatment effect for Caplacizumab on recurrence may be larger than reported in the HERCULES trial.

Table 10: Recurrence of disease in HERCULES

	Follow-up	**CAPLA (n=72)**	**SoC (n=73)**	**Treatment effect[a]**
Relapse, n (%)	Final 28 day follow-up*	6 (8.3%)	0 (0%)	Peto OR 8.06 (95% CI 1.58, 41.07)
Exacerbation, n (%)	Final 28 day follow-up	3 (4.2%)	28 (38.4%)	RR 0.11 (95% CI 0.03, 0.34)
Patients with recurrence of disease, n (%)	Final 28 day follow-up	9 (12.5%)	28 (38.4%)	RR 0.33 (95% CI 0.17, 0.64)
Patients with refractory disease, n (%)[b]	Final 28 day follow-up	[redacted]	[redacted]	[redacted]

Key: CAPLA, caplacizumab; ITT, intention-to-treat; NR, not reported; SoC, standard care.

Note: [a] Calculated by ERG. b as defined by international consensus definition (lack of sustained platelet count increment or platelet counts <50 x 109/L and persistently raised LDH [>1.5 x ULN] despite 5 PEX treatments and steroid treatment]

Source: CS, Document B, p. 50

Finally, the ERG found some variation in the counts of exacerbations and relapses (and consequently on treatment effects) depending on the approach taken, as shown in Table 11 and Table 12. There appears to be a discrepancy in the results: Figure 2B of Scully et al. shows three relapses after the end of the trial treatment period in SoC allocated patients who switch, whereas the uncensored counts show only one event in one subject over the overall study period. Altered counts are also presented when the company reinterprets certain trial-defined relapses as 'true exacerbations' (Document B, p.73).

Though the differences in data may be small, they are influential because the data are sparse (see calculated risk ratios in Table 11 and Table 12). In this specific regard, information from TITAN is helpful for comparison, given the sparseness of data for these outcomes. The ERG noted that there are indications from both trials that the risk of exacerbation is lower on caplacizumab (Table 12) but the risk of relapse is lower on SoC (Table 11). Follow-up for relapses is longer in TITAN (one year, though not for all patients given early stopping) than HERCULES (28 days). However, this follow-up is subject to problems including attrition (Section

4.2.1.2). Relapse information from the trials is not used in the economic model, where the rate of relapse is assumed to be equivalent for Caplacizumab and SoC, and the model does not allow differential relapse rates (see Section 4.2.4.1).

Table 11: Risk of relapse

	CAPLA	SoC	Risk Ratio[a]	Notes/Source
HERCULES	6/72	0/73	-	As presented in Scully et al. 2019, Table 2 and CS Document B, Table 9
	0/72	0/73	-	Redefining relapses as late exacerbations (CS p73, p100)
	6/72	3/73	2.03 (0.53 to 7.80)	using Figure 2B of Scully et al. 2019
TITAN	11/36	3/39	3.97 (1.20 to 13.1)	As presented in Peyvandi et al. 2016 Table 2 (12 month follow-up) and CS Document B, Table 9
	4/36	3/39	1.44 (0.35 to 6.02)	New relapses from fig 2 of Peyvandi et al. 2016

Key: Capla, caplacizumab; SoC, standard care

Notes: [a] calculated by ERG

Table 12: Risk of exacerbation

	CAPLA	SoC	Risk Ratio[a]	Notes/Source
HERCULES	3/72	28/73	0.11 (0.03 to 0.34)	As presented in Scully et al. 2019 Table 2 and CS Document B, Table 9
	9/72	28/73	0.33 (0.17 to 0.64)	If redefining relapses as exacerbations (CS, p73, p100)
TITAN	3/36	11/39	0.29 (0.09 to 0.97)	As presented in Peyvandi et al 2016, Table 2 and CS Document B, Table 9

Key: CAPLA, caplacizumab; SoC, standard care

Notes: [a] calculated by ERG

3.2.5.5. Reduction of time-to-recovery

To evaluate the impact of caplacizumab on time to recovery, the company reported data for five outcomes related to resource use: days of PEX therapy; volume of plasma; hospitalisation days; patients admitted to ICU; and ICU days. These outcomes were specified as independent outcomes in the NICE scope and are presented below (volume and frequency of plasma exchange in Section 3.2.5.10; and length of hospital stay in Section 3.2.5.9). Based on clinical advice, the ERG regarded that days of PEX therapy in particular, but also volume of plasma, were key indicators for this outcome, though the additional outcomes presented—specifically ICU days—were also informative for this outcome. Time to platelet count response may also be an indicator of time to recovery, but clinical advice received by the ERG noted that this is a short-term outcome.

The ERG considered that, given the specification of the outcome as time to recovery, it would have been useful to present time to event data for response outcomes. However, the company only report one time to event outcome, which is Time to platelet count response, reported in Section 3.2.5.6.

3.2.5.6. Time to platelet count response

Time to platelet count response was the primary outcome for HERCULES. The results as reported in the CS are shown in Table 13.

In the HERCULES ITT population, the vast majority of participants in both arms of the trial exhibited a platelet count response during the study period (91.0%, 132/145). The proportion of those exhibiting a platelet count response was similar in both arms of the trial: 91.7% of participants in the caplacizumab arm (66/72) and 90.4% of participants in the SoC arm (66/73) exhibited a response.

The CS reported that those in the caplacizumab arm experienced a platelet count response earlier than those in the SoC arm: median time to platelet response in the caplacizumab arm was 2.69 days (95% CI 1.89 – 2.83), compared to 2.88 days (95% CI 2.68 – 3.56) in the SoC arm. This difference corresponds to an approximate difference of 4.56 hours. Clinical advisors to the ERG considered this difference to be clinically meaningful to patients, due to the perceived benefits of earlier treatment for avoiding complications.

Table 13: Time to platelet count response in HERCULES and TITAN (ITT)

	HERCULES		TITAN	
	CAPLA (n=72)	**SoC (n=73)**	**CAPLA (n=36)**	**SoC (n=39)**
Patients with event, n	66	66	31 (86.1)	28 (71.8)
Median days to response (95% CI)	2.69 (1.89, 2.83)	2.88 (2.68, 3.56)	2.97 (2.74, 3.65)	4.79 (3.51, 5.94)
HR for time to platelet count response (95% CI)	1.55 (1.09, 2.19)		2.20 (1.28, 3.78)	
p-value	0.01		0.005	

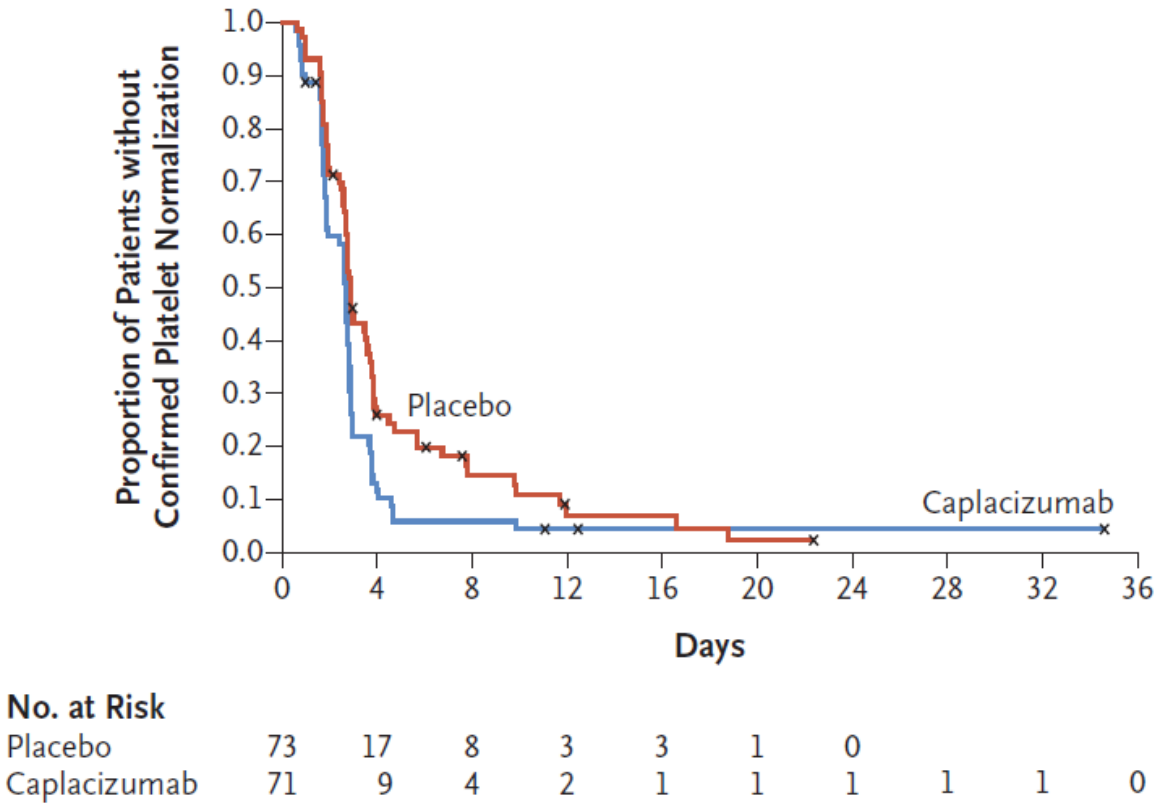
Key: CAPLA, caplacizumab; CI, confidence interval; HR, hazard ratio; ITT, intention to treat; SoC, standard care;.

Notes: platelet count response defined as ≥150,000/uL with subsequent stop of daily PEX treatment within 5 days in the HERCULES trial, and recovery of platelets ≥150,000/uL confirmed at 48 hours by a de novo measure of platelets ≥150,000/uL and LDH ≤2 x ULN in the TITAN trial.

Source: CS p.48

Hazard ratio data demonstrated that treatment with caplacizumab was associated with a statistically significant increase in the chance of a platelet response at any time during the follow-up period (HR 1.55, 95% CI 1.09 – 2.19). The ERG noted that 95% CIs were wide, indicating some uncertainty in the size of the effect, and the lower 95% CI approaches the line of null effect. The ERG therefore considered that further data would increase confidence in the findings. At clarification the company provided a Kaplan-Meier plot (Figure 3), which seems to show that platelet count response is similar between trial arms until Day 3, at which point a benefit for caplacizumab over SoC appears until Day 12, when the trial arms then merge.

Figure 3: Kaplan-Meier curve for time to platelet count response in HERCULES



Note: the 'x' symbols indicate censored data

Source: Scully et al. 2019[4]

In the per protocol population, median time to response was similar to the ITT population: [redacted] days for patients receiving caplacizumab ([redacted]) and [redacted] days for patients receiving SoC ([redacted]). Hazard ratio data indicated a bigger impact of caplacizumab on time to platelet response ([redacted]), although again the 95% CIs were wide, and approached the line of null effect ([redacted]).

Overall, the ERG considered the evidence from HERCULES to indicate that caplacizumab may not impact on the number of patients who overall exhibit a platelet count response within approximately a month of starting treatment; but that the use of caplacizumab may reduce the time until patients exhibit a response, with potentially clinically meaningful benefits. However, due to the uncertainty in the size of the effect, owing to wide 95% CIs around the outcomes, and the short follow-up period used in HERCULES, the ERG did consider that more evidence would

lead to firmer conclusions on the effect of caplacizumab on platelet response, and on any potential downstream benefits.

3.2.5.7. TTP-related events

To address this outcome, the company only presents data for those TTP events that were judged by the investigating team as being 'treatment-emergent and clinically significant'. It is unclear from the CS how these criteria were judged, and what data may have been excluded.

The data presented by the company are shown in Table 14. The proportion of cardiovascular and neurological events, TTP-related death, and 'other' TTP events were similar between trial arms, with no statistically significant differences. Overall, the ERG did not consider there to be evidence that caplacizumab is associated with a change in the proportion of TTP-related events.

Table 14: Treatment-emergent clinically significant TTP-related events in HERCULES

n (%)	Study drug treatment period		Overall study period		Treatment effect (overall study period)[a]
	CAPLA (n=71)	SoC (n=73)	CAPLA (n=72)	SoC (n=73)	
Cardiovascular event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neurological event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TTP-related death	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: CAPLA, caplacizumab; CI, confidence interval; ITT, intention-to-treat; SoC, standard care; TTP, thrombotic thrombocytopenic purpura; RR, risk ratio

Note: [a] Calculated by ERG

Source: CS, Document B, p. 53; HERCULES CSR[16]; Scully et al. 2019[4].

3.2.5.8. Neuro-psychological impact following an episode

No data were presented in the CS for this outcome.

3.2.5.9. Length of hospital stay

Several outcomes measured in the HERCULES trial represented hospital resource use following treatment: length of hospital stay, length of ICU stay, and the proportion of patients admitted to ICU (data shown in Table 15). Overall, the data showed that patients receiving caplacizumab spent fewer days in hospital (at clarification, the company clarified that this

included days spent on a general ward and in ICU), although this difference was not statistically significant. An equivalent number of participants in the caplacizumab and SoC arms were admitted to ICU, although participants in the caplacizumab arm spent statistically significantly fewer days in ICU than those in the SoC arm (a mean difference of -6.3 days [95% CI -10.77, -1.83] [Table 15]). Clinical advisors to the ERG suggested that patients receiving caplacizumab may still require admission to ICU to receive PEX, which is a possible reason for the lack of difference in the number of patients admitted to ICU; and clinician preference may be to admit all aTTP patients to ICU. A difference in the length of time in ICU may reflect patients on caplacizumab requiring less time on treatment (which is supported by evidence presented in Section 3.2.5.10). Evidence presented in Section 3.2.5.7, however, suggests that a reduced time in ICU is not caused by a lower incidence of TTP-related events as there were no differences between arms in events.

Table 15: Hospital resource use in HERCULES

	CAPLA (n=72)	SoC (n=73)	Treatment effect[a]
Hospitalisation days			
Mean (95% CI)	9.9 (8.5, 11.3)	14.4 (12.0, 16.9)	MD -4.5 (95%CI -7.32, -1.68)
Median (range)	9.0 (2.0-37.0)	12.0 (4.0-53.0)	
Patients admitted to ICU, n (%)	28 (39)	27 (37)	RR 1.05 (95%CI 0.69, 1.59)
ICU days			
Mean (95% CI)	3.4 (2.6, 4.2)	9.7 (5.3, 14.1)	MD -6.3 (95%CI -10.77, -1.83)
Median (range)	3.0 (1.0-10.0)	5.0 (1.0-47.0)	

Key: CAPLA, caplacizumab; CI, confidence interval; ICU, intensive care unit; ITT, intention-to-treat; L – litre; NR, not reported; PEX, plasma exchange; MD, mean difference; RR, risk ratio; SoC, standard care

Note: [a] calculated by ERG

Source: Peyvandi et al. 2016[12]; Scully et al. 2019[4]

3.2.5.10. Volume and frequency of plasma exchange

The volume of plasma received by participants in HERCULES, and the number of days of PEX therapy received, are reported in Table 16. No outcome data related to the frequency of PEX were reported, though clinical advice received by the ERG suggested that PEX is generally a daily treatment, and only rarely twice daily. The data show a statistically significant difference in

both outcomes, with participants in the caplacizumab arm receiving fewer days of PEX therapy, and receiving fewer litres of plasma.

Table 16: Volume and frequency of plasma exchange

	CAPLA (n=72)	SoC (n=73)	Treatment effect[a]
Days of PEX therapy			
Mean (95% CI)	5.8 (4.8, 6.8)	9.4 (7.8, 11.0)	MD -3.60 (95%CI -5.49, -1.71)
Median (range) [min-max]	5.0 (1.0-35.0)	7.0 (3.0-46.0)	
Volume of plasma - L			
Mean (95% CI)	21.3 (18.1, 24.6)	35.9 (27.6, 44.2)	MD -14.60 (95%CI -23.51, -5.69)
Median (range) [min-max]	18.1 (5.3-102.2)	26.9 (4.0-254.0)	

Key**:** CAPLA, caplacizumab; CI, confidence interval; ICU, intensive care unit; ITT, intention-to-treat; L – litre; NR, not reported; PEX, plasma exchange; MD, mean difference; SoC, standard care

Note: [a] Calculated by ERG

Source: CS, Document B, p. 52; Peyvandi et al. 2016[12]; Scully et al. 2019[4]

3.2.5.11. Health-related quality of life

No health-related quality of life data were reported.

3.2.5.12. Subgroup analyses

The company presented subgroup analyses for three subgroup categories: baseline disease severity (assessed using the French severity score); previous TTP episode; and baseline ADAMTS13. Not all outcomes specified in the NICE scope were analysed in subgroup analysis; the company reports subgroup analyses for time to platelet count response, recurrence, and risk of refractory TTP only. All analyses were conducted in the ITT population. No statistical tests were reported that compared outcomes between subgroups.

Data from the subgroup analysis according to patients' baseline disease severity are summarised in Table 17 below. On the basis of the small number of outcomes reported, the ERG did not consider there to be conclusive evidence of effect modification between patients defined as less and very severe; although the ERG noted that the effect of caplacizumab on time to platelet count response was slightly larger in patients with very severe TTP (although note wide 95% CIs). The ERG also noted that all TTP recurrences in the caplacizumab arm that occurred during the double-blind period were in those patients who were very severe.

Table 17: HERCULES subgroup analysis: Baseline disease severity (ITT)

Efficacy outcome	Less severe		Very severe	
	CAPLA (n=42)	SoC (n=48)	CAPLA (n=30)	SoC (n=25)
Time to platelet count response, HR (95% CI)	[redacted]		[redacted]	
Recurrence of TTP during the DB study drug treatment period, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence of TTP during the FU period, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence of TTP during overall study period, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Refractory TTP, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Key: CAPLA, caplacizumab; CI, confidence interval; DB, double-blind; FU, follow-up; HR, hazard ratio; ITT, intention-to-treat; soC, standard care; TTP, thrombotic thrombocytopenia purpura.

Notes: [a], 41 patients were assessable for this event; [b], 40 patients were assessable for this event; [c], 26 patients were assessable for this event.

Very severe disease is defined as French severity score ≥ 3 or severe neurological involvement or cardiac involvement (cTnI >2.5 x ULN).

Source: HERCULES CSR[16]

Data from the subgroup analysis according to whether this was patients' first or subsequent episode are summarised in Table 18 below. There were no discernable differences in treatment response between patients for whom this was their first, compared to recurrent, episode, and the ERG did not consider there to be evidence of an effect modifier of TTP episode. However, the ERG took note of clinical advice that patients experiencing a recurrent episode may experience a quicker treatment response if earlier diagnosis facilitates treatment being administered at a time when symptoms are less severe. As randomisation in the HERCULES trial was stratified by severity of neurological symptoms at baseline, the ERG considered it possible that this may have partially occluded an effect modifier of TTP episode. It was not possible for the ERG to validate this assumption using TITAN, as no subgroup analysis for TTP episode was reported. On the basis of the evidence and clinical advice given, the ERG did not consider there to be sufficient evidence to rule out the possibility of a treatment effect modifier of TTP episode.

Table 18: HERCULES subgroup analysis: Previous TTP episode (ITT)

Efficacy outcome	Initial episode		Recurrent episode	
	CAPLA (n=48)	SoC (n=34)	CAPLA (n=24)	SoC (n=39)

Efficacy outcome	Initial episode		Recurrent episode	
Time to platelet count response, HR (95% CI)	[redacted]		[redacted]	
Recurrence of TTP during the DB study drug treatment period, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence of TTP during the FU period, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence of TTP during overall study period, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Refractory TTP, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Key: CAPLA, caplacizumab; CI, confidence interval; DB, double-blind; FU, follow-up; HR, hazard ratio; ITT, intention-to-treat; SoC, standard care; TTP, thrombotic thrombocytopenia purpura

Notes: [a] 41 patients were assessable for this event; [b] 40 patients were assessable for this event; [c] 26 patients were assessable for this event.

Very severe disease is defined as French severity score ≥ 3 or severe neurological involvement or cardiac involvement (cTnI >2.5 x ULN).

Source: HERCULES CSR[16]

Data from the subgroup analysis according to ADAMTS13 level at baseline are reported in Table 19 below. The data suggest that caplacizumab may have a greater impact on the time to platelet count response in patients who meet UK aTTP diagnostic criteria of ADAMTS13 <10%; however, 95% CIs around the effect for patients with ADAMTS13 ≥10% were extremely wide, meaning that the true effect for this group is extremely uncertain. Due to the small proportion of patients with ADAMTS13 ≥10% in the trial, and the low rate of events subject to subgroup analysis, the ERG did not consider there to be sufficient evidence in respect of effect modification between these groups.

Table 19: HERCULES subgroup analysis: ADAMTS13 level at baseline (ITT)

Efficacy outcome	ADAMTS13 <10%		ADAMTS13 ≥10%	
	CAPLA (n=58)	SoC (n=65)	CAPLA (n=13)	SoC (n=7)
Time to platelet count response, HR (95% CI)	[redacted]		[redacted]	
Recurrence of TTP during the DB study drug treatment period, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence of TTP during the FU period, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Recurrence of TTP during overall study period, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Refractory TTP, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Key: CAPLA, caplacizumab; CI, confidence interval; DB, double-blind; FU, follow-up; HR, hazard ratio; ITT, intention-to-treat; SoC, standard care; TTP, thrombotic thrombocytopenia purpura

Notes: [a], 53 patients were assessable for this event; [b], 33 patients were assessable for this event; [c], 6 patients were assessable for this event.

Source: HERCULES CSR[16]

3.2.6. Safety

Safety evidence provided by the company for the HERCULES trial is summarised in Sections 3.2.6.1 - 3.2.6.4 below. In addition to the data presented in the CS, the ERG notes that an integrated summary of safety was developed as part of the Biologics License Application that included seven clinical trials investigating caplacizumab across aTTP and percutaneous coronary intervention indications. Overall, caplacizumab was generally well tolerated across the HERCULES and TITAN trials. Adverse events (AEs) were predictable and resolved without treatment, and with only a small number of treatment-related AEs leading to discontinuation. In addition, the company present evidence from a post-hoc analysis suggesting that caplacizumab may be associated with a reduced number of PEX-related complications, possibly reflecting the reduced duration of PEX therapy in the caplacizumab arm (see Section 3.2.5.10).

The European Medicines Agency (EMA) noted a favourable assessment of safety data of caplacizumab from both TITAN and HERCULES trials; however, because of the shared concerns of the EMA and ERG regarding the quality of the TITAN trial (as discussed in Section 3.2.1.2 and 3.2.2), the ERG reports only a detailed critique of the safety data from the HERCULES trial.

3.2.6.1. Common adverse events

Common AEs are summarised in the CS (Document B, Table 15, p. 59-61). As expected, the most common AEs reported were bleeding events (see Section 3.2.6.3). Other common reactions (occurring in at least 10% of patients in the caplacizumab arm) were pyrexia, fatigue, nausea, headache, and urticaria. In most cases these were relatively minor and resolved without treatment. Nevertheless, the company reported that ‘one quarter’ of randomised patients did not complete 1-month follow-up due to adverse events (CS p. 43). Further data for this outcome was not reported in the CS, although it was reported that discontinuation due to a treatment-emergent AE (TEAE) was less common (see Section **Error! Reference source not found.**).

3.2.6.2. Treatment-related adverse events

Rates of treatment-related adverse events (TEAEs) in HERCULES are summarised in Table 20 below. Overall rates of TEAEs were similar between trial arms, with the vast majority of patients reporting at least one TEAE. However, Caplacizumab was not associated with a higher rate of death or study withdrawal due to a TEAE. At least one hypersensitivity reaction was reported in similar proportions of the study groups, however there were no treatment-related events of drug-induced anaphylaxis in the double-blind caplacizumab group. The most frequently reported TEAEs were:

- TTP: reported in 9/71 (12.7%) and 29/73 patients (39.7%) in the double-blind caplacizumab and SoC groups, respectively.
- Epistaxis: reported in 23/71 (32.4%) and 2/73 patients (2.7%) in the double-blind caplacizumab and SoC groups, respectively.
- Headache reported in 16/71 (22.5%) and 6/73 patients (8.2%) in the double-blind caplacizumab and SoC groups, respectively.

During the overall study period, excluding TTP as an event, [redacted] of patients in the caplacizumab arm and [redacted] in the SoC arm discontinued study drug due to AEs.[16]

Table 20: Summary table of adverse events in HERCULES

n (%)	HERCULES		
	Caplacizumab (n=71)	**SoC (n=73)**	Relative risk[a]
TEAE	69 (97.2)	71 (97.3)	RR 1.00 (95%CI 0.95, 1.06)
TEAE leading to death	1 (1.4) [a]	3 (4.1)	RR 0.34 (95%CI 0.04, 3.22)
TEAE leading to withdrawal	5 (7.0)	9 (12.3)	RR 0.57 (95%CI 0.20, 1.62)
TEAE leading to interruption	NR	NR	-
TEAE possibly treatment-related[b]	41 (57.7)	32 (43.8)	RR 1.32 (95%CI 0.95, 1.83)

Key: NR, not reported;RR, risk ratio; SoC, standard care; TEAE, treatment emergent adverse event

Notes: [a] Calculated by the ERG; b the CS did not define this outcome, and therefore interpretation of this data is unclear

Source: CS, Document B, Table 14

A post-hoc analysis of HERCULES data reported that a lower proportion of patients in the caplacizumab arm exhibited a complication of PEX compared to SoC ([redacted]). The ERG agreed with the company that this may reflect the reduced duration of PEX therapy received by patients in the caplacizumab arm (see Section 3.2.5.10). ..

3.2.6.3. Bleeding-related adverse events in HERCULES

Overall rates of bleeding events are reported in Table 21 below. The figures indicate that bleeding events were more common in the Caplacizumab arm (RR 1..34, 95%CI 1.01, 1.79; calculated by the ERG), but approximately two thirds of patients in both arms of the trial reported haemorrhage. Clinically relevant bleeding was more commonly reported in the caplacizumab arm and this has been reflected in Section 4.4 of the SmPC[17] where warnings have been introduced and a patient alert card will be given to patients. In the CS, the company state that clinical expert consensus is that the bleeding risk associated with caplacizumab is usually minor and generally manageable. Clinical advisors to the ERG are in agreement with this statement.

The company reported that bleeding events reported were largely mucocutaneous bleeding. Haemorrhage events mostly consisted of von Willebrand disease-like mild to moderate mucosal and skin/subcutaneous tissue haemorrhage. After removing TTP and thrombotic microangiopathy, no major difference between groups in terms of treatment-emergent thromboembolic events is noted; however, this data was not reported.

There was a statistically significant higher risk of serious adverse events of bleeding in the caplacizumab arm compared to SoC (RR 8.23; 95%CI 1.06, 64.09); however the true size of this effect is uncertain, due to low event rates in the trial. The most commonly reported serious adverse event of bleeding was epistaxis/nose bleeds, which occurred in 4/71 (5.6%) patients in the caplacizumab group; although only one serious bleeding event of epistaxis required medical intervention. No temporal relationship between the occurrence of bleeding and the duration of exposure to caplacizumab was observed.

Severe bleeding-related adverse events were more commonly reported for patients treated with caplacizumab (RR 3.08, 95%CI 0.33, 28.96), though again low event rates meant that there is considerable imprecision in this effect, as evidenced by the wide confidence intervals. Severe bleeding events reported were epistaxis/nose bleeds (1/71; 1.4%), gingival/gum bleeding (1/71;

1.4%), upper gastrointestinal haemorrhage (1/71; 1.4%) in the caplacizumab arm, and a haemorrhagic transformation stroke (1/73; 1.4%) in the SoC arm.

Table 21: Bleeding events reported in HERCULES

n (%)	HERCULES		
	Caplacizumab (n=71)	SoC (n=73)	Relative risk[a]
Bleeding event – SMQ 'haemorrhage'	49 (69.0%)	49 (67.1)	RR 1.03 (95%CI 0.82, 1.29)
Bleeding event – CRF	47 (66.2%)	36 (49.3)	RR 1.34 (95%CI 1.01, 1.79)
Serious bleeding event	8 (11.3%)	1 (1.4%)	RR 8.23 (95%CI 1.06, 64.09)
Severe bleeding event	3 (4.2%)	1 (1.4%)	RR 3.08, 95%CI 0.33, 28.96

Key: CRF, clinical report form; NR, not reported; RR, risk ratio; SoC, standard care; SMQ, standardized MedDRA queries; TEAE, treatment emergent adverse event

Notes: a Calculated by the ERG

Source: Adapted from CS, Document B, Table 14

3.2.6.4. Deaths, serious adverse events and other significant adverse events in HERCULES

As summarised in Section 3.2.5.2, four patients died during the HERCULES trial: 3/73 (4.1%) in the SoC arm during the study drug treatment period, and 1/71 (1.4%) patients in the caplacizumab arm during the treatment-free follow-up period (CS, Document B, p.62). The ERG requested further information from the company on AEs leading to death (Clarification Question A11), who then confirmed that all patients in the HERCULES trial died of TTP-related adverse events. In the SoC arm, one participant died due to hypoxia with bleeding into the lung; a second participant died due to purpura followed by septic shock; and a third participant died due to stroke (worsened massive ischemic stroke with haemorrhage transformation). One death (stroke in the SoC arm) was judged to be related to PEX. In the caplacizumab arm, the participant died of cerebral ischemia. None of the deaths were stated to be related to corticosteroid drug treatment.

Serious adverse events (SAEs) occurring in HERCULES are reported in Table 22. SAEs were relatively common (occurring in 39.4% and 53.4% of the caplacizumab and SoC arms, respectively), and likely reflect the serious nature of the disease. Of these, a third in the caplacizumab arm were considered to be related to treatment. Treatment-related SAEs were significantly more common in the caplacizumab arm than for SoC.

As reported in Section 3.2.6.3, the majority of treatment related SAEs in HERCULES were bleeding events. Generally, serious adverse events (SAEs) occurring in more than one patient treated with caplacizumab were epistaxis and headache. Other SAEs occurring in more than one patient in the SoC arm of HERCULES were anaphylactic transfusion reaction (reported in 3/71, 4.2%, of patients), which is a risk associated with PEX, and septic shock (reported in 2/73, 2.7% patients).

Table 22: Serious adverse events reported in HERCULES

n (%)	HERCULES		
	Caplacizumab (n=71)	SoC (n=73)	Relative risk[a]
SAE	28 (39.4)	39 (53.4)	RR 0.74 (95%CI 0.52, 1.06)
SAE possibly treatment-related	10 (14.1)	4 (5.5)	RR 2.57 (95CI 0.84, 7.82)

Key: NR, not reported; RR, risk ratio; SoC, standard care; TEAE, treatment emergent adverse event

Notes: [a] Calculated by the ERG

Source: CS, Document B, Table 14

3.3. Critique of the meta-analysis

The CS presented an 'integrated analysis' (CS, Document B, Section B.2.8), findings are summarised in Table 23, which shows key information from both trials and a synthesis of them.

Table 23: Findings from integrated data analysis of HERCULES and TITAN

	HERCULES		TITAN		Integrated analysis	
	CAPLA (n=72)	SoC (n=73)	CAPLA (n=36)	SoC (n=39)	CAPLA (n=108)	SoC (n=112)
Primary outcome						
Median days to platelet count response (95% CI)	2.69 (1.89, 2.83)	2.88 (2.68, 3.56)	2.97 (2.74, 3.65)	4.79 (3.51, 5.94)	[redacted]	[redacted]
HR (95% CI)	1.55 (1.09, 2.19)		2.20 (1.28, 3.78)		[redacted]	
p-value	0.01		0.005		[redacted]	
Secondary outcomes						
Composite endpoint: TTP-death, TTP-recurrence or MTE, n (%)	9 (12)	36 (49)	NR	NR	[redacted]	[redacted]

	HERCULES		TITAN		Integrated analysis	
p-value	<0.001		NR		[redacted]	
Recurrence of disease[a], n (%)	9 (12)	28 (38)	13 (36.1)	13 (33.3)	[redacted]	[redacted]
p-value	<0.001		NR		[redacted]	
Refractory disease						
PCD, n (%)	0	3 (4)	NR	NR	[redacted]	[redacted]
p-value	NSD		NR		[redacted]	
ICD, n (%)	[redacted]	[redacted]	NR	NR	[redacted]	[redacted]
p-value	[redacted]		NR		[redacted]	
Days of PEX			(n=35)	(n=37)	[redacted]	[redacted]
Mean (95% CI) [SD]	5.8 (4.8, 6.8)	9.4 (7.8, 11.0)	6.7 [3.7]	8.4 [6.7]	[redacted]	[redacted]
Median (range)	5.0 (1–35)	7.0 (3–46)	6.0 (3–22)	6.0 (3–36)	[redacted]	[redacted]
p-value	0.001		NR		NR	
Mortality - treatment period, n	0	3	0	1	[redacted]	[redacted]
p-value	NR		NR		[redacted]	

Key: CAPLA, caplacizumab; CI, confidence interval; HR, hazard ratio; ICD, ; ICU, intensive care unit; NR, not reported; PCD, ; PEX, plasma exchange; SD, standard deviation; SoC, standard care; TTP, thrombotic thrombocytopenic purpura

Source: CS, Document B, Section B.2.8, Table 13

The ERG notes the company's decision to exclude TITAN trial data from decision making on grounds of quality, making the integrated analysis superfluous. This meta-analytic step is at odds with the decision to exclude information from TITAN, owing to concerns about trial conduct (discussed in Section 4.2.2.2 and 4.2.3), and could be criticised on grounds of differences between the two trials in conduct and reporting. But neither the pooled HR estimate, nor the HR from HERCULES, are used in the company's economic model.

Moreover, the ERG found interpretation of the integrated data analysis difficult and opaque, and responses to clarification queries did not fully resolve the interpretation of this analysis. 'Integrated' recurrences from the CS (Document B, Section B.2.8, Table 13), over the entire study period for both trials are given as [redacted] and [redacted] for caplacizumab and SoC respectively. In response to clarification question A9, the company noted that recurrence data presented

were for the blinded treatment period only and gave revised figures of [redacted] and [redacted], a less extreme difference between arms. Certain other counts appear discrepant or unclear, for example in Document A, Table 4 the number of patients who are refractory in the caplacizumab arm is given as three in HERCULES but NR in TITAN, with an 'integrated' figure of [redacted].

3.4. Critique of the indirect comparison and/or multiple treatment comparison

As no evidence for any comparators to caplacizumab was identified in the SLR, the company were unable to conduct any network meta-analysis (NMA) of evidence in this disease area.

3.5. Additional work on clinical effectiveness undertaken by the ERG

Due to the fact that the company searches for relevant clinical trials limited to the drug name, caplacizumab, and, given the paucity of evidence for aTTP, the ERG considered that some non-drug trials might have been missed. Therefore the ERG carried out broader searches for trials concerning the aTTP population (not only for caplacizumab). These searches were carried out in WHO ICTRP and in ClinicalTrials.gov, and no additional relevant trials were found.

Due to concerns about the generalisability of the HERCULES trial population to the UK aTTP population, as raised by the company and discussed in Sections 3.2.1.3 and 3.2.3, the ERG considered that relative treatment effect estimates would be more informative for understanding the effectiveness of caplacizumab than absolute treatment estimates. As the company provided only absolute treatment estimates, the ERG calculated relative treatment effect estimates for all clinical outcomes (Section 3.2.4).

3.6. Conclusions of the clinical effectiveness section

The company presented an SLR that included two trials: HERCULES and TITAN, both of which tested the effectiveness of caplacizumab against SoC, to include PEX, and immunosuppression (including, where indicated, rituximab). Methods for the SLR were reasonable and the ERG agreed that it was unlikely any further studies would have been found.

The company noted that due to issues with the conduct of TITAN, it was not used for EMA decision-making; the ERG's own assessment of quality coincided and thus TITAN was not presented in depth. The ERG's quality assessment of HERCULES also noted several important issues with the trial, including a high number of protocol deviations, though the cumulative impact and direction of that impact on effectiveness estimates remains uncertain.

Follow-up in HERCULES ran for 28 days after an initial treatment period conicident with PEX and an additional 30 days of study drug. Thus, follow-up was short-term, which the ERG regarded as an issue given the potential long-term impacts of caplacizumab and the possibility for late relapse. In addition, the size of the trials meant that estimation of some key outcomes, including mortality, was highly uncertain and was hampered by sparse data. The ERG highlighted a number of ambiguities and inconsistencies in trial analysis methods, including the use of censoring to account for treatment switching, that while individually may not have had a major impact on counts of events (e.g. censoring only affected a small number of events across outcomes), might collectively alter the trustworthiness of trial estimates. An integrated data analysis incorporating TITAN and HERCULES was presented. The ERG did not regard that this integrated data analysis was probative given the inclusion of TITAN in these estimates and the range of inconsistencies identified by the ERG.

On the whole, the ERG regarded that HERCULES yielded reasonable evidence that as compared to SoC, caplacizumab is both safe and effective at reducing time to normalisation of platelet count, the trial's primary outcome, reduced the volume and frequency of plasma exchange, and reduced the length of days spent in ICU. However, evidence for other outcomes presented, including mortality, major thromboembolic events and recurrence of disease, was less convincing, though overall risk of recurrence and refractory disease was lower in caplacizumab than in SoC. Subgroup analyses for selected outcomes stratified by ADAMTS13 at baseline, previous episode and severity of disease did not yield convincing evidence of effect modification.

4. COST EFFECTIVENESS

4.1. ERG comment on company's systematic literature review

The following section includes searches for the cost effectiveness analysis review (Section 4.1.1), measurement and evaluation of health effects (Section 4.1.2) as well as for the measurement and evaluation of healthcare resource use and costs (Section 4.1.2.3). Targeted literature reviews were also conducted to inform other model input parameters and these are summarised and critiqued in Section 4.1.4.

4.1.1. Cost-effectiveness review

4.1.1.1. Searches

The searches for the cost effectiveness review were the same as for the clinical effectiveness review; see Section 4.1.1.

4.1.1.2. Inclusion/exclusion criteria: cost-effectiveness review

Inclusion and exclusion criteria for the review of economic evaluations are presented in Table 24.

Table 24: Eligibility criteria: cost-effectiveness review

PICOS	Inclusion criteria	Exclusion criteria
Population	Patients of any age with a diagnosis of aTTP[1]	Patients with a diagnosis of congenital or inherited TTP Patients with known causes of thrombocytopenia Patients with clinical evidence of enteric infection with *E. coli* 0157 or related organism Patients with a diagnosis of aHUS Patients with haematopoietic stem cell, bone marrow or organ transplantation-associated thrombotic microangiopathy Patients with known or suspected sepsis Patients with a diagnosis of disseminated intravascular coagulation
Intervention	Caplacizumab (of any length of treatment) alone or in combination with any other therapy or standard of care	

PICOS	Inclusion criteria	Exclusion criteria
Comparator	Any other intervention or combination of interventions for the treatment of aTTP	
Outcomes	Measures of cost-effectiveness such as QALYs and ICERs	
Study design	Economic evaluations	• Case reports • Case studies • News reports • Commentary • Editorials • Letters
Other	No date restriction No language restriction	

Key: aHUS, atypical haemolytic uraemic syndrome; aTTP, acquired thrombotic thrombocytopenic purpura; HRQL, health-related quality of life; ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; LDH, lactate dehydrogenase; PEX, plasma exchange; QALYs, quality-adjusted life years; ULN, upper limit of normal

Notes: [1] Where possible data was collected separately for the following subgroups of patients: adults (over the age of 18) and children; use of rituximab (yes, no); prior aTTP episodes (yes, no); severity of ADAMTS13 activity (<10% vs ≥10%); patients with serious aTTP (defined by clinical score); refractory patients

Source: Adapted from CS, Appendix G, Table 16

In general the ERG agreed that the eligibility criteria are suitable to fulfil the company's objective to identify cost-effectiveness studies; however, the restriction to cost-effectiveness analyses including caplacizumab was noted as a potential limitation as cost-effectiveness models of other treatments could also have been useful in addressing this decision problem, especially given the focus elsewhere in the company's submission on proxy conditions.

4.1.1.3. Included/excluded studies: cost-effectiveness review

The systematic literature review yielded no full text publications evaluating the cost-effectiveness of caplacizumab. No previous NICE health technology appraisals (HTAs) were identified in the population of interest. The ERG conducted a broader search combining population terms with an economics filter in Medline (Appendix A). A total of 36 records were identified but no economic evaluations evaluating caplacizumab or other interventions of relevance to the scope were identified.

4.1.2. Health-related quality of life and health state utilities

The company conducted a systematic review of health-related quality of life (HRQoL) (Section 4.1.2.1). In addition, due to the paucity of data identified for the estimated utility associated with an acute episode, the company conducted a targeted literature review (TLR) to identify data for the proxy conditions suggested by UK clinicians participating in an advisory board (Section 4.1.2.2).

4.1.2.1. Health-related quality of life

Searches

The searches for HRQoL data for aTTP/TTP were carried out in a variety of databases and sources in July 2018 and comprised a mixture of different elements:

- terms for aTTP, AND
- terms for quality of life OR
- terms for costs and resource use (not a recognised tested filter) OR
- terms for hospitalisation/length of stay OR
- terms for seven named instruments.

Inclusion/exclusion criteria

Inclusion and exclusion criteria for the review of HRQoL are presented in Table 25.

Table 25: Eligibility criteria: utilities

PICOS	Inclusion criteria	Exclusion criteria
Population	Patients of any age with a diagnosis of aTTP or TTP[1] Where possible data was also collected separately for patients who use RTX	Patients with known causes of thrombocytopenia Patients with clinical evidence of enteric infection with E. coli 0157 or related organism Patients with a diagnosis of aHUS Patients with haematopoietic stem cell, bone marrow or organ transplantation-associated thrombotic microangiopathy Patients with known or suspected sepsis Patients with a diagnosis of disseminated intravascular

PICOS	Inclusion criteria	Exclusion criteria
		coagulation
Intervention	Any or no intervention / comparator	
Comparator		
Outcomes	HRQoL data, including: • EQ-5D • TTO derived utilities • SG derived utilities • SF-36 and its variants • RBANS • HIT • MoCA • CPT-3 • BDI II • IDS-SR • FLei 5	Studies not reporting HRQoL data
Study design	• Economic evaluations • Utility elicitation studies • Utility mapping studies / reviews • RCT • Technology assessments • Systematic reviews for reference checking of eligible studies only	• Case reports • Case studies • Conference abstracts • News • Comments • Editorials • Letters
Other	NA	NA

Key: aHUS, atypical haemolytic uraemic syndrome; aTTP, acquired thrombotic thrombocytopenic purpura; BDI, beck depression inventory; CPT, continuous performance test; EQ-5D, euroqol 5 dimensions; FLei 5, Fragebogen zur subjektiven Einschatzung der geistigen Leistungsfahigkeit German questionnaire for complaints of cognitive disturbance; HIT, headache impact test; HRQoL, health-related quality of life; IDS-SR, inventory of depressive symptomatology (self-report); MoCA, Montreal cognitive assessment; RBANS, repeatable battery for neuropsychological status; RCT, randomised controlled trials; RTX, rituximab; SF-36, 36-item short-form; SG, standard gamble; TTO, time trade off; TTP, thrombotic thrombocytopenic purpura

Notes, [1] Due to the paucity of literature on aTTP, following a protocol amendment, studies assessing resource use and utilities in TTP were also eligible for this review

Source: Adapted from CS, Appendix H, Table 17

Included/excluded studies

The ERG noted discrepancies between the text reporting the number of studies identified (Appendix H, p.36) and the numbers reported in the PRISMA flow diagram (CS, Appendix H,

Figure 4, p.37); for example, “no further records were retrieved from other sources” whereas the PRISMA flow diagram indicated seven studies were identified via other sources. However, none of these were considered to materially affect the conclusions of the review.

A total of 78 full text publications were reviewed, of which five studies met the inclusion criteria (Table 26). The quality and relevance of each of the identified publications was assessed according to a number of pre-specified criteria namely: (1) selection of participants; (2) generalisability of the target population (age, disease severity, co-morbidities); (3) reasonable pilot testing approach; (4) validity of utility elicitation methods; (5) reasonable attempts to reduce potential for bias by study authors; (5) assessment of the limitations of the study approach.

All five studies were conducted in patients with a previous history of a diagnosis and treatment for TTP and in clinical remission. Three studies were conducted in US patients[18-20], one included both US and UK patients[21] and the final study was in patients in Germany[22] Two studies used the SF-36 as the instrument to assess patients’ quality of life,[20,21] two studies assessed the BDI-II to assess the prevalence of depression among patients,[18,19] and one assessed the inventory of depressive symptomatology (self-report) (IDS-SR), and Fragebogen zur subjektiven Einschatzung der geistigen Leistungsfahigkeit (FLei) (German Questionnaire for complaints of cognitive disturbances), to assess depression and cognitive symptoms.[22] A summary of study characteristics of the included studies are reported in the CS (Appendix H, Table 19).

Table 26: Included studies: HRQoL

Study	Study design	HRQoL measure	Population (Country)	Used in economic model	ERG Comment
Chaturvedi, 2017[23]	XS online survey (February 2016)	BDI-II	Adult aTTP patients (US)	No	No usable utility reported. Prevalence of symptoms of PTSD and depression in survivors of TTP
Han, 2015[19]	Retrospective cohort	BDI-II	TTP patients in remission (US)	No	No usable utility reported. Frequency, severity, and clinical course of depression and cognitive impairment

Study	Study design	HRQoL measure	Population (Country)	Used in economic model	ERG Comment
Lewis, 2009[20]	Retrospective chart review (1998 and 2007)	SF-36	Outpatients with previous history of a diagnosis and treatment for TTP (US) vs general population (US)	No	Utility by domain for initial assessment.
Cataland, 2011[21]	XS (2008-2009)	SF-36	Previous history of a diagnosis and treatment for TTP in clinical remission (US/UK) vs age-and gender-matched population (US)	No	No usable utility reported.
Falter, 2007[22]	Observational cohort	IDS-SR; FLei	Patients with a previous history of acute TTP (Germany)	No	No usable utility reported. Prevalence of depressive symptoms and cognitive deficits in patients having survived acute TTP episodes

Key: BDI-II, Beck Depression Inventory-II; ERG, Evidence Review Group; FLei, Fragebogen zur subjektiven Einschatzung der geistigen Leistungsfahigkeit (German Questionnaire for complaints of cognitive disturbances); HRQoL, health-related quality of life; IDS-SR, inventory of depressive symptomatology (self-report); SF-36, 36 item short-form survey; TTP, thrombotic thrombocytopenic purpura; vs, versus; XS, cross-sectional

Source: CS, Appendix H.1, Table 19

None of the five publications identified in the systematic review were used in the company model. The ERG concurred with the company's rationale for not using in the economic model. The company also referenced a poster presentation by Burns et al. (2008),[24] which described a mapping analysis of SF-36 scores from patients with aTTP in remission to EQ-5D utility values. The company noted that conference abstracts and posters were not formally included but presented for information purposes (CS, Document B, p.110). The ERG recognised that relaxing the inclusion criteria to include conference abstracts was a pragmatic decision; however, the company did not present a list of conference abstracts in the submission and as such the ERG was not able to assess whether the presented source was the most appropriate.

Despite these concerns, the ERG broadly agreed that Burns et al (2008)[24] was a valid source for remission utility in the absence of more robust sources.

4.1.2.2. Targeted literature review: utilities (acute episode)

Given the paucity of data identified for the acute episode, the company asked clinicians to suggest proxy conditions for which HRQoL may be representative of an acute aTTP episode. Proxy conditions suggested included: severe brain injury; cerebral vein thrombosis; sepsis (young patients without comorbidities); Guillain Barré syndrome; meningitis; patients in critical care or ICU. A targeted literature review was conducted to identify utility values for aTTP and the proxy conditions listed.

Searches

For the targeted literature review, the searches were carried out more recently in April 2019, in Medline only. No additional sources were searched. Data were identified for aTTP or proxy conditions with a 'similar disease burden' (CS Appendix H p 55). Searches for aTTP and proxies were combined with search terms for utilities (not a recognised tested filter). Some relevant supplementary sources were also searched.

Inclusion/exclusion criteria

The inclusion/exclusion criteria for the TLR of utilities are not provided in the CS. While the ERG assumed that an adapted version of the criteria for the systematic review of utilities was used, namely studies reporting utilities in a population with aTTP or a listed proxy condition, it was not possible to formally assess this. In addition, the ERG noted that conference abstracts were not eligible for inclusion in the eligibility criteria specified for utilities review (Section 4.1.2), but in the CS the company note that while abstracts were not formally included they were listed for information. The ERG considered this noteworthy because the company included a conference abstract as a source in its base case; the ERG highlighted the potential for selection bias.

Included/excluded studies

The TLR identified an additional 487 unique publications, of which 98 were screened at full text. A total of 33 publications were considered to meet inclusion criteria (CS, Appendix H, Figure 5, p.58). Summary characteristics of these studies are reported in the CS (Appendix H, Table 21).

The included studies were categorised as of low, medium, or high relevance to the economic model; however, as the criteria against which relevance was assessed were not reported, the ERG was unable to judge suitability. The ERG's scrutiny of this categorisation suggested that relevance was judged on the basis of a) proximity to the target condition and b) consideration of acute ICU hospitalisation. Of the seven studies considered highly relevant by the company (Table 27), three did not report the quality of life instrument used, one reported utilities in the remission state (Burns et al. 2008 [referenced above]), and of the remaining three only one was judged by the company to inform the utility associated with an acute episode. The ERG highlighted concerns

Table 27: Utilities classed as high relevance by the company

Author (Year) (Country)	Disease area	QoL Instrument	Source utility/ disutility values	Relevance	Used in economic model	ERG Comment
Burns et al. (2018) (US)[24]	aTTP	Mapped SF-36 to EQ-5D-3L (UK tariff)	N/A	High	Yes – remission state	Conference abstract. Remission. SF-36 from US Registry data (n=72). Utilities mapped from SF-36 to EQ-5D-3L using an algorithm (Rowen, 2009), and included a specific decrement for neuro-psychological symptoms
Davies et al. (2005) (UK)[25]	Sepsis/ICU	EQ-5D	Drabinski et al. (2001)[26]	High	No – rationale not given	Unclear; a single utility value of 0.69 applied at all points post-hospitalisation

Author (Year) (Country)	Disease area	QoL Instrument	Source utility/ disutility values	Relevance	Used in economic model	ERG Comment
Ersson et al (2018) (Sweden)[27]	ICU	NR	Vainiola et al. (2011)[28]	High	No – utility measure not reported	
Hernandez et al. (2013) (UK)[29]	Intensive care follow-up programmes	EQ-5D (UK tariff)	N/A	High	No – utility measure not reported	
Kim (2011) (US)[30]	Thrombosis	NR	Earnshaw et al. (2006)[31]	High	No – utility measure not reported	
Pappas et al (2018) (US)[32]	Nonvalvular atrial fibrillation	EQ-5D-3L	McPhail et al. (2010)[33]; Chit et al. (2015)[34];	High	Yes – acute episode	Baseline utility before episode
Shankar et al (2017) (US)[35]	West Nile virus	NR	N/A	High	No – utility measure not reported	

Key: AQoL, assessment of quality of life; aTTP, acquired thrombotic thrombocytopenic purpura; CI, confidence interval; DVT, deep vein thrombosis; EQ-5D-3L, three-level EQ-5D; HUI, Health utility indices; ICH, intracerebral haemorrhage; ICU, intensive care unit; LOS, length of stay; mRS, Modified Rankin Scale; PE, pulmonary embolism; QoL, quality of life; N/A: not applicable; NR, not reported; QWB, Quality of Well-Being Index; SD, standard deviation; SE, standard error; SF-36, 36-Item Short Form Survey; TTO, time trade-off; VAS, visual analogue scale

Source: Adapted from CS, Appendix H.2, Table 22

4.1.2.3. Targeted literature review: carer quality of life

The company described a targeted literature review relating to carer quality of life and associated disutilities in relevant proxy conditions (CS, Document B, p.117)

. Specifically, the company described identification of a systematic review including studies of utilities for informal caregivers for patients with stroke. The company referenced an advisory board report in which clinicians had considered stroke to be a good proxy for the worst forms of cognitive impairment. However, the specific systematic review was not referenced, nor the process for identifying included studies specified. The ERG regarded that this was a serious but unquantifiable threat to validity of utility identification.

4.1.3. Healthcare resource use and costs

4.1.3.1. Searches

The search for healthcare resource use and costs was conducted alongside the search for utilities (Section 4.1.2.2).

4.1.3.2. Inclusion/exclusion criteria, healthcare resource use and costs

Inclusion and exclusion criteria for the review of healthcare resource use and costs are provided in Table 28

Table 28: Eligibility criteria: Healthcare resource use and costs

PICOS	Inclusion criteria	Exclusion criteria
Population	Patients of any age with a diagnosis of aTTP or TTP[1]. Where possible data will also be collected separately for patients who use RTX	Patients with known causes of thrombocytopenia Patients with clinical evidence of enteric infection with E. coli 0157 or related organism Patients with a diagnosis of aHUS Patients with haematopoietic stem cell, bone marrow or organ transplantation-associated thrombotic microangiopathy Patients with known or suspected sepsis Patients with a diagnosis of disseminated intravascular coagulation
Intervention	Any or no intervention / comparator	
Comparator		
Outcomes	Resource use data, including, Hospital-related resource use, • Number of hospitalisations • Bed days Staff utilisation • Other secondary care usage, • Psychological support services Other support services; • Primary care resource use, • GP/nurse/other staff visits • Home visits PE and RTX cost Resource use and cost associated	Studies not reporting resource use data

PICOS	Inclusion criteria	Exclusion criteria
	with short term treatment of AEs, e.g. • Stroke or cerebrovascular accident • AMI • TIA • DVT • PE • Bleeding Long term consequences of aTTP episode	
Study design	Any design reporting resource use data among patients with aTTP/TTP Systematic reviews for reference checking of eligible studies only	Case reports Case studies Conference abstracts News Comments Editorials Letters
Other	NA	NA

Key: AEs, adverse events; AMI, acute myocardial infarction; aTTP, acquired thrombotic thrombocytopenic purpura; DVT, deep vein thrombosis; GP, general practitioner; HUS, atypical haemolytic uraemic syndrome; NA, not applicable; PE, pulmonary embolism; RTX, rituximab; TIA, transient ischaemic attack; TTP, thrombotic thrombocytopenic purpura

Notes: [1] Due to the paucity of literature on aTTP, following a protocol amendment, studies assessing resource use and utilities in TTP were also eligible for this review

Source: Adapted from CS, Appendix I, Table 24

4.1.3.3. Included/excluded studies: healthcare resource use and costs

A total of 11 studies reported in 13 separate publications were considered eligible for inclusion. Most of the studies were retrospective studies reviewing healthcare activities, often within a single organisation or institution. There was one prospective analysis and one Phase 2 non-randomised trial. Four studies were conducted in the USA, two in the UK, one in Australia, one in Israel and one in Spain. No full economic evaluations or economic analyses based on RCTs were identified, and no previous NICE HTAs were identified in the population of interest. Summary characteristics of included studies are provided in the CS (Appendix I, Table 25).

Of the 11 studies identified, the company considered two to be fully applicable to UK practice (Table 29).[36,37] The remaining nine studies were judged to be either partly applicable (Australia, Israel, Italy, Spain) or to have low applicability (South Africa, US) to clinical practice in England. It appears that applicability was judged on the basis of country setting and by that healthcare system; however, this was not explicitly stated in the CS.

Table 29: Studies reporting healthcare resource use and costs

Study identifier	Country of study	Date of study	Applicability to clinical practice in England	Cost valuations used in the study	Costs for use in the economic analysis	Technology costs
Scully 2011 [36]	UK	2006 to 2009	Fully applicable	NA	RTX use: 4 treatments, 1 per week for 4 weeks	NR
Westwood 2012 [37]	UK	January 2004 to December 2011	Fully applicable	NA	NA	NR

Key: NA, not applicable; NR, not reported; RTX, rituximab; UK, United Kingdom

Of the studies judged fully applicable, only Scully et al. (2011) contributed costs relevant to the economic model. The ERG agreed that of the information presented in the CS, this was the only study of high relevance to the decision problem that also contributed relevant costs.

4.1.4. Other

4.1.4.1. Targeted literature review: clinical burden

The company conducted a TLR evaluating the clinical burden of disease in people with aTTP (Ablynx, 2018).[38] In general, the ERG considered the review to have been well conducted: the research question, PICO, and methods for study selection, data extraction, data synthesis and risk of bias were well specified prior to the conduct of the review. However, the search was limited to one database, MEDLINE, and relied on a basic search string with one single reviewer per abstract. Details relating to the methods used for random effects meta-analysis of proportions were not provided. This is potentially important as meta-analysis of rare events routinely uses transformations to the included study-level estimates to prevent bias in pooled estimates. However, the quantity of studies included in the meta-analysis may have mitigated this potential bias.

In total, 141 studies consisting of 20,131 patients that suffered from at least one acute TTP episode were included. Most importantly, 129 studies measuring acute phase mortality from aTTP where PEX was a first-line treatment were included in a meta-analysis.

The ERG agreed with limitations noted by the review authors including: incomplete reporting of outcome measurements, small sample size, and a high degree of heterogeneity between studies (population, outcome definition, treatment strategy and methodological quality).

4.1.4.2. Targeted literature review: surrogacy

The company conducted a TLR to quantify a relationship between the outcomes reported in HERCULES following treatment of an acute episode of aTTP (time spent in hospital or ICU; exacerbation; refractory disease; number of days/volume of PEX), and its relative effect on long-term cognitive impairment. The company anticipated there would be limited data in the aTTP patient population so included proxy conditions (lacunar stroke, and haemolytic-uremic syndrome (HUS)). The ERG noted that the proxy conditions selected differed from the proxy conditions specified in the TLR to identify utilities; however the impact of this difference was unclear. Eligibility criteria were clearly specified in terms population, outcomes, study design (any), and publication type. A language restriction was applied.

Of 1,372 title/abstracts retrieved, 86 were screened at full text and two were included (Han et al., 2015[19] and Falter et al., 2017[22]); these studies are presented below (Table 30). The company note that the majority of studies were excluded because they did not include one of the populations of interest or did not address the research question (did not quantify a link between acute outcomes reported in the HERCULES trial and cognitive impairment, or no link between the magnitude of cognitive impairment and other clinical outcomes reported). It was not possible for the ERG to assess the reasons for the exclusion of the 84 studies as a list was not provided in the systematic review report.

Table 30: Included studies: surrogacy

Study, year	Population	Outcomes	Study conclusions
Han, 2015	aTTP	**Outcomes** Relapse and ADAMTS13 activity; time since initial TTP episode; depression BDI-II	Magnitude of cognitive impairment not associated with duration since initial aTTP episode, relapse or ADAMTS13 activity
		Cognitive RBANS	Association between cognitive impairment and depression not supported

Study, year	Population	Outcomes	Study conclusions
Falter, 2017	aTTP[a]	**Outcomes** Relapse / recurrence[c] ; TTP-induced neurological abnormalities[d]; Depression: IDS-SR (clinically relevant depression: IDS-SR >25) **Cognitive** FLei	No significant correlation between cognitive deficits and the number or severity of acute TTP episodes Highly significant correlation between severity of depression and the degree to which cognitive performance was reduced

Key: ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aTTP, acquired thrombotic thrombocytopenic purpura; BDI-II, Beck Depression Inventory-II; FLei, Fragebogen zur geistigen Leistungsfähigkeit (German questionnaire for complaints of cognitive disturbances); IDS-SR, Inventory of Depressive Symptomatology, Self-Report; RBANS, Repeatable Battery for Assessment of Neuropsychological Status; TTP, thombotic thrombocytopenic purpura

Notes: a One patient with hereditary TTP; b c Microangiopathic haemolytic anaemia, thrombocytopenia (<150 x 10^9/L), and ADAMTS13 <10% in acute TTP episode (commercial FRETS-assay or, since July 2014, fluorogenic assay using FRETSVWF73 substrate); d Deatures occurring at any time during the acute episode; neurological signs graded as severe, mild or absent;

The ERG noted that this represented another instance of apparent inconsistency in the selection of evidence, including the selection and use of proxy conditions, to inform the model. Reporting in the CS was not explicit enough to assess the rationale for the selection (or not) of evidence used in the model. The ERG did not run its own searches in this regard, but the ERG's clinical advisors agreed that there was little or no evidence in the literature quantifying a surrogate relationship between aTTP and long-term morbidity.

4.1.5. Conclusions

The ERG recognise the paucity of data in the population of interest and the lack of precedent in terms of previous NICE HTA submissions in this population.

In general, the ERG consider that the company adopted a robust approach to the identification and selection of economic evidence in respect of each of the systematic reviews documented. However, the ERG noted concerns regarding the TLRs; specifically, regarding the selection of studies. This was impossible to audit across the TLRs undertaken. Moreover, given the paucity of evidence relating strictly to aTTP, it was justifiable to account for evidence from proxy conditions. However, these proxy conditions were inconsistently described and used in searching and study selection, and evidence from these proxy conditions was inconsistently included in final evidence tables. The ERG regard that this may have generated inconsistencies in which evidence was considered most relevant for inclusion in the economic model; indeed,

the linchpin of their utility estimation is a report from a conference abstract, and the lack of an excluded studies list precludes broader consideration of this potential threat to review validity.

4.2. Summary and critique of the company's economic evaluation

4.2.1. NICE reference case checklist

Table 31 evaluates the company's *de novo* economic model against the NICE reference case requirements.

Table 31: NICE reference case checklist

Attribute	Reference case and TA Methods Guidance	Does the de novo economic evaluation match the reference case?
Comparator(s)	Plasma exchange therapy (with or without spun apheresis, steroids or rituximab), without caplacizumab.	Yes
Patient group	Adults experiencing an episode of aTTP.	Yes
Perspective on costs	NHS & PSS	Yes
Perspective on benefits	All direct health effects, whether for patients or, when relavant, carers.	Yes, albeit long-term consequences lack data
Form of economic evaluation	Cost-utility analysis with fully incremental analysis	Yes
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared.	Yes, lifetime
Synthesis of evidence on outcomes	Based on systematic review.	Yes. Company conducted meta-analysis of HERCULES and TITAN but only HERCULES used in economic model due to quality concerns by EMA.
Measuring and valuing health effects	Health effect should be expresed in QALYs. The EQ-5D is the preferred measure of health related quality of life.	Yes
Source data for measurement of HRQOL	Reported directly by patients and carers.	Yes, albeit proxies used from some conditions
Source of preference data for valuation of changes in HRQoL	Representative sample of UK population.	Yes, HERCULES age/sex data applied to regression coefficients for a UK general population from Ara (2010). Burns et al mapped using UK tariff (Rowen et al,

Attribute	Reference case and TA Methods Guidance	Does the de novo economic evaluation match the reference case?
		2009)(Rowen, 2009}
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	Yes
Discounting	The same annual rate for both costs and health effects (currently 3.5%).	Yes
Probabilistic modelling	PSA is preferred to simultaneously explore the uncertainty associated with parameters.	Yes, albeit the uncertainty around many parameters is arbitrary.

Key: HRQoL, health-related quality of life; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life year; TA, technology appraisal

The ERG also conducted a critical appraisal of the company's economic analysis using the Drummond checklist (Table 32).[39]

Table 32: Drummond checklist

Question	Critical appraisal	ERG comment
Was a well-defined question posed in answerable form?	Yes	OK
Was a comprehensive description of the competing alternatives given?	Yes	OK
Was the effectiveness of the programme or services established?	Partially	HERCULES included healthier patients than UK practice. Evidence lacking on long-term consequences.
Were all the important and relevant costs and consequences for each alternative identified?	Yes	OK
Were costs and consequences measured accurately in appropriate physical units?	Yes	OK
Were the cost and consequences valued credibly?	Partially	Long-term benefits derived using numerous assumptions
Were costs and consequences adjusted for differential timing?	Yes	Costs & benefits discounted at 3.5% per annum
Was an incremental analysis of costs and consequences of	Yes	ICER calculated correctly

alternatives performed?		
Was allowance made for uncertainty in the estimates of costs and consequences?	Yes	Deterministic, scenario, threshold, and probabilistic sensitivity analysis undertaken, although some many parameters in PSA varied arbitrarily.
Did the presentation and discussion of study results include all issues of concern to users?	Yes	OK

Key: ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis

4.2.2. Population

The population entering the *de novo* economic model is adults with a confirmed diagnosis of aTTP (i.e. ADAMTS13<10%). This differs slightly from the HERCULES population which includes 20 patients (14%) who have ADAMTS13≥10% (i.e. unconfirmed aTTP) and two patients with missing data. However, the company include a subgroup analysis of patients with ADAMTS13<10% albeit with the qualification that this breaks randomisation. The confirmed aTTP subgroup matches the NICE scope and caplacizumab product licence hence may be more appropriate for the base case analysis. However, clinical advice to the ERG is that ADAMTS13 10-20% is a "grey area" over whether patients can be diagnosed with aTTP. Of the 20 patients in HERCULES, the majority (n=13) (CSR, Section 10.3.2) fell into this category.

The economic model includes all aTTP patients; no subgroup analysis by disease severity was conducted. As reported in Section 3.2.5.12, a subgroup analysis of severe patients for platelet response and rates of recrurrence was reported in the HERCULES CSR, using the French severity score ≥3 or severe neurological involvement or cardiac involvement (troponin >2.5 x upper limit of normal) as a marker of 'very severe' aTTP. This severe aTTP group comprised 30/72 (42%) caplacizumab and 25/73 (34%) SoC patients. Appendix E Table 6 shows caplacizumab maintains superiority over SoC for exacerbations in the "less severe" (n=90) and "very severe" (n=55) subgroups. Because aTTP presents as a "spectrum of disease", the ERG would have liked to have seen a subgroup analysis of severe patients (requested in Clarification Question B15). Without this, the ERG was unclear whether cost-effectiveness extends to the severe and non-severe subgroups. In response to Clarification Question B15, the company provided subgroup analysis from HERCULES for the very severe and less severe subgroups. There was very little impact on the company-presented ICER for either of these subgroups (Clarification Response Tables 12 and 13). Our experts also identified elevated cardiac troponin

level as indicative of more severe patients. No subgroup analysis by troponin level was conducted in HERCULES and the company responded that elevated troponin was only one factor indicative of more severe disease (response to Clarification Questions A5 and B16).

As discussed in Section 3.2.1.3, a discrepancy between HERCULES and the UK population was also noted in the CS. HERCULES was deemed to include fitter or “stably unwell” patients (CS, Document B, p.73) than typically observed in UK clinical practice. It is unclear whether this could bias the results in favour of caplacizumab albeit it is noted that there were a higher proportion of severe patients in the caplacizumab arm. In Clarification Question A16 the ERG requested baseline characteristics of the UK compassionate use programme in order to contrast with HERCULES, however a comparison of HERCULES with the compassion use programme was not possible as these data were not recorded (Clarification Response A14). The ERG believed mortality was likely to be higher in UK clinical practice than HERCULES, but as individuals start in the model with diagnosed aTTP having started PEX it is plausible that much of this additional mortality may have already occurred.

HERCULES was also conducted at specialist centres which are unlikely to be universal across the UK. The CS reports plans are afoot for a highly specialised aTTP service in the UK. However, the ERG understand that the scope of this service has yet to be confirmed. We understand there are significant capital and personnel requirements needed to introduce such a service. Where patients do not have access to specialist services, it seems unlikely that the efficacy reported in HERCULES could be achieved across UK centres. Clinical advisors to the ERG advise that following the introduction of the specialist aTTP service, many patients will nevertheless present to non-specialist centres and will require transfer. Travel to specialist centres is likely to delay treatment and increase mortality and patient deterioration.

Whilst the ITT population in the caplacizumab arm comprises 72 participants, one participant who withdrew consent prior to receiving the drug was dropped from the economic analysis.

4.2.3. Interventions and comparators

Individuals with a confirmed diagnosis of aTTP (ADAMTS13<10%) were given either caplacizumab plus standard of care (SoC) or SoC alone. SoC was defined as PEX, steroids, and RTX.

The caplacizumab regimen aligned with HERCULES and the product license. Immusupresssants (steroids and RTX) were used in the model according to their UK licensed

doses. RTX was administered as 375 mg/m^2 weekly for four weeks (with body surface area [BSA] estimated from HERCULES) in line with the license and UK guidance. Vial sharing was excluded in the base case. In HERCULES, 39% of caplacizumab and 48% of SoC participants were given RTX. However, the company noted that clinicians attending their advisory board believed RTX would be more widely used in UK practice than observed in HERCULES, perhaps more indicative of a sicker population. UK Registry data indicate RTX usage in aTTP is approximately 78%,[5] and the ERG's clinical advisors confirmed that RTX use would likely be higher than observed in HERCULES. The ERG's clinical advisors indicated that RTX was a component of SoC rather than a distinct comparator.

There was a disconnect between the use of other TTP therapies used in HERCULES and those recommended in UK clinical practice. Other regimens used in fewer than 5% of patients in HERCULES and which did not align with UK practice were not included in the economic model. These "other regimens" (including mycophenloate mofetil, hydroxychloroquine, splenectomy, and immune globulin concentrate infusion) hence could contribute towards the efficacy and safety outcomes observed in the trial and therefore the economic model, but their costs are excluded (CS, Document B, Sections B.3.2.3 and B.3.5.1).

Although these "other regimens" were each used in fewer than 5% patients, two (mycophenloate mofetil, and immune globulin concentrate infusion) were used in more than 5% of participants in the caplacizumab arm. The ERG believes it is unlikely that these differences could have influenced outcomes observed in the trial. Three individuals (two caplacizumab, one SoC) were also given splenectomy during the trial. These costs were not included in the model as splenectomy was "not standard practice in the UK". The company reported splenectomy has not been used in this indication in the UK since 1970 hence this omission appears reasonable.

4.2.4. Modelling approach and model structure

The company built a *de novo* cost-effectiveness model consisting of a decision-tree component and a Markov model component.

The decision tree component modelled the individual through the acute phase of illlness and was described in Document B (Section B.3.2.2), and reproduced in Figure 4 below. Individuals started on admission to hospital with confirmed diagnosis of aTTP (ADAMTS13<10%) and were given either caplacizumab plus SoC or SoC alone. Patients either responded or were initially

refractory before responding. They then have disease exacerbation or no exacerbation and patients alive at the end of the decision tree process progress to the lifetime Markov model.

The Markov component was also described in Section B.3.2.2 and reproduced below in Figure 5. All individuals entering the Markov process start in the remission state. At the end of each model cycle they remain in remission or transition to the “true relapse” or death states (the term “true relapse” was used to distinguish between relapse as per the Markov model and acute relapse defined in HERCULES). The remission health state was further split into sub-states for long-term complications (cognitive impairment, neuropsychological impairment, both conditions, and neither condition). These substates were not explicitly modelled as they were not considered to alter the risk of death.

The decision tree data were partly informed by data from the HERCULES trial, whilst long-term data were informed by literature searches and clinical opinion.

Base case clinical efficacy in the acute stage was driven by the following data from HERCULES:

- Proportions of patients having “early” (recurrence during the 30-day period post-PEX) and “late” exacerbations (recurrence after the 30-day period post-PEX): summarised in Section 3.2.5.4 .
- Hospitalisation/ICU days: summarised in Section 3.2.5.9.
- Proportions of patients with refractory disease: summarised in Section 3.2.5.4.
- Caplacizumab treatment compliance and duration.

Figure 4: Decision tree component of economic model

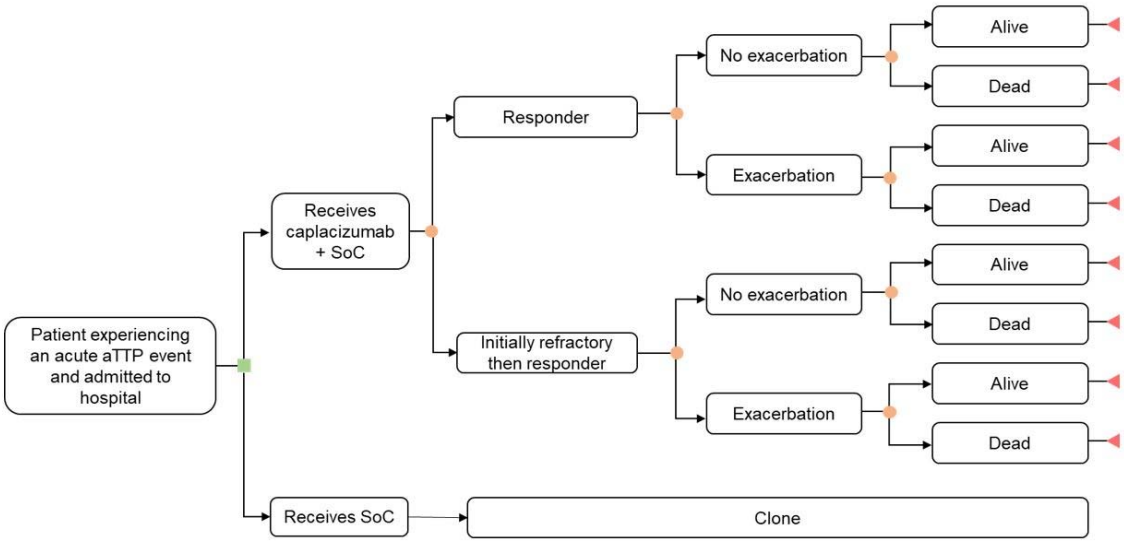
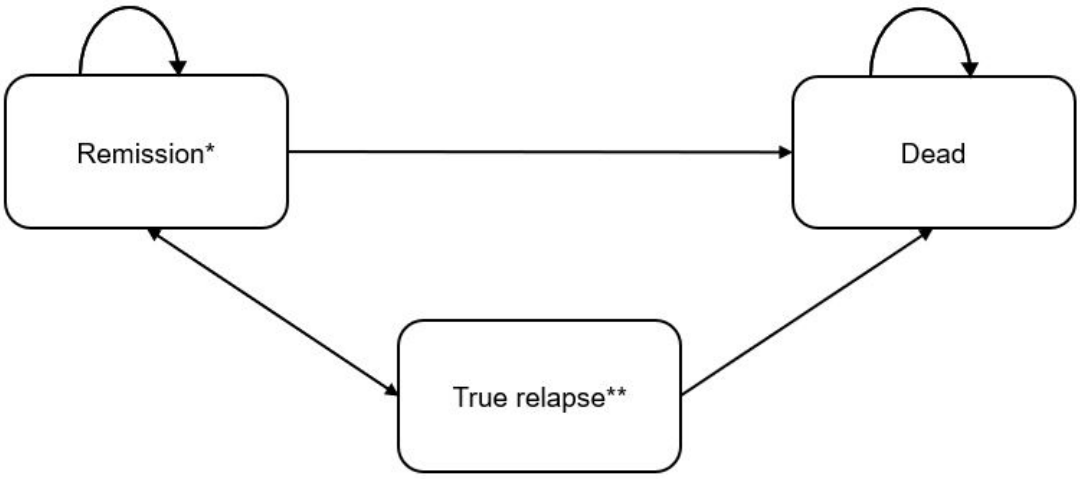


Figure 5: Markov component of economic model



The diagnosis of confirmed aTTP takes place pre-model and individuals in the model have also started receiving PEX. However, the ERG cannot think of any reason the costs and benefits of diagnosis would differ by arm.

An updated model was submitted in response to the ERG clarification questions. Only the probabilistic and one-way sensitivity analyses were impacted. The base case ICER was unaffected. The following changes were made by the company:

- Minor omissions in the probabilistic sensitivity analysis (PSA) parameterisation (see Clarification Response B13).

4.2.4.1. Summary of model assumptions

The company's model included the assumptions reported in the CS (Document B, Table 47) and summarised in Table 33.

Table 33: Model features

Factor	Company base case	Company's justification	ERG Comments
Exacerbations	Individuals in the decision tree model can have a maximum of one exacerbation during the acute period.	Simplifying conservative assumption	OK.
Exacerbations	The probability of acute exacerbation was the same for responders and refractory disease patients	Lack of data available	OK
Discounting	No discounting was applied in the decision tree model	Short 3-month time horizon	OK
Mortality	No additional mortality associated with an exacerbation	Conservative assumption given lack of data; SoC patients switched to caplacizumab on exacerbation.	OK
Relapse	No individuals enter the Markov model in the "true relapse" state	Consistent with definition of true relapse	OK
Utility	Acute utility was based on utility for hospitalisation	Clinically validated proxy as collection of utilities during acute episode not ethically justifiable.	OK
Long-term complications	Long-term complications other than cognitive impairment and neuropsychological impairment are excluded	Lack of data	OK

Factor	Company base case	Company's justification	ERG Comments
Long-term complications	The risk of cognitive impairment and neuropsychological impairment are independent	Lack of data	OK. The ERG note that the impact of a possible relationship between cognitive impairment and neuropsychological impairment is likely to have limited impact, as duration of neuropsychological impairment is 12-months.
Long-term complications	A lifetime duration (55 years) was used for risk of cognitive impairment	Clinical experts agreed cognitive impairment is likely to persist over patient's lifetime.	OK
Long-term complications	A 12-month duration was used for risk of neuropsychological impairment	Based on published sources, likely conservative.	OK, conservative
QALYs	Stroke was a proxy for moderate/severe cognitive function utility value	Based on clinical opinion	OK; ERG clinical experts concur
Patients body surface are (BSA)	BSA calculated from HERCULES	HERCULES population assumed to be generalisable to clinical practice	Unclear but effect likely to be minimal
Relapse rate	Risk of relapse was independent of long-term complications. Individuals with cognitive impairment are no more or less likely to relapse	No data	OK
Relapse rate	True relapse is constant over time and assumed to be 1% annually.	Based on UK current experience	OK
Relapse	Probability of relapse was not dependent on treatment given in acute phase.	Clinical opinion	OK, no reduction in relapse rate with addition of caplacizumab likely to be conservative. Evidence that RTX in the acute phase reduces risk of subsequent relapse

Factor	Company base case	Company's justification	ERG Comments
			(ERG expert) but given to both arms so no likely impact.
Relapse	Individuals having a true relapse are given the same treatment as in the acute phase	Conservative, caplacizumab would be used if available	OK
Mortality	Individuals having a true relapse have the same mortality as those in the acute phase	Simplifying assumption, varied in sensitivity analysis	OK
Long-term complications	There was no cumulative effect of relapse on long-term complications	Simplification, given low probability of relapse	OK
Utilities	Utility for true relapse same as exacerbation in acute phase	No evidence of relationship between number of relapses and utility	OK

Key: BSA, body surface area; ERG, Evidence Review Group; HRQoL: health-related quality of life; QALY: quality-adjusted life year; RTX, rituximab; SoC, standard of care; TA: technology appraisal

One of the ERG's clinical advisors diagreed with the assumption that the probability of relapse was independent of acute treatment. However, since both arms received rituximab we believe the impact of this to be minimal besides suporting the company's argument of a low relapse rate. Furthermore, the ERG believed the company intended this assumption to relate to any difference between caplacizumab and SoC.

Table 9 in the company's clarification response summarised all the data used in the economic model including those omissions identified in Clarification Question B13.

4.2.4.2. Perspective, time horizon and discounting

The model used an NHS and PSS perspective. Carer quality of life associated with long-term cognitive impairment was included (refer to Section 4.1.2.3 and Section 4.2.7). A lifetime horizon (55 years) was used for the Markov model and costs and benefits were both discounted at 3.5%.

The model was sensitivite to a shorter time horizon: a 20-year scenario conducted by the company yielded an ICER of £47,416. However, the ERG's clinical advisors concurred that the

benefits of caplacizumab in terms of reduced mortality and cognitive impairment would continue to accrue until death.

4.2.5. Treatment effectiveness

4.2.5.1. Acute outcomes

The decision tree model only used data from HERCULES; TITAN was excluded due to the EMA concerns with the "conduct of the Phase II" trial (nevertheless, the ERG noted the TITAN publication had not been retracted).

Due to the short duration of HERCULES it was assumed observed "relapses" were actually late exacerbations for the purposes of the economic model. These "late" exacerbations only occurred in the caplacizumab arm (CS, Document B, Table 9 and reproduced in Table 34 below). The ERG's experts agreed this assumption aligned with the definition. In any case a scenario was carried out in which late exacerbations were excluded which had little impact on the ICER (CS, Document B, Table 51).

Table 34: Exacerbation data from HERCULES used in the economic model (ITT)

	HERCULES	
	CAPLA (n=71[a])	**SoC (n=73)**
Patients with exacerbation, n (%)	3 (4.23%)	28 (38.36%)
Patients with "late" exacerbation, n (%)	6 (8.45%)	0
Total early and "late" patients with exacerbations, n (%)	9 (12.68%)	28 (38.36%)

Key: CAPLA, caplacizumab; CS, company submission; ITT, intention to treat; SoC, standard care

Note: [a] Whilst the 72 caplacizumab ITT patients are included in the CS Table 9, the one patient who did not receive treatment was excluded in the model.

Treatment switching was permitted for SoC patients following disease recurrence: 38% (28/73) SoC participants switched to caplacziumab. No formal adjustment for crossover was carried out by the company which suggests the analysis will be conservative for caplacizumab as this most likely benefits SoC (however, an important caveat to this relates to the calculation of hospitalisation/ICU days and AEs, discussed below).

The ERG queried whether proportional hazards held for time-to-event outcomes given a Cox proportional hazards model was used. A Kaplan-Meier curve was reported for the primary outcome (time to platelet count response) in the CSR (Figure 9). Although not explicitly

modelled, platelet count informs the exacerbation/relapse endpoint. The company confirmed the proportional hazards assumption was not violated (Clarification Response A8).

There were [redacted] refractory patients in the caplacizumab arm of HERCULES and either [redacted] in the SoC arm, depending on the definition of refractory used. The company used the highest estimate in the base case in line with HERCULES. A scenario analysis investigated using a 17% refractory rate for SoC paired with a RR of 0.2 for caplacizumab had little impact on the ICER (CS, Document B, Table 51). One of the ERG's experts agreed that there are unlikely to be refractory individuals when using caplacizumab but estimated that 10–20% of patients on SoC would experience refractory disease.

Acute mortality in HERCULES (0% caplacizumab, 4.2% SoC) was much lower than expected in UK clinical practice according to the company's experts. This may in part be a result of the healthier individuals or use of specialist centres in HERCULES. Hence, alternative sources were preferred for the economic model. A figure of 13.2% mortality in the acute phase of aTTP was used for SoC. In response to Clarification Question B7, the company confirmed this figure was obtained from a meta-analysis (discussed above in Section 4.1.4.1). Mortality for caplacizumab was estimated as 4.28% (8/187) from the company's compassionate use programme which gave a RR of 0.32. The response to Clarification Question A14 confirmed these deaths occurred in the acute period.

4.2.5.2. Long-term outcomes

The link between aTTP and long-term consequences appears to be generally accepted.

According to the CS, there is a "wealth" of literature supporting long-term complications following acute aTTP. The company refer to a systematic literature review of burden of disease related to mortality, exacerbation, relapses, stroke, transient ischemic attach (TIA), renal impairment, acute renal failure, acute myocardial infarction (AMI), mesenteric ischemia, pulmonary embolism and deep venous thrombosis (DVT) Section 4.1.4.1).

Long-term complications included in the economic model were limited to cognitive impairment (a mix of mild/moderate/severe), and neuropsychological impairment (comprising depression, anxiety, and post traumatic stress disorder [PTSD]). The company commented that the impact of aTTP on cognitive impairment is "universally recognised". The ERG's clinical advisors agreed that some patients would experience cognitive impairment; however, while some studies indicated an association, it considered that the evidence base was not sufficient to estimate the

proportion of patients who experience cognitive impairment or to dermine the impact of cognitive impairment. Other potential long-term consequences were omitted from the model due to a lack of data and clinical consensus (CS, Document B, Section B.3.2.2).

The ERG assumed that the company had used the studies identified in the burden of disease search. The company identified the baseline (SoC) risk of cognitive impairment used in the model from Kennedy et al. (2009)[40] with alternative values from Cataland et al. (2011)[21] explored in a sensitivity analysis. Both papers were cited in the burden of disease review provided by the company (discussed in Section 4.1.4.1) but not formally included given the review's focus on comorbid conditions on presentation, and complications developing during the acute phase. Both papers were judged to be of poor quality by the ERG and concerned small numbers of individuals. Neverthless they play a pivotal role in the company's model in terms of baseline estimates of cognitive impairment. Kennedy (2009)[40] reported 54.2% of aTTP patients had mild cognitive impairment and 20.8% had moderate/severe cognitive impairment. Cataland (2011)[21] reported 63% of patients had cognitive impairment; which split by severity was assumed to be the same as Kennedy (2009).[40] A lifetime duration of cognitive impairment was used based upon clinical opinion. An additional paper was cited (Lewis et al. 2009) in the burden of disease review, but this study did not include an estimate of 'caseness' arising from cognitive impairment. The ERG scrutinised the presented burden of disease review and was satisfied that while of poor quality, the data sources presented for this parameter were the best available given those presented in the company submission. However, the ERG was unable to undertake its own search for evidence.

The proportion of individuals with neuropsychological impairment was taken from Chaturvedi et al. (2017).[18] The authors reported depression in 36.8% and PTSD in 35.1% of aTTP survivors using two validated questionnaires. Measures were highly correlated. The company thus used the Chaturvedi rate of depression in the model to indicate neuropsychological impairment. The ERG was satisfied that this data source was the best available given its sample size (n=236), though the study did rely on a convenience sample to recruit patients as opposed to a systematic or hospital-based sampling frame. Higher and lower rates were explored in the scenario analysis. A duration of 12 months was assumed.

The proportion of individuals with SoC experiencing long-term complications is reported in the CS (Document B, Table 24). Altering the baseline proportions of individuals with long-term complications had little impact on the ICER.

Reduction in long-term outcomes with caplacizumab

There were no long-term data on the effectiveness of caplacizumab. The CS noted the UK TTP Registry has been collecting data since 2008, but has only begun to collect long-term data beyond the acute phase from 2018. The company's estimation of long-term consequences thus relied on literature searches and clinical opinion (refer to Section 4.1.4.2).

The company's clinical experts claimed that since caplacizumab shortens the time in which brain cells are destroyed then there is a "biological plausibility" of a treatment effect of caplacizumab on long-term complications.

No studies were identified which associated long-term complications with characteristics of individuals with aTTP. Two studies described by the company found no evidence of an association between cognitive impairment and recurrence/relapse (Han et al., 2015; Falter et al., 2017),[19,22] and no studies were found that investigated an association between time spent at risk of microvascular thrombosis (using proxies of TTPN, hospitalisation/ICU stay and PEX days), and long-term complications. In terms of neuropsychological impairment, the company cited one study by Hatch et al. (2018)[41] to support their assertion, but it was unclear how this study supported a link between length of ICU stay and neuropsychological symptoms, given the cited study's goal was to link psychiatric diagnoses after ICU stay to survival.

To quantify the reduction in risk of long-term complications with caplacizumab, the company presented their expert advisers with a selection of potential proxies for the reduced risk (CS, Document B, Table 23). In the event, we are told the experts preferred a combination of hospitalisation and ICU days as being the strongest proxy (Clarification Response B6). Thereafter the company used the following formula based on the proportion of and duration of hospital and ICU stay for caplacizumab versus SoC.

$$RR\ for\ long\ term\ complications = \frac{p(hospitalisation\ cap) * hospitalisation\ days\ cap + p(ICU\ cap) * ICU\ days\ cap}{p(hospitalisation\ SoC) * hospitalisation\ days\ SoC + p(ICU\ SoC) * ICU\ days\ SoC}$$

A relative risk (RR) of 0.62 was calculated, inferring a 38% reduction in long-terms events from treatment with caplacizumab. This figure was applied to the SoC baseline estimates of cognitive impairment, neuropsychological impairment, and mortality. The calculation was unclear hence the ERG sought further clarification.

The response to Clarification Question B6 outlined the calculation (refer to Clarification Response, Table 4). However, in response to ERG Clarification Question A6 the company also revealed that hospitalisation days included ICU days which implied an element of double counting in the calculation of the RR above.

Rather than recalculate the RR, the company referred to the previous calculations for hospitalisation (RR 0.79) and ICU (RR 0.35) presented in the CS (Document B, Table 23). These yielded ICERs of £56,216 and £23,158 per QALY, respectively. Importantly, however, the original calculation failed to take account that ICU stay was embedded in the hospitalisation days. However, the company did not change their base case noting the "original RR of 0.62 applied in the model still falls in the middle of the range of RRs presented". The ERG found this puzzling, and would have preferred an updated RR was used in a revised base case. Following FAC, the Company clarified the ICU average stay was calculated for individual attending ICU rather than the whole population. The Company and ERG agreed the simplest calculation was to divide the hospitalisation including ICU days, which resulted in a slightly higher RR compared to the Company's original 0.62:

$RR =$ [redacted] $= 0.6875$.

Whilst the ERG's clinical advisors agreed with the biological plausibility argument of a reduction in long-term complications from an effect of caplacizumab on microthrombi they stated that hospitalisation was only a surrogate marker for this. One clinical advisor suggested alternative proxies for reduction in long-term complications could be serial measurements of troponin or degree of renal dysfunction. However, none of these were available.

Whilst the calculations by the company made sense they gave rise to an inconsistency in the modelled data (Table 35):

- There were a higher proportion of individuals with neuropsychological impairment only in the caplacizumab arm than the SoC arm
- In the SOC group, the proportion of individuals with both cognitive and neuropsychological impairment was higher than the proportion with neuropsychological impairment only. In the caplacizumab group the opposite was true.

There is no evidence or suggestion that caplacizumab would increase the likelihood of neuropsychological impairment only or decrease the likelihood of individuals having both conginitive impairment and neuorpsychological impairment, which is what the model suggested.

Table 35: Proportions of patients with long-term complication used in the economic model

	SoC	CAPLA	Ratio (CAPLA to SoC)
Proportions with both cognitive impairment and neuropsychological impairment	27.63%	10.62%	0.38
Proportions with cognitive impairment only	47.37%	35.88%	0.76
Proportions with neuropsychological impairment only	9.21%	12.22%	1.32
Proportions with neither	15.79%	41.28%	2.61
Total	100%	100%	

Key: CAPLA, caplacizumab; SoC, standard care

There is no straightforward way to adjust for this imbalance in the economic model, so it is highlighted as an area of further uncertainty.

Mortality

The company identified two literature sources (Deford et al., 2013; Upreti et al., 2019)[42,43] to estimate the increase in mortality of an aTTP population. Both of these sources involved calculations by the company to yield a standardised mortality ratio of 7.8 and 8.3 relative to the general population. The latter was chosen for the model due to it being a more recent source. The study by Deford et al. (2013)[43] was cited in the burden of disease review (although the ERG note that the burden of disease review did not formally synthesise evidence for long-term mortality). However, it was not clear how Upreti et al. (2019)[42] was identified or whether alternative sources were available. Both sources provided plausible estimates of long-term mortality after aTTP, drawing on several years of follow-up data per patient.

The same RR for a reduction in long-term mortality with caplacizumab was used as for long-term complications; i.e. 0.62. The ERG noted that this approach was unsupported by the scarce literature.

Relapse

The company included an annual relapse rate of 1% in the model on the basis that "true relapse" is rare in UK practice due to "proactive monitoring and pre-emptive treatment with RTX". For individuals in remission it was assumed 10% receive four RTX doses per year suffice in response to elevated ADAMTS13 scores. One of our experts believed a higher proportion of individuals would receive RTX in remission, possibly 30%. No treatment effect for caplacizumab is applied to the long-term relapse rate. Relapse rates of 0% and 2% were explored in the company's sensitivity analysis.

4.2.6. Adverse events

Adverse events costs were not included in the base case model since these were assumed to be included in hospitalisation costs. However, they were included in a scenario analysis. AEs included patients experiencing short-term (acute phase) serious adverse events as observed in HERCULES. On the advice of clinical experts, PEX complications including DVT and infection were also included, as were renal and urinary disorders (CS, Document B, Table 31).

The adverse event calculations exclude those 38% (28/73) SoC patients who switched to caplacziumab following exacerbation. Hence, AEs may be conservative towards caplacizumab.

AEs in the acute period did not have a material impact on the ICER.

4.2.7. Health-related quality of life

No quality of life data were collected alongside HERCULES. The company argued it would be unethical to solicit quality of life data from critically ill patients. As a result, quality of life data used in the model were obtained from the literature.

Baseline utility prior to an initial aTTP event (0.87) was estimated using HERCULES age/sex data and applying the regression coefficients for a UK general population from Ara (2010).[44] Multipliers for acute hospitalisation (0.64) and post-hospital discharge (0.82) were applied based on a study by Pappas et al. (2018)[32] of intracranial haemorrhage and ischaemic stroke. While the ERG agreed with the use of a proxy condition, the face validity of the estimates and the data source, they were unable to reconstruct the chain of inference that yielded these multipliers.

Utility in remission (0.736) was estimated from Burns et al. (2018).[45] The company had conducted a systematic literature review (refer to Section 4.1.2.1), and targeted literature

review of utilities (Section 4.1.2.2). While the ERG acknowledged the limitations of this source (including that the format was a poster presentation, and that it was company authored), it considered it was the best source available. Using registry data (n=72), utilities were mapped from SF-36 to EQ-5D-3L using an algorithm (Rowen, 2009), and included a specific decrement for neuro-psychological symptoms.

Utility multipliers for long-term complications were sourced from the literature using a range of proxies. A multiplier of 0.93 was used for mild cognitive impairment (Gage et al. [1996]).[46] A moderate/severe cognitive impairment multiplier of 0.61 was based on stroke sufferers from Gage et al. (1996). A neuropsychological impaiment multiplier of 0.77 was taken from Sullivan et al. (2011)[47] in individuals with depressive disorder. Finally, a caregiver multiplier of 0.83 from Van Exel (2005)[48] was used for moderate/severe cognitive impairment.

Utlities values and multipliers used in the base case model are summarised in the company's clarification response (Table 7).

Disutilities for AEs were sourced from the literature and previous NICE submissions (TA327[49] and TA420[50]; CS, Document B, Table 32).

There appeared to be a disconnect between the economic model and the CS with respect to utilities for long-term complications. This was clarified in Clarification Response B10. The utility multiplier of 0.73 for neuropsychological impairment reported in the CS (CS, Document B, Table 34), should have been 0.77 as per the economic model.

Only the utility for baseline remission (0.736) had the potential for a substantive impact on the ICER. This was varied by the SE (0.031) reported in Burns et al. (2018)[45] in the company's one-way sensitivity analysis (OWSA) and PSA. Given the small sample size of Burns et al., and the fact that it is an unpublished study, the ERG would have liked to have seen greater uncertainty explored around this variable.

4.2.8. Resources and costs

4.2.8.1. Acute model

Treatment costs for caplacizumab given by the company included a patient access scheme (PAS) discount. The cost per dose of RTX was estimated from the *British National Formulary*. Whilst the ICER was sensitive to the cost of caplacizumab, it was not sensitive to imunosuppressant (corticosteroids or RTX) dosage or cost.

Hospitalisation/ICU and PEX days and volume were calculated from HERCULES whilst outpatients visits and ADAMTS13 activity tests were based on assumptions. RTX doses were based on UK treatment guidelines. None of these assumptions had a material impact on the ICER.

Caplacizumab compliance and treatment duration were taken from HERCULES. Assuming 100% compliance had little effect on the ICER. The model was sensitive to caplacizumab treatment duration from HERCULES; [redacted] in the double blind period and [redacted] in open-label period following exacerbation, respectively.

No administration costs were included for either arm; it was assumed these were included in the hospitalisation costs. It was also assumed that caplacizumab post-discharge was self-administered or given by the individual's carer. This was deemed reasonable by our experts.

Resource unit resource costs for the acute period were taken from official sources including NHS Reference costs (CS, Document B, Table 37). The ERG found a number of issues with the data sources used in this table. Firstly, there was a discrepancy for PEX procedure cost. This was reported in the CS (Document B, Table 37) as £602.34 but does not agree with the citation (17/18 NHS Reference Costs, code SA44A) which reports this cost as £1,265. The ERG's expert ackowledged the cost of PEX is likely to differ depending upon supplier and whether it is provided in the unit, ward or ICU. Whilst the company used clinical expert opinion for a haematologist outpatient visit at £250, NHS Reference Costs 17/18 reported a clinical haematology, consultant led visit at £171. Expert opinion was used for the ADAMTS13 activity test but this made little impact on cost-effectivenesss. One of the ERG's experts noted that MRI is the "modality of choice" for cerebral imaging rather than CT scan, which is the least useful.

Hospitalisation days and ICU stay were both substantively reduced in the caplacizumab arm (CS, Document B, Table 10; CSR Table 14.2.1.6.3; Scully, 2019[4] [Table 2]). The ERG queried whether hospitalisation days reported are inclusive or exclusive of ICU days (to be sure to avoid double counting). The company responded that reported hospitalisation was inclusive of ICU days (Clarification Question A6). Furthermore, there was a lack of clarity on the association between reported hospitalisation/ICU days reported in the CS tables and the data used in the model (Clarification Question B8).

Clarification Question B6 revealed these aggregate data for hospitalisation and ICU days were not used in the economic model. Instead hospitalisation and ICU days were calculated in a post-

hoc subgroup analysis of HERCULES according to each of the decision tree model branches and excluding SoC switchers (CS, Document B, Table 38). The company stated this was to avoid overcounting resource use from those SoC patients who switched to caplacizumab on exacerbation. In calculating resource use for the SoC switchers, rather than use the open-label period the company assumed this would be equal to the initial double blind period, an assumption supported by the company's clinical experts (Clarification Response B8). These post-hoc subgroup data used in the model are reported in the CS (Appendix S, Table 40). Back calculating the subgroup data to get to the aggregate data reported in the paper (and Table 4 of the clarification response) was not provided. Nor could the ERG replicate the aggregate data; presumably because of the exclusion of switchers.

The ERG was also concerned whether ICU stay in HERCULES could be higher than observed in UK practice. The footnote to Table 2 in HERCULES (Scully, 2019[4]) noted admission to ICU for PEX "is standard practice at some centres". The ERG believed this could have inflated (absolute) ICU stay. In addition, in the economic model, it was noted that "For hospitalization days excluding ICU: some subjects have Value 0. Which means they did not have general ward stay days, only ICU days." Discharge directly from ICU seemed unlikely unless there was a fatal event. Percentages of participants admitted directly to ICU were similar across arms (caplacizumab 39%, SoC 37%). Clarification Question A14 queried whether direct admission to ICU was standard practice at the four UK HERCULES centres. In their response to Clarification Question A12, the company confirmed that 2/3 UK centres had a policy to admit all individuals with acute aTTP directly to the ICU whilst another admitted about half. The ERG therefore agreed with the company assertion that ICU days are unlikely to be inflated relative to UK practice by direct admission to ICU. The classification of HERCULES participants as "stably unwell" also did not suggest admission to ICU but if they are healthier than UK practice then this could be a conservative estimate. One of the ERG's experts commented that most indivduals will be admitted to the ICU in the UK but that it was unlikely that they would be discharged directly from ICU. Nevertheless, the ERG requested a scenario whereby ICU days were reduced across both arms (Clarification Question B11). The company reported a scenario with a 20% absolute reduction in ICU days across both arms which had little impact on the ICER (Table 8, clarification responses).

Costs and calculations reported in the CS were checked against sources (CS, Document B, Table 45 and Table 46).

4.2.8.2. Long-term model

Resource use in remission (long-term Markov model) was based on assumptions (CS, Document B, Table 39).

Clinical opinion was used to estimate the resource usage proportion of patients incurring such resource for being free of chronic condition, having cognitive impairment, neuropsychological impairment, or both conditions combined (CS, Document B, Table 39 and Table 40). One of the ERG's experts suggested higher proportions for usage of psychology/counselling/mental health services, antidepressants and haematology clinic time. Altering these variables had little impact on the ICER.

Costs for resource use of long-term complications were reported in the CS (Document B, Table 41). These were checked against sources. As in the acute setting, the ERG's clinical advisors considered that MRI was a more suitable modality than CT scan.

Lifetime costs and QALYs for the relapse state (including long-term complications) were modelled using a "payoff" approach[51] to avoid explicitly modelling computationally intensive tunnel states in the Markov model. The method appears to have been implemented correctly and is calculated as the area under the SMR curve to estimate time spent in the relapse state, and then applying costs, utilities, and discounting.

The ERG observed that no inflation of 17/18 NHS Reference Costs was conducted.

5. COST-EFFECTIVENESS RESULTS

5.1. Company's base case results

The company base case results are shown in Table 36 (refer also to the CS, Document B, Table 48, section 3.7.1).

Table 36: Discounted base case results, with PAS discount applied for caplacizumab

	Total			Incremental			ICER incremental (£/QALY)
Technologies	**Costs (£)**	**LYs**	**QALYs**	**Costs (£)**	**LYs**	**QALYs**	
SoC	[redacted]	[redacted]	[redacted]				
CAPLA	[redacted]	[redacted]	[redacted]	[redacted]	5.48	[redacted]	£37,986

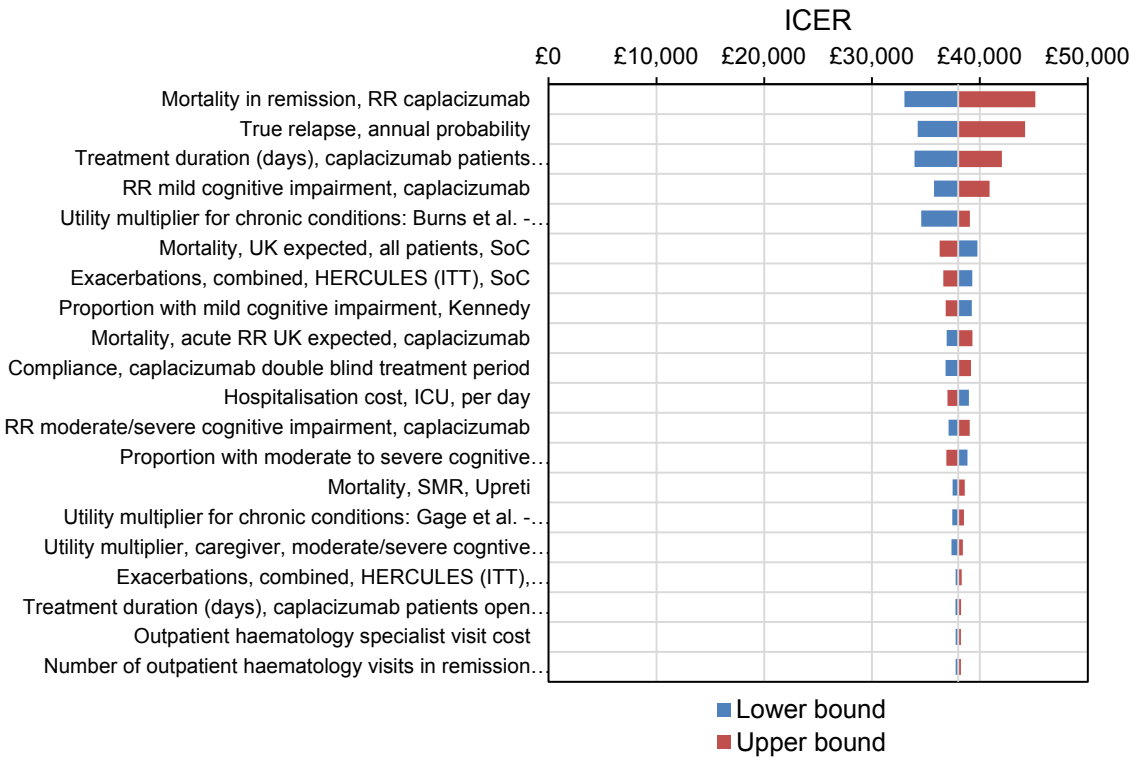
Key: CAPLA, caplacizumab; ICER, incremental cost-effectiveness ratio; LY, life years; PAS, patient access scheme; QALY, quality-adjusted life year; SoC, standard of care

Source: CS, Document B, Table 48

5.2. Company's one-way sensitivity analysis

A set of 133 parameters were investigated in the company's one-way sensitivity analysis (OWSA); the Tornado plot captured the most influential 20 (Figure 6). The company stated that there was "no notable impact" on the results compared to the original model. Whilst the company stated the parameters were varied according to their 95% CI, many of these estimates were arbitrary; e.g. costs and resource use were mostly assigned a 10% standard error.

Figure 6: Tornado plot of one-way sensitivity analysis



Key: ICER, incremental cost-effectiveness ratio; ICU, intensive care unit; ITT, intention-to-treat; RR, relative risk; SMR, standardised mortality ratio

Source: Reproduced from the updated model following ERG Clarification Questions

Parameters having the greatest impact on cost-effectiveness were RR for mortality in remission, annual probability of relapse, caplacizumab treatment duration, the RR of experiencing long-term mild cognitive impairment, and the utility multiplier for neurological symptoms.

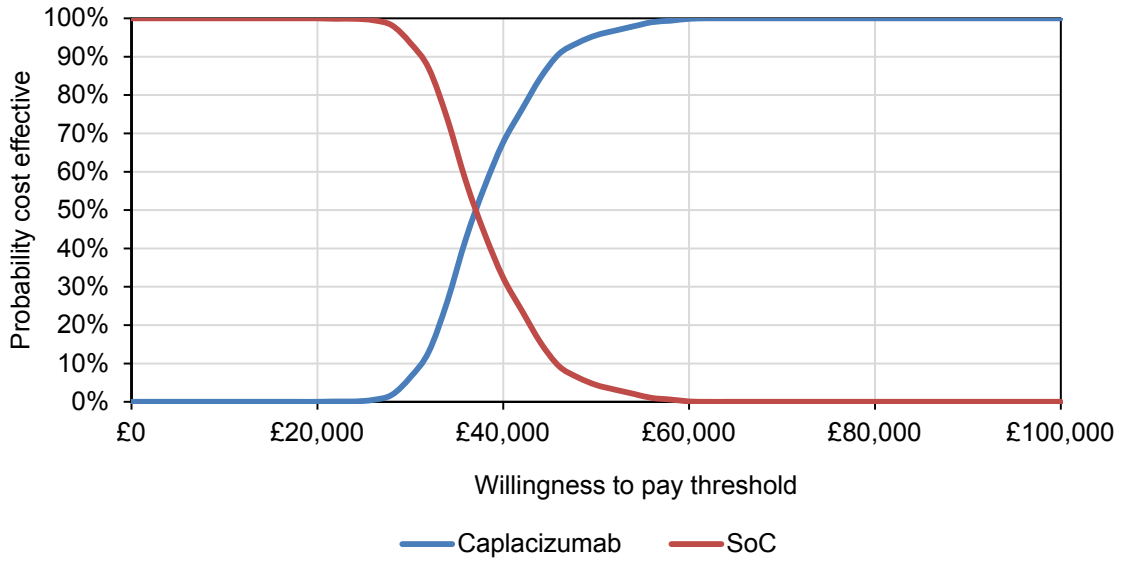
5.3. Company's probabilistic sensitivity analysis

The PSA results were taken from the "updated" model and the company reported that there was "no notable impact" on the results compared to the original model. The ICER from the PSA was £37,478 (95% CI: 28,303 to 53,077) per QALY. These figures showed modest variation from the deterministic. As noted above, limited variation was explored around many parameters. The cost-effectiveness acceptability curve (CEAC) is taken from the updated model (Figure 7).

In the original company model "parameters" worksheet, "Refractory, Scully HERCULES (aTTP only), caplacizumab" and "Refractory, Scully HERCULES (aTTP only), SOC" were missing the β

parameter (Cells J23 & J27) and compliance caplacizumab, open-label period was missing a standard error (Cell G117). Clarification Question B13 asked the company to explain these inconsistencies. The company corrected these in the updated ERG model (Clarification Response B13). These changes only applied to the OWSA and PSA.

Figure 7: Cost-effectiveness acceptability curve



Key: SoC, standard of care

5.4. Company's scenario analyses

The company conducted a wide range of scenario analyses presented in the CS (Document B, Table 51).

ICERs were reported to be sensitive to acute and long term mortality and the RR of long-term complications. The ERG also noted a higher ICER for a 20-year time horizon. The company reported favourable ICERs (i.e. <£30,000 per QALY) under two scenarios: (1) when a 1.5% discount rate was used, and (2) when a QALY multiplier of 1.7 was used.

The 1.5% discount rate scenario was applied to both costs and benefits. The rationale used by the Company was that costs are front-loaded with caplacizumab whilst benefits (potentially) accrue long-term. The ERG is aware of the current debate around using a lower discount rate for benefits following recent Treasury guidance[52]. Nevertheless, the use of 1.5% discount rate is not consistent with the present NICE reference case.

The company rationale for considering a 1.7 QALY multiplier scenario relates to “life-saving treatments at the end of life” (section B.3.8.3). However, the ERG noted that caplacizumab in this indication does not meet formal end-of life criteria and there is insufficient evidence to support extension to life. The ICER for the subgroup of aTTP patients (ADAMTS13<10%) resembled the base case (refer to CS, Document B, Table 54).

5.5. Company’s threshold analyses

The company also conducted two sets of threshold analyses on the most uncertain of the input parameters. Firstly they jointly varied the RRs for acute (0.32) and long-term mortality (0.62) (CS Table 52). The model was most sensitive to the RR for mortality in the acute period. If the RR of acute mortality was above 0.5 (base case was 0.32) then caplacizumab was not cost-effective at a threshold of £30,000 per QALY regardless of the RR of mortality in remission.

The company also jointly varied the RRs for long-term cognitive impairment (base case 0.62) and long-term neuropsychological impairment (base case 0.62) with caplacizumab (CS, Document B, Table 53). The model was most sensitive to the RR of cognitive impairment with caplacizumab. When the RR for cognitive impairment was above 0.3 (base case 0.62), caplacizumab was not cost-effective at a threshold of £30,000 per QALY regardless of the RR of neuropsychological impairment. This was unsurprising since neuropsychological impairment is only applied in the 12 months following hospital discharge.

5.6. Model validation

The model concept was informed by a clinical expert advisory board whilst a Delphi panel was used to quantify the evidence on long-term consequences. Each was attended by seven clinical experts in treating aTTP. Further teleconferences with these experts were conducted to validate model inputs and assumptions. The economic model also also underwent quality checks by senior analysts not involved in the model development (CS section B.3.10.1). No independent external review of the economic model appeared to have been conducted.

5.6.1. Model verification procedures

The ERG conducted a series of checking/verification procedues on the model inputs, calculations, and outputs:

- Model inputs were cross-checked against those reported in the CS.

- Model inputs were checked against published sources
- A series of extreme value and logical checks were conducted to ensure the model behaved as expected.
- Model outputs were checked against those reported in the CS including the base case, PSA, OWSA, and scenarios, and
- Equations and formulae within the model were checked.

Generally, the company model was well conducted and no substantive implementation errors were identified.

The ERG determined the principal drivers of the economic model were:

- RR of acute mortality;
- RR of long-term complications;
- RR of mortality in remission;
- caplacizumab price;
- model time horizon;
- relapse rate; and
- utility in remission.

6. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

6.1. ERG corrections to company analyses

The ERG implemented a minor correction to the company model:

- The PEX procedure cost reported as £602.34 in the CS (Document B, Table 37), did not agree with the citation "17/18 NHS Reference Costs, non-elective long stay (SA44A): single PEX or other intravenous blood transfusion, 19 years and over", which reported this cost as £1,265. On investigation, the company has used the non-elective short stay value.

The resulting ERG-corrected base case is provided in Table 37; effects were negligible.

Table 37: Company base case results with ERG corrections applied

	Total			Incremental			ICER incremental (£/QALY)
Technologies	**Costs (£)**	**LYs**	**QALYs**	**Costs (£)**	**LYs**	**QALYs**	
SoC	[redacted]	[redacted]	[redacted]				
CAPLA	[redacted]	[redacted]	[redacted]	[redacted]	5.48	[redacted]	£36,937

Key: CAPLA, caplacizumab; ICER, incremental cost-effectiveness ratio; LY, life years; PAS, patient access scheme; QALY, quality-adjusted life year; SoC, standard of care

6.1.1. Probabilistic sensitivity analyses

A number of minor inconsistencies were found between the model PSA inputs and those reported in the CS:

- There were a couple of missing PSA parameters (see Section 5.3 and Clarification Question B13). The company corrected these in their updated model (Clarification Response B13). These changes only applied to the OWSA and PSA.
- In the PSA worksheet, the summary LYs and QALYs for SoC (Cells F16:G16) were wrongly sourced from the deterministic results (Cells K47 and I47) rather than the mean of the probabilistic (Cells K48 and I48). However, this did not effect the calculation of the probabilistic ICER, which was correctly calculated in Cell Q48.

6.1.2. One-way sensitivity analyses

The ERG did not re-run the OWSA as the identified corrections would have a negligible impact.

6.1.3. Scenario analyses

The ERG did not re-run the scenario analyses as the identified corrections would have a negligible impact.

6.2. Exploratory and sensitivity analyses undertaken by the ERG

6.2.1. ERG scenario analyses

A range of scenario analyses were conducted to explore the impact of the ERG base case assumptions on the model results. These scenarios are applied to the company model as corrected in section 5.3.2 above and are provided with sources in Table 38.

Table 38: Potential ERG scenarios

Factor	Company base case	ERG scenario	ICER (£)
Company base case (corrected)			**36,937**
Relapse rate	1%	5% (Testing limits of reasonable assumptions)	44,801
ITT population CAPLA	N=71	N=72	36,929
Refractory rate (SoC)	6.85%	15% (ERG expert average)	36,570
Proportion receiving RTX in acute phase	48% SoC 39% CAPLA	78% RTX CAPLA and SoC (Shin et al., 2018)	37,155
Proportion of patients receiving RTX in remission	10%	30% (ERG expert)	38,132
RR long-term complications (cognitive impairment only)	0.62	0.6875 (ERG corrected calculation to avoid double counting hospitalisation days)	38,937
RR long-term complications (neuropsychological impairment only)	0.62	0.6875 (ERG corrected calculation to avoid double counting hospitalisation days)	36,993
RR long-term complications (cognitive impairment and neuropsychological impairment)	0.62	0.6875 (ERG calculation to avoid double counting hospitalisation days)	38,997
Resource use costs (acute and long-term)	CT (£90)	MRI (£141 [NHS Reference Costs 17/18, Code IMAGOP RD01A, MRI of one area without contrast, 19 years-plus]) rather than CT scan in	36,887

Factor	Company base case	ERG scenario	ICER (£)
		acute and long-term phases	
Haematology outpatient visit	£250	£171 (ERG source: NHS Reference Costs 17/18)	36,543
Resource use for long-term complications		ERG expert:	36,921
Psychology/counselling	33%	100%	
Antidepressants	20%	50%	
Haematology clinic time	50%	75%	

Key: CAPLA, caplacizumab; CT, computed tomography; ERG, Evidence Review Group; ICER, incremental cost-effectiveness ratio; MRI, magnetic resonance imaging; PEX, plasma exchange; RR, relative risk; RTX, rituximab; SoC, standard of care

Whilst the ERG favoured a lower RR for long-term complications, on reflection it was decided that the impact of caplacizumab on mortality was likely to be greater therefore the ERG retained the company RR of 0.62 for mortality.

6.2.2. Impact on the ICER of additional clinical and economic analyses

As expected, the parameters having a substantive impact on the ICER were the RRs of reduction of long-term complications with caplacizumab. The majority of other factors had a relatively minor impact on the ICER.

6.2.3. ERG preferred assumptions

The ERG's preferred base case is described in Table 39. Results are shown in Table 40 below.

Table 39: Potential ERG base case

Factor	Company base case	ERG base case
ITT CAPLA	N=71	N=72 (includes patient who withdrew consent prior to receiving treatment)
Refractory rate SoC	6.85%	15% (ERG expert average)
Proportion receiving RTX in acute phase	48% SoC 39% CAPLA	78% RTX CAPLA and SoC (Shin et al., 2018)
RR long-term complications (cognitive impairment/ neuropsychological	0.62 (combined in company base case)	0.6875 (ERG corrected calculation without double counting of hospitalisation days)

Factor	Company base case	ERG base case
impairment		
RR mortality		0.62
Resource use for long-term complications		ERG expert:
Psychology/counselling, proportion of patients	33%	100%
Antidepressants	20%	50%
Clinic time (haematology)	50%	75%
RTX use in remission	10%	30% (ERG expert)
Resource costs		
Cerebral imaging (long-term)	£90 CT scan	£141 MRI (NHS Reference Costs 17/18, Code IMAGOP RD01A, MRI of one area, without contrast, 19 years+)
PEX procedure cost	£602.34	£1,265 (ERG correction)
Haematology OP visit	£250	£171 (ERG source NHS Reference Costs 17/18)

Key: CAPLA, caplacizumab; CT, computed tomography; ERG, Evidence Review Group; MRI, magnetic resonance imaging; OP, outpatient; PEX, plasma exchange; RR, relative risk; RTX, rituximab; SoC, standard of care

Table 40: ERG base case results

	Total			Incremental			ICER incremental (£/QALY)
Technologies	**Costs (£)**	**LYs**	**QALYs**	**Costs (£)**	**LYs**	**QALYs**	
SoC	[redacted]	[redacted]	[redacted]				
CAPLA	[redacted]	[redacted]	[redacted]	[redacted]	5.48	[redacted]	£39,630

Key: CAPLA, caplacizumab; ICER, incremental cost-effectiveness ratio; LY, life years; PAS, patient access scheme; QALY, quality-adjusted life year; RTX, rituximab; SoC, standard of care

The ICER is £39,630 per QALY, which is higher than the company base case estimate. As noted above, the increase in the ICER is driven by the higher RR for the effect of caplacizumab on long-term complications favoured by the ERG.

Furthermore, the ERG also acknowledged the evidence is weak for impact of caplacizumab on long-term mortality, utility in remission, and baseline (SoC) rates of long-term complications but was unable to obtain better sources to those used by the company as there are no good quality studies to make confident predictions. This is compounded by the likely effect of caplcacizumb on the reduction in these long-term complications. Whilst the balance of opinion seems to

suggest a plausible impact, the RR methodology and estimates used in the ERG model are highly speculative and thus highly uncertain.

6.3. Conclusions of the cost-effectiveness section

To summarise, the ERG considered the base case economic model to be highly uncertain since reliable data to populate the model were limited. The company PSA applied arbitrary and limited uncertainty around many parameters. Limited short-term data were utilised from HERCULES as results were deemed atypical of a UK population. Furthermore, there was a lack of data on long-term outcomes and the impact of caplacizumab, which thus relied upon the use of proxies and clinical advice. Where literature sources were used, these were generally of poor quality. However, the ERG often did not have better sources of data for the model inputs and thus relied on their own clinical experts. Nevertheless, the ERG believed that, in many cases, the company used the best estimates available.

Key drivers of the model were short-term mortality, long-term mortality, long-term complications, and the cost of caplacizumab.

7. END OF LIFE

According to the evidence submitted by the company, caplacizumab is expected to yield substantial decreases in mortality for people with aTTP. This is especially given that aTTP is relatively rare and life threatening in nature (CS, Document B, p.74). However, caplacizumab does not meet the end-of-life criterion on life expectancy set by NICE, nor did the company specifically present any evidence to support an application under end-of-life criteria.

References

1. Scully M, Hunt B, Benjamin S, Liesner R, Rose P, Peyvandi F, et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. British Journal of Haematology. 2012;158(3):323-35.
2. NHS England. Service specification 1668: Schedule 2 - The Services. Draft for consultation. Available from: https://www.engage.england.nhs.uk/consultation/thrombocytopenic-purpura/user_uploads/thrombotic-thrombocytopenic-purpura-service-specification.pdf.
3. Scully M, Cataland S, Coppo P, de la Rubia J, Friedman KD, Kremer Hovinga J, et al. Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies. Journal of Thrombosis and Haemostasis. 2017;15(2):312-22.
4. Scully M, Cataland SR, Peyvandi F, Coppo P, Knöbl P, Kremer Hovinga JA, et al. Caplacizumab treatment for acquired thrombotic thrombocytopenic purpura. New England Journal of Medicine. 2019;380(4):335-46.
5. Shin JS, Alwan F, Austin S, Crowley M, Dutt T, Clark A, et al. Thrombotic thrombocytopenic purpura: demographic analysis of the UK TTP registry from 2009 to 2018. British Society for Haematology 59th Annual Scientific Meeting 1-3 April; Glasgow: Scotland; 2019.
6. NICE. Caplacizumab for treating adults experiencing an episode of acquired thrombotic thrombocytopenic purpura [ID1185]. Final scope. Available from: http://nicedsu.org.uk/wp-content/uploads/2017/06/Partitioned-Survival-Analysis-final-report.pdf.
7. EMA. Cablivi: Assessment report. Available from: https://www.ema.europa.eu/en/documents/assessment-report/cablivi-epar-public-assessment-report_en.pdf.
8. Dutt T, Scully M. A proposal: the need for thrombotic thrombocytopenic purpura Specialist Centres – providing better outcomes. British Journal of Haematology. 2015;170(5):737-42.
9. CRD. Systematic reviews. CRD's guidance for undertaking reviews in health care. Available from: https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf.
10. NICE. Single technology appraisal: User guide for company evidence submission template 2017. Available from: https://www.nice.org.uk/About/What-we-do/Our-Programmes/NICE-guidance/NICE-technologyappraisal-guidance.
11. Ablynx NV. Integrated Summary of Efficacy. Caplacizumab. Zwijnaarde, Belgium; 2018.
12. Peyvandi F, Scully M, Kremer Hovinga JA, Cataland S, Knöbl P, Wu H, et al. Caplacizumab for acquired thrombotic thrombocytopenic purpura. New England Journal of Medicine. 2016;374(6):511-22.
13. Benhamou Y, Boelle PY, Baudin B, Ederhy S, Gras J, Galicier L, et al. Cardiac troponin-I on diagnosis predicts early death and refractoriness in acquired thrombotic thrombocytopenic purpura. Experience of the French Thrombotic Microangiopathies Reference Center. Journal of Thrombosis and Haemostasis. 2015;13(2):293-302.
14. Ablynx NV. TITAN CSR: a phase II, single-blind, randomised, placebo-controlled trial to study the efficacy and safety of anti-von willebrand factor nanobody administered as adjunctive treatment to patients with acquired thrombotic thrombocytopenic purpura. Clinical Study Report2015.
15. Sanofi. HTA advisory board 2019 06 March.
16. Ablynx NV. HERCULES CSR: a phase III double-blind, randomized, parallel group, multicenter placebo-controlled trial to study the efficacy and safety of caplacizumab in patients with acquired thrombotic thrombocytopenic purpura. ALX0681-C301. 2017.

17. Ablynx NV. Cablivi 10mg powder and solvent for solution for injection. Summary of product characteristics (SPC). Available from: https://www.ema.europa.eu/documents/product-information/cablivi-epar-product-information_en.pdf.
18. Chaturvedi S, Oluwole O, Cataland S, McCrae KR. Post-traumatic stress disorder and depression in survivors of thrombotic thrombocytopenic purpura. Thrombosis Research. 2017;151:51-6.
19. Han B, Page EE, Stewart LM, Deford CC, Scott JG, Schwartz LH, et al. Depression and cognitive impairment following recovery from thrombotic thrombocytopenic purpura. American Journal of Hematology. 2015;90(8):709-14.
20. Lewis QF, Lanneau MS, Mathias SD, Terrell DR, Vesely SK, George JN. Long-term deficits in health-related quality of life after recovery from thrombotic thrombocytopenic purpura. Transfusion. 2009;49(1):118-24.
21. Cataland SR, Scully MA, Paskavitz J, Maruff P, Witkoff L, Jin M, et al. Evidence of persistent neurologic injury following thrombotic thrombocytopenic purpura. American Journal of Hematology. 2011;86(1):87-9.
22. Falter T, Schmitt V, Herold S, Weyer V, von Auer C, Wagner S, et al. Depression and cognitive deficits as long-term consequences of thrombotic thrombocytopenic purpura. Transfusion. 2017;57(5):1152-62.
23. Chaturvedi S, Oluwole O, Cataland S, McCrae KR. Post-traumatic stress disorder and depression in survivors of thrombotic thrombocytopenic purpura. Thromb Res. 2017;151:51-6.
24. Burns D, Lee D, Vesely S, George J, Cerdobbel A, De Naeyer L, et al. Patient health-related quality of life associated with remission of aTTP. A regression analysis using non-randomised observational data from the Oklahoma TTP registry. ISPOR; 10-14 November 2018; Barcelona: Spain; 2018.
25. Davies A, Ridley S, Hutton J, Chinn C, Barber B, Angus DC. Cost effectiveness of drotrecogin alfa (activated) for the treatment of severe sepsis in the United Kingdom. Anaesthesia. 2005;60(2):155-62.
26. Drabinski A, Williams G, Formica C. Observational evaluation of health state utilities among a cohort of sepsis patients. Value in Health. 2001;4(2):128-9.
27. Ersson A, Beckman A, Jarl J, Borell J. Effects of a multifaceted intervention QI program to improve ICU performance. BMC Health Services Research. 2018;18(1):838.
28. Vainiola T, Roine RP, Pettila V, Kantola T, Rasanen P, Sintonen H. Effect of health-related quality-of-life instrument and quality-adjusted life year calculation method on the number of life years gained in the critical care setting. Value in Health. 2011;14(8):1130-4.
29. Hernandez RA, Jenkinson D, Vale L, Cuthbertson BH. Economic evaluation of nurse-led intensive care follow-up programmes compared with standard care: the PRaCTICaL trial. European Journal of Health Economics. 2014;15(3):243-52.
30. Kim AS, Nguyen-Huynh M, Johnston SC. A cost–utility analysis of mechanical thrombectomy as an adjunct to intravenous tissue-type plasminogen activator for acute large-vessel ischemic stroke. Stroke. 2011;42(7):2013-8.
31. Earnshaw SR, Joshi AV, Wilson MR, Rosand J. Cost-effectiveness of recombinant activated factor VII in the treatment of intracerebral hemorrhage. Stroke. 2006;37(11):2751-8.
32. Pappas MA, Vijan S, Rothberg MB, Singer DE. Reducing age bias in decision analyses of anticoagulation for patients with nonvalvular atrial fibrillation - A microsimulation study. PLoS One. 2018;13(7):e0199593.
33. McPhail S, Haines T. Response shift, recall bias and their effect on measuring change in health-related quality of life amongst older hospital patients. Health and Quality of Life Outcomes. 2010;8:65.
34. Chit A, Becker DL, DiazGranados CA, Maschio M, Yau E, Drummond M. Cost-effectiveness of high-dose versus standard-dose inactivated influenza vaccine in adults aged 65

years and older: an economic evaluation of data from a randomised controlled trial. Lancet Infectious Diseases. 2015;15(12):1459-66.
35. Shankar MB, Staples JE, Meltzer MI, Fischer M. Cost effectiveness of a targeted age-based West Nile virus vaccination program. Vaccine. 2017;35(23):3143-51.
36. Scully M, McDonald V, Cavenagh J, Hunt BJ, Longair I, Cohen H, et al. A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura. Blood. 2011;118(7):1746-53.
37. Westwood JP, Webster H, McGuckin S, McDonald V, Machin SJ, Scully M. Rituximab for thrombotic thrombocytopenic purpura: benefit of early administration during acute episodes and use of prophylaxis to prevent relapse. Journal of Thrombosis and Haemostasis. 2013;11(3):481-90.
38. Ablynx Pharma. Data on File: Systematic review on the clinical burden of disease in thrombotic thrombocytopenic purpura. Ablynx Pharma; 2018.
39. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes. Oxford, UK: Oxford University Press; 2015.
40. Kennedy AS, Lewis QF, Scott JG, Kremer Hovinga JA, Lammle B, Terrell DR, et al. Cognitive deficits after recovery from thrombotic thrombocytopenic purpura. Transfusion. 2009;49(6):1092-101.
41. Hatch R, Young D, Barber V, Griffiths J, Harrison DA, Watkinson P. Anxiety, depression and post traumatic stress disorder after critical illness: A UK-wide prospective cohort study. Critical Care. 2018;22(1):310.
42. Upreti H, Kasmani J, Dane K, Braunstein EM, Streiff MB, Shanbhag S, et al. Reduced ADAMTS13 activity during TTP remission is associated with stroke in TTP survivors. Blood. 2019;134(13):1037-45.
43. Deford CC, Reese JA, Schwartz LH, Perdue JJ, Kremer Hovinga JA, Lammle B, et al. Multiple major morbidities and increased mortality during long-term follow-up after recovery from thrombotic thrombocytopenic purpura. Blood. 2013;122(12):2023-9; quiz 142.
44. Ara R, Brazier JE. Populating an economic model with health state utility values: moving toward better practice. Value in Health. 2010;13(5):509-18.
45. Burns D, Lee D, Vesely S, George J, Cerdobbel A, De Naeyer L, et al. PSY192 - Patient health-related quality of life associated with remission of aTTP, a regression analysis using non-randomised observational data from the Oklahoma TTP registry. Value in Health. 2018;21:S469.
46. Gage BF, Cardinalli AB, Owens DK. The effect of stroke and stroke prophylaxis with aspirin or warfarin on quality of life. Archives of Internal Medicine. 1996;156(16):1829-36.
47. Sullivan PW, Slejko JF, Sculpher MJ, Ghushchyan V. Catalogue of EQ-5D scores for the United Kingdom. Medical Decision Making. 2011;31(6):800-4.
48. van Exel NJ, Koopmanschap MA, van den Berg B, Brouwer WB, van den Bos GA. Burden of informal caregiving for stroke patients. Identification of caregivers at risk of adverse health effects. Cerebrovascular Diseases. 2005;19(1):11-7.
49. NICE. TA327: Dabigatran etexilate for the treatment and secondary prevention of deep vein thrombosis and/or pulmonary embolism (Technology appraisal guidance). Available from: https://www.nice.org.uk/guidance/ta327.
50. NICE. TA420: Ticagrelor for preventing atherothrombotic events after myocardial infarction (Technology appraisal guidance). Available from: https://www.nice.org.uk/guidance/ta420.
51. Woods B, Sideris E, Palmer S, Latimer N, Soares M. NICE DSU Technical Support Document 19: Partitioned survival analysis for decision modelling in health care: A critical review (report by the Decision Support Unit. Sheffield, UK: Decision Support Unit, ScHARR, University of Sheffield; 2017.

52. HM Treasury. The Green Book: Central Government Guidance on Appraisal and Evaluation. London: HM Treasury; 2018.

Appendix A: Additional ERG targeted literature searches

The ERG conducted additional targeted literature searches for:

- cost-effectiveness studies

Cost-effectiveness studies

Database: Ovid MEDLINE(R) ALL <1946 to November 27, 2019>

Date of search 2 December 2019

Search Strategy:

1	Purpura, Thrombotic Thrombocytopenic/	4461
2	(thrombotic adj3 thrombocytop?eni$1 adj3 purpura$).ti,ab,kf.	4647
3	(thrombotic adj3 thrombop?eni$1 adj3 purpura$).ti,ab,kf.	83
4	((acquired or autoimmune) adj5 ttp).ti,ab,kf.	344
5	((Moschcowitz$ or Moschowitz$ or Moschkowitz$) adj (disease$1 or syndrome$1 or disorder$1)).ti,ab,kf.	125
6	attp.ti,ab,kf.	598
7	or/1-6	6336
8	Economics/	27102
9	exp "Costs and Cost Analysis"/	230537
10	Economics, Nursing/	3996
11	Economics, Medical/	9041
12	Economics, Pharmaceutical/	2898
13	exp Economics, Hospital/	24061
14	Economics, Dental/	1908

15	exp "Fees and Charges"/	30013
16	exp Budgets/	13596
17	budget*.ti,ab,kf.	28438
18	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.	220472
19	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	275213
20	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	154166
21	(value adj2 (money or monetary)).ti,ab,kf.	2277
22	exp models, economic/	14542
23	economic model*.ab,kf.	3159
24	markov chains/	13833
25	markov.ti,ab,kf.	21329
26	monte carlo method/	27469
27	monte carlo.ti,ab,kf.	47249
28	exp Decision Theory/	11709
29	(decision* adj2 (tree* or analy* or model*)).ti,ab,kf.	22369
30	or/8-29	702384
31	7 and 30	36

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check

Caplacizumab for treating adults experiencing an episode of acquired thrombotic thrombocytopenic purpura [ID1185]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on 6 January 2020** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Appropriate proxy for the RR for long-term complications

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
In the company submission, the RR for long-term complications was calculated based on hospitalisation + ICU days in the overall treatment period. This assumption was accepted by the ERG in their report with an adjustment to remove ICU days from hospitalisation days, given ICU days are included within hospitalisation days in the overall treatment period data used in the initial calculation (page 105-106 of ERG report). However this calculation and the resulting RR are incorrect, as the ERG have not adjusted ICU days for the proportion of patients admitted to ICU in their calculation. Using the ERG's methodology, with the adjustment of ICU days by proportion of patients admitted to ICU, the corrected RR is **0.688.** Please see calculation below: ICU days are weighted by the proportion requiring ICU, and these are subtracted from hospitalisation days (including ICU) to determine hospitalisation days excluding ICU. Then the calculation is performed with hospitalisation days excluding ICU and weighted ICU days as below: [redacted] **= 0.688** This is also supported by a simpler calculation. Given that it is now clear that the hospitalisation days reported include ICU days, the simplest way to get to the calculation of the RR including both hospitalisation and ICU days for the overall study drug treatment period is[redacted] This again results in a corrected RR of	The RR should be amended to **0.688** to correct for the calculation error.	The RR was calculated incorrectly Impact on cost-effectiveness results: Using an RR of **0.688** for long-term complications reduces the ICER from **£49,077 to £39,630**	Thank you for this clarification. The ERG had assumed that the ICU days were aggregated across the whole HERCULES population; the Company FAC response and CSR (Table 25) makes it clear this was an error, and that the ICU days are only for the subgroup of patients who attended ICU. The ERG also accept the Company's argument for the simpler calculation (i.e. dividing hospitalisation plus ICU days). The correct HR is thus 0.688. The text was amended (ERG report p.17, p.104-105, and p. 118-120). An updated version of the ERG model is also provided. The ERG is unclear why there is an inconsistency between Table 4 in the clarification responses and Table 2 of the NEJM paper but this is a minor issue. The updated ERG base case

0.688.			ICER is £39,630.

Issue 2 Estimating uncertainty where data not available

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On Page 121 of the report, the ERG state that *"The company PSA applied arbitrary and limited uncertainty around many parameters."* (See also Page 15 and Table 32 on Page 93) As stated in section B.3.6 of the company submission, uncertainty information such as SEs and 95% CIs were obtained from the input source where available. Where uncertainty information was not reported, an SE of 10% was assumed. Throughout the submission the uncertainty in estimates was addressed upfront and an extensive range of sensitivity analyses presented to account for the uncertainty in both parameter estimates (through OWSA, PSA) and alternative modelling assumptions (through extensive scenario testing and threshold analyses).	Text should be amended to state that an SE of 10% was used where uncertainty information was not available from the original source. Phrases such as *"arbitrary and limited uncertainty around many parameters"* should be removed as these could be considered misleading.	Amendment required to accurately reflect systematic modelling approach. Impact on cost-effectiveness results: None	The ERG disagrees, with no evidence to support the choice of a 10% SE, it is arbitrary. Therefore, this is not a factual correction. **No change required.**

Issue 3 Calculation of utility multipliers

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 108 states that *"[the utility for baseline remission] was **only varied** by the SE (0.031) reported in Burns et al. (2018) in the company's one-way sensitivity*	Statement should be amended to:	Amendment required to increase accuracy of ERG report.	This is a misunderstanding. The ERG intended the use of "only" to refer to the magnitude

analysis (OWSA)." This statement omits that the baseline utility value was also varied in the PSA.	*"[the utility for baseline remission] was **varied** by the SE (0.031) reported in Burns et al. (2018) in the company's one-way sensitivity analysis (OWSA) **and PSA"***	Impact on cost-effectiveness results: None	of the variation around the mean used in the OWSA and PSA. The text was reworded as follows (p.108): "Given the small sample size of Burns et al., and the fact that it is an unpublished study, the ERG would have liked to have seen greater uncertainty explored around this variable"
Page 108 also states that: *"The same source (CS, Document B, Table 34 [see also the company's clarification response, Table 7]), also incorrectly references the moderate/severe cognitive impairment multiplier as "Utilities" worksheet cell E83, whereas it should be E98 but again this was correctly modelled."*	This sentence should be removed as E83 is set as equal to E98 in the economic model.	Amendment required to increase accuracy of ERG report. Impact on cost-effectiveness results: None	Agreed, this sentence was removed (p.108).

Issue 4 Description of International Consensus definition of relapse

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 41 of the ERG report, the ERG state the following: *"The International Consensus definition of relapse requires a follow-up period of greater than 30 days following the resolution of symptoms, meaning that relapse could not be evaluated in HERCULES, and was only evaluated at the one-year follow-up for TIITAN."*	The statement in the ERG report needs amending to accurately reflect the International Consensus definition, which is: "a fall in platelet count to below the lower limit of the established reference range	Amendment required to accurately reflect the International Consensus definition and true potential of trials to observe relapse as per this definition.	Thank you for highlighting this point. The ERG agree with the company regarding the specification of the International Consensus definition of relapse, and have clarified the definition in the

This is factually inaccurate as it does not reflect the IC definition of relapse,and there is subsequent misinterpretation of relapse data available from the caplacizumab studies. This misinterpretation is further referred to on page 42 of the ERG report.	(e.g. < 150 x 109 L-1), with or without clinical symptoms, >30 days after stopping of PEX for an acute TTP episode, requiring initiation of therapy." Subsequent interpretation also needs updating to acknowledge that relapse (as per IC definition) would thus have been captured in part as both HERCULES and TITAN included study treatment and follow-up periods that extended to a <u>minimum</u> of 58 days after stopping of PEX for an acute TTP episode. That is, all patients in both studies were treated for at least 30 days after stopping PEX, excluding treatment extensions, and the follow up visit was 28 days after end of treatment in HERCULES and 30 days after end of treatment in TITAN. When added together this equals a minimum 58-day follow-up period after stopping PEX, well beyond the minimum period stated in the Consensus definition.		text (p.41). Subsequently, on p.42 it was clarified that relapse was measured following the optional treatment continuation phase, and thus was evaluated more than 30 days after the end of PEX.

Issue 5 Description of follow-up period

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On pages 13 and 41 of the ERG report, the ERG note that the follow-up was variable between patients and between treatment arms, as total time under follow-up was related to total days receiving daily PEX. This is a misrepresentation of the study design, in which the treatment period could vary but the follow-up period was set after the end of study drug treatment (28 days in HERCULES and 30 days for first follow-up in TITAN)	The language of the ERG report needs amending. An example edit is provided below: *"The follow-up period was set after the end of study drug treatment; the treatment period was variable based on response. This meant that the total study period was variable between patients and treatment arms".*	Amendment required to accurately reflect the study design and true variability observed.	This is not a factual error. The ERG believes it is clear that what is being described is the total time that patients are 'under surveillance' for experiencing an outcome. Indeed, it is not inaccurate to state that patients had different follow-up times either in this sense or in the sense of when the post-study drug period began after randomisation. **No change required.**

Issue 6 Data presentation and confidential marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 40, in the 'Intervention' section, "…re-initiated for 7-day periods...' should state 'extension', not re-initiation as treatment would not stop after the initial 30 days of treatment.	Please change description of dosing on page 40 to: *"This dosing schedule continued for 30 days after the conclusion of daily PEX treatment, but could be **extended** for 7-day periods up to 28 days when clinically indicated*	Factual accuracy of caplacizumab dosing description	Thank you for highlighting this error –the text was amended as suggested (p.40).

	(i.e. based on disease activity).		
On page 22 description of dosing of caplacizumab is incorrect. The ERG report states "…for the duration of daily PEX and up to 30 days after the last daily PEX". This does not match the licence. Dosing should be for a minimum of 30 days after last PEX, potentially extended if ADAMTS13 activity is still suppressed at this point. The dosing was more accurately described later on page 40 of ERG reporting the "intervention" section (when changing 're-initated' to 'extended' as per point above).	Please change description of dosing on page 22 of the ERG report to align with description on page 40.	Factual accuracy of caplacizumab dosing description	Thank you for highlighting this –the text was amended as suggested (p.22).
On pages 40-41 and 51 of the ERG report, there is discussion of RTX use and how it may bias against caplacizumab. The ERG appear to agree with the company submission that it may bias against caplacizumab in discussion on page 51 but make contradictory statement on pages 40-41.	Please align discussion on RTX use and how it may bias against caplacizumab throughout ERG report.	Consistency.	This is not a factual error because these two assertions are making different points. On pages 40-41 of the ERG report, the discussion of RTX is in respect of generalisability of the treatment to clinical practice in the UK. On page 51, the discussion of RTX use relates to imbalance between treatment arms. The assertion of the ERG on pages 40-41 that bias against caplacizumab 'was not clearly evidenced' relates directly to evidence (or rather, the lack of evidence) in the company submission

			to support the company's assertion. **No change required.**
On page 58, the ERG report states: "Clinical advice to the ERG is that this is plausible, and is consistent with the perceived benefit of rituximab in this population." In the context of this piece of text, it should state caplacizumab, not rituximab	Please change this sentence to: "Clinical advice to the ERG is that this is plausible, and is consistent with the perceived benefit of **caplacizumab** in this population."	Factual inaccuracy	The company's proposed amendment was implemented in the report (p.58).
On page 69 of the ERG report, common reactions described as "occuring in at least 10% of patients in the caplacizumab arm" include confusion, dizziness, rash, insomnia, hypokalaemia and hypertension. These events did not occur in at least 10% of patients in the caplacizumab arm, as summarised in Table 15 of the company submission.	Please remove these events from the list or correct the definition of common reactions that has been used to categorise the events listed.	Factual inaccuracy	Thank you for highlighting this. These events occurred in at least 10% of patients in the placebo arm of the trial. The ERG has now deleted these events so that the following non-bleeding events occurring in at least 10% of patients in the caplacizumab arm are presented: fatigue, pyrexia, nausea, headache, paraesthesia and urticaria. (p.69).
On page 70 of the ERG report, TTP is reported as a treatment-emergent adverse event but relapse and exacerbation of TTP were not included as adverse events under the system organ class adopted, but were reported as secondary efficacy outcomes.	Please align to the company submission and HERCULES manuscript and not include TTP as an adverse event.	Factual accuracy of summary reporting	The ERG has reported TTP as a treatment-emergent event, as consistent with the approach used by the EMA. **No change required**

On page 71 of the ERG report, the following statements are referenced to the company but these are not taken from the company submission: *"The company reported that bleeding events reported were largely mucocutaneous bleeding, while haemorrhage events mostly consisted of von Willebrand disease-like mild to moderate mucosal and skin/subcutaneous tissue haemorrhage. The company stated that, after removing TTP and thrombotic microangiopathy, no major difference between groups in terms of treatment-emergent thromboembolic events is noted; however, this data was not reported"*	Please reword to make it clear where these statements were taken from (not the company submission).	Factual accuracy of summary reporting.	The ERG agree that the statement regarding adverse events after accounting for TTP was not based on evidence reported in the CS, but rather was based on evidence presented by the EMA. The words 'The company stated that' have been removed from the text (p.71).
On page 75, the ERG report states '...to include PEX, immunosuppression and where indicated, rituximab.' This implies that rituximab is separate to immunosuppression which is incorrect.	When referring to immunosuppression throughout the ERG report, please indicate that this can include both corticosteroids and rituximab, as stated in the company submission.	Factual inaccuracy	Thank you for noting this ambiguity. The sentence was altered to clarify that immunosuppression may include rituximab (p.75).
On page 104, the ERG report describes the UK TTP registry inaccurately. The report states that the UK registry has only been running since December 2018 – this is incorrect. The registry has been collecting data since 2008. The change in 2018 was to begin to collect data beyond the acute phase: routine assessments in remission, elective rituximab to prevent relapse, serial assessments of cognition / memory, depression.	Please amend text on page 104 to: "The CS noted the UK TTP Registry has been collecting data since 2008, and from 2018 onwards has begun to collect long-term data beyond the acute phase."	Factual inaccuracy	The ERG agree that a change to the text would be useful to clarify the role of the TTP registry, and has changed the text to (p.104): "The CS noted the UK TTP Registry has been collecting data since 2008, but has only begun to collect long-term data beyond the acute phase from 2018."

On page 107 the description regarding RTX use around relapse is misleading.	Please consider amending text on page 107 to: *"…it was assumed 10% would receive four RTX doses per year: this would suffice to elevate ADAMTS13 activity/scores."*	Accuracy of RTX dosing description	This is not a factual error. **No change required.**
On page 110, the number of HERCULES centres is incorrect - HERCULES had 3 participating centres in the UK, not 4. Also the ERG report refers to Clarification Question A14 querying whether direct admission to ICU was standard practice at UK centres – this is actually Clarification Question A12.	Please amend wording to: *"Clarification Question **A12** queried whether direct admission to ICU was standard practice at the **three** UK HERCULES centres."*	Factual inaccuracy	The ERG are aware that the trial CSR for HERCULES states that 3 centres in the UK participated in the trial. However, four UK centres are stated to have participated in supplementary information of the HERCULES trial publication (Scully et al. 2019). These are listed as follows: 1. Bristol Haemophilia Centre Bristol UNITED KINGDOM 2. Royal Liverpool & Broadgreen University Hospital NHS Trust, Liverpool UNITED KINGDOM 3. McDonald, Vickie St. Thomas' Hospital London UNITED KINGDOM 4. Scully, Marie University College London Hospital London UNITED KINGDOM

			No change required.
There are several instances of data not being marked up in alignment with the company submission marking.	Please mark up the following data as academic in confidence: - Baseline platelet count data from TITAN (page 50) - Cognitive function data taken from the HERCULES CSR (Table 9, pages 56-57) - Refractory dsease outcome data according to the International Consensus definition (page 58, page 101 and Table 10 [page 59]) - Per-protocol sensitivity analyses from HERCULES (page 63) - TTP-related events data from HERCULES (Table 14 [page 64]) - Discontinuation due to AE data excluding TTP as an event taken from the HERCULES CSR (page 70) - Post-hoc analysis of PEX complications (page 71)	Accuracy of confidential markings.	Thank you, the confidential marking was checked and mark-up was corrected where required (p.50, 56-57, 59, 63-65, 70-71,102, 109, 115). The ERG also noted that the page reference given by the company in Bullet 3 should have been page 102 not page 101. The confidential marking was checked and the mark-up corrected.

	- RR for acute mortality (Page 115) Please mark up the following data as commercial in confidence: - Treatment duration in the double blind and open label period of HERCULES (Page 109) Please remove marking up of the following data: - Hospital resource use data from HERCULES (Table 15 [page 65])		

Issue 7 Minor factual inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
On page 35 of the ERG report, the description of the study design includes the statement: *"…and were indicated rituximab"*	Statement corrected to: *"…and where indicated rituximab"*	Spelling error.	Not a factual error. **No change required.**
In Table 3 (page 36), the format of the intervention and comparator rows suggest some differences between treatment arms of individual studies and details are incomplete e.g. immunuosuppression of HERCULES not detailed and listing of 'other immunosuppressive treatment' in the comparator row only suggests this was not permitted in both arms.	Please align to formatting of Table 4 in the company submission.	Formatting error.	Not a factual error. **No change required.**

On page 39 of the ERG report, evidence from registry data cited in the company submission is reported as: *"…in a French cohort of patients with aTTP, 25% experienced refractory disease…"* This is not the correct data.	Statement corrected to: *"…in a French cohort of patients with aTTP, **17%** experienced refractory disease…"*	Transcription error.	The company's proposed amendment was implemented. [p. 39]
On page 45 of the ERG report, there appears to be words missing from the opening sentence that currently reads: *"The ERG had regard to the quality assessment for both HERCULES and TITAN"*	Please add missing words.	Transcription error.	Not a factual error. **No change required.**
On page 49 of the ERG report, it is acknowledged that there is a: *"…significant minority of patients of Black ethnicity (28/145, 19.3%)."* The use of minority in this sentence could be confusing.	Please replace minority with proportion.	Confusing language.	Not a factual error. **No change required.**
On page 50 of the ERG report, the relatively low proportion of patients with GCS ≤12 at baseline is attributed to: *"…to the exclusion of those unconscious or unstable of arrival"* Patients who were unconscous were eligible for enrolment as long as a legally acceptable representative or independent physician could provide informed consent and assent.	Please amend to accurately reflect the HERCULES study design. An example edit is provided below: *"…and the exclusion of those unstable on arrival"*	Factual inaccuracy.	Not a factual error. This was based on the ERG's reasonable reading of the evidence presented. Indeed, based on the statement presented, it is reasonable that not all unconscious people were eligible for enrolment. **No change required.**

On page 52 of the ERG report, stratification factor for primary outcome analyses in HERCULES is reported as: *"Glasgow Coma Scale score of ≤12 vs ≥13"* The higher score group should be >13.	Please correct to: *"Glasgow Coma Scale score of ≤12 vs >13"*	Factual inaccuracy.	This is a mathematical problem with the notation used by the company, as by the company's notation those with GCS >13 would not be included in stratification. Not a factual error. **No change required.**
On page 54 of the ERG report, it is stated that: *"Censoring is properly accounted for in the survival analysis for platelet normalisation…"* This should state KM analysis.	Please correct to: *"Censoring is properly accounted for in the KM analysis for platelet normalisation…"*	Transcription error.	KM analysis is a form of survival analysis. Not a factual error. **No change required.**
Table 9 of the ERG report (pages 56-57) reports cogntive function data referenced to the CSR but data have not been transcribed verbatim.	Please align data to that reported in the CSR.	Transcription error.	This is not a factual error. Percentages reported in the trial CSR were inconsistent with the number of patients in each arm, as reported; these were corrected accordingly in the ERG report. **No change required**
Section 3.2.6.2 of the ERG report (pages 70-71) is incorrectly titled "Treatment-related adverse events" and introduced as such at first mention - events reported are not treatment-related.	Please correct to treatment-emergent adverse events throughout.	Transcription error.	Methods for determining whether AEs were treatment-emergent were not described in the CS The ERG's referencing to 'treatment-

			related adverse events' is congruent with referencing to treatment-related adverse events' in the EMA report. **No change required**

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft technical report

Caplacizumab for treating acute acquired thrombotic thrombocytopenic purpura [ID1185]

This document is the draft technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

1. Topic background

1.1 Disease background.

- Acquired thrombotic thrombocytopenic purpura (aTTP): rare blood disorder, where clotting in small blood vessels restricts blood supply to tissue, resulting in a lack of oxygen and organ damage (particularly the heart, brain and kidney).
- Autoimmune disease, where body's immune system mistakenly attacks itself. An autoantibody against the ADAMTS13 enzyme, which is involved in blood clotting and decreases its activity, leads to overproduction of ultra large von Willibrand factor (vWF, a protein needed for the blood to clot normally).
- aTTP:
    - Is acquired: patients can be born with the disease (known as inherited TTP), but only in rare cases.
    - Is thrombotic: causes blood clots
    - Is thrombocytopenic: decreases the number of platelets in the blood.
    - Causes purpura: purple bruising because of bleeding under skin.
- It is diagnosed when patients present with thrombocytopaenia and microangiopathic haemolytic anaemia (a type of anaemia, or low oxygen in blood cells, caused by damage to red blood cells) in the absence of any other identifiable cause. A blood sample is taken and diagnosis is confirmed as aTTP if ADAMTS13 activity is less than 10% of normal activity.

- Early signs include fatigue, headache and bruising, but people can quickly progress to more severe symptoms (e.g. confusion, stroke and coma). Heart, kidney failure or strokes can lead to long-term complications (including physical disability and cognitive impairment from cerebral damage) or death. Therefore, rapid control is essential to minimise the damage, with mortality rates over 90% if untreated.

- Lifetime risk of relapse can cause severe anxiety for patients, in addition to the physical, cognitive and neurological symptoms.

- 100-150 people in England each year have an acute episode. Particularly affects young adults (mean age 43) and women (73% are female). People of Afro-Caribbean family origin and people with HIV are at increased risk of having this condition.

1.2 Treatment pathway and technology.

- No NICE guidance on this condition, but British Committee for Standards in Haematology issued treatment guidance in 2012 (Scully et al 2012).

- Aim of treatment: replenish ADAMTS13 with plasma exchange therapy (PEX), and to control underlying autoimmune activity with immunosuppressants, including corticosteroids and rituximab. Medications to prevent blood clot formation using, for example low molecular weight heparin and aspirin.

- PEX removes blood from a vein and separates the plasma from the blood cells and platelets. The plasma which is removed includes the ADAMTS13 enzyme and the antibodies against it. Donated plasma replaces the ADAMTS13 enzyme. The plasma exchange process takes several hours

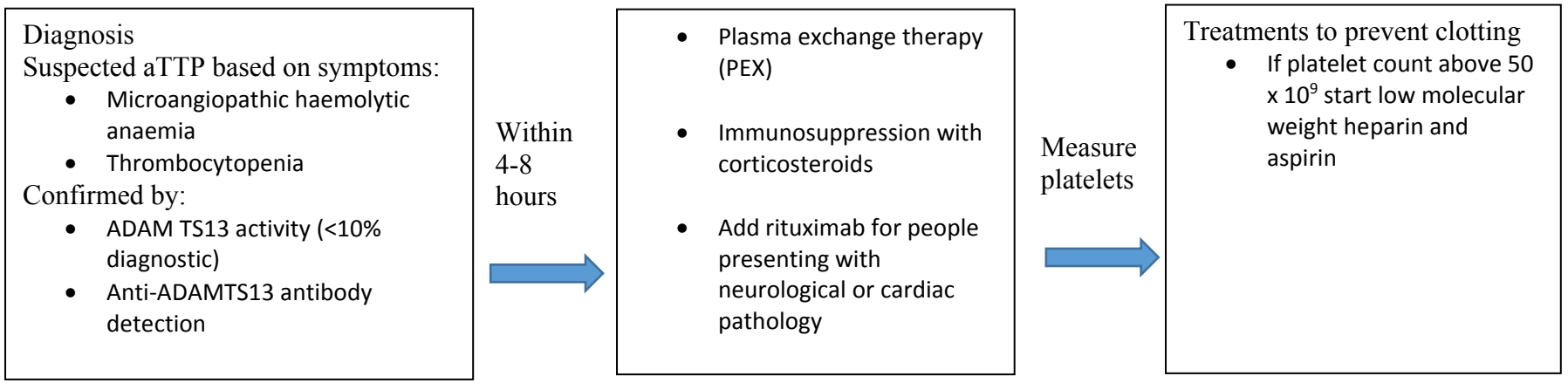
- Treatment should be started within 4-8 hours of diagnosis at specialised centre. Platelet levels measured during treatment to determine when treatment can be stopped or escalated.

- Caplacizumab: humanised nanobody which directly targets vWF-mediated platelet aggregation to prevent clotting. Taken alongside PEX and immunosuppressants.

- First dose taken intravenously before plasma exchange. Thereafter, subcutaneously daily for up to 30 days after stopping plasma exchange. But treatment can continue, together with immunosuppression, if there is unresolved immunological disease. Treatment stops when immunological disease is resolved, that is, when ADAMTS13 activity is normalised. In the main trial (HERCULES), this was given in 7-day periods, up to an additional 28 days. The summary of product characteristics states that caplacizumab has been taken daily for up to 65 days.

- Company and ERG note that use of rituximab for aTTP is becoming more widespread than at the time the BCSH 2012 guidelines were written. Clinical advice to the ERG is that it is now standard to offer rituximab to everyone presenting with an aTTP episode. The company stated that it is given pre-emptively when a person's aTTP is in remission, to prevent relapse.

Figure 1: diagram of treatment pathway outlined in BCSH 2012 guidelines



1.3 Clinical evidence.

- Main data comes from HERCULES (N = 145), double-blind placebo-controlled trial.

- Another trial (TITAN) was carried out before HERCULES, but the European Medicines Agency determined it was not suitable for regulatory submission because of a large number of protocol violations. Company presented some data from TITAN in its submission but did not use it in the cost effectiveness modelling.

- Observational data from a compassionate use programme for caplacizumab and registry data of people with aTTP (in the US) also used to supplement the trial data (this is referred to as the Oklahoma Registry). A UK TTP registry has been collecting data since 2008 but has only begun to collect data beyond the acute phase of treatment (when a person is in hospital) from 2018. The company did not use data from this registry in its submission.

- HERCULES was a double-blind placebo-controlled trial, where people were randomised to plasma exchange therapy followed by either caplacizumab with immunosuppressants or placebo with immunosuppressants for 30 days. The duration of plasma exchange was defined by the treating clinician. People at risk of recurrence (for example people with persistent deficiency of ADAMTS13) could have weekly extended treatment for a period of up to 28 days. There was a 28 day follow up period after stopping the study drug.

- Primary outcome: time to platelet normalisation. This was defined as recovery of platelets to ≥150,000/uL with subsequent stop of daily PEX treatment within 5 days. Secondary outcomes included duration and volume of plasma exchange therapy, time in intensive care unit (ICU) and in hospital; rates of disease recurrence and refractory disease and rates of aTTP-events (such as cardiovascular or neurological events or death).

- Analysis for the primary outcome was carried out in the intention to treat (ITT) population and statistical significance was tested at the 5% level. Secondary efficacy analyses were conducted in the per protocol population which included all

patients assigned to treatment arms ‘as randomised’ who had no major protocol violations. Safety analyses were carried out in people who had received at least 1 dose of capalcizumab or placebo

- People in placebo arm could cross over to open label caplacizumab if they had disease recurrence (26/73 people crossed over). Two out of 72 patients in caplacizumab arm had open label caplacizumab after double-blind period.
- Patients had to be “stably unwell” to be eligible for treatment, and those with most severe disease were excluded.
- Quality of life data were not collected in HERCULES.
- The issues in the other trial TITAN included:
    - It stopped early because it did not enrol enough people to be able to detect a statistically significant difference between capalcizumab and placebo, if there was one. The trial enrolled 75 and it needed to enrol 110 according to its statistical analysis plan
    - It had 12 protocol amendments including allowing people to start PEX before being randomised to caplacizumab or placebo
    - Issues with the laboratory sampling and analysis of platelet counts, and missing data
    - 64% of people had a major protocol deviation. The most common was treatment noncompliance (53% in the caplacizumab arm and 49% in the placebo arm)

1.4 Key trial results.

- Trial results from HERCULES describe caplacizumab plus standard of care compared with placebo plus standard of care, hereafter referred to as caplacizumab compared with placebo (Table 1).
- Compared with placebo, caplacizumab decreased time to platelet normalisation, days spent having and the volume of plasma exchange therapy, days spent in ICU and hospital, recurrence of disease and lowered the proportion of people with refractory disease.
- No difference between caplacizumab and placebo for rates of major thromboembolic events or deaths during trial follow up period

Table 1: Overview of key clinical efficacy results from HERCULES

Outcome	**Caplacizumab n=72**	**Placebo n=73**	**Effect size (N.b. ERG calculated relative results except primary outcome)**
Primary outcome: Median days to platelet normalisation (95% confidence interval)	2.7 (1.89 to 2.83)	2.9 (2.68 to 3.56)	Hazard ratio 1.55 (95% CI 1.09 to 2.19) Median difference 4.6 hours

			P value 0.01
Mean days of plasma exchange (95% confidence interval)	5.8 (4.8 to 6.8)	9.4 (7.8 to 11.0)	Mean difference -3.6 (95% CI -5.49 to -1.71)
Mean volume of plasma exchange in litres (95% confidence interval)	21.3 (18.1 to 24.6)	35.9 (27.6 to 44.2)	Mean difference -14.60 (95% CI -23.51 to -5.69)
Mean days in hospital (95% confidence interval)	9.9 (8.5 to 11.3)	14.4 (12.0 to 16.9)	Mean difference -4.5 (95% CI -7.32 to -1.68)
Mean days in intensive care (95% confidence interval)	3.4 (2.62 to 4.2)	9.7 (5.3 to 14.1)	Mean difference -6.3 (95% CI -10.77 to -1.83)
% with recurrence of disease	12.5%	38.4%	Relative risk 0.33 (95% CI 0.17 to 0.64)
% with refractory disease	0%	[redacted]	[redacted]

% Major thromboembolic events	8%	8%	NR
TTP related death (overall study period)	[redacted]	[redacted]	[redacted]
Composite of TTP related death, recurrence of TTP or major thromboembolic event	12%	49%	P<0.001 (relative treatment effect not reported)

*Peto odd ratio: a measure of treatment effect when the outcome is binary (i.e. refractory/ non-refractory). CI, confidence interval

1.5 **Safety.**

- Bleeding events more common with addition of caplacizumab to standard care (n.b. bleeding is also a risk of standard care alone). Relative risk for bleeding events for caplacizumab compared with standard care was 1.34 (95% CI 1.01 to 1.79).

- People treated with caplacizumab would have a patient alert card because of increased risk of bleeding. Company clinical advisors and ERG clinical advisors agreed that bleeding risk associated with caplacizumab is usually minor and generally manageable.

- Summary of product characteristics states “In case of active, clinically significant bleeding, treatment with caplacizumab should be interrupted. If needed, the use of von Willebrand Factor concentrate could be considered to correct haemostasis. caplacizumab should only be restarted upon the advice of a physician experienced in the management of thrombotic microangiopathies”.

1.6 **Patient experience of aTTP.**

- Patient experts stated symptoms of aTTP have a large impact on daily life. Once condition is in remission symptoms of relapse can be quite ambiguous, so patients experience constant worry about relapse. Their families and carers may share this anxiety.

- Patients noted difficulties in being treated at specialist centre which may be far from home and that there is regional variation outside of these centres with regards to clinicians' knowledge of the condition, monitoring and prophylactic treatment.

- Patients particularly commented on unpleasantness of, and reactions to, plasma exchange therapy, and their concerns about use of large volumes of donated blood product.

- Patients would welcome treatment which reduces the length of relapses and hospital stays.

1.7 **Model structure.**

- Short term outcomes (reflecting the trial period) and costs were modelled using a decision tree model.

- Long term outcomes and costs were modelled using Markov model with 3 health states, remission, relapse and dead. Lifetime time horizon, cycle length of 3 months and 3.5% discounting was used.

- Model population reflected trial population from HERCULES.

Table 2: a summary of the sources of data which were used to model clinical outcomes

Short or long term	Modelled clinical outcome	Source of data
Short term outcomes (reflecting trial period)	Chance person responds to treatment	HERCULES
	Chance person has an exacerbation of their disease	
	Time spent in hospital and ICU	
	Drugs and plasma exchange received	
	Chance person dies	Caplacizumab: compassionate use programme Standard care only: references not publicly available
Long term outcomes when a person is in remission	Chance a person's aTTP relapses	Assumption that people in both modelled treatment arms would have same chance of relapse, 1% of the modelled cohort would have a relapse annually and each person would have only 1 relapse. On relapse it was

		assumed that people would have the same treatment they had as their first treatment
	Chance a person has long term cognitive impairment Chance a person has neuro-psychological impairment Death rate	Assumption: no long-term trial or comparative observational data (see section 1.12) Standard care only: published data (see table 3) Caplacizumab: assumed a relative risk compared with standard care which was based on the time spent in hospital/ICU for capalcizumab compared with placebo in HERCULES

1.11 **Naïve comparison of death rates with capalcizumab plus standard care compared with standard care only during short term phase of the model (that is, trial period)**

- Company used naïve comparison rather than data from HERCULES to model short term mortality rates with capalcizumab compared with standard of care. A naïve comparison means that the data came from 2 separate populations for each treatment and, unlike a randomised trial, would not necessarily share the same demographic and clinical characteristics.
- Data for short term mortality on capalcizumab came from the global compassionate use programme which estimated mortality as 4.28%.
- Data for short term mortality on standard care only was based on a meta-analysis of literature sources (which were not publicly available). This was estimated as a 13.2% mortality rate. The company stated that this estimate was within published estimates of mortality of 13 to 15% (Lester et al. 2015, Orpha.net))

1.12 **Approach for long term outcomes in absence of trial or other comparative data.**

- Company: cognitive impairment, depression, anxiety post-traumatic stress disorder, premature mortality, cardiac failure, renal failure, arterial hypertension and stroke are potential long-term complications of aTTP, but most robust data for long term outcomes associated with aTTP were for cognitive impairment and neuro-psychological impairment (depression/anxiety PTSD) so only included these outcomes in cost effectiveness modelling.

- Prevalence of cognitive impairment, neuropsychological impairment, having concomitant cognitive and neurological impairment and death rates over the long term with current care were estimated from literature (US studies) (see table 3 below).

- Relative risk (of 0.62) for these outcomes for caplacizumab compared with standard care estimated by calculating ratio of hospitalisation/ICU stays for people having caplacizumab compared with standard care in HERCULES.
- Company suggested that the quicker disease resolved (and quicker people left hospital/ICU), the less time people would have microthrombi, leading to reduced organ damage and death caused by these blood clots.
- For purposes of modelling cognitive and neuropsychological impairment assumed to be independent.

Table 3: Company estimates of the risk of aTTP related mortality, neuro-psychological impairment and cognitive impairment after being treated with current standard care for aTTP.

Complication	Risk	Duration of risk	Source in company base case
Cognitive impairment	Prevalence • Mild (54.2%) • Moderate to severe (20.8%)	Lifetime with no improvement (on clinical advice)	Kennedy et al.2009 (risk) 24 patients enrolled in the Oklahoma TTP-HUS Registry for their initial episode of TTP, 1995-2006

Neuro-psychological impairment (depression, anxiety, PTSD)	Prevalence • Depression (36.8%) • PTSD (35.1%) • Company clinical experts say represents "mid-range estimate"	Company clinical experts say will gradually improve over time. 12 month duration based on clinical advice and CG91 (depression in adults with a chronic physical health problem)	Chaturvedi et al. 2017 (risk) cross sectional study (US)
Mortality in remission (due to organ damage, cardiac adrenal failure)	Standardised mortality ratio • 8.3 applied to general population mortality	Not applicable	Upreti et al. 2019 Cohort study 170 consecutive patients treated for TTP The Johns Hopkins Hospital 1995 - 2018

1.13 **Utility values.**

- No health-related quality of life data collected in HERCULES.
- Utility values were estimated from a number of sources (see table 4).

- Utility values during remission had the greatest effect on the modelled incremental cost effectiveness ratio (ICER) when varied in sensitivity analyses.

Table 4: Utility values used in the company model

State	Utility value: mean (standard error)	Population	Quality of life measure and adjustments
Acute phase (reflecting the trial period)			
Baseline utility – prior to acute episode	0.87	Age-matched general population	Utility derived using HERCULES data for patient age
Acute episode – hospitalised (multiplier)	0.64	People with intracranial haemorrhage or stroke (Pappas et al) Australia	Quality of life measure not stated in company submission. Adjustments: average of utility at admission and discharged divided by age-matched general population utility
Acute episode – post discharge (multiplier)	0.82	People with intracranial haemorrhage or stroke (Pappas et al) Australia	Quality of life measure not stated in company submission. Adjustments utility at discharge divided by age-matched general population utility
QALY decrement for AEs, caplacizumab	0.003085	Disutilities based on a targeted search of previous NICE submissions and standard utility sources were identified for adverse events, durations based on assumptions	Quality of life measure not stated in company submission
QALY decrement for Adverse events, SoC	0.002202		

State	Utility value: mean (standard error)	Population	Quality of life measure and adjustments
remission			
Baseline utility	0.77	People with aTTP (Oklahoma registry) (Burns et al 2018)	Mapped SF-36 data to EQ-5D utilities 0.736, adjusted for age, gender and proportion with neuro-psychological impairment
Mild cognitive impairment (multiplier)	0.93	People with aTTP (Oklahoma registry) (Burns et al 2018)	As above Decrement of -0.054 reported for neurological symptoms vs baseline of 0.736 for aTTP patients. Average multiplier for combined impairment severity applied
Moderate /severe cognitive impairment (multiplier)	0.61	People with stroke (no aTTP specific data available) (Gage et al 1996)	Quality of life measure not stated in company submission. Adjustments: stroke utility per severity taken weighted according to stroke severity proportions.
Neuro-psychological impairment (multiplier)	0.73	No aTTP specific utility data available. Assumed comparable to depressive disorder (Sullivan et al 2011)	EQ-5D (from catalogue of EQ-5D results for UK)
Carer disutility for moderate /severe cognitive impairment (multiplier)	0.83	For caregivers of patients with moderate to severe cognitive impairment. Stroke carer HRQL used as stroke considered a good proxy for the worst forms of cognitive impairment (several references cited)	Quality of life measure not stated in company submission

1.14 Key model assumptions

- Same annual risk of relapse after stopping treatment over long term in caplacizumab and standard of care (assumed to be 1% company, tested up to 5% by ERG)

- Mortality during acute phase from observational (non-comparative) data, not HERCULES
- Assumption used for relative risk of long- term complications and death with caplacizumab compared with standard care
- Utility values from literature, some from people with aTTP, some using other conditions (which were considered to have a similar effect to aTTP on quality of life)

1.15 **Cost effectiveness results**

- The ERG noted some minor modelling errors which when corrected decreased the company base case from £37,986 to £36,397 per QALY gained. The ERG exploratory base case was £39,630 per QALY gained

1.16 **Overview of how quality-adjusted life years accrue in the model.**

- Caplacizumab:
  - extends modelled survival
  - decreases time spent in hospital and intensive care (which are associated with poorer quality of life).
  - decreases rate of long term cognitive and neuropsychological impairment (associated with poorer quality of life).
- ERG exploratory base case includes company assumptions on mortality and therefore models same number of life years.

- However, ERG considered that treatment effect of caplacizumab to reduce risk of long term cognitive and neuropsychological complications to be smaller than company's assumption. This reduces modelled QALY gain with caplacizumab in ERG base case.

1.17 **Overview of how drug costs of caplacizumab are offset in the model.**

- Reducing time in hospital/ICU and the amount of plasma exchange and immunosuppression and treating complications of aTTP could in part offset the cost of caplacizumab.

2. Summary of the draft technical report

2.1 In summary, the technical team considered the following:

- **The population in HERCULES may be fitter than the population who would have caplacizumab in UK clinical practice**
- **Treatments received in HERCULES may not reflect those received in clinical practice**
- **Protocol violations and imbalances between treatment arms in HERCULES may affect reliability of the trial**
- **Trial data does not show that caplacizumab reduces mortality or cognitive or neuropsychological impairment**
- **The company used a naive comparison of observational data from two different sources to model mortality in the short term with caplacizumab compared with standard care**
- **There are no data available to test whether caplacizumab reduces mortality or cognitive or neuropsychological impairment in the long term.**

- **Relationship between hospital/ICU stay and long-term complications has not been validated**
- **Utility values did not come from a trial and long-term utility associated with complications of aTTP was not derived from people with aTTP.**
- **The model assumes relapse rate at 1%**
- **Has the model accounted for all the potential costs that can be offset by using capalcizumab, and the wider benefits of reducing use of a blood product?**
- **The company base case was over £30,000 per QALY gained. The company considered that special consideration of 1) the rarity of aTTP 2) discounting rate (costs are accrued during acute episode but benefits over a lifetime horizon) and that 3) caplacizumab is life-saving but acknowledges it does not meet end of life criteria**
- **Caplacizumab may be an innovative technology**

2.2 No issues around resource and drug costs, general model structure or safety were identified

2.3 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- Uncertainties about the effect of caplacizumab compared with standard care in reducing aTTP related deaths, cognitive impairment, and neuropsychological impairment in the absence of further clinical data.
- The effect of caplacizumab compared with standard care on quality of life without further data collected in people with aTTP

- Uncertainties around the relationship between time to recovery (time spent in hospital/ICU) and long-term clinical outcomes without clinical data to validate this relationship.

2.4 The cost-effectiveness results include a commercial arrangement (patient access scheme) for caplacizumab.

2.5 The company base case £36,937 (with ERG corrections) and ERG exploratory base case £39,630 are similar. However, the technical team consider that the committee should consider scenarios assuming a lower benefit of caplacizumab compared with standard care on acute and long-term mortality and long-term complications because of the lack of robust comparative data for these outcomes. The technical team consider that there are potential benefits which have not been captured by the QALY calculation and there are also cost and wider benefits of adding caplacizumab to standard care which may not have been fully accounted for in the model.

2.6 Taking these aspects into account, the technical team's preferred assumptions result in an incremental cost-effectiveness ratio (ICER) which is greater that the company's or ERG's exploratory base case. The technical team consider that scenarios which assume no short- or long-term benefit in survival with caplacizumab compared with standard of care should be taken into account (resulting in an ICER of £172,429 per QALY gained). However, it considers this may be a "worst-case" ICER because it is plausible there are benefits of caplacizumab that are not captured in the company base case, or in these scenarios (see table 5). If the company were able to provide data to support its assumptions on the survival benefit the most plausible ICER would still likely be around £40,000 per QALY gained, which is above the range usually considered cost effective that is, below £20,000 to £30,000 per QALY gained.

3. Key issues for consideration

Issue 1 – Generalisability of HERCULES. The trial population may be fitter than people who would have caplacizumab in UK clinical practice and capalcizumab started later than it would be in clinical practice

<table>
<tr><td>Questions for engagement</td><td colspan="3">Were people in HERCULES fitter than people who would be treated with caplacizumab in UK clinical practice?
How long after starting plasma exchange was caplacizumab given in HERCULES?
Would outcomes be expected to differ between the trial and clinical practice?</td></tr>
<tr><td>Background/description of issue</td><td colspan="3"><table>
<tr><td>Potential difference</td><td>HERCULES</td><td>Expected in UK clinical practice</td></tr>
<tr><td>Eligibility criteria: fitness</td><td>Trial included stably unwell people and excluded people who were on admission at imminent or high risk of death</td><td>Broader</td></tr>
<tr><td>Only people fit enough to consent were included</td><td>Patients who were in a coma and could not provide consent by proxy may have been omitted from the trial</td><td>People who are in a coma or are unconscious can have caplacizumab</td></tr>
<tr><td>Only people who survived long enough to have 1st treatment with PEX and be randomised were included</td><td>All patients needed to have had one PEX treatment prior to randomisation</td><td>Summary of product characteristics: caplacizumab is started at the same time as PEX.
Company: may mean sickest patients died before randomisation.
ERG: clinicians acknowledged that in some cases, caplacizumab may be</td></tr>
</table></td></tr>
</table>

			administered before confirmed diagnosis, in an effort to arrest further deterioration in patient condition.
	Setting -->Time from onset of symptoms to diagnosis/treatment	Because people were recruited in specialist centre, time from onset to treatment may be shorter than non-specialist centres.	Likely it would take longer for diagnosis/treatment start than in clinical trial because people would present in non-specialist centres, may be 1st rather than recurrent episode.
	Diagnostic criteria International Consensus Guidelines specify ADAMTS13 activity levels of <10% are diagnostic for aTTP.	Some people with higher ADAMTS13 activity were included in the trial and more people in the caplacizumab arm had ADAMTS13 activity ≥10% Caplacizumab 13/72 (18.1%) Standard care 7/73 (9.6%)	Clinical advice to the ERG is that ADAMTS13 10-20% is a "grey area" over whether patients can be diagnosed with aTTP. ERG: A subgroup analysis provided by the company shows some variation in treatment effect between the groups. However, this analysis was inconclusive, and based on clinical advice, the ERG was not concerned that this factor alone would bias effect estimation.
	The **company** only included patients who were 'stably unwell', and therefore were fitter than the general population who would receive caplacizumab in clinical practice. The **ERG** and the **technical team** noted that: • Mortality and response rates (in standard care arm) varied widely from UK population data, and the expectation of clinical advisors to both the company and the ERG. • It is unclear whether caplacizumab is likely to be more or less effective in patients excluded from the trials. Clinical advice to the ERG was conflicting as to whether the mechanism of		

	action of caplacizumab would vary in sicker patients, and the ERG stated it was not aware of any empirical evidence investigating this • The company subgroup analyses based on disease severity (assessed using the French severity score), initial/recurrent episode or ADAMTS13 activity on the time to platelet normalisation (primary outcome), which did not suggest different treatment effect in these groups, but noted the small group size. These data are from tables 17-19 ERG report. **Less severe** | **Very severe** **CAPLA (n=42)** | **SoC (n=48)** | **CAPLA (n=30)** | **SoC (n=25)** [redacted] | [redacted] **Initial episode** | **Recurrent episode** CAPLA (n=48) | SoC (n=34) | CAPLA (n=24) | SoC (n=39) [redacted] | [redacted] **ADAMTS13 <10%** | **ADAMTS13 ≥10%** CAPLA (n=58) | SoC (n=65) | CAPLA (n=13) | SoC (n=7) [redacted] | [redacted] The **technical team** noted that a scenario analysis using results for ADAMTS13< 10% (the group of people who have aTTP according to diagnostic criteria) only had a minimal impact on cost-effectiveness results (company base case changed from £37,986 --> £37,493).
Why this issue is important	• Uncertainty about the relative clinical effectiveness in UK clinical practice • Company use this as justification for using alternative source of data for estimating short term mortality (see issue 4)
Technical team preliminary judgement and rationale	It is likely that the trial population is fitter than the population who would have caplacizumab in clinical practice, and it is not possible to quantify effect this has on clinical effectiveness results.

Issue 2 – Concomitant treatments received in the caplacizumab arm in HERCULES may not be consistent with either the comparator arm or clinical practice

Questions for engagement	• How is rituximab used in aTTP in current clinical practice? When is it stopped? • Is rituximab standardly given to during remission to prevent relapse? • Is there any clinical effectiveness data for rituximab in aTTP? • Do more people have rituximab in UK clinical practice than in the trial? If so, what is the likely effect of this on clinical outcomes in the trial? • In the trial, people in the caplacizumab had use of rituximab. Does this represent a benefit of treatment with caplacizumab (that is, were people having caplacizumab less likely to need rituximab than people having placebo), or an imbalance across arms which was independent of study drug? • Do imbalances in rituximab use between treatment arms bias results?
Background/description of issue	

	HERCULES	Expected in UK clinical practice
Rituximab	Rituximab was permitted in the trial and used in accordance with local protocols of the trial	ERG: 2012 guidelines are outdated as they don't refer to rituximab

	centres. 43% of the trial population had rituximab	as part of emergency treatment which would now be regarded as part of standard care (SoC)
Splenectomy	7% of patients in the SoC arm of HERCULES (5/73) No patients in the caplacizumab arm had already received splenectomy at baseline.	ERG: has not been used to treat TTP in the UK since 1970.

The **company** used rituximab in the clinical trial as directed by local protocols (see above). However, the **ERG** stated that, according to clinical advice, more people received rituximab in clinical practice than the guidelines suggest. A lower proportion of patients received rituximab in the caplacizumab arm (39%) compared with the standard of care arm (48%). Furthermore, a small number of patients in the standard of care arm had already received splenectomy at baseline, which the ERG stated is not standard practice.

In the decision tree the proportion of people who had rituximab in the acute phase in each arm was based on HERCULES. In the Markov model 10% of people in both treatment arms had rituximab whilst their aTTP was in remission

The **technical team** noted that if fewer people in the trial receive an effective treatment such as rituximab than in standard practice, trial outcomes may differ from NHS practice. Furthermore, if there are imbalances between arms in the broader treatments received, this may bias the trial outcomes.

The ERG carried out 2 scenarios around rituximab use (which had a small effect on the ICER).

- 78% of people in each treatment arm had rituximab in the acute phase of the model. This increased the company base case (ERG corrected) to £37,155

	• 30% rather than 10% had rituximab during remission (both treatment arms). This increased the company base case (ERG corrected to £38,132)
Why this issue is important	Imbalances in concomitant treatments between treatment arms may bias results. Furthermore, if treatments in the trial are not representative of treatments given in clinical practice, the trial results become less representative of what we could expect to happen in the NHS.
Technical team preliminary judgement and rationale	When comparing either both treatment arms with each other, and both treatment arms with NHS practice, any variations in concomitant treatments were not substantial, so it is unlikely that this had a substantial impact on results. However, if there were any biases, it is likely these would be against caplacizumab, because fewer people received rituximab (compared with NHS practice) and fewer people received splenectomy (compared with the standard of care arm) in the caplacizumab arm

Issue 3 – Protocol violations in HERCULES may affect reliability of the trial

Questions for engagement	• Would protocol violations in HERCULES affect outcomes in study? • Were there any differences in the characteristics of the people who had a protocol violation compared with those who did not?
Background/description of issue	• The **company** noted that 44.1% of patients in HERCULES had a major protocol deviation (see table below). It stated that these were 'not thought to materially impact the outcomes of the study'. • The **ERG** and **technical team** noted that this was an unusually high rate of protocol deviations to see in a clincial trial. The ERG stated that the opinion of the company that this would not materially impact outcomes was not substantiated, noting in particular the inclusion of 21 patients who did not meet the selection criteria.

		HERCULES	
		CAPLA (n=72)	**SoC (n=73)**
	Patients with a treatment non-compliance protocol deviation, n	[redacted]	[redacted]
	Missed daily PEX (HERCULES) and/or had an excursion of dosing time window (TITAN), n	[redacted]	[redacted]
	Daily PEX not continued for at least 2 days after platelet count normalisation, n	[redacted]	[redacted]
	Study drug administration interrupted, n	[redacted]	[redacted]
	Incorrect storage conditions for study drug, n	[redacted]	[redacted]
	Administration of the wrong study drug dose, n	[redacted]	[redacted]
	Use of the wrong route of administration, n	[redacted]	[redacted]
	Administration of the wrong study drug, n	[redacted]	[redacted]
	Received two doses of study drug in error, n	[redacted]	[redacted]
	(table 4 ERG report page 37)		
Why this issue is important	An important aspect of clinical trials is that the methods of data collection are set out clearly prior to the data being collected. If the methods change after the trial started, this can bias the results, for example through inconsistent data collection in different patients.		
Technical team preliminary judgement and rationale	The HERCULES trial had an unusual amount of protocol deviations. It would be useful for the company to provide a clearer explanation of why it believes the protocol deviations do not materially affect results, and/or provide analyses exploring the impact of this, if possible.		

Issue 4 – HERCULES trial data does not suggest that caplacizumab reduces mortality or cognitive or neuropsychological impairment in the short term

Questions for engagement	• Could HERCULES capture any potential differences between caplacizumab and standard of care for mortality, cognitive or neuropsychological impairment? • What is the relationship between time at exposure to thrombi/anti-ADAMTS13 antibodies and death in the short term (would a difference of 4.6 hours in time to platelet normalisation result in a difference in these outcomes)? • Are there any published studies reporting on a relationship between platelet levels in aTTP and death rate? • Was the difference in treatment times between the study arms accounted for in survival analysis?
Background/description of issue	• One person in each treatment arm had a TTP-related death during the trial period • Follow up in the trial was 28 days following end of treatment, and the total treatment duration was different between arms in the double-blind period [redacted]. This suggested that different arms experienced different 'potential time' for events to accrue • These outcomes were secondary outcomes meaning the study may not have been statistically powered to detect a difference • Clinical advisors to the ERG considered the reduction of time to platelet normalisation of 4. 6 hours with caplacizumab observed in HERCULES to be clinically meaningful to patients "due to the perceived benefits of earlier treatment for avoiding complications" The company noted that deaths were lower than expected, which was likely due to an inclusion criterion requiring patients to be stably unwell (and so, fitter than the general population). It therefore used observational mortality data from 2 sources to crudely estimate the effect of caplacizumab on mortality in the short term compared with standard care (see issue 5).

Why this issue is important	A potential important benefit of caplacizumab is that it might reduce mortality compared with current care. This has a big impact on cost-effectiveness results (assuming no difference in acute mortality (over the trial period) increases the company base case from around £37,000 to around £56,000 per QALY gained table 52 company submission)
Technical team preliminary judgement and rationale	There is uncertainty in whether there is an acute mortality benefit to caplacizumab. It would be useful for the company to explore varying levels of mortality benefit, including no benefit. Whether the difference in time to platelet normalisation observed in the trial is clinically relevant in preventing deaths should also be assessed.

Issue 5 – A naive comparison of observational data from two different sources (used by the company to model mortality in the short term with caplacizumab compared with standard care) is not robust

Questions for engagement	• Do the real-world data sources reflect UK clinical practice/ people with aTTP in England? • Does the real-world data (naïve comparison) give a robust estimate of survival and the treatment effect of caplacizumab during the acute phase? • What is the most plausible estimate, real world naïve comparison or trial, for the effect of caplacizumab on survival during the acute phase?
Background/description of issue	The **company** stated that fewer people died in the short-term in the HERCULES trial than would be expected in clinical practice in both arms and this was likely because the trial excluded sicker patients. The company considered alternative sources for mortality in the acute phase of the model • Standard of care arm: 13.2% based on clinical expert advice, which itself was based on a meta-analysis of literature sources. The company stated this is also validated by alternative estimates taken from sources authored by expert clinicians stating an acute mortality on standard of care of between 13-15%. • Caplacizumab: 4.28%, based on mortality data from a compassionate use programme of caplacizumab, where there were 8 deaths in 187 patients as of 30 September 2019. The company stated this rate should be considered a maximum rate, because patients received caplacizumab later than they would have done in NHS practice (treatment with caplacizumab is made available through individual requests and caplacizumab is not available on site). • This results in an acute mortality relative risk of 0.32 for people treated with caplacizumab compared with standard care.

	The **ERG** and the **technical team** note that there are few data to inform mortality in the acute phase. The company does not use randomised controlled data to estimate how caplacizumab affects mortality. This approach is unlikely to be robust and may be affected by confounding.
Why this issue is important	Acute mortality is an important assumption in the model. Assuming no difference in acute mortality d increases the company base case from around £37,000 to around £56,000 per QALY gained (table 52 company submission setting RR for acute mortality to 1, RR for mortality in remission to 0.62 (company base case- see issue 7))
Technical team preliminary judgement and rationale	Data from randomised controlled trials are preferred to naïve comparisons of observed data. It is unclear how generalisable the treatments received by the people in the cohorts were to current UK practice. It is unclear how similar the people in these observed cohorts were to people who would be treated with caplacizumab in UK clinical practice. In order for the committee to assess the uncertainty around the company's naive comparison the company, where possible, should provide: • Mortality rates in people receiving current standard care in UK clinical practice • Mortality rates in people receiving caplacizumab in the UK • A description of the methods used for the company's naïve comparison, including an assessment of the comparability of patient characteristics to UK clinical practice and between the 2 cohorts • An assessment of potential confounding factors in the naïve comparison and a matched analysis to account for potential confounding factors Based on the data submitted in the company submission an estimate of acute mortality from HERCULES is preferred for the cost effectiveness estimates.

Issue 6 – There are no data available to test whether caplacizumab reduces mortality or cognitive or neuropsychological impairment in the long term

Questions for engagement	• Is there any ongoing data collection assessing the clinical effectiveness of caplacizumab in reducing mortality or cognitive or neuropsychological impairment in the long term (after acute phase)? • Is it biologically plausible that a person who is in remission after caplacizumab should have a reduced risk of death, or neuropsychological or cognitive impairment compared with someone who is in remission after standard care? • Is it biologically plausible that the time a person stayed in hospital/ICU for their acute treatment is related to their risk of death, or neuropsychological or cognitive impairment when in remission?
Background/description of issue	The **company** stated that cognitive impairment, depression, anxiety PTSD, premature mortality, cardiac failure, renal failure, arterial hypertension and stroke are potential long-term complications of aTTP. The company considered that there would be a long-term benefit of caplacizumab for these outcomes. Clinical experts to both the company and **ERG** say it is biologically plausible that caplacizumab may affect long term outcomes. The technical team also agree, however note that there are no data for this outcome, which is a cause of uncertainty. The company also noted that • Follow up in HERCULES was short • The UK TTP registry has been collecting data since 2008, but has only begun to collect data beyond the acute phase from 2018 (and wasn't used in its submission)
Why this issue is important	It is plausible that caplacizumab may help to improve long term outcomes, but given the nature of the trial, it is not currently possible to demonstrate this. This is a cause of uncertainty in the evidence. This can impact the cost-effectiveness results, for example:

	• Assuming no difference between caplacizumab and standard care in both mortality in remission and acute mortality (table 52 setting relative risk for both acute mortality and mortality in remission to 1 increases the ICER to around 172,000 per QALY gained) • Assuming no difference between caplacizumab and standard care in neuropsychological impairment or cognitive impairment (setting relative risk for these outcomes as 1 in table 53 company submission) increases the ICER to £53,000 per QALY gained)
Technical team preliminary judgement and rationale	Without data any estimates of rates of death, neuropsychological or cognitive impairment once a person is in remission are highly uncertain. It would be useful for the company to provide any further available data (including requesting data from the UK registry) to the committee for decision making.

Issue 7 – The relationship between hospital stays and risk of cognitive impairment, neuropsychological impairment or death in the long term has not been validated.

Questions for engagement	• Do the rates of mortality in remission, cognitive impairment or neuropsychological impairment used in the standard care arm of the model reflect the expected rates for people having standard care in UK clinical practice? See table 3 above • Is there a relationship between hospital/ICU stay and risk of long-term complications? Are there data to support this? • Does time in hospital ICU/hospital reflect a) exposure to microthrombi b) exposure to microthrombi + damage caused by exposure to microthrombi? • Is the modelled survival gain for caplacizumab compared with standard care (5.48 years) plausible? • Is there any evidence to support a relationship between any other outcome measured in HERCULES (such as time to platelet normalisation) and long-term outcomes?

	• Which is a more valid assumption on the relative risk of caplacizumab on cognitive or neuropsychological impairment compared with standard care; the company's or ERG's? • Is the ERG's approach of assuming that the potential treatment effect of caplacizumab on mortality in remission is greater than the treatment effect of caplacizumab on neuropsychological or cognitive impairment plausible?
Background/description of issue	Based on clinical advice, the **company** used time in hospital/ICU as a proxy for the risk of cognitive impairment, neuropsychological impairment or death during remission. It calculated a relative risk for time in hospital/ICU for caplacizumab compared with standard care using data from HERCULES. Rates of mortality in remission, cognitive impairment or neuropsychological impairment derived from cohorts of patients with aTTP in the US were used to model the rates of these outcomes on standard care. The relative risk (0.62) was applied to these rates to derive the rates of these outcomes with caplacizumab. • Time in hospital/ICU was calculated with the formula $$RR\ for\ long\ term\ complications = \frac{p(hospitalisation\ cap) * hospitalisation\ days\ cap + p(ICU\ cap) * ICU\ days\ cap}{p(hospitalisation\ SoC) * hospitalisation\ days\ SoC + p(ICU\ SoC) * ICU\ days\ SoC}$$ The **ERG** stated that it was ambiguous whether hospitalisation days included ICU days in the company submission. Following a factual accuracy check the company clarified the ICU average stay was calculated for individuals attending ICU rather than the whole population. The company and ERG agreed the simplest calculation was to divide the hospitalisation including ICU days, which resulted in a slightly higher relative risk compared to the company's original 0.62: • $RR =$ [redacted] $= 0.6875$.

	The **ERG** preferred to use its corrected relative risk of 0.688 (a smaller treatment effect of caplacizumab) for cognitive and neuropsychological impairment (but retained the RR of 0.62 for mortality in its exploratory base case). Whilst the ERG favoured a lower relative risk for long-term complications, on reflection it was decided that the impact of caplacizumab on mortality was likely to be greater therefore the ERG retained the company relative risk of 0.62 for mortality. The **technical team** noted that the relationship between time to recovery (time in hospital/ICU) and long-term outcomes has not been validated and is highly uncertain. The company stated, "Despite there being a wealth of qualitative evidence to show that quicker resolution of the acute episode can be linked to a reduced long-term risk of conditions and mortality, there is a lack of data demonstrating the quantitative relationship".
Why this issue is important	See issue 6 above: assumptions on a treatment effect of caplacizumab on these outcomes have a large effect on the cost effectiveness estimates, therefore it is important that they are as accurate as possible.
Technical team preliminary judgement and rationale	The calculation of relative risk should be 0.688 for all 3 outcomes (mortality, cognitive and neuropsychological impairment) which the company provided in its fact check of the ERG report. The estimates of relative risk are highly uncertain because there has been no validation of the exact relationship between time in hospital/ICU and mortality rates, neuropsychological impairment or cognitive impairment. Without such validation it should be considered that there may not be a benefit of caplacizumab on these outcomes and the committee will consider scenarios showing no benefit of caplacizumab on cognitive impairment, neuropsychological impairment or death rates during the modelled remission period.

Issue 8 – The utility values in the model do not come from trial data and utility associated with long term complications of aTTP is based on other conditions

Questions for engagement	• Is stroke a good proxy for the utility experienced during an acute episode for aTTP • Do the utility values for acute aTTP reflect the impact of treatment with caplacizumab/ standard of care on quality of life?

	• Is the quality of life of people in the US with aTTP likely to be similar to the quality of life of patients in the UK? • Are the neuropsychological impairments experienced with aTTP similar to those experienced by people with depressive disorder? • Is the quality of life of people caring for people with aTTP expected to be similar to people caring for people with aTTP?
Background/description of issue	The HERCULES trial did not collect health related quality of life data (HRQoL). The **company** stated it was not possible to collect HRQoL at the time of the acute episode due to ethical concerns. The **ERG** disagreed, stating it considered that HRQoL data measured at timepoints following the acute episode would have been both ethical and possible. It also considered that the company submisison does not provide sufficient evidence for understanding the potential effect of caplacizumab on patients' HRQoL. It noted that although baseline utility values in the model were based on data from people with aTTP, quality of life associated with long term complications of aTTP were not derived from people with aTTP The **technical team** noted that the patient expert statements referred to plasma exchange and fear of relapse as having a large impact on quality of life. Because much of the utility data comes from people without aTTP these may not be captured.
Why this issue is important	The effect of complications of aTTP and treatment for aTTP may not have been fully captured by the model because the utility values come from people with other conditions. In particular, patients stated that plasma exchange therapy is unpleasant.
Technical team preliminary judgement and rationale	The utility values used in the model are uncertain. Further data on quality of life in UK patients with aTTP would help to resolve uncertainty. The effect of plasma exchange therapy and immunosuppression on quality of life should be accounted for in the model. It is expected that being on plasma exchange and immunosuppressants may lower quality of life for some people so if caplacizumab the decreases time a person needs to be on these treatments it would be expected to improve quality of life compared with standard care.

Issue 9 – The relapse rate modelled by the company of 1% is uncertain

Questions for engagement	• Is the company assumption of a 1% relapse rate plausible? • Are there any data on the current relapse rate in the UK?
Background/description of issue	People who have aTTP can relapse after treatment. The **company** assumed that 1% of patients would relapse in the model. It stated that this was because "true relapse" is rare in UK practice due to "proactive monitoring and pre-emptive treatment with [rituximab]", and tested rates of 0% and 2% in sensitivity analyses. It further noted that "In current practice, patients formally referred to specialist centres receive follow-up care in line with BCSH guidance such that true relapse rates are low (estimated to occur in ~1% of patients annually). This may not be the case for patients not formally referred to expert or specialist centres, and relapse has historically been reported in up to 40% of patients". The **ERG** stated one of its clinical experts suggested this rate would be higher and possibly as high as 30% over a person's lifetime. The ERG tested a rate of 5% in its exploratory analyses. Applying an annual relapse rate of 5% which the ERG states is testing limits of reasonable assumptions increases the company base case (from £36,937 to 44,801). The technical team noted that both the company and ERG estimates are not evidence based, therefore there is a large amount of uncertainty in the model.
Why this issue is important	The ERG scenario analyses show that increasing the assumed relapse rate increases the ICER
Technical team preliminary judgement and rationale	It is unclear whether the company and ERG assumptions on relapse rate are too low. An up-to-date estimate of the relapse rate in the UK would help to resolve this uncertainty.

Issue 10 – Have all potential costs that may be offset by using caplacizumab, and the wider benefits of reducing use of a blood product, been accounted for in the model?

Questions for engagement	• Will reducing the volumes of a blood product for plasma exchange have a wider impact (besides the costs of giving the infusion itself)? • Would needing a lower volume of plasma reduce the likelihood of any PEX related complications? • Are there any issues with the availability of plasma for PEX in clinical practice? • Would a shorter time to platelet normalisation observed with caplacizumab be expected to also mean that people treated with caplacizumab have fewer doses of rituximab in clinical practice?
Background/description of issue	In HERCULES people having caplacizumab had around 15 fewer litres of plasma than people having standard care. The **technical team** noted that this might have wider benefits for the NHS that might not be captured in the model, for example reducing the need for donated plasma might reduce costs and also allow a finite resource in the NHS to be made more easily available. The **technical team** noted the uncertainty surrounding how rituximab is used in clinical practice compared with in the trial. It is unclear whether rituximab use would change if caplacizumab were available.
Why this issue is important	Although the costs of plasma exchange were accounted for in the cost effectiveness model, reducing the use of blood products (which is a finite resource) may increase its availability for other conditions. If the use of capalcizumab means that people have less rituximab this would mean that the costs of caplacizumab may be in part offset by lower rituximab costs.
Technical team preliminary judgement and rationale	There may be cost savings and wider benefits to the NHS which are not captured in the model.

Issue 11 – The company base case is over £30,000 per QALY gained

Questions for engagement	• Is there reason to consider an ICER of above £30,000 per QALY gained a cost-effective use of NHS resources? • Are there any benefits of caplacizumab that the company have not included in its modelling? • Have the benefits of reduced use of blood products (which are a limited resource) been captured?
Background/description of issue	The company submission includes a base case ICER which is above the range normally considered a cost-effective use of NHS resource. The **company** argued that it should be allowed some flexibility with the normal threshold. It stated that: • aTTP is an ultra-rare, life threatening condition. Although it does not strictly meet the criteria for end-of-life, the company argued that the threshold could "arguably be increased" to something similar (that is, £50,000 per QALY gained) and is "cost-effective when considered under an increased willingness-to-pay (WTP) threshold similar to that used for end-of-life and/or highly specialised life-saving treatments in acute ultra-rare, life-threatening diseases". • Caplacizumab is a treatment with high upfront costs for the acute episode but long-term benefits through reduced acute mortality, and therefore the use of a 3.5% discount rate biases against caplacizumab as benefits are heavily discounted but not costs. It noted that a discount rate of 1.5% for both costs and QALYs reduces the ICER to £29,970. • The treatment is innovative (discussed further in Issue 12) and there are uncaptured benefits with "difficulties in including all relevant potential benefits of treatment (other long-term complications, carer impact, impact on long-term mortality)". • A NICE Citizens Council report that discusses how society should place a higher value on life-saving interventions in situations of urgent need (under the principle or "rule of rescue") which states that using a QALY modifier of 1.7, equivalent to the end-of-life criteria allowing for a £50,000 threshold should be considered for life-saving treatments at the end of life.

	The **technical team** note that the topic is being considered within the normal single technical appraisal process, and therefore the maximum acceptable ICER is £20,000 to £30,000 per QALY gained. It further notes that under principle 7 of the NICE principles NICE "cannot apply the 'rule of rescue', which refers to the desire to help an identifiable person whose life is in danger no matter how much it costs". However, the company base case might exclude some cost savings (see Issue 10) and it may be innovative (see issue 12), and it is possible these might reduce the ICER to within the range normally considered to be cost-effective use of NHS resources.
Why this issue is important	The company base case is above the level normally considered a cost-effective use of NHS resources.
Technical team preliminary judgement and rationale	Neither of the company scenarios are consistent with NICE methods. The NICE methods guide says (on appropriateness of using a 1.5% discount rate) "In cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), cost-effectiveness analyses are very sensitive to the discount rate used". The long-term benefits of caplacizumab have not been demonstrated. The NICE methods guide says the QALY modifier of 1.7 for treatments used for end of life can only be used when specific criteria are met. That is: • the treatment is indicated for patients with a short life expectancy, normally less than 24 months and • there is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment. In addition, the Appraisal Committees will need to be satisfied that:

	• the estimates of the extension to life are sufficiently robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review) and • the assumptions used in the reference case economic modelling are plausible, objective and robust The lack of robust data for survival gain and no data presented for life expectancy means that end of life criteria are not met in this case. However, there might be uncaptured cost savings and QALYs, which could reduce the ICER to a cost-effective level.

Issue 12 – Caplacizumab may be an innovative technology

Questions for engagement	• Are there any benefits not captured by QALY calculation?
Background/description of issue	The **company** stated that: • Caplacizumab is o the first nanobody developed from camelid heavy-chain-only antibodies to be approved for any indication. o the first treatment specific to aTTP directly targeting the pathologic mechanism of the disease. o A step change in the management of the disease

	• Having a treatment that can quickly control the disease is of reassurance to patients and their family and friends which cannot be captured in the QALY calculation The **technical team** noted that NICE considers a technology innovative if the innovation adds demonstrable and distinctive benefits of a substantial nature which may not have been adequately captured in the reference case QALY measure
Why this issue is important	If there are benefits not captured in the QALY, then this may underestimate the cost-effectiveness of caplacizumab.
Technical team preliminary judgement and rationale	Caplacizumab is likely to be innovative. It shows a step change in treatment by decreasing the time to recovery and reducing hospital stays and plasma exchange therapy. Potential benefits not captured in QALY are • limiting time patients need plasma exchange and immunosuppression and the impact this has on their quality of life. • impact on patient anxiety of having an effective treatment Although the effect of caplacizumab on mortality, neuropsychological impairment and cognitive impairment is unclear, the company model considers the potential for caplacizumab to have a benefit on these outcomes

4. Issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 5: Technical team preferred assumptions and impact on the cost-effectiveness estimate

Alteration	Technical team rationale	ICER	Change from base case
Company base case	–	£37,986	
1. ERG correction of minor errors	Technical team and company agree with amendments	£36,937	-£1049
2. Correction of the estimated relative risk of hospitalisation/ICU with caplacizumab vs. standard care. This should be applied for all outcomes which this relative risk is used for	Company proposed this change during the factual accuracy check	To be provided by company	
3. Use of trial data rather than crude comparison to model mortality (suggesting no effect of caplacizumab on acute mortality)	Trial data is more robust than indirect observational comparison	~£56,000	+ £18,014
4. Scenario in which survival during remission is the same for people initially treated with caplacizumab as people initially treated with standard care	There are no data suggesting a difference and the relationship between hospital/ICU stay and long-term survival has not been validated	~£65,000	+£27,014
5. Assuming that caplacizumab does not neuropsychological or cognitive impairment compared with standard care	There are no robust data showing a treatment effect and the relationship between hospital/ICU stay and long-term survival has not been validated	~£53,000	+£15,014
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate	**In the absence of data to robustly show that caplacizumab improves survival compared with standard care in the short term (when a person has their initial treatment in hospital)**	£172,429	+£134,443

Alteration	Technical team rationale	ICER	Change from base case
	or in the long-term when a person is in remission a scenario showing no effect of caplacizumab on mortality should be considered as a worst case		

Table 6: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Uncertainties about the effect of caplacizumab compared with standard care in reducing aTTP related deaths, cognitive impairment, and neuropsychological impairment in the absence of further clinical data.	It is not likely to be possible to collect this data, but it is required for the model, and impacts cost-effectiveness results.	Unknown
The effect of caplacizumab compared with standard care on quality of life without further data collected in people with aTTP	Quality of life is a key aspect of the cost-effectiveness calculation	Unknown
Uncertainties around the relationship between time to recovery (time spent in hospital/ICU) and long-term clinical outcomes without clinical data to validate this relationship.	This may impact cost-effectiveness results. The technical team that observational data on this relationship would be very valuable if available.	Unknown

Table 7: Other issues for information

Issue	Comments
Equality considerations	The company noted higher incidence of aTTP is found in people from Afro-Carribbean decent and in people with HIV. It was not considered by the technical team that access to caplacizumab would be different in these two groups compared with the whole population with aTTP. The technical team therefore considered there were no equality issues.

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References

Burns D, Lee D, Vesely S, et al. Patient health-related quality of life associated with remission of aTTP. A regression analysis using non-randomised observational data from the Oklahoma TTP registry. ISPOR. Barcelona, Spain. 10-14 November 2018 PSY192

Chaturvedi S, Abbas H and McCrae KR. Increased morbidity during long-term follow-up of survivors of thrombotic thrombocytopenic purpura. *Am J Hematol.* 90 (10): E208

Gage BF, Cardinalli AB and Owens DK. The effect of stroke and stroke prophylaxis with aspirin or warfarin on quality of life. *Arch Intern Med.* 1996;156(16): 1829-36

Kennedy AS, Lewis QF, Scott JG, et al. Cognitive deficits after recovery from thrombotic thrombocytopenic purpura. *Transfusion*. 2009; 49 (6): 1092-101.

Lester W, Begaj I, Ray D and Pagano D. Trends in diagnosis and mortality from thrombotic thrombocytopenic purpura in England from 2003 to 2013: are we improving outcomes? 55th Annual Scientific Meeting of the British Society for Haematology. Edinburgh, UK. 20-22 April 2015

Orpha.net. Acquired thrombotic thrombocytopenic purpura. 2015. Available at http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=93585.

Pappas MA, Vijan S, Rothberg MB and Singer DE. Reducing age bias in decision analyses of anticoagulation for patient with nonvalvular atrial fibrillation. A microsimulation study. PLoS One. 2018; 13(7):e0199593

Scully M, Hunt B, Benjamin S, et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. *Br J Haematol.* 2012; 158:323-35

Sullivan PW, Slejko JF, Sculpher MJ and Ghushchyan V, Catalogue of EQ-5D scores for the United Kingdom. *Med Decis Making.* 2011; 31 (6): 800-4.

Upreti H, Kasmani J, Dane K, et al. Reduced ADAM TS13 activity during TTP remission is associated with stroke in TTP survivors. *Blood.* 2019:blood.2019001056.

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NICE National Institute for Health and Care Excellence

Technical engagement response form

Caplacizumab for treating adults experiencing an episode of acquired thrombotic thrombocytopenic purpura [ID1185]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **13 March 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Sanofi**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Sanofi**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Company summary

Sanofi welcome the technical engagement step and have addressed issues raised in the document. Sanofi have submitted a revised PAS of "Commercial in confidence information removed" which has been accepted by PASLU. With the revised PAS, using a range of data sources for mortality and a potential utility decrement due to fear of relapse, a new range of ICERs are presented from £26,357 to £31,712, detailed in response to Issue 11 below.

Questions for engagement

Issue 1: Generalisability of HERCULES. The trial population may be fitter than people who would have caplacizumab in UK clinical practice and caplacizumab started later than it would be in clinical practice	
• Were people in HERCULES fitter than people who would be treated with caplacizumab in UK clinical practice?	HERCULES enrolled patients with a clinical diagnosis of aTTP who had already received one PEX treatment and there were no inclusion / exclusion criteria which would have excluded patients with more severe disease. In fact, the trial allowed for consent to be obtained from the legally acceptable representative or independent physician when the patient was unconscious or unable to give consent. The HERCULES trial is as generalisable as it is possible to be within the context of a clinical trial in an acute setting. We therefore do not believe that there are major differences between the HERCULES trial population and that seen in UK clinical practice barring: • The trial being run only in centres with expertise in management of aTTP who can run acute clinical trials • The impact of the requirement for one PEX prior to randomisation

	The trial design required one PEX treatment within 24hrs prior to randomisation, which was implemented mainly for logistical reasons. In view of the sudden acute and life-threatening nature of the disease, this measure allowed the patient and relatives more time to be informed about their disease and the trial, and the trial staff to get organized. As a result, those patients who did not survive long enough between the prior PEX and the randomization, would not have been included in the trial. Additionally, for those that were randomised, initiation of PEX treatment would have resulted in improvement of their condition prior to administration of caplacizumab. Clinicians at an advisory board meeting considered the mortality figures in the HERCULES trial to be lower than what they would expect to see in UK practice ((0 deaths in the caplacizumab arm vs 4.2% in the SOC arm). As such, alternative sources for mortality were sought. For caplacizumab, mortality data were obtained from an ongoing global compassionate scheme. As of 30 September 2019, 187 patients had been treated with caplacizumab globally, and there were 8 deaths, equating to a mortality of 4.3%. For the SOC arm, a mortality rate of 13.2% (based on the literature and 13 – 15% in UK reported studies[1,2]) was used. Prior PEX before randomisation and recruitment of patients from specialised centres as well as the use of open label caplacizumab to treat disease exacerbations in HERCULES (which mainly happened in the placebo group) are likely to have caused this difference in mortality. As a result, the term “stably unwell” was used in the CS to highlight why outcomes from HERCULES do not reflect what would be expected in real world practice (for the SOC arm). We acknowledge that this terminology has caused some confusion, but we can confirm that there was no such criteria in the trial; patients who were, on admission, at imminent or high risk of death were **not** excluded from the HERCULES trial. For reference, the inclusion and exclusion criteria for HERCULES are provided in Table 1 of Appendix 1.

• How long after starting plasma exchange was caplacizumab given in HERCULES?	A single loading dose of 10 mg caplacizumab was to be administered by intravenous bolus injection from "academic in confidence information removed" hours to "academic in confidence information removed" minutes prior to the first PEX done after randomization. The maximum time allowed between the first PEX prior to randomisation and the first exchange after randomisation was 24 hours.
• Would outcomes be expected to differ between the trial and clinical practice?	Acute mortality observed within the clinical trial is lower than is expected in clinical practice. As noted within clinical expert consultation conducted, real-world mortality would be expected to be higher than in the trial for the SoC arm and would not be expected to be 0 for caplacizumab[3]. The acute mortality rates from the clinical trial programme are considered to be lower than would be expected in practice because some patients might have died before PEX could be initiated or prior to potential randomisation and the use of open label caplacizumab to treat disease exacerbations in HERCULES (which occurred mainly in placebo patients). Estimates from real-world datasets are also thought to underestimate acute mortality due to patients dying before PEX can be initiated in clinical practice or prior to consent for inclusion in registry (and physicians tending not to ask their families for consent). Clinical expert input indicated that the difference in mortality would be increased in a real-world setting (i.e. caplacizumab use would be even more beneficial) as patients with more severe disease are more likely to be rescued[3]. The overarching design of the caplacizumab clinical trials generally reflects clinical practice and clinical experts consulted indicated that the HERCULES population generally reflected clinical practice[3]. It is worth noting that three UK sites (UCH, Liverpool and Bristol) were involved in the trial with 21 UK patients (mostly from UCH) enrolled – the second highest contributor after the US. Other than for acute mortality and other

	outcomes impacted by the use of open-label caplacizumab (such as hospitalisation days), real-world outcomes are expected to be similar to the trial. Where they are not similar the bias is against caplacizumab. There is consensus across the clinical community that the clinical benefits shown in the caplacizumab data would translate to longer-term benefits based on biological rationale. There is also strong clinical support for the addition of caplacizumab to routine care for an acute episode of aTTP. Caplacizumab is currently being supplied free of charge to specialist centres in the UK as part of a compassionate use program to fulfil unsolicited requests from clinicians, and in recognition of the urgent clinical need caplacizumab addresses. Clinician feedback from this compassionate use programme has been extremely positive with several comments highlighting improved outcomes in patient who received caplacizumab.
Issue 2: Concomitant treatments received in the caplacizumab arm in HERCULES may not be consistent with either the comparator arm or clinical practice	
• How is rituximab used in aTTP in current clinical practice? When is it stopped?	Firstly, we would like to make it clear that rituximab should not be considered as a comparator to caplacizumab as is currently indicated within the technical report. The two drugs have very different mechanisms of action and very different purposes for use. When treating aTTP in the acute setting, the aim is to: • replenish functional ADAMTS13 via PEX, • suppress autoantibody that is interfering with ADAMTS13 activity / clearance (steroids and / or rituximab), to restore normal vWF processing

	Caplacizumab as an addition to the current care pathway immediately prevents von Willebrand factor (vWF) proteins binding to platelets an in doing so, speeds up time to platelet normalisation (TTPN); effectively bridging the gap to ADAMTS13 normalisation. In current practice, rituximab is given upfront as soon as possible. However, it takes several days for treatment to have an effect, during which time microvascular thrombosis is ongoing and patients remain at risk of tissue ischemia, organ damage and death [4, 5, 6]. According to the latest UK aTTP registry publication, rituximab is used in 75-80% of acute cases. Typically, this is done at the standard dose and schedule for lymphoma, which is 375 mg/m^2, weekly for 4 weeks. [ref J-S Shin abstract BSH 2019, Scully et al Blood 2011] Rituximab is also used in remission to raise and/or maintain ADAMTS13 activity and in doing so, prevent relapses. According to recently consulted upon draft ITSH guidelines, rituximab is recommended: • *"For patients experiencing a first acute event or relapse, the Panel suggests the addition of rituximab to corticosteroids and PEX over corticosteroids and PEX alone (conditional recommendation in the context of very low certainty evidence)"* • *"For patients who are in remission, and still have low ADAMTS13 activity but no other signs/symptoms of TMA, the Panel suggests the use of rituximab for prophylaxis (conditional recommendation in the context of very low certainty evidence)"*

	Clinical experts have confirmed at the technical engagement call that the use of rituximab in aTTP will not change regardless of whether caplacizumab is recommended or not.
• Is rituximab standardly given to during remission to prevent relapse?	The BSH guideline from 2012 recommends monitoring of ADAMTS13 activity in remission, and reports that elective rituximab when ADAMTS13 activity has fallen out of the normal range has shown good effectiveness in preventing acute relapse. The draft ITSH guidelines (see above) also recommend use in this setting.
• Is there any clinical effectiveness data for rituximab in aTTP?	Westwood et al (Journal of Thrombosis and Haemostasis, 2012) report a retrospective analysis of 52 cases where rituximab was administered during the acute phase of TTP[7]. Patients were treated between 1 January 2004 and 31 December 2011). Earlier administration of rituximab (≤ 3 days) was associated with faster attainment of remission (12 vs. 20 days, P < 0.001), fewer plasma exchanges (16 vs. 24, P = 0.03) and shorter hospital stay (16 vs. 23 days, P = 0.01). 95% of patients achieved complete remission within 14 days (4–52 days); four patients died acutely. Rituximab prophylaxis was associated with normalization of ADAMTS13 levels within 3 months in all but one case, with only one acute relapse at follow-up. Westwood et al (Blood Advances 2017) report 76 cases where prophylactic rituximab was administered to prevent relapse in aTTP[8]. Patients were treated between 2005 and 2016. 79% of cases showed ADAMTS13 normalisation, with at least a partial response in 92%. Reduced-dose rituximab was associated with a higher rate of re-treatment than the standard dose. The use of rituximab for prevention of relapse has been instrumental in reducing relapse rates within aTTP. However, as mentioned above, rituximab takes on average 6-10 days to take effect during which time patients remain in an occluded state. This is an unmet need that is addressed by caplacizumab.

• Do more people have rituximab in UK clinical practice than in the trial? If so, what is the likely effect of this on clinical outcomes in the trial?	According to the UK aTTP registry approximately 75-80% of acute cases of TTP are managed with rituximab. The UK centres in HERCULES enrolled a total of 21 patients – 19 received rituximab in the acute phase (90%). This is greater than the proportion who received rituximab in the clinical trial (caplacizumab arm [39%] compared with the standard of care arm [48%]). This is due to evolving nature of proactive use of rituximab in aTTP globally. More and more centres are now using it routinely and earlier. The lower use of rituximab in the clinical trial is not expected to have a substantial impact on results. However, as the technical team states, if there were any biases, it is likely these would be against caplacizumab, because differentially fewer people received rituximab (compared with NHS practice) in the caplacizumab arm versus the standard of care arm
• In the trial, people in the caplacizumab had use of rituximab. Does this represent a benefit of treatment with caplacizumab (that is, were people having caplacizumab less likely to need rituximab than people having placebo), or an imbalance across arms which was independent of study drug?	Per protocol, centres were free to use additional immunosuppressive therapy per investigator decision or site policy. All subjects were to receive corticosteroids. In current UK practice, rituximab is expected to be administered at the same time as caplacizumab and the course length does not vary dependent upon response. Given this and the different aspects of the disease that these two medications address, the difference in use of rituximab between the two arms is an imbalance which is thought to be independent of study drug. We do note, however, that the imbalance may have some impact on outcomes with the bias being against caplacizumab.
• Do imbalances in rituximab use between treatment arms bias results?	HERCULES results and outcomes have been analysed according to the initial immunosuppressive regimen at enrolment – rituximab at initiation or otherwise. 24 cases were managed with rituximab at presentation in

	addition to corticosteroids. A similar treatment effect for caplacizumab was seen in both groups, consistent with the overall analysis. These results were presented as a poster at the ASH congress in December 2019. There is no way of knowing the full impact of rituximab use on the dataset, however, the Committee can be confident that the impact is unlikely to be substantial and in any case biases against rather than for caplacizumab.
Issue 3: Protocol violations in HERCULES may affect reliability of the trial	
• Would protocol violations in HERCULES affect outcomes in study?	As noted by the EMA the *"protocol deviations were not deemed likely to favour the experimental arm, or to challenge the overall results of the study"*[6]. This is because the nature and frequency of major protocol deviations were similar between study groups and the majority consisted of deviations from the protocol treatment schedule. Additional detail is provided below on the nature of the protocol deviations to provide reassurance on this point. Overall, 64 subjects (44.1%) had a major protocol deviation; 31 subjects (43.1%) in the caplacizumab group and 33 subjects (45.2%) in the placebo group. Overall, the most commonly reported category of major protocol deviations was "treatment non-compliance", reported in 36 subjects (24.8%) (caplacizumab group: 15 subjects

	[20.8%]; placebo group: 21 subjects [28.8%]), followed by “selection criteria not met” reported in 21 subjects (14.5%) (caplacizumab group: 11 subjects [15.3%]; placebo group: 10 subjects [13.7%]). Most major protocol deviations in the category of “treatment non-compliance” included deviations from the expected study drug administration schedule, as well as the expected PE treatment schedule. See Tables 3 and 4 in Appendix 1 for a list of major protocol deviations The relatively high number of protocol deviations in the HECULES trial, acknowledged upfront in the CS (page 47 of Document B), should be expected when taken in the context of a clinical trial, in an acute emergency setting, where the first and foremost priority is to save a life. The challenges of running a trial in such a setting have been documented and include difficulty in obtaining consent; heterogenous patient casemix and patients presenting often outside normal “office” hours[9, 10, 11]. There were no major protocol deviations due to treatment with prohibited concomitant medications or due to subjects not withdrawn as per protocol in either group. The nature and frequency of major protocol deviations were similar between study groups and the majority consisted of deviations from the protocol treatment schedule as would be expected for a treatment in the acute setting with the top four reasons for deviation being: • Missed daily PEX (HERCULES) • Daily PEX not continued for at least 2 days after platelet count normalisation • Study drug administration interrupted • Inclusion criterion 3 - required initiation of daily PE treatment and had received 1 PE treatment prior to randomization

	As presented in Appendix L of the company submission, the results of the per protocol analysis (see **Error! Reference source not found.** in Appendix 1) confirm the results presented for the ITT population. In the per protocol population, median time to response was similar to the ITT population: "academic in confidence information removed" for patients receiving caplacizumab (95% CI "academic in confidence information removed") and "academic in confidence information removed" for patients receiving SoC (95%CI "academic in confidence information removed). Hazard ratio data indicated a greater impact of caplacizumab on time to platelet response (HR "academic in confidence information removed"), although again the 95% CIs were wide (HR "academic in confidence information removed", 95% CI "academic in confidence information removed").
• Were there any differences in the characteristics of the people who had a protocol violation compared with those who did not?	Table 5 in Appendix 1 provides compares the baseline characteristics of the ITT population of HERCULES with the those of the population that had a major protocol violation.
Issue 4: HERCULES trial data does not suggest that caplacizumab reduces mortality or cognitive or neuropsychological impairment in the short term	
• Could HERCULES capture any potential differences between caplacizumab and standard of care for mortality, cognitive or neuropsychological impairment?	It is not possible to capture differences in cognitive or neuropsychological outcomes in the short-term; especially within the context of an acute setting trial. The trial would also never have been able to capture acute mortality generalisable to the wider UK context (see answer to Issue 1) even if sufficient patients had been available in the context of an ultra-rare disease to do so. Despite this it is notable that there is an observed numerical difference in mortality within the HERCULES trial (0 vs 3 deaths in the caplacizumab and placebo arms respectively during the arm during the drug

	treatment period). It is also notable that, pooled analysis of HERCULES and TITAN demonstrated a significant improvement in mortality rate during the treatment period ("academic in confidence information removed") as shown in Table 13 in the company submission.
• What is the relationship between time at exposure to thrombi/anti-ADAMTS13 antibodies and death in the short term (would a difference of 4.6 hours in time to platelet normalisation result in a difference in these outcomes)?	The vWF-mediated platelet aggregation in aTTP is characterized by consumption of platelets into microthrombi and is reflected by low platelet counts. When sustained, this microthrombotic process leads to tissue ischemia and ultimately may result in organ damage and death. As such, low platelet count is a measure of the pathogenic microvascular thrombosis and associated potential morbidity. Faster normalization of platelet counts therefore is an indirect measure of clinical benefit as it reflects a faster recovery from the acute episode of the disease and represents an immediate and direct inhibition of the pathological formation of microthrombi. In general, the mortality rate during the acute phase ranges between 10–20%. Most deaths occur within 2 weeks of diagnosis. Patients treated with caplacizumab achieve a faster resolution of the acute aTTP episode (Phase III HERCULES study data show that patients treated with caplacizumab are 55% more likely to achieve platelet count response at any timepoint versus Placebo).
• Are there any published studies reporting on a relationship between platelet levels in aTTP and death rate?	Rock et al 1991 compared plasma exchange to plasma infusion in TTP. They reported that the plasma exchange group had a higher rate of response (as defined by an increase in platelet count (24/51 patients) than those who received plasma infusion (13/51); P = 0.025. Mortality was lower in the plasma exchange group (2/51) compared to the plasma infusion group (8/51); P =0.035) The plasma exchange group demonstrated better outcomes after 6 months with 11 deaths compared to 19 in the plasma-infusion group[12].

• Was the difference in treatment times between the study arms accounted for in survival analysis?	Yes, the time (hours and minutes) was taken into account.
Issue 5: A naive comparison of observational data from two different sources (used by the company to model mortality in the short term with caplacizumab compared with standard care) is not robust	
• Do the real-world data sources reflect UK clinical practice/ people with aTTP in England?	Both Sanofi and clinical advisers considered the mortality rates in the HERCULES trial do not reflect what will be seen in clinical practice as they appear very low for both caplacizumab and placebo. This is an issue also raised by the technical team in terms of generalisability in Issue 1. As discussed earlier, this is likely due to the design and setting of the trial (prior PEX before randomisation, the trial being conducted in centres with expertise in management of aTTP, use of open-label caplacizumab) rather than the condition of the patients recruited into the trial. As such, Sanofi used a real-world data source on acute mortality for caplacizumab derived from the compassionate use program. In this program, clinicians request caplacizumab once they identify an aTTP case. There is, therefore, a delay between diagnosis and administration of caplacizumab that will be reduced if caplacizumab is available in hospitals. As such, the mortality estimates from the compassionate programme are conservative to caplacizumab. This interpretation was supported by clinicians on clinical validation calls and on the technical engagement call[3]. It is also noteworthy that mortality rates within the compassionate use data are decreasing as centres become more experienced with the product and how to obtain it reducing delays. The data originally provided covering to 30 September 2019 indicated a mortality rate of 4.3% (8/187 patients). The latest data indicate (as of February 2020) 9 deaths out of 239 patients (3.77% mortality).

	For the placebo arm, clinical advisers suggested a mortality rate of between 10% and 20% in clinical practice. Sanofi chose to use a mortality rate of 13.2% based on a meta-analysis. The full report for this meta-analysis was provided as a reference with the company submission[13]. Briefly, the mortality rate used for the standard of care arm was taken from a systematic literature review (SLR) and meta-analysis of TTP studies. The SLR was designed to provide insight into the presentation, progression and outcomes of acute TTP. Prospective, retrospective studies as well as case reports and clinical trials were included in the search criteria. The population focused on adults and children suffering from one or more acute episodes of TTP and acquired or congenital patients treated with plasma exchange. A meta-analysis was performed using a random effects model, to summarize the descriptive data. The overall prevalence was calculated using the weight of different studies (higher weight for studies with more patients), to avoid bias of exceptionally small or large study populations. A total of 627 studies were identified in the systematic literature review. 414 of these were eliminated after primary screening. Of the 213 remaining, a further 79 studies were excluded after full text screening. 7 studies were included after scanning the references of the included studies leaving a total of 141 studies in the systematic literature review. The 141 studies included a total of 20,131 patients that suffered from at least one acute TTP. The patients had a median age of 41 years (ranging from neonatal to 93 years) and were predominantly female (67.7%). ADAMTS13 was determined in 5,326 patients in 61% of studies (84.8% of patients had ADAMTS13 activity of <10%). Mortality rates and timing of mortality was extracted from each study if reported. Only studies using plasma exchange as first line treatment were included due to the reduced mortality rates after introducing this as standard of care. Out of the 141 studies included in the

	review, mortality rates during the first acute phase was reported in 129 studies. Mortality rates varied between studies ranging from 0% to 57% due to the variation in patient populations and patient numbers. For the first acute phase (including exacerbations which occur mostly in the first 15 days after diagnosis), the average mortality was 13.2% (95% CI: 11.9%-14.5%). Analysis looking at the impact of study timing showed that despite a greater understanding of the disease pathogenesis and the use of additional treatments, the acute mortality rate has not changed over the years after introduction of PEX. This figure was validated by clinical advisers and is consistent with recent estimates taken from sources authored by expert clinicians stating an acute mortality on SoC of between 13-15%[1, 2]. Since submission additional data has become available: • **French matched-cohort analysis:** A matched-cohort analysis conducted in France based upon the temporary authorization scheme for caplacizumab use which has been running since September 2018 was recently published in abstract form by a consortium of French clinicians. "Academic in confidence information removed"[14]. o "Academic in confidence information removed" o "Academic in confidence information removed" o "Academic in confidence information removed" o "Academic in confidence information removed"

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Given the convergence of these values (as shown in the table below) we would consider that the real-world data sources presented in the original submission are consistent with the evidence for SoC and that the compassionate use data originally presented likely over-estimates mortality for caplacizumab (as was noted by clinicians at the time). We have therefore revised our base case to use the latest compassionate use data of 3.77%.

	Caplacizumab	SOC	P value
HERCULES (study treatment period)	0/72(0%)	3/73(4.1%)	N/A
HERCULES/TITAN pooled analysis (study treatment period) (Appendix 2)	0/108(0%)	4/112 (3.6%)	0.047
French matched cohort study[14]	"AIC information removed"	"AIC information removed	"AIC information removed
Caplacizumab UK Registry (treated within 48 hours of PEX) (Appendix 2)	"AIC information removed	-	NA
Caplacizumab UK Registry (treated	"AIC information removed	-	NA

	within 7 days of PEX) (Appendix 2			
	Compassionate use all patients February 2020 (n=239)	9/239 (3.77%)	-	NA
	Compassionate use all patients August 2019 (n=187)	8/187 (4.3%)	-	NA
	UK Literature (References 1 and 13 in technical report response)	-	13.0% - 15.0%	NA

• Does the real-world data (naïve comparison) give a robust estimate of survival and the treatment effect of caplacizumab during the acute phase?	As noted above the data reflects real-world practice and is conservative for caplacizumab due to delay in administration. This data is supported by a recent French matched cohort study, mortality in those who received caplacizumab and (corticosteroids, rituximab and plasma exchange) was "AIC information removed" % vs. "AIC information removed" % in the matched historical control group respectively A naïve comparison was necessary as Sanofi do not have access to the data on patient characteristics within the compassionate use programme and a matched comparison is therefore not possible**.** Limited data has become available since the submission via the UK registry on the characteristics of UK patients enrolled in the programme. The mean age of patients treated was "AIC information removed" years, (range "AIC information removed" years) and "AIC information removed" (n="AIC information removed") cases were female, reflecting the female to male predominance reported in aTTP. Sixty seven percent (n="AIC information removed") were Caucasian. These demographics are very similar to HERCULES where the mean age was 46.1 (range 18 – 79); 69% of cases were female and 72.9% were white.

	In the UK compassionate use programme the median time taken for patients to receive the first dose of caplacizumab after initiation of plasma exchange (PEX) for aTTP was "AIC information removed" days (range "AIC information removed" days), and "AIC information removed"% (n="AIC information removed") of patients received caplacizumab within "AIC information removed" days of starting plasma exchange. This is a considerably longer time period than seen in HERCULES and results primarily from access issues due to caplacizumab not being available routinely. The impact of this on mortality can be seen in the dataset (mortality is considerably lower when caplacizumab is given earlier).
• What is the most plausible estimate, real world naïve comparison or trial, for the effect of caplacizumab on survival during the acute phase?	As above, we consider the real-world estimates to be more plausible than the HERCULES data. The trial was not powered to measure differences in mortality between the two arms, however, we note that the meta-analysis with the TITAN study does indicate a statistically significant benefit. We would consider that the real-world data sources presented in the original submission are consistent with the evidence for SoC and therefore 13.2% is the most plausible estimate of survival for SoC and that the compassionate use data originally presented likely over-estimates mortality for caplacizumab (as was noted by clinicians at the time). We present scenario analysis using the French matched cohort study for information.
Issue 6: There are no data available to test whether caplacizumab reduces mortality or cognitive or neuropsychological impairment in the long term	
• Is there any ongoing data collection assessing the clinical effectiveness of caplacizumab in reducing mortality or cognitive or	The Post-HERCULES trial is collecting data on long-term safety, effectiveness of repeat exposure, and QoL.

neuropsychological impairment in the long term (after acute phase)?	Post- HERCULES includes the Repeatable Battery for the Assessment of Neuropsychological Status; SF-36 and Headache Impact Test (HIT6). Last patient last visit is scheduled for "AIC information removed" however, no data is expected until "AIC information removed" at the earliest.
• Is it biologically plausible that a person who is in remission after caplacizumab should have a reduced risk of death, or neuropsychological or cognitive impairment compared with someone who is in remission after standard care?	Yes. In a modified-Delphi process was conducted to explore the potential longer-term benefits of caplacizumab treatment.10 During this process, ten UK clinical experts agreed that it is biologically plausible that caplacizumab plus PEX and immunosuppression would reduce the risk of long-term consequences associated with acute organ damage, such as neurocognitive complications, and that adding caplacizumab to the NHS formulary would offer several benefits to both the patient and the healthcare system[4].
• Is it biologically plausible that the time a person stayed in hospital/ICU for their acute treatment is related to their risk of death, or neuropsychological or cognitive impairment when in remission?	Yes. A range of estimated relative risk was provided to clinical experts and they agreed that the time spent in hospital/ICU is one reasonable proxy for calculating the relative risk of death and neuropsychological or cognitive impairment when in remission. Disease resolution (i.e. TTPN without exacerbation) was considered another reasonable proxy. Both give similar relative risks; 0.62 (for time spent in hospital/ICU and 0.65 for TTPN without exacerbation) [15].
Issue 7: The relationship between hospital stays and risk of cognitive impairment, neuropsychological impairment or death in the long term has not been validated.	

• Do the rates of mortality in remission, cognitive impairment or neuropsychological impairment used in the standard care arm of the model reflect the expected rates for people having standard care in UK clinical practice? See table 3 above	Since submission, new data from a non-interventional, cross-sectional online survey investigating the quality of life of UK aTTP patients (n=50) and carers (n=10) has become available (Appendix 2). Outcome measures selected to explore the HRQL in patients and carers were: • Short Form 36 (SF-36) – patients only due to a data programming error • Hospital Anxiety and Depression Scale (HADS) – patients only • Patient-Reported Outcomes Measurement Information System (PROMIS) – patients only • Modified Caregiver Strain Index (MCSI) – carers only • Work Productivity and Activity Impairment Questionnaire (WPAI) • Bespoke questions to measure outstanding concepts as identified by expert patient and carer input The study concluded that survivors of aTTP appeared to report lower overall HRQoL and greater cognitive dysfunction than the UK general population. These patients also seem to experience moderate levels of both anxiety and depression. Similarity, the majority of carers for survivors of aTTP reported an overall loss in work productivity and general impairment in non-work related activities. Nearly all the carers who were surveyed reported that they are very worried about the patient they care for having another episode of aTTP. The study investigators acknowledged that patients and carers may not be representative of the total patient and caregiver population of interest due to recruitment methods used. However, the direction of bias is unclear. It may be that those with more severe disease were sufficiently engaged to participate or that

	patients and carers who decided to participate were those whose level of HRQL was sufficient to allow participation. Based upon the quality of life impact study conducted, the rates of cognitive impairment assumed within the model appear reasonable "AIC information removed". (See quality of life study report Sections 4.1.4 and 4.1.6.1) "AIC information removed". (See quality of life study report Sections 4.1.2.8, 4.1.3 and 4.1.6.2) A comparison of rates of cognitive impairment and neuropsychological impairment based on the quality of life study, versus modelled rates is presented in Table 6 of Appendix 1.
• Is there a relationship between hospital/ICU stay and risk of long-term complications? Are there data to support this?	For the purposes of clarity, we have not assumed a direct relationship between hospital stays and the risk of cognitive impairment, neuropsychological impairment or death. Rather, as guided by clinical input,[3] we have assumed that a quicker disease resolution and less time spent in hospital / ICU will reduce the long-term consequences of aTTP, as a result of acute organ damage from uncontrolled microvascular thrombosis in the acute phase. Similarly, at a modified Delphi panel attended by seven clinical experts and one pharmacist, all agreed that *"Based on its mode of action, caplacizumab plus PEX and immunosuppression would substantially reduce the relative risk of mortality, organ damage, myocardial and cerebral ischaemia, length of intensive care unit (ICU)/hospital stay, number of PEX and plasma exchange, and exacerbations (compared to PEX and immunosuppression alone)"* and that *"it is biologically plausible that caplacizumab plus PEX and immunosuppression would reduce the risk of long-term consequences associated with acute*

	organ damage, such as neurocognitive complications which are prevalent in this population (compared to PEX and immunosuppression alone)"[4] Initially, time to platelet count response (the primary endpoint of HERCULES) was considered a surrogate for long-term outcomes, however a White Paper based on a review of literature sources found no quantitative relationship between time to platelet count response and long-term morbidity or mortality.{Sanofi, 2019 #96} Furthermore, clinicians attending an expert advisory board agreed that there was a lack of quantitative evidence linking time to platelet count response to long-term outcomes. Instead, clinicians suggested considering a composite of outcomes (in particular ICU, time to platelet count response and exacerbation) rather than relying on a single surrogate measure.[15] Following this input, a targeted literature review (TLR) was conducted to investigate the link between outcomes in HERCULES and long-term cognitive impairment in aTTP patients and similar proxy conditions. The full TLR report is presented in Appendix R of the company submission. The TLR concluded that there is no evidence on how the time spent at risk of microvascular thrombosis (hospitalisation days, ICU days and PEX days) links to cognitive impairment in aTTP or similar diseases. We acknowledge that further clinical input was required in order to quantify this relationship. This is perhaps unsurprising given the extremely rare nature of aTTP. Given data were not available from literature clinical expert opinion was sought.{Sanofi, 2019 #107} A range of proxy relative risks (RRs) and hazard ratios (HRs) were presented to three clinicians on expert validation TCs based on HERCULES data, as presented in Table 23 of the company submission, and in Table 7 in Appendix 1

	As shown in Table 7, the proxy RRs/HRs are largely aligned ranging from 0.33 for all recurrences (termed early and late exacerbations in the submission) and 0.69 for hospitalisations (including ICU). The RR used in the base-case analysis of 0.62, therefore represents a mid-range estimate in the context of all calculated proxy RRs/HRs, reducing the reliance on one datapoint alone. It should be emphasised that the ratio of hospitalisation/ICU days alone is not the only relevant outcome and should be considered alongside the other potential surrogates presented above. We note that the ERG stated in their report that *"Whilst the ERG's clinical advisors agreed with the biological plausibility argument of a reduction in long-term complications from an effect of caplacizumab on microthrombi they stated that hospitalisation was only a surrogate marker for this. One clinical advisor suggested alternative proxies for reduction in long-term complications could be serial measurements of troponin or degree of renal dysfunction. However, none of these were available."* This acknowledges both the difficulty in quantifying the long-term benefit of caplacizumab treatment and the biological plausibility of a relationship. Finally, whilst there are no data in aTTP we do note that there is a wealth of literature available supporting the link between ICU stay in general and long-term mortality and quality of life impacts. [16, 17, 18, 19, 20, 21] These data demonstrate improved long-term mortality for patients with shorter ICU stays. This provides some support to the notion of differential long-term mortality but cannot provide quantitative input given that long-term mortality for aTTP would also be expected to be influenced by accrued organ damage from exposure to microthrombi.
• Does time in hospital ICU/hospital reflect a) exposure to microthrombi	Clinical experts consulted prior to the CS and during the technical engagement meeting have confirmed this to be case. In addition, this aligns with the ERG's clinical advisor's input: "Whilst the ERG's clinical advisors

b) exposure to microthrombi + damage caused by exposure to microthrombi?	agreed with the biological plausibility argument of a reduction in long-term complications from an effect of caplacizumab on microthrombi they stated that hospitalisation was only a surrogate marker for this."
• Is the modelled survival gain for caplacizumab compared with standard care (5.48 years) plausible?	The modelled survival gain for caplacizumab encompasses both caplacizumab's benefit in reducing acute mortality, as demonstrated by HERCULES data, and the long-term benefits on mortality expected by clinicians through reducing organ damage to the heart and kidneys[3]. As patients are relatively young at the time of an acute episode (mean age in HERCULES was 46), any benefits in reducing mortality will be realised over the patients remaining lifetime and a small mortality benefit can have a large impact, this is why the modelled survival gain of 5.48 may appear high compared to other indications such as oncology, where typically an older population with a lower remaining life expectancy is modelled.
• Is there any evidence to support a relationship between any other outcome measured in HERCULES (such as time to platelet normalisation) and long-term outcomes?	As described above, a targeted literature review (TLR) was conducted to investigate the link between outcomes in HERCULES and long-term cognitive impairment in aTTP patients and similar proxy conditions. The full TLR report is presented in Appendix R of the company submission. The TLR concluded that there is no evidence on how the time spent at risk of microvascular thrombosis (hospitalisation days, ICU days and PEX days) links to cognitive impairment in aTTP or similar diseases; therefore, future research is necessary to quantify this relationship. The range of diseases considered in the TLR was narrow, as only studies in aTTP and cerebral small vessel diseases (such as lacunar stroke and haemolytic uraemic syndrome) were included. The rationale for this was that these conditions have a similar impact on long-term outcomes as a result of persistent damage in

	the microvasculature and are related to cognitive impairment and depression. No data was found to quantify a relationship.
• Which is a more valid assumption on the relative risk of caplacizumab on cognitive or neuropsychological impairment compared with standard care; the company's or ERG's?	Both the company's and ERG's assumptions for the relative risk of long-term complications are similar (company: 0.62 versus ERG: 0.6875). However, the 0.62 originally submitted by the company falls in the upper-mid range of proxy RRs/HRs presented to clinicians, whereas 0.6875 is at the very top of this range. See company submission Table 23 (also presented in response to Issue 7, Question 2) Therefore the company consider 0.62 as appropriate.
• Is the ERG's approach of assuming that the potential treatment effect of caplacizumab on mortality in remission is greater than the treatment effect of caplacizumab on neuropsychological or cognitive impairment plausible?	The acute microvascular thrombotic process of aTTP impacts multiple organs causing long-term damage. The model explicitly considers the impact on cognitive impairment and anxiety/depression as separate health states with no increased mortality risk. There are however influencers of mortality (for example cardiovascular and renal issues) that the model does not capture. This is perhaps why the ERG assumed a greater effect might be plausible.
Issue 8: The utility values in the model do not come from trial data and utility associated with long term complications of aTTP is based on other conditions	
• Is stroke a good proxy for the utility experienced during an acute episode for aTTP	In the model, stroke is not used for the utility due to an acute episode. Rather literature values were sourced for the disutility due to hospitalisations in general[22]. Utility values specific to patients with aTTP were not available for the acute episode, likely as it is unethical to collect such data from patients with very severe disease. Furthermore, as the worst patients present in a comatose state, these patients would not be able to

participate in health-related quality of life (HRQL) data collection. Therefore, utilities in the model are currently likely to underestimate the impact of the acute episode.

SF-36 data from the QoL survey were mapped to EQ-5D using the Rowen et al. algorithm (for consistency with the analysis presented by Burns et al [23, 24].). The average utility for patients who had experienced an episode within the last year vs those who had experienced an episode longer ago is presented below.

The comparison of mapped to modelled utility values shows that the model slightly overestimates utility for patients in the first year following an acute aTTP episode, however mapped values are aligned with model predictions following the first year. These data, data from an aTTP population, validate the modelling approach. The differences on acute utility between the mapped and modelled analyses are expected as the data available to populate the model was taken from a healthier population (i.e. sufficiently healthy to participate in data collection during the period of hospitalisation). This indicates that the impact of the acute period may have been underestimated.

Characteristic	Category	Patient numbers (n=50) [%]	Mean utility in survey	Modelled utility
Acute (episode within a year)	Yes	"AIC removed" "AIC removed"	"AIC removed"	"AIC removed"
	No	"AIC removed" "AIC removed"	"AIC removed"	"AIC removed"

- Do the utility values for acute aTTP reflect the impact of treatment with

As noted above the modelled values are generally reflective of recently collected data for QoL in UK patients.

caplacizumab/ standard of care on quality of life?	
• Is the quality of life of people in the US with aTTP likely to be similar to the quality of life of patients in the UK?	Please see the table above for a comparison of modelled utility versus EQ-5D values mapped from SF-36 responses in aTTP patients. The mapping analysis validates modelled utility.
• Are the neuropsychological impairments experienced with aTTP similar to those experienced by people with depressive disorder?	New data from the aTTP quality of life study show that "AIC information removed". % (n = "AIC information removed"., N = "AIC information removed".) of patients experienced flashbacks following an acute aTTP episode, and "AIC information removed". % (n = "AIC information removed"., N = "AIC information removed".) of patients reported that these were moderately to extremely severe. The model currently does not capture the benefits of caplacizumab in reducing the fear of relapse for patients and carers through the availability of an effective treatment. New quality of life data for patients with aTTP suggest that: • "AIC information removed". % (n = "AIC information removed"., N = "AIC information removed".) of patients experienced flashbacks following an acute aTTP episode, and "AIC information removed". % (n = "AIC information removed"., N = "AIC information removed".) of patients reported that these were moderately to extremely severe • "AIC information removed". % (n = "AIC information removed"., N ="AIC information removed".) worry about relapse, with "AIC information removed". % (n = "AIC information removed"., N="AIC information removed".) worrying "very much"

	The technical engagement papers circulated by NICE, detail input from members of the patient support group, TTP Network. Patients were asked about what it is like to live with the condition and about the impact on carers. Responses were: • "My mum is living with TTP I worry about her every day shes being monitored every 2 weeks,but currently her white blood cells are dangerously low & is having to check her temperature every day & if it gets to 38 she needs to get to hospital it's very worrying" • "Stressful and draining. It affects all aspects of life including work and personal as it causes fatigue. It is always there in the background and any infection causes anxiety of a relapse. Very debilitating. Every day is exhausting I go to bed tired and I wake up tired. I have on going memory issues and I feel very low at times simply because I have no energy. I wish I could be back to my old self. I also pick up colds, flu, infections much quicker since diagnosed so I become unwell quickly and it lasts longer. My energy and stamina are affected and I can't do what I should be able to do at my age. - I have not been the same since I was diagnosed. Every part of me aches constantly" • "Sometimes it can be very difficult, it's every time at the back of your mind, you never know when you can have a relapse. When there's a health problem your first thought is am I heading for a relapse. It affects your family as well, especially children. I still have problems with my daughter anxiety issues and it's been three years. But with time you somehow manage to learn to live with it." • "Always on edge wondering if and when the next attack might happen"

	• "Difficult, I'm surprised how much it has affected my life. The symptoms of relapse quite ambiguous, therefore, it is always just at the back of your mind. The thought of a relapse, and having to stop your life for weeks on end while you receive treatment, is always hanging over you. I'm not the same person, I'm often exhausted, my memory is causing me severe problems at home and at work." • "For 25 years I have lived with a constant worry of relapsing. I am hyper vigilant and live with anxiety about my health. I have a daily battle with my memory and Aphasia. I have low energy levels and must balance my work/life in favour of taking regular rest. I tire very quickly and feel extreme tiredness. My whole body aches at times. My family, particularly parents, remain constantly worried about my health despite me being nearly 50." • "Extremely tired, confused, headachy, sickly like I want to be sick, forgetful, scared but won't show it. Body feels like a ton weight and on (the treatment)machine like I have a tap on fast forward pouring fluid into my body - very fast feeling which makes me feel sickly and heart pound. I had three strokes on initial diagnoses, so I get worried I will have more. Family / carers have always felt scared and a bit isolated. Anxious and stressed." In order to model the benefit of caplacizumab in reducing fear of relapse, a targeted literature review (TLR) was conducted to identify proxy utilities for fear of relapse/recurrence after recovery for severe acute episodes. (Appendix 2) Through searches of the NICE website and Tufts CEA registry a range of sources reporting disutility due to fear in multiple indications were included. The studies varied greatly by indication, country in which they were conducted and sample size. More consistently, the EQ-5D was used and valued using the UK general

	population tariff. Disutility due to fear ranged from 0.021 to 0.33. The highest quality studies reported a disutility of 0.04-0.0597, therefore as a mid-range estimate and consistent with the highest quality studies a disutility of 0.05 was considered for application in the model. The next important parameter was the improvement in disutility of fear through the availability of an effective intervention. Only one study in anaphylaxis reported a value for this parameter of 25%. This was reported as potentially conservative. As such, scenarios are presented using values from 25 to 100%.
• Is the quality of life of people caring for people with aTTP expected to be similar to people caring for people with stroke?	As aTTP is a rare disease, searches of previous NICE submissions and published literature identified no data on the utility impact for carers of aTTP survivors. The publication used for the disutility of carers of stroke patients was considered the most appropriate proxy given that clinical experts previously discussed how utility values for patients with the worst forms of cognitive impairment are comparable to those of patients who have suffered stroke[3]. Therefore, in the model, the impact is only applied to carers of patients with moderate or severe cognitive impairment. The new data above provides quality of life data for carers of patients with aTTP (n=10), which shows that: • "AIC information removed". % of carers reported experiencing an overall loss in work productivity • "AIC information removed". % reported general impairment in non-work-related activities • The majority of carers reported aTTP had some sort of an impact on their overall daily life ("AIC information removed". %), sex life ("AIC information removed". %), and finances ("AIC information removed". %)

	• "AIC information removed". % were very worried about the patient they care for having another episode of aTTP In the context of this new data, the current approach of assuming only an impact for carers of patients with high levels of cognitive impairment could be considered conservative.
Issue 9: The relapse rate modelled by the company of 1% is uncertain	
• Is the company assumption of a 1% relapse rate plausible?	It should be noted that the 1% relapse rate applied in the model is an annual rate rather than a lifetime rate, and was calculated based on clinical expert input, which suggested that out of 100 patients undergoing monitoring each year, approximately one patient will relapse [3]. In the model, this equates to a lifetime relapse rate of approximately 16%. This is aligned with published UK estimates and clinical expert opinion (see next question). Therefore, modelled estimates are considered appropriate[3, 25].
• Are there any data on the current relapse rate in the UK?	The Shin et al. publication reporting outcomes for patients in the UK TTP registry between 2009-2018 reports relapse rates of 19%,{Shin, 2019 #77} albeit before protocols were in place for preventing relapse with appropriate rituximab use. Clinical expert opinion suggested that 10% of patients will relapse at some point during the course of their remaining lifetime[3]. This aligns with the estimate given on the technical engagement call (10%). Lower relapse rates reduce the ICER.
Issue 10: Have all potential costs that may be offset by using caplacizumab, and the wider benefits of reducing use of a blood product, been accounted for in the model?	

• Will reducing the volumes of a blood product for plasma exchange have a wider impact (besides the costs of giving the infusion itself)?	There are many benefits to reducing the number of plasma exchange procedures and the volume of plasma exchanged that cost per QALY calculation does not fully reflect, such as the benefit to patient quality of life through reducing the volume of plasma exchanged, the number of days the patient has to undergo unpleasant plasma exchange, the requirement for multiple lines (which has a major impact on the patient) and the risk of plasma exchange complications including infections. As noted on the technical engagement call this has the potential for a major impact given that over ¼ of all UK plasma usage is for aTTP. Data is not available to quantify the impact. The technical engagement papers circulated by NICE detail patient and carer thoughts on current treatments and care available on the NHS. Responses were: • "Plasma for me was the worse ever 4hours twice a day for god knows how long , made me feel sick , got mad tingles so then had to have calcium drip, omg every time they came in to my ward with the trolley I cried" • "I had an allergic reaction to ffp. I don't know what triggered it and have never had a reaction to any food or drinks so it is a worry that there is something that will do that to me! I do feel guilty for using so much ffp during an episode of ttp too, it takes such a huge volume of donations to recover, and sometimes if the plasma exchange doesn't go well it can actually be wasted which is terrible considering people have taken the time to donate! I do find it a worry that with the overuse

	of antibiotics if something was to slip through the net during testing of the donated plasma, it may be very dangerous."
• Would needing a lower volume of plasma reduce the likelihood of any PEX related complications?	Yes. Clinical experts explained that deep vein thrombosis and bacteraemia are both complications of PEX, the risk of which can be reduced through reducing the duration of plasma exchange[3]. The model assumes that the costs for treating these adverse events is included within the cost of hospitalisation itself, therefore the impact of PEX complications may not be fully reflected.
• Are there any issues with the availability of plasma for PEX in clinical practice?	It is also worth noting that there are major issues with the availability of beds in intensive care units (ICU) across the NHS. One clinician noted on the technical engagement call that their hospital (which has the 3rd biggest ITU in Europe) has had to implement a protocol where other patients are moved to theatre recovery rooms from ICU to allow aTTP patients access to ICU. This indicates the strain on ICUs within the NHS and the major benefits that could be realised from reduction in ICU stays. Within HERCULES there as a 65% shorter duration of care in an ICU with caplacizumab (even with use of open label caplacizumab on the SoC arm).
• Would a shorter time to platelet normalisation observed with caplacizumab be expected to also mean that people treated with caplacizumab have fewer doses of rituximab in clinical practice?	No. They have different modes of action and in UK practice are initiated simultaneously in the acute setting. In the preventative setting differential use would not be expected either. As noted previously the imbalanced between the arms in the HERCULES trial may have an impact on effectiveness assessment but would not be expected to impact on cost.
• Will reducing the volumes of a blood product for plasma exchange	Yes (see answers provided above).

have a wider impact (besides the costs of giving the infusion itself)?	
Issue 11: The company base case is over £30,000 per QALY gained	
• Is there reason to consider an ICER of above £30,000 per QALY gained a cost-effective use of NHS resources?	In May 2019, Sanofi requested that NICE consider routing caplacizumab through the HST appraisal process rather than through the standard STA process. Sanofi provided evidence for caplacizumab applicability to HST as part of the HST criteria company proforma. NICE concluded that caplacizumab did not meet the following criteria: • *The condition is chronic and severely disabling* • *The technology has the potential for lifelong use* However, caplacizumab did meet the following criteria: • *The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS* • *The technology is expected to be used exclusively in the context of a highly specialised service* • *The need for national commissioning of the technology is significant* Due to the narrow criteria for entry to HST evaluation, caplacizumab was routed into the standard STA process, despite the treatment and disease demonstrating characteristics more suited to HST. Sanofi urge the Committee to consider this previous unsuccessful application for HST in their decision making, and the fact that multiple HST criteria were still met and more will be met in the near future.

	Sanofi feel that applying rigid cost-effectiveness thresholds to all treatments that fail to meet all specific criteria of EOL or HST is not flexible enough to appropriately evaluate new medicines, and that social value judgements should underpin considerations. We urge that the Committee discuss the additional value elements of caplacizumab such as the rarity of aTTP, the sudden and severe onset of disease, the need for a new and targeted treatment to reduce the time spent in the occluded state as well as the numerous benefits unable to be captured in the QALY calculation and apply flexibility in their decision. HRQL data are not available from the caplacizumab clinical trial programme and it is extremely difficult to capture robust HRQL data relating to the treatment of an acute episode of aTTP. In the real-world setting, we would expect a treatment that results in rapid control of microvascular thrombi and thus limits tissue ischaemia and organ damage and the long-term consequences of such damage to positively impact patient and carer wellbeing. Not only is the value of a treatment that can quickly control the disease physical, but it provides hope and reassurance to patients' and their loved ones, and confidence to healthcare professionals. Patient and carer interviews highlight the struggle patients have coming to terms with the life-changing nature of their condition with patients feeling snappy, angry, sad and frustrated that they cannot do things for themselves and are suffering with short-term memory problems. Some patients report feeling very isolated and fearful but the psychological impact extends to the people close to them. These benefits cannot be adequately captured in a clinical trial setting or QALY measurement. Caplacizumab is a truly innovative treatment, representing the first nanobody developed from camelid heavy-chain-only antibodies to be approved in any indication. Caplacizumab is the first licensed treatment specific to aTTP and has a unique mode of action that directly targets the pathologic mechanism of this disease. The approval of caplacizumab is the first advancement in acute phase therapeutics for 30 years

	and offers a step-change in the management of this ultra-rare, life-threatening disease. The innovative nature of caplacizumab is recognised by the clinical community and there is strong support for it to be made available[3, 4]. Clinician feedback from an ongoing compassionate use programme has been extremely positive with several comments relating to the remarkability of outcomes with caplacizumab. Flexibility is particularly important in light of the ongoing review of the HST criteria and the recognition amongst stakeholders for a broader consideration of rare disease medicines that can utilise this appraisal route. Committees have previously considered rarity and severity of disease in their decisions on whether to recommend a treatment at a given threshold. The final appraisal document (FAD) for nusinersen for treating spinal muscular atrophy (SMA) (TA588) states that 'the decision making takes into account the rarity and severity of the disease'. The FAD goes on to explain that although nusinersen has several features that are commonly seen in the HST programme, it was considered as an STA. This was because the population covered by the marketing authorisation was larger than what can be considered in HST evaluations, and because SMA is not commissioned through a highly specialised service. Therefore, similarly to caplacizumab, nusinersen also failed to meet the very specific and narrow HST criteria. The FAD for nusinersen explains how the committee was aware that SMA is both rare and a very serious condition. It also reflected on the benefits associated with nusinersen, and how they are highly valued by patients and families. The committee was mindful during its decision making of the need to consider whether any adjustments to its normal considerations were needed to take into account the rarity and severity of the disease[26]. The NICE methods review is due to be completed in Summer 2020, with changes due to be implemented in 2021 onwards[27]. As the first Appraisal Committee meeting for caplacizumab is due to take place in Q2 2020,

	updated guidance on the acceptance of decision modifiers will not be published in time for consideration by the Committee. We feel it is, however, pertinent to draw this to the attention of the ERG and Committee, as the implications of this are that decision modifiers may be considered within a more formal framework in the near future, however due to the timing of this appraisal caplacizumab would miss out.
• Are there any benefits of caplacizumab that the company have not included in its modelling?	Yes. As noted by the technical team the patient expert statements referred to plasma exchange and fear of relapse as having a large impact on quality of life. This impact was not included within the economic model at the time of submission and this variable is difficult to populate due to lack of data for patients with aTTP. A targeted literature review has therefore been undertaken to assess the possible impact of fear of relapse (appendix 2). The potential impact is explored within the economic model and indicates the potential for a reduction in the ICERs. These are presented two rows below. Other potential cost savings identified by the technical team on blood products have not been included due to lack of data and short-term impact, so the original conservative assumptions remain in the model. Finally, we would request the Committee to consider the potential benefits to the NHS unable to be captured within the QALY measure: • Reduced requirement for and duration of ICU stays which has the potential to be a major benefit as most hospitals are at capacity. Within HERCULES there as a 65% shorter duration of care in an intensive care unit (ICU) with caplacizumab (even with use of open label caplacizumab on the SoC arm). • Reduced requirement for plasma – TTP currently uses over 25% of all plasma in the UK (based upon clinician comments in the technical engagement meeting). Reducing plasma use has multiple

<table>
<tr><td></td><td>benefits including removing the requirement for multiple lines to be put in which is a major issue for patients and reduces the risk of infection

• Reduced damage to organs such as the kidneys, heart and brain stemming from reduced exposure to micro thrombi – the impact of which could not be included in the economic model

• Impact on the wider family is not included in the economic model and the impact on carers has likely been underestimated given that an impact is only included currently for carers of patients with severe cognitive impairment</td></tr>
<tr><td>• Have the benefits of reduced use of blood products (which are a limited resource) been captured?</td><td>As noted above this has not been captured within the model and will need to be considered qualitatively.</td></tr>
<tr><td>• Scenarios based on revised PAS and alternative assumptions</td><td>The impact of the revised PAS is presented below along with scenarios demonstrating the impact of alternative assumptions around the data source used for acute mortality, fear of relapse, the benefit of caplacizumab in reducing long-term complications and long-term mortality.

<table>
<tr><th rowspan="2">Scenario</th><th colspan="2">Acute Mortality</th><th rowspan="2">RR long-term complications</th><th rowspan="2">RR long-term mortality</th><th rowspan="2">ICER* £/QALY</th><th rowspan="2">ICER** £/QALY</th></tr>
<tr><th>Caplacizumab</th><th>SOC</th></tr>
<tr><td>Revised company base case with revised PAS, ERG correction to PEX procedure cost (£602.34 to £1265) and updated</td><td>3.8%</td><td>13.2%</td><td>0.62</td><td>0.62</td><td>£27,856</td><td>£26,357</td></tr>
</table>
</td></tr>
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	mortality from the compassionate use scheme (RR 0.267)						
	Original company base case with revised PAS and mortality from French Matched Cohort Study (Ref. 14 in technical response document)	"AIC information removed"	"AIC information removed"	0.62	0.62	£28,126	£26,495
	Original company base case with revised PAS and ERG correction to PEX procedure cost (£602.34 to £1265)	4.3%	13.2%	0.62	0.62	£28,358	N/A
	Original company base case with revised PAS	4.3%	13.2%	0.62	0.62	£29,407	N/A
	Original company base case with revised PAS and mortality from Hercules	0%	4.1%	0.62	0.62	£31,712	£29,252
	Revised PAS with NICE technical team ICER	13.2%	13.2%	0.62	1	£128,910	N/A
	Notes: *Cost of treatment of acute episode is £"CIC information removed" based on revised PAS ("CIC information removed"%); ** Cost of treatment of acute episode is £"CIC information removed" based on revised PAS ("CIC information removed"%**) and fear of relapse disutility (50%)						
Issue 12: Caplacizumab may be an innovative technology							

• Are there any benefits not captured by QALY calculation?	Yes. These are discussed above in the response to Issue 11 “Are there any benefits of caplacizumab that the company have not included in its modelling?”

References

1. Lester W, Begaj I, Ray D and Pagano D. Trends in diagnosis and mortality from thrombotic thrombocytopenic purpura in England from 2003 to 2013: are we improving outcomes? 55th Annual Scientific Meeting of the British Society for Haematology. Edinburgh, UK. 20-22 April 2015. 100.

2. Orphan.net. Acquired thrombotic thrombocytopenic purpura. 2015 Availblabe at: http://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=93585. Accessed: 13 March 2020.

3. Sanofi. HTA model review and clinical validation June 2019.

4. Sanofi. Expert consensus to support the use of caplacizumab in aTTP. (SA8248A Version 2.0) 18 April 2019.

5. Scully M, Cataland SR, Peyvandi F, et al. Caplacizumab Treatment for Acquired Thrombotic Thrombocytopenic Purpura. *N Engl J Med*. 2019; 380(4):335-46.

6. European Medicines Agency (EMA). Cablivi: Assessment report. 2018. Available at: https://www.ema.europa.eu/en/documents/assessment-report/cablivi-epar-public-assessment-report_en.pdf. Accessed: 13 March 2020.
7. Westwood J, Webster H, McGuckin S, et al. Rituximab for thrombotic thrombocytopenic purpura: benefit of early administration during acute episodes and use of prophylaxis to prevent relapse. *Journal of Thrombosis and Haemostasis*. 2012; 11: 481–490
8. Westwood J, Thomas M, Alwan F, et al. Rituximab prophylaxis to prevent thrombotic thrombocytopenic purpura relapse: outcome and evaluation of dosing regimens. *Blood advances.* 2017; 1(15):1159-1166.

9. Good A, Driscoll P, et al. Clinical research in emergency medicine: putting it together. *Emerg Med J.* 2002;19:242–246.

10. Columb M, Haji-Michael P, Nightngale P. Data collection in the emergency setting. *Emerg Med J.* 2003; 20:459–463.

11. Nee P, Griffiths R. Ethical considerations in accident and emergency research. *Emerg Med J*, 2002;19:423–427.

12. Rock G, Shumak K, Buskard N, et al. Comparison of plasma exchnage with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. The New England jounal of Medcine. 1991; 325(6):393-397
13. Ablynx. Systematic review on the clinical burden of disease in thrombotic thrombocytopenic purpura. 2018.
14. Coppo P, Malot S, Azoulay E, et al. Treatment of autoimmune thrombotic thrombocytopenic purpura with caplacizumab prevents the onset of unfavorable course until improvement in ADAMTS13 activity. 2020.
15. Sanofi. HTA advisory board 06 March 2019.
16. Gayat E, Cariou A, Deye N, et al. Determinants of long-term outcome in ICU survivors: results from the FROG-ICU study. *Critical Care.* 2018; 22:8.
17. Mahesh B, Choong K, Goldsmith K, et al. Prolonged Stay in Intensive Care Unit Is a Powerful Predictor of Adverse Outcomes After Cardiac Operations. *The Society of Thoracic Surgeons.* 2012; 94:109 –16.
18. Moitra V, Guerra C, Linde-Zwirble W, et al. Relationship Between ICU Length of Stay and Long-term Mortality for Elderly ICU Survivors. *Crit Care Med.* 2016; 44(4): 655–662.
19. Oeyen S, Vandjick D, Benoit D, et al. Quality of life after intensive care: A systematic review of the literature. *Crit Care Med*. 2010; 38(12):2386-2400.
20. Sricharoenchai T, Parker A, Zanni J, et al. Safety of physical therapy interventions in critically ill patients: A single-center prospective evaluation of 1110 intensive care unit admissions. *Journal of Critical Care*. 2014; 29:395-400.
21. Williams T, Ho K, Dobb G, et al. Effect of length of stay in intensive care unit on hospital and long-term mortality of critically ill adult patients. *British Journal of Anaesthesia.* 2010; 104: 459–64.
22. Chit A, Becker DL, DiazGranados CA, et al. Cost-effectiveness of high-dose versus standard-dose inactivated influenza vaccine in adults aged 65 years and older: an economic evaluation of data from a randomised controlled trial. *Lancet Infect Dis*. 2015; 15(12):1459-66.
23. Rowen D, Brazier J and Roberts J. Mapping SF-36 onto the EQ-5D index: how reliable is the relationship? *Health Qual Life Outcomes*. 2009; 7:27.
24. Burns D, Lee D, Vesely S, et al. Patient health-related quality of life associated with remission of aTTP. A regression analysis using non-randomised observational data from the Oklahoma TTP registry. ISPOR. Barcelona, Spain. 10-14 November 2018 2018. PSY192.
25. Shin JS, Alwan F, Austin S, et al. Thrombotic thrombocytopenic purpura: demographic analysis of the UK TTP registry from 2009 to 2018. British Society for Haematology 59th Annual Scientific Meeting Glasgow, Scotland. 1-3 April 2019. BSH19-OR-032.

26. National Institute for Health and Care Excellence (NICE). Final appraisal document: nusinersen for treating spinal muscular atrophy. 2019. Available at: https://www.nice.org.uk/guidance/ta588/documents/final-appraisal-determination-document-2. Accessed: 13 March 2020.
27. National Institute for Health and Care Excellence (NICE). Changes we're making to health technology evaluation. 2019. Available at: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation. Accessed: 13 March 2020

Appendix 1: Tables

Table 1: HERCULES inclusion and exclusion criteria

Inclusion Criteria	Exclusion Criteria
• Male or female ≥18 years of age (adults) • Clinical diagnosis of acquired TTP • Required initiation of PEX therapy and had received one PEX treatment prior to randomisation within 24 hours of study PEX • Patient, or legally acceptable representative or independent physician where the patient was unconscious or unable to give consent, to provide informed consent and assent • Negative pregnancy test and willing to accept an acceptable contraceptive regimen	Platelet count ≥100,000/uL Serum creatinine level >200 umol/L in case platelet count was >30 x 10^9/L (to exclude possible cases of aHUS) Known other causes of thrombocytopenia, including (but not limited to): – Clinical evidence of enteric infection with E.coli 0157 or related organism – Atypical aHUS – Haematopoietic stem cell or bone marrow transplantation-associated thrombotic microangiopathy – Known or suspected sepsis – Diagnosis of disseminated intravascular coagulation Known 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 Malignant arterial hypertension Clinical condition other than that associated with TTP with life expectancy <6 months Known hypersensitivity to the active substance or excipients of the study drug Enrolled in a clinical study with another investigational drug or device currently or <28 days prior to enrolment in this study Considered by the investigator to be an unsuitable candidate for the study Previously enrolled in a clinical study with caplacizumab and received caplacizumab or for whom the assigned treatment arm was unknown Pregnancy or breastfeeding

Table 2: Time to platelet count response - sensitivity analyses

	HERCULES	
	CAPLA	**PBO**
PP population, n	"AIC information removed"	"AIC information removed"
Median days to response (95% CI)	"AIC information removed"	"AIC information removed"
HR for time to platelet count response (95% CI)	"AIC information removed"	
p-value	"AIC information removed"	
mITT population, n	"AIC information removed"	"AIC information removed"
Median days to response (95% CI)	"AIC information removed"	"AIC information removed"
HR for time to platelet count response (95% CI)	"AIC information removed"	
p-value	"AIC information removed"	
Constrained response definition - ITT, n	"AIC information removed"	"AIC information removed"
Median days to response (95% CI)	"AIC information removed"	"AIC information removed"

HR for time to platelet count response (95% CI)	"AIC information removed"	
p-value	"AIC information removed"	
Response definition excluding PEX stop - ITT, n	"AIC information removed"	"AIC information removed"
Median days to response (95% CI)	"AIC information removed"	"AIC information removed"
HR for time to platelet count response (95% CI)	"AIC information removed"	
p-value	"AIC information removed"	

Key: CAPLA, caplacizumab; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; mITT, modified intention-to-treat; PBO, placebo; PEX, plasma exchange; PP, per protocol; ULN, upper limit of normal.

Notes: platelet count response defined as ≥150,000/uL with subsequent stop of daily PEX treatment within 5 days unless otherwise stated; constrained response defined as…

Source: HERCULES CSR.[1]

Table 3: Major protocol deviations in the category of "treatment non-compliance"

	HERCULES	
	CAPLA (n=72)	**SoC (n=73)**
Patients with a treatment non-compliance protocol deviation, n	"AIC information removed"	"AIC information removed"
Missed daily PEX (HERCULES), n	"AIC information removed"	"AIC information removed"
Daily PEX not continued for at least 2 days after platelet count normalisation, n	"AIC information removed"	"AIC information removed"
Study drug administration interrupted, n	"AIC information removed"	"AIC information removed"
Incorrect storage conditions for study drug, n	"AIC information removed"	"AIC information removed"
Administration of the wrong study drug dose, n	"AIC information removed"	"AIC information removed"
Use of the wrong route of administration, n	"AIC information removed"	"AIC information removed"
Administration of the wrong study drug, n	"AIC information removed"	"AIC information removed"
Received two doses of study drug in error, n	"AIC information removed"	"AIC information removed"

Table 4: Major protocol deviations in the category of "selection criteria not met"

	HERCULES	
	CAPLA (n=72)	**SoC (n=73)**
Inclusion criterion 3 - Required initiation of daily PE treatment and had received 1 PE treatment prior to randomization, n	"AIC information removed"	"AIC information removed"

Inclusion criterion 3 - PE treatment starting more than 24 hours prior to randomization	"AIC information removed"	"AIC information removed"
Inclusion criterion 5 = Subjects provided informed consent prior to initiation of any study specific activity/procedure	"AIC information removed"	"AIC information removed"
Key: *("AIC information removed")		

Table 5: Baseline characteristics of participants in caplacizumab trials

	HERCULES		HERCULES (ITT with major protocol deviation	
	CAPLA (n=72)	**PBO (n=73)**	**CAPLA (n=31)**	**PBO (n=33)**
Mean age, years (range)	45 (18-77)	47 (21-79)	"AIC information removed"	"AIC information removed"
Gender, female n (%)	49 (68)	51 (70)	"AIC information removed"	"AIC information removed"
Race, n (%) White Black Asian	 47 (65) 15 (21) 4 (6)	 50 (68) 13 (18) 0	"AIC information removed"	"AIC information removed"
BMI, mean (range)	30 (18-53)	30 (19-59)	"AIC information removed"	"AIC information removed"
Median platelet count, per mm^3 (range)	24,000 (3,000-119,000)	25,000 (9,000-133,000)	"AIC information removed"	"AIC information removed"

	HERCULES		HERCULES (ITT with major protocol deviation	
	CAPLA (n=72)	**PBO (n=73)**	**CAPLA (n=31)**	**PBO (n=33)**
TTP episode, n (%) Initial Recurrent	 48 (67) 24 (33)	 34 (47) 39 (53)	"AIC information removed"	"AIC information removed"
ADAMTS13 activity, n (%) <10% ≥10%	 58 (81) 13 (18)	 65 (89) 7 (10)	"AIC information removed"	"AIC information removed"
Median cTnI, ug/L (range)	0.09 (0.01-75.96)	0.07 (0.01-7.28)	"AIC information removed"	"AIC information removed"
Median LDH, U/L (range)	449 (120-2,525)	403 (151-3,343)	"AIC information removed"	"AIC information removed"
Median serum creatinine, umol/L (range)	77 (35-717)	82 (52-482)	"AIC information removed"	"AIC information removed"

Key: BMI, body mass index; CAPLA, caplacizumab; cTnI, cardiac troponin I; LDH, lactate dehydrogenase; TTP, thrombotic thrombocytopenic purpura.

Table 6*:* Data available from the QoL study for rates of cognitive impairment or neuropsychological impairment in the UK

	Data available from the QoL study	**Assumption within the economic model**

Cognitive impairment	"AIC information removed"	"AIC information removed"		Base case using Kennedy et al. 2009:{Kennedy, 2009 #29} 20.8% moderate / severe cognitive impairment 54.2% mild cognitive impairment Scenario: total 63%
	"AIC information removed"	"AIC information removed"		
	"AIC information removed"	"AIC information removed"		
	"AIC information removed"	"AIC information removed"		
	"AIC information removed"	"AIC information removed"		
	"AIC information removed"	"AIC information removed"		
	"AIC information removed"			
Neuropsychological impairment	"AIC information removed"			Base case using Chaturvedi et al 2015:{Chaturvedi, 2017 #42} 36.8% Scenarios: 14.3% to 47.6%

Key: aTTP, acquired thrombotic thrombocytopenic purpura; HADS, Hospital Anxiety and Depression Scale; MH, mental health; PROMIS SF CFA, Patient-Reported Outcomes Measurement Information System Short-Form Cognitive Function Abilities; QoL, quality of life; SD, standard deviation; SF-36, Short Form-36.

Table 7: Estimates of RRs/HRs for long-term complications based on HERCULES trial data

Parameter	Caplacizumab	SoC	HR* / Proxy RR**	Source
Exacerbations (early and late)	12.68%	38.36%	0.33**	Economic model; Efficacy G81
Time to platelet count response, initial (days); HR: SoC versus caplacizumab	1.55		0.65*	HERCULES CSR table 18
Time to platelet count response, initial and exacerbation	N/A	N/A	0.57**	Calculation*
Number of days PEX (mean) – overall treatment period	5.8	9.4	0.62**	HERCULES CSR, Table 14.2.1.5.2
Volume of PEX (litres) – overall treatment period	21.3	35.9	0.59**	HERCULES CSR, Table 14.2.1.5.3
Number of days hospitalisation (mean) – overall treatment period	9.9	14.4	0.69**	HERCULES CSR, Table 14.2.1.6.3

Number of days in ICU for those admitted (mean) – overall treatment period	3.4	9.7	0.35**	HERCULES CSR, Table 14.2.1.6.4

Key: HR, hazard ratio; ICU, intensive care unit; PEX, plasma exchange; RR, relative risk; SoC, standard of care.

Notes: *Formula: HR time to platelet count response*(1-RR exacerbations) + HR time to platelet count response2 * RR exacerbations

NICE National Institute for Health and Care Excellence

Appendix 2 – Supplementary materials

1. Draft aTTP QoL report
2. Fear and Anxiety TLR
3. HERCULES-TITAN integrated analysis
4. UK Registry data

Melinda Goodall
National Institute for Health and Care Excellence
Level 1 A
City Tower
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M1 4BT

4 March 2020

Dear Melinda

RE: Caplacizumab for treating acute acquired thrombotic thrombocytopenic purpura (aTTP)
NICE ID 1185.

Following the Technical Engagement meeting on 24th February 2020 and subsequent email discussion between the NICE Technical Team and Sanofi, I thought it would be helpful at this stage to clearly outline the correct mortality data to utilise within the Draft Technical Engagement Report, as I realise there has been some confusion in this regard.

This letter is to provide a formal document that can be referred to within the appraisal process rather than relying upon the multiple emails between the NICE technical team and us as the manufacturer.

The technical team utilised acute mortality figures from Table 11 in the CS (which reflects Table 22 of the HERCULES trial CSR) in the Draft Technical Report (Table 1 page 9). The TTP related death (overall study period) in this table is [redacted]. This led the technical team to conclude that HERCULES did not show a difference in acute mortality. As we highlighted to NICE prior to, and during the call, Table 8 in the company submission (CS) should have been used to determine the efficacy endpoint for mortality based upon number of deaths in each arm in the study drug treatment period.

As requested, to clarify the data presented in Table 11 of the CS (which presents SAE not efficacy data), I can confirm that Table 22 in the CSR (corresponding to Table 11 in the CS) is not erroneous; however, without the CRF as context, it is difficult to interpret.

Table 11 in the CS (Table 22 in the CSR) reports the SAEs including investigator-assessed TTP related deaths; those that were categorised as TTP related at the time of reporting by the investigator, indicated by a checkbox in the CRF. Table 11 reports this information directly from the CRF for both the study drug treatment and follow up period. One of the three deaths on placebo was categorized as TTP related at time of reporting in the CRF, and the one death in the follow up period for caplacizumab was also categorised as TTP related at time of reporting in the CRF. This accounts for the reporting of one death per arm, at [redacted] as referred to within the Draft Technical Engagement report in Table 1 (page 9). The three tables have been inserted at the end of this letter for your reference.

All reports of major thromboembolic events or deaths were, according to study design, referred for adjudication to an independent, blinded committee. In each case, the investigator was asked to provide additional information to ensure the event could be assessed effectively. The adjudication committee

assessed all deaths in the study period as being TTP-related. This meant that two additional deaths were categorized as TTP-related on the placebo arm when the investigator had not initially categorized them as such on the CRF. These deaths are thus not listed in Table 11 of the CS, but are listed in Table 8 of the CS, which should be the data source.

To confirm, in the study drug treatment period, there were 3 deaths in the placebo arm (all in the double-blind PEX period), and 0 in the caplacizumab arm, as reported in Table 8 of the CS. In the total study period including follow up, there were 3 deaths in the placebo arm and 1 in the caplacizumab arm. The adjudication committee categorized all deaths as TTP-related. Therefore, the correct percentages are 0 and 4.1% for caplacizumab and placebo respectively in the study drug treatment period shown in Table 19 of the CSR and replicated within Table 8 of CS (see below). We hope this confirms that the mortality data referenced in the Draft Technical Report should be from the efficacy in Table 8 of CS.

In light of this factual inaccuracy, which is not down to a difference in interpretation but an incorrect citing of evidence, I think it is important for the credibility of both Sanofi and NICE that the Draft Technical Report be re-issued with the correct mortality data in Table 1, and the references to mortality updated in the following sections:

- Page 21, Section 2.1, (bullet point 4) which states that trial data does not show any difference in acute mortality between the two treatment arms.
- Page 23, Sections 2.5 and 2.6 also refer to no short-term survival benefit for caplacizumab.
- Page 31, Issue 4 (title) states “trial data does not suggest that caplacizumab reduces mortality…..”. Also, In the rows for questions for engagement (bullet point 1) and background/description of issue (bullet 1).
- Page 32 TT preliminary judgement states that there is uncertainty in acute mortality benefits.

Finally, we would recommend the result in Table 5 of the Draft Technical Report be checked for accuracy with revised mortality figures in the model.

Many thanks for all your work and understanding throughout this appraisal process. The technical engagement meeting was most helpful to us, and we very much look forward to the discussion with clinical experts that your team are arranging.

Best wishes

Jessamy Baird

Director of Patient Access,
Sanofi UK/ROI

Tables referred to in text

HERCULES CSR

Table 1: Proportion of subjects with treatment-emergent clinically significant TTP-related events by category of events (ITT Population)

Time point, n(%)	Caplacizumab N=72	Placebo N=73
DB Treatment Period	[redacted]	[redacted]
At least one TE clinically significant TTP-related event	[redacted]	[redacted]
Cardiovascular events	[redacted]	[redacted]
Neurological events	[redacted]	[redacted]
TTP-related death	[redacted]	[redacted]
TTP	[redacted]	[redacted]
Other	[redacted]	[redacted]
Overall Study Period	[redacted]	[redacted]
At least one TE clinically significant TTP-related event	[redacted]	[redacted]
Cardiovascular events	[redacted]	[redacted]
Neurological events	[redacted]	[redacted]
TTP-related death	[redacted]	[redacted]
TTP	[redacted]	[redacted]
Other	[redacted]	[redacted]

Abbreviations:; FU = follow-up; N = number of subjects within the population of interest (by treatment group); n = number of subjects with treatment-emergent clinically significant TTP-related events in that category; TE = treatment-emergent

When considering adverse events reported in the CSR it is important to note that "treatment emergent" can relate to the PEX procedure, infused plasma, immunosuppressive medication, other medications permitted per protocol, or study drug.

Company Submission

Table 2: Composite of TTP-related death, recurrence or major thromboembolic event in HERCULES (ITT – study drug treatment period)

	CAPLA (n=72)	PBO (n=73)	p-value
Composite outcome, n (%)	9 (12)	36 (49)	<0.001
TTP-related death, n (%)	0	3 (4)	NR
Recurrence of TTP[a], n (%)	3 (4)	28 (38)	NR
Major thromboembolic event, n (%)	6 (8)	6 (8)	NR

Key: CAPLA, caplacizumab; ITT, intention-to-treat; NR, not reported; PBO, placebo; TTP, thrombotic thrombocytopenic purpura.
Notes: [a], based on exacerbation of TTP episode.
Source: Scully et al. 2019.[16]

Company Submission

Table 3 : Treatment-emergent clinically significant TTP-related events in HERCULES (ITT)

n (%)	Study drug treatment period		Overall study period	
	CAPLA (n=71)	PBO (n=73)	CAPLA (n=72)	PBO (n=73)
At least one TTP-related event	[redacted]	[redacted]	[redacted]	[redacted]
Cardiovascular event	[redacted]	[redacted]	[redacted]	[redacted]
Neurological event	[redacted]	[redacted]	[redacted]	[redacted]
TTP-related death	[redacted]	[redacted]	[redacted]	[redacted]
TTP	3 (4.2)	28 (38.4)	9 (12.5)	28 (38.4)
Other	[redacted]	[redacted]	[redacted]	[redacted]

Key: CAPLA, caplacizumab; CI, confidence interval; ITT, intention-to-treat; TTP, thrombotic thrombocytopenic purpura.
Source: HERCULES CSR.[43]; Scully et al. 2019.[16]

Melinda Goodall
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Level 1 A
City Tower
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16th March 2020

Dear Melinda

RE: Caplacizumab for treating acute acquired thrombotic thrombocytopenic purpura (aTTP)
NICE ID 1185.

Thank you for the technical engagement report and the subsequent technical engagement meetings and correspondence. Sanofi have reviewed the technical report content and have submitted a revised PAS (a discount of [redacted]%) which brings the ICER in the base case below accepted cost-effectiveness thresholds. This represents a substantial additional discount (a further [redacted]%) and is offered in the spirit of the technical engagement process to provide the Committee with the potential to recommend caplacizumab without the need for additional Committee meetings.

Within this document we present a revised base case and scenario analyses with the new PAS. We would, however, also request the Committee to take into account the ultra-rare nature of aTTP when deliberating both on the presented ICERs and the ability of Sanofi to generate evidence to support the economic case for caplacizumab.

Committee Considerations

Request for consideration of decision modifiers within deliberations

This appraisal has been previously listed under both HST and STA but was finally routed through STA, although the treatment and disease demonstrate characteristics more suited to HST. Sanofi urge the Committee to consider this previous consideration for HST in their decision making, and the fact that multiple HST criteria were still met including:

- The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS
- The technology is expected to be used exclusively in the context of a highly specialised service
- The need for national commissioning of the technology is significant

In meetings with NICE subsequent to the STA routing, Sanofi were directed to the EOL criteria, which allow a higher threshold for EOL medicines for patients with a short life-expectancy:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months;
- there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment
- the treatment is licensed or otherwise indicated, for a small patient population)

The original spirit behind the EOL criteria were to recognise the additional willingness to pay within society for cancers which were severe, limited the individual's life expectancy but also in addition recognised the limited commercial potential due to small populations.

Caplacizumab meets the criterion regarding the small population, with only 100-150 episodes per year in the UK and it meets the criterion of incremental survival gain of greater than 3 months. There is sufficient evidence that mortality is improved with the use of caplacizumab in the acute setting and clinical consensus that the benefits of reduced exposure to micro-thrombi will result in long-term benefits from reduced complications. For life expectancy in aTTP, it is more binary: the patient either lives (around 80-90% of patients), potentially with reduced life expectancy due to microvascular damage, or they die immediately within the acute phase. Thus, the average life expectancy in the population is higher than 24 months due to the life-threatening nature of the acute event, but also due to the young age at which patients present.

Therefore, whilst all the EOL criteria may not be directly applicable for a treatment such as caplacizumab, we would urge the committee to consider the rarity, the severity, that aTTP presents as an acute medical emergency and the potential to offer life extension with improved quality of life for these acutely unwell patients.

There is an urgent clinical need for a new intervention to complement current standard of care (SoC) and reduce the time patients spend in the occluded state during an acute episode and reduce the risk of recurrence and refractory disease. Caplacizumab addresses this need resulting in quicker resolution of the acute episode and a likely reduced risk of long-term and disabling complications, which have an impact on patients and their families.

Sanofi believe that medicines for ultra-rare conditions, that do not meet all specific criteria for HST or EOL, represent a real challenge in terms of NICE Committee decision making and the application of an ICER threshold intended for "standard" medicines for larger populations. NICE committees have previously considered rarity and severity of disease in their decisions on whether to recommend a treatment, at a given threshold, and have exercised their right to discretion as indicated in section 6.3.3 of the NICE methods guide. For example, the final appraisal document (FAD) for nusinersen for treating spinal muscular atrophy (SMA) (TA588) states that 'the decision making takes into account the rarity and severity of the disease'.

Benefits not captured within the QALY calculation

The technical team noted that the patient expert statements referred to the plasma exchange procedure and fear of relapse as having a large impact on quality of life. This impact was not included within the economic model at the time of submission and this variable is difficult to populate due to lack of data for patients with aTTP. A targeted literature review has therefore been undertaken to assess the possible impact of fear of relapse (Appendix 2 of the technical report response). The potential impact is explored within the economic model and indicates the potential for a reduction in the ICERs, presented in Table 2.

Other potential cost savings identified by the technical team on blood products have not been included due to lack of data and short-term impact, so the original conservative assumptions remain in the model. Finally, we would request the Committee to consider the following potential benefits to the NHS that were unable to be captured within the QALY measure:

- Reduced requirement for and duration of ICU stays which has the potential to be a major benefit as most hospitals are at capacity. Within HERCULES there was a 65% shorter duration of care in an intensive care unit (ICU) with caplacizumab (even with use of open label caplacizumab on the SoC arm).
- Reduced requirement for plasma – TTP currently uses over 25% of all plasma in the UK (based upon clinician comments in the technical engagement meeting). Reducing plasma use has multiple benefits including removing the requirement for multiple lines to be put in which is a major issue for patients. During the technical engagement call, clinicians stated typically before caplacizumab became available, patients often had at least two central lines which were replaced every 5-7 days due to infection risks, and this was typically done for 2-3 weeks. Since caplacizumab has been available, this need has been reduced with often only one single central line, for around one week with no need to replace it.
- Reduced damage to organs such as the kidneys, heart and brain stemming from reduced exposure to micro thrombi – the impact of which could not be included in the economic model
- Impact on the wider family is not included in the economic model and the impact on carers has likely been underestimated given that an impact is only included currently for carers of patients with severe cognitive impairment

Additional evidence

Due to the rarity of the condition and difficulty in collecting data at an acute life-threatening event, Sanofi recognise there is uncertainty in the data. Attempts have been made to find data to support the necessary assumptions.

A QOL study in patients with aTTP and their carers undertaken by Sanofi in 2019 has investigated quality of life, anxiety and depression, cognitive function and work productivity. Data from this study are first presented in the response to Issue 7 and show that survivors of aTTP appeared to report lower overall HRQoL and greater cognitive dysfunction than both UK

and U.S. general populations respectively. These patients also appear to experience moderate levels of both anxiety and depression, as well as markedly reduced productivity at work and participation in daily activities. These findings were generally consistent across those patients who experienced an aTTP episode within the last 12 months and those who had not, suggesting these issues may persist for aTTP patients beyond the initial acute episode(s). (Appendix 2 of technical report response).

CPRD-HES data was explored, however, due to the rarity of the condition, the data coding is problematic, and the dataset provided appears unreliable and unrepresentative of aTTP patient experience. Only a small percentage of patients classified as aTTP received PEX, which further discredits the dataset.

TTP Registry data is provided for caplacizumab patients treated in the UK for acute mortality, and this acute morality has been presented in Table 1 below and Appendix 2 in the technical report response. The registry has recently been updated to begin collecting longer term data, it does not yet provide long-term cognitive impairment outcomes or quality of life as these data will take several years to collect, and the data is not yet mature.

Mortality

The technical team assertion of caplacizumab having no effect on mortality both Sanofi and clinicians believe to be incorrect. There is no evidence of no effect, and there is evidence of an effect from various sources outlined below.

While the HERCULES study was not powered to demonstrate a significant effect on mortality, there was a significant effect on the first key secondary composite endpoint, of TTP-related death, recurrence or major thromboembolic event (P<0.001; Table 8, CS). The individual (exploratory) endpoint of mortality rate during the treatment period, whilst not part of the hierarchical ranked endpoints and hence not tested for significance, showed a clinically relevant reduction in mortality of 0 vs 3. This is the second study showing no acute deaths during the treatment period. The significance of this effect is shown by a pooled analysis of HERCULES and TITAN, demonstrating a significant reduction in mortality during the treatment period due to increased power of the pooled analysis (Table 1).

An updated figure from the compassionate use study is presented, and data from a matched cohort study in France. In France, the reference network for Thrombotic Microangiopathies (CNR-MAT), conducted a prospective real-world study (Caplavie study). Sixty-eight aTTP patients were treated with Caplacizumab together with plasma exchange and immunosuppression (corticosteroids and rituximab). Outcomes were compared to 160 aged-matched historical control patients. An abstract has been accepted for Societe Haemologique Francais 2020. Only the information from the abstract is available to Sanofi at this time, and this has been supplied as academic in confidence from the author (Ref. 14 in technical report response). These mortality figures are presented in Table 1 and in company preferred scenarios in Table 2 at the end of this letter.

These data from the matched cohort study are of particular relevance as they demonstrate real world mortality for caplacizumab which is lower than that in the compassionate use scheme, as

would be expected given that in the compassionate use programme, treatment with caplacizumab is started later than it would be if it was made available through routine funding (as requests are individual and caplacizumab is not available on site). Additionally, a similar mortality for standard of care is shown to that demonstrated in the meta-analysis and UK literature sources.

These data are also used as scenario inputs for assumptions in the company preferred case.

Table 1: Sources of Acute Mortality

	Caplacizumab	SOC	P value
HERCULES (study treatment period)	0/72(0%)	3/73(4.1%)	NA
HERCULES/TITAN pooled analysis (study treatment period) (Appendix 2)	0/108(0%)	4/112 (3.6%)	0.047
French matched cohort study (Ref. 14 in technical report response)	[redacted]	[redacted]	[redacted]
Caplacizumab UK Registry (treated within 48 hours of PEX) (Appendix 2 of technical report response)	[redacted]	-	NA
Caplacizumab UK Registry (treated within 7 days of PEX) (Appendix 2 of technical report response)	[redacted]	-	NA
Compassionate use all patients February 2020 (n=239)	9/239 (3.77%)	-	NA
Compassionate use all patients August 2019 (n=187)	8/187 (4.3%)	-	NA
UK Literature (Refs.1 and 13 in technical report response)	-	13.0% - 15.0%	NA

These data from the matched cohort study are of particular relevance as they demonstrate real world mortality for caplacizumab which is lower than that in the compassionate use scheme, as would be expected given that in the compassionate use programme, treatment with caplacizumab is started later than it would be if it was made available through routine funding (as requests are individual and caplacizumab is not available on site). Additionally, a similar mortality for standard of care is shown to that demonstrated in the meta-analysis and UK literature sources. Only the information from the abstract is available to Sanofi at this time and has been supplied as academic in confidence from the author (Ref. 14 in technical response document). These mortality figures are presented in scenarios in Table 2

Revised base case

Sanofi has considered the changes implemented by the ERG and technical team and has adopted the following amendments within our revised base case:

- ERG costing amendments (PEX procedure cost amended from £602.34 to £1265)
- Revised mortality information from the compassionate use scheme data for caplacizumab (9/239)

The impact of the revised PAS is presented below along with scenarios demonstrating the impact of alternative assumptions around the data source used for acute mortality, fear of relapse, the benefit of caplacizumab in reducing long-term complications and long-term mortality.

Sanofi appreciate the complex deliberations and responsibility of the NICE Committee and have therefore provided a significantly revised PAS alongside the additional analyses to reduce uncertainty, in order to reach a range of ICERs close to, either below or above the £30K threshold. We believe caplacizumab represents an important step forward for management of aTTP and gives hope to patients suffering from this terrible rare condition and we would therefore be grateful if the Committee could give due consideration to the additional value elements of caplacizumab such as the rarity of aTTP, the sudden and severe onset of disease, the acute mortality threat, the need for a new and targeted treatment to reduce the time spent in the occluded state when making their decision.

This is a medicine for a very rare, severe and life-threatening disease, and we hope our response, additional analyses and adjustment of the PAS will enable the Appraisal Committee to reach a recommendation for patients within England and Wales to gain prompt access alongside the new NHSE Highly Specialised Service for TTP.

Best wishes

Jessamy Baird

Director of Patient Access,
Sanofi UK/ROI

Table 2: Company preferred assumptions and base case with revised PAS and revised PAS plus fear of relapse disutility

Scenario	Acute Mortality		RR long-term complications	RR long-term mortality	ICER* £/QALY	ICER** £/QALY
	Caplacizumab	SOC				
Revised company base case with revised PAS, ERG correction to PEX procedure cost (£602.34 to £1265) and updated mortality from the compassionate use scheme (RR 0.267)	3.8%	13.2%	0.62	0.62	£27,856	£26,357
Original company base case with revised PAS and mortality from French Matched Cohort Study (Ref. 14 in technical response document)	[redacted]%	[redacted]%	0.62	0.62	£28,126	£26,495
Original company base case with revised PAS and ERG correction to PEX procedure cost (£602.34 to £1265)	4.3%	13.2%	0.62	0.62	£28,358	N/A
Original company base case with revised PAS	4.3%	13.2%	0.62	0.62	£29,407	N/A
Original company base case with revised PAS and mortality from Hercules	0%	4.1%	0.62	0.62	£31,712	£29,252
Revised PAS with NICE technical team ICER	13.2%	13.2%	0.62	1	£128,910	N/A

Notes: *Cost of treatment of acute episode is £[redacted] based on revised PAS ([redacted]%); ** Cost of treatment of acute episode is £[redacted] based on revised PAS ([redacted]%**) and fear of relapse disutility (50%)

Table 3: Base case with original PAS

Scenario	Acute Mortality		RR long-term complications	RR long-term mortality	ICER* £/QALY
	Caplacizumab	SOC			
Original company base case	4.3%	13.2%	0.62	0.62	£37,986
With ERG correction to PEX procedure cost (£602.34 to £1265)	4.3%	13.2%	0.62	0.62	£36,937
NICE technical team	13.2%	13.2%	0.62	1	£172,429
Revised company base case with original PAS – ERG correction to PEX procedure cost (£602.34 to £1265) and updated mortality from the compassionate use scheme (RR 0.267)	3.8%	13.2%	0.62	0.62	£36,252
Notes: *Cost of treatment of acute episode is £[redacted] with original PAS ([redacted]%)					

NICE National Institute for Health and Care Excellence

Technical engagement response form

Caplacizumab for treating adults experiencing an episode of acquired thrombotic thrombocytopenic purpura [ID1185]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments **13 March 2020**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	Professor Marie Scully
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	RCPath, UK TTP forum
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	I have undertaken advisory boards and had speaker fees from Ablynx and Sanofi and was PI in both the TITAN and HERCULES studies.

Questions for engagement

Issue 1: Generalisability of HERCULES. The trial population may be fitter than people who would have caplacizumab in UK clinical practice and capalcizumab started later than it would be in clinical practice	
• Were people in HERCULES fitter than people who would be treated with caplacizumab in UK clinical practice?	There was no difference In the cohort admitted in HERCULES than normal clinical practice. In the UK cases (n=18), these were consecutive patients. Furthermore, the demographics of the cases in Hercules suggested by chance, more de novo and more with GCS < 12, so more severe. From registry data, 10% of patients required intubation and ventilation. No patient is well, but the degree of organ involvement will vary at presentation. This and refractory disease predicts those who may die during an acute admission. Please see attached document re TTP data in the patient access scheme compared to non capla cases
• How long after starting plasma exchange was caplacizumab given in HERCULES?	24 hours as per protocol. In the UK we ensured the patients had TTP by testing ADAMTS 13 activity levels, which was not an absolute requirement for trial entry, but samples were taken centrally to confirm diagnosis.
• Would outcomes be expected to differ between the trial and clinical practice?	No difference. We would not start capla until TTP is confirmed by ADAMTS 13 activity, as is the process throughout the UK. Many patients present after working hours-the mainstay of therapy is PEX and steroids and analysis of ADAMTS 13 levels. Therefore initiation of capla is comparable to the HERCULES protocol. Please see attached doc re our real world experience in the patient access scheme. Two further comments: 1. The importance of starting capla on confirmation of diagnosis of TTP 2. The reason TITAN did not recruit to target was because of the protocol-requiring capla pre 1st PEX. This is logistically impossible with a clinical study given the time criticality of initiating PEX.

Issue 2: Concomitant treatments received in the caplacizumab arm in HERCULES may not be consistent with either the comparator arm or clinical practice	
• How is rituximab used in aTTP in current clinical practice? When is it stopped?	Rituximab is used in >90% of cases during the acute presentation within the UK. Initially 4 infusions are given, but up to 8 depending on ADAMTS 13 activity levels.
• Is rituximab standardly given to during remission to prevent relapse?	Yes, throughout the UK. Patients are monitored after acute episodes and with a reduction in ADAMTS 13, rituximab is given in the outpatient setting to prevent relapse
• Is there any clinical effectiveness data for rituximab in aTTP?	Multiple papers, from the UK and internationally
• Do more people have rituximab in UK clinical practice than in the trial? If so, what is the likely effect of this on clinical outcomes in the trial?	All the UK patients entered into the trial had rituximab-it is SOC. Availability remains an issue at an international level. Rituximab use is to clear ADAMTS 13 antibodies. This is not the method of action of capla; Caplacizumab has no effect on ADAMTS 13. The effect of rituximab is on a different part of the TTP pathway.
• In the trial, people in the caplacizumab had use of rituximab. Does this represent a benefit of treatment with caplacizumab (that is, were people having caplacizumab less likely to need rituximab than people having placebo), or an imbalance across arms which was independent of study drug?	The effect of rituximab in the trial has been attempted to be looked at-but any impact would be descriptive only. There was an ASH 2019 abstract. The numbers that received rituximab were comparable in each arm. But rituximab and capla are not comparative. They work in completely different ways
• Do imbalances in rituximab use between treatment arms bias results?	No-different mechanisms of action in TTP. Plus ritux takes a median of 10 days to start to work, which is an important period covered by capla. Its in the 1st 10 days that mortality in acute TTP is at its greatest. Therefore, capla provides a very important protective effect during this time.
Issue 3: Protocol violations in HERCULES may affect reliability of the trial	
• Would protocol violations in HERCULES affect outcomes in study?	Please remember this is a clinical trial in an acute life threatening disorder.

• Were there any differences in the characteristics of the people who had a protocol violation compared with those who did not?	I do not have this data, but expect these would have been reviewed by EMA and FDA in detail.
Issue 4: HERCULES trial data does not suggest that caplacizumab reduces mortality or cognitive or neuropsychological impairment in the short term	
• Could HERCULES capture any potential differences between caplacizumab and standard of care for mortality, cognitive or neuropsychological impairment?	What both TITAN and HERCULES have provided is NO mortality in the capla arms. There were deaths in the placebo arm. Furthermore, there was no refractory disease with capla, which would impact the mortality levels positively. Furthermore, there was an open capla arm in HERCULES for those patients who had an exacerbation, again preventing mortality. Re neurocognitive/psychological effects 1. Inhibiting further microthrombi formation as proven in vitro, will prevent further organ microvascular thrombi and end organ damage 2. Neurocognition/psychology will be available in post Hercules follow up, which includes capture of these effects. The remit for many years was to ensure diagnosis and get patients through the acute disease. Only recently, perhaps the last 3 years, has the longer term impact of TTP started to be addressed, hence the paucity of published data. However, there are a number of national and international groups who are looking specifically at longer term effects of acute TTP.

• What is the relationship between time at exposure to thrombi/anti-ADAMTS13 antibodies and death in the short term (would a difference of 4.6 hours in time to platelet normalisation result in a difference in these outcomes)?	The faster the platelet count increases, the safer patients will be re mortality and morbidity. I don t understand the 4.6 hours-has this really been calculated correctly? Patients die because of 1. Delayed diagnosis, so more severe, refractory disease 2. A very brisk, severe disease, not often even allowing for therapy 3. Between 7-10 days from diagnosis/treatment initiation Rituximab takes approximately 10 days to have an effect. Hence during this time, patients are at greatest risk from significant morbidity and mortality. This is the rationale to start capla as soon as possible, providing a swifter time to platelet normalisation which is sustained. Thereafter, the effect of immunosuppressive therapy takes time to normalise ADAMTS 13activity-explaining why capla is continued until this is achieved.
• Are there any published studies reporting on a relationship between platelet levels in aTTP and death rate?	There is no initial platelet count that predicts mortality. Refractory disease does predict mortality and morbidity. Refractory disease affects 10-20% of all cases. We have presented the mortality risk with ADAMTS 13 results at presentation, with troponin T and GCS (Alwan et al, Blood 2017) and peyvandi et al showed that mortality is 3 fold increased with IgG antibodies and mortality.

	There is no one paper looking at base line platelets and mortality-it relies on other features. But the quicker platelets are increased, they are no longer binding to UL VWF multimers, so microvascular thrombi are reduced and mortality reduced.
• Was the difference in treatment times between the study arms accounted for in survival analysis?	No. Regardless of immunosuppressives used (and these could not be analysed post trial completion), the capla arm had more severe cases by chance, but results were better in this arm re mortality, refractory disease and time to remission.
Issue 5: A naive comparison of observational data from two different sources (used by the company to model mortality in the short term with caplacizumab compared with standard care) is not robust	
• Do the real-world data sources reflect UK clinical practice/ people with aTTP in England?	Compassionate use scheme – <5% mortality. However, at the initiation of the scheme, there were some cases where capla was started much later in the disease course Placebo – 13.2% . Even within the UK, some centres mortality was 50%, hence the drive to have specialist units. UCLH-mortality <5% nad has been this for a number of years. Overall, the mortality pre capla is quoted as 10-20%, in the UK and from international data, but is a median for all sites, specialist or not.
• Does the real-world data (naïve comparison) give a robust estimate of survival and the treatment effect of caplacizumab during the acute phase?	Re real world data, All centres now use a common protocol. The time to remission is quicker. The time to platelets in a safe level, reducing the mortality risk is quicker. Length of stay is significantly reduced and amount of PEX/ plasma used is significantly reduced. Included is the UCLH experience. UK experience should also follow.

• What is the most plausible estimate, real world naïve comparison or trial, for the effect of caplacizumab on survival during the acute phase?	The effects of capla demonstrated in the trials are exactly that in real world. Response above and UCLH data
Issue 6: There are no data available to test whether caplacizumab reduces mortality or cognitive or neuropsychological impairment in the long term	
• Is there any ongoing data collection assessing the clinical effectiveness of caplacizumab in reducing mortality or cognitive or neuropsychological impairment in the long term (after acute phase)?	Yes post Hercules data-3 years Uk TTP registry Study to be open via Liverpool hospital, including UK TTP registry data and a quality of life assessment. We will be publishing shortly data on patients who have had MRI and neurocognitive assessments.
• Is it biologically plausible that a person who is in remission after caplacizumab should have a reduced risk of death, or neuropsychological or cognitive impairment compared with someone who is in remission after standard care?	Yes definitively re effect on preventing microvascular thrombi. The time to normal platelet count is undoubtably longer in patients who do not receive capla and this results in significant risk to patients from increased morbidity, in the short and longer term and mortality.

• Is it biologically plausible that the time a person stayed in hospital/ICU for their acute treatment is related to their risk of death, or neuropsychological or cognitive impairment when in remission?	Yes, sicker patients require ICU admission, worse prognostic factors, based on troponin and Glasgow coma scale, as well as ADAMTS 13 assay results. The longer the admission, associated with exacerbation/refractory disease, increases mortality and long term risk of complications
Issue 7: The relationship between hospital stays and risk of cognitive impairment, neuropsychological impairment or death in the long term has not been validated.	
• Do the rates of mortality in remission, cognitive impairment or neuropsychological impairment used in the standard care arm of the model reflect the expected rates for people having standard care in UK clinical practice? See table 3 above	Not sure I understand this
• Is there a relationship between hospital/ICU stay and risk of long-term complications? Are there data to support this?	As above, refractory disease-associated with on going microvascular thrombi and effect on end organ damage and mortality. This is demonstrated by delayed time to platelet normalisation, more therapy, including plasma exchange and immunosuppressive treatments, aside from steroids and rituximab.
• Does time in hospital ICU/hospital reflect a) exposure to microthrombi b) exposure to microthrombi + damage caused by exposure to microthrombi?	Already answered above
• Is the modelled survival gain for caplacizumab compared with standard care (5.48 years) plausible?	Absolutely. Capla provides extremely important protection, by increasing platelet counts and inhibiting microvascular thrombi formation which has been missing within the treatment pathway

• Is there any evidence to support a relationship between any other outcome measured in HERCULES (such as time to platelet normalisation) and long-term outcomes?	This will be captured in the post Hercules data. However, from the underlying pathophysiology of TTP, by preventing further microthrombi formation, with capla, ongoing end organ damage will be averted.
• Which is a more valid assumption on the relative risk of caplacizumab on cognitive or neuropsychological impairment compared with standard care; the company's or ERG's?	As above
• Is the ERG's approach of assuming that the potential treatment effect of caplacizumab on mortality in remission is greater than the treatment effect of caplacizumab on neuropsychological or cognitive impairment plausible?	It impacts both equally, one goes with the other
Issue 8: The utility values in the model do not come from trial data and utility associated with long term complications of aTTP is based on other conditions	
• Is stroke a good proxy for the utility experienced during an acute episode for aTTP	No-only 70% of patients have neurological symptoms, and not all of these are strokes.
• Do the utility values for acute aTTP reflect the impact of treatment with caplacizumab/ standard of care on quality of life?	I m unclear what a utility value is, but quality of life has not formally assessed to ate-only in the post Hercules study and this data is not currently available.
• Is the quality of life of people in the US with aTTP likely to be similar to the quality of life of patients in the UK?	No. The treatment of TTP is highly variable in the US and there are many factors relating to this, including expertise by the treating centre in TTP, ADAMTS 13 measurement. capability and long term follow up and support and prevention of relapse. The UK follows a national protocol.

• Are the neuropsychological impairments experienced with aTTP similar to those experienced by people with depressive disorder?	No. Depression, which is severe in up to 50% of patients is related to the acuteness of the condition and the treatments in a young population. However, microtthrombi affecting the eg frontal lobe may be associated with depression. The neuropsychological symptoms, including intelligence, executive functions (such as planning, abstraction, conceptualization), attention, memory, language, perception, sensorimotor functions are quite separate and can be documented through neuropsychological assessments to be affected. These may relate to areas of ischaemia (stroke), but more often white matter changes, relating to microvasular thrombi during the acute episode, evident on MRI scanning (manuscript from UCLH nearly ready for submission).
• Is the quality of life of people caring for people with aTTP expected to be similar to people caring for people with aTTP?	Sorry I m not sure I understand the question.
Issue 9: The relapse rate modelled by the company of 1% is uncertain	
• Is the company assumption of a 1% relapse rate plausible?	Confirm it is annualised rate – 10% over 10 years = 1% Risk of relapse pre rituximab was 30-50% Only reduced to 10-15% in those monitored and given elective rituximabv There remains those cases not followed up or lost to follow up that are at risk of relapse.
• Are there any data on the current relapse rate in the UK?	Yes SE England Registry data (BJH), confirmed in ISTH 2019 oral presentation re the UK TTP registry-comparable results. Blood paper re early use of rituximab demonstrated its reduced relapse risk (Scully et al, Blood 2014), Other confirmation: ohio registry (USA) data and the risk of relapse and impact, french registry and oklahoma data (USA) - suggests the risk goes out to 10 years, not just in the first 2-3 years. UCLH and french data on the prevention of relapse risk

Issue 10: Have all potential costs that may be offset by using caplacizumab, and the wider benefits of reducing use of a blood product, been accounted for in the model?	
• Will reducing the volumes of a blood product for plasma exchange have a wider impact (besides the costs of giving the infusion itself)?	Absolutely-it is a blood product providing proteins aside from ADAMTS 13 which are unnecessary in disease treatment. Despite being safe (the UK use Octaplas-solvent detergent prion reduced plasma), there are the associated risks of repeat central venous access insertions, reactions are less but exist, compared to standard FFP and the mantra is to try and avoid unnecessary blood and blood component use.
• Would needing a lower volume of plasma reduce the likelihood of any PEX related complications?	Definitely and all the subsidiary effects eg lines, impact of citrate reactions, plasma reactions and potential risk of pathogens
• Are there any issues with the availability of plasma for PEX in clinical practice?	No, not in the UK. It is non UK sourced
• Would a shorter time to platelet normalisation observed with caplacizumab be expected to also mean that people treated with caplacizumab have fewer doses of rituximab in clinical practice?	No, these are not comparable therapies and too much of this report suggests they are. Rituximab is required to remove underlying abs to ADAMTS 13. . Capla has no effect on ADAMTS 13, but provides a very safe situation while the underlying disease is being treated.
• Will reducing the volumes of a blood product for plasma exchange have a wider impact (besides the costs of giving the infusion itself)?	Yes as above

Issue 11: The company base case is over £30,000 per QALY gained: Unable to commnet MS	
• Is there reason to consider an ICER of above £30,000 per QALY gained a cost-effective use of NHS resources?	
• Are there any benefits of caplacizumab that the company have not included in its modelling?	
• Have the benefits of reduced use of blood products (which are a limited resource) been captured?	
Issue 12: Caplacizumab may be an innovative technology	
• Are there any benefits not captured by QALY calculation?	

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About you

Your name	[redacted]
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**TTPNetwork**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**

Questions for engagement

Issue 1: Generalisability of HERCULES. The trial population may be fitter than people who would have caplacizumab in UK clinical practice and capalcizumab started later than it would be in clinical practice	
• Were people in HERCULES fitter than people who would be treated with caplacizumab in UK clinical practice?	Any patient presenting as likely to have aTTP and commencing standard treatment will be in a very unwell state. They will have a very low platelet count, a very low haemoglobin count (Hb) and a raised lactate dehydrogenase (LDH) count. They will be at immediate and serious risk of organ damage and/or Stroke. We know from our contact with patients (including those involved in the trial) that at this point they experience severe psychological distress. It feels disingenuous of NICE to not recognise the seriousness of the condition on presentation and beyond. The trial appears to have been carried out at centres of excellence, in that respect, patients were getting the very best and most prompt treatment. It is fair to say that many patients do not get that level of care normally**.**
• How long after starting plasma exchange was caplacizumab given in HERCULES?	

• Would outcomes be expected to differ between the trial and clinical practice?	We would hope that in clinical practice, outcomes were even better than in trial as we move towards a commissioned Specialist Service for aTTP and where we could see Caplacizumab (if licenced by NICE) included in the treatment protocol which all specialist sites would work to.
Issue 2: Concomitant treatments received in the caplacizumab arm in HERCULES may not be consistent with either the comparator arm or clinical practice	
• How is rituximab used in aTTP in current clinical practice? When is it stopped?	It is our understanding that Rituximab is used to supress the immune system. It is routinely used in some centres to avoid a relapse – so when a patients ADAMST13 protease reading is low, prior to evidence of an acute episode. It is also given to patients during a full episode of aTTP. Rituximab is used for a different purpose than Caplacizumab. It is our understanding, from talking to patients that the two are used in tandem.
• Is rituximab standardly given to during remission to prevent relapse?	Some centres (typically centres of excellence) will treat with Rituximab if through regular monitoring a patients ADAMST13 levels are shown to be dropping and reach (for example) in the region of less than 20 (centres appear to differ on the trigger point).
• Is there any clinical effectiveness data for rituximab in aTTP?	We believe there have been papers written. i.e. JP Westwood et al.
• Do more people have rituximab in UK clinical practice than in the trial? If so, what is the likely effect of this on clinical outcomes in the trial?	As above Rituximab is given typically in centres of excellence. As we move towards a commissioned Specialist TTP Service we would expect that Rituximab would be used more widely but that it would be used in addition to Caplacizumab.

• In the trial, people in the caplacizumab had use of rituximab. Does this represent a benefit of treatment with caplacizumab (that is, were people having caplacizumab less likely to need rituximab than people having placebo), or an imbalance across arms which was independent of study drug?	Rituximab does a very different job to Caplacizumab and is used for a different purpose
• Do imbalances in rituximab use between treatment arms bias results?	
Issue 3: Protocol violations in HERCULES may affect reliability of the trial	
• Would protocol violations in HERCULES affect outcomes in study?	Cannot answer
• Were there any differences in the characteristics of the people who had a protocol violation compared with those who did not?	Cannot answer
Issue 4: HERCULES trial data does not suggest that caplacizumab reduces mortality or cognitive or neuropsychological impairment in the short term	
• Could HERCULES capture any potential differences between caplacizumab and standard of care for mortality, cognitive or neuropsychological impairment?	From the trial it appears that there were less deaths among those having Caplacizumab. Caplacizumab enables a patient to achieve normal counts in a quicker time frame. This would reduce time they are exposed to the small clots travelling around their body and brain, this would reduce the risk of neuro impairment and organ damage and death. It would reduce the exposure to donor plasma (and associated risks). Essentially the longer

	you have the clots travelling around your body the higher the risk of Stroke, or organ damage, having a treatment that shortens that time even by a day, reduces that risk. In terms of psychological damage – the impact of a TTP diagnosis should not be underestimated. The stress of knowing you have aTTP and worrying about relapse is immense. Many patients report Post Traumatic Stress symptoms or have PTSD diagnosis.
• What is the relationship between time at exposure to thrombi/anti-ADAMTS13 antibodies and death in the short term (would a difference of 4.6 hours in time to platelet normalisation result in a difference in these outcomes)?	Yes. Every moment of exposure to thrombi, is a moment of risk of organ damage or stroke. 4.6hrs is a long time when you consider speed at which blood travels around the body and therefore the thrombi in that blood. Reducing the time to platelet normalisation would without doubt reduce the risk of death, organ damage and damage to the brain.
• Are there any published studies reporting on a relationship between platelet levels in aTTP and death rate?	Unable to answer
• Was the difference in treatment times between the study arms accounted for in survival analysis?	Unable to answer
Issue 5: A naive comparison of observational data from two different sources (used by the company to model mortality in the short term with caplacizumab compared with standard care) is not robust	

• Do the real-world data sources reflect UK clinical practice/ people with aTTP in England?	Unable to answer
• Does the real-world data (naïve comparison) give a robust estimate of survival and the treatment effect of caplacizumab during the acute phase?	Unable to answer
• What is the most plausible estimate, real world naïve comparison or trial, for the effect of caplacizumab on survival during the acute phase?	We hear from our patient community that the use of Caplacizumab was welcomed and tolerated well. Some said that even with some side effects they were happy to have the drug given the reduced exposure to low platelets and plasma exchange and the fact that it would get them to 'being well' quicker. They told us that psychologically this was much healthier too. We understand that death from TTP without use of Caplacizumab is 1 in 10 with treatment. Death in those using Caplacizumab 1 in 100. Patients with aTTP typically are of working age and a diagnosis of aTTP affects the ability to work, either in the short term with usually several months being absent from work. Also, in the long term with many patients reporting they have reduced their working hours or changed their job role, due to dealing with the effects of aTTP. aTTP also impacts on personal relationships with the change of lifestyle and long-term health prospects being altered

Issue 6: There are no data available to test whether caplacizumab reduces mortality or cognitive or neuropsychological impairment in the long term	
• Is there any ongoing data collection assessing the clinical effectiveness of caplacizumab in reducing mortality or cognitive or neuropsychological impairment in the long term (after acute phase)?	We believe there are studies taking place to look at neuro / psych effect of TTP on patients and would expect there to be Caplacizumab patients within that study due to the compassionate use scheme. Many patients live with long term disability such as weakness, and / or organ damage following a TTP episode where the disease had taken hold. Virtually all patients talk of memory problems and fatigue, these are long term, and disabling, often affecting their ability to return to full time employment. This results in a reduction in salary and in some cases reliance on benefits. There is emerging anecdotal evidence from our patient group that there is a link between the small thrombi in the brain (likely as ADAMST13 values lower) and anxiety/depression. Patients report notable increasing anxiety prior to discovering at a check-up that their ADAMST13 had dropped.
• Is it biologically plausible that a person who is in remission after caplacizumab should have a reduced risk of death, or neuropsychological or cognitive impairment compared with someone who is in remission after standard care?	Yes absolutely. Caplacizumab reduces the time to normal platelet count. This means that there is less time for clots to be circulating the body. This means less risk of Stroke or organ damage due to circulating clots.

	In turn this could enable patients to return to near normal working and personal lives.
• Is it biologically plausible that the time a person stayed in hospital/ICU for their acute treatment is related to their risk of death, or neuropsychological or cognitive impairment when in remission?	Yes absolutely. Staying in hospital comes with its own risks. If you are required to stay in hospital you are likely very unwell, if aTTP is refractory then the risks are higher that you will not survive the episode or will have long lasting damage, and regardless of the type of aTTP (refractory or not) you will experience unpleasant and frightening medical procedures that could and does have a long term psychological effect on patients.
Issue 7: The relationship between hospital stays and risk of cognitive impairment, neuropsychological impairment or death in the long term has not been validated.	
• Do the rates of mortality in remission, cognitive impairment or neuropsychological impairment used in the standard care arm of the model reflect the expected rates for people having standard care in UK clinical practice? See table 3 above	Unable to answer
• Is there a relationship between hospital/ICU stay and risk of long-term complications? Are there data to support this?	Unable to answer
• Does time in hospital ICU/hospital reflect a) exposure to microthrombi b) exposure to microthrombi + damage caused by exposure to microthrombi?	Unable to answer
• Is the modelled survival gain for caplacizumab compared with standard care (5.48 years) plausible?	Unable to answer

• Is there any evidence to support a relationship between any other outcome measured in HERCULES (such as time to platelet normalisation) and long-term outcomes?	Unable to answer
• Which is a more valid assumption on the relative risk of caplacizumab on cognitive or neuropsychological impairment compared with standard care; the company's or ERG's?	Unable to answer
• Is the ERG's approach of assuming that the potential treatment effect of caplacizumab on mortality in remission is greater than the treatment effect of caplacizumab on neuropsychological or cognitive impairment plausible?	Unable to answer
Issue 8: The utility values in the model do not come from trial data and utility associated with long term complications of aTTP is based on other conditions	
• Is stroke a good proxy for the utility experienced during an acute episode for aTTP	No. The impact of a TTP diagnosis should not be underestimated. Patient are incredibly unwell on admission to hospital. Their platelets are incredibly low (usually less than 10) and their Hb is also low – resulting in breathlessness and headaches, but these symptoms are the lower end of the scale. They will often be confused, disorientated and sometimes unconscious. They are hooked up to a Plasma Exchange machine for many many hours during the first week. This is with tubes and needles in the crook of each elbow or a central line fitted into the neck, chest or groin. Patients are frequently reminded about the risk of infection which adds a further worry.

	When patients are told/realise that they have a risk of relapse, their anxiety continues. Patients talk of their first thought each morning, being: 'do I have bruises' (a first sign of low platelets) That constant, intense worry, plus the issue of living with any effects of organ or stroke damage. It's like living with a ticking time bomb. Patients with an aTTP diagnoses report that they struggle to go back to work on full time hours due to fatigue and memory problems. Many change their working hours permanently and some cease work altogether, relying on the benefit system. Due to the typical age range of patients being 20-30's these are people who should ordinarily be fully contributing members of our community. There is also an impact on interpersonal relationships and next of kin family members experience worry and anxiety about their loved one's health.
• Do the utility values for acute aTTP reflect the impact of treatment with caplacizumab/ standard of care on quality of life?	
• Is the quality of life of people in the US with aTTP likely to be similar to the quality of life of patients in the UK?	No. The US appear to have a patchwork of patient care and treatment for TTP. Among our group we have members from the USA, and they tell us that they have additional worries about insurance and paying for care and treatments. We are unsure if there is a standard of care in the

	US.
• Are the neuropsychological impairments experienced with aTTP similar to those experienced by people with depressive disorder?	We hear from patients via our group that a great many suffer from long term psychological issues such a depression, anxiety and PTSD. There is a real fear of relapse for very good reason – many patients do relapse and repeatedly. In the general population, depressive disorders appear to be more of a chemical imbalance and people may be depressed even if they are living healthy and good lives. Anxiety and depression in TTP are due to a physical reason: disability, reduced cognitive ability and constant worry about their future health and livelihood.
• Is the quality of life of people caring for people with aTTP expected to be similar to people caring for people with aTTP?	This question does not make sense but on seeking advice we are told the comparison should be with Stroke. The comparison would not be fair. With Stroke although there may be some risk of another stroke, patients in that group are generally closely monitored for a time. In aTTP the risk of relapse is lifelong. We know of patients who have been in remission for over 10 or 15 years who then experience relapse or threatened relapse (avoided using Rituximab). This has a massive impact of family members and carers. Family members anxiety levels would be similar to the patients: the fear of the unknown. Added to that they would be living with/caring for someone suffering anxiety, PTSD and depression, a huge strain on a relationship.

Issue 9: The relapse rate modelled by the company of 1% is uncertain	
• Is the company assumption of a 1% relapse rate plausible?	We are unable to answer this but would imagine there are some research papers somewhere.
• Are there any data on the current relapse rate in the UK?	Centres of excellence (mainly UCL and Liverpool) will follow patients up regularly (1 or 2 times a year) this care enables patients to be monitored and when there are signs of ADAMST13 dropping they will seek to start patients on a course of Rituximab which appears to help raise the ADAMST13. However, many patients are not currently being seen at a centre of excellence and are not being followed up regularly. In fact, some patients are told that they were unlucky to have aTTP and that it won't happen again. Even when we get the commissioned service, there will be number of patients who will fall through the net and those individuals are at risk of relapse without intervention.
Issue 10: Have all potential costs that may be offset by using caplacizumab, and the wider benefits of reducing use of a blood product, been accounted for in the model?	
• Will reducing the volumes of a blood product for plasma exchange have a wider impact (besides the costs of giving the infusion itself)?	
• Would needing a lower volume of plasma reduce the likelihood of any PEX related complications?	
• Are there any issues with the availability of plasma for PEX in clinical practice?	

• Would a shorter time to platelet normalisation observed with caplacizumab be expected to also mean that people treated with caplacizumab have fewer doses of rituximab in clinical practice?	Rituximab and Caplacizumab are used for different things. As we understand it, Rituximab is used to supress the immune system. Caplacizumab does something very different (to reduce time to normal platelet count). We are unable to answer if one would reduce the use of the other.
• Will reducing the volumes of a blood product for plasma exchange have a wider impact (besides the costs of giving the infusion itself)?	Yes. There are risks associated with blood transfusions/plasma exchange. Risk of reaction, infection etc. Reducing the volume of blood product transfused, reduces those risks. Blood and plasma transfusions are also frightening for patients, reducing the need, reduces the worry.
Issue 11: The company base case is over £30,000 per QALY gained	
• Is there reason to consider an ICER of above £30,000 per QALY gained a cost-effective use of NHS resources?	We were very disappointed that Caplacizumab was not appraised under the Highly Specialised Technology scheme. Despite presenting evidence of its eligibility for HST we find ourselves in the position of responding to the Single Technology Appraisal. We are concerned that the numbers will not stack up for treatment of this ultra-rare disease and that patients with this condition will be disadvantaged in comparison to patients living with more common disorders.
• Are there any benefits of caplacizumab that the company have not included in its modelling?	
• Have the benefits of reduced use of blood products (which are a limited resource) been captured?	

Issue 12: Caplacizumab may be an innovative technology	
• Are there any benefits not captured by QALY calculation?	Caplacizumab is absolutely innovative. There has been no drug or treatment in the past 25 years that has significantly altered the path of TTP. For many years patients would expect to be in hospital for the best part of 2-3 weeks whilst doctors tried to get their aTTP under control. This would be followed by many weeks of outpatient appointments, some several times a week. Caplacizumab enables normalisation of platelets to take place within days, and patients to be home much faster. The socio-economic effect of this change has the potential to be significant.

Caplacizumab for treating adults experiencing an episode of acquired thrombotic thrombocytopenic purpura [ID1185]

ERG Review of Company's Response to Technical Engagement Response

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Produced by

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1. INTRODUCTION

The National Institute for Health and Care Excellence (NICE) considered evidence for caplacizumab (Caplivi®) for the treatment of acute thrombocytopenia purpura (aTTP) within its single technology appraisal (STA) programme. Following submission of the Evidence Review Group's (ERG's) report, the company were provided with the opportunity to present further evidence or clarification regarding key issues identified by NICE during the technical engagement process.

As part of this process, the company increased the PAS discount applicable to caplacizumab, and submitted a revised model incorporating this, alongside further changes to model inputs. The ERG critique of the company's updated model and the ERG preferred base case are presented in Section 2.

In Section 3, the ERG present their critique of the company's response to each of the key issues raised by NICE. These issues were:

1. The generalisability of the HERCULES trial to UK practice
2. The generalisability of concomitant treatments received in the caplacizumab arm of the HERCULES trial
3. The implications of protocol violations in the HERCULES trial
4. The absence of data showing an impact of caplacizumab on short-term mortality, cognitive, or neuropsychological outcomes
5. The robustness of mortality data following treatment with caplacizumab
6. The absence of data showing an impact of caplacizumab on long-term mortality, cognitive, or neuropsychological outcomes
7. The validity of any relationship between hospital stays and long-term (mortality, cognitive, neuropsychological) outcomes
8. The validity of utility values used in the company model
9. Uncertainty surrounded the relapse rate of 1% used in the company model

10. Whether all potential costs that may be offset by caplacizumab have been included in the company model

11. The ICER is over £30,000 per QALY gained

12. Whether there are additional potential benefits of caplacizumab that are not included in the QALY.

Finally, as agreed with NICE, the company provided further evidence to accompany their submission that came from studies that were ongoing or started following the time of their original submission. New mortality data and the findings of a targeted literature review (TLR) to identify evidence for the impact of 'fear of relapse' on outcomes are both discussed within the relevant key issues in Section 2. The findings of a cross-sectional survey containing patient-reported outcome (PRO) data for patients with aTTP and carers are partially discussed within Issue 7, with ERG critique on the remaining outcomes presented in Section 0.

2. UPDATED COMPANY ALTERNATIVE ERG BASE CASE ANALYSES

In response to the technical engagement report, the company presented the following updated analyses:

- A revised PAS discount
- An alternative source for estimates of acute mortality, and
- Introducing a fear of relapse effect on quality of life and treatment effect from caplacizumab …

The Company increased the PAS discount offered from [redacted] to [redacted]

New estimates of acute mortality were obtained from a French cohort study of [redacted] patients matched to the general population. However, these data were sourced from a conference abstract and no details were provided. Nevertheless, in the view of the ERG, the additional French data reinforces the evidence for a mortality reduction with caplacizumab in the acute phase.

The Company's range of scenarios with the revised PAS and various sources for acute mortality led to costs per QALY of £27,856 to £31,712 (see Table 2 of the Company's TE response letter). The revised Company base case was the lower estimate of this range.

In addition, a range of scenarios exploring the impact of "fear of relapse" on quality of life reportedly reduced the ICER by up to 15% (see Figure 1 of the Company's TE response letter). A disutility of 0.05 for fear of relapse (finding from the Company's commissioned literature review) was coupled with an improvement of 25% following intervention although it is unclear how these figures were applied to the economic model and no updated model was provided alongside the TE response. In addition, these figures were derived from proxy conditions hence their validity could be questioned. It is also unclear whether these values are applied to all patients. Furthermore, it is unclear whether the fear of relapse could have already been built into the remission utility estimate from the Burns et al study[1].

We have updated the ERG base case updated to include the new PAS discount (see Table below). All other ERG preferred parameters remain unchanged.

Table 1: ERG updated base case results

	Total			Incremental			ICER incremental (£/QALY)
Technologies	**Costs (£)**	**LYs**	**QALYs**	**Costs (£)**	**LYs**	**QALYs**	
SoC	[redacted]	15.85	[redacted]				5.48
CAPLA	[redacted]	21.33	[redacted]	[redacted]	5.48	[redacted]	£30,665

Key: CAPLA, caplacizumab; ICER, incremental cost-effectiveness ratio; LY, life years; PAS, patient access scheme; QALY, quality-adjusted life year; RTX, rituximab; SoC, standard of care

The ERG base case ICER has reduced from £39,630 per QALY to £30,665 per QALY as a result of the revised PAS. This revised figure is marginally above the generally accepted cost-effectiveness threshold. However, although the new evidence provided by the Company supports the long-term morbidity faced by aTTP patients, these results remain highly uncertain as no new data have been provided to address the uncertainty around a beneficial effect of caplacizumab on long-term complications or mortality.

3. ERG REVIEW OF KEY ISSUES

Issue 1: Generalisability of HERCULES. The trial population may be fitter than people who would have caplacizumab in UK clinical practice and caplacizumab started later than it would be in clinical practice

In their response, the company state that while patients in the HERCULES trial were defined as "stably unwell', this was not a requirement in the trial inclusion/exclusion criteria. However, they agree with the ERG assessment that procedures for the recruitment of patients to the HERCULES trial is likely to have resulted in 'fitter' patients being included. These procedures include recruitment from specialist centres, the requirement for patients to consent to being included in the trial (while the trial allowed for consent to be given by proxy, it is unclear how frequent this was possible), and the requirement for all patients to receive PEX prior to treatment. That patients may be fitter than those treated in clinical practice is supported by the reduced mortality rates in both arms of the trial, highlighted by clinical advice to the company and to the ERG. As noted by the company in their response, absolute rates of mortality are therefore likely to vary between the trial and clinical practice; however the ERG consider this to also be the case for other outcomes in the trial, since differences in baseline risk for mortality are likely to reflect that the trial population is a different population, with a different prognosis.

While the company state in their response that caplacizumab would be even more beneficial amongst a population with a higher baseline risk, the ERG are not aware of any empirical evidence supporting this. Clinical advice to the ERG on this was also conflicting. The ERG therefore consider this to not yet be established. The company further state that "*There is consensus across the clinical community that the clinical benefits shown in the caplacizumab data would translate to longer-term benefits based on biological rationale.*". Clinical advisors to the ERG agree that there is biological plausibility for a reduced risk of long-term complications from caplacizumab, although the ERG did not consider the company to have presented evidence of "*consensus across the clinical community*". The ERG stress that there is no empirical evidence to support the presence or size of an association between use of caplacizumab and long-term benefits; this was a key area of uncertainty highlighted in the ERG report.

Issue 2: Concomitant treatments received in the caplacizumab arm in HERCULES may not be consistent with either the comparator arm or clinical practice

The company notes, and the ERG agree, that rituximab is not a comparator for caplacizumab in aTTP, including because these drugs have different purposes related to their different mechanisms for action. However, it remains unclear when rituximab is stopped as part of acute treatment, and how this relates to rituximab initiation during remission; that is, is there a treatment holiday?

The company suggests that rituximab is used during remission when there is some evidence of impending relapse via falling ADAMTS13 activity. This coincides with clinical advice received by the ERG.

The company has not presented any high-quality evidence in relation to the effectiveness of rituximab, drawing on two case series to support improvements in expected outcomes. While noting the poor-quality evidence used to support the effectiveness of rituximab, the ERG notes that this is a common issue with this relatively rare disease, and the effectiveness of rituximab was not taken to be an issue by clinical advice contained in the original ERG report.

The company agrees with the ERG's original assertion that more people with aTTP receive rituximab than in the trial, but go on to note that the lower use of rituximab would not substantially impact trial results. As commented by the ERG in their original report, this statement is not clearly evidenced, especially if lower use of rituximab reflected earlier stabilisation and response, or if worse outcomes accrued due to lower rituximab use. Thus, it is unclear that the higher level of rituximab in the comparator arm is in fact a bias against caplacizumab, or independent of the study drug, as the company asserts. It is possible, however, that assuming RTX improves outcomes, effectiveness will be different in the trial population than would be seen in UK practice. In sum, the ERG regards this as a continuing area of uncertainty that has not been clearly resolved by the TE process.

Issue 3: Protocol violations in HERCULES may affect reliability of the trial

The ERG agree with the company that protocol violations may be inevitable events within trials conducted in emergency medicine, and are not necessarily a result of poor practice. However, despite this, it is the case that protocol violations can affect the reliability of trial data. This may particularly be the case where violations involve enrolment of patients not meeting the selection

criteria and deviation in the delivery of treatment, as were present in the HERCULES trial. In their response, the company provided a table with some key baseline characteristics for those who had a protocol violation compared to the full trial sample. The ERG reproduce this table below (), adapted to include categorical data calculated for those who did not experience a violation in each trial arm, and also for the full sample of those with and without a protocol deviation irrespective of trial arm.

Table 1), adapted to include categorical data calculated for those who did not experience a violation in each trial arm, and also for the full sample of those with and without a protocol deviation irrespective of trial arm.

Table 1: Baseline characteristics of participants in caplacizumab trials

	HERCULES All patients		HERCULES (no violation; each treatment arm)*		HERCULES (major protocol deviation; each treatment arm)		HERCULES (no violation; arms combined)*	HERCULES (violation; arms combined)*
	CAPLA (n=72)	**PBO (n=73)**	**CAPLA (n=41)**	**PBO (n=40)**	**CAPLA (n=64)**	**PBO (n=33)**	**ITT population n=81**	**ITT population n=97**
Mean age, years (range)	45 (18-77)	47 (21-79)	Not calculable	Not calculable	Not calculable	[redacted]	Not calculable	Not calculable
Gender, female n (%)	49 (68)	51 (70)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race, n (%) White Black Asian	 47 (65) 15 (21) 4 (6)	 50 (68) 13 (18) 0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI, mean (range)	30 (18-53)	30 (19-59)	Not calculable	Not calculable	[redacted]	[redacted]	Not calculable	Not calculable

	HERCULES All patients		HERCULES (no violation; each treatment arm)*		HERCULES (major protocol deviation; each treatment arm)		HERCULES (no violation; arms combined)*	HERCULES (violation; arms combined)*
	CAPLA (n=72)	**PBO (n=73)**	**CAPLA (n=41)**	**PBO (n=40)**	**CAPLA (n=64)**	**PBO (n=33)**	**ITT population n=81**	**ITT population n=97**
Median platelet count, per mm^3 (range)	24,000 (3,000-119,000)	25,000 (9,000-133,000)	Not calculable	Not calculable	[redacted]	[redacted]	Not calculable	Not calculable
TTP episode, n (%) Initial Recurrent	48 (67) 24 (33)	34 (47) 39 (53)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADAMTS13 activity, n (%) <10% ≥10%	58 (81) 13 (18)	65 (89) 7 (10)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median cTnI, ug/L (range)	0.09 (0.01-75.96)	0.07 (0.01-7.28)	Not calculable	Not calculable	[redacted]	[redacted]	Not calculable	Not calculable

	HERCULES All patients		HERCULES (no violation; each treatment arm)*		HERCULES (major protocol deviation; each treatment arm)		HERCULES (no violation; arms combined)*	HERCULES (violation; arms combined)*
	CAPLA (n=72)	**PBO (n=73)**	**CAPLA (n=41)**	**PBO (n=40)**	**CAPLA (n=64)**	**PBO (n=33)**	**ITT population n=81**	**ITT population n=97**
Median LDH, U/L (range)	449 (120-2,525)	403 (151-3,343)	Not calculable	Not calculable	[redacted]	[redacted]	Not calculable	Not calculable
Median serum creatinine, umol/L (range)	77 (35-717)	82 (52-482)	Not calculable	Not calculable	[redacted]	[redacted]	Not calculable	Not calculable

Key: BMI, body mass index; CAPLA, caplacizumab; cTnI, cardiac troponin I; LDH, lactate dehydrogenase; TTP, thrombotic thrombocytopenic purpura

Notes: *Calculated by the ERG. ^ These percentages to do correspond to the figures presented, and therefore the ERG are uncertain about these figures, and those calculated by the ERG using them. ≠Reproduced from the company's table.

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In their response, the company did not comment on the data they provided, but the ERG considered the data to show that those who had a protocol violation (across both trial arms) were more likely to be male, and more likely to be experiencing their first episode of aTTP. [redacted] who did not experience a violation. Across both trial arms, there was no clear difference in whether ADAMTS was above or below 10%; however, [redacted] respectively; although the ERG note some errors in the company reporting of this data, and so cannot be sure of the reliability of these figures). As the data was not provided, the ERG could not evaluate whether there were difference between those who did and did not experience a violation on the other prognostic markers at baseline (including platelet count and median LDH).

As protocol deviations such as those occurring in the HECULES trial are largely driven by human decisions, it is highly likely that at least some of these decisions will have been influenced by patient characteristics. As such, the presence of some differences, as reported above, are unsurprising. In the case of the HERCULES trial, based on the data provided, it is not possible for the ERG to determine a significant, consistent bias in the effect of protocol deviations on trial outcomes, and therefore the potential effect of protocol deviations on trial outcomes in HERCULES therefore remains uncertain.

Issue 4: HERCULES trial data does not suggest that caplacizumab reduces mortality or cognitive or neuropsychological impairment in the short term

The ERG agree with the company that within the short follow-up period of HERCULES, it was not possible to meaningfully evaluate cognitive or neuropsychological impairment. In their response, the company report a numerical difference in mortality, though the ERG note that the company do not report that 1 death did occur in the caplacizumab arm during follow-up (CS, document B, p.53). As there were 3 deaths in the SoC arm, the ERG calculated a risk ratio (RR) of 0.34 for mortality (95% CI 0.04, 3.22). Due to the low mortality rate in both arms of the trial, there is a high degree of uncertainty about this finding, which is demonstrated in the wide 95% confidence intervals around the effect. As acknowledged by the company, these mortality rates

were considered not to represent UK clinical practice. Due to limitations in the trial evidence for short-term mortality, the company referred to other sources of evidence. The ERG appraisal of the available sources of evidence for mortality is provided for Issue 5. The ERG agree with the company that faster resolution of platelet count may be associated with the risk of acute mortality. However, the company have not provided evidence that a difference of 4.6 hours in time to platelet response could lead to a difference in clinical outcome. As noted by the ERG in their report, this is a key area of uncertainty.

Issue 5: A naive comparison of observational data from two different sources (used by the company to model mortality in the short term with caplacizumab compared with standard care) is not robust

Do the real-world data sources reflect UK clinical practice/ people with aTTP in England?

The company present information from 1) the UK aTTP registry, 2) an international compassionate use scheme treated with caplacizumab, 3) a SLR of acute mortality in aTTP patients, and 4) an unpublished matched cohort study.

The ERG believes that, though the sources are relevant, limitations in background information make it difficult to fully appraise their correspondence to acute mortality in the UK setting. In particular the ERG notes potential ambiguities and sources of bias in the compassionate use program (details below) including unknown follow-up periods, unclear recruitment process, and that it draws from an international population.

The ERG would anticipate that the UK registry data presented better reflects UK practice than the international data presented in the compassionate use scheme. However it is not clear to the ERG whether the UK registry data excludes those data used in the compassionate use scheme (as implied by CS doc B p67). The follow-up period for deaths in the registry is also not clear, in particular whether these are deaths in the acute setting only. From the registry data, the company report two mortality risks of [redacted] for those treated within 48 hours and [redacted] for those treated within 7 days. The ERG notes that the source document also presents a total of [redacted] when including those treated after 7 days. The ERG is not aware of any information presented to indicate a plausible pattern of treatment delays in the UK setting which could be linked to these mortality risks.

The compassionate use data is an international dataset and so may not closely reflect UK practice. The company points out that under the programme there is an atypical delay in obtaining treatment, and that 'requests are individual', which appears to indicate some selective recruitment. Patient characteristics are not well understood since the information is largely inaccessible. The compassionate use programme has no set follow-up period and information on deaths is derived from the adverse event reports only (company clarification to A14 and A15), so the ERG believes the recorded deaths may not be restricted to the acute period.

The SLR collates mortality information over the acute phase (defined as 15 days of treatment) from a variety of studies. There is a high degree of heterogeneity between studies (population, outcome definition, treatment strategy and methodological quality) (ERG report p90). Furthermore, there were no particular restrictions to UK practice.

With respect to the newly submitted information from the French cohort study, since the study is only published in an abstract form which the ERG could not locate, the ERG can only note that it appears to loosely corroborate UK and SLR evidence. For example, the ERG does not have information to interpret the comparator ('historical practice'), does not know the follow-up period for mortality outcomes, nor have any background information on severity of cases.

Does the real-world data (naïve comparison) give a robust estimate of survival and the treatment effect of caplacizumab during the acute phase?

The company submission divides caplacizumab acute mortality of 4.28% (from compassionate use study) by 13.2% mortality (from SLR) to give a risk ratio of 0.32 (CS doc B, table 22). An updated mortality from compassionate use of 3.77% is used in the Technical Engagement response. Given that available trial data is not typical of the UK (see Issue 5c and Issue 1), the company used observational figures for short term mortality in their base case. Estimates of uncertainty of the risks (and uncertainty in the resultant risk ratio) are not available.

The ERG stresses that naïve comparisons across studies such as this are at particular risk of selection bias, allowing differences between the characteristics of the comparison groups other than caplacizumab. For example, patient characteristics may differ between the comparison groups because of dissimilar recruitment processes, but there is limited scope and data to examine this. The SLR restricted mortality data to the acute period, defined as 15 days of treatment, while the compassionate use data has no set follow-up period (see Issue 5a), so the comparison appears to be made between different and indistinct time-points.

The ERG notes that estimates from the SLR source, selected to represent SoC in the comparison, appear to correspond with the company's clinical advisors' estimates. The company indicate that the compassionate use programme estimates selected to represent caplacizumab in the comparison are, if anything, too high.

While the newly-presented French matched cohort study improves on a naïve comparison because it is a comparative study, it does not provide robust evidence because inter alia it lacks the randomisation design to balance the characteristics (measured and unmeasured) of the groups being compared. The abstracted information made available from the study will not provide sufficient information for full appraisal, for example allowing a comparison of known baseline information between the two groups.

The ERG notes the availability of multiple sources of observational information entails subjectivity in the selection of the sources for use in a quantitative comparison. In this instance, compassionate use and SLR data were used quantitatively, while UK registry data and matched cohort study were not.

What is the most plausible estimate, real world naïve comparison or trial, for the effect of caplacizumab on survival during the acute phase?

The ERG believes that naïve comparisons do not provide dependable estimates, and in this particular case the accompanying information required to appraise a naïve comparison is limited (as discussed in the response to Issues 5a and 5b). Trial (RCT) information is preferred as trials ensure fair and unbiased comparison and estimates have quantified uncertainty, but in this particular case the rarity of the condition and outcome lead to low precision from the trial data (see below), and the primary trial (HERCULES) was carried out in an atypical setting (in specialist centres after PEX commenced). Moreover, the naïve comparisons, either as presented or as used in the modelling, do not use any method to improve causal inference, such as weighting, matching, etc.

The ERG notes that effect sizes from trials (risk ratios, hazard ratios etc.) can remain valid even when absolute event rates may vary. In the present context, this means the estimated efficacy of caplacizumab from the trial may be plausible even in another setting with a differing baseline mortality. The ERG agrees with the company that acute mortality will be higher in a real world UK setting as many patients will present to non-specialist centres (ERG report p95). To reflect mortality over the entire acute setting the effect of caplacizumab treatment provided by the trial

must be combined with information on mortality prior to the trial setting (before the initiation of PEX).

Mortality information from the relevant trials is limited: mortality was a component of a secondary composite outcome in HERCULES and an adverse event in TITAN, so the data obtained are sparse, which has consequences for trial analysis and interpretation (see below). Confidence intervals when obtained will be wide (but this is appropriate as it reflects the sparsity of the data).

Available trial data for acute mortality are shown in Table 2, including from TITAN. The ERG reiterates that numerous trial quality issues attending TITAN must be balanced against the increased value of further information when data is sparse.

Table 2. Trial deaths recorded (HERCULES or HERCULES/TITAN combined), with associated risk estimates and confidence intervals (calculated by the ERG).

Data	Follow-up	CAPLA	Risk estimate (95% CL)	SoC	Risk estimate (95% CL)
HERCULES	Treatment period [a] only	0/72	0 (0 to 0.04) [c]	3/73	0.04 (0.01 to 0.11)
	Treatment and follow-up [b]	1/72	0.01 (0.0004 to 0.075)	3/73	0.04 (0.01 to 0.11)
Pooled HERCULES/ TITAN	Treatment period[a] only	0/108	0 (0 to 0.03) [c]	4/112	0.04 (0.01 to 0.09)
	Treatment and follow-up [b]	1/108	0.01 (0.0002 to 0.05)	5/112	0.05 (0.02 to 0.10)

[a] daily PEX, 30 days post daily-PEX and in HERCULES up to 28 days treatment extension

[b] follow-up was 28 or 30 days after the end of study drug treatment in the two trials

[c] approximate upper 95% CL calculated using 'rule of three'

The preferred approach to estimation of survival at the timepoint of interest (the end of follow-up) would be taken from the Kaplan-Meier curve, which takes account of censoring, but the data here are too sparse for this approach. A statistical comparison of the proportion of deaths in the pooled HERCULES/TITAN data over the treatment period only has been made by the company (response to Issue 5a) and appears to be a chi-squared analysis without continuity correction giving a p-value of [redacted]. The ERG believes that with such sparse data this comparison should have been made with Fisher's exact test, and there is no evidence of a significant difference in

mortality under this test (p=[redacted]), which reflects the limited data and that, as stated by the company, the trial was not powered for this outcome.

Mortality in the treatment period arguably aligns with acute/ short-term mortality. The estimated risk ratio for the pooled trial data in the treatment period is 0 but confidence intervals cannot be obtained by the standard approximation. The ERG notes that under circumstances with zero events in one arm, other trials have obtained CLs by Bayesian methods.

A risk ratio obtained from the entire trial follow-up for primary and secondary outcomes (this includes 28 or 30 days after end of drug treatment) calculated by the ERG is 0.21 (95% CLs 0.03 to 1.75). This figure is fairly close to the risk ratio used in the base case (see Issue 5b), though it may be argued is derived from information incorporating some follow-up beyond the acute period.

The ERG believes that these trial-based risk ratios are important and plausible estimates of the effect of caplacizumab on acute mortality in specialist centres once PEX has commenced, and the uncertainty they carry is properly expressed in wide CLs (where computable). In the real world setting these would ideally be combined with further mortality that occurs in the acute phase prior to PEX including in non-specialist centres, but this information has not been presented. However, this needs to be balanced against the quantity of information provided by the existing approach, and thus the ERG has not sought to alter the risk ratio for short-term mortality. In the event, risk ratios between sources as estimated appear to broadly agree, though the ERG acknowledges that this parameter is one of the most important to variation in the ICER.

Issue 6: There are no data available to test whether caplacizumab reduces mortality or cognitive or neuropsychological impairment in the long term

There are no long-term data on the effectiveness of caplacizumab. The ERG consider that evidence from the post-HERCULES trial, currently underway, will therefore be crucial for understanding whether treatment with caplacizumab has any impact on long-term mortality, cognitive or neuropsychological impairment.

Following advice from clinical experts, the ERG agree that it is biologically plausible that a person in remission following caplacizumab may have a lower risk of long-term mortality, and of poor long-term cognitive or neuropsychological outcomes, than a patient treated using standard

care. If caplacizumab limits the damage to organs caused during an acute TTP episode, for example by resolving platelet count faster, then these organs may continue to function at a higher level in the long-term. caplacizumab resolved patients' platelet count a mean of 4.6 hours earlier than placebo. It is possible that this timeframe is enough to cause sufficient benefit to translate into long-term gains, though this has not been demonstrated empirically. Further, it needs to be considered whether any such an effect would continue for patients who continue to experience multiple acute TTP episodes in their lifetime. In the CS, the company use time in hospital/ICU as a surrogate for the damage of the acute TTP episode on the body. Based on clinical advice, the ERG agree that there is biological plausibility that time in hospital/ICU may be associated with the risk of long-term adverse outcomes, although again there is no empirical evidence for this. Estimates of relative risk for long-term outcomes are based on conjecture only, and therefore the existence and size of any possible effect remains highly uncertain.

Issue 7: The relationship between hospital stays and risk of cognitive impairment, neuropsychological impairment or death in the long term has not been validated

As discussed above, the systematic review conducted by the company did not identify any evidence to validate a relationship between hospital/ICU stay and risk of long-term complications. As noted by the company in their response, there are studies in other populations that report an association between ICU/hospital stay and long-term outcomes; although these studies do not appear to have been identified using systematic methods, and so the ERG is unable to ascertain if the effects reported are reliable.

It is unclear whether the rates of mortality in remission and of cognitive and neuropsychological impairment used in the standard care arm of the company's model reflect the expected rates for people have standard care in UK clinical practice. In order to support the rates of cognitive and neuropsychological impairments used in their model, in their response, the company report the findings of an online, cross-sectional survey conducted with 50 patients and 10 carers, recruited via the TTP network in the UK. This survey collected information across a range of validated patient-reported outcomes (PROs), including two validated questionnaires measuring cognition (the short form of the Cognitive Function Abilities (v6a) measure from the Patient Reported Outcome Measurement Information System (PROMIS)) and anxiety and depression (the Hospital Anxiety and Depression Scale (HADS)).

To explore the proportion of patients with aTTP who experience cognitive difficulties while in remission, the company cite results from the Cognitive Function Abilities scale, which is a 6-item measure that assesses a person's perceptions of their concentration, thinking, memory, and 'sharpness' of mind over the previous week (e.g. "I have been able to keep track of what I am doing, even if I am interrupted").

[redacted]

This figure is difficult to interpret, since the report provided by the company does not state whether the general population in the USA used for comparison was matched for demographic characteristics, such as age. It is also important to note that this measure is not intended to assess for the presence of 'clinically significant' cognitive impairments; i.e. those that impact meaningfully on a person's HRQoL, including those that require additional support or medical care. It was not possible for the ERG to validate the proportion of patients with cognitive impairment used in the standard care arm of the company's model with this data, since the company do not report the proportion of patients who reported cognitive difficulties on the scale. In addition to the findings from the Cognitive Function Abilities scale, the company cite a statistic in their response that

[redacted]. This figure is based on patients' responses to a single question that was included in the questionnaire as part of a battery of 'bespoke' questions. These questions asked patients about various possible impacts of aTTP on their lives. However, the ERG note that these do not appear to have been validated in any sample, and it's not clear whether this question can accurately, and adequately, measure the cognitive impairment that may be experienced by patients with aTTP. Therefore, the ERG did not consider this statistic to provide any validation of the proportion used in the company's model. In sum, the ERG did not believe that the proportion of patients with cognitive impairment used for the standard care arm in the company's model have been validated in technical engagement.

To validate the proportion of patients with neuropsychological impairment, in their response the company report that

[redacted] as assessed using the HADS questionnaire, Moreover, the company present findings from the SF-36, which includes (individual and summary) domains to assess for the presence of emotional or mental health difficulties that may impact on wellbeing and functioning. The findings showed that patients with aTTP reported poorer scores on these domains as compared to a 'general

population' from the USA. The ERG agree with the company that these data support that many patients with aTTP may experience symptoms of anxiety and depression, and that these difficulties may significantly impact on their HRQoL. The figures suggest that the proportion of patients with aTTP who experience long-term neuropsychological impairments in both arms of the trial (36.84% and 23.02% for standard care and caplacizumab, respectively) may be underestimates. However, the ERG note that these scales are not diagnostic tools for depressive or anxiety disorders. Accounting for the incidence of symptoms of depression and anxiety that do not meet the criteria for a mental health diagnosis, the true rate of anxiety and depressive disorders may therefore be lower than the figures reported in the survey. Following advice from clinical experts, the ERG noted in their report that the proportions of patients with long-term neuropsychological impairment used in the company model may be underestimates. Accordingly, in the ERG's preferred basecase, the proportion of patients who would receive psychological therapy or counselling was increased to 100%, and the proportion of patients who would receive antidepressants was increased to 50%. These changes were found to have little impact on the ICER.

Is the ERG's approach of assuming that the potential treatment effect of caplacizumab on mortality in remission is greater than the treatment effect of caplacizumab on neuropsychological or cognitive impairment plausible?

The ERG regarded that this was a plausible assumption because of the mechanism of action of caplacizumab and its place in the treatment pathway. Given that patients often already accrue significant harm as a result of thrombi in aTTP even before treatment, the ERG believed that an impact on long-term complications would likely be less than an impact on mortality, including where the mortality impact was due to early and more effective management of the disease. We acknowledge that this, along with many other inputs to the model in the long-term phase, is an assumption.

Issue 8: The utility values in the model do not come from trial data and utility associated with long term complications of aTTP is based on other conditions

For the acute episode, utility estimates were not available. The Company conducted an SLR to identify health-related quality of life and utility estimates specific to aTTP, but none were identified. The ERG concurred with the Company that this was likely due to the fact that it was likely not possible to collect data from patients as they would typically present with severe disease. Given the paucity of data identified for the acute episode, the company asked clinicians

to suggest proxy conditions for which HRQoL may be representative of an acute aTTP episode. Proxy conditions suggested included: severe brain injury; cerebral vein thrombosis; sepsis (young patients without comorbidities); Guillain Barré syndrome; meningitis; patients in critical care or ICU. Multipliers for acute hospitalisation (0.64) and post-hospital discharge (0.82) were applied based on a study by Pappas et al. (2018)[32] of intracranial haemorrhage and ischaemic stroke. The ERG agreed with the use of a proxy condition in the absence of estimates within the aTTP population. The ERG reiterated that the face validity of the estimates and the data source but were unable to reconstruct the chain of inference that yielded these multipliers.

In the TE response, the company compared modelled utility with the mean utility from the survey: for acute episode within a year the modelled utility was [redacted] vs the mean utility in the survey of [redacted].While this gives some confidence in the modelled utility, the ERG note limitations in the survey data Section 3.1.

The ERG does not anticipate any significant differences between the quality of life of people in the US with aTTP and the quality of life of epople in the UK with aTTP.

Are the neuropsychological impairments experienced with aTTP similar to those experienced by people with depressive disorder?

In its response to technical engagement the company presented data from the aTTP quality of life study. The study presented by the company is a UK based, non-interventional, cross-sectional survey that collected quantitative data on the HRQoL of people with aTTP (n=50) and carers (n=10). Data were reported directly by all participants. Data for this study were collected using a close-ended, online survey designed to capture HRQoL and health outcomes in patients with aTTP and in carers of patients with aTTP. The survey has been appraised in Section 3.1. The ERG considered that despite limitations also acknowledged by the company the data were insightful in respect of a meaningful impact on the lives of patients and carers. In terms of the impact on patients, the company highlighted that [redacted] worried about relapse with [redacted] of patients worrying very much. In addition, statements from members of the patient support group, TTP network, are presented by the company which indicate what it is like to live with the condition and the impact on carers in which the fear of relapse is also presented.

The company presented a targeted literature review to ascertain health state utility values associated with fear of relapse. This TLR used a limited and non-reproducible search that did not include any academic databases. The proxy conditions used to understand disutility associated with fear of relapse were, as with other targeted literature reviews used in the

original submission, seemingly arbitrary and inconsistent with proxy conditions used elsewhere in this particular appraisal.

The findings of the TLR did not include any studies relevant to aTTP, instead locating one study on venom anaphylaxis, two on diabetes and two on fear of falling in older adults. The estimate of disutility associated with fear of recurrence varied substantially between studies, from 0.33 0.021. Studies were appraised using a scheme that was not presented. The company posited that the highest quality studies suggested a disutility of 0.05. While the ERG regarded that the judgement of which studies were the highest quality had face validity, the generalizability of the chosen disutility value was unclear as the value was the midpoint of disutilities from both fear of falling and fear of recurrence related to venom anaphylaxis.

The company then asserted that the degree to which an intervention would reduce the disutility arising from fear of relapse was a different question, but no TLR was presented for this nor a reference provided to suggest how an intervention would reduce disutility from fear of relapse. This compounds the uncertainty arising in this aspect of the cost-effectiveness modelling.

Is the quality of life of people caring for people with aTTP expected to be similar to people caring for people with stroke?

The ERG recognised the paucity of data reporting the utility impact for carers of aTTP survivors. The ERH noted that in the main submission, the company described identification of a systematic review including studies of utilities for informal caregivers for patients with stroke. The company referenced an advisory board report in which clinicians had considered stroke to be a good proxy for the worst forms of cognitive impairment. The ERG concurred with the company's assumption regarding the use of stroke as a proxy in the absence of population-specific data; however, was unable to validate the utility estimate cited as the company did not reference the systematic review, or document the process for identifying included studies specified.

In its response to technical engagement, the company referenced new data which provided quality of life data for carers of patients with aTTP (n=10) (see above), in which a high proportion [redacted] reported general impairment in non-work related activities and an overall loss in work productivity, impact on overall daily life [redacted], sex life ([redacted]) and finances ([redacted]), and 90% worried about the patient they cared for having another episode of aTTP. The ERG noted that while these population-relevant data suggest a meaningful HRQoL decrement for carers which suggested assumptions made in the original company submission may be conservative in

that the model currently assumes an impact for carers of patients with the worst forms of cognitive impairment. The ERG also notes limitations of the survey (refer to Section 3.1), in particular a small sample comprising 10 carers.

Issue 9: The relapse rate modelled by the company of 1% is uncertain

The company included an annual relapse rate of 1% in the model. This estimate was based on clinical input that "true relapse" is rare in UK practice due to "proactive monitoring and pre-emptive treatment with RTX". This was in accordance with clinical advice provided to the ERG. The company comment that over the lifetime of the model this equates to a relapse rate of approximately 16% which they compared to UK data reported in Shin et al. (2019)[2] – 19%.

Shin et al. (2019)[2], report data from the UK aTTP Registry (January 2009 to 2018), Out of a total of 564 recorded episodes, 475 were acute presentations (first diagnosis or relapse), with a relapse rate in immune-mediated TTP of 19%. The company highlight a difference in treatment suggesting that this rate may indeeed be higher.The ERG also noted that this publication is available only in abstract format and a full publication was not available. In addition, the company commented that 10% of patients would relapse at some point in their lifetime.

The ERG reflected that although the relapse rate is uncertain it is broadly aligned with clinical opinion – as given to the ERG, to the company, and to NICE, and the limited clinical evidence available taking into account the changes in rituximab treatment protocols noted by the company.The ERG identified relapse rate as one of the key drivers of cost-effectiveness. The ERG tested the assumption in its scenario analyses by assuming a higher relapse rate of 5% (testing limits of reasonable assumptions).

Issue 10: Have all potential costs that may be offset by using caplacizumab, and the wider benefits of reducing use of a blood product, been accounted for in the model?

Will reducing the volumes of a blood product for plasma exchange have a wider impact (besides the costs of giving the infusion itself)?

The Company report that anecdotal evidence suggests an impact on reduced plasma requirements from caplacizumab and the benefit to patients but no data to quantify the impact has been presented.

Would needing a lower volume of plasma reduce the likelihood of any PEX related complications?

Clinical advice to the company indicates that PEX can lead to serious complication but no data or literature sources to quantify this effect is provided

Are there any issues with the availability of plasma for PEX in clinical practice?

No response to this specific question was provided. However, in their response the company notes that 25% of plasma used in the NHS is for aTTP patients.

Would a shorter time to platelet normalisation observed with caplacizumab be expected to also mean that people treated with caplacizumab have fewer doses of rituximab in clinical practice?

The company state that caplacizumab and rituximab are initiated concurrently and have different modes of action. Based on clinical evidence the ERG agrees with this assertion.

Will reducing the volumes of a blood product for plasma exchange have a wider impact (besides the costs of giving the infusion itself)?

The company asserts it will have an impact. As noted above, aTTP patients account for a high proportion of plasma usage in the UK. The usage of caplacizumab should free up plasma for other uses.

Issue 11: The company base case is over £30,000 per QALY gained

Is there reason to consider an ICER of above £30,000 per QALY gained a cost-effective use of NHS resources?

The ERG understand that NICE considered this prior to the ERG's appraisal of the evidence, and concluded that caplacizumab did not meet criteria to be considered within the Highly Specialised Technology program.

Are there any benefits of caplacizumab that the company have not included in its modelling?

The company argue that fear of relapse has a large impact on quality of life and should be included in the modelling. They commissioned a literature review to attempt to quantify its potential impact. According to the company, modelling the effect of fear to relapse led to a reduction in the ICER of up to 15%. However, the figures applied to the model (a disutility of 0.05 coupled with an improvement of 25% following intervention) were derived from proxy conditions, hence their validity could be questioned. It is also unclear whether these values were applied to all patients. Furthermore, the ERG also considered that fear of relapse could have

already been considered in the model as included in the remission utility estimate from the Burns et al study. Further critique of the company's TLR on fear of relapse is provided in Section **Error! Reference source not found.**.

The company also argue that reduced ICU stay, reduced plasma requirements, and reduced organ damage from reduced exposure to micro-thrombi should be considered but could not be modelled. The ERG considered that the opportunity cost of reductions in ICU stay or plasma requirements will have an opportunity cost, albeit this has not been quantified. The impact of additional organ damage may be included in the mortality reduction, but additional impact on mortality will not have been captured. However, this effect has not been quantified nor literature sources provided.

Have the benefits of reduced use of blood products (which are a limited resource) been captured?

The company and ERG agree this has not been captured in the model. No new evidence has been presented to quantify this impact.

Issue 12: Caplacizumab may be an innovative technology

Are there any benefits not captured by QALY calculation?

The ERG agrees with the company that there are further potential benefits from this technology, including reduced ICU stay, reduced plasma requirements and reduced exposure to micro-thrombi as stated in Issue 11. However, these benefits have not been quantified and thus are not captured in the model.ERG CRITIQUE OF ADDITIONAL EVIDENCE

3.1. Patient-reported outcome (PRO) data for patients and carers

The company provided the fndings of a survey administered to 50 patients with aTTP and 10 carers. This included outcomes of measures assessing patients' experience of cognitive and neuropsychological difficulties, which have been appraised by the ERG for Issue 7. In addition to this data, the survey provided further data on HRQoL and the impact of aTTP on work for patients, and on the burden and impact of caring for someone with aTTP on work for carers (Issue 8).

The ERG considered the assessment of HRQoL in patients with aTTP and their carers to be important for understanding the potential benefits of treatment with caplacizumab. As the evidence presented is from a cross-sectional survey, conducted only with patients who had not

received caplacizumab, there is still not evidence for the potential impact of caplacizumab on the HRQoL of patients or carers.

The ERG considered that the survey was informative for understanding some of the impacts of aTTP on the lives of patients and carers. While the company note that the sample included in the survey may not be representative of UK patients and carers (and the sample was small, particularly for carers), the evidence presented suggests that patients with aTTP may experience meaningful deficits in their HRQoL, and that both patients and carers experience a negative impact on their ability to work. Carers also reported experiencing burden from caring, though the ERG note that the tool used by the company to evaluate burden does not provide thresholds for understanding how scores translate to carers' lives, and therefore is difficult to interpret. As noted above, the ERG did not consider the findings from the company's 'bespoke' questions to be informative, as these are close-ended, subject to bias, and do not appear to have been validated in any sample.

In sum, the evidence presented by the company speaks to a need for an effective treatment to improve the lives of patients and carers, though it remains unclear whether caplacizumab is able to do this.

4. REFERENCES

1. Burns D, Lee D, Vesely S, George J, Cerdobbel A, De Naeyer L, et al. Patient health-related quality of life associated with remission of aTTP. A regression analysis using non-randomised observational data from the Oklahoma TTP registry. ISPOR; 10-14 November 2018; Barcelona: Spain; 2018.

2. Shin JS, Alwan F, Austin S, Crowley M, Dutt T, Clark A, et al. Thrombotic thrombocytopenic purpura: demographic analysis of the UK TTP registry from 2009 to 2018. British Society for Haematology 59th Annual Scientific Meeting 1-3 April; Glasgow: Scotland; 2019.