NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Caplacizumab with plasma exchange and immunosuppression for treating acute acquired thrombotic thrombocytopenic purpura [ID1185]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Caplacizumab with plasma exchange and immunosuppression for treating acute acquired thrombotic thrombocytopenic purpura [ID1185]

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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

SingleTechnology Appraisal

Caplacizumab with plasma exchange and immunosuppression for treating acute acquired thrombotic thrombocytopenic purpura

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Consultee	Comment [sic]	Response

Sanofi	Sanofi are encouraged to see that the appraisal consultation document (ACD) recognises that aTTP is a life-threatening, stressful condition associated with long-term morbidity and mortality. We are pleased that the committee concluded that caplacizumab was clinically effective versus standard of care and that they agreed caplacizumab is an innovative medicine. We were disappointed however that the committee felt unable to recommend caplacizumab at this stage despite being presented with an ICER below £30,000/QALY. Sanofi are committed to securing access to caplacizumab through a positive NICE recommendation as soon as possible but acknowledge the committees concerns regarding the level of uncertainty in the cost-effectiveness analyses. Given the rarity of aTTP and the existing evidence base, it is impossible to eliminate all uncertainty, however Sanofi propose 2 options to the committee to help mitigate the existing decision uncertainty. 1. An additional discount (equating to a discount of [redacted] discount from the list price) is proposed were caplacizumab to be recommended for routine commissioning. At this revised PAS price caplacizumab can be considered cost-effective under more conservative assumptions. The revised base case analysis provided within this response reports an ICER of £20,300/QALY using credible assumptions. This should provide reassurance to the committee and aligns with comments in the ACD and from the methods guide that state where plausible ICERs are above £20,000 the degree of certainty in those ICER estimates should be taken into account. This is the simplest, fastest route to achieve access for patients involving minimum burden for all parties. 2. If, however the committee feel unable to recommend caplacizumab for routine commissioning Sanofi would be willing to consider a managed access arrangement, as suggested in the ACD, to collect further data on caplacizumab that will reduce the existing level of uncertainty. Discussions with NICE and NHS England are ongoing. We are mindful however that this may delay access to caplacizumab in the short term given there is no standard process for agreeing an MAA outside of the CDF and HST programme. Our response is structured around the key uncertainties identified by the committee and in summary includes: 1. Updated evidence to inform acute mortality estimates 2. New evidence to inform rates of long-term complications and mortality	Summary of company response noted. Individual comments are addressed as they are raised.

Consultee	Comment [sic]	Response
	3. Discussion of the available evidence to inform quality of life estimates including fear of relapse 4. A revised base case (incorporating revised PAS discount) 5. Scenario analyses as requested by the committee	

Sanofi	• Sanofi acknowledges the committee's concerns with the use of observational data and naïve comparison in the company submission (CS). However, we consider that the substantial amount of available evidence from the clinical trial programme, UK registry, compassionate use scheme and French matched-cohort analysis prove that caplacizumab reduces mortality [compared to standard of care (SoC)] during an acute episode of aTTP. This view is supported by clinical experts consulted prior to the submission, during the technical engagement meeting and at the first ACM. We therefore consider that it is inappropriate to explore scenarios in which no effect of caplacizumab on acute mortality is assumed. • A summary of trial and real-world evidence of caplacizumab's benefit on acute mortality is provided below. **HERCULES data and integrated HERCULES/TITAN analysis** • Sanofi would like to reiterate that in the phase III HERCULES trial, there were no deaths among patients randomised to caplacizumab during the study drug treatment period arm; compared to 3 deaths in the standard of care (SoC) arm. There was 1 death in the caplacizumab arm during the follow-up period). In the phase II TITAN trial, no patient died in the caplacizumab group, versus 2 in placebo. One death in the placebo arm occurred outside the placebo treatment period. • An integrated analysis of the Phase II TITAN and HERCULES trials to assess treatment differences that may have gone undetected in individual trials, was conducted to assess the efficacy and safety of caplacizumab in aTTP. Caplacizumab also significantly reduced deaths (0 vs 4; [redacted]) during the blinded treatment period. This integrated analysis confirms the individual trial results and provides further evidence that caplacizumab has the potential to reduce mortality in aTTP patients. • In its response to Sanofi's response to the technical engagement report, the ERG, stated that "the statistical comparison of the proportion of deaths in the pooled HERCULES/TITAN data over the treatment period only has been made by the company and appears to be a chi-squared analysis without continuity correction giving a p-value of 0.047." The ERG also stated that "with such sparse data this comparison should have been made with Fisher's exact test" which resulted in a non-significant difference in mortality (p=0.12), reflecting the limited data and the fact that the trial was not powered for this outcome (as acknowledged by the ERG). A risk ratio obtained from the entire trial follow-up for primary and secondary outcomes (this	The committee's deliberations of acute mortality estimates on caplacizumab compared with standard care are discussed in sections 3.11 and 3.12 of the Final Appraisal Determination.

	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 close to the risk ratio used in Sanofi's base case (0.29). **UK real-world data** • UK registry data (obtained by clinicians) on acute mortality among aTTP patients who received caplacizumab (as part of the compassionate use scheme) shows the acute mortality rate among those who received caplacizumab within 48 hours of first PEX (as per SmPC) to be lower compared to those who received caplacizumab more than 48 hours after first PEX; [redacted] respectively. Forty-eight hours is a considerably longer time period than mandated in the HERCULES protocol - to start caplacizumab within 24 hours of the first PEX delivered on-study - and results primarily from access issues due to caplacizumab not being available routinely on-site in the treating centre. • In the UK registry data, the median time taken for patients to receive the first dose of caplacizumab (as part of the compassionate use programme) after initiation of plasma exchange (PEX) for aTTP was [redacted] days (range [redacted] days); and [redacted] (n=[redacted]) of patients received caplacizumab within 7 days of starting PEX • The impact of this on mortality can be seen in the dataset; mortality is lower when caplacizumab is given earlier. Furthermore, as highlighted in paragraph 3.5 of the ACD, clinicians would administer caplacizumab within the same day as plasma exchange is initiated. As such, Sanofi would consider outcomes among those who received caplacizumab more than 48 hours after PEX ([redacted] to be comparable to the most likely acute mortality in the absence of caplacizumab. • In addition to the acute mortality rate, the UK data also provided characteristics of UK patients enrolled in the compassionate use programme. The mean age of patients treated was [redacted] years, (range [redacted] – [redacted] years) and [redacted] (n=[redacted]) cases were female, reflecting the female to male predominance reported in aTTP; [redacted] (n=[redacted]) 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 highlighting the generalisability of the mortality data from HERCULES to expected UK practice if caplacizumab were to be recommended. **French Matched Cohort Analyses** During Technical Engagement, Sanofi presented a draft abstract of a French matched-cohort analysis based upon the temporary authorization scheme for caplacizumab use which has been	

Consultee	Comment [sic]	Response
	running since September 2018. The final analysis by a consortium of French clinicians, which has now been submitted to a leading medical journal for peer review compares [redacted] historical patients matched in terms of severity and treated according to the historical practice to [redacted] aTTP patients treated first line with caplacizumab, PEX and rituximab. Acute mortality in the caplacizumab regimen was [redacted] compared to [redacted]) in the historical cohort. Please note that the mortality has changed from the draft abstract.	

Consultee	Comment [sic]	Response
	Use of observational data • Clinical experts advised that mortality in HERCULES was much lower than expected in UK clinical practice (both for caplacizumab and placebo groups). 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). Clinicians stated that a mortality of 13.2% for SOC, based on a meta-analysis of literature sources, was a more realistic estimate. This figure was validated by alternative estimates taken from sources authored by expert clinicians that estimated acute mortality on SoC of between 13-15%. • For caplacizumab, Sanofi used real-world data on acute mortality derived from the compassionate use program [3.77% (9/239)] in the base case. 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 routinely available on site in hospitals treating aTTP. As such, the mortality estimates from the compassionate programme are conservative to caplacizumab. This interpretation was supported by clinicians on validation calls and on the technical engagement call. • 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 thus reducing delays. The data originally provided, covering period up to 30 September 2019, indicated a mortality rate of 4.3% (8/187). The latest data indicate (as of February 2020) 9 deaths out of 239 patients (3.77%). • Regarding the size of the association between treatment with caplacizumab and acute mortality, Sanofi believes the relative effect estimates from the clinical trial programme are generalisable to the real-world setting. This has been substantiated by the ERG who, in their review of Sanofi's response to the technical engagement report, noted that "the estimated efficacy of caplacizumab from the trial may be plausible even in another setting with a differing baseline mortality" (Pages 16 of ERG response to company TE response) **We therefore consider the most robust source of relative treatment effect to be the caplacizumab clinical trials; 0.21 (95% CLs 0.03 to 1.75) as calculated by the ERG. This is consistent with the RR used in the original submission (0.29).**	

Sanofi	**Meta-analysis of SoC** • As mentioned above Sanofi used a mortality rate of 13.2% in the original submission based on a global systematic literature review (SLR) and meta-analysis of available literature in TTP patients on standard of care. This figure was validated by UK 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%. • To address the committee's recommendation that the meta-analysis should reflect current UK practice using studies from the UK only, or those most relevant to UK clinical practice, an assessment of the most appropriate UK sources was conducted. As the search dates of the previous SLR only included studies up until 16th March 2017, a further basic search of studies for mortality in aTTP patients was conducted using PubMed on 1st June 2020 restricted to studies published 2017 onwards. Search terms were (mortality) AND (acquired thrombotic thrombocytopenia purpura). • Seven studies were identified from the original SLR that were specific to the UK. In addition to the meta-analysis, a further two sources, authored by clinical experts, were cited in the company submission, as highlighted by clinical experts and through communications with NICE.[8, 9]These sources were not picked up in the original SLR as the only source searched was MEDLINE – via PubMed. • A further 33 publications were identified in the updated search. However, except for the clinical trial publications for caplacizumab, no further studies were identified that were UK-specific. Therefore, the existing evidence base of nine studies was considered comprehensive, in the context of the limited search terms and sources searched. Summaries of patient/study characteristics and outcomes for all studies are presented in **Error! Reference source not found.** and **Error! Reference source not found.** respectively (Appendix 1). • Seven of the nine UK-specific studies identified were based on data from the UK TTP registry/South East England TTP registry or conducted at University College London Hospitals (UCLH), a global leader in aTTP management. Professor Marie Scully, who was one of the clinical experts in attendance at the Appraisal Committee meeting, was primary author or co-author on all of these studies. For the remaining two studies, one was an analysis of ONS/HES statistics, and the other did not specify the data source. • As per the inclusion criteria of the original SLR, all patients were suffering with acute TTP. Scully et al. (2014) only considered outcomes in pregnant women, and Patriquin et al. only considered bortezomib treatment in severe or refractory disease. Therefore these two studies were considered less reflective of UK clinical practice and were excluded from further	The committee's deliberations of acute mortality on standard care are described in section 3.10 of the Final Appraisal Determination.

	consideration. Most patients in the remaining studies had acquired or idiopathic TTP (confirmed by low ADAMSTS13 activity) with various expected comorbidities such as HIV; therefore, the remaining studies were deemed relevant to the decision problem. • The seven remaining studies varied according to dates conducted, however in most of the older studies, patients were treated with experimental rituximab, therefore the relevance to current practice was considered to be high. Caplacizumab was not mentioned in any of the included studies. Across all studies, median/mean age and female:male ratio closely mirrored UK expectations; patients were relatively young (~40s) and there was a greater proportion of female patients. This is also in line with the HERCULES trial. • Mortality across the seven remaining studies ranged from 5.8% to 15%. We are unclear as to the methods used by NICE to derive the 7% estimate noted in the ACD, however, when we assessed the data, naïve pooling of patient numbers and event numbers was considered inappropriate due to the high probability of overlap between sources. There is, therefore, a significant risk of double counting as the majority of studies were conducted on UK registry patients at around the same time. • Majority of data in the UK registry is from UCLH which is a specialised centre regarded as having the best outcomes for TTP patients across the UK and is recognised globally as a centre of excellence. It is therefore unsurprising that mortality for the studies from the registry and UCLH are at the lower end of this scale. Outcomes for aTTP patients who are treated in UCLH are most likely not generalisable to those for aTTP patients in the rest of the country**.** • All mortality estimates based on registry data should be interpreted as a conservative estimate of mortality for patients on SoC in the UK. As discussed in Section A.9 (Document A) of the Company Submission; patients were often not consented to the aTTP registry (and similar UCLH analyses) if the outcome was death. This was because it is often considered inappropriate to ask family members to consent to the deceased patient's inclusion. Furthermore, the study by Lester et al. explains how mortality across England is highly heterogenous and varies between 8% and 20%. This is further substantiated in paragraph 3.4 of the ACD where it is states that the estimates of death rates were 10% to 20% in non-specialist centres and less than 5% in specialist centres. **We therefore consider the Lester et al. study, which is one of the more recent publications and covers the whole of the UK to be the most generalisable (mortality rate 12.6%). This study is therefore used in the revised base case analysis presented in this response. A rate of 7% which may be more reflective of mortality in specialist centres is explored in scenario analyses (**Error! Reference source not found. **of Appendix 1) but this does not have a significant impact on the base case ICER.**	

Consultee	Comment [sic]	Response
Sanofi	**Adjustment for confounding** • An adjusted indirect comparison between the compassionate use data collected for caplacizumab and data on real-world mortality with SoC is not possible because Sanofi do not have access to the data on patient characteristics within the compassionate use programme; the sole exception to this is information on adverse events of which mortality is clearly a constituent. • Limited data has become available since the submission via the UK registry on the characteristics of UK patients enrolled in the programme (See comment 2 above). The demographics are very similar to HERCULES. The median time taken for patients to receive the first dose of caplacizumab after initiation of plasma exchange (PEX) for aTTP was [redacted] days (range [redacted] days), and [redacted] (n=[redacted]) of patients received caplacizumab within [redacted] 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). Our ability to conduct a matching analysis between the compassionate use data and the available data for SoC was considered with the new availability of this data. Unfortunately, data are only available to Sanofi from the publication and not in a patient level data format which precludes the use of methods such as MAIC as data is not available to Sanofi in a patient level format for SoC either. Furthermore, Sanofi believes that conducting a MAIC is unlikely to be that informative given the limited number of covariates available and that they are similar.	Comments and new data noted.
Sanofi	**Validation of acute mortality** Sanofi validated assumption on acute mortality during an advisory board and clinical validation meetings. Clinical opinion suggested that overall mortality for the acute episode (13.2%, as reported in a meta-analysis of studies identified in the literature) is generalisable to the UK. 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 neither appropriate nor realistic).	Comment noted.

Consultee	Comment [sic]	Response
Sanofi	**Acute mortality summary** • The ERG notes that effect sizes from trials (risk ratios, hazard ratios etc.) can remain valid even when absolute event rates may vary. 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 Sanofi 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). 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). • **The base case has been revised to use an acute mortality rate of 12.6% (based on Lester et al) for SoC given that this is the estimate that is most generalisable to the whole of the UK and for caplacizumab, 2.65% based on applying a RR of 0.21 taken from the clinical trial program as the most robust data source.** Alternative estimates of acute mortality are provided in **Error! Reference source not found.** of Appendix 1.	Summary noted. The committee's preferred assumptions in the acute sub-model are described in section 3.20 of the Final Appraisal Determination.
Sanofi	• Sanofi acknowledges the committee's concerns with the lack of evidence on long-term effects of caplacizumab. Given the rarity of the disease and the fact that until recently, management has focussed solely on ensuring survival during an acute episode, it is not surprising that there is a lack of data on long-term outcomes. Nonetheless, Sanofi has systematically searched for and included all available relevant evidence and sought clinical opinion to substantiate all assumptions made in the CS. Below, we summarise the available evidence, assumptions made and their validation. We also present results of the recommendations made by the committee in the ACD.	Comment noted.

Sanofi	**Prevalence of long-term complications in people with aTTP (on SOC)** • Sanofi conducted an SLR on the clinical burden of disease in aTTP. A number of studies were identified that reported multiple long-term complications following an acute episode of aTTP. These conditions include cognitive impairment, neuro-psychological impairment, headache, hypertension, chronic kidney disease, stroke and an increased risk of premature death. A number of studies identified in an SLR on the clinical burden of disease also indicate the presence of persistent cognitive impairment in remission, with abnormalities found upon magnetic resonance imaging (MRI) scans. • Two studies cited in the SLR were used to estimate the baseline risk of cognitive impairment. Kennedy et al. reported the proportion of patients experiencing mild impairment (54.2%) and moderate to severe impairment (20.8%) Cataland et al (2011), reported 63% of patients had cognitive impairment. While Kennedy et al. reported cognitive functions among patients who were enrolled in the Oklahoma TTP registry, Cataland et al. included patients with a history of idiopathic TTP from existing patient cohorts at both the Ohio State University (n = 12) and the University College London Hospitals (n = 15). 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 • The proportion of individuals with neuropsychological impairment was taken from Chaturvedi et al. (2017) who reported depression in 36.8% and PTSD in 35.1% of aTTP survivors using two validated questionnaires. The ERG was satisfied that this data source was the best available given its sample size (n=236). 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. Alternative scenarios were presented using higher and lower proportions of neuro-psychological impairment. • For long-term mortality, a number of literature sources report reduced life expectancy in aTTP patients compared to general population. Two publications, Deford et al., 2013 (n =70) and Upreti et al., 2019 (n =170) were used to estimate the increase in mortality of an aTTP population. Deford et al. and Upreti et al. compare mortality based on Oklahoma registry data and John Hopkins Hospital aTTP patients respectively with matched general population mortality. Standardised mortality ratios of 7.8 and 8.3 relative to the general population were calculated for both sources respectively. Upreti et al. was chosen for the model due to it being	The company's discussion of the available data on prevalence of long-term complications is noted. The committee's deliberation on the studies presented by the company are described in section 3.14 of the Final Appraisal Determination.

Consultee	Comment [sic]	Response
	a more recent source. The ERG concluded that *"both sources provide plausible estimates of long-term mortality after aTTP, drawing on several years of follow-up data per patient."* • Since submission, new data from a Sanofi funded and initiated non-interventional, cross-sectional study investigating the quality of life of UK aTTP patients (n=50) and carers (n=10) has become available. The study concluded that survivors of aTTP appeared to report worse cognitive dysfunction than the UK general population. These patients also seem to experience moderate levels of both anxiety and depression. Based on this study, the rates of cognitive impairment assumed within the model appear reasonable as the majority of patients state that they have not been able to put their thoughts into words without extra effort (88%) and the PROMIS score indicated cognitive function abilities one standard deviation lower than the U.S. average. (See Appendix 2: Quality of life study report - Sections 4.1.4 and 4.1.6.1) • Based upon the quality of life impact study conducted the rates of neuropsychological impairment used in the standard care arm of the model appear low as the majority of patients reported moderate or severe symptoms on the HADS anxiety and depression scales (72% and 84%) and the Mental Health (MH) domain on the SF-36 was well below the UK norm. Additionally, scores did not vary much between the acute patients (an episode within the last year) and non-acute patients indicating that the duration of impact may have been underestimated. Finally, the majority of patients (84%) reported feeling 'quite a bit' or 'very much' worried about having another aTTP episode which illustrates the ongoing impact on patients' lives of fear of recurrence. (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 **Error! Reference source not found.** of Appendix 1. • Sanofi conducted validation teleconferences (TCs) with clinical experts who confirmed 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. 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.	

Sanofi	**Platelet count as a surrogate measure for long-term outcomes** • Sanofi recognises the committee's position that platelet count could be a surrogate measure for more meaningful outcomes reflecting morbidity and mortality. There is a volume of evidence showing that delay in initiating PEX adversely impacts survival and thrombotic sequelae backing up the benefit from reduced time spent in the occluded state with rapid treatment.[29] The same principle applies to the time saving that can be achieved with caplacizumab. However, the evidence available does not allow robust estimation of a surrogacy relationship between potential short-term predictors and longer-term complications (including mortality). • Clinical experts at the advisory board, technical engagement meeting and during the first ACM have affirmed that reducing the time to platelet normalisation and stable platelet counts, reduced risk of exacerbation and /or refractory disease is likely to improve outcomes for patients with aTTP. There is, therefore, extensive clinical support for a long-term treatment benefit of caplacizumab due to reduced time spent in the occluded state, However, directly quantifying this expected treatment benefit with caplacizumab is challenging, as the HERCULES trial considered the acute episode only and 26/28 patients who exacerbated on the standard of care arm received caplacizumab. Furthermore, as caplacizumab is a relatively new treatment, there is currently a lack of evidence demonstrating its long-term benefit. • In light of the above reasons, Sanofi performed a targeted literature review (TLR) to establish surrogacy relationships between HERCULES outcomes and long-term mortality and complications. No data on the relationship between the time spent at risk of microvascular thrombosis (measured by TTPN, hospitalisation/ICU/PEX days) and long-term mortality and complications were identified. The lack of data on surrogate measures in aTTP is not surprising given that until very recently, the focus of management of the condition has been on keeping patients alive in the acute phase. It was only in early 2019 that the UK TTP registry started regular follow-up and data collection at regular intervals during remission. • In addition to the TLR, clinicians were consulted on the expected improvement in long-term outcomes for patients treated with caplacizumab. At the clinical advisory board, clinicians explained that it is biologically plausible that reducing the time with active disease will benefit patients and improve long-term cognitive and neuro-psychological impairment. As a starting point for discussions on how to quantify the expected long-term improvement in the cost-effective model, proxy RRs and HRs were calculated based on HERCULES trial outcomes and presented to attending clinicians (**Error! Reference source not found.** of Appendix 1). All calculated results are in alignment and patients on caplacizumab perform better than patients	Comments noted. The committee's deliberation of platelet count as a surrogate measure for long term outcomes is described in section 3.16 of the Final Appraisal Determination

	on SoC. While emphasising uncertainty, the clinicians 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 (RR -0.62). This was based on two rationales; that quicker resolution of disease and a reduced overall time spent in the occluded state lessens the microthrombi burden, which leads to a reduction in acute organ damage with long-term consequences and, most importantly, on the rationale that the ratio of hospitalisation/ICU days was consistent with outcomes for other proxies such as TTPN and PEX days. • As discussed in the technical engagement response, a number of publications are available that suggest that the greater the time spent in ICU the greater the long-term mortality risk.[31-35] A limitation of all of these publications is that they are not specific to aTTP, so any estimates of long-term mortality will not consider the accrued organ damage through prolonged exposure to microthrombi. • Two papers that do provide some supportive evidence in aTTP patients are Rock (1991) and Liu (2013).[36, 37] The first study, Rock (1991), discussed during in the company's response to technical engagement, was an RCT comparing plasma exchange and plasma infusion in the treatment of TTP. Response was defined as a platelet count of more than 150 x 10^9/L for two consecutive days and no new neurologic events. Based on this publication, response at the end of the first treatment cycle was 47% in the plasma exchange group versus 25% in the plasma infusion group. For the patients who received plasma exchange, 22% had died by 6 months versus 37% of those who received plasma infusion. In conclusion, an 85% increase in response resulted in a 73% reduction in mortality, supporting a near 1:1 relationship. • Data from HERCULES could not be used directly to estimate long-term mortality based on Rock (1991) due to limitations in the frequency of platelet count measurements. In the daily plasma exchange period, platelet count was measured daily. However, in the post-daily plasma exchange period, only weekly measurements were taken, precluding any useful assessment of response as per the Rock (1991) criteria. Additionally the Rock paper only reports mortality per arm (and according to whether patients crossed over or not) and not by directly by response status (although it should be noted that the number of non-responders and deaths in the initial period in the plasma exchange arm is identical which is not unexpected as patients who are refractory to treatment have a very poor prognosis). Therefore, an alternative approach was required. • As reported in Table 23 of the company submission, the RR for time to platelet count response based on HERCULES (initial and exacerbation) is 0.57. Assuming that response as assessed	

in HERCULES will have a similar relationship with mortality to response assessed in Rock (1991) this was adjusted using the relationship reported in Rock (1991) as follows:

$$\frac{0.57 * 85\%}{73\%} = 0.66$$

Scenarios presented in **Error! Reference source not found.** of Appendix 1 investigate the impact of assuming an RR for long-term mortality of 0.66.

- The second study, Liu (2013), which was identified in the burden of disease SLR showed that platelet recovery rate by Day 3 is a predictor of both short term and long-term outcomes. The study showed that survival is significantly better in patients with a platelet recovery rate of >=5 x 10^9/L per 24 hours, than in patients with a platelet recovery rate below this cut off ($p < 0.001$), hazard ratio 23.2 ($p < 0.005$). In patients with a platelet recovery rate at Day 3 of <5 x 10^9/L per 24 hours, the estimated rates of survival were 74.7% at 1 month, 64.8% at 3 months, and 58.9% at 1 year, compared with an unchanged rate of 100% at all three time points in patients with a platelet recovery rate at Day 3 of >=5 x 10^9/L per 24 hours.
- To incorporate a scenario using the relationship reported by Liu (2013) into the model, data were required on the proportion of patients in each treatment arm of HERCULES who were responders (i.e. above cut-off) and non-responders (i.e. below cut-off) according to the definition in Liu (2013). This data is shown below based on a post-hoc analysis of HERCULES data.

	N	**N**	**% responders**	**% non-responders**
Responders SoC	[redacted]	[redacted]	[redacted]	[redacted]
Responders capla	[redacted]	[redacted]	[redacted]	[redacted]

- To implement the relationship reported by Liu (2013) into the model, survival curves were generated for responders and non-responders. The responder curve was assumed the same as general population survival as Liu (2013) reports survival of 100% over all time points measured.

	• To generate the non-responder curve mortality for non-responders was taken from Liu (2013). Based on the paper, survival was 64.8% at 3 months, and 58.9% at 12 months, a 5.9% difference in survival over this time frame. The non-responder curve was calibrated using Solver, via the application of an SMR (of 45.7) to the general population hazard until the difference between survival at Month 3 and Month 12 was 5.9%. • Following generation of responder and non-responder curves, the hazards were then weighted according to the proportion of responders and non-responders in each treatment arm based on HERCULES data to generate survival curves for each treatment. It is important to note that as 100% of caplacizumab patients were responders, the long-term survival for caplacizumab patients is assumed to be equal to the general population. This may be overly optimistic, thus results based on the Liu (2013) data are provided as a scenario only. • All calculations are provided in the "Long-term mortality" sheet of the updated cost effectiveness model. The user can select to apply the Liu (2013) mortality on the "Controls" sheet, G70. • Key limitations of these papers include: 1. Rock (1991): age of the study, Canadian population [although practice is not expected to be overly different to the UK], small patient numbers as would be expected given the rarity of the condition (n=51 in each arm; note to get this number of patients across 16 Canadian centres a 7 year enrolment period was required), definition of response cannot be replicated with the data collected in HERCULES 2. Liu (2013): single centre US study [although practice is not expected to be overly different to the UK and this study includes patients enrolled relatively recently; 2003 – 2010], retrospective review, excluded some deaths due to lack of response measurement, some patients with ADAMTS13 >10% included, small patient numbers as would be expected (n=64) • Despite these limitations both the Rock (1991) and Liu (2013) papers are consistent in that a link is shown between response to treatment (platelet count response) and mortality and the impact on cost-effectiveness is explored in scenario analyses. Finally, draft manuscript of the UK registry states: [redacted]	

Sanofi	**Validation of long-term outcomes** Long-term complications • 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 the brain is subjected to thrombotic assault, and that it was biologically plausible that quicker time to resolution of disease leads to lessening of the microthrombi burden. Clinicians explained that reducing a lengthy and stressful hospital or ICU stay should also result in a reduced risk of developing long-term complications. 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.[7] This is due to proactive monitoring and pre-emptive treatment with rituximab if ADAMTS13 activity falls below acceptable levels. 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. Experts at the clinical validation meeting explained that it is biologically 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. 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 thrombotic episode.	Comments on the company's validation of the long-term outcomes noted. These comments were taken into account in the committee's assessment that it was plausible that caplacizumab had long-term effects in section 3.15 of the Final Appraisal Determination

Sanofi	**Quality of life in the acute period** • In the CE model, literature values were sourced for disutility due to hospitalisations in general to explore the impact of the acute episode on quality of life. Utility values specific to patients with aTTP were not available for the acute episode as it is unethical and challenging to collect such data from patients with very severe disease. It is an extremely traumatic experience for both patients and carers; the onset is unexpected, and the treatment is unpleasant, particularly PEX. The more severely affected 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. These patients would not be able to participate in health-related quality of life (HRQL) data collection. • 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.[7] Suggestions included: o Severe brain injury o Cerebral vein thrombosis o Sepsis (young patients without comorbidities) o Guillain–Barré syndrome o Meningitis o Patients in critical care or intensive care (ICU) • To investigate the available evidence base for the listed proxy conditions, a TLR was conducted and a number of useful sources reporting EQ-5D utility scores for patients with the associated proxy conditions were identified. 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. 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 and finally, utility estimates from this study demonstrate face validity in that patient-reported quality of life is low on admission, then improved at discharge, but does not exceed quality of life estimates for remission.	Comments on quality of life in the acute period noted. The committee's deliberations on how the company estimated utility values are described in section 3.18 of the Final Appraisal Determination.

Consultee	Comment [sic]	Response
	• 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. • In the ACD, Paragraph 3.3, Page 7, the committee concluded that plasma exchange and hospital stays are unpleasant, and that people with acquired TTP would welcome a treatment that reduces these. In the ACD, Paragraph 3.16, Page 20, it noted that there were benefits which may not have been captured in the QALY calculation such as: "The effect of caplacizumab in reducing plasma exchange duration on the number of central lines replacements a patient would need, how this reduces the risk of infection and how this would affect a patient's quality of life". It is clear from patient and clinical representatives that any treatment which reduces the requirement for plasma exchange and the volume of plasma required would benefit patients greatly, and that current model approach underestimates this benefit. In light of this, the updated base case assumes that patients on SoC have half the utility of patients on caplacizumab to account for reductions in the duration and volume of plasma exchanged and reductions in associated complications such as line infections and thromboses. Alternative scenarios are presented in **Error! Reference source not found.** of Appendix 1 with little impact on model results.	

Sanofi	**Long-term quality of life** • For long-term quality of life, new data from a Sanofi initiated and funded non-interventional, cross-sectional study investigating the quality of life of UK aTTP patients (n=50) and carers (n=10) became available during the appraisal and was presented in Sanofi's technical engagement response. In this study, 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 individuals reported moderate levels of both anxiety and depression. Similarly, 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. Whilst there are limitations to the study, we do still consider this relevant as the only such evidence available for UK aTTP patients. • SF-36 data from the UK QoL study were mapped to EQ-5D using the Rowen et al. algorithm (for consistency with the analysis presented by Burns et al). The average utility for patients who had experienced an episode within the last year vs those who had experienced an episode more than a year ago is presented below. The comparison of mapped to modelled utility values, which are based on US registry analysis in aTTP patients (Burns et al.), show that the model slightly overestimates utility for patients in the first year following an acute aTTP	Comments on quality of life after the acute period are noted. The committee's deliberations on how the company estimated utility values are described in section 3.18 of the Final Appraisal Determination.

<table>
<tr><th>Consultee</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td></td><td>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.
<table>
<tr><th>Characteristic</th><th>Category</th><th>Patient numbers (n=50) [%]</th><th>Mean utility in survey</th><th>Modelled utility</th></tr>
<tr><td>Acute (episode within a year)</td><td>Yes</td><td>[redacted] ([redacted]%)</td><td>[redacted]</td><td>[redacted]</td></tr>
<tr><td></td><td>No</td><td>[redacted] ([redacted]%)</td><td>[redacted]</td><td>[redacted]</td></tr>
</table></td><td></td></tr>
<tr><td>Sanofi</td><td>Fear of relapse

• The committee noted that quality-of-life estimates for acquired TTP should include an estimate of the fear of relapse.
• Data from the aTTP quality of life study show 92% (33/36) of patients experienced flashbacks following an acute aTTP episode, and 64% (23/36) of patients reported that these were moderately to extremely severe. 96% (48/50) worry about relapse, with 52% (n = 26, N=50) worrying “very much”

The model has been revised to capture the benefits of caplacizumab in reducing the fear of relapse for patients and carers through the availability of an effective treatment.</td><td>Comments on fear of relapse noted. The committee’s deliberations on how the company estimated utility values are described in section 3.18 of the Final Appraisal Determination.</td></tr>
</table>

Sanofi	**Relapse rates** • The use of rituximab during remission has dramatically reduced the relapse rate among people who have suffered an acute episode of aTTP. This was affirmed by clinicians at the Technical Engagement meeting. During validation exercises, clinical expert opinion suggested that 10% of patients will relapse at some point during their remaining lifetime. This aligns with the estimate given on the technical engagement call (10%). • 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. Therefore, Sanofi considers 1% relapse rate a reasonable assumption due to monitoring and use of rituximab during remission. We have tested a rate of 2% in sensitivity analysis based on the Shin paper but as noted above this is an upper bound as relapse rates are expected to reduce due to more consistent use of rituximab prevent relapse in centres in England. • With regards to the committee's concerns on the effectiveness of caplacizumab on re-exposure, Sanofi can confirm that there are no data available on re-exposure to caplacizumab in patients with aTTP. All subjects who enrolled in the post-Hercules study will have access to caplacizumab in the event of relapse, however those data are not yet available. As part of the safety assessments in Hercules we investigated the development of anti-drug antibodies following exposure. Results of antibody assessments can be difficult to interpret in aTTP due to the infusion of donor plasma, which may contain cross-reacting antibodies. o Positive results for treatment-emergent anti-drug antibodies were seen in a very small minority of patients (n=4) exposed to caplacizumab, and one randomised to placebo o there was no correlation between duration of exposure to the drug and a positive anti-drug antibody test; o these antibodies did not impact pharmacokinetics of the drug, nor assessments of pharmacodynamics by RICO assessment (vWF platelet-binding activity remained fully suppressed); o there was also no effect on clinical safety (achievement of primary endpoint) or tolerability in these subjects [redacted]There is however anecdotal evidence. [redacted] [redacted]	Comments on relapse rates noted. The committee's deliberations on relapse rates are described in section 3.17 of the Final Appraisal Determination.

Consultee	Comment [sic]	Response
	[redacted] As such, Sanofi has no reason to believe the effect of caplacizumab would be different on re-exposure. The post-ACD CE model retains a relapse rate of 1% (with sensitivity analysis of 2% as the upper bound). In addition, scenarios have been presented with reduction of efficacy of caplacizumab on subsequent use.	
Sanofi	**Proportion of people with a major thromboembolic event** While the same proportion (8%) of people in both arms of HERCULES experienced a major thromboembolic event, Sanofi would like to highlight that the thrombotic process in large vessel disease is not vWF-mediated. Those clots are rich in fibrin and red cells, and the clotting is driven by thrombin. This is why LMWH is used for prophylaxis, for its anti-Xa activity, reducing thrombin generation. This has been substantiated in informal discussion with clinicians. vWF has its greatest effect in the microcirculation, and thrombi in TTP are vWF and platelet-rich, hence why the effect of caplacizumab is greatest there.	Comment noted. The company explanation is described in section 3.15 of the Final Appraisal Determination.

Consultee	Comment [sic]	Response
Sanofi	**Frequency of plasma exchange** Paragraph 3.3 states that caplacizumab "may reduce the frequency" of plasma exchange. Sanofi would like to highlight that in HERCULES, there was a statistically significant reduction in the number of days of plasma exchange therapy and the volume of plasma exchanged: 38% shorter duration of PEX therapy in the caplacizumab group compared to the placebo group and a 41% lower volume of plasma exchanged. (Ref). Therefore, caplacizumab reduces the days of PEX therapy and volume of plasma and not necessarily, the frequency of PEX.	Comments noted. The Final Appraisal Determination section 3.3 has been updated.
Sanofi	**Marketing authorisation** • Paragraph 2.1 of the ACD mentions the recent Committee for Human Medicinal Products (CHMP) adoption of a positive opinion recommending a change to the terms of the marketing authorisation for caplacizumab to include adolescents. Sanofi would like to highlight that the official adoption of the CHMP opinion by the European Commission and the Market Authorisation was received on 9th June 2020. ***Cablivi is indicated for the treatment of adults*** *and adolescents of 12 years of age and older weighing at least 40 kg* ***experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in conjunction with plasma exchange and immunosuppression.*** **"**	Noted. The recommendations cover the full population for whom caplacizumab is licensed. NHS England has a policy in which technologies recommended by NICE within specialised services for adults are also made available for younger people.

Consultee	Comment [sic]	Response
Sanofi	**Validation of assumptions** • The ACD mentions in a number of places what steps were taken to validate assumption in the CS. Sanofi sought extensive clinical input during the model conceptualisation and development process. 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 health economists not involved in the model development. **A summary of the model verification/validation is presented in** Error! Reference source not found. **of Appendix 1**	Comments noted.

Consultee	Comment [sic]	Response
Sanofi	• In light of the ACD and responses above, Sanofi has revised its base case based on the following: o Acute episode cost based on revised PAS ([redacted]) o Acute mortality ▪ SOC -12.6% (0.49/3.88) SoC ▪ Caplacizumab – 2.5% (RR 0.2 applied to caplacizumab) o Duration of depression increased in line with cognitive impairment (55 years) o Utilities in acute episode based on literature for caplacizumab, patients on SoC assumed to have half the utility of patients on caplacizumab as discussed in comment No. 11 above o Complete improvement in fear of relapse due to availability of caplacizumab • Caplacizumab is associated with 5.80 incremental life years, [redacted] incremental QALYs and incremental costs of [redacted] per patient, compared with SoC. The incremental cost-effectiveness ratio (ICER) is £20,377 per additional QALY gained. Error! Reference source not found. **in Appendix 1 presents the impact of individual changes above to the ICER.**	The committee's preferred assumptions and base case are described in sections 3.20 to 3.22 of the Final Appraisal Determination.
Sanofi	• **Error! Reference source not found.** of Appendix 1 presents a range of scenarios based on the ACD. Each scenario is varied by switching off long-term mortality benefit only (conservative scenario) and by switching off long-term benefits for mortality and complications (highly conservative scenario).	Scenarios noted.

Consultee	Comment [sic]	Response
Sanofi	• There is an acknowledgement that there is currently a large gap between the STA and HST willingness to pay thresholds and a lack of clarity regarding which medicines should be assessed via HST. Whilst we hope that this gap can be addressed via the methods review, we would ask that the committee exert some flexibility in their decision making given caplacizumab falls into this gap (it was originally scoped for HST). There is precedent for applying a modifier to the STA willingness to pay threshold in the end of life criteria, however this largely only applies to medicines for late stage cancers. There are however other types of medicines for which society would be prepared to accept a higher price and medicines for rare or particularly severe conditions such as aTTP fall into this group. Were a severity and or a rarity modifier (per ABPI proposals) to be implemented in the STA process, caplacizumab would likely be assessed at a higher cost-effectiveness threshold. Under even the most conservative assumptions (i.e. assuming no long-term benefit) the ICER for caplacizumab does not exceed £50,000/QALY. • Sanofi believe the existing PAS (submitted at technical engagement) would provide caplacizumab at a net price to the NHS that is considerably lower than would be expected for this type of medicine (given its assessment via STA and not HST) and that this doesn't reflect the significant value offered by this innovative therapy. However, given our commitment to securing access for patients to caplacizumab Sanofi have offered a further level of discount in an attempt to de-risk a committee decision for routine commissioning. It is also important to note that given the rarity of aTTP and that this is a clearly defined patient population, the overall budgetary impact of introducing caplacizumab will be small, again minimising the risk associated with a positive recommendation. **Sanofi would encourage the appraisal committee to reconsider their preliminary decision in the context of the additional discount and revised analyses that have been presented and the considerable unmet need for this very rare but particularly severe condition.**	During the topic selection process, it was decided that evaluation of caplacizumab through the Technology Appraisals programme was appropriate. The Appraisal Committee can only make decisions in accordance with the methods of the technology appraisals programme.
TTPNetwork	As the leading patient group for people with a TTP diagnosis we are concerned that the Committee has not understood the clear and present danger of blood clots circulating the body during the crisis phase of the disorder. Until such time as the platelet count is back within the normal range, clots will form and circulate in the brain and vital organs. On current treatments alone, every single day until normalized platelets is critical to the long term health of the patient.	Comments noted.

Consultee	Comment [sic]	Response
TTPNetwork	We believe that as a patient group with an ultra-rare blood disorder we are being disadvantaged because we do not believe the Committee had the experience to review a technology designed for such a rare condition (we revert to our opinion that a HST would have been a more appropriate assessment tool). We also fear for the Afro-Caribbean members of our patient community who are disproportionately affected by TTP. This decision causes their healthcare needs to be once again side-lined, in a system that already causes healthcare disadvantage for the BAME community. This is discrimination, when the technology is proven to work in the real world.	During the topic selection process, it was decided that evaluation of caplacizumab through the Technology Appraisals programme was appropriate. The Appraisal Committee can only make decisions in accordance with the methods of the technology appraisals programme. The comments on potential equality issues were discussed by the appraisal committee over the course of the appraisal.
TTPNetwork	We know that at the best treatment centres, Caplacizumab is being used as part of the standard treatment of care because Consultant Haematologists know patients will have a better outcome with its use, and it is morally and ethically wrong not to give Caplacizumab when a patient would benefit from it. This evidence should help inform any decision about authorising its use via the NHS. It's imperative that this technology is included in the Treatment Specification for the soon to be commissioned Specialist Treatment Centres, in order to give patients the best level of care and hope of returning to a near normal personal and work life. Below, please find comments from patients/their family members- some of whom tried to comment via your website portal but were unable to do so.	Comments noted.

Consultee	Comment [sic]	Response
TTPNetwork	I am writing on behalf of my daughter who was recently diagnosed with TTP – April 2020. She was 16 at the time. Her plasma level was at 7 and her condition was extremely acute. She had immediate danger of heart attack, stroke or death. Luckily, she was treated with Caplacizumab and she only needed 5 plasma exchanges. We were able to go home within the week, which bearing in mind we were in the middle of a pandemic with its own risks, was extremely important. We were shown how to self-inject and carried on the procedure for a further month at home. 3 months on, she is probably as far on as we could possibly hope. She is a keen golfer and is out playing 4 or 5 times a week, which when you look back to 1 April was something that you could only hope and pray for. **The treatment was invaluable in allowing my daughter to return to a near normal lifestyle extremely quickly. I would urge Nice to ensure that this drug is available to others.**	Thank you for sharing this patient experience. The benefit of caplacizumab in reducing plasma exchanges was noted to be of importance to patients in section 3.3 if the Final Appraisal Determination
TTPNetwork	I am a 67Year old retired nurse recovering from my first episode of TTP. I was admitted to hospital on 5th May and discharged on 13th May 2020, on Caplacizumab. I completed the course on 6th June but as my Adamst13 was only 3% on 10th June my consultant prescribed a further 25-day course of Caplacizumab to give oral immunosuppressants to be effective. If the Caplacizumab resulted in a shorter hospital stay, less plasma exchanges and reduced risk of my suffering long term neurological damage, strokes or even death then it is a valuable treatment. I appreciate this treatment may be very expensive but so are plasma exchanges, longer hospital stays, rehabilitation following strokes and or organ damage caused by clots. Caplacizumab is apparently the biggest breakthrough in the treatment of TTP for 30 years, and I count myself lucky to have been able to avail myself of this treatment and hope that others diagnosed in the future will be able to benefit.	Thank you for sharing this patient experience. The benefit of caplacizumab in reducing plasma exchanges was noted to be of importance to patients in section 3.3 of the Final Appraisal Determination. The innovative nature of the technology was taken into account in the committee's decision making (section 3.21 of the Final Appraisal Determination)

Consultee	Comment [sic]	Response
TTPNetwork	As a patient treated for acute TTP in 2017, before Caplacizumab became available, I feel very lucky to have made it through. I spent 9 days in the ICU at UCLH under Professor Marie Scully and had countless plasma transfusions in order to try and get my platelets to a normal level. All of those 9 days were spent in a critical condition, and I was lucky enough not to suffer any serious strokes or organ damage by the end of it. The length of time spent in ICU has significant effects on the life of not only the patient but the extended family too. And as with my own experience, the longer you are in the ICU, the longer you are in an acute critical condition. I have listened very carefully to Professor Scully discuss the beneficial effects of this drug on current TTP patients and the fact that it has now been the standard of care for the last 2 years. It reduces the number of plasma exchanges needed, increases the blood platelet numbers more quickly and therefore shortens the time spent in acute condition in the ICU. Prof. Scully and her colleagues around the world do so much to forward the research on this deadly disease, but as we are such a small cohort of TTP patients it is very difficult just to keep us alive, let alone get large quantities of data on the long-term efficacy of drugs used to treat us. Suffice to say that the short-term efficacy of Caplacizumab is such that we DO NOT DIE. Long-term data will only come if we are kept alive long enough to provide it. At one time or another nearly all TTP patients relapse, and I very much hope that if and when I relapse – and with my current number trend it could be as soon as 3 month – I will be fortunate enough to be treated by Professor Scully and her fantastic team, to whom I owe my life, with Caplacizumab.	Thank you for sharing this patient experience. Reducing time in intensive care was one of the aspects taken into account when committee determined that caplacizumab was an innovative treatment (section 3.21).

Consultee	Comment [sic]	Response
TTPNetwork	I am appealing to NICE to give Caplacizumab a place in treating TTP patients. We go through very traumatic plasma exchanges, to have a chance to cut down on the amount of treatments we have would be so much easier to cope with. I had 10 plasma exchange so if I had the choice, I would opt for Caplacizumab, so I didn't have to have so many. It also helps platelets recover more quickly which has got to be good for our brains and vital organs. Once I was diagnosed, I was in hospital for a week on plasma exchange and then had 3 treatments as an outpatient. If we can go home sooner it helps our mental and emotional torment that we go through with this devastating disease. I have read about Caplacizumab and heard about how it saves lives, simply because of cutting the time it takes to get us in a safe zone more quickly. I wouldn't hesitate to have Caplacizumab. We as patients need something to hope for and Caplacizumab is certainly that. It is the best breakthrough we have had for TTP treatment. Please make this available for us because if I relapsed I would be asking for Caplacizumab because when you are clinging onto life it is so important to know there is a treatment that could improve my chance of survival.	Thank you for sharing this patient experience. The benefit of caplacizumab in reducing plasma exchanges was noted to be of importance to patients in section 3.3 if the Final Appraisal Determination

Consultee	Comment [sic]	Response
TTPNetwork	Having arrived in the Intensive Care Unit with platelets at level 6 and Adamst13 at 0 and having my life's blood exchanged with plasma for 3 to 4 hours twice a day I thought my life was over and that there was no hope. Having such a rare blood disorder and not knowing the cause is truly frightening and it comes with the fear that it could happen again. But I was given, what I consider a lifeline, Caplacizumab. Knowing it was developed for acute TTP with the aim of raising my platelet levels and to help prevent relapses and the need for future plasma exchanges certainly made my future seem a bit brighter. It is ten months since my first acute TTP episode and Caplacizumab was part of my treatment. My platelets levels rose and have remain at my normal level for 10 months as have all the other blood components including Adamts13 and hence no relapses. I have had no side-effects. I have been able to return to work and a normal life. I find it almost unbelievable. Therefore, I would highly recommend and support the use of Caplacizumab for use in acute stage of TTP. It is a lifeline that's gives us, the patients, hope that we can achieve a better outcome from a rare blood disorder that at one time (and not too long ago) had limited treatment and a high risk of death. Caplacizumab has been a major step in the treatment of TTP. To lose such a wonder drug from the NHS that could benefit a small group of people with a very rare and life-threatening disease would be catastrophic. To summarise, Caplacizumab enables the less time spent in Intensive care, less plasma exchanges, faster normalising and stabilising of platelet levels, less time in hospital, and the chance of returning to some level of a normal life. Caplacizumab must be retained as treatment for TTP within the NHS.	Thank you for sharing this patient experience. The benefit of caplacizumab in reducing plasma exchanges was noted to be of importance to patients in section 3.3 if the Final Appraisal Determination. Reducing time in intensive care was one of the aspects taken into account when committee determined that caplacizumab was an innovative treatment (section 3.21).
TTPNetwork	This treatment is instrumental in thrombotic thrombocytopenic purpura, it's a drug that has & will save life, I feel we are at a severe disadvantage as this disease is extremely rare. This treatment shortens patients stay battling this illness in hospital which no doubt improves the patients Physiological Health & recovery. We are being discriminated against, thrombotic thrombocytopenic purpura is a rare & life-threatening illness therefore only very limited people can trial, as a patient with this illness should I relapse absolutely id expect to be able to access this drug. It's in our basic Human Rights's to be able to access the best treatment and for us with TTP this is without a doubt Caplacizumab, NICE should not use this process as a tick box exercise, TTP is a rare & life threatening disorder & we deserve the best treatment, I genuinely feel we are being discriminated against, as we are unable to test this on a vast patient base.	Thank you for sharing this patient experience. The committee took into account that much of the data limitations were because aTTP is a rare condition (Final Appraisal Consultation).

Consultee	Comment [sic]	Response
TTPNetwork	In summary, though we and our patient community are incredibly disappointed with the NICE Committee decision, we seek a positive way forward to enable patients to continue to receive this technology whilst the required evidence is gathered to satisfy NICE of its effectiveness. To that end, we would urge NICE, NHSE and Sanofi to come to a Managed Access Agreement as soon as possible but with some urgency, and furthermore we, TTPNetwork as the leading UK TTP patient group for the past 23yrs, must be involved in this discussion just as other Patient Advocacy Groups are, in other Managed Access Agreements.	Comments noted. Since the first meeting the recommendation was changed and caplacizumab will be available through routine commissioning.

Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
Prof Marie Scully	Age should not be a consideration-the presence of antibody TTP requires treating with caplacuzimab to aid time to clinical remission	Comment noted. The recommendation applies to the whole population covered by the marketing authorisation for caplacizumab

Nominating organisation	Comment [sic]	Response
Prof Marie Scully	[Comments on the draft recommendation in the Appraisal Consultation Document] TTP is an ultra rare, acute life threatening disorder and the process would have fit better within the highly specialised route, but did not meet the requirements as a chronic disease. The remit for TTP has been survival through the acute episode given the high mortality even following diagnosis and treatment. The long term effects of disease are increasingly recognised as important but the literature base is sparse. The presentation for NICE approval was based on an international randomised controlled study (HERCULES) and outcomes relating to acute disease. Longer term outcomes were not captured. They will however, be available following analysis of the post HERCULES data. Further data will be required from all TTP patients in the UK, via the uK TTP regisdtry, which can be captured, but this will take time to mature ie years. The data presented is from the HERCULES study but also international real world data from the company's patient access scheme, which includes the UK cases. Also submitted to NICE was the UCLH data set of consecutive patients treated with caplacizumab in contrast to consecutive patients treated following the same protocol, but without caplacuzimab. From all of these data sets, the benefit of caplacuzimab is clear. In summary, the improved time to platelet normalisation, significant reduction in the exacerbation rate and refractory disease. The mortality rate in all data sets is favourable to caplacuzimab. But there are some assumptions in the NICE recommendation and from the ERG report that would suggest otherwise that require re-discussion. Long term data and modelled scenarios are a necessary accompaniment to the application as required for the process but clinically this the data is not satisfactorily available.	Comments noted. The data limitations have been noted in the Final Appraisal Determination.

Nominating organisation	Comment [sic]	Response
Prof Marie Scully	[Comment on text on page 5 of the Appraisal Consultation Document] "*imbalances in the proportion of people who had rituximab between the arms of the HERCULES trial would not be expected to have a large effect on the cost-effectiveness estimates (issue 2, see technical report page 27)* *protocol violations in HERCULES would not be expected to have a large effect on the cost-effectiveness estimates (issue 3, see technical report page 29)".* As discussed in the committee meeting, all UK patients in the study received rituximab. The impact of rituximab is not comparable to caplacuzimab as they target completely different areas of the treatment pathway. Protocol violations: this is an acute and complex disease	Comments noted. These potential issues identified at the technical engagement stage were not key issues in the committee's decision making.
Prof Marie Scully	Comment on text on page 9 of the Appraisal Consultation Document "*some of their patients have had caplacizumab for the last 2 years via a global compassionate use scheme*" Patients have NOT had caplacuzimab for 2 years. The patient access scheme has been opened for 2 years, but patients receive treatment for a maximum of 60 days as per the Smpc	Comment noted. This sentence has been updated to: since 2018, some patients under her care have had caplacizumab via a global compassionate use scheme

Nominating organisation	Comment [sic]	Response
	Comment on subheading on page 9 of the Appraisal Consultation Document *"The outcomes in HERCULES are clinically relevant, but do not test for short- or long-term morbidity or mortality"* Short term morbidity and mortality ie during an acute TTP episode to the point of complete remission were measured within HERCULES. Data on long term morbidity and mortality will be addressed in the post HERCULES study	Comment noted.
Prof Marie Scully	Comment on text on page 9 of the Appraisal Consultation document *"However, people must have also stopped plasma exchange within 5 days of their platelet counts returning to normal* " *This is not correct. Patients continued plasma exchange until the platelet count is in the normal range and for 48 hours after. 5 days relates to the time at which patients who do not normalise their platelet count are defined as refractory TTP.*	This text has been deleted in the Final Appraisal Determination.

Nominating organisation	Comment [sic]	Response
Prof Marie Scully	Comment on text on page 9 of the Appraisl Consultation Document *"The committee heard about (but did not see) evidence that the faster the platelet count is normalised, the lower the risk of complications".* Complications related to acute TTP including mortality are based on time to platelet normalisation. Exacerbations and refractory disease and morbidity and mortality result in longer hospital admissions, more treatments and an understanding of the underlying pathophysiology of TTP. That is platelet microthrombi and organ damage. There are many publications describing this but it does require an inference of understanding the pathology of the disease	Comment noted. This sentence has been updated to: the committee heard that the faster the platelet count in normalised, the lower the risk of complications. In response to the appraisal consultation document the company provided some studies supporting an association between quicker time to platelet normalisation and reduced death in the longer term. No data showing an association between microthrombi and organ damage were presented to the committee.
Prof Marie Scully	Comment on text on page 9 of the Appraisal Consultation Document *"Other secondary outcomes such as volume and duration of plasma exchange, time in hospital or intensive care, and death were not tested statistically".* *Within the HERCULES data set, there was a clear statistical difference in these measures between placebo and caplacuzimab arms for these specific parameters.*	Comment noted. This section was referring to the pre-specified statistical tests in the HERCULES statistical analysis plan

Nominating organisation	Comment [sic]	Response
Prof Marie Scully	Comment on text on pages 10,11 of the Appraisal Consultation Document "*The committee concluded that the primary surrogate and the secondary outcomes in HERCULES were clinically relevant. However, it noted that the trial did not measure the effect of caplacizumab on survival, quality of life, disability or mental health in the long term*. "*One clinical experts explained that she had seen a similar reduction in number of plasma exchanges and hospital stay with caplacizumab when using caplacizumab through the compassionate use programme in her centre".* *"The committee concluded that caplacizumab is clinically effective in the acute period compared with standard of care alone".* *"However, it concluded that the size of this reduction was unlikely to be as large as that estimated from unadjusted observational analyses, and remained uncertain"*. The committee have accepted the HERCULES data set and the UK data as comparable and already commented that it is clinically effective. This last statement appears contradictory.	Comments noted. The last quoted statement refers to the comparison of data for caplacizumab (from the global compassionate use scheme) with data for standard care which came from a meta-analysis of international studies rather than HERCULES or the clinical expert's experience of using caplacizumab in her centre in the UK.

Nominating organisation	Comment [sic]	Response
Prof Marie Scully	Comments on text on page 15 of the Appraisal Consultation Document *"In the long term, there is no evidence that caplacizumab reduces the risk of complications"* *"the company assumed that time in intensive care or hospital was causally related to the prevalence of long-term outcomes including cognitive impairment and mental health (including depression, anxiety, post-traumatic stress), and the relative risk of death"* *"The committee noted that a relationship between length of stay and the development of subsequent complications had not been validated"* *An explanation about long term data has already been commented on. The impact of ICU stay and depression, anxiety and PTSD is well described (1800 references on Pubmed in the last 10 years, the 1st one was:* *Crit Care 2018 Nov 23;22(1):310.* ***Anxiety, Depression and Post Traumatic Stress Disorder After Critical Illness: A UK-wide Prospective Cohort Study*** *Robert Hatch[1 2], Duncan Young[3 2], Vicki Barber[4], John Griffiths[5], David A Harrison[6], Peter Watkinson* Other groups aside from the Oklahoma registry have described the impact of TTP and depression, anxiety and PTSD, This is clinically recognised and the reason the presence of a clinical psychologist is part of the national TTP service specification.	Comments noted. The statements in the Appraisal Consultation Document were specific to the lack of evidence for the exact relationship between time in hospital or intensive care for aTTP and the risk of long-term complications. At the second meeting the committee considered that using time to platelet normalisation was a better surrogate outcome for estimating how well caplacizumab could prevent long term complications than time in hospital/intensive care. See sections 3.15 and 3.16 of the Final Appraisal Determination.

Nominating organisation	Comment [sic]	Response
Prof Marie Scully	Comment on text on page 15 of the Appraisal Consultation Document *It recalled that the same proportion of people in each arm of HERCULES developed a major thromboembolic complication during short-term follow up in this trial.* The risk of VTE was comparable between placebo and caplacuzimab. This is unsurprising and in an international study, thromboprophylaxis is not SOC in most centres. TTP carries a number of risk factors, increased weight, prolonged immobility. Caplacuzimab is associated with severe reduction in VWF and a potential risk of bleeding-which was not severe. The study provided important information re the need to consider thromboprophylaxis, even when receiving caplacuzimab.	Comment noted. The Final Appraisal Determination also notes the company comment that major thromboembolic events would not capture differences in microvascular damage between caplacizumab and standard care.

Nominating organisation	Comment [sic]	Response
Prof Marie Scully	Comment on text on pages 16 and 20 of the Appraisal Consultation Document *"Modelled rate of relapse is low, and it is uncertain whether caplacizumab works equally well when reused"* *"Caplacizumab is innovative but the extent to which it is a step change in treatment remains unclear"* "*the committee thought the extent to which it is a step change in the treatment of acquired TTP was unclear because of the uncertainty about its effect on overall survival and long-term complications*" While the long term impact of acute TTP episodes is an important area for ongoing research, there is no dispute clinically the major advance of caplacuzimab in acute TTP. It is standard of care with plasma exchange and immunosuppression (steroids, rituximab). The impact on patient care is highly significant re time to platelet count normalisation and improvement in clinical symptoms	Comment noted
Prof Marie Scully	Comment on text on page 21 of the Appraisal Consultation Document *"The committee concluded that the feasibility of a managed access agreement should be explored using the committees preferred assumptions around modelling"* This idea would be welcomed to meet the committees requirement for long term impact following acute TTP.	Comment noted. In the Final Appraisal Determination the committee were able to recommend caplacizumab within routine commissioning

Nominating organisation	Comment [sic]	Response
Dr Will Lester	I'm concerned that the innovative nature of this treatment is not fully appreciated. It does not impact on ADAMTS13 and its inhibition however it is the first licensed drug which inhibits VWF-platelet binding which is the cause of microvascular ischaemia in TTP. Although there is insufficient direct evidence of long term benefits (as this is a new drug) the HERCULES trial does show a clear reduction in the number of ITU days (which in turn directly reflects improvement in organ function due to reversal of microvascular ischaemia) and improvement in platelet count (which reflects reduced consumption of platelets in microvascular thrombus). To argue that prolonging the duration of microvascular ischaemia has long term consequences on brain injury is highly plausible.	Comments noted.
Dr Will Lester	I'm concerned that there is insufficient attention to refractory patients. It is a similar situation to mortality in that numbers were small in the Hercules trial so statistical significance wasn't quite met. There were no refractory patients in the Capla arm of Hercules and 4 in the control arm (p=0.06). The real world incidence of refractory disease is historically higher – 10-20% (Coppo P, Cuker A, George JN. Thrombotic thrombocytopenic purpura: Toward targeted therapy and precision medicine. Research and practice in thrombosis and haemostasis. 2018;3(1):26-37) so as with mortality, the benefit is likely underestimated. Refractory patients require additional therapies which can be expensive (eg plasma cell therapy like Bortezemib) and they require twice daily exchange transfusion which doubles the main material cost and complications	Comments noted. Section 3.19 of the Final Appraisal Determination states: the committee noted that the company modelling did not include the costs of escalating treatment for people whose condition was refractory to treatment. Not including these costs would favour standard care because more people in HERCULES were refractory to treatment in the standard care arm than the caplacizumab arm (section 3.7).
Dr Will Lester	I'm concerned that the proposed review date of 3 years is too long as further comparative data between patients on and off caplacizumab should become available before then	Comment noted.
Dr Will Lester	I can only state again (as I did in the TA) that using the drug through the compassionate access scheme has had huge benefits for patients and to lose access to the drug will be very difficult for those of us who treat this condition	Comment noted.

Summary of comments received from members of the public

Theme	Response
Comments from people with aTTP and their carers described the severity of aTTP and associated anxiety of having a relapse. They described the extreme nature of plasma exchange, and the impact on their lives of being in intensive care and the impact on their quality of life. They also highlighted the negative impact of long-term complications of aTTP on quality of life	The appraisal committee took into account the personal testimonies of people who have aTTP and their carers. The severity of aTTP and patient experience of living with this condition and having treatment for aTTP is reported in sections 3.1 and 3.3 of the Final Appraisal Determination.
People with personal experience of aTTP were extremely disappointed with the draft recommendation in the Appraisal Consultation Document, noting that they had been denied a life-saving treatment which would reduce long term complications of aTTP which reduce their quality of life. Some respondees felt that they had been penalised because of the rarity of aTTP.	
People with personal experience of aTTP stated that caplacizumab is an innovative treatment and those respondees who had had it reported their positive experiences.	

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**

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]**
Name of commentator person completing form:	**[Omar Saeed]**

Comment number	Comments
	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Sanofi are encouraged to see that the appraisal consultation document (ACD) recognises that aTTP is a life-threatening, stressful condition associated with long-term morbidity and mortality. We are pleased that the committee concluded that caplacizumab was clinically effective versus standard of care and that they agreed caplacizumab is an innovative medicine. We were disappointed however that the committee felt unable to

	recommend caplacizumab at this stage despite being presented with an ICER below £30,000/QALY. Sanofi are committed to securing access to caplacizumab through a positive NICE recommendation as soon as possible but acknowledge the committees concerns regarding the level of uncertainty in the cost-effectiveness analyses. Given the rarity of aTTP and the existing evidence base, it is impossible to eliminate all uncertainty, however Sanofi propose 2 options to the committee to help mitigate the existing decision uncertainty. 1. An additional discount (equating to a discount of [redacted] discount from the list price) is proposed were caplacizumab to be recommended for routine commissioning. At this revised PAS price caplacizumab can be considered cost-effective under more conservative assumptions. The revised base case analysis provided within this response reports an ICER of £20,300/QALY using credible assumptions. This should provide reassurance to the committee and aligns with comments in the ACD and from the methods guide that state where plausible ICERs are above £20,000 the degree of certainty in those ICER estimates should be taken into account. This is the simplest, fastest route to achieve access for patients involving minimum burden for all parties. 2. If, however the committee feel unable to recommend caplacizumab for routine commissioning Sanofi would be willing to consider a managed access arrangement, as suggested in the ACD, to collect further data on caplacizumab that will reduce the existing level of uncertainty. Discussions with NICE and NHS England are ongoing. We are mindful however that this may delay access to caplacizumab in the short term given there is no standard process for agreeing an MAA outside of the CDF and HST programme. Our response is structured around the key uncertainties identified by the committee and in summary includes: 1. Updated evidence to inform acute mortality estimates 2. New evidence to inform rates of long-term complications and mortality 3. Discussion of the available evidence to inform quality of life estimates including fear of relapse 4. A revised base case (incorporating revised PAS discount) 5. Scenario analyses as requested by the committee

Acute mortality	
2	• Sanofi acknowledges the committee's concerns with the use of observational data and naïve comparison in the company submission (CS). However, we consider that the substantial amount of available evidence from the clinical trial programme, UK registry, compassionate use scheme and French matched-cohort analysis prove that caplacizumab reduces mortality [compared to standard of care (SoC)] during an acute episode of aTTP. This view is supported by clinical experts consulted prior to the submission, during the technical engagement meeting and at the first ACM. We therefore consider that it is inappropriate to explore scenarios in which no effect of caplacizumab on acute mortality is assumed. • A summary of trial and real-world evidence of caplacizumab's benefit on acute mortality is provided below. **HERCULES data and integrated HERCULES/TITAN analysis** • Sanofi would like to reiterate that in the phase III HERCULES trial, there were no deaths among patients randomised to caplacizumab during the study drug treatment period arm; compared to 3 deaths in the standard of care (SoC) arm.[1] There was 1 death in the caplacizumab arm during the follow-up period). In the phase II TITAN trial, no patient died in the caplacizumab group, versus 2 in placebo.[2] One death in the placebo arm occurred outside the placebo treatment period. • An integrated analysis of the Phase II TITAN and HERCULES trials to assess treatment differences that may have gone undetected in individual trials, was conducted to assess the efficacy and safety of caplacizumab in aTTP. Caplacizumab also significantly reduced deaths (0 vs 4; [redacted]) during the blinded treatment period. This integrated analysis confirms the individual trial results and provides further evidence that caplacizumab has the potential to reduce mortality in aTTP patients.[3] • In its response to Sanofi's response to the technical engagement report, the ERG, stated that "the statistical comparison of the proportion of deaths in the pooled HERCULES/TITAN data over the treatment period only has been made by the company and appears to be a chi-squared analysis without continuity correction giving a p-value of 0.047." The ERG also stated that "with such sparse data this comparison should have been made with Fisher's exact test" which resulted in a non-significant difference in mortality (p=0.12), reflecting the limited data and the fact that the trial was not powered for this outcome (as acknowledged by the ERG). 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 close to the risk ratio used in Sanofi's base case (0.29). **UK real-world data** • UK registry data (obtained by clinicians) on acute mortality among aTTP patients who received caplacizumab (as part of the compassionate use scheme) shows the acute mortality rate among those who received caplacizumab within 48 hours of first PEX (as per SmPC) to be lower compared to those who received caplacizumab more than 48 hours after first PEX; [redacted] and [redacted] respectively. Forty-eight hours is a considerably longer time period than mandated in the HERCULES protocol - to start caplacizumab within 24 hours of the first PEX delivered on-study - and results primarily from access issues due to caplacizumab not being available routinely on-site in the treating centre. • In the UK registry data,[4] the median time taken for patients to receive the first dose of caplacizumab (as part of the compassionate use programme) after initiation of plasma exchange (PEX) for aTTP was [redacted] days (range [redacted] – [redacted] days); and [redacted] of patients received caplacizumab within 7 days of starting PEX[i]. • The impact of this on mortality can be seen in the dataset; mortality is lower when caplacizumab is given earlier. Furthermore, as highlighted in paragraph 3.5 of the ACD, clinicians would administer caplacizumab within the same day as plasma exchange is initiated. As such, Sanofi would consider outcomes among those who received caplacizumab more than 48 hours after PEX [redacted] to be comparable to the most likely acute mortality in the absence of caplacizumab. • In addition to the acute mortality rate, the UK data also provided characteristics of UK patients enrolled in the compassionate use programme. The mean age of patients treated was [redacted] years, (range [redacted] – [redacted] years) and [redacted] (n= [redacted]) cases were female, reflecting the female to male predominance reported in aTTP; [redacted] (n=[redacted]) 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 highlighting the generalisability of the mortality data from HERCULES to expected UK practice if caplacizumab were to be recommended. **French Matched Cohort Analyses** • During Technical Engagement, Sanofi presented a draft abstract of a French matched-cohort analysis based upon the temporary authorization scheme for caplacizumab use which has been running since September 2018.

	The final analysis by a consortium of French clinicians, which has now been submitted to a leading medical journal for peer review compares [redacted] historical patients matched in terms of severity and treated according to the historical practice to [redacted] aTTP patients treated first line with caplacizumab, PEX and rituximab. Acute mortality in the caplacizumab regimen was [redacted] compared to [redacted] in the historical cohort.[5] Please note that the mortality has changed from the draft abstract.
3	**Use of observational data** • Clinical experts advised that mortality in HERCULES was much lower than expected in UK clinical practice (both for caplacizumab and placebo groups). 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). Clinicians stated that a mortality of 13.2% for SOC, based on a meta-analysis of literature sources,[6, 7] was a more realistic estimate. This figure was validated by alternative estimates taken from sources authored by expert clinicians that estimated acute mortality on SoC of between 13-15%.[8, 9] • For caplacizumab, Sanofi used real-world data on acute mortality derived from the compassionate use program [3.77% (9/239)] in the base case. 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 routinely available on site in hospitals treating aTTP. As such, the mortality estimates from the compassionate programme are conservative to caplacizumab. This interpretation was supported by clinicians on validation calls and on the technical engagement call.[10] • 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 thus reducing delays. The data originally provided, covering period up to 30 September 2019, indicated a mortality rate of 4.3% (8/187). The latest data indicate (as of February 2020) 9 deaths out of 239 patients (3.77%). • Regarding the size of the association between treatment with caplacizumab and acute mortality, Sanofi believes the relative effect estimates from the clinical trial programme are generalisable to the real-world setting. This has been substantiated by the ERG who, in their review of Sanofi's response to the technical engagement report, noted that "the estimated efficacy of caplacizumab from the trial may be plausible even in another setting with a differing baseline mortality" (Pages 16 of ERG response to company TE response)

	• **We therefore consider the most robust source of relative treatment effect to be the caplacizumab clinical trials; 0.21 (95% CLs 0.03 to 1.75) as calculated by the ERG. This is consistent with the RR used in the original submission (0.29).**
4	**Meta-analysis of SoC** • As mentioned above Sanofi used a mortality rate of 13.2% in the original submission based on a global systematic literature review (SLR) and meta-analysis of available literature in TTP patients on standard of care. This figure was validated by UK 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%.[8, 9] • To address the committee's recommendation that the meta-analysis should reflect current UK practice using studies from the UK only, or those most relevant to UK clinical practice, an assessment of the most appropriate UK sources was conducted. As the search dates of the previous SLR only included studies up until 16th March 2017, a further basic search of studies for mortality in aTTP patients was conducted using PubMed on 1st June 2020 restricted to studies published 2017 onwards. Search terms were (mortality) AND (acquired thrombotic thrombocytopenia purpura). • Seven studies were identified from the original SLR that were specific to the UK.[11-17]. In addition to the meta-analysis, a further two sources, authored by clinical experts, were cited in the company submission, as highlighted by clinical experts and through communications with NICE.[8, 9]These sources were not picked up in the original SLR as the only source searched was MEDLINE – via PubMed. • A further 33 publications were identified in the updated search. However, except for the clinical trial publications for caplacizumab, no further studies were identified that were UK-specific. Therefore, the existing evidence base of nine studies was considered comprehensive, in the context of the limited search terms and sources searched. Summaries of patient/study characteristics and outcomes for all studies are presented in Table 1 and Table 2 respectively (Appendix 1). • Seven of the nine UK-specific studies identified were based on data from the UK TTP registry/South East England TTP registry or conducted at University College London Hospitals (UCLH), a global leader in aTTP management.[11-17] Professor Marie Scully, who was one of the clinical experts in attendance at the Appraisal Committee meeting, was primary author or co-author on all of these studies. For the remaining two studies, one

	was an analysis of ONS/HES statistics,[8] and the other did not specify the data source.[9] • As per the inclusion criteria of the original SLR, all patients were suffering with acute TTP. Scully et al. (2014) only considered outcomes in pregnant women,[15] and Patriquin et al. only considered bortezomib treatment in severe or refractory disease.[13] Therefore these two studies were considered less reflective of UK clinical practice and were excluded from further consideration. Most patients in the remaining studies had acquired or idiopathic TTP (confirmed by low ADAMSTS13 activity) with various expected comorbidities such as HIV; therefore, the remaining studies were deemed relevant to the decision problem. • The seven remaining studies varied according to dates conducted, however in most of the older studies, patients were treated with experimental rituximab, therefore the relevance to current practice was considered to be high. Caplacizumab was not mentioned in any of the included studies. Across all studies, median/mean age and female:male ratio closely mirrored UK expectations; patients were relatively young (~40s) and there was a greater proportion of female patients. This is also in line with the HERCULES trial. • Mortality across the seven remaining studies ranged from 5.8% to 15%. We are unclear as to the methods used by NICE to derive the 7% estimate noted in the ACD, however, when we assessed the data, naïve pooling of patient numbers and event numbers was considered inappropriate due to the high probability of overlap between sources. There is, therefore, a significant risk of double counting as the majority of studies were conducted on UK registry patients at around the same time. • Majority of data in the UK registry is from UCLH which is a specialised centre regarded as having the best outcomes for TTP patients across the UK and is recognised globally as a centre of excellence. It is therefore unsurprising that mortality for the studies from the registry and UCLH are at the lower end of this scale. Outcomes for aTTP patients who are treated in UCLH are most likely not generalisable to those for aTTP patients in the rest of the country. • All mortality estimates based on registry data should be interpreted as a conservative estimate of mortality for patients on SoC in the UK. As discussed in Section A.9 (Document A) of the Company Submission; patients were often not consented to the aTTP registry (and similar UCLH analyses) if the outcome was death. This was because it is often considered inappropriate to ask family members to consent to the deceased patient's inclusion. Furthermore, the study by Lester et al. explains how mortality across England is highly heterogenous and varies between 8% and 20%.[8] This is further substantiated in paragraph 3.4 of the ACD where it is states

	that the estimates of death rates were 10% to 20% in non-specialist centres and less than 5% in specialist centres. • **We therefore consider the Lester et al. study, which is one of the more recent publications and covers the whole of the UK to be the most generalisable (mortality rate 12.6%). This study is therefore used in the revised base case analysis presented in this response. A rate of 7% which may be more reflective of mortality in specialist centres is explored in scenario analyses (Table 8 of Appendix 1) but this does not have a significant impact on the base case ICER.**
4	**Adjustment for confounding** • An adjusted indirect comparison between the compassionate use data collected for caplacizumab and data on real-world mortality with SoC is not possible because Sanofi do not have access to the data on patient characteristics within the compassionate use programme; the sole exception to this is information on adverse events of which mortality is clearly a constituent. • Limited data has become available since the submission via the UK registry on the characteristics of UK patients enrolled in the programme (See comment 2 above). The demographics are very similar to HERCULES. The median time taken for patients to receive the first dose of caplacizumab after initiation of plasma exchange (PEX) for aTTP was [redacted] days (range [redacted] days), and [redacted] of patients received caplacizumab within [redacted] 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). • Our ability to conduct a matching analysis between the compassionate use data and the available data for SoC was considered with the new availability of this data. Unfortunately, data are only available to Sanofi from the publication and not in a patient level data format which precludes the use of methods such as MAIC as data is not available to Sanofi in a patient level format for SoC either. Furthermore, Sanofi believes that conducting a MAIC is unlikely to be that informative given the limited number of covariates available and that they are similar.
5	**Validation of acute mortality** • Sanofi validated assumption on acute mortality during an advisory board and clinical validation meetings. Clinical opinion suggested that overall mortality for the acute episode (13.2%, as reported in a meta-analysis of

	studies identified in the literature) is generalisable to the UK. 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 neither appropriate nor realistic).
6	**Acute mortality summary** • The ERG notes that effect sizes from trials (risk ratios, hazard ratios etc.) can remain valid even when absolute event rates may vary. 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 Sanofi 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). 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). • **The base case has been revised to use an acute mortality rate of 12.6% (based on Lester et al) for SoC given that this is the estimate that is most generalisable to the whole of the UK and for caplacizumab, 2.65% based on applying a RR of 0.21 taken from the clinical trial program as the most robust data source.** • Alternative estimates of acute mortality are provided in Table 3 of Appendix 1.
Long-term mortality	
7	• Sanofi acknowledges the committee's concerns with the lack of evidence on long-term effects of caplacizumab. Given the rarity of the disease and the fact that until recently, management has focussed solely on ensuring survival during an acute episode, it is not surprising that there is a lack of data on long-term outcomes. Nonetheless, Sanofi has systematically searched for and included all available relevant evidence and sought clinical opinion to substantiate all assumptions made in the CS. • Below, we summarise the available evidence, assumptions made and their validation. We also present results of

	the recommendations made by the committee in the ACD.
8	**Prevalence of long-term complications in people with aTTP (on SOC)** • Sanofi conducted an SLR on the clinical burden of disease in aTTP.[6]A number of studies were identified that reported multiple long-term complications following an acute episode of aTTP. These conditions include cognitive impairment[18-21], neuro-psychological impairment [19, 20, 22, 23], headache[24], hypertension[22, 23], chronic kidney disease[25], stroke[26] and an increased risk of premature death.[23, 27] A number of studies identified in an SLR on the clinical burden of disease[6] also indicate the presence of persistent cognitive impairment in remission[18-21, 28], with abnormalities found upon magnetic resonance imaging (MRI) scans.[18] • Two studies cited in the SLR were used to estimate the baseline risk of cognitive impairment. Kennedy et al. reported the proportion of patients experiencing mild impairment (54.2%) and moderate to severe impairment (20.8%)[21] Cataland et al (2011)[18], reported 63% of patients had cognitive impairment. While Kennedy et al. reported cognitive functions among patients who were enrolled in the Oklahoma TTP registry, Cataland et al. included patients with a history of idiopathic TTP from existing patient cohorts at both the Ohio State University (n = 12) and the University College London Hospitals (n = 15). 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 • The proportion of individuals with neuropsychological impairment was taken from Chaturvedi et al. (2017) who reported depression in 36.8% and PTSD in 35.1% of aTTP survivors using two validated questionnaires.[22] The ERG was satisfied that this data source was the best available given its sample size (n=236). 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.[10] Alternative scenarios were presented using higher and lower proportions of neuro-psychological impairment. • For long-term mortality, a number of literature sources report reduced life expectancy in aTTP patients compared to general population.[23, 26, 28] Two publications, Deford et al., 2013 (n =70) and Upreti et al., 2019 (n =170) were used to estimate the increase in mortality of an aTTP population. Deford et al. and Upreti et al. compare mortality based on Oklahoma registry data and John Hopkins Hospital aTTP patients respectively with

	matched general population mortality. Standardised mortality ratios of 7.8 and 8.3 relative to the general population were calculated for both sources respectively. Upreti et al. was chosen for the model due to it being a more recent source. The ERG concluded that *"both sources provide plausible estimates of long-term mortality after aTTP, drawing on several years of follow-up data per patient."* • Since submission, new data from a Sanofi funded and initiated non-interventional, cross-sectional study investigating the quality of life of UK aTTP patients (n=50) and carers (n=10) has become available. The study concluded that survivors of aTTP appeared to report worse cognitive dysfunction than the UK general population. These patients also seem to experience moderate levels of both anxiety and depression. Based on this study, the rates of cognitive impairment assumed within the model appear reasonable as the majority of patients state that they have not been able to put their thoughts into words without extra effort (88%) and the PROMIS score indicated cognitive function abilities one standard deviation lower than the U.S. average. (See Appendix 2: Quality of life study report - Sections 4.1.4 and 4.1.6.1) • Based upon the quality of life impact study conducted the rates of neuropsychological impairment used in the standard care arm of the model appear low as the majority of patients reported moderate or severe symptoms on the HADS anxiety and depression scales (72% and 84%) and the Mental Health (MH) domain on the SF-36 was well below the UK norm. Additionally, scores did not vary much between the acute patients (an episode within the last year) and non-acute patients indicating that the duration of impact may have been underestimated. Finally, the majority of patients (84%) reported feeling 'quite a bit' or 'very much' worried about having another aTTP episode which illustrates the ongoing impact on patients' lives of fear of recurrence. (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 5 of Appendix 1. • Sanofi conducted validation teleconferences (TCs) with clinical experts who confirmed 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.[10] 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.

9	**Platelet count as a surrogate measure for long-term outcomes** • Sanofi recognises the committee's position that platelet count could be a surrogate measure for more meaningful outcomes reflecting morbidity and mortality. There is a volume of evidence showing that delay in initiating PEX adversely impacts survival and thrombotic sequelae backing up the benefit from reduced time spent in the occluded state with rapid treatment.[29] The same principle applies to the time saving that can be achieved with caplacizumab. However, the evidence available does not allow robust estimation of a surrogacy relationship between potential short-term predictors and longer-term complications (including mortality). • Clinical experts at the advisory board, technical engagement meeting and during the first ACM have affirmed that reducing the time to platelet normalisation and stable platelet counts, reduced risk of exacerbation and /or refractory disease is likely to improve outcomes for patients with aTTP. There is, therefore, extensive clinical support for a long-term treatment benefit of caplacizumab due to reduced time spent in the occluded state,[7, 29, 30] However, directly quantifying this expected treatment benefit with caplacizumab is challenging, as the HERCULES trial considered the acute episode only and 26/28 patients who exacerbated on the standard of care arm received caplacizumab. Furthermore, as caplacizumab is a relatively new treatment, there is currently a lack of evidence demonstrating its long-term benefit. • In light of the above reasons, Sanofi performed a targeted literature review (TLR) to establish surrogacy relationships between HERCULES outcomes and long-term mortality and complications. No data on the relationship between the time spent at risk of microvascular thrombosis (measured by TTPN, hospitalisation/ICU/PEX days) and long-term mortality and complications were identified. The lack of data on surrogate measures in aTTP is not surprising given that until very recently, the focus of management of the condition has been on keeping patients alive in the acute phase. It was only in early 2019 that the UK TTP registry started regular follow-up and data collection at regular intervals during remission. • In addition to the TLR, clinicians were consulted on the expected improvement in long-term outcomes for patients treated with caplacizumab. At the clinical advisory board, clinicians explained that it is biologically plausible that reducing the time with active disease will benefit patients and improve long-term cognitive and neuro-psychological impairment.[7] As a starting point for discussions on how to quantify the expected long-term improvement in the cost-effective model, proxy RRs and HRs were calculated based on HERCULES trial outcomes and presented to attending clinicians (

	• Table 4 of Appendix 1). All calculated results are in alignment and patients on caplacizumab perform better than patients on SoC. While emphasising uncertainty, the clinicians 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 (RR -0.62). This was based on two rationales; that quicker resolution of disease and a reduced overall time spent in the occluded state lessens the microthrombi burden, which leads to a reduction in acute organ damage with long-term consequences and, most importantly, on the rationale that the ratio of hospitalisation/ICU days was consistent with outcomes for other proxies such as TTPN and PEX days. • As discussed in the technical engagement response, a number of publications are available that suggest that the greater the time spent in ICU the greater the long-term mortality risk.[31-35] A limitation of all of these publications is that they are not specific to aTTP, so any estimates of long-term mortality will not consider the accrued organ damage through prolonged exposure to microthrombi. • Two papers that do provide some supportive evidence in aTTP patients are Rock (1991) and Liu (2013).[36, 37] The first study, Rock (1991), discussed during in the company's response to technical engagement, was an RCT comparing plasma exchange and plasma infusion in the treatment of TTP. Response was defined as a platelet count of more than 150 x 10^9/L for two consecutive days and no new neurologic events. Based on this publication, response at the end of the first treatment cycle was 47% in the plasma exchange group versus 25% in the plasma infusion group. For the patients who received plasma exchange, 22% had died by 6 months versus 37% of those who received plasma infusion. In conclusion, an 85% increase in response resulted in a 73% reduction in mortality, supporting a near 1:1 relationship. • Data from HERCULES could not be used directly to estimate long-term mortality based on Rock (1991) due to limitations in the frequency of platelet count measurements. In the daily plasma exchange period, platelet count was measured daily. However, in the post-daily plasma exchange period, only weekly measurements were taken, precluding any useful assessment of response as per the Rock (1991) criteria. Additionally the Rock paper only reports mortality per arm (and according to whether patients crossed over or not) and not by directly by response status (although it should be noted that the number of non-responders and deaths in the initial period in the plasma exchange arm is identical which is not unexpected as patients who are refractory to treatment have a very poor prognosis). Therefore, an alternative approach was required. • As reported in Table 23 of the company submission, the RR for time to platelet count response based on

HERCULES (initial and exacerbation) is 0.57. Assuming that response as assessed in HERCULES will have a similar relationship with mortality to response assessed in Rock (1991) this was adjusted using the relationship reported in Rock (1991) as follows:

$$\frac{0.57 * 85\%}{73\%} = 0.66$$

Scenarios presented in Table 8 of Appendix 1 investigate the impact of assuming an RR for long-term mortality of 0.66.

- The second study, Liu (2013), which was identified in the burden of disease SLR showed that platelet recovery rate by Day 3 is a predictor of both short term and long-term outcomes. The study showed that survival is significantly better in patients with a platelet recovery rate of >=5 x 10^9/L per 24 hours, than in patients with a platelet recovery rate below this cut off ($p < 0.001$), hazard ratio 23.2 ($p < 0.005$). In patients with a platelet recovery rate at Day 3 of <5 x 10^9/L per 24 hours, the estimated rates of survival were 74.7% at 1 month, 64.8% at 3 months, and 58.9% at 1 year, compared with an unchanged rate of 100% at all three time points in patients with a platelet recovery rate at Day 3 of >=5 x 10^9/L per 24 hours.

- To incorporate a scenario using the relationship reported by Liu (2013) into the model, data were required on the proportion of patients in each treatment arm of HERCULES who were responders (i.e. above cut-off) and non-responders (i.e. below cut-off) according to the definition in Liu (2013). This data is shown below based on a post-hoc analysis of HERCULES data.

	N	**N**	**% responders**	**% non-responders**
Responders SoC	[redacted]	[redacted]	[redacted]	[redacted]
Responders capla	[redacted]	[redacted]	[redacted]	[redacted]

- To implement the relationship reported by Liu (2013) into the model, survival curves were generated for responders and non-responders. The responder curve was assumed the same as general population survival as Liu (2013) reports survival of 100% over all time points measured.

	• To generate the non-responder curve mortality for non-responders was taken from Liu (2013). Based on the paper, survival was 64.8% at 3 months, and 58.9% at 12 months, a 5.9% difference in survival over this time frame. The non-responder curve was calibrated using Solver, via the application of an SMR (of 45.7) to the general population hazard until the difference between survival at Month 3 and Month 12 was 5.9%. • Following generation of responder and non-responder curves, the hazards were then weighted according to the proportion of responders and non-responders in each treatment arm based on HERCULES data to generate survival curves for each treatment. It is important to note that as 100% of caplacizumab patients were responders, the long-term survival for caplacizumab patients is assumed to be equal to the general population. This may be overly optimistic, thus results based on the Liu (2013) data are provided as a scenario only. • All calculations are provided in the "Long-term mortality" sheet of the updated cost effectiveness model. The user can select to apply the Liu (2013) mortality on the "Controls" sheet, G70. • Key limitations of these papers include: 1. Rock (1991): age of the study, Canadian population [although practice is not expected to be overly different to the UK], small patient numbers as would be expected given the rarity of the condition (n=51 in each arm; note to get this number of patients across 16 Canadian centres a 7 year enrolment period was required), definition of response cannot be replicated with the data collected in HERCULES 2. Liu (2013): single centre US study [although practice is not expected to be overly different to the UK and this study includes patients enrolled relatively recently; 2003 – 2010], retrospective review, excluded some deaths due to lack of response measurement, some patients with ADAMTS13 >10% included, small patient numbers as would be expected (n=64) • Despite these limitations both the Rock (1991) and Liu (2013) papers are consistent in that a link is shown between response to treatment (platelet count response) and mortality and the impact on cost-effectiveness is explored in scenario analyses. • Finally, draft manuscript of the UK registry states: [redacted]

	[redacted] [4]
10	**Validation of long-term outcomes** Long-term complications • 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 the brain is subjected to thrombotic assault, and that it was biologically plausible that quicker time to resolution of disease leads to lessening of the microthrombi burden.[7] Clinicians explained that reducing a lengthy and stressful hospital or ICU stay should also result in a reduced risk of developing long-term complications. 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.[7] This is due to proactive monitoring and pre-emptive treatment with rituximab if ADAMTS13 activity falls below acceptable levels. 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.[29] Experts at the clinical validation meeting explained that it is biologically 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.[7] 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 thrombotic episode.

Quality of life in aTTP	
11	**Quality of life in the acute period** • In the CE model, literature values were sourced for disutility due to hospitalisations in general to explore the impact of the acute episode on quality of life.[38] Utility values specific to patients with aTTP were not available for the acute episode as it is unethical and challenging to collect such data from patients with very severe disease. It is an extremely traumatic experience for both patients and carers; the onset is unexpected, and the treatment is unpleasant, particularly PEX. The more severely affected 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. [39] These patients would not be able to participate in health-related quality of life (HRQL) data collection. • 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.[7] Suggestions included: o Severe brain injury o Cerebral vein thrombosis o Sepsis (young patients without comorbidities) o Guillain–Barré syndrome o Meningitis o Patients in critical care or intensive care (ICU) • To investigate the available evidence base for the listed proxy conditions, a TLR was conducted and a number of useful sources reporting EQ-5D utility scores for patients with the associated proxy conditions were identified. 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.[38, 40, 41]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 and finally, utility estimates from this study demonstrate face validity in that patient-reported 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. • In the ACD, Paragraph 3.3, Page 7, the committee concluded that plasma exchange and hospital stays are unpleasant, and that people with acquired TTP would welcome a treatment that reduces these. In the ACD, Paragraph 3.16, Page 20, it noted that there were benefits which may not have been captured in the QALY calculation such as: "The effect of caplacizumab in reducing plasma exchange duration on the number of central lines replacements a patient would need, how this reduces the risk of infection and how this would affect a patient's quality of life". It is clear from patient and clinical representatives that any treatment which reduces the requirement for plasma exchange and the volume of plasma required would benefit patients greatly, and that current model approach underestimates this benefit. In light of this, the updated base case assumes that patients on SoC have half the utility of patients on caplacizumab to account for reductions in the duration and volume of plasma exchanged and reductions in associated complications such as line infections and thromboses. • Alternative scenarios are presented in Table 8 of Appendix 1 with little impact on model results.
12	**Long-term quality of life** • For long-term quality of life, new data from a Sanofi initiated and funded non-interventional, cross-sectional study investigating the quality of life of UK aTTP patients (n=50) and carers (n=10) became available during the appraisal and was presented in Sanofi's technical engagement response.[42] In this study, 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 individuals reported moderate levels of both anxiety and depression. Similarly, 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.[42]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. Whilst there are limitations to the study, we do still consider this relevant as the only such evidence available for UK aTTP patients. • SF-36 data from the UK QoL study were mapped to EQ-5D using the Rowen et al. algorithm (for consistency with the analysis presented by Burns et al).[43, 44] The average utility for patients who had experienced an episode within the last year vs those who had experienced an episode more than a year ago is presented below. The comparison of mapped to modelled utility values, which are based on US registry analysis in aTTP patients (Burns et al.), show 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	[redacted]	[redacted]	[redacted]
	No	[redacted]	[redacted]	[redacted]

13

Fear of relapse

- The committee noted that quality-of-life estimates for acquired TTP should include an estimate of the fear of relapse.
- Data from the aTTP quality of life study show 92% (33/36) of patients experienced flashbacks following an acute aTTP episode, and 64% (23/36) of patients reported that these were moderately to extremely severe. 96% (48/50) worry about relapse, with 52% (n = 26, N=50) worrying “very much”
- The model has been revised to capture the benefits of caplacizumab in reducing the fear of relapse for patients and carers through the availability of an effective treatment.

Other issues raised in the ACD

14

Relapse rates

- The use of rituximab during remission has dramatically reduced the relapse rate among people who have suffered an acute episode of aTTP. This was affirmed by clinicians at the Technical Engagement meeting. During validation exercises, clinical expert opinion suggested that 10% of patients will relapse at some point during their remaining lifetime. This aligns with the estimate given on the technical engagement call (10%).

	• 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.[10] Therefore, Sanofi considers 1% relapse rate a reasonable assumption due to monitoring and use of rituximab during remission. We have tested a rate of 2% in sensitivity analysis based on the Shin paper but as noted above this is an upper bound as relapse rates are expected to reduce due to more consistent use of rituximab prevent relapse in centres in England. • With regards to the committee's concerns on the effectiveness of caplacizumab on re-exposure, Sanofi can confirm that there are no data available on re-exposure to caplacizumab in patients with aTTP. All subjects who enrolled in the post-Hercules study will have access to caplacizumab in the event of relapse, however those data are not yet available. As part of the safety assessments in Hercules we investigated the development of anti-drug antibodies following exposure. Results of antibody assessments can be difficult to interpret in aTTP due to the infusion of donor plasma, which may contain cross-reacting antibodies. o Positive results for treatment-emergent anti-drug antibodies were seen in a very small minority of patients (n=4) exposed to caplacizumab, and one randomised to placebo o there was no correlation between duration of exposure to the drug and a positive anti-drug antibody test; o these antibodies did not impact pharmacokinetics of the drug, nor assessments of pharmacodynamics by RICO assessment (vWF platelet-binding activity remained fully suppressed); o there was also no effect on clinical safety (achievement of primary endpoint) or tolerability in these subjects • There is however anecdotal evidence. [redacted]

	• As such, Sanofi has no reason to believe the effect of caplacizumab would be different on re-exposure. • **The post-ACD CE model retains a relapse rate of 1% (with sensitivity analysis of 2% as the upper bound). In addition, scenarios have been presented with reduction of efficacy of caplacizumab on subsequent use.**
15	**Proportion of people with a major thromboembolic event** • While the same proportion (8%) of people in both arms of HERCULES experienced a major thromboembolic event, Sanofi would like to highlight that the thrombotic process in large vessel disease is not vWF-mediated. Those clots are rich in fibrin and red cells, and the clotting is driven by thrombin. This is why LMWH is used for prophylaxis, for its anti-Xa activity, reducing thrombin generation. This has been substantiated in informal discussion with clinicians. vWF has its greatest effect in the microcirculation, and thrombi in TTP are vWF and platelet-rich, hence why the effect of caplacizumab is greatest there.
16	**Frequency of plasma exchange** • Paragraph 3.3 states that caplacizumab "may reduce the frequency" of plasma exchange. Sanofi would like to highlight that in HERCULES, there was a statistically significant reduction in the number of days of plasma exchange therapy and the volume of plasma exchanged: 38% shorter duration of PEX therapy in the caplacizumab group compared to the placebo group and a 41% lower volume of plasma exchanged. (Ref). Therefore, caplacizumab reduces the days of PEX therapy and volume of plasma and not necessarily, the frequency of PEX.
17	**Marketing authorisation** • Paragraph 2.1 of the ACD mentions the recent Committee for Human Medicinal Products (CHMP) adoption of a positive opinion recommending a change to the terms of the marketing authorisation for caplacizumab to include adolescents. Sanofi would like to highlight that the official adoption of the CHMP opinion by the European Commission and the Market Authorisation was received on 9th June 2020. o *Cablivi is indicated for the treatment of adults **and adolescents of 12 years of age and older weighing at least 40 kg** experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in*

	conjunction with plasma exchange and immunosuppression."
18	**Validation of assumptions** • The ACD mentions in a number of places what steps were taken to validate assumption in the CS. Sanofi sought extensive clinical input during the model conceptualisation and development process. 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 health economists not involved in the model development. • A summary of the model verification/validation is presented in Table 6 of Appendix 1
Revised base case	
19	• In light of the ACD and responses above, Sanofi has revised its base case based on the following: o Acute episode cost based on revised PAS [redacted] o Acute mortality ▪ SOC -12.6% (0.49/3.88) SoC ▪ Caplacizumab – 2.5% (RR 0.2 applied to caplacizumab) o Duration of depression increased in line with cognitive impairment (55 years) o Utilities in acute episode based on literature for caplacizumab, patients on SoC assumed to have half the

	utility of patients on caplacizumab as discussed in comment No. 11 above o Complete improvement in fear of relapse due to availability of caplacizumab • Caplacizumab is associated with 5.80 incremental life years, [redacted] incremental QALYs and incremental costs of [redacted] per patient, compared with SoC. The incremental cost-effectiveness ratio (ICER) is £20,377 per additional QALY gained. • Table 7 in Appendix 1 presents the impact of individual changes above to the ICER.
Scenarios	
20	• Table 8 of Appendix 1 presents a range of scenarios based on the ACD. Each scenario is varied by switching off long-term mortality benefit only (conservative scenario) and by switching off long-term benefits for mortality and complications (highly conservative scenario).
Committee decision making	
21	• There is an acknowledgement that there is currently a large gap between the STA and HST willingness to pay thresholds and a lack of clarity regarding which medicines should be assessed via HST. Whilst we hope that this gap can be addressed via the methods review, we would ask that the committee exert some flexibility in their decision making given caplacizumab falls into this gap (it was originally scoped for HST). There is precedent for applying a modifier to the STA willingness to pay threshold in the end of life criteria, however this largely only applies to medicines for late stage cancers. There are however other types of medicines for which society would be prepared to accept a higher price and medicines for rare or particularly severe conditions such as aTTP fall into this group. Were a severity and or a rarity modifier (per ABPI proposals) to be implemented in the STA process, caplacizumab would likely be assessed at a higher cost-effectiveness threshold. Under even the most conservative assumptions (i.e. assuming no long-term benefit) the ICER for caplacizumab does not exceed £50,000/QALY.[45] • Sanofi believe the existing PAS (submitted at technical engagement) would provide caplacizumab at a net price to the NHS that is considerably lower than would be expected for this type of medicine (given its

	assessment via STA and not HST) and that this doesn't reflect the significant value offered by this innovative therapy. However, given our commitment to securing access for patients to caplacizumab Sanofi have offered a further level of discount in an attempt to de-risk a committee decision for routine commissioning. It is also important to note that given the rarity of aTTP and that this is a clearly defined patient population, the overall budgetary impact of introducing caplacizumab will be small, again minimising the risk associated with a positive recommendation. • Sanofi would encourage the appraisal committee to reconsider their preliminary decision in the context of the additional discount and revised analyses that have been presented and the considerable unmet need for this very rare but particularly severe condition.

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, 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 our consultations 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.

Appendix 1: Tables

Table 1: Study and patient characteristics, SLR/meta-analysis of SoC mortality

Author (year)	Inclusion period	Country/setting/registry	Sample size	Patient population (type of TTP/secondary diagnoses)	ADAMTS13 activity	Additional info on patient characteristics
Hughes et al. (2009)[11]	2004-2007	University College London Hospitals	41	Idiopathic, congenital, HIV, pancreatitis	<5% in 88% of patients	• Types of TTP: 1 congenital TTP, 34 aTTP, 6 secondary aTTP (HIV, pancreatitis) • Mean age: 40 (range: 12-73) • Male: female ratio: 1:2.2 • Treatment: All had PEX and 73% treated with rituximab • ADAMSTS13 activity >10% in 4/41 patients
Patriquin et al. (2016)[13]	2013-2015	UK TTP registry (2 UK centres)	6	Idiopathic, bortezomib-treated refractory patients	<10%	• Mean age 49.5 (range: 27-76) • Male: female: 1:1 • Rituximab use: 100% • All patients were severe/refractory with ADAMSTS13 activity <10%
Scully et al. (2014)[15]	2009-2013	UK TTP registry	35	Acquired and congenital during pregnancy	<10%	• 47 women who had 91 pregnancies are included • 35 women presented with de novo TTP in pregnancy • 23 women had late onset cTTP with no previous episodes of TTP before their presentation in pregnancy • 12 women had acquired antibody mediated TTP presenting for the first

						time in pregnancy
Westwood et al. (2013)[17]	2004-2011	UK TTP registry	86 (104 episodes)	Idiopathic	<5%, range <5-39% with some patients where activity was measured after 1 PEX	• Treatment: All patients were treated with rituximab, 15 were also treated with prophylactic rituximab to prevent relapse. • Female: male of 61:25 • 74 patients presented with de novo aTTP, 12 with relapses • Mean age: 43 (range: 12-75)
Scully et al. (2011)[14]	2006-2009	South East England TTP study group	40	Idiopathic, rituximab treated + historic controls. Patients who died prior to screening excluded. Secondary TTP excluded	Median <5% (<5-32%)	• 34 de novo, 6 relapses • Median age 42 (range: 21-76) • Female: Male 26:14 • Treatment: All patients given rituximab
McDonald et al. (2010)[12]	2007-2009	University College London Hospitals	30	Idiopathic, HIV	Median <5% (<5-31%)	• Mean age 39 (13-76) in Group 1 (ritux) and 54(28-61) in Group 2 (control)
Scully et al. (2008)[16]	2002-2006	South East England TTP registry	178	Idiopathic, congenital, pregnancy, HIV, malignancy, transplant, infection Cases presenting to hospitals not included on the registry, who died on admission, before referral was possible or were treated locally, were excluded.	<5% in 67%, 5-10% in 6%, >10% in 27% of patients	• 236 total episodes, 124 were relapses. Some patients initial episode was prior to data collection. • Median age 46 (range: 0-81) • 75% female, 25 % male

Lester (2015)[8]	2003-2013	England	3.88 per million per year	Deaths were included from ONS data where TTP (ICD-10 M31.1) code was recorded as one of first 3 causes of death Admissions from HES data with diagnostic code for TTP	NR	NR
Orpha.net[9]	2015	England	Annual incidence of TTP ~ 1/250, 000	Acquired 95%, congenital 5%	NR	Median age: 40 Female-to-male ratio: 3:1

Key: ADAMSTS 13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; aTTP, acquired thrombotic thrombocytopenic purpura; cTTP, congenital thrombotic thrombocytopenic purpura; HIV, human immunodeficiency virus; PEX, plasma exchange; SLR, systematic literature review; SoC, standard of care; TTP, thrombotic thrombocytopenic purpura.

Table 2: Outcomes, SLR/meta-analysis of SoC mortality

Author (year)	Sample size	Mortality during hospitalisation	Timing of mortality	Additional info on outcomes
Hughes et al. (2009)	41	9.8% (4/41)	See 'Additional info' column	• 3 patients died with 24 hours • The fourth received 13 plasma exchanges prior to death • No info provided for the 5th death and do not believe included in the 41 included patients as no data was available • Mortality in subgroup of patients with ADAMSTS13<10%: 4/37 = 10.8%.
Patriquin et al. (2016)	6	16.7% (1/6)	Death occurred on Day 9 post-admission	NA
Scully et al. (2014)	35	0.0% (0/35)	NA	• 0 deaths of women • 58% of fetus lost

Westwood et al. (2013)	86 (104 episodes)	5.8% (6/104)	Deaths occurred at a median of 12.5 days following admission (range 4–18 days)	• During the 8-year period (2004–2011) rituximab was given in 104 episodes of acute TTP, to 86 patients who were rituximab-naive and 14 patients (18 episodes) who had been previously treated • Of the rituximab-naive group, 74 were de novo cases and 12 were relapses. • 6 out of 104 episodes resulted in death, including both acute events and relapses (5.8%) • Of the 104 patient episodes there were six deaths (four in the rituximab-naive group, two in the previously treated group). • The overall mortality rate was thus 5.8%; four were male and two female, with a median age of 37.5 years (26–81).
Scully et al. (2011)	40	7.5% (3/40)	NA	• 3/40 during the trial for ritux. • 3/40 in the historical controls group. • 7 deaths prior to admission and therefore excluded due to screen failure
McDonald et al. (2010)	30	10.0% (3/30)	Within 18 days of admission	• 3 deaths (10%) • Only Group 1 included; Group 2 in remission and not receiving PEX
Scully et al. (2008)	178	7.3% (13/178)	46.2% within 24 hours, 23.1% day 2-3, 38.5%> day 7	• Thirteen cases (8.5%) died (10 women, three men), six within 24 h of presentation, one on day 2, two on day 3 and 5 after 7 d of treatment • Mortality estimate conservative as patients excluded if died prior to referral. • Post-January 2004, adjuvant therapy was reduced and rituximab therapy increased.
Lester (2015)	3.88 per million per	0.49 per million per year (i.e. 12.6%)	NR	• Regional variation was between 8% and 20%.

	year			
Orpha.net	Annual incidence of TTP ~ 1/250, 000	15%	NR	NR

Key: ADAMSTS, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; SLR, systematic literature review; SoC, standard of care; TTP, thrombotic thrombocytopenic purpura.

Table 3: Alternative sources of acute mortality for caplacizumab and SoC

	Caplacizumab	**SoC**	**P value**	**Setting in which people had treatment**	**Generalisability to UK population**
HERCULES/TITAN pooled analysis (study treatment period) (Appendix 2)	1/108(0.9%)	5/112 (3.6%)	0.12	Clinical trial in specialised centres	Generalisable to UK population as concluded by the committee in the ACD
Caplacizumab UK Registry (treated within 48 hours of PEX for Caplacizumab arm and >48 hours after first PEX for SOC arm)	[redacted]	[redacted]	NA	UK hospitals under real-world settings as part of the compassionate use scheme	Yes; however, we expect the numbers to be lower if caplacizumab is available in hospitals
Caplacizumab UK Registry (treated within 7 days of PEX)	[redacted]	-	NA	UK hospitals under real-world settings as part of the compassionate use scheme	Yes; however, we expect the numbers to be lower if caplacizumab is available in hospitals
Compassionate use all patients February 2020 (n=239)	9/239 (3.77%)	-	NA	Global compassionate use scheme	UK hospitals participate in the scheme
UK Literature[8, 9]	-	13.0% - 15.0%	NA		
French Matched cohort analysis	[redacted]	[redacted]	N/A	French expert centres	The mortality rate in SoC is similar to that expected in UCLH based on meta-analysis of UK only studies.

* Assume mortality rate among those who received caplacizumab >48 hrs after first PEX is representative of acute management in the absence of caplacizumab;
** This value has been updated from the [redacted] provided at technical engagement phase which was based on interim data matched only on age. This have now been updated in the draft manuscript.

Table 4: Estimates of RRs/HRs for long-term complications based on HERCULES trial data

Parameter	Caplacizumab	SoC	HR* / Proxy RR**
Exacerbations (early and late)	12.68%	38.36%	0.33**
Time to platelet count response, initial (days); HR: SoC versus caplacizumab	1.55		0.65*
Time to platelet count response, initial and exacerbation	N/A	N/A	0.57**
Number of days PEX (mean) – overall treatment period	5.8	9.4	0.62**
Volume of PEX (litres) – overall treatment period	21.3	35.9	0.59**
Number of days hospitalisation (mean) – overall treatment period	9.9	14.4	0.69**
Number of days in ICU for those admitted (mean) – overall treatment period	3.4	9.7	0.35**
Number of days PEX (mean) – all phases, per modelled resource use	[redacted]	[redacted]	0.62**
Volume of PEX (litres) – all phases, per modelled resource use	[redacted]	[redacted]	0.60**
Number of days hospitalisation (mean) – all phases, per modelled resource use	[redacted]	[redacted]	0.79**
Number of days in ICU for those admitted (mean) – all phases, per modelled resource use	[redacted]	[redacted]	0.35**

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*

Table 5: Data available from the QoL study for rates of cognitive impairment or neuropsychological impairment in the UK

<table>
<tr><th></th><th>Data available from the QoL study</th><th>Assumption within the economic model</th></tr>
<tr><td>Cognitive impairment</td><td>
<table>
<tr><td>How much as aTTP affected the following? (n=50)</td><td>I have been able to put my thoughts into words without extra effort…</td></tr>
<tr><td>Not at all</td><td>[redacted]</td></tr>
<tr><td>A little bit</td><td>[redacted]</td></tr>
<tr><td>Somewhat</td><td>[redacted]</td></tr>
<tr><td>Quite a bit</td><td>[redacted]</td></tr>
<tr><td>Very much</td><td>[redacted]</td></tr>
</table>

The PROMIS Short-Form Cognitive Function Abilities 6a (PROMIS SF CFA 6a) was used to assess general patient-perceived cognitive deficits. The scores in the PROMIS SF CFA 6a are calculated to a standardised T-score metric where the mean of 50 represents the average level of the domain for US general population and 10 is the SD. The mean T-score for patients with aTTP was [redacted]), suggesting the cognitive function abilities are one standard deviation lower than the U.S. average.
</td><td>Base case using Kennedy et al. 2009

• 20.8% moderate / severe cognitive impairment

• 54.2% mild cognitive impairment

• Scenario: total 63%</td></tr>
</table>

Neuropsychological impairment	The Hospital Anxiety and Depression Scale (HADS) was used to assess both anxiety and depression. A higher score on each scale indicates a greater severity of symptoms. The cut-off scores for quantification of symptom severity were as follows: 8-10 points was defined as 'mild'; 11-14 points was defined as 'moderate'; and 15-21 was defined as 'severe'. The lowest possible scale score is 0 and the highest possible scale score is 21. According to the cut-off scores [redacted] had mild symptoms, [redacted] had moderate symptoms and [redacted] had severe symptoms. The mean anxiety score for patients with aTTP was [redacted]), suggesting a moderate level of anxiety symptom severity. The mean depression scale score of patients with aTTP was [redacted]), suggesting a moderate level of depression symptom severity. According to the cut-off scores [redacted] had mild symptoms [redacted] had moderate symptoms and [redacted] had severe symptoms. The mean MH domain score for patients with aTTP on the SF-36 was [redacted]) while the mean UK norm score was [redacted]), tentatively suggesting patients with aTTP have poor mental health (i.e. frequent feelings of nervousness and depression) than the general population in the UK.	• Base case using Chaturvedi et al 2015: 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 6: 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.		

Table 7: Changes to model and effect on ICER

Change	ICER	Rationale
Original tech engagement model	£27,856	-
[redacted] per vial; discount [redacted]	£25,531	PAS updated
Mortality 12.6% (0.49/3.88) SoC; RR 0.2 applied to caplacizumab (capla mortality 2.5%)	£24,873	Most representative UK source which takes into account data from all centres not just specialist centres. Also validated by UK registry estimate for those receiving treatment post 48 hours. RR from HERCULES and TITAN used in lieu of matched data as recommended by the ERG. From ACD 3.5; Page 8 – The clinical experts considered that people in the trial may have had better outcomes than would be seen in overall NHS practice. However, this was unlikely to have affected caplacizumab's treatment effect.
Duration of depression increased in line with cognitive impairment (55 years)	£24,183	ACD 3.1; Page 5 – Even when acquired TTP is in 'remission', people with the condition fear relapse. Also, the signs and symptoms of relapse may be non-specific. One patient expert suggested that anxiety itself is a symptom of an upcoming relapse and can lead to long-term depression. The committee concluded that acquired TTP is a life-threatening, stressful condition associated with long-term morbidity and mortality. ACD 3.16, Page 20 – the effect that knowing another treatment exists would have on anxiety
Utilities in acute episode based on literature for caplacizumab, patients on SoC assumed to have half the utility of patients on caplacizumab	£23,469	ACD 3.3; Page 7 – The committee concluded that plasma exchange and hospital stays are unpleasant, and that people with acquired TTP would welcome a treatment that reduces these. ACD 3.16, Page 20 – It noted that there were benefits which may not have been captured in the QALY calculation such as: the effect of caplacizumab in reducing plasma exchange duration on the number of central lines replacements a patient would need, how this reduces the risk of infection and how this would affect a patient's quality of life
Complete improvement in fear of relapse with caplacizumab available	£20,377	ACD 3.13; Page 16 – It also noted that quality-of-life estimates for acquired TTP should include an estimate of the fear of relapse. This was because people with the condition stated this affected their mental health (see section 3.1), not because caplacizumab would lessen relapse, but because they would know a treatment exists. ACD 3.16, Page 20 – [the committee] noted that there were benefits which may not have been captured in the QALY calculation such as: the effect that knowing another treatment exists would have on anxiety ACD 3.1; Page 5 – Even when acquired TTP is in 'remission', people with the condition fear relapse.
Final base case ICER:	**£20,377**	

Table 8: Scenarios

Scenario #	Scenario description	Base case including mortality and long-term complication benefits	No long-term mortality benefit (conservative)	No long term benefit on mortality or complications (extremely conservative)	Rationale
0	BASE CASE	£20,377	£28,174	£47,482	-
1	Base case using long-term mortality of 0.9	£25,738	N/A	N/A	• Using RR of 0.9
2	Relapse rate 2%	£22,219	£30,490	£50,127	• ACD 3.12; Page 16 – modelled rate of relapse is low. Average of clinician estimates of 1% and 1-5% [3%]) =2% scenario. In addition, the use of rituximab during remission has dramatically reduced the relapse rate among people who have suffered an acute episode of aTTP. This was affirmed by clinicians at the Technical Engagement meeting. During validation exercises, clinical expert opinion suggested that 10% of patients will relapse at some point during their remaining lifetime. This aligns with the estimate given on the technical engagement call (10%).
3	Reduced efficacy on retreatment –	£20,791	£28,903	£49,350	• ACD 3.12; Page 16 –

	(i.e. same mortality on relapse for caplacizumab and SoC [12.6%]), base case relapse 1%				**it is uncertain whether caplacizumab works equally well when reused.** • **As discussed in comment No. 14., Sanofi has no reason to believe the effect of caplacizumab would be different on re-exposure**
4	**Reduced efficacy on retreatment – same mortality on relapse for caplacizumab and SoC (12.6%), relapse rate 2%**	**£23,098**	**£32,027**	**£53,916**	
5	**Long-term mortality based on Liu (2013)**	**£14,555**	**Scenario not applicable**	**£20,085**	**Evidence-based long-term mortality scenario**
6	**Long-term mortality based on Rock (1991) – RR 0.66**	**£21,041**	**Scenario not applicable**	**£31,327 (only applicable to complications only)**	**Evidence-based long-term mortality scenario**
7	**Long-term mortality and long-term complications based on Rock (1991) – RR 0.66**	**£21,876**	**Scenario not applicable**	**Scenario not applicable**	**Evidence-based long-term mortality scenario**
8	**Treatment duration [redacted] days**	**£14,535**	**£19,244**	**£33,642**	**Based on Dutt et al. (2020) – reflects caplacizumab's use in real world practice rather than in a trial context**
9	**Mortality rate SoC 7% reflective of specialist centres; mortality RR 0.2 (1.4%) caplacizumab based on HERCULES + TITAN RR (conservative)**	**£21,776**	**£32,069**	**£60,984**	• **ACD 3.9; Page 12.** • **As discussed in the section of acute mortality, mortality in the SoC should be higher than 7%;**

					which is based on mortality in UCLH, a world-leading centre.
10	Mortality rate SoC 12.6%; mortality RR 0.333 (4.2%) caplacizumab based on HERCULES RR	£21,220	£29,954	£52,180	Alternative RR based on HERCULES alone
11	Mortality rate SoC 7%; mortality RR 0.333 (2.3%) caplacizumab based on HERCULES RR (conservative)	£22,332	£33,409	£65,483	Alternative RR based on HERCULES alone
12	Mortality 12.6% SoC, versus compassionate use 9/239 (3.77%) for caplacizumab	£20,988	£29,458	£50,840	Representative comparison of non-specialist centres
13	Mortality 7% SoC, versus UK registry <48 hours 1/54 (1.85%) mortality for caplacizumab (conservative)	£22,041	£32,702	£63,073	Representative comparison of specialist centres
14	Scenarios around alternative assumptions for baseline risk of long-term complications and long term mortality	LT mort; Deford (2013); £20,233	£27,744	£46,821	• ACD 3.10; Page 14 • Alternative assumptions have little effect on the ICER
		LT cog; Cataland (2011); £20,594	£28,915	£46,184	
		LT neuro: Deford (2013); £20,535	£28,936	£45,654	
		LT neuro: Falter (2013); £20,282	£27,733	£48,652	
		LT neuro: Falter (2017); £20,576	£29,139	£45,204	
		LT neuro: Han (2015); £20,447	£28,509	£46,650	
15	Acute utility various scenarios	Caplacizumab, 0.0; SoC, 0; £21,081	£29,673	£51,514	ACD Section 3.13, Page 16; Section 3.15 Page 20 – Alternative quality-of-life scenarios, including the modelling of worse
		Caplacizumab 0.3; SoC 0.15 £20,763	£28,990	£49,647	
		Caplacizumab 0.6; SoC 0.3; £20,455	£28,338	£47,911	

		Caplacizumab 0.6; SoC 0.6; £20,949	**£29,415**	**£50,805**	**quality of life during an acute episode of acquired TTP (see section 3.11) should be provided. Alternative assumptions have little effect on the ICER**

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

Consultation on the appraisal consultation document – deadline for comments **5pm on Friday 3 July 2020** email: **NICE DOCS**

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NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments **5pm on Friday 3 July 2020** email: **NICE DOCS**

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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.	**No links or funding from the tobacco industry**
Name of commentator person completing form:	[redacted]

Comment number	**Comments**

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	As the leading patient group for people with a TTP diagnosis we are concerned that the Committee has not understood the clear and present danger of blood clots circulating the body during the crisis phase of the disorder. Until such time as the platelet count is back within the normal range, clots will form and circulate in the brain and vital organs. On current treatments alone, every single day until normalized platelets is critical to the long term health of the patient.
2	We believe that as a patient group with an ultra-rare blood disorder we are being disadvantaged because we do not believe the Committee had the experience to review a technology designed for such a rare condition (we revert to our opinion that a HST would have been a more appropriate assessment tool). We also fear for the Afro-Caribbean members of our patient community who are disproportionately affected by TTP. This decision causes their healthcare needs to be once again side-lined, in a system that already causes healthcare disadvantage for the BAME community. This is discrimination, when the technology is proven to work in the real world.
3	We know that at the best treatment centres, Caplacizumab is being used as part of the standard treatment of care because Consultant Haematologists know patients will have a better outcome with its use, and it is morally and ethically wrong not to give Caplacizumab when a patient would benefit from it. This evidence should help inform any decision about authorising its use via the NHS. It's imperative that this technology is included in the Treatment Specification for the soon to be commissioned Specialist Treatment Centres, in order to give patients the best level of care and hope of returning to a near normal personal and work life. Below, please find comments from patients/their family members- some of whom tried to comment via your website portal but were unable to do so.
4	I am writing on behalf of my daughter who was recently diagnosed with TTP – April 2020. She was [redacted] at the time. Her plasma level was at 7 and her condition was extremely acute. She had immediate danger of heart attack, stroke or death. Luckily, she was treated with Caplacizumab and she only needed 5 plasma exchanges. We were able to go home within the week, which bearing in mind we were in the middle of a pandemic with its own risks, was extremely important. We were shown how to self-inject and carried on the procedure for a further month at home. 3 months on, she is probably as far on as we could possibly hope. She is a keen golfer and is out playing 4 or 5 times a week, which when you look back to 1 April was something that you could only hope and pray for. The treatment was invaluable in allowing my daughter to return to a near normal

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	lifestyle extremely quickly. I would urge Nice to ensure that this drug is available to others.
5	I am a [redacted] recovering from my first episode of TTP. I was admitted to hospital on [redacted] May and discharged on [redacted] May 2020, on Caplacizumab. I completed the course on [redacted] June but as my Adamst13 was only 3% on [redacted] June my consultant prescribed a further 25-day course of Caplacizumab to give oral immunosuppressants to be effective. If the Caplacizumab resulted in a shorter hospital stay, less plasma exchanges and reduced risk of my suffering long term neurological damage, strokes or even death then it is a valuable treatment. I appreciate this treatment may be very expensive but so are plasma exchanges, longer hospital stays, rehabilitation following strokes and or organ damage caused by clots. Caplacizumab is apparently the biggest breakthrough in the treatment of TTP for 30 years, and I count myself lucky to have been able to avail myself of this treatment and hope that others diagnosed in the future will be able to benefit.
6	As a patient treated for acute TTP in 2017, before Caplacizumab became available, I feel very lucky to have made it through. I spent 9 days in the ICU at [redacted] under [redacted] [redacted] [redacted] and had countless plasma transfusions in order to try and get my platelets to a normal level. All of those 9 days were spent in a critical condition, and I was lucky enough not to suffer any serious strokes or organ damage by the end of it. The length of time spent in ICU has significant effects on the life of not only the patient but the extended family too. And as with my own experience, the longer you are in the ICU, the longer you are in an acute critical condition. I have listened very carefully to [redacted] [redacted] [redacted]discuss the beneficial effects of this drug on current TTP patients and the fact that it has now been the standard of care for the last 2 years. It reduces the number of plasma exchanges needed, increases the blood platelet numbers more quickly and therefore shortens the time spent in acute condition in the ICU. [redacted] [redacted] and her colleagues around the world do so much to forward the research on this deadly disease, but as we are such a small cohort of TTP patients it is very difficult just to keep us alive, let alone get large quantities of data on the long-term efficacy of drugs used to treat us. Suffice to say that the short-term efficacy of Caplacizumab is such that we DO NOT DIE. Long-term data will only come if we are kept alive long enough to provide it. At one time or another nearly all TTP patients relapse, and I very much hope that if and when I relapse – and with my current number trend it could be as soon as 3 month – I will be fortunate enough to be treated by [redacted] [redacted] and her fantastic team, to whom I owe my life, with Caplacizumab.
7	I am appealing to NICE to give Caplacizumab a place in treating TTP patients. We go through very traumatic plasma exchanges, to have a chance to cut down on the amount of treatments we have would be so much easier to cope with. I had 10 plasma exchange so if I had the choice, I would opt for Caplacizumab, so I didn't

	have to have so many. It also helps platelets recover more quickly which has got to be good for our brains and vital organs. Once I was diagnosed, I was in hospital for a week on plasma exchange and then had 3 treatments as an outpatient. If we can go home sooner it helps our mental and emotional torment that we go through with this devastating disease. I have read about Caplacizumab and heard about how it saves lives, simply because of cutting the time it takes to get us in a safe zone more quickly. I wouldn't hesitate to have Caplacizumab. We as patients need something to hope for and Caplacizumab is certainly that. It is the best breakthrough we have had for TTP treatment. Please make this available for us because if I relapsed I would be asking for Caplacizumab because when you are clinging onto life it is so important to know there is a treatment that could improve my chance of survival.
8	Having arrived in the Intensive Care Unit with platelets at level 6 and Adamst13 at 0 and having my life's blood exchanged with plasma for 3 to 4 hours twice a day I thought my life was over and that there was no hope. Having such a rare blood disorder and not knowing the cause is truly frightening and it comes with the fear that it could happen again. But I was given, what I consider a lifeline, Caplacizumab. Knowing it was developed for acute TTP with the aim of raising my platelet levels and to help prevent relapses and the need for future plasma exchanges certainly made my future seem a bit brighter. It is ten months since my first acute TTP episode and Caplacizumab was part of my treatment. My platelets levels rose and have remain at my normal level for 10 months as have all the other blood components including Adamts13 and hence no relapses. I have had no side-effects. I have been able to return to work and a normal life. I find it almost unbelievable. Therefore, I would highly recommend and support the use of Caplacizumab for use in acute stage of TTP. It is a lifeline that's gives us, the patients, hope that we can achieve a better outcome from a rare blood disorder that at one time (and not too long ago) had limited treatment and a high risk of death. Caplacizumab has been a major step in the treatment of TTP. To lose such a wonder drug from the NHS that could benefit a small group of people with a very rare and life-threatening disease would be catastrophic. To summarise, Caplacizumab enables the less time spent in Intensive care, less plasma exchanges, faster normalising and stabilising of platelet levels, less time in hospital, and the chance of returning to some level of a normal life. Caplacizumab must be retained as treatment for TTP within the NHS.
9	This treatment is instrumental in thrombotic thrombocytopenic purpura, it's a drug that has & will save life, I feel we are at a severe disadvantage as this disease is extremely rare. This treatment shortens patients stay battling this illness in hospital which no doubt improves the patients Physiological Health & recovery. We are being discriminated against, thrombotic thrombocytopenic purpura is a rare & life-

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

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	threatening illness therefore only very limited people can trial, as a patient with this illness should I relapse absolutely id expect to be able to access this drug. It's in our basic Human Rights's to be able to access the best treatment and for us with TTP this is without a doubt Caplacizumab, NICE should not use this process as a tick box exercise, TTP is a rare & life threatening disorder & we deserve the best treatment, I genuinely feel we are being discriminated against, as we are unable to test this on a vast patient base.
10	In summary, though we and our patient community are incredibly disappointed with the NICE Committee decision, we seek a positive way forward to enable patients to continue to receive this technology whilst the required evidence is gathered to satisfy NICE of its effectiveness. To that end, we would urge NICE, NHSE and Sanofi to come to a Managed Access Agreement as soon as possible but with some urgency, and furthermore we, TTPNetwork as the leading UK TTP patient group for the past 23yrs, must be involved in this discussion just as other Patient Advocacy Groups are, in other Managed Access Agreements.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**None**]
Name of commentator person completing form:	[**Dr Will Lester**]

Comment number	**Comments**

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	I'm concerned that the innovative nature of this treatment is not fully appreciated. It does not impact on ADAMTS13 and its inhibition however it is the first licensed drug which inhibits VWF-platelet binding which is the cause of microvascular ischaemia in TTP. Although there is insufficient direct evidence of long term benefits (as this is a new drug) the HERCULES trial does show a clear reduction in the number of ITU days (which in turn directly reflects improvement in organ function due to reversal of microvascular ischaemia) and improvement in platelet count (which reflects reduced consumption of platelets in microvascular thrombus). To argue that prolonging the duration of microvascular ischaemia has long term consequences on brain injury is highly plausible.
2	I'm concerned that there is insufficient attention to refractory patients. It is a similar situation to mortality in that numbers were small in the Hercules trial so statistical significance wasn't quite met. There were no refractory patients in the Capla arm of Hercules and 4 in the control arm (p=0.06). The real world incidence of refractory disease is historically higher – 10-20% (Coppo P, Cuker A, George JN. Thrombotic thrombocytopenic purpura: Toward targeted therapy and precision medicine. Research and practice in thrombosis and haemostasis. 2018;3(1):26-37) so as with mortality, the benefit is likely underestimated. Refractory patients require additional therapies which can be expensive (eg plasma cell therapy like Bortezemib) and they require twice daily exchange transfusion which doubles the main material cost and complications
3	I'm concerned that the proposed review date of 3 years is too long as further comparative data between patients on and off caplacizumab should become available before then
4	I can only state again (as I did in the TA) that using the drug through the compassionate access scheme has had huge benefits for patients and to lose access to the drug will be very difficult for those of us who treat this condition
5	
6	

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE
Appraisal consultation document
Caplacizumab for treating acute acquired thrombotic thrombocytopenic purpura

Comments from Professor Marie Scully in Italics
Clinical Lead for TTP-UK TTP forum, UK TTP Registry and NHSE specialist commissioning
Consultant Haematologist UCLH and Professor of Haemostasis and Thrombosis, UCL

The appraisal committee is interested in receiving comments on the following:

- Has all the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity? *Age should not be a consideration-the presence of antibody TTP requires treating with caplacuzimab to aid time to clinical remission*

Why the committee made these recommendations

Standard care for an acute episode of acquired TTP includes plasma exchange and immunosuppressant medicines. Trial results show that, compared with standard care alone, caplacizumab plus standard care reduces:

- • _the time it takes to bring platelet levels back to normal
- • _the number of plasma exchange treatments needed
- • _time in_hospital and intensive care

Adding caplacizumab may reduce the long-term complications of acquired TTP and risk of death around the time of an acute episode. But, the trial does not look at whether adding caplacizumab improves either length or quality of life over the long term. Alternative ways estimating these outcomes are not proven, so this needs confirming.

The limitations in the clinical evidence mean that the cost-effectiveness estimates for caplacizumab compared with standard care are very uncertain. However, they may be higher than the range normally considered a cost-effective use of NHS resources. So, caplacizumab is not recommended for treating acute acquired TTP.

Comment

TTP is an ultra rare, acute life threatening disorder and the process would have fit better within the highly specialised route, but did not meet the requirements as a chronic disease. The remit for TTP has been survival through the acute episode given the high mortality even following diagnosis

and treatment. The long term effects of disease are increasingly recognised as important but the literature base is sparse. The presentation for NICE approval was based on an international randomised controlled study (HERCULES) and outcomes relating to acute disease. Longer term outcomes were not captured. They will however, be available following analysis of the post HERCULES data. Further data will be required from all TTP patients in the UK, via the uK TTP regisdtry, which can be captured, but this will take time to mature ie years.
The data presented is from the HERCULES study but also international real world data from the companys patient access scheme, which includes the UK cases. Also submitted to NICE was the UCLH data set of consecutive patients treated with caplacuzimab in contrast to consecutive patients treated following the same protocol, but without caplacuzimab. From all of these data sets, the benefit of caplacuzimab is clear. In summary, the improved tme to platelet normalisation, significant reduction in the exacerbation rate and refractory disease. The mortlaoty rate in all data sets is favourable to caplacuzimab. But there are some assumptions in the NICE recommendation and from the ERG report that would suggest otherwise that require re-discussion.
Long term data and modelled scenarios are a necessary accompaniment to the application as required for the process but clinically this the data is not satisfactorily available.

Committee discussion

- imbalances in the proportion of people who had rituximab between the arms of the HERCULES trial would not be expected to have a large effect on the cost-effectiveness estimates (issue 2, see technical report page 27)

- • _protocol violations in HERCULES would not be expected to have a large effect on the cost-effectiveness estimates (issue 3, see technical report page 29).

Comment

As discussed in the committee meeting, all UK patients in the study received rituximab. The impact of rituximab is not comparable to caplacuzimab as they target completely different areas of the treatment pathway.

Protocol violations: this is an acute and complex disease

- • _some of their patients have had caplacizumab for the last 2 years via a global compassionate use scheme

Comment

Patietns have NOT had caplacuzimab for 2 years. The patient access scheme has been opened for 2 years, but patients receive treatment for a maximum of 60 days as per the Smpc

The outcomes in HERCULES are clinically relevant, but do not test for short- or long-term morbidity or mortality

Comment
Short term morbidity and mortality ie during an acute TTP episode to the point of complete remission were measured within HERCULES. Data on long term morbidity and mortality will be addressed in the post HERCULES study

- However, people must have also stopped plasma exchange within 5 days of their platelet counts returning to normal

Comment
This is not correct. Patients continued plasma exchange until the platelet count is in the normal range and for 48 hours after. 5 days relates to the time at which patients who do not normalise their platelet count are defined as refractory TTP.

- The committee heard about (but did not see) evidence that the faster the platelet count is normalised, the lower the risk of complications.

Comments
Complications related to acute TTP including mortality are based on time to platelet normalisation. Exacerbations and refractory disease and morbidity and mortality result in longer hospital admissions, more treatments and an understanding of the underlying pathophysiology of TTP. That is platelet microthrombi and organ damage. There are many publications describing this but it does require an inference of understanding the pathology of the disease.

- Other secondary outcomes such as volume and duration of plasma exchange, time in hospital or intensive care, and death were not tested statistically.

Comments
Within the HERCULES data set, there was a clear statistical difference in these measures between placebo and caplacuzimab arms for these specific parameters.

- The committee concluded that the primary surrogate and the secondary outcomes in HERCULES were clinically relevant. However, it noted that the trial did not measure the effect of caplacizumab on survival, quality of life, disability or mental health in the long term.

- One clinical experts explained that she had seen a similar reduction in number of plasma exchanges and hospital stay with caplacizumab when using caplacizumab through the compassionate use programme in her centre.

• The committee concluded that caplacizumab is clinically effective in the acute period compared with standard of care alone.

• However, it concluded that the size of this reduction was unlikely to be as large as that estimated from unadjusted observational analyses, and remained uncertain.

Comment

The committee have accepted the HERCULES data set and the UK data as comparable and already commented that it is clinically effective. This last statement appears contradictory.

In the long term, there is no evidence that caplacizumab reduces the risk of complications

• the company assumed that time in intensive care or hospital was causally related to the prevalence of long-term outcomes including cognitive impairment and mental health (including depression, anxiety, post-traumatic stress), and the relative risk of death

• The committee noted that a relationship between length of stay and the development of subsequent complications had not been validated

Comment:
An explanation about long term data has already been commented on. The impact of ICU stay and depression, anxiety and PTSD is well described (1800 references on Pubmed in the last 10 years, the 1st one was:

Crit Care 2018 Nov 23;22(1):310.

Anxiety, Depression and Post Traumatic Stress Disorder After Critical Illness: A UK-wide Prospective Cohort Study

Robert Hatch[1 2], Duncan Young[3 2], Vicki Barber[4], John Griffiths[5], David A Harrison[6], Peter Watkinson

Other groups aside from the Oklahoma registry have described the impact of TTP and depression, anxiety and PTSD, This is clinically recognised and the reason the presence of a clinical psychologist is part of the national TTP service specification.

• It recalled that the same proportion of people in each arm of HERCULES developed a major thromboembolic complication during short-term follow up in this trial.

Comment
The risk of VTE was comparable between placebo and caplacuzimab. This is unsurprising and in an international study, thromboprophylaxis is not SOC in most centres. TTP carries a number of risk factors, increased weight, prolonged immobility. Caplacuzimab is associated with severe reduction in VWF and a potential risk of bleeding-which was not severe. The study provided important information re the need to consider thromboprophylaxis, even when receiving caplacuzimab.

Modelled rate of relapse is low, and it is uncertain whether caplacizumab works equally well when reused

Caplacizumab is innovative but the extent to which it is a step change in treatment remains unclear

- the committee thought the extent to which it is a step change in the treatment of acquired TTP was unclear because of the uncertainty about its effect on overall survival and long-term complications

Comment
While the long term impact of acute TTP episodes is an important area for ongoing research, there is no dispute clinically the major advance of caplacuzimab in acute TTP. It is standard of care with plasma exchange and immunosuppression (steroids, rituximab). The impact on patient care is highly significant re time to platelet count normalisation and improvement in clinical symptoms

- The committee concluded that the feasibility of a managed access agreement should be explored using the committees preferred assumptions around modelling

Comment
This idea would be welcomed to meet the committees requirement for long term impact following acute TTP.

Comments on the ACD received from the public through the NICE Website

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

Name	[redacted]
Role	
Other role	
Organisation	No
Location	
Conflict	
Notes	
Comments on the ACD:	
I have very damaged veins after several plasma exchanges, drug infusions and repeated blood tests for TTP relapses. My neck and groin veins are badly scared. So much so at my second TTP relapse they had great difficulty in putting in the lines for my plasma exchanges and a few days after the entry points of those lines went septic causing me additional problems. I have had numerous plasma exchanges when the lines haven't been put in correctly because of my scared veins so any drug that can reduce my requirement for repeated plasma exchanges would be a god send for me I have previously during my relapses spent weeks and weeks in hospital and even 3 weeks in intensive care on one occasion so any drug such as Caplacuzimab that will mean I spend less time in hospital will help me enormously and also save NHS resources. If I can reduce the time that I am most ill too by having Caplacuzimab to reduce my worst time I can save myself some very serious long term damage, During my last relapse I spent 18 months afterwards having to learn how to walk again as I suffered blood clots in my right vestibular function which wiped out my coordination and I had blood clots in my brain. So having caplacuzimab could have saved me 18 months of rehabilitation after my relapse	

Name	[redacted]
Role	
Other role	
Organisation	No
Location	
Conflict	
Notes	
Comments on the ACD:	
This drug could drastically improve my treatment of TTP. When I relapse, it takes a long time and an incredibly huge volume of ffp to get my blood back to normal. With Caplacizumab, recovery time would be shorter. The advantages of this being, reduced number of nights spent as an inpatient, reduced number of days with a central line (and therefore a reduced risk of infection and bleeding) lower risk of associated ttp issues such as stroke, bleeds, organ failure and organ damage. Personally I struggle with my mental health and the longer I am an inpatient, the longer it takes me to mentally recover as well as physically. If I were to have Caplacizumab and have a reduced hospital stay, I know I would recover from my acute episode much more quickly and be back to my full life. I am a mother and I	

need to be there for my son. If anything can help me to recover more quickly, I think it is extremely important that it should be available.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
I have had two Acute Episodes of Acquired TTP. The first was in 2013. I was seen by my GP who arranged blood tests and sent me to [redacted]. The next day I was taken to the [redacted] where I stayed for 6 weeks on the Haematology Ward and had 29 plasma exchange sessions, 6 x Retuximab and high dose steroids. I was then discharged home with appointments on alternate days for the first week, requiring me to attend the [redacted], a 130 mile round trip. This caused enormous emotional distress and financial hardship, and this was only week 1 of discharge, there were more to follow. I suffered PTS and had very real fears of my platelets falling and being readmitted for more treatment. In 2017, my Adamts 13 level fell again and I received 4 doses of Retuximab to prevent a full relapse. In 2019, I had a second Acute Episode of Acquired TTP. I was admitted to [redacted] and told that my Adamts 13 level had fallen sharply. I was blue lighted to [redacted] the same day in a critical condition. I was intubated for 5 days, and received kidney dialysis in ITU, staying for three weeks in all. I received Plasma Exchange over a 14 days period and 4 doses of Retuximab with high dose steroids. I was discharged with a supply of Caplacizumab which my husband and I administered at home. I am told that my most recent TTP episode was so much worse than the first, my family were told they should attend. I still have fears of my Adamts 13 levels falling again, to have to undergo another episode is my worst nightmare, but I am reassured by the progress being made with research and new drugs. The treatment, in terms of Plasma Exchange and Retuximab, for my second episode was approximately half that of the first, despite my health being so much worse. I am told that Caplacizumab made this difference for me and that it is hoped that remission will be lengthened because of it. This does give me hope for the future and eases some of the stress associated with TTP episodes and indeed each blood test and appointment. I hope that I and others, who will undoubtedly follow, can be saved by this new drug. Please, I will beg, please, reconsider this drug for TTP patients. There is no cure, but a chance of better treatment to prevent death and enable us to continue to live a better life is absolutely priceless. Thank you for your time.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
Has all of the relevant evidence been taken into account?	

I don't believe so from the evidence of the top professionals in the TTP field, the UK national TTP support network and from the logic of the conclusions stated. I write as a former regulator myself (FSA).

Are the summaries of clinical and resource savings reasonable interpretations of the evidence?
From my experience: I had 26 Plasma exchanges and 5 weeks in hospital after acute TTP in 2017/18; an unnecessary cost to the NHS and pain/discomfort for me that I understand with caplacizumab would have been substantially reduced. Had 1 relapse in 2019 requiring 4 visits x 100 miles each way to [redacted] (the nearest TTP specialist centre to [redacted].)
I have lost 50% of my income permanently + significant family costs.

Are the recommendations sound and a suitable basis for guidance to the NHS?
No. I understand from the evidence available (although not necessarily statistically valid in NICE terms) that I and others may have been unable to access a valuable treatment that lengthened and may be threatened my recovery. This does not seem to represent a sensible cost saving from NICE's point of view.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
The quality of life data seems incomplete yet there seems to be substantial indications of improving quality of life over the long term, which is difficult for most TTP sufferers. The LRBUT Connect study should be relevant.
[redacted] case study in the Sanofi paper.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
As a patient having experienced acute TTP twice, any less time on plasma exchange or in hospital would be beneficial, for mental health as well, as the treatment is gruelling and	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
his is a really important medicine to have access to . My sister has TTP and a young son at home who needs her and she cannot afford to spend weeks in	

hospital like she has previously had to. Please consider this medication for better quality of life to not only the patient but also their family.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

Has all of the relevant evidence been taken into account?

I don't believe so, this treatment is instrumental in ttp, Its a drug that has & will save life, i feel we are being penalised as this disease is extremely rare. this treatment shortens patients stay in hospital which no doubt improves the patients Physiological Health.

Are the summaries of clinical and resource savings reasonable interpretations of the evidence?
absoutley where possible this can only be trialed on those presenting with this rare & complex blood disorders

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
we are being discriminated against as this is a rare ilness therefore only very limited people can trial, this as a patient with ttp, should I relapse absolutely id expect to be able to access this drug.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	

Has all of the relevant evidence been taken into account?

I am responding to the decision not to authorize the use of Caplacizumab in the treatment of TTP.

As a long term chronic relapsing patient of 20 years and 8 relapses behind me I was delighted to hear of this new treatment.

Caplacizumab would shorter my hospital stays which have been approx eight weeks each relapse receiving plasma exchange daily at 25 bag plus on each day. As you can imagine this takes its toll on my body and my overall general health. I have had hundreds of plasma exchange treatments over the years and I was more than delighted to hear of this new treatment which would more than halve my hospital - inpatient stays.

I had awaited this medication for so long and now to see and it has not been authorized is completely heartbreaking to say the least.

After 8 relapses and 3 strokes I am more than lucky to still be alive as you can imagine any positive results for a shorter treatment and less hospital time is a huge positive for all TTP patients alike.

It is on this note that I do not think that all the evidence has been taken into account and patients should be asked and consulted on this matter as it is an imperative part of our future health and welfare.

Caplacizumab is also the first treatment for many many years that would reduce the risk of the long term organ damage and strokes - heart attacks that TTP can and does cause as a 3 times stroke survivor I live with these issues daily

Are the recommendations sound and a suitable basis for guidance to the NHS?

No they are not sound and suitable

The longer a TTP patient is in hospital the higher the risks are of infection and death

the more treatment needed ie PPE the higher the cost

If caplacizumab was agreed this would mean shorter hospital stays - with platelets getting to within a more normal range quicker

Less complications and infections from the condition and the treatment

less reactions to Plasma Exchange (which I have had many)

Less time spent in hospital

The overall benefits of this new drug truly outweigh the negatives - the overall cost would be less too

since diagnoses I have developed another auto immune condition which also needs treatment so my quality of life has been affected greatly

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group

of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
Yes I think that TTP is a disability
Any illness or impairment to your life last lasting longer than 12 months is a disability -

TTP leaves on going issues for the majority of patients for many many years and as time goes on these 'issues' seem to become worse and more debilitating
Life changes completely with TTP - I am unable to enjoy the things in life I took for granted and I have to plan anything I do.
I cannot even book to go for a meal or have a break just incase I am not well or I end up in relapse.

My hospital admissions have been long and the treatment has been aggressive and affected me in many ways any new treatment which would shorter a relapse would literally be a god send for all of us patients and also our carers and our families

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

Plasma exchange is unpleasant, and people with acquired TTP would welcome a treatment that reduces plasma exchange and hospital stays

This is certainly true for me. I have had TTP since 2010 and I have found the plasma exchange to be one of the more stressful experiences of what is already a difficult and stressful time.
The insertion of the IV catheter (whether in the neck, leg or arm) is distressing and, whilst the line is in situ, particularly for long periods of time I am very conscious of the infection risk. Trying to keep the site dry whilst attending to personal hygiene can also be challenging, depending on where the line is. It makes it more difficult to sleep too. Anything that reduces the number or duration of plasma exchanges needed would be a big positive for me, and I relapse roughly every 2 years, so the benefit of any reduction could be considerable.

people would be willing to accept these if treatment reduced hospital stays and the need for plasma exchange.

I would certainly be willing to accept this. I live a significant distance away from my treatment centre, so anything that would mean that I could get home sooner and spend more time with my family would be welcome.

Information on quality of life is not available from HERCULES, and caplacizumab's effect on quality of life remains uncertain

how severely an acute episode affected people.

I have had a number of acute episodes of TTP and the effects have been significant. For all my acute relapses, I have been in hospital, over 100 miles away

for over 2 weeks each time. My concentration has been significantly affected each time, making me unable to work for weeks and months after discharge and I have suffered from fatigue, which has impacted on all areas of my daily life. It has also been a challenge to come to terms with the diagnosis of having a chronic, life-threatening illness when I had previously been healthy. The acute episodes I have had have, indeed, had a severe effect on me and my family, and the longer the treatment episode, the longer it has taken me to get back on my feet afterwards.

estimate of the fear of relapse. This was because people with the condition stated this affected their mental health (see section 3.1), not because caplacizumab would lessen relapse, but because they would know a treatment exists.

The fear of relapse for me is nearly always present. My relapse pattern so far has been roughly every 2 years, but I am really only relatively confident that I will not relapse for around 12 months after Rituximab. After that, the fear is present in the background every day until relapse is confirmed. I show very few symptoms until I am in relapse, but check my body every day for bruises and try to track my levels of fatigue as an early indicator. That in itself is tiring and and makes me more anxious than I otherwise would be, not only about the treatment that I will need, but about having to be away from my family to receive it. Whilst I am fortunate that I have, so far, responded well to Rituximab, that may not always be the case, and it would be reassuring to know that there is an alternative treatment which might reduce such a stay in hospital, were it needed, and mean that I could be back home sooner.

Caplacizumab is innovative but the extent to which it is a step change in treatment remains unclear

The effect of caplacizumab in reducing plasma exchange duration on the number of central lines replacements a patient would need, how this reduces the risk of infection and how this would affect a patient's quality of life

Whilst I have not received Capla, I have now received Rituximab on an elective basis as an outpatient to prevent my last relapse, and the difference between being an inpatient, having plasma exchange and becoming institutionalised, miles away from home and having outpatient treatment over a number of weeks was huge. If it were possible to avoid some of the plasma exchange (with the associated line issues) and get home faster, with an injection, the positive impact on quality of life would be huge. It is difficult to explain the relief of being home with family when you have had to (again) confront your own mortality during a period of relapse. We are all, I think, pretty well aware of how dangerous TTP can be, and whilst treatment is good, and prospects of success are good, people do still die from it and that knowledge doesn't get any lighter, no matter how many episodes I have survived.

the effect that knowing another treatment exists would have on anxiety
For myself, I think knowing there was another treatment out there would have a positive effect on my anxiety. So far, Rituximab has worked for me, but there is no guarantee that this will continue. I need to travel a long way at present for treatment, and this comes with a cost, both personal and financial. If Capla were made available, not only would I not worry so much about what might happen if my current treatment stopped being so effective, there would be an alternative to a lengthy inpatient stay miles away from home with attendant worries associated with being away from my children. I appreciate that the need for inpatient treatment would not necessarily be removed, but it would be reduced, and my anxiety with it.

Caplacizumab is innovative but the extent to which it is a step change in treatment remains unclear

the broader positive effect on the NHS of reducing the use of scarce NHS resources, such as plasma

have received a significant quantity of plasma in the last 10 years of having TTP. In my first admission, I had at least 20 full volume plasma exchanges and 2 double volume exchanges, although this has lessened in recent years as the monitoring of my condition has improved. The cost to the NHS as a result is considerable and I have always been conscious that, not only was I utilising both FFP and Octaplas, but I was occupying a bed (and in some cases at my local hospital before transfer, 2 beds - one in ICU for transfusion and one in haematology). If the number of bed days, use of plasma, plasmapharesis bed, inpatient bed and associated nursing costs can be reduced so that those resources can be available to others, so much the better.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
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Comments on the ACD:

Has all of the relevant evidence been taken into account?

As a very rare disease, any possible treatment / medication for the patients is an absolute lifeline for us. It could simply be the difference between life and death. Extension of life and improvement of one's quality of life will be given through the use of this medication. Reduced time in hospital having treatment - less plasma infusions needed for a quicker recovery. Enables the patient to continue their recovery at home and allows them to return to a new normal of living. Using this medication as a standard treatment alongside other established medication gives the patient a greater chance of life longevity and could reduce the risk of relapse. As a TTP patient myself this medication could be the difference to me coming out of hospital after a relapse in remission or the possibility of never seeing my family again. I therefore please urge you to reconsider your position on your initial decision and please give these patients, including myself, the chance of living a life without the constant worry of relapsing and ultimately not surviving. Long term analysis and results of this medication cannot be made without this treatment being licensed and surely it is worth giving this the green light please to allow as many patients as possible a healthy, disease free future. Many thanks.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
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Comments on the ACD:

I was diagnosed with acquired TT P in 2017 and received daily plasma exchange (6 litres per day) for a period of nearly 6 weeks and my platelet levels were refractory. Had Capla been available my platelet levels may have recovered more quickly and the associated risk of PE X and a venal line may have been reduced. PE X is slow for the patient and Labour intensive for staff. It causes considerable anxiety for the patient and the psychological impact of refractory platelet levels - which meant I could not be discharged from hospital - was considerable. The biggest danger for a TT P patient is reduced platelet levels and associated clotting. It's what makes this condition a life threatening medical emergency. My platelet levels were virtually zero on admission to hospital. I was [redacted] and had suffered no previous health conditions. Any drug that significantly improves platelet recovery has to be a good thing from a patient perspective and could potentially reduce the cost and potential risk of extended plasma exchange treatment as well.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
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Comments on the ACD:

Dear NICE
I am one of very few TTP specialist Nurses in the UK and I very privileged to look after over 60 patients with TTP.
I have looked after over 20 patients who have received Caplacizumab. Some of these patients would have died at diagnosis without access to this treatment and we have used it to treat patients who have had an acute relapse. I can't stress enough what difference this make to patients such as less days of plasma exchange, reduced time in ITU/as an inpatient, less organ damage , a quicker rise in platelet count and this all improves QOL for the patients. Diagnosis in this patient group is already a very stressful and difficult time and this experience can be improved by the use of Caplacizumab, it makes such a difference to their QOL on discharge such as going back to work sooner, being able to spend quality time with their families and reducing any long term symptoms that they might have.

Caplacizumab is the first new treatment for TTP for many years and this treatment should be standard of care for all patients who are diagnosed or having a relapse.

Best wishes
[redacted]

Name	[redacted]
Role	

Other role	
Organisation	
Location	
Conflict	
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Comments on the ACD:	
I was diagnosed with TTP in 2003 and spent 6 weeks away from my young family having daily plasmapheresis to save my life along with numerous medication as at that time very little was known about the disease, 17 years later I am amazed at the research that has enabled me to live a full life and I cannot tell you how important this drug is to those of us unfortunate to have this rare disease . This disease has a huge impact both physically and mentally and to be able to have reduced time In hospital on plasmapheresis , improves outcome for not dying in an acute relapse and the opportunity to live life to the full is amazing. I personally have not received this drug although I have over the years had acute relapses and prevenatative treatment , recently I have had to travel to uclh in London from Bournemouth to have prevenataive treatment this impacts enormously on my family , work and financially . Therefore I would like NICE to consider and recognise the impact this disease has in us rare ttp patients and how this drug will improve our lives and those who develop ttp	

Name	[redacted]
Role	
Other role	
Organisation	
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Comments on the ACD:	
My Sister has been in and out of hospital with TTP since she was 18. Thankfully she has only had a handful of serious occasions when she has had to be in hospital for long periods of time. When this has happened it has been a very worrying and stressful time for the whole family. If this could help to reduce the amount of time she would need to spend in hospital then it would be so beneficial all round. Not only for her health, but for the entire familys peace of mind. It would be such a relief to think that even though she can not be cured this could make such a difference her quality of life**.**	

Name	[redacted]
Role	
Other role	
Organisation	
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Comments on the ACD:	
Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?	

As a family member the impact our daughter's treatment has on us through having access to this drug would be remarkable. This drug could massively reduce the time she needed treatment with plasma exchange, it means reduced time in the hospital, reduced time with a central line which in turn means a reduced risk of infection and bleeding. A quicker recovery could mean less chance of organ damage, stroke and bleeding. Also, the use of this drug would have a much more positive outcome from a mental health perspective to have a shorter hospital stay.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
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Comments on the ACD:

Has all of the relevant evidence been taken into account?
Yes

Are the summaries of clinical and resource savings reasonable interpretations of the evidence?
No

Are the recommendations sound and a suitable basis for guidance to the NHS?
No

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
No

Caplacizumab keeps patients from suffering unnecessary relapse during treatment. Meaning, longterm patients aren't susceptible to damage to their organs and memory from relapsing. Caplacizumab allows patients to live their lives, as normally as possible, while keeping them out of the hospital. Hospital stays range from 2 weeks to a month to recover from TTP episodes. The longterm benefits of staying out of the hospital are as follows: decrease risk of infection, decreased risk of complications with central line, decreased risk of losing financial independence (ability to pay bills & eat), increased risk of psychological happiness (less stress, being with family, & living a normal life). All of these factors effect TTP patients longterm & short-term outcomes either positively or negatively.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	

Notes	
Comments on the ACD:	
. have been diagnosed with acquired TTP in December 2019. I had an acute phase and ended up in intensive care in the nearest specialist centre. I have been treated as per guidelines with plasma exchanges, steroids, caplacizumab and rituximab. Due to the fast reaction and prompt treatment I was able to be discharged after 6 days. As I have responsibilities at home and wanted to return to my own home environmental as quick as possible I was more then happy to participate and receive the drug caplacizumab as this has shown to minimise the hospital stay. I was more then happy to administer caplacizumab at home on my own as the injections are very straight forward and easy to administer. Due to my quick discharge I was able to commence my “normal” life and try to learn how to life with something which come as a great shock. I was able to return to work faster and thereby have less impact financially as well as mentally. To return to work and be part of society again and return to my normal life. As my mother has aTTP as well I have seen the other side of it when she was diagnosed in the 1990s there wasn’t any treatment like caplacizumab available. So she used to have lengthy hospital stays and I have had to have a long time away from my mother at a young age. I don’t wish my children to go through a similar time then I have and if caplacizumab is the answer for a shorter hospital stay then it should be considered as frontline treatment. It has helped me financially and emotionally after the worst time of my life. Furthermore, I have recognised how busy the wards are and if something could minimise the stay even if it’s just for a few day’s it could greatly help the anyway overly full wards.	

Name	[redacted]
Role	
Other role	
Organisation	
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Notes	
Comments on the ACD:	
This drug is an amazing treatmeant for those with TTP. It reduces the time needed in hospital and also reduces the amount of plasma infusions needed. The long term affects for TTP patients are.very positive with this drug too. Please reconsider licensing it for use with TTP. I had TTP in 2015. This drug was not available at the time. I had a long stay in hospital and many procedures. If this drug had been available my recovery time would have been much quicker saving the NHS time and money.	

Name	[redacted]
Role	
Other role	
Organisation	
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Conflict	
Notes	
Comments on the ACD:	
. his recommendation is absurd . I’m a TTP patient , and caplizumab greatly reduces the time of recovery for us patients . Also reducing the stress emotionally and the toll plasma exchange has on the body . I had a terrible allergic reaction to	

retuximab , ending up with toxic epidermal necrolysis , which hospitalised ne for weeks more , and was hoping for caplizumab as an alternative treatment , eso also suffering a stroke/vascular bleed . Please Re.consider For the sake of people's lives . Thank you

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

I feel that the decision taken by NICE not to recommend the use of Caplacizumab in the treatment of aTTP does not adequately take into consideration the long term financial impact of aTTP initial episodes or relapses. Research has shown that prior to the use of Caplacizumab in the UK there were extended ITU and hospital stays in acute relapses, additional plasmapheris treatments and an increased likelihood of ongoing lifelong cognitive impairment. The aTTP population has an average age of 45 so sufferers are commonly of working age and have dependent children. It is imperative therefore that they are able to regain independence and have the ability to return to work where able thus reducing dependence on our health and social care systems.

I feel that the recommendation not to approve Caplacizumab for use in acute episodes of aTTP is denying the population of aTTP sufferers in the UK the opportunity to have the optimum chance of recovery from this life threatening condition. As a daughter of a TTP sufferer I can confirm it has a devastating effect on those who are diagnosed with it, their families and loved ones. I am also an NHS Parkinson's nurse specialist so feel lucky in many respects that I am in a position to utilise my medical knowledge and skills to help me navigate through the process of understanding TTP. I have had to thoroughly research all aspects of this complex and harrowing condition in order to educate myself with regards to the best available treatments and support my mother both physically and emotionally. Research has shown that Caplacizumab has been clinically proven to reduce the length of hospital stay (both ITU and ward based) and the number of invasive plasmaphereis treatments needed during an acute aTTP episode. The introduction of Caplacizumab as a treatment for relapse in aTTP has been a breakthrough in altering the pathophysiology of the condition. This treatment is widely recognised as the gold standard of treatment in the UK, the US and throughout Europe due to it's proven benefit in reducing clot formation during the period following plasmapheresis. The resulting benefits of Caplacizumab use are a faster overall recovery, a reduced hospital stay and return to independent living and a reduction in long term complications. I have become a member of many TTP support groups in the UK and internationally and aTTP sufferers consistently report problems with memory and recall, headaches and cognitive impairment in addition to the ongoing psychological symptoms of anxiety around possible relapse and depression. Caplacizumab given following an initial or acute episode has been proven to minimise the risk of clot formation and therefore improve long term cognitive outcomes. This is a rare condition however aTTP sufferers should not be denied the chance to improve their prognosis following initial episodes and subsequent relapses. The average age of suffers is mid 40's and this group of patients typically need to remain independent, continue their employment and support their families. Caplacizumab improves mortality rates in acute episodes

which is crucial in this generally young and otherwise healthy patient group. Denying aTTP sufferers the option of accessing Caplacizumab will have a devastating impact on sufferers and is I feel a short sighted decision as it will increase the dependency of this patient population not only on their families but on the health and social care system. It is highlighted in this consultation document that the long term benefits of Caplacizumab have not been demonstrated however this medication has only been in use since 2017 so it is not possible to produce evidence from a long term study. It should not be concluded that Caplacizumab is not approved for use in aTTP due to lack of evidence of the long term benefits as research is still ongoing and all findings to date with regards to health benefits and improved quality of life measures have been positive. QALY (Quality Adjusted Life Years) is an outcome measure when considering the approval of medication through NICE. The prevention of micro emboli in an acute aTTP episode has a direct impact on the QALY as this reduces the incidence of cognitive impairment and stroke like symptoms which are common in aTTP sufferers.

Name	[redacted]
Role	
Other role	
Organisation	
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Conflict	
Notes	
Comments on the ACD:	
. As the husband of a TTP patient I have over the years seen the impact of the condition on both the physical and mental health of my wife. Due to the disease the prolonged hospital stays and the plasma exchange therapy my wife experiences extreme tiredness and periods of high anxiety and we have needed to adjust our lifestyle based on her need to work reduced hours. This has a significant impact on our day to day activities through travel itineraries and venues. Having researched caplacizumab I am of the belief that this would make an episode of TTP considerably less impactful to other episodes that she has suffered. The side effects reported seem to be few and are massively outweighed by the benefit. I would urge you reconsider your initial view. TTP patients are a very small group who are adversely affected by this life threatening condition and this treatment offers them hope of a speedy recovery, something that until recently seemed unreachable.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
I have had an episode of TTT and was given a few days of Caplacizumab before stopping due to side effects. Prolonged plasma exchange and time in intensive care is detrimental to health and any medicine that decreases the amount of plasma exchanges received and time in intensive care will improve recovery times.	

Plasma as a blood based product carries its own risks and decreasing number of exchanges will decrease this risk.
I was extremely fit and well prior to my first episode and have taken a significant amount of time to return to work . My physical / psychological health is improving. However, any prolonged courses of treatment will cause significant physical and psychological health problems which will impact on quality of life and possible earlier mortality. This disease is acute and life threatening when it initially occurs in usually a young population. The recovery can be prolonged and some people will never fully recover. I do not agree with your recommendation and feel that Caplacizumab can benefit quality of life and length of life. I and feel the decision needs to be urgently reviewed.

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	

Comments on the ACD:

. **Has all of the relevant evidence been taken into account?**
no; as a parent of a young person who has had multiple episodes of TTP i do not think NICE has reasonably considered the impact on the life of that sufferer or their family by an acute episode. the amount of time spent in hosp undergoing intrusive plasma exchange can be shortened by this proposed drug and that has untold benefits in terms of reduced trauma to the sufferer and the family (i cannot stress how much trauma and uncertainty within the family this illness causes). the reduced risk of clots by use of this drug has to have a positive long term effect on the sufferer and potential costs to the NHS in their care should clots occur. To reduce the amount of time a sufferer is on plasma exchange and to bring their blood levels back to manageable means they can leave hospital for out patient treatment and therefore an obvous cost saving to the NHS

Are the summaries of clinical and resource savings reasonable interpretations of the evidence?
no; i do not think NICE have taken into account the savings to the NHS of enabling a sufferer to leave hospital and undertake outpatient treatment and the reduced risk of clots by use of this proposed drug

Are the recommendations sound and a suitable basis for guidance to the NHS?
i do not believe it is sound guidance given the issues raised in the previous questions

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?
I think there is indirect discrimination to all groups by not enabling a useful and effective drug to be used to benefit all

Name	[redacted]

Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
This is vital medication that would help my Daughter should she have a TTP relapse. It would reduce her time in hospital and avoid her having to have traumatic distressing treatments with risk of infection. As a mum I have seen my beautiful daughter struggle with her condition for many years and if this medication can help her I beg you to approve it's use for TTP as soon as possible. [redacted]	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
As a TTP patient since 2003 when I was admitted to [redacted] with my first acute episode, and with 6 subsequent relapses,I can still remember vividly the many, many days of plasma exchange. Having to be in hospital away from my young family for so long, I could only dream about having a treatment that could shorten the time spent in hospital, shorten the many plasma exchanges and allow me to be at home with my family sooner. Now with Capla as a safe treatment in conjunction with plasma exchange, this dream could come to fruition if Capla is approved for ttp patients. Please make this happen,.	

Name	[redacted]
Role	
Other role	
Organisation	
Location	
Conflict	
Notes	
Comments on the ACD:	
I would like to comment on the decision not to use Caplacizumab in the treatment of TTP. I think this would be a huge mistake. I've had personal experience of this wonderful drug as last year I was suddenly and unexpectedly struck down with acute TTP and nearly died. Along with plasma exchange, Caplacizumab had a hand in saving my life. I'm not sure of the specifics of my case but I don't think my ADAMTS13 was responding to plasma exchange, so I was put onto Caplacizumab. I tolerated it well and was able to go home and continue Caplacizumab at home. Nobody who has not suffered with TTP understands the full extent of how frightening it is and what a lonely road it is to travel. I would ask NICE to reconsider this decision. Thank you. [redacted]	

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. The difference in the proportion of patients experiencing their first episode was particularly pronounced for patients receiving placebo: 58% of patients in the placebo arm who had a protocol violation were experiencing their first episode of aTTP compared to 37.5% who did not experience a violation. Across both trial arms, there was no clear difference in whether ADAMTS was above or below 10%; however, those in the placebo arm who had a protocol violation were more likely than those who did not have a violation to have ADAMTS above 10% (15.2% vs. 5.0%, 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.

ID 1185: Caplacizumab in aTTP – Sanofi response to Committee's preferred assumptions post-second ACM

14 August 2020

Thank you for the opportunity to discuss the committee's preferred assumptions with the technical team last week. As discussed, we accept most of the committee's preferred assumptions, and have updated the economic model accordingly. However, there are a couple of assumptions, namely the relative risks for acute and long-term mortality, that we are particularly concerned with as they do not appear to be a reasonable reflection of the available evidence.

We provide in the following pages a summary of the available evidence for these two variables and Sanofi's position on each. In addition we have provided details regarding how the committee's preferred assumptions have been incorporated into the model and provided the resulting ICERs for a small number of scenarios that vary key assumptions (based on the existing PAS price submitted in response to the ACD).

To reiterate, we will continue to work with NICE to ensure that caplacizumab can be made available to patients in England as soon as possible but we would again highlight that this is a severe, life threatening, ultra-rare condition for which uncertainty is inevitable. Given caplacizumab is indicated for a small, defined patient population, it should be considered low risk. We strongly believe that with reasonable assumptions that reflect the available clinical trial and real-world evidence, caplacizumab can be deemed a cost-effective use of NHS resources.

1. Committee preferred assumptions (post 2nd ACM)

Table 1 below shows the committee's preferred assumptions that were communicated to Sanofi (via email from the NICE technical team) after the second ACM and the impact of these assumptions on the ICER.

Table 1: Committee's preferred assumptions and impact on ICER

Variable	Original base case assumption	AC preferred assumption*	ICER (cumulative impact of the NICE preferred assumptions)
Company base case following response to ACD	-	-	£20,377
Acute mortality, (standard care)	12.6%	10%	£20,993
RR acute mortality	0.2	0.5	£22,718
Reduction in acute quality of life for SoC patients	50% reduction	25% reduction	£23,087
RR for long-term complications	0.62	0.66 for (based on Rock et al.)	£24,093
RR for long-term mortality	0.62	0.9	£32,557
Fear of relapse disutility	On	Off	£43,177

Relapse rate	1%	1.5%**	£45,102
Revised SMR calculation	England and Wales general population mortality	US general population mortality	£41,470

*Based on email communication and teleconference between Sanofi and NICE technical team

**Relapse rate of 1.5% as agreed with NICE technical team on teleconference on 7th August 2020

2. Sanofi response to committee preferred assumptions (post 2nd ACM)

Table 2 and Table 3 below summarise the existing sources of RR for acute and long-term mortality.

Table 2: Acute mortality (caplacizumab) - Relative risk

No.	Source	RR	Comment
1	HERCULES RR	0.34	Based on HERCULES mortality during treatment and follow-up; 1/72 in the caplacizumab arm vs 3/73 in the SoC arm
2	Pooled HERCULES/TITAN RR (ERG calculated)	0.21	ERG calculated risk ratio obtained from pooled HERCULES/TITAN treatment and follow-up periods; 1/108 in the caplacizumab arm vs 5/112 in the SoC arm. See Page 18 of ERG response to company response to technical engagement report.
3	UK registry data	[redacted]	Based on UK mortality among patients who received caplacizumab who received caplacizumab within 48 hours of first PEX (as per SmPC) compared to those who received caplacizumab ≥ 48 hours after first PEX (in effect, mortality rate without caplacizumab); [redacted] respectively
4	UK registry data	[redacted]	Calculated using [redacted] (see preceding row) for caplacizumab and committee's preferred assumption of 10% for SOC mortality
5	Committee preferred assumption	0.5	"Risk ratio of acute mortality caplacizumab compared with standard care is likely to be greater than 0 but less than 1, therefore a midpoint of 0.5 should be used with sensitivity analyses (n.b. the committee noted that a naïve comparison between the acute mortality on caplacizumab from the global compassionate use scheme (3.8%) and the estimated value for UK centres (7%) may represent a unmatched estimate for specialist centres, and this may give a risk ratio slightly higher than the 0.5 midpoint)"
Sanofi response			
The committee's preferred assumption of a RR of 0.5 for acute mortality appears to have been calculated using acute mortality (for caplacizumab) from the global compassionate scheme (3.8%) and for SOC, 7% mortality rate derived from UCLH studies. Sanofi would like to highlight the following points: 1. This approach is similar to the one employed in the original CS. As discussed in the ACD, the committee did not consider a "naïve comparison" approach to be robust. 2. The compassionate use scheme is a global program and as such, a better comparison would be with UK specific data. Mortality rate among patients who received caplacizumab (as part of the compassionate scheme) and within 48 hours of first PEX is [redacted]. A naïve comparison with UCLH mortality rate (7%) results in a RR of [redacted]. 3. Based on the committee's preferred assumption of 10% as SOC mortality in the UK, a naive comparison with UK caplacizumab mortality rate results in a RR of [redacted]		

4. The available clinical trial and real-world evidence show RR ranges from **0.14 to 0.29.**

Sanofi considers a RR of 0.5 to be extremely conservative and not easily substantiable given the existing data. We would therefore urge the committee to consider using a value representing the upper end of the available evidence (RR = 0.34).

Table 3: Long-term mortality (caplacizumab) - Relative risk

	Source	RR	Comment
1	Company original submission	0.62	Proxy RR calculated based on ratio of days spent in hospital/ICU between caplacizumab and SoC arms in HERCULES.
2	ERG calculated RR	0.69	Proxy RR calculated based on ratio of hospitalisation including ICU days between caplacizumab and SoC arms in HERCULES
3	Company revised submission (post-ACD)	0.66	Based on Rock et al (1991)
4	Company revised submission (post-ACD)	0.59	Scenario based on Liu et al (2013); RR calculated at 1 year
5	Committee preferred assumption	0.9	"Risk ratio of death in long term model caplacizumab vs. standard care should use more conservative estimate of 0.9 (The potential benefits of caplacizumab on long term morbidity and mortality remain highly uncertain. The committee considered that a benefit of caplacizumab on complications was plausible, but whether this would translate to a benefit in survival was more uncertain)".
Sanofi response			
Following the committee's preference (in the ACD) for platelet count as a surrogate measure for more long-term morbidity and mortality, 2 papers that provide some supportive evidence in aTTP patients -Rock et al (1991) and Liu et al (2013) were used to estimate RR for long-term outcomes. Each have limitations as discussed during the ACM, however, they both support the concept that faster resolution of acute episodes leads to improved survival outside of the acute period. Using Rock et al (1991) and assuming that response as assessed in HERCULES will have a similar relationship with mortality to response assessed in Rock et al (1991), we calculated a RR of **0.66** (please see comment No. 9 of company's ACD stakeholder comments form for detailed calculations). This study demonstrated a near 1:1 relationship between mortality and response to treatment (platelet count of more than 150 x 10^9/L for two consecutive days and no new neurologic events). This paper provides the best available evidence to inform the likely impact of treatment with caplacizumab on long-term mortality. The analysis presented using the Rock et al (1991) paper was supported with information from the Liu et al (2013) paper which also demonstrated a link between platelet count response and mortality. Both the Rock (1991) and Liu (2013) papers are consistent in that a link is shown between response to treatment (platelet count response) and mortality.			

The relative risks produced using the data from these papers are considerably more favourable than the 0.9 currently being considered by the Committee and are in line with the original company and ERG preferred values (0.62 and 0.69).

Sanofi believes a RR of 0.66 is a reasonable assumption for long-term mortality. However, given the uncertainty, Sanofi has amended its base case to use 0.8. This lies between 0.66 and the committee's preferred assumption of 0.9

Incorporation of committees preferred assumptions into the economic model

Table 4 summarises the committee's assumption accepted by Sanofi and incorporated in the model.

Table 4: Committee's assumptions accepted by Sanofi and implemented in CE model

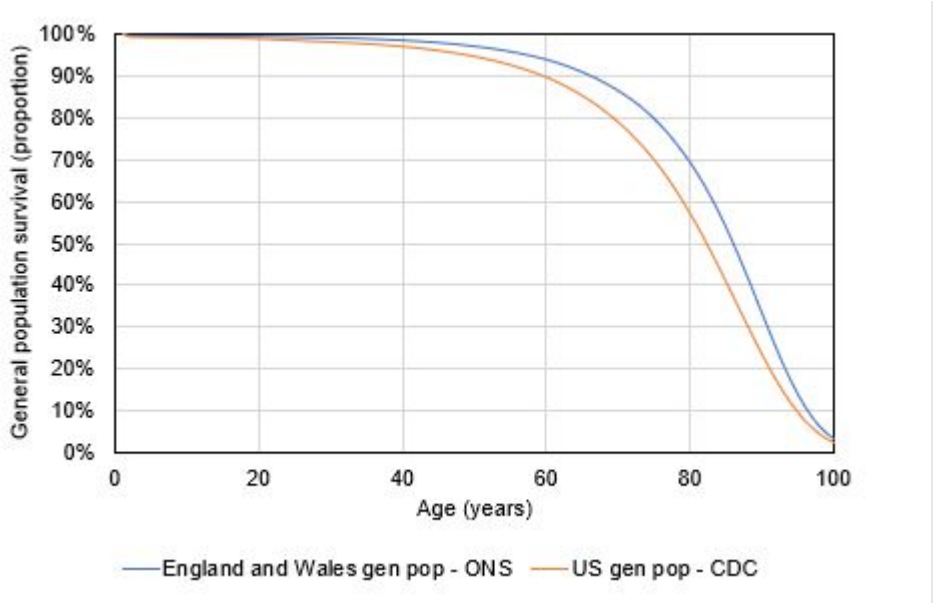
<table>
<tr><th></th><th></th><th>Committee's preferred assumption</th><th>Sanofi response</th></tr>
<tr><td>1</td><td>Acute mortality (SOC)</td><td>10%

"Acute absolute mortality rates on standard care for the duration of the acute episode likely falls between 7% and 12.6%, therefore a midpoint of 10% should be used with sensitivity analyses"</td><td>Sanofi would like to highlight that there are a number of sources providing evidence that the mortality rate on SOC is higher than the 10% assumed by the committee.

<table>
<tr><td>Lester et al</td><td>12.6%</td><td>TTP mortality for all of England based on ONS/HES data</td></tr>
<tr><td>Meta-analysis</td><td>13.2%</td><td>Global SLR – value validated by clinicians</td></tr>
<tr><td>UK registry data*</td><td>[redacted]</td><td>UK mortality among patients who received caplacizumab ≥48 hours after first PEX. Sanofi considers this to reflect the real-world acute mortality rate in the absence of caplacizumab. For those who received caplacizumab within 48 hours of first PEX (as per marketing authorisation), mortality rate was [redacted].</td></tr>
<tr><td>Meta-analysis of UK studies</td><td>7%</td><td>Requested by committee in the ACD. As previously highlighted, all UK studies were UCLH specific (a global leading centre for aTTP management) and as such not generalisable to the rest of England. A mortality rate of 7% can be achieved once the NHS specialised service is instituted and all centres are able to provide a similar level of care to UCLH.</td></tr>
</table>

Sanofi considers the UK registry data that shows mortality among patients who received caplacizumab ≥ 48 hrs after first PEX [redacted] to be an accurate representation of aTTP mortality in the absence of caplacizumab. In addition, this is very close to the mortality rate in Lester et al (12.6%) and the meta-analysis of global studies (13.2%); confirmation that mortality will be higher in centres other than UCLH.

However, we have revised our base case to 10% in line with the committee's preferred assumption.</td></tr>
</table>

2	Standardised mortality ratio (SMR)	Recalculating the standardised mortality ratio underlying the estimate of the absolute risk of dying for people on standard care using general population relevant to Upreti et al (n.b this was to control for the possibility that people in the general population in UK had greater life expectancy than people in the region Upreti collected data from)"	The SMR for patients on standard care in remission has been recalculated using general population mortality for the region Upreti et al collected data from. The Upreti study considers 170 consecutive patients treated for TTP at the Johns Hopkins Hospital in Baltimore, Maryland, US, between 1995 and 2018. US general population mortality was taken from US life tables published by the Centers for Disease Control and Prevention (CDC). Life tables from 2002 were used as this is the mid-point year between the study inclusion dates of 1995 and 2018. A comparison of general population mortality for England & Wales (current base case) and the US is presented below:  As anticipated by the NICE, general population mortality in the US is slightly higher than that of England & Wales. When US mortality is used in the SMR calculation, this leads to a lower **SMR of 5.10**.
3	Relapse rate	Relapse rate should be between 1% and 5%	Sanofi considers a relapse rate of 1% to be valid due to monitoring and use of rituximab in remission. We anticipate this rate will further decrease once the NHS specialised service is

			instituted. 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. In the model, this equates to a lifetime relapse rate of approximately 16%. Similarly, during the technical engagement process, one clinician stated that 10% of patients will relapse at some point over the course of their remaining lifetime, equating to an annual relapse rate of <1%. If a 2% annual relapse rate is tested in the model, this results in a lifetime relapse rate of 32-34% which is vastly beyond clinical plausibility. **Sanofi has revised its base case assumption to a more conservative relapse rate of 1.5%. This is in line with the committee's preferred assumptions.**
3	Utility values (acute phase)	"Assuming half the quality of life on standard care is likely to overestimate the negative impact of having longer stays in hospital and more plasma exchange than with caplacizumab (The committee noted that scenarios around utility values in the acute decision tree model had limited impact on the ICER- NICE technical team would suggest that a scenario using a mid-point between original company base case and the company's revised base case – i.e. a 25% reduction in quality of life for standard care compared with caplacizumab is relevant)."	Completed as per committee's preference
4	Prevalence of LTCs in SOC	In absence of other data, the company's estimates are reasonable	No action required

5	Duration of LTC	Duration of neuropsychological impairment should be lifetime (n.b. as per revised base case after ACD).	No action required
6	Fear of relapse	Do not model fear of relapse modelled separately (*this would be captured by lifetime neuropsychological impairment – see bullet above)*	Fear of relapse has been switched off as per committee's preference

3. Cost-effectiveness results using committee's preferred assumptions

Table 5 presents ICERs for the committee's preferred assumptions, a revised Sanofi base case and some alternative scenarios. All scenarios incorporate the committee's preferred assumptions (implemented as detailed above) except for the variables highlighted. ICERs are based on the PAS price submitted in response to the ACD.

Table 5: ICERs

Scenario	Acute mortality RR	Relapse rate	LTM RR	Treatment duration	ICER at post-ACD PAS
AC preferred assumptions	0.5	1.5%	0.9	Trial	£41,470
Sanofi revised base case	0.34	1.5%	0.8	Trial	£33,620
A	0.34	1%	0.66	Trial	£27,615
B	0.34	1.5%	0.66	Trial	£28,963
C	0.5	1%	0.66	Trial	£29,491
D	0.5	1.5%	0.66	Trial	£30,997
E	0.5	1.5%	0.9	UK registry (mean); [redacted] days	£33,526

It is also worth noting that treatment duration with caplacizumab in the real world may be shorter than modelled here (based on UK registry data) meaning that these ICERs would be lower if the shorter duration is applied (see scenario E). This should provide some reassurance regarding the existing level of uncertainty.

In addition, there are a number of benefits rightly recognised by NICE as uncaptured within the economic analysis. These include:

- The effect of caplacizumab in reducing plasma exchange duration on the number of central lines replacements a patient would need on quality of life and risk of infection – a benefit for which there is clear support from patient and clinical representatives.
- The impact of caplacizumab in reducing the need for ICU stays – a key benefit in terms of NHS capacity.