NICE National Institute for Health and Care Excellence

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Caplacizumab for acute acquired thrombotic thrombocytopenic purpura [ID1185]

Chair's presentation

2nd appraisal committee meeting
Committee B, 16 July 2020

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Evidence Review Group: Peninsula Technology Assessment Group (PenTag)

Technical team: Amanda Adler, Mary Hughes, Carl Prescott, Nicole Elliott

Company: Sanofi

Recommendations - Appraisal Consultation Document

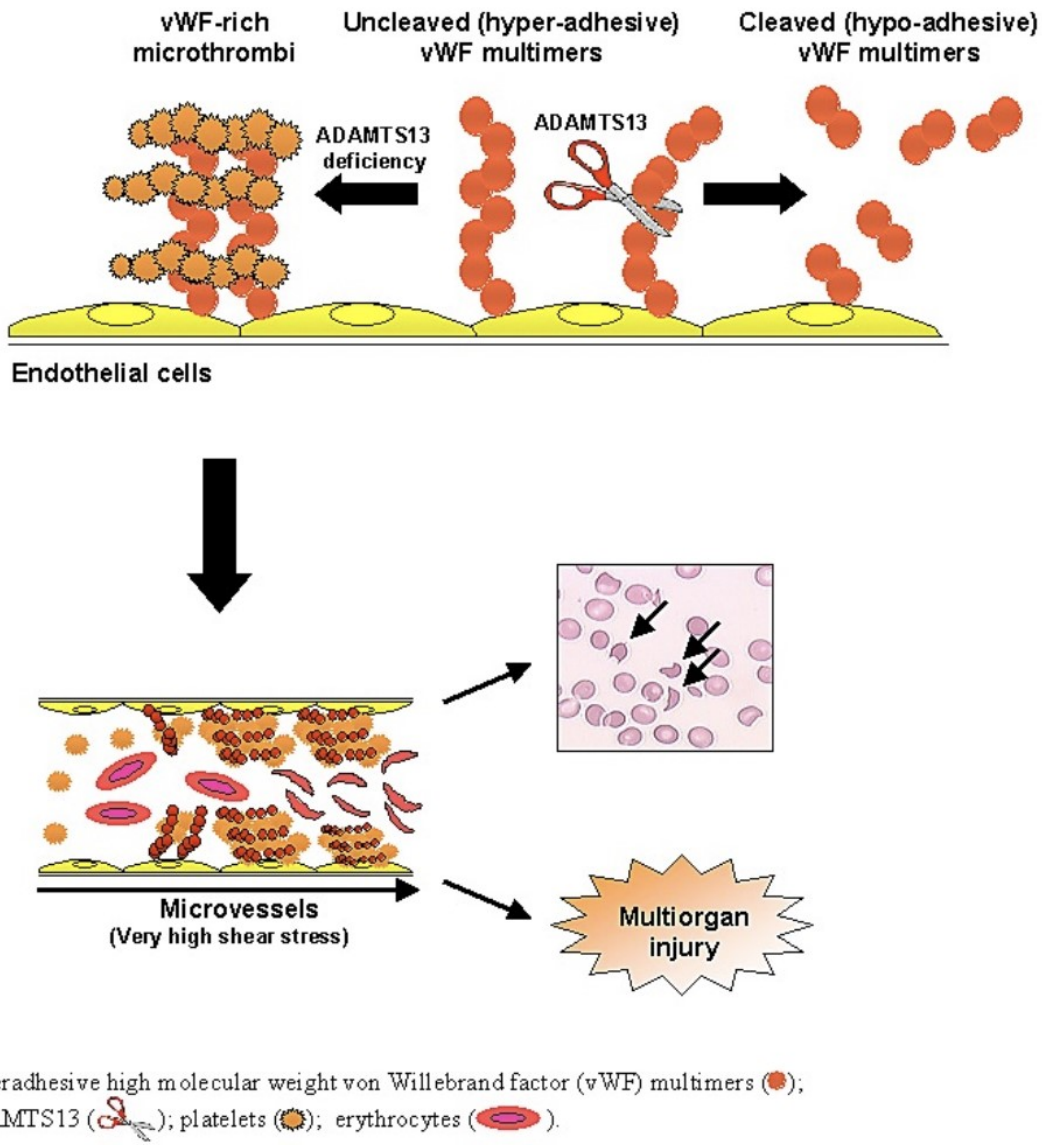
- For acute episode of acquired TTP, standard care includes plasma exchange and immunosuppressants
- Trial results in acute disease show caplacizumab + standard care vs standard care alone reduces:
  - time it takes to normalise platelet levels
  - number of plasma exchange treatments
  - time in hospital and intensive care
- Trial does not look at whether adding caplacizumab improves length or quality of life over long term
- Limitations in clinical evidence mean that cost-effectiveness for caplacizumab vs standard care is ‘very uncertain.’
- Caplacizumab not recommended

History of appraisal

- May 2020 committee included patient access scheme discount
- Committee recognised evidence generation difficult given rare nature of disease, therefore managed access agreement (MAA) potential should be explored
- June 2020: Company, NHS England & NICE discussed MAA:
  - Possible, but several issues with feasibility
- July 2020: Company open to MAA but making a case for routine commissioning in first instance
- Committee decision on routine commissioning is in part 2 of this meeting

Thrombotic thrombocytopenic purpura, acquired

- Autoimmune (‘acquired’) condition against an enzyme ADAMTS13
- Normally, ADAMTS13 cuts up von Willebrand factor into small pieces
- If not cut up, von Willebrand factor will trigger clots ‘thrombi’
- So, without enough ADAMTS13, multiple thrombi develop
- Leads to ischaemic injury: may include myocardial infarction, stroke, renal failure disability and death
- Treatment in acute setting aims to remove antibodies, prevent new antibodies, prevent clots
- Episodes can recur
- Caplacizumab is a von Willebrand factor–directed antibody



Ref Predictive Features of Severe Acquired ADAMTS13 Deficiency in Idiopathic Thrombotic Microangiopathies: The French TMA Reference Center Experience

Acute management of aTTP

Pathway as per British Committee for Standards in Haematology (2012)

Diagnosis

- Microangiopathic haemolytic anaemia
- Thrombocytopenia
- ADAMTS13 activity <10%
- Anti-ADAMS13 antibody

Blue light to specialist centre 8 hours to treat

Plasma exchange + rituximab corticosteroids

Caplacizumab?

Platelet count > 50K/μL platelet start antithrombotics

- Aspirin
- Heparin

Stop PEX if platelets >150K for 2 days

- If relapse consider adding cyclosporin A

Rituximab offered to low ADAMTS13 after acute episode chronically to prevent relapse

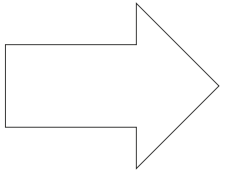
Caplacizumab (Cablivi, Sanofi)

Marketing authorisation	Adults and adolescents of 12 years of age and older weighing ≥ 40 kg experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP) In conjunction with plasma exchange and immunosuppression.
Administration	1st dose 10 mg (IV) caplacizumab before plasma exchange (PEX) Subsequent doses Daily 10 mg (subcutaneous): • after each PEX for duration of daily PEX treatment • for 30 days after stopping PEX If still unresolved, optimise immunosuppression and continue daily caplacizumab until …sustained normalisation of ADAMTS13 activity level. In clinical development program caplacizumab administered daily for up to 65 days No data on re-treatment with caplacizumab

Company proposes treatment improves length and quality of life in acute setting and long term

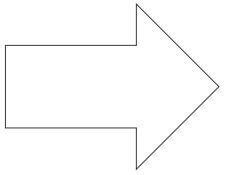
Trial evidence limited to acute setting; did not show improved length or quality of life
Company did not use 1º endpoint of trial.

	Acute setting	Long term
Length of life	YES. Uncontrolled pharmaco-epidemiological evidence naively vs. meta-analysis standard care	YES. Multiplied time in intensive care by death rate from standard care, itself based on SMR
Quality of life	NO. No quality of life data collected in trial	YES. Assumed fewer complications in trial led to longer gains



↑ Length of life

↑ QALYS



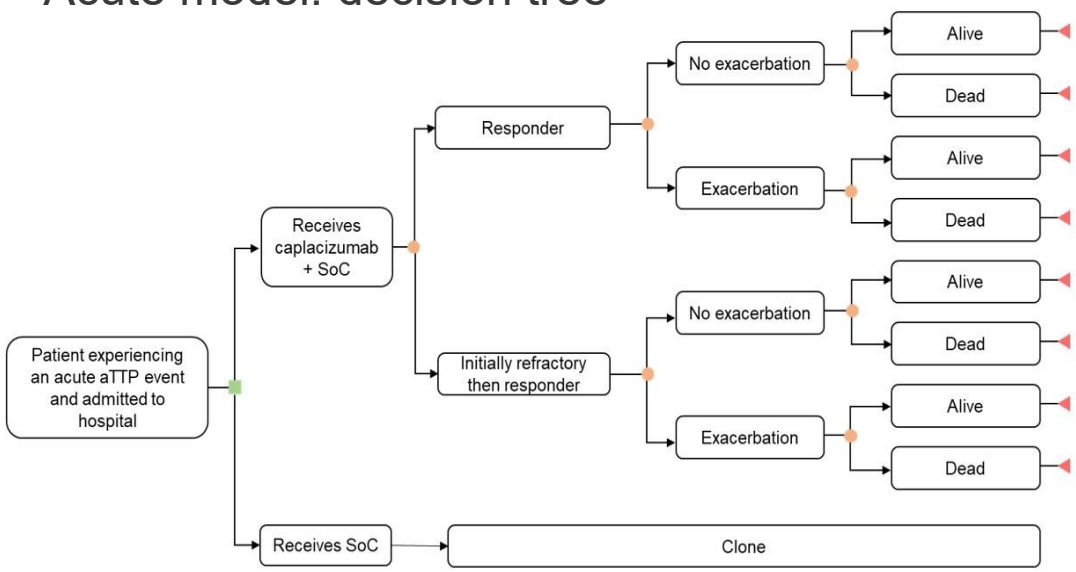
↑ Quality of life

NICE

SMR: standardised mortality ratio

Acute and long term effects of aTTP were modelled by company

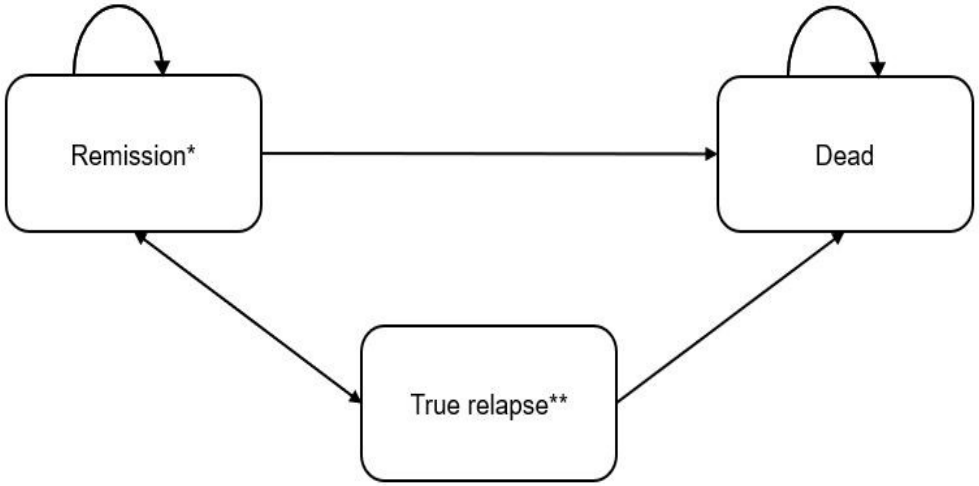
Acute model: decision tree



Modelling takes into account

- In acute phase around an acute episode of aTTP:
  - % who respond to treatment
  - People who have disease recurrence (exacerbation)
  - % who die
  - Time spent in hospital
  - Amount of plasma exchange

Long-term model: Markov



- In long term after acute episode has been treated:
  - % who relapse
  - % who have long term complications (cognitive impairment, mental health problems)
  - % who die because of aTTP complications

If people relapse go back to acute model

Acute outcomes

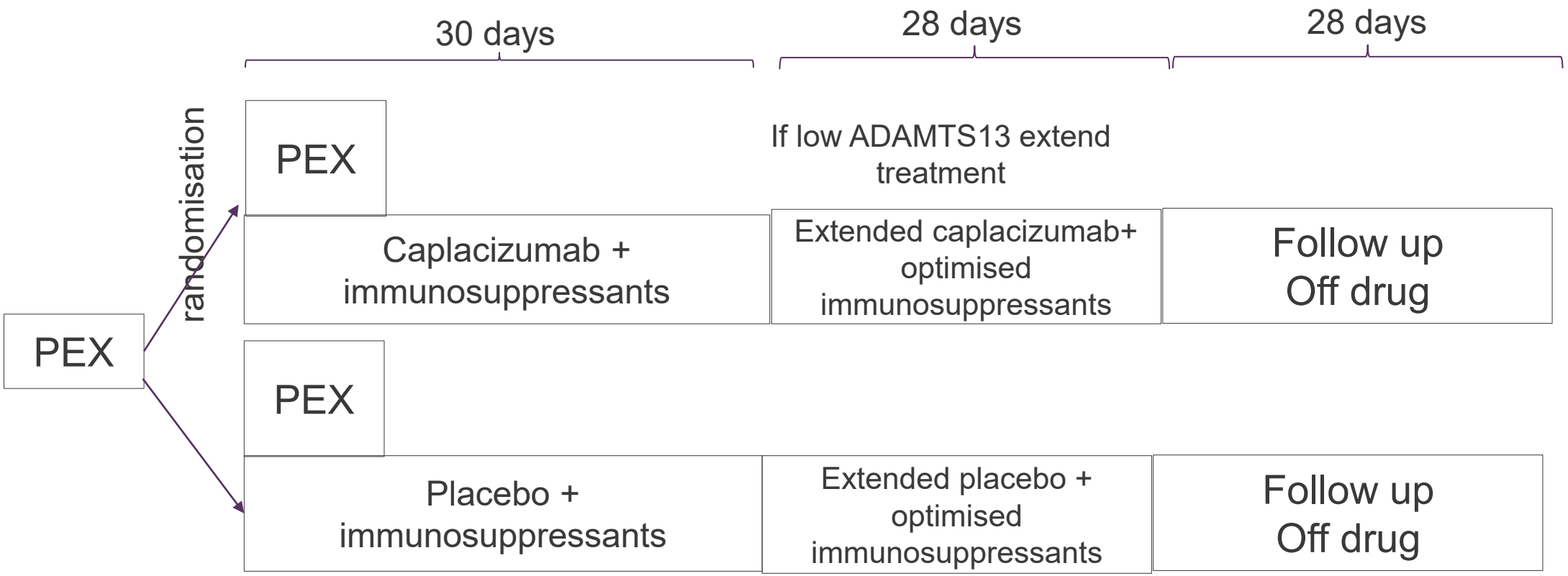
Clinical effectiveness evidence: trial data

HERCULES was the trial that informed the regulatory submission

Trial	Company used in regulatory submission	Company uses in model
HERCULES N=145 double-blind placebo-controlled trial	Yes	Yes, but does not use data on death – instead uses observational data
Post-HERCULES study **ongoing** providing quality of life and survival data not expected to complete before October 2020	No	No
TITAN N=75 needed to enrol 110	No. European Medicines Agency determined unsuitable • stopped early did not recruit to target because protocol said to start caplacizumab before plasma exchange • 12 protocol amendments • Issues with lab sampling/ analysis • 64% had major protocol deviation	Not in 1st meeting

HERCULES: trial design n= 145

- *Double blind placebo controlled trial in international specialist centres*
- *Caplacizumab started at same time as plasma exchange (PEX)*
- *30 days of treatment. Continue for 28 further days if low ADAMTS13 levels at 30 days*
- *No data on quality of life*



People in placebo arm with recurrence in treatment period could **switch** to open label caplacizumab*

Committee at 1st meeting: HERCULES broadly generalisable to UK practice (ACD 3.5), but did not test for short or long term morbidity or mortality (ACD 3.6)

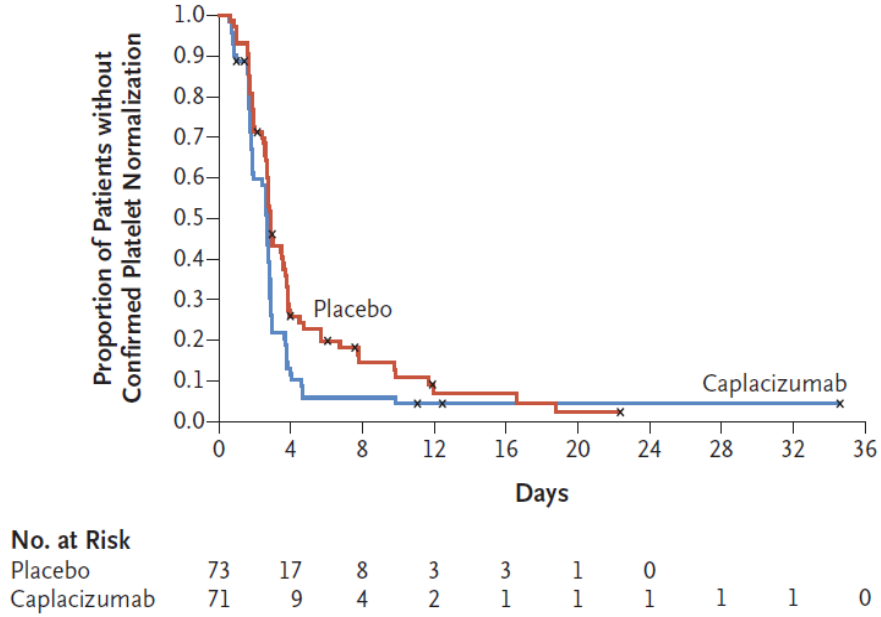
* Trial results not adjusted for treatment switching, PEX duration determined by clinician

HERCULES 1◦ outcome: days to normalising platelet count – company did not use in model

Platelet levels normalised 0.2 day earlier with caplacizumab than placebo

Outcome	Caplacizumab n=72	Placebo n=73
Median days to platelet normalisation (95% confidence interval [CI])	2.7 (1.9 to 2.8)	2.9 (2.7 to 3.6)
Hazard ratio (95% CI)	1.6 (1.1 to 2.2)	

Kaplan Meier curve of time to platelet normalisation



HERCULES 2◦ outcomes used in acute model

Caplacizumab → lower disease recurrence, fewer people with refractory disease, reduced hospital stays and plasma exchange

Outcome	CAPLA n= 72	PLACEBO n= 73	Effect measure/ p value
% recurrence = thrombocytopenia needing PEX restart	13%	38%	RR* 0.33 (95% CI 0.17 to 0.64)
% refractory = no improvement in platelet count	0%	*AIC*	*AIC*
Secondary outcomes not tested for statistical significance			
Mean days plasma exchange	6	9	RR 0.62
Mean volume plasma exchange litres	21	36	RR 0.59
Mean days in hospital	10	14	RR 0.69
Mean days in intensive care	3	10	RR 0.35

Committee at 1st meeting: plasma exchange and hospital stays are unpleasant; people with aTTP welcome a treatment that reduces these (ACD 3.3)

CAPLA, caplacizumab; NR, not reported; RR relative risk; OR, odds ratio; *Calculated by ERG

Deaths in HERCULES and TITAN trials

Company did not used in model

- Trials not powered to test difference between deaths caplacizumab and standard care
- Company noted that deaths in both arms in trials lower than expected in clinical practice

Data	Follow-up	caplacizumab	Standard care	Risk ratio calculated by ERG
HERCULES alone	Treatment and follow-up	1/72	3/73	0.34 95% CI 0.04 to 3.22
HERCULES and TITAN pooled	Treatment and follow-up	1/108	5/112	0.21 95% CI 0.03 to 1.75

Observational data used by company to model treatment benefit for mortality

Made naïve comparison of observational data unadjusted for confounding

- **Company base case** absolute death rates around an acute episode:
  - Caplacizumab: 3.8%
    - *observational data from global compassionate use scheme (February 2020)*
  - Standard care: 13.2%
    - *meta-analysis of 129 international studies*
  - Company carried out naïve comparison to give relative risk of death caplacizumab vs. standard care 0.29. Attributes all effect to caplacizumab

Committee at 1st meeting: considered this estimate very uncertain

- No assessment or adjustment for potential confounding with caplacizumab
- Death rates on standard care around acute episode vary depending on hospital
  - Specialist centre< 5%; non-specialist centre up to 50%
- Studies in meta-analyses gave very heterogeneous results. Company presented limited detail on populations included and if generalisable to NHS clinical practice, no information on how meta-analysis addressed confounding (ACD 3.9)
- If restricted meta-analysis to studies from UK, death rate on standard care ~ 7% around acute event

Long-term outcomes

Long term modelled complications of aTTP

- *No long-term observational or trial data for caplacizumab*
- *Baseline risks of complications/death modelled for **standard care** from literature*
- *Assumed relative risk of time in hospital/ITU in HERCULES caplacizumab vs. standard care (0.62 company, 0.69 ERG)≈ relative risk of death/complications for caplacizumab vs standard care in long term model*
- *Company assumed 1% have relapse/year*

Risk of long term complications in standard care arm of company model

Complication	Risk	Duration	Source in base case
Cognitive impairment	Prevalence • Mild (54.2%) • Moderate to severe (20.8%)	Lifetime with no improvement	Kennedy 2009 Oklahoma TTP-HUS Registry 1995-2006, n=24
Neuro-psychological impairment depression, anxiety, post-traumatic stress	Prevalence • Severe depression (37%) • PTSD (35%)	12 month duration	Chaturvedi et al. 2017 (risk) cross sectional study
Mortality during remission	Standardised mortality ratio 8.3 applied to general population mortality	Not applicable	Upreti et al. 2019 Cohort study 170 patients at Johns Hopkins Hospital 1995 - 2018

Committee view on long term model

Caplacizumab for acute episode, not disease modifying

- Unclear if modelled prevalence of long term complications were generalisable to people in UK with aTTP (ACD 3.10)
- Modelled rate of relapse low (1% annually) and may be between 1-5% (ACD 3.12)
- Unclear if caplacizumab is as effective if used repeatedly (ACD 3.12)
- Using
  - risk ratio of hospital/ITU stay caplacizumab vs. standard care in the acute period to estimate
  - risk ratio of complications or death for caplacizumab vs. standard care in the long term model

  not validated and company presented no evidence for a benefit of caplacizumab on these long-term outcomes (ACD 3.11)
- Was relevant to consider scenarios in which there was **no** long term benefit of caplacizumab on long term complications of aTTP

Quality of life

- No quality of life data collected in HERCULES
- Utility value in acute model of company base case
  - Based on people hospitalised for stroke
  - Assumed to be the same if in hospital treated with caplacizumab or standard care
  - Did not include the impact of fear of relapse on quality of life
    - Company scenario included disutility of 0.05 for fear of relapse and 25%or 50% reduction of fear of relapse with caplacizumab

- Committee concluded:
  - Utility value of being in hospital of 0.64 did not seem to reflect severity of condition (ACD 3.13)
  - Fear of relapse should be included in the modelling of quality of life (ACD 3.13)
    - N.b. caplacizumab not shown to reduce relapse
  - Effect of caplacizumab in reducing plasma exchange duration/ number of central lines on quality of life may not be captured in model (ACD 3.16)

1st meeting recommendation

Not recommended – caplacizumab has clinical benefits but too much uncertainty in assumptions around short term mortality and long term complications

Issue	Committee conclusion	ACD section
Death rates in acute phase based on naïve comparison of observational data	Caplacizumab may reduce risk of dying but size of reduction uncertain Confounding not addressed/ adjusted	3.9
Rates of long-term complications	Company had not shown rate of complications on standard care generalisable to UK	3.10
Using hospital stay as a proxy to estimate long term outcome benefit with caplacizumab	Not possible to validate a causal link between former treatment with caplacizumab and long-term complications. Conservative assumption of no benefit relevant	3.11, 3.14
Relapse rates	Modelled rates low Uncertain if caplacizumab effective on repeated use	3.12
Utility values	Baseline utility value for people in hospital seems high Should include an estimate of fear of relapse	3.13
Innovation - potential benefits not included in model	Possibly innovative, but ‘step change’ unclear because of uncertainties around clinical effectiveness. Impact of reduced plasma use/hospital stay and fear of relapse not in QALY calculation	3.16

Appraisal consultation

- Comments were received from:
  - Company
  - Clinical expert who attended first meeting
  - aTTP Network
  - Public

Company response to ACD

Issue	Company response	In revised base case?
Death rates in acute phase based on naïve comparison of observational data	• New estimate for annual death rate on standard care • Risk ratio based on trial data not naïve comparison	Yes
Rates of long-term complications	• No new rates presented, but supportive data presented	No
Using hospital stay as a proxy to estimate long term outcomes benefit with caplacizumab	• No new data to validate hospital stay/long term outcomes relationship • Scenarios: time to platelet normalised to estimate long term benefit with caplacizumab • Conservative assumption scenarios presented	No Scenarios only
Relapse rates	• Scenario assuming annual relapse of 2%. • Scenario assuming caplacizumab not effective on retreatment	No Scenarios only
Utility values in acute model	• New assumption on acute utility (standard care) • Fear of relapse utility assumption	Yes
Innovation (benefits not included in model)	• See above scenarios to capture unaddressed potential utility benefits	Yes

Company: new death rates in acute period

Naïve comparison (confounding) vs. risk ratio from trials (small no. events)

Original base case:

- Risk ratio 0.29 naïve comparison of estimated absolute acute mortality rates of:
  - Caplacizumab 3.8% - global compassionate use scheme
  - Standard care 13.2% - meta-analysis of 129 international studies*

*Committee estimated UK centres only mortality ~7%: Company suggested UK studies used same data from UK aTTP registry from specialist centres

New base case:

- Risk ratio 0.21 (95% CI 0.03 to 1.75) calculated from pooled data from caplacizumab trials HERCULES and TITAN: 1 death caplacizumab (1%), 5 deaths standard care (4%)
  - Caplacizumab: calculated as 2.7%
    - risk ratio of 0.21 applied to estimated death rate on standard care below
  - Standard care: new estimate 12.6%
    - Lester 2015, aTTP-related mortality from ONS code as proportion of newly diagnosed cases (HES TTP code) in England 2003 to 2013

  N.b. assumes that risk ratio constant even if absolute risk differs

◉ Is *there a mortality benefit of caplacizumab acute? If so, what is the best estimate?*
◉ *Which is best estimate for acute death on standard care?*

ONS: Office for National Statistics; HES: Hospital Episode Statistics

Alternative acute mortality estimates..

…suggest a risk ratio 0.1 to 0.3 for caplacizumab vs. standard care

	Caplacizumab	Standard care	Risk ratio
Company original base case	3.8%	13.2%	0.29
Company revised base case	2.7%	12.6%	0.21
Company alternative estimates			
UK registry: people treated with caplacizumab (if treated > 48hrs caplacizumab assumed to have same % dying as standard care)	*AIC*	*AIC*	*AIC*
French matched cohort: compassionate use caplacizumab vs. historical cohort. Matched on disease severity	*AIC*	*AIC*	*AIC*
ERG preferred (used in ERG revised base case)			
UK registry data for caplacizumab Committee estimate of 7% for standard care	*AIC*	7%	*AIC*

◉ Do these data support the company's new acute death rate estimates?

Company: validation of prevalence of long term outcomes on standard care – unchanged in company's model

Company suggests its base case assumptions are conservative

Complication	Risk in original base case	Duration	ACD response: supportive data for original base case
Cognitive impairment	Prevalence • Mild (54%) • Moderate to severe (21%)	Lifetime	Cross sectional study 50 patients/10 carers UK aTTP registry • 88% report 'not able to put thoughts into words without extra effort' • PROMS score indicated cognitive function 1 SD lower than US average
Neuro-psychological impairment depression, anxiety, post-traumatic stress	Prevalence • Severe depression (37%) • PTSD (35%)	Changed from 12 months to lifetime in revised base case	Cross sectional study • 72% & 84% reported moderate or severe symptoms the HADS anxiety and depression scales • Mental health domain on SF-36 'well below UK norm' • 84% patients reported feeling 'quite a bit' or 'very much' worried about having another aTTP episode

◉ *Are these estimates plausible? Is there evidence that previous treatment with caplacizumab prevents long term complications? If so, is this a way to capture it?*

Company: alternative approaches to modelling benefit of caplacizumab on long term outcomes

- **Original base case**
  - Time in hospital/ITU proxy for long term outcomes including death in model.
  - Some publications report association between time in hospital/ITU and long term outcomes, none specific for aTTP
  - Committee aware that co-morbidities could relate both to long stay and post-hospital complications and caplacizumab would not treat these
- **Assumption retained in revised model**, but exploratory scenarios presented, using time to platelet normalisation as alternative proxy
  - Based on 1 RCT and 1 retrospective cohort study suggesting an association between time to platelet normalisation (Rock et al.; Liu et al. – see next slides)
  - Used to estimate treatment effect of caplacizumab vs. standard care in reducing long-term complications
- At consultation company noted:
  - its clinical advisers considered it plausible that less time spent in occluded state in short term = less chance of long term complications
  - time in hospital relates to time to platelet normalisation

Rock et al. RCT plasma exchange vs infusion

Company uses to support assumption time to platelet normalisation linked to longer-term outcome death

Population	People with aTTP	
Intervention	Plasma exchange vs. plasma infusion	
Outcome	Short term outcome	Longer term outcome
	Response at end of first treatment cycle = platelet count normalised 150 x 10^9/L for 2 consecutive days and no new neurological events	Death at 6 months
Results	Plasma exchange: 47% Plasma infusion: 25%	Plasma exchange 22% n=11 Plasma infusion: 37% n=19

How company used this in new scenario

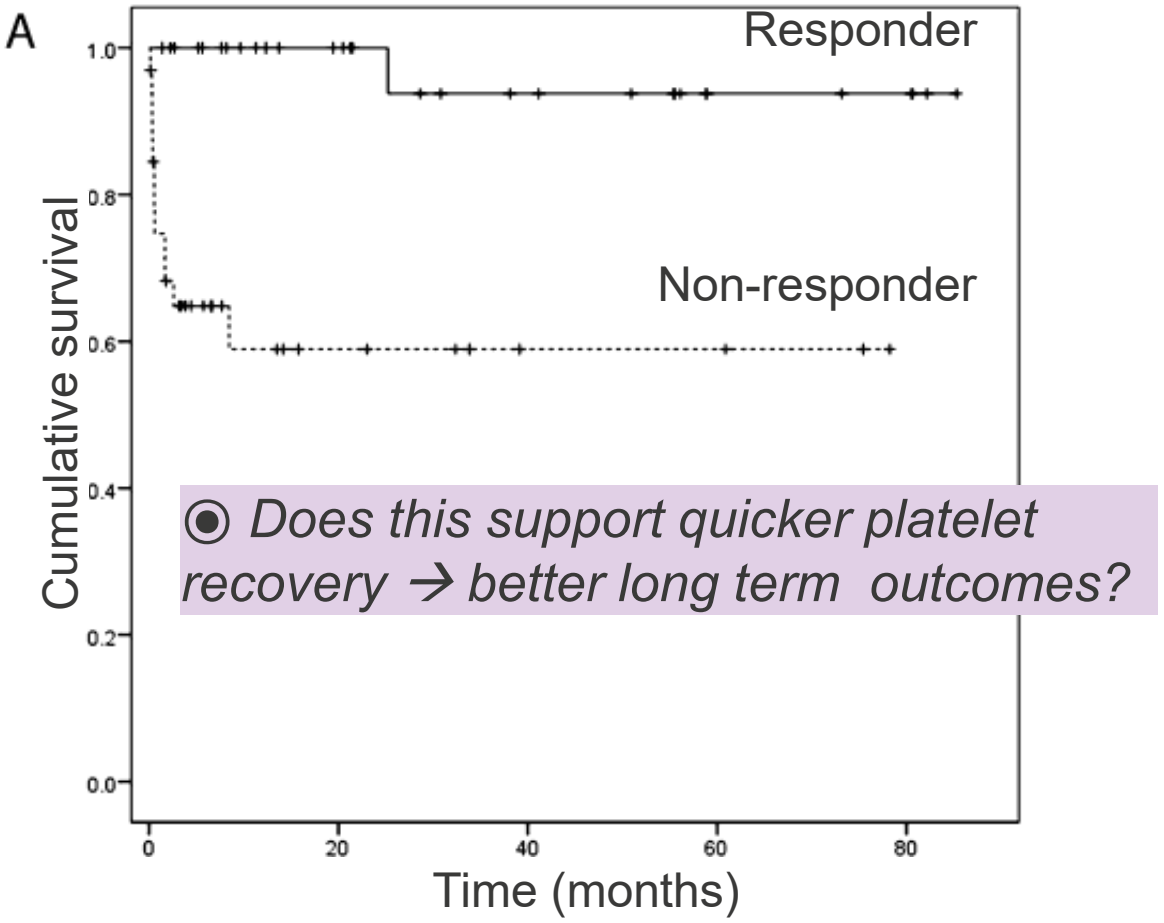
- Company suggest shows that an 85% improvement in response with more effective treatment results in a 73% improvement in survival at 6 months
- Company adjusted the risk ratio for time to platelet count response in HERCULES (0.57) with the relationship between platelet count response in Rock et al 0.57 * 85%/73% = 0.66
- ERG: calculations “opaque and uninterpretable”

◉ *Is this approach valid using short term surrogate to estimate long term outcomes? Can modelling of stroke/MI inform the model? Does death at 6 months double count acute deaths?*

Liu et al. retrospective cohort study

Company uses to support assumption quicker platelet recovery = better long-term survival

- Retrospective analysis of 64 people who had PEX between 2003 and 2010 in US centre
- People who had platelet recovery by 3 days had:
  - Better survival including after stopping treatment (long-term)
- Company used 1 year data from this study in its scenario
- ERG consider:
  - Valuable data showing a relationship between short and long term outcomes



◉ *Does this support quicker platelet recovery → better long term outcomes?*

Platelet recovery rate at 3 days	% surviving at 1 month	% surviving at 3 months	% surviving at 1 year
<5 x 10^9/L per 24 hrs (non-responder)	75%	65%	59%
≥5 x 10^9/L per 24 hrs (responder)	100%	100%	100%

Company scenario using Liu et al data

Used Liu et al data to make new survival curves for caplacizumab and standard care

How company used this in new scenario

1. Reassessed data from HERCULES according to Liu et al response by 3 days criteria
    1. Response on standard care *AIC*
    2. Response on caplacizumab *AIC*
2. Calibrated survival curve for people without aTTP to make a survival curve for people not responding to treatment using data from Liu et al
3. Made weighted survival curves for caplacizumab and standard care using proportion of responders in HERCULES i.e. took into account poorer survival for non-responders

Company considered this optimistic scenario: all people having caplacizumab met Liu et al response criteria at day 3 → survival curve for caplacizumab is the same as the general population over the long term

ERG noted company used survival data only from 3- 12 months to calibrate non-responder survival curve (not 80 months of follow up)

◉ *What is the committee's views on this approach using short term outcomes to estimate long term outcomes with caplacizumab vs. standard care?*

Company: new utility values in acute model

Now assumes difference in quality of life between people treated with caplacizumab vs. standard care

New assumptions

- In acute phase: standard care utility 1/2 caplacizumab because committee noted possible uncaptured benefit of caplacizumab reducing PEX duration and central lines replacements and reduced infection risk
- Still assumed that utility if hospitalised and taking caplacizumab was 0.64

- Company noted utility value changes do not have large impact on results
- ERG consider 50% reduction of utility on standard care arbitrary assumption

◉ *Is assuming quality of life on standard care is half that on caplacizumab + standard care appropriate?*

Company: includes fear of relapse in long term model in revised base case

Company presented scenario analysis incorporating disutility for fear of relapse in original submission – now includes in revised base case

- Fear of relapse disutility (0.05) applied to standard care arm based on fear of relapse from other conditions
- Assumed all people having caplacizumab won't fear relapse and won't have associated disutility
  - N.b in company scenario at 1st meeting it was assumed 50% of people having caplacizumab wouldn't have this disutility
- ERG considered that:
  - caplacizumab does not reduce the risk of further relapses so not reasonable to assume no fear of relapse if have caplacizumab
  - Assumption appears contradictory to other changes to company's model increasing the duration of depression (12 months to lifetime), which the company states reflects ongoing anxiety

◉ *Has caplacizumab been shown to reduce frequency of relapse? Would the availability of caplacizumab completely resolve anxiety about having a future relapse?*

Company: newly mapped utility data from UK survey of people with aTTP

Company: supports utility values in its long-term model

- Company presented data from UK survey of aTTP patients (n=50) and carers (n=10) at 1st meeting. Survey collected SF-36 data (generic quality of life survey).
- New: mapped SF-36 data to EQ-5D data using Rowen et al. algorithm
- Found that modelled utility values it had used to estimate baseline utility in its original long term model, based on Burns et al, higher in 1st year after aTTP episode than mapped survey results, but similar thereafter

	Yes/No	Original base case utility (based on Burns et al)	NEW supportive data: Mean utility in UK survey
Acute (episode within a year)	Yes	*AIC*	*AIC*
	No	*AIC*	*AIC*

◉. *Are the company's estimates of long-term utility reasonable?*

Changes to the company deterministic base case in response to ACD

Parameter	Original base case	Updated base case	ICER
Company deterministic base case at first meeting			£27,856
Discount (PAS)	Discount	Increased discount	£25,531
Acute mortality caplacizumab	Global compassionate use scheme 3.8%	Relative risk 0.2 from HERCULES/TITAN data applied to standard of care =2.5%	£24,873
Acute mortality standard care	13.2%	12.6% (Lester et al, hospital episode statistics and ONS data)	
Duration of depression	12 months	Same as duration of cognitive impairment 55 years	£24,183
Utility values in acute episode	Same utility value multiplier in both modelled arm if hospitalised with aTTP (0.64)	Patients on standard care assumed to have half utility of patients on caplacizumab	£23,469
Fear of relapse	Not modelled in base case (scenario only)	disutility (0.05) for fear of relapse in standard care arm	£20,377
Company base case after consultation on ACD			£20,377

Company scenario analyses using alternative long term outcome estimates

Scenario	Assumption	ICER assumptions applied for survival only	ICER assumptions for survival + complications
Company base case	Mortality rate standard care based on Upreti et al, hazard ratio 0.62 applied for caplacizumab	Not applicable	£20,377
Scenario using Rock et al data	Hazard ratio of 0.66 applied to standard care arm for caplacizumab	£21,041	£21,876
Scenario using Liu et al data	New survival curves both treatment arms	£14,555	-
Limited long term benefit	Assumed hazard ratio of 0.9 for risk of long term mortality caplacizumab vs standard care	£25,738	-

Company: further scenario analyses around revised deterministic base case

Scenario	Rationale	ICER
Company revised base case		£20,377
Acute mortality rate 7% on standard care	Reflective of UK specialist centres in meta analyses	£21,776
Annual relapse rate 2%	ACD: original relapse rate of 1% may be low	£22,219
Reduced efficacy on retreatment (assume same acute mortality on relapse (12.6%) in both arms)	ACD: it is uncertain if caplacizumab works equally well on re-exposure	£20,791
Caplacizumab treatment duration *AIC* days	UK registry data May 2018 to June 2020 Company: reflects use in NHS practice rather than trial (had caplacizumab 30 days)	£14,535
No long term mortality benefit with caplacizumab	More conservative assumption	£28,174
No long term complication benefit with caplacizumab	More conservative assumption	£47,482

ERG: further scenario analyses around company revised deterministic base case

Scenario	Rationale	ICER
Company revised base case		£20,377
Annual relapse rate 5%	Clinical expert at 1st meeting said annual relapse 1-5%	£25,631
25% improvement in fear of relapse with caplacizumab	Presented by company as scenario in response to technical engagement	£25,681

Combination scenarios around company base case

ICERs rounded to nearest £1000 (£1) black: company, red:ERG

		Risk ratio acute mortality			Annual relapse			No long term mortality benefit	No long term benefits
		0.1	0.2	0.3	1%	2%	5%		
Risk ratio acute mortality (standard care acute mortality 12.6%)	0.1	-	-	-	£19	£22	£25	NA	£45
	0.2	-	-	-	£20	£22	£26	£28	£48
	0.3	-	-	-	£21	£23	£27	NA	£51
Annual relapse	2%	£21	£22	£23	-	-	-	£58	£148
	5%	£25	£26	£27	-	-	-	£68	£153
Caplacizumab retreatment not effective		NA	NA	NA	£21	£23		NA	NA
No long term mortality benefit		NA	28	NA	£28	£58	£68	-	-
No long term benefits		£45	48	£51	£48	£148	£153	-	-

ERG revised base case

Did not include company revised base case assumptions of

- *50% utility in acute model for standard care vs. caplacizumab*
- *Disutility for fear of relapse in long –term model*

But does include both short and long term mortality benefit

	assumptions	ICER
ERG original base case	Differed from company: • % refractory standard care • Risk ratio long-term mortality • Resource use long term complications and monitoring • N for ITT population	£30,665
Revised base case	New PAS	£28,180
	Acute mortality Standard care 7% Caplacizumab *AIC*	£28,180
	Duration of depression 55 years not 12 months (same as company revisions)	£31,024
	All of the above	£30,005

Comments from clinical expert

- Innovative
- Highly plausible that prolonging microvascular ischaemia in short term has long term consequences. HERCULES data shows, with caplacizumab, a:
  - Reduction in ITU days reflects improvement in organ function due to reversal of microvascular ischaemia
  - Improvement in platelet count which reflects reduced consumption of platelets in microvascular thrombus
- Important reduction in proportion of refractory patients. In HERCULES:
  - 0 refractory patients on caplacizumab
  - 4 on standard care
- Patients with refractory disease need additional expensive treatments e.g. bortezomib and need twice rather than once daily PEX
- Comparative data between patients on and off caplacizumab soon available
- “Caplacizumab through the compassionate access scheme has had huge benefits for patients”

Comments from aTTP network

- “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. … On current treatments alone, every single day until normalized platelets is critical to the long term health of the patient”
- Rare condition – should be appraised through the highly specialised technology programme.
- Preliminary decision discriminates against people of African Caribbean family origin who are disproportionately affected by the condition
  - N.b.from NICE - Considered in equality impact assessment for this appraisal and not considered an equality issue. Issues related to incidence of a disease cannot be addressed in a technology appraisal
- Caplacizumab now part of standard treatment of care. “Morally and ethically wrong” not to give caplacizumab when patient would benefit from it.

Patient and public comments

- Reducing plasma exchange important because:
  - Scarring can make venous access difficult,
  - May affect ability to have plasma exchange for relapses
  - Infection risk
- Less time in hospital
  - The longer an inpatient, the longer it takes to recover mentally and physically
- Long-term complications/organ damage
  - First drug in years that may reduce risk of long term organ damage or stroke
  - Rehab can be intensive e.g. 18 months learning to walk after stroke
- Travel to (sometimes distant) hospital huge burden to patients including financially
- Fear of relapse
  - Constant
  - ‘That another treatment exists would have a positive effect on my anxiety’
- Stress/impact on quality of life for family and carers of people with aTTP