NICE National Institute for Health and Care Excellence

Caplacizumab for treating acute acquired thrombotic thrombocytopenic purpura [ID1185]

Lead team presentation

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How treatment affects quality adjusted life years (QALYs) in company's base-case model

- *Company does not assess effect of caplacizumab vs standard care directly on quality of life*
- *Indirect data and assumptions used to estimate effect of caplacizumab on survival*

Quality of life

Reduces

- hospital stay
- complications of acute acquired thrombotic thrombocytopenic purpura (aTTP) for example stroke, anxiety, depression

+

Length of life

Reduces chance of dying

- short term around time of acute episode
- Long term when aTTP in remission

⇨ Increased QALYs

Costs with caplacizumab

- Extra drug costs of caplacizumab
- Lower costs→ reduced hospital stay, plasma exchange, treating fewer complications of aTTP[2]

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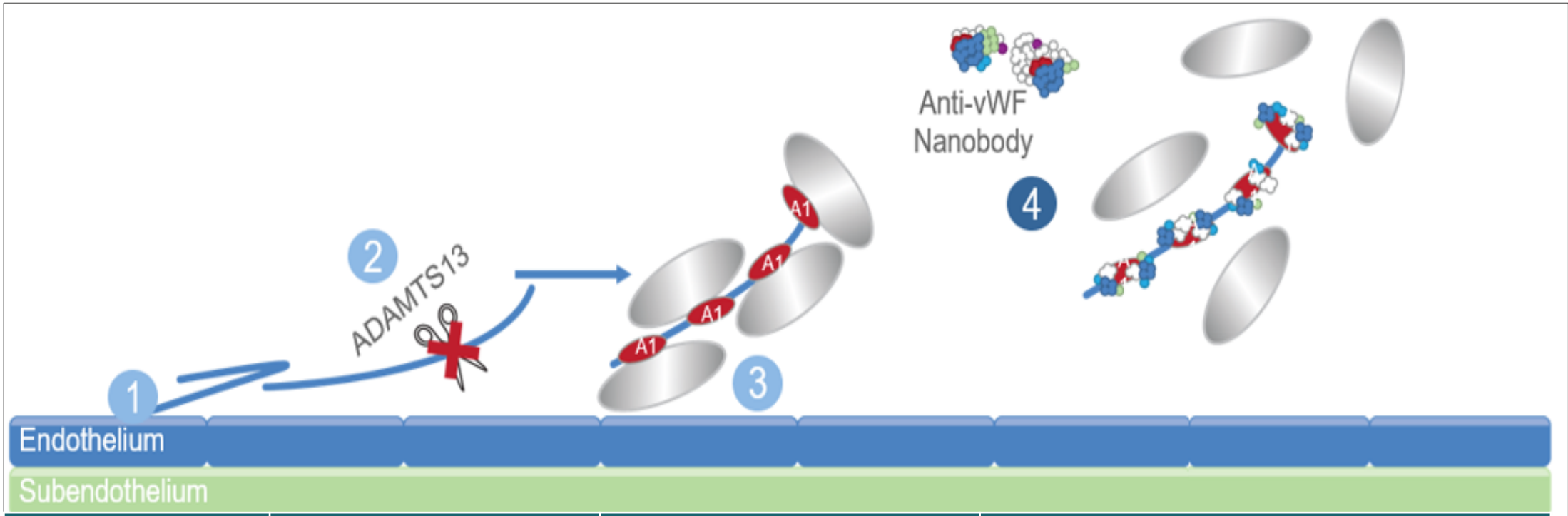
Key issues

- **Limited comparative evidence base**:
  - What are the best sources of data and what are the limitations?
- **Mortality in short term**:
  - Company does not take this from key trial
  - Has big impact on incremental cost effectiveness ratio (ICER).
  - Does indirect (naïve) comparison reasonably estimate death rates with caplacizumab vs standard care during aTTP episode?
- **Upcoming specialised service for TTP:** variability of outcomes depending on where presenting with symptoms- what is “average” standard care?
- **Long term outcomes**: Data not available, therefore company use short term outcomes to estimate long term outcomes. Plausible?
- **Quality of life**: no trial data, some proxy conditions used. Have effects of disease and its treatment on QoL been captured in model?
- **Wider benefits not captured in modelling?** Caplacizumab may reduce time in intensive care and plasma use; are benefits fully captured in model?

Acquired thrombotic thrombocytopenic purpura: autoimmune disease which stops ADAMTS13 activity



1.Ultra long von Willebrand factor (vWF) released from blood vessel walls	2.Normally ADAMTS13 breaks down vWF. Autoimmune antibody stops this	3.If not broken down, long vWF units form, platelets stick to it making blood clots	4.Caplacizumab blocks platelets binding to vWF - stopping platelets aggregating/blood clots forming

Acquired thrombotic thrombocytopenia

- Rare: In England 100-150 patients present with acute episode each year
- Median age 43 years, 73% female; disproportionately affects people of African-Caribbean family origin
- Autoimmune (so ‘acquired’) - antibodies against ADAMTS13 protein
- Thrombotic: persistence of ultra-large von Willebrand factor multimers spontaneously capture platelets, resulting in microvascular thrombi (blood clots)
- Thrombocytopenic: decreases number of platelets in blood
- Early signs include fatigue, headache and bruising
- Can quickly progress to ischaemic damage, particularly heart, brain and kidneys
- Can be fatal or lead to physical disability and cognitive impairment
- Carries lifetime risk of relapse and this is cause of anxiety to patients
  - Have severe or moderate depression: 40%
  - Acute symptoms reoccur needing re-starting of treatment ~35%
  - Refractory to treatment i.e. limited or no change in platelet counts ~10%
- Specialist care improves outcomes and lowers risk of death

Caplacizumab (Cablivi, Sanofi)

Marketing authorisation (MA)	Adults experiencing an episode of acquired thrombotic thrombocytopenic purpura (aTTP), in conjunction with plasma exchange and immunosuppression 30th April 2020 +ve opinion to extend MA for adolescents of 12 years of age and older weighing at least 40kg. Expectation that efficacy/safety of caplacizumab in adolescents = adults
Administration	1st dose 10 mg (IV) caplacizumab before plasma exchange (PEX) Subsequent doses Daily 10 mg (subcut): • after each PEX for duration of daily PEX treatment • for 30 days after stopping PEX If still unresolved immunological disease, optimise immunosuppression and continue daily caplacizumab until underlying immunological disease resolved e.g. sustained normalisation of ADAMTS13 activity level. In clinical development program caplacizumab administered daily for up to 65 days There are no data on re-treatment with caplacizumab

Current treatment: plasma exchange (PEX) and immunosuppression

- **PEX**
  - Removes blood from vein and separates plasma from blood cells
    - Techniques for separating blood components include “spun apheresis”
  - Discarded plasma includes ADAMTS13 enzyme and antibodies against it
  - Donated plasma replaces ADAMTS13 enzyme
  - PEX takes several hours or days
    - Clinical expert: range of number of plasma exchanges 5~36
  - Clinical expert (technical engagement) stated
    - Patients often have ≥2 central lines, replaced every 5-7 days, for 2-3 weeks
      - Risk of multiple line insertions and infection
    - Plasma infusion
      - Risk of reactions
      - Can use up blood supplies: may account for 25% of plasma usage in UK

- **Immunosuppression**
  - with corticosteroids + rituximab
  - used to control underlying autoimmune disease

Treatment pathway – no NICE guidance

- *Pathway as per British Committee for Standards in Haematology (2012)*
- *Marketing authorisation- start caplacizumab before plasma exchange, key trial HERCULES started caplacizumab after plasma exchange*
- *Starting treatment quickly key to better outcomes*

Diagnosis

Suspected
- Microangiopathic haemolytic anaemia
- Thrombocytopenia

Confirmed by:
- ADAMTS13 activity <10% diagnostic
- Anti-ADAMTS13 antibody detected

Within 4-8 hrs refer to specialist centre and start treatment

Plasma exchange

Immunosuppression with corticosteroids + rituximab

Platelet count

Thromboprophylaxis
If platelets above 50,000/µL blood
Start low molecular weight heparin and aspirin to prevent thrombosis

Start caplacizumab?

Stopping/ treatment escalation
- Continue PEX for minimum of 2 days after platelet count > 150,000/µL blood
- If symptoms progress, or signs of refractory disease or early relapse, increase PEX and offer rituximab or cyclosporin A
- Can give rituximab to prevent relapses

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Patient perspectives on living with aTTP

Symptoms have large impact on daily life:

- Extreme fatigue
- Constant body aches
- Bruising
- Memory problems and aphasia
- Mobility problems
- Frequent infections which takes longer to recover from
- People of working age can have difficultly going back to work full time because of fatigue and memory problems, some may stop working altogether.
- Anxiety about relapse
  - "symptoms of relapse are quite ambiguous, therefore, it is always just at the back of your mind. The thought of a relapse, and having to stop your life for weeks on end while you receive treatment, is always hanging over you"
  - family and carers also anxious, "constant state of worry"

Reference: Quotations from patients with aTTP presented in submission from TTP Network

Patient perspectives on current treatment

- “Care at specialist centres is very good but elsewhere medical professionals often not aware of the condition or its treatment”
- Difficulties in being treated in regional centre; can be hours from home, makes experience scarier
- Regional variation in monitoring and prophylactic treatment

Plasma exchange therapy

- “Plasma for me was the worst ever 4 hours twice a day for God knows how long, made me feel sick… had to have calcium drip…every time they came into my ward with the trolley I cried”
- Patients described allergic reactions to fresh frozen plasma, rituximab
- Patients would welcome treatment which would reduce lengths of relapses and hospital stays

Reference: Quotations from patients with aTTP presented in submission from TTP Network

Decision problem

	Final scope	Company submission
Population	Adults* experiencing an episode of aTTP	
Intervention	Caplacizumab in addition to plasma exchange (PEX) + immunosuppression	
Comparator	• PEX with or without spun apheresis, corticosteroids or rituximab	• PEX with or without spun apheresis, corticosteroids or rituximab
Outcomes	• time to normalising platelet count • aTTP recurrence, • aTTP related complications • death • time in hospital • time + volume of plasma exchange • adverse events • health related quality of life	No EQ-5D data. Instead company mapped available SF-36 data to EQ-5D using a mapping algorithm Company considered 'acute episode' and 'long term' separately
Subgroup	• Severe refractory disease	Company did not assess because • 1) cannot tell who will be refractory when starting treatment • 2) refractory disease does not correlate with severity

* Recommendations would reflect the extended marketing authorisation and include adolescents

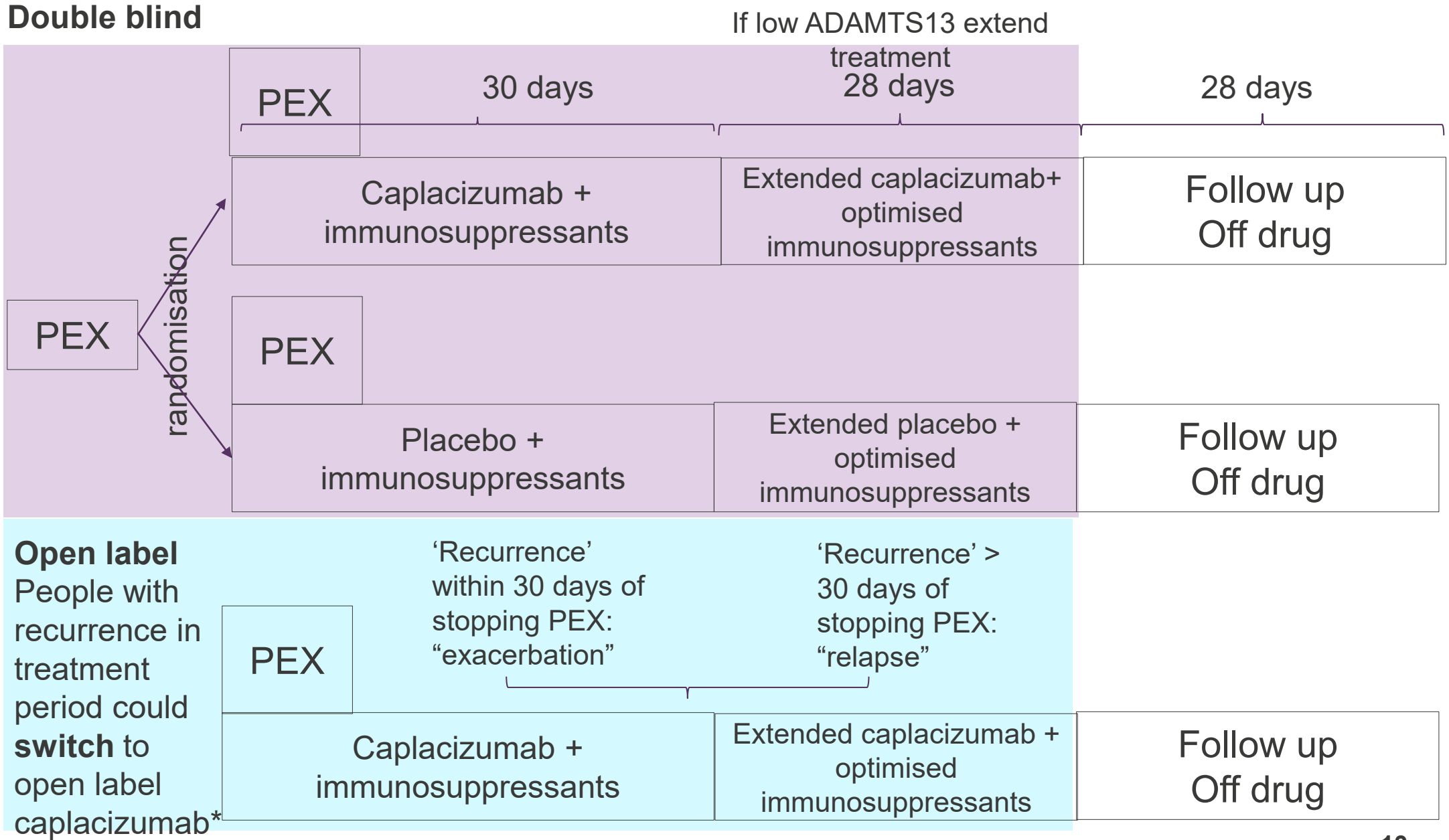
Clinical effectiveness evidence: trial data

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 trial providing quality of life and survival data not expected to complete before October 2020	No	No
TITAN N=75 (needed to enrol 110 to meet statistical testing requirements)	No; European Medicines Agency determined unsuitable • stopped early did not recruit to target because initial protocol said to start caplacizumab before plasma exchange • 12 protocol amendments • Issues with lab sampling/ analysis • 64% had major protocol deviation	No

HERCULES: trial design n= 145

1◦ endpoint time to platelet count ≥150,000/uL then stopping daily PEX within 5 days



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

Outcomes in statistical analysis plan

1◦ outcome in trial not used in model; composite endpoints for power;
Intention to treat population tested at 5% alpha
Death not a formal outcome; data collected, but not used in model

Statistical analysis plan	Outcome	Used in company model
1◦ outcome	Time to ≥150,000/uL blood then stopping daily PEX within 5 days	No
2◦ outcomes with pre-planned statistical testing. Fixed-sequence to analyse key 2◦ outcomes hierarchically ordered on clinical relevance. Protocol amendment	1) Composite % TTP-related death, TTP recurrence, or ≥1 treatment-emergent major thromboembolic event excluding 28 day follow up	No
	2) % recurrence of TTP including 28 day follow-up period	Yes
	3) % refractory TTP	Yes
	4) Time to normalisation 3 organ damage marker levels	No
Other prespecified 2◦ outcomes not in statistical analysis plan	Volume/duration of plasma exchange	Yes (costs)
	Time in hospital/ intensive care	Yes (costs/quality of life)
	aTTP related death	No - estimated from observational data

Generalisability HERCULES to UK practice

Trial starts caplacizumab later than in clinical practice and only has data from specialist centres

Trial	Clinical practice
Start caplacizumab 24 hours after plasma exchange	Would start caplacizumab before plasma exchange as per marketing authorisation
Recruited in specialised centres	Currently people are referred to specialist centres for treatment and time to referral and starting treatment affects outcomes. N.b. anticipated NHS England's specialised service for TTP ~October 2020 (aims 8 specialised centres and reduced time to treatment)

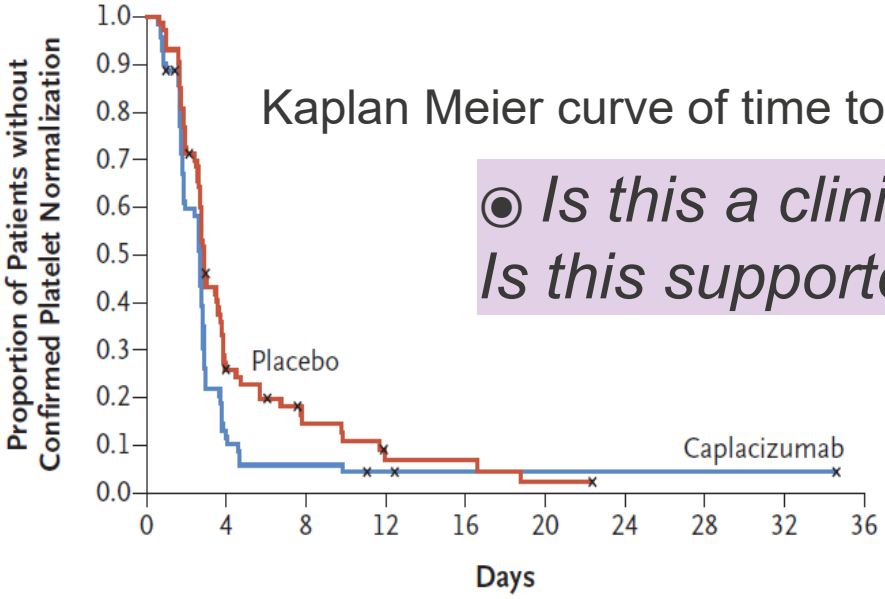
- **Clinical expert response**: no difference in cohort admitted in HERCULES vs normal clinical practice. 18 UK participants in HERCULES
- **Patient expert response:** patients at specialised centres get best/ most prompt treatment. Many patients do not get that level of care normally

◉ *Is HERCULES generalisable to NHS clinical practice and for purposes of disease modelling?*

Results: 1◦ outcome: days to normalising platelet count

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)	2.7 (1.9 to 2.8)	2.9 (2.7 to 3.6)
Hazard ratio (95% confidence interval)	1.6 (1.1 to 2.2)	



Kaplan Meier curve of time to platelet normalisation

◉ *Is this a clinically meaningful effect?*
Is this supported by fewer deaths/ complications?

HERCULES 2◦ outcomes

Caplacizumab reduces composite endpoint

Outcome	Follow up period	Capla n= 72	Plac n= 73	Effect measure/ p value	In model?
Composite (all bullets below)	Excluding follow up period	9 (12%)	36 (49%)	<0.001	
• aTTP related death		0	3 (4%)	NR	Scenario only
• Recurrence within 30 days of stopping PEX		3 (4%)	28 (38%)	NR	No
• Major thromboembolic event		6 (8%)	6 (8%)	NR	No
% recurrence = recurrent thrombocytopenia needing PEX restart	Including follow up period	12.5%	38.4%	RR* 0.33 (95% CI 0.17 to 0.64)	Yes
% refractory = no improvement in platelet count	No improvement after 5 PEX treatments and corticosteroids	0%	*AIC*	*AIC*	Yes

◉ *Is randomisation to caplacizumab associated with fewer complications?*

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

HERCULES results 2◦ outcomes

Caplacizumab decreased amount and duration of plasma exchange, time in hospital and time in intensive care compared with standard care alone – not statistically tested

HERCULES	Caplacizumab n=72	Placebo n=73
Mean days of plasma exchange	5.8	9.4
(95% confidence interval)	(4.8 to 6.8)	(7.8 to 11.0)
Mean volume of plasma exchange in litres	21.3	35.9
(95% confidence interval)	(18.1 to 24.6)	(27.6 to 44.2)
Mean days in hospital	9.9	14.4
(95% confidence interval)	(8.5 to 11.3)	(12.0 to 16.9)
Mean days in intensive care	3.4	9.7
(95% confidence interval)	(2.62 to 4.2)	(5.3 to 14.1)

Clinical experts (during engagement): before caplacizumab ≥ 2 central lines replaced every 5-7 days for 2-3 weeks. With caplacizumab one single central line, for around 1 week with no need to replace.

◉ What are the benefits of reducing plasma exchange and hospital/ICU stays?

Death rates in trial

Company argues lower than expected and so choose to include in model naïve comparison (without adjusting for difference) of observational data on death rates from 2 separate sources for caplacizumab and for standard care

	Caplacizumab	Standard care	P value
HERCULES study treatment period	0/72 (0%)*	3/73 (4.1%)	N/A
* *There was 1 death in follow up period in caplacizumab arm*			

ERG:

- Low mortality rate in both arms, so high degree of uncertainty
- Plausible that drug might improve survival, but not provided with robust evidence

◉ *Is it reasonable to assume that caplacizumab makes people live longer?*
◉ *Is company's reason for naïve comparison of observational data justified?*

Company: death rates from observational data

Company "naïve comparison" uses data from separate populations to estimate effect of caplacizumab vs. standard care on death in acute period
No data on patient characteristics/ how well matched/ generalisability

Caplacizumab or standard care	Source of mortality data	In model?
Caplacizumab	Caplacizumab: global compassionate use scheme(Feb 2020) n= 239 (superseded data in company original submission from August 2019 n=187)	Company revised base case
Standard care	Meta-analysis of 129 international studies of people with aTTP who had PEX (7 UK studies)	Company base case
Caplacizumab and standard care	French matched cohort study * AIC*	Company scenario
Caplacizumab	UK registry • *AIC*	no

◉ *What are the challenges associated with naïve comparison of caplacizumab vs. standard of care? Are data from global compassionate use schemes generalisable to UK?*

Company: death rates from observational data

Observational data suggests a death rate on caplacizumab of < 5%
Estimates of death rates with standard care vary and may depend on where patients present/treated

Source of mortality data	Capla	SoC	RR	CI	In model?
• **Caplacizumab: global compassionate use (Feb 2020) *** • **Standard care: company meta-analysis**	3.8%	13.2%	0.29		Company revised base case
French matched cohort study	*AIC*	*AIC*	*AIC*	*AIC*	Company scenario
UK registry • ***AIC*** • ***AIC***	*AIC* *AIC*	-	-	-	no

Estimates of standard of care mortality
- specialist centre < 5%
- average (specialist and non specialist) 10-20%
- non-specialised centre up to 50%

◉ *Is there a causal association between caplacizumab and fewer deaths in acute setting?*
◉ *Is the observational data generalisable to current practice? Variability specialist vs. general practice?*

Capla, caplacizumab; SoC standard care; RR, relative risk; CI, 95% confidence interval

Compassionate use scheme : NHS specialist centre

Provided by clinical expert with her comments. Shows similar effect to HERCULES on plasma exchange and hospital stay. No deaths on caplacizumab. Not used in model.

	AIC	*AIC*
Time period	*AIC*	*AIC*
Severity	*AIC*	
ICU during admission	*AIC*	*AIC*
Time to diagnosis protocol	*AIC*	
Median time to platelet normalisation	*AIC*	*AIC*
Median no. plasma exchanges	*AIC*	*AIC*
Median hospital stay	*AIC*	*AIC*
Deaths	*AIC*	*AIC*

◉ *How were patients chosen to receive caplacizumab?*
Are these effects likely to reflect what would be observed in NHS specialised service?

Cost effectiveness

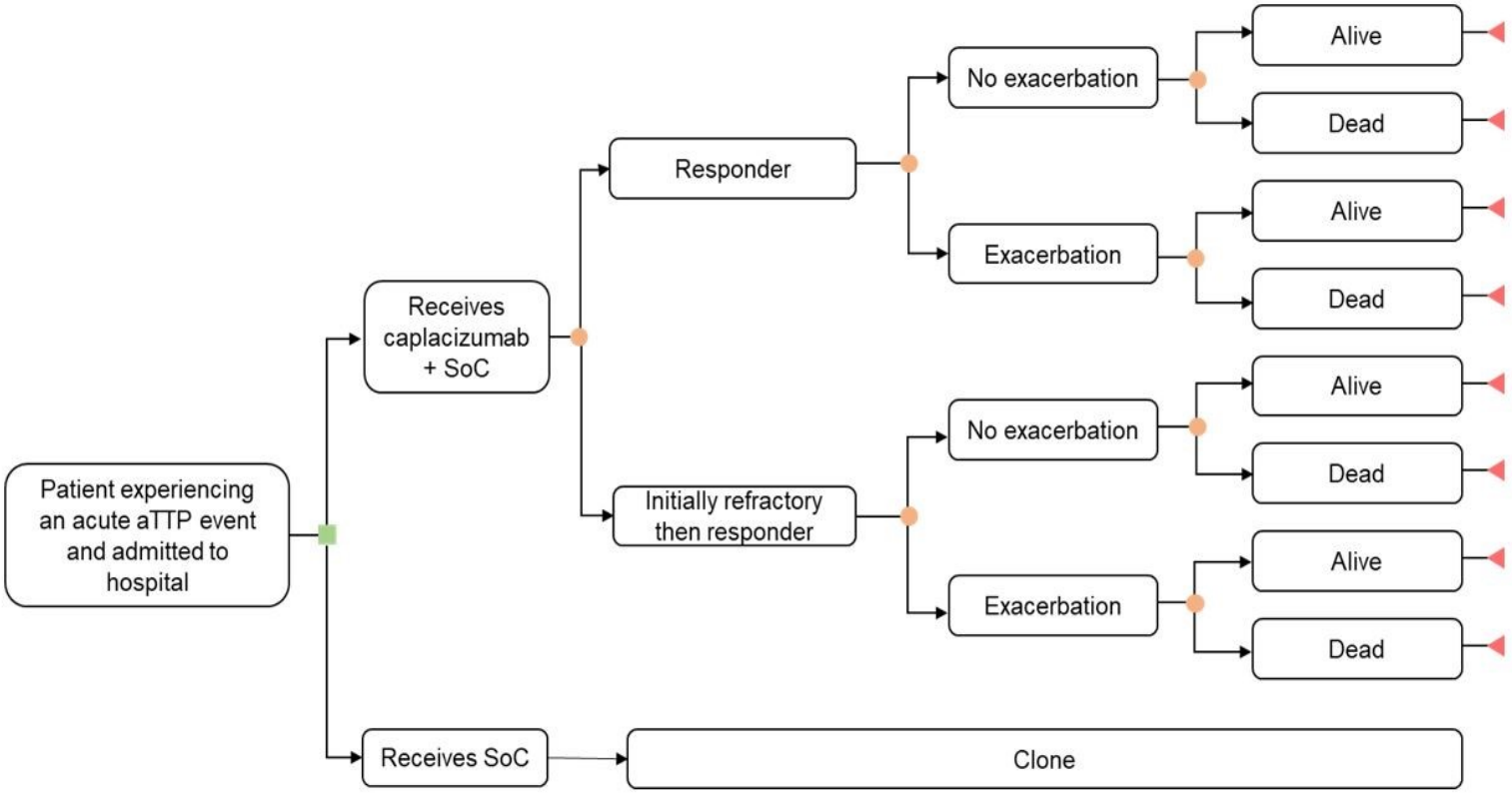
Company's cost effectiveness model: overview

Company models an acute episode, then after acute period

Component	How modelled	Source of data	Comment
Acute period	Decision tree 3 months	• Hercules trial • Naïve comparison	
After acute period	Markov model for rest of life	• Assumptions based on acute period data from Hercules trial • Observational data • Clinical opinion	
Exacerbation	In acute period	• Hercules trial	Not same as relapse
Relapses	After acute period	• Clinical opinion	
Utility	• Acute aTPP • Complications • Carer disutility	• From literature for people **without** aTTP with exception post treatment without complications	Fear of relapse in scenario
Costs	NHS costs for standard care. Duration of treatment from Hercules	• Trial for treatments • NHS reference costs	Can get caplacizumab more than once – no data for repeat use
Discount rate	3.5% in Markov model		
Horizon	Life-time		

Company's model: acute event decision tree

Does not use HERCULES 1◦ endpoint
Used data from HERCULES 2 ◦ endpoints except death rates



Death rates - acute:

Caplacizumab: global compassionate use programme
Feb 2020 data

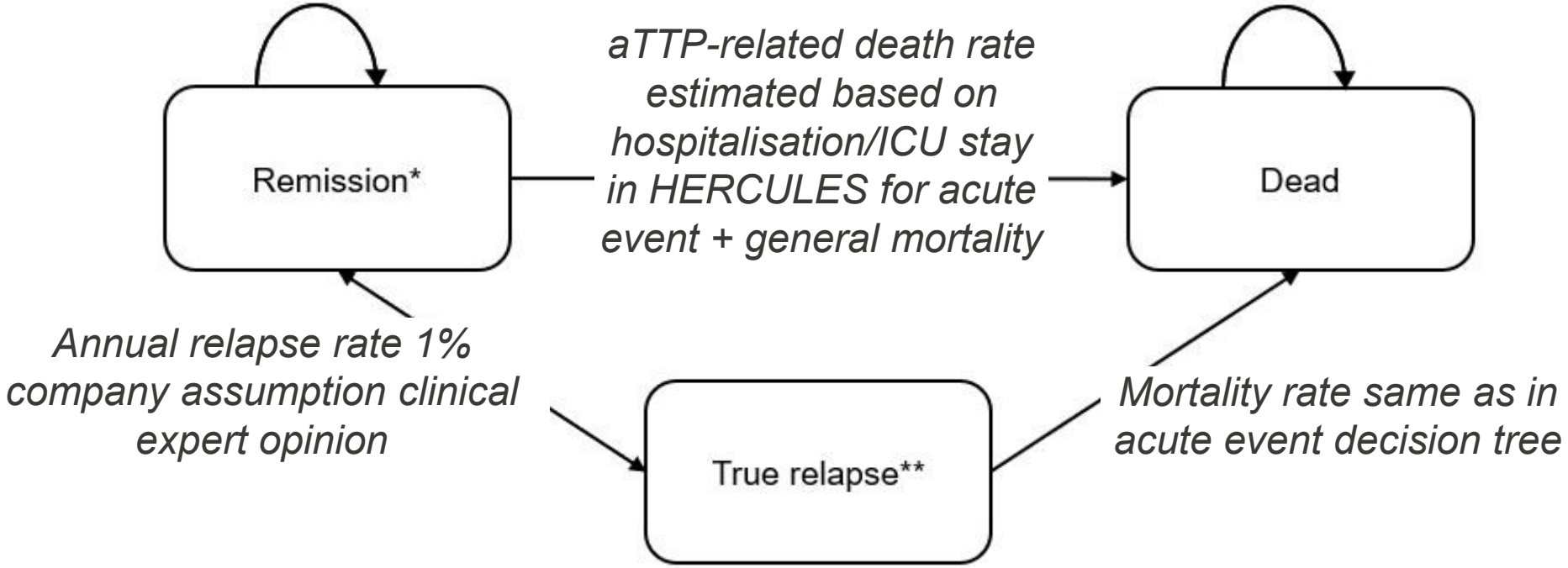
Standard care: company's meta-analysis of observational studies

Exacerbation in model: recurrent thrombocytopenia after initial response to treatment requiring a re-initiation of daily PEX therapy within the trial period from HERCULES

◉ *Is it reasonable to assume that everyone responds to caplacizumab?*

Markov cost effectiveness model: long-term

Model based on assumptions. No trial or comparative data.



Chance a person had a long term complications with caplacizumab compared with standard care based on “relative risk” of hospital/ICU stay in HERCULES.

Long term complications aTTP

Baseline risks of complications/death modelled for standard care from literature
No long-term observational or trial data for caplacizumab
An assumed relative risk applied to estimate rates of complications for caplacizumab

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

Company did not model headache, hypertension, chronic kidney disease, stroke

◉ *Is it plausible that taking caplacizumab to treat an acute episode of aTTP reduces the likelihood of long term complications of aTTP after stopping caplacizumab?*

Estimating treatment benefit for long term complications caplacizumab vs. standard care

No comparative long term data on long-term complications or death
Company assumes relative risk of long term outcomes ≈ "relative risk" for short term outcomes

- Company chose "hospitalisation/ICU days" from HERCULES trial to estimate the relative risks of cognitive impairment, neuro-psychological impairment and death with caplacizumab vs. standard care. Based on clinical advice
- Resulted in an estimated "relative risk" of 0.69* (95% CI 0.67 to 0.71)
- Company considered platelet normalisation as another proxy -estimated hazard ratio 0.65- but not used in model. Other proxy outcomes were estimated but not used in base case
- No data to validate association between hospitalisation/ICU days and these long term outcomes
- Engagement: stakeholders agreed plausible time in hospital/ICU or time to platelet normalisation associated with better long term outcome

◉ *Has the committee seen evidence that treatment improved long term outcome? How does the committee interpret an association between these proxies and complications?*

* Recalculation by company at factual accuracy check of ERG report

Health related quality of life in acute phase

Company uses values for stroke in people without aTTP to reflect general health-related quality of life with aTTP

State	Utility value	Population
Baseline utility – prior to acute episode	0.87 value	Age-matched general population
Acute episode – hospitalised	0.64 multiplier*	People with intracranial haemorrhage or stroke (Pappas et al) Australia
Acute episode – post discharge	0.82 Multiplier*	People with intracranial haemorrhage or stroke (Pappas et al) Australia
Adverse events, caplacizumab	0.0031 decrement	Targeted search of previous NICE submissions and standard utility sources for adverse events, durations based on assumptions
Adverse events, standard care	0.0022 decrement	

* Utility value is a scale of health related quality of life from 0 worst possible to 1 perfect quality of life. “multiplier” shows the % change in quality of life from baseline. Decrement is utility value subtracted from baseline value

Health related quality of life in remission

Utility values associated with moderate cognitive or neuropsychological impairment estimated from conditions other than aTTP
Includes carer disutility

State	Utility value	Population
Baseline utility	0.77	People with aTTP (Oklahoma registry) (Burns et al 2018)
Mild cognitive impairment	0.93 multiplier	People with aTTP (Oklahoma registry) (Burns et al 2018)
Moderate /severe cognitive impairment	0.61 multiplier	People with stroke (no aTTP specific data available) (Gage et al 1996)
Neuro-psychological impairment	0.73 multiplier	No aTTP specific utility data available. Assumed comparable to depressive disorder (Sullivan et al 2011)
Carer disutility for moderate /severe cognitive impairment	0.83 multiplier	For caregivers of patients with moderate to severe cognitive impairment. Stroke carer HRQL used (several references cited)

* Utility value is a scale of health related quality of life from 0 worst possible to 1 perfect quality of life. “multiplier” shows the % change in quality of life from baseline.

Health-related quality of life - discussion

Stroke utilities not proxy for quality of life with aTTP
Company does not include disutility of PEX treatment

Engagement comments:

- Using stroke to estimate QoL for people hospitalised with aTTP **not appropriate**
  - "Patients are incredibly unwell on admission to hospital" (patient group)
  - Only 70% of patients have neurological symptoms. Not all are strokes (clinical expert)
- Plasma exchange therapy (PEX)
  - PEX involves tubes and needles in "crook of each elbow or central line fitted into neck, chest or groin". Risk of infection adds further worry (patient group)
- Fear of relapse constant worry
  - "Patients talk of their first thought each morning, being 'do I have bruises' (a first sign of low platelets)… constant, intense worry, plus the issue of living with any effects of organ or stroke damage - it is like living with a ticking time bomb" (patient group)

- ◉ *What is the committee's view of the company's estimates of health related quality of life?*

Costs

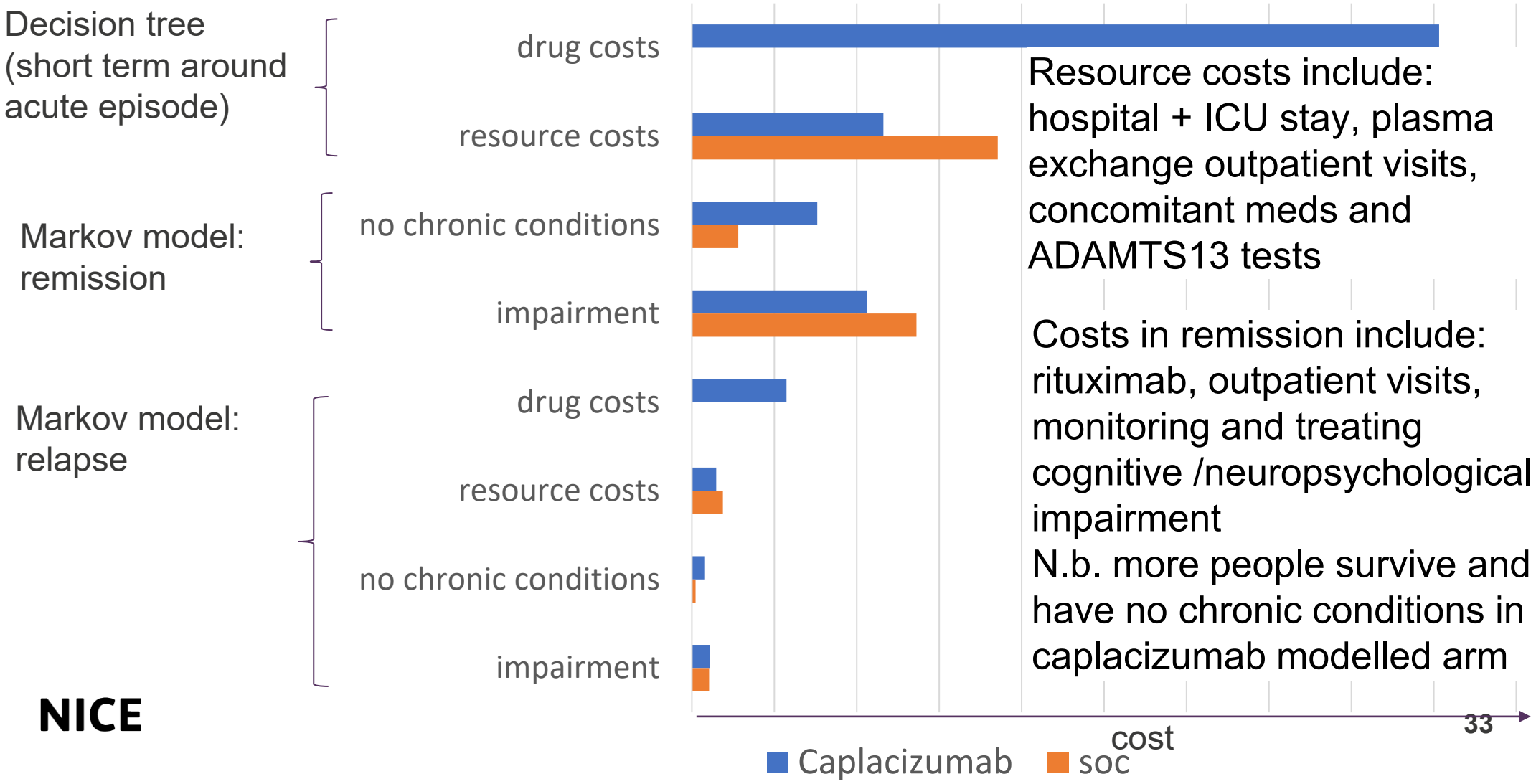
No cost issues identified in the technical report

Item	Amount/duration	Cost
Caplacizumab	Treatment duration and compliance from HERCULES	Patient access scheme
Plasma exchange	Duration and volume from HERCULES	Procedure NHS ref costs, plasma NHS blood and transplant
Other concomitant medication	Based on what received in HERCULES	eMIT and BNF prices
Hospital/ICU stay	Duration based on HERCULES	NHS reference costs
ADAMTS13 testing + outpatient visits	Clinicians survey by company	Clinicians survey cost source not stated
Adverse events	Adverse events in HERCULES	NHS reference costs
Cognitive and neuropsychological impairment	Proportions needing treatment and frequency appointments - company's clinicians survey	NHS reference costs

◉ *What determines duration of treatment of a relapse?*

How costs accrue in the company's model

Caplacizumab added to standard care decrease plasma exchange and hospital stay but costs of caplacizumab mean overall costs increased



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Cost effectiveness results company deterministic base case

Company base case revised from original company submission after technical engagement. All results are the revised base case

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental life years	Incremental QALYs	ICER incremental (£/QALY)
Standard care	*CIC*	15.85	*CIC*			
Caplacizumab	*CIC*	21.46	*CIC*	5.48	*CIC*	£27,856

Probabilistic ICER £28,934

LYs, Life Years; QALYs Quality Adjusted Life Years; ICER Incremental Cost Effectiveness Ratio

Company scenarios using alternative acute mortality estimates- deterministic

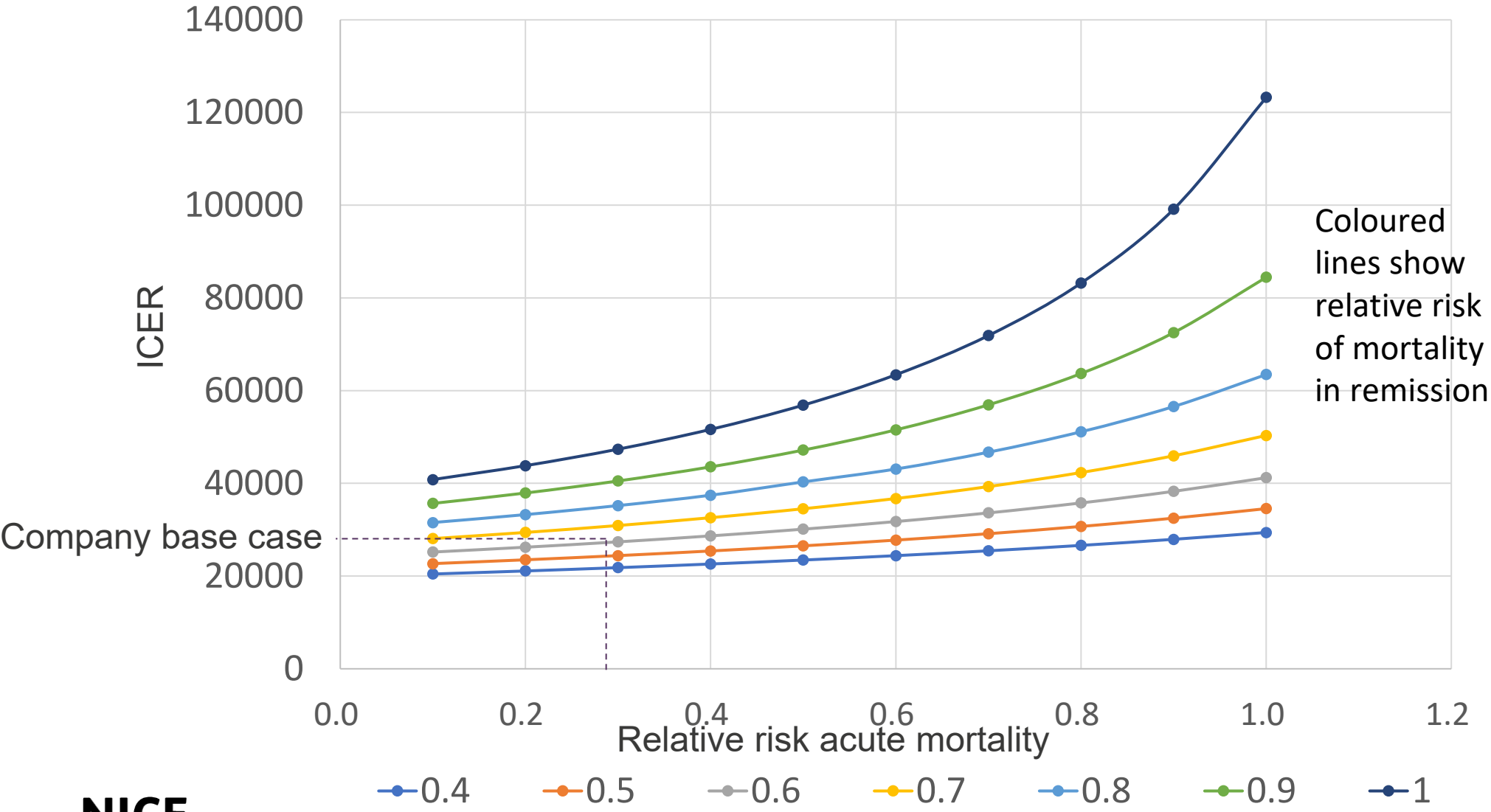
probabilistic results not presented

Scenario	Acute Mortality		ICER £/QALY
	Caplacizumab	SOC	
Caplacizumab mortality estimate global compassionate use scheme (August 2019 n=187)	**4.3%**	**13.2%**	**£28,358**
Revised company base case Caplacizumab mortality estimate global compassionate use scheme Feb 2020 n=239)	**3.8%**	**13.2%**	**£27,856**
mortality from French Matched Cohort Study	***AIC***	***AIC***	**£28,126**
mortality from Hercules	**0%**	**4.1%**	**£31,712**

1 further scenario applied a further disutility for “fear of relapse” of “50%” → decreased revised base case to £26,357

Scenario analysis: relative risk of mortality in remission caplacizumab vs. standard care

Large impact on cost effectiveness if assume no or very limited survival benefit



Same analysis as in company original submission table 52. Calculated by NICE around company revised base case

ERG preferred assumptions

Did not have a large impact on ICER. Broadly agree with the company short and long term mortality estimates which are biggest driver in model

Factor	Company	ERG	ICER
Company base case ICER			27,856
Size of ITT population in caplacizumab arm	N=71	N=72	28,353
Refractory rate on standard of care	6.85%	15% *	27,993
Proportion receiving rituximab in acute phase	48% SoC 39% CAPLA	78% both arms	28,578
RR long-term complications	0.62	0.68§	30,033
RR mortality (remission)		0.62	No change
Resource use for long-term complications			
Psychology/counselling, proportion of patients	33%	100%*	28,344
Antidepressants	20%	50%*	
Clinic time (haematology)	50%	75%*	
Rituximab use in remission	10%	30%*	29,556
Resource costs			
Cerebral imaging (long-term)	£90 CT scan	£141 MRI†	28,311
Haematology outpatient visit	£250	£171 †	27,996

* Advice from ERG clinical expert, § recalculation by company; † NHS reference costs 2017/18

ERG exploratory base case- deterministic

	Total			Incremental			ICER
Technologies	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs	incremental (£/QALY)
SoC	*CIC*	15.85	*CIC*				
CAPLA	*CIC*	21.33	*CIC*	*CIC*	5.48	*CIC*	£30,665

Innovation

Step change, uncaptured benefits

Company submission

- 1st nanobody developed from camelid heavy-chain-only antibodies in any indication
- 1st licensed treatment specific to aTTP
- Unique mode of action

Patient experts

- no [other] drug or treatment in last 25 years that has significantly altered path
- With caplacizumab → normalisation of platelets within days, patients home much faster "socio-economic impact likely to be significant"

Benefits not in modelling

- Reduced ICU/hospital stays frees beds (company/ clinical experts)
- Reduced plasma use →fewer replacement lines (company/clinical experts)
- People report fear of relapse

◉ *Is caplacizumab innovative?*

Equality issues

- Disproportionately affects women and people of African Caribbean family origin
- People with HIV are at increased risk
- No evidence has been presented to suggest caplacizumab has better or worse outcomes in any group of people

◉ *Are there any equality issues?*