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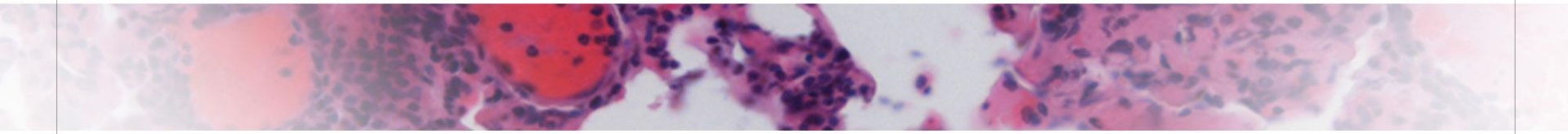


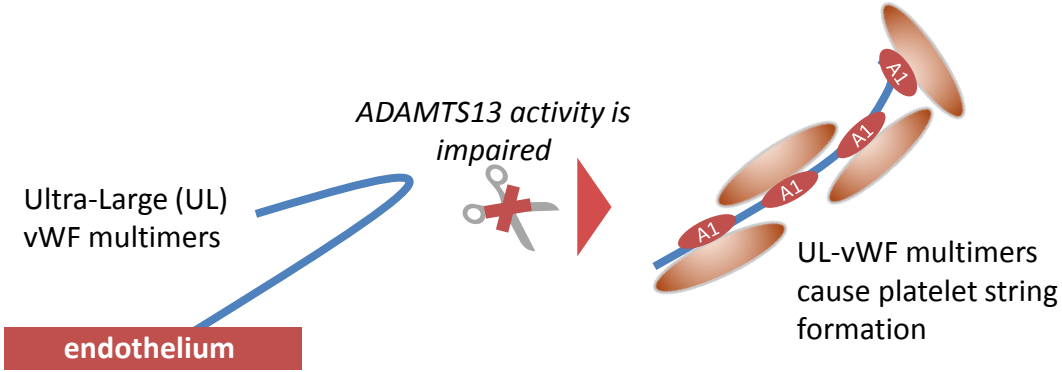
Results of the Randomized, Double-Blind, Placebo-Controlled, Phase 3 Hercules Study of Caplacizumab in Patients with Acquired Thrombotic Thrombocytopenic Purpura

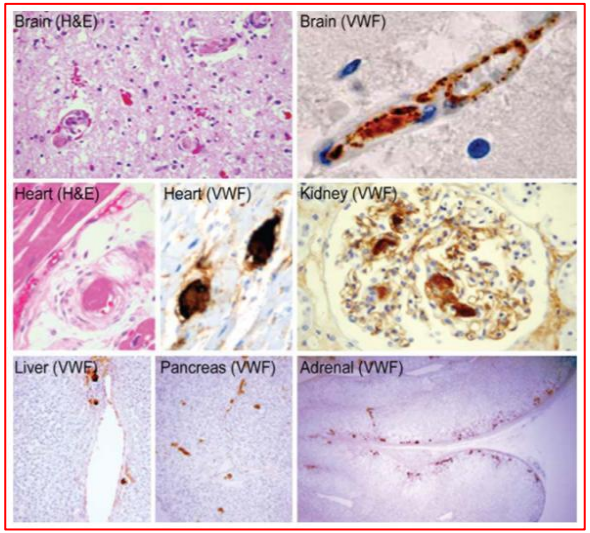
Marie Scully, Spero Cataland, Flora Peyvandi, Paul Coppo, Paul Knoebl, Johanna A. Kremer Hovinga, Ara Metjian, Javier de la Rubia, Katerina Pavenski, Filip Callewaert, Debjit Biswas, Hilde De Winter, Robert K. Zeldin
for the HERCULES Investigators

Acquired Thrombotic Thrombocytopenic Purpura (aTTP)

- Acute, life-threatening thrombotic microangiopathy

- Disseminated vWF-platelet microthrombi caused by a deficiency in the vWF-cleaving enzyme ADAMTS13
  - tissue ischemia and end organ damage
  - mortality >90% if untreated





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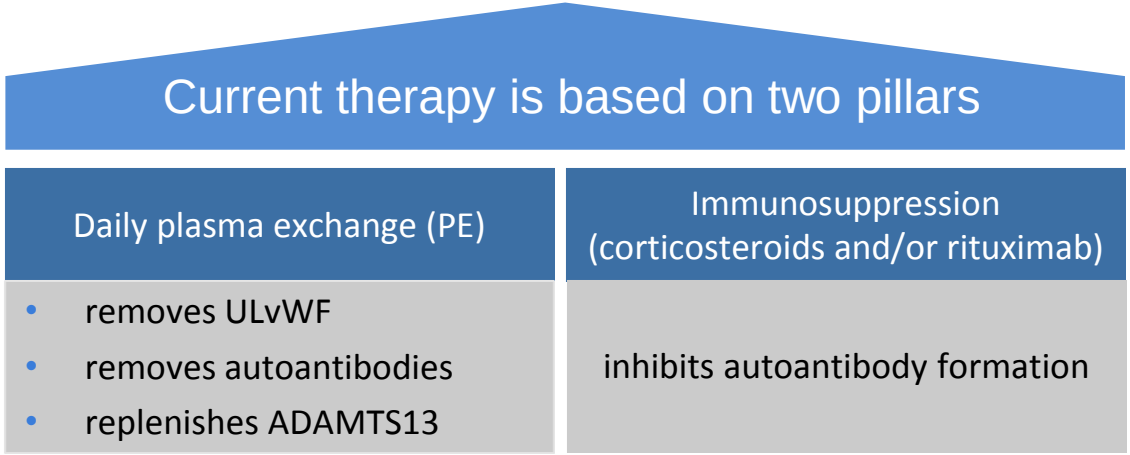
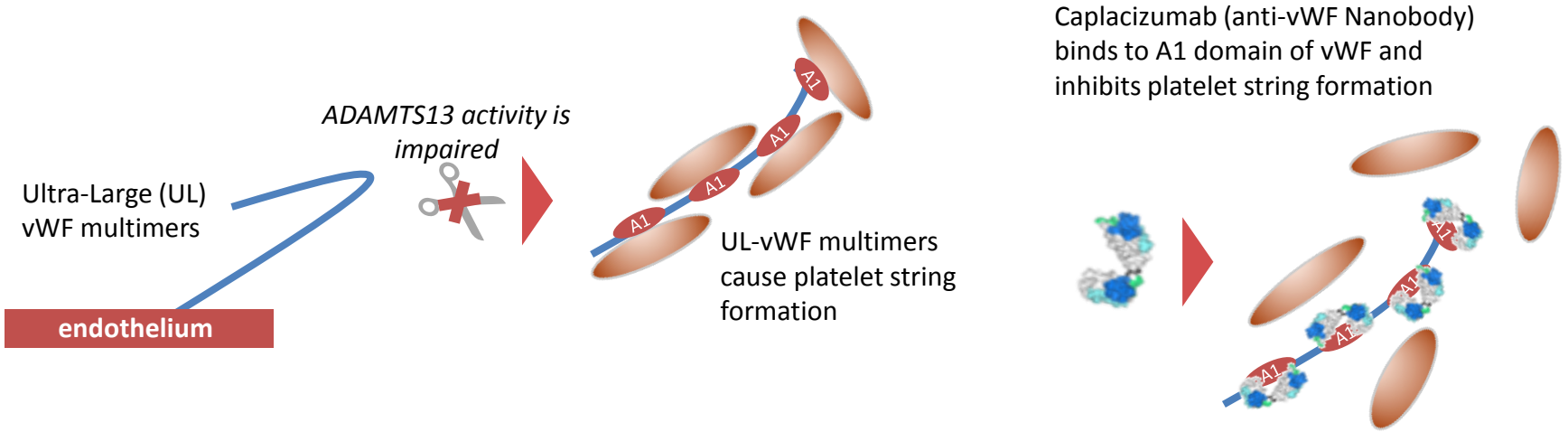
aTTP - Current Treatment and Issues



The unmet medical need remains high

- Mortality of 10-20%
- Refractoriness to treatment (associated with poor outcomes)
- Disease exacerbations within weeks after stopping plasma exchange
- PE-related complications

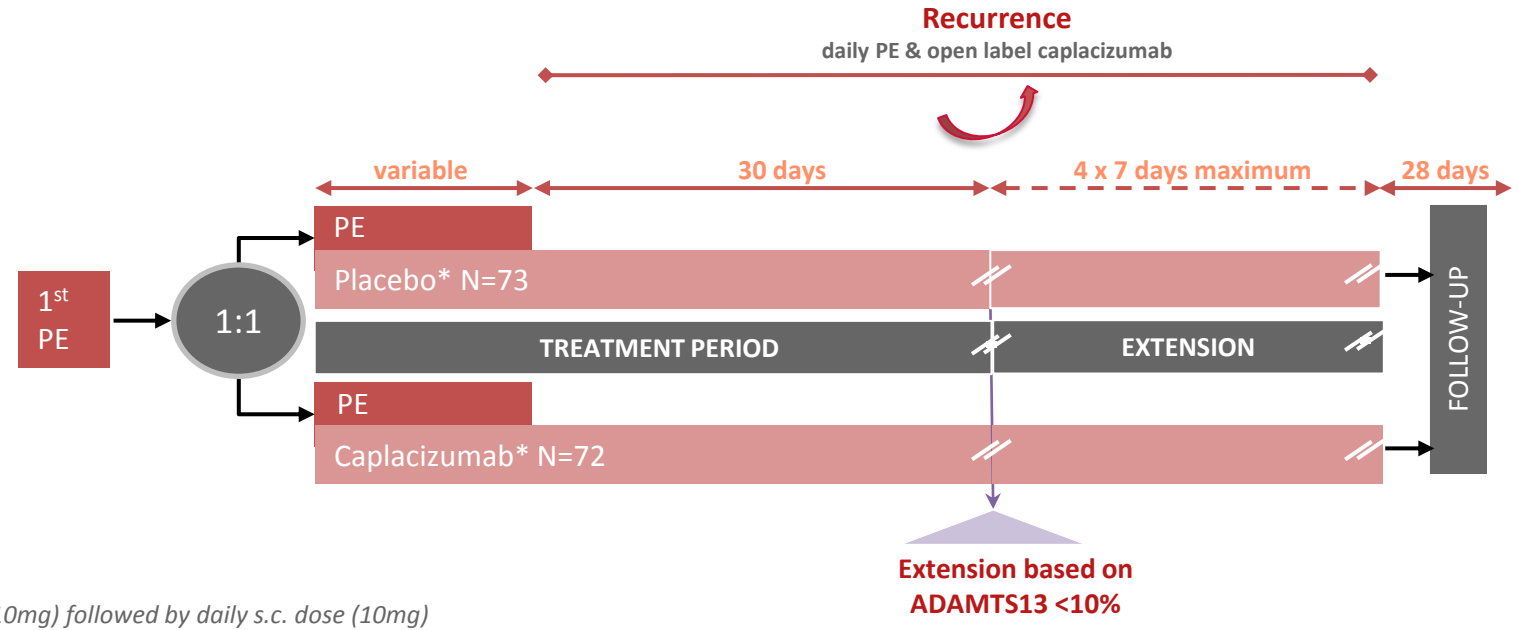
Caplacizumab in aTTP



Caplacizumab blocks the binding of vWF to platelets which has an immediate effect on platelet aggregation and the ensuing formation of microthrombi

Caplacizumab - Phase III HERCULES study design

- Randomized, double-blind, placebo-controlled, multi-national study



* *i.v. bolus (10mg) followed by daily s.c. dose (10mg)*
PE = plasma exchange

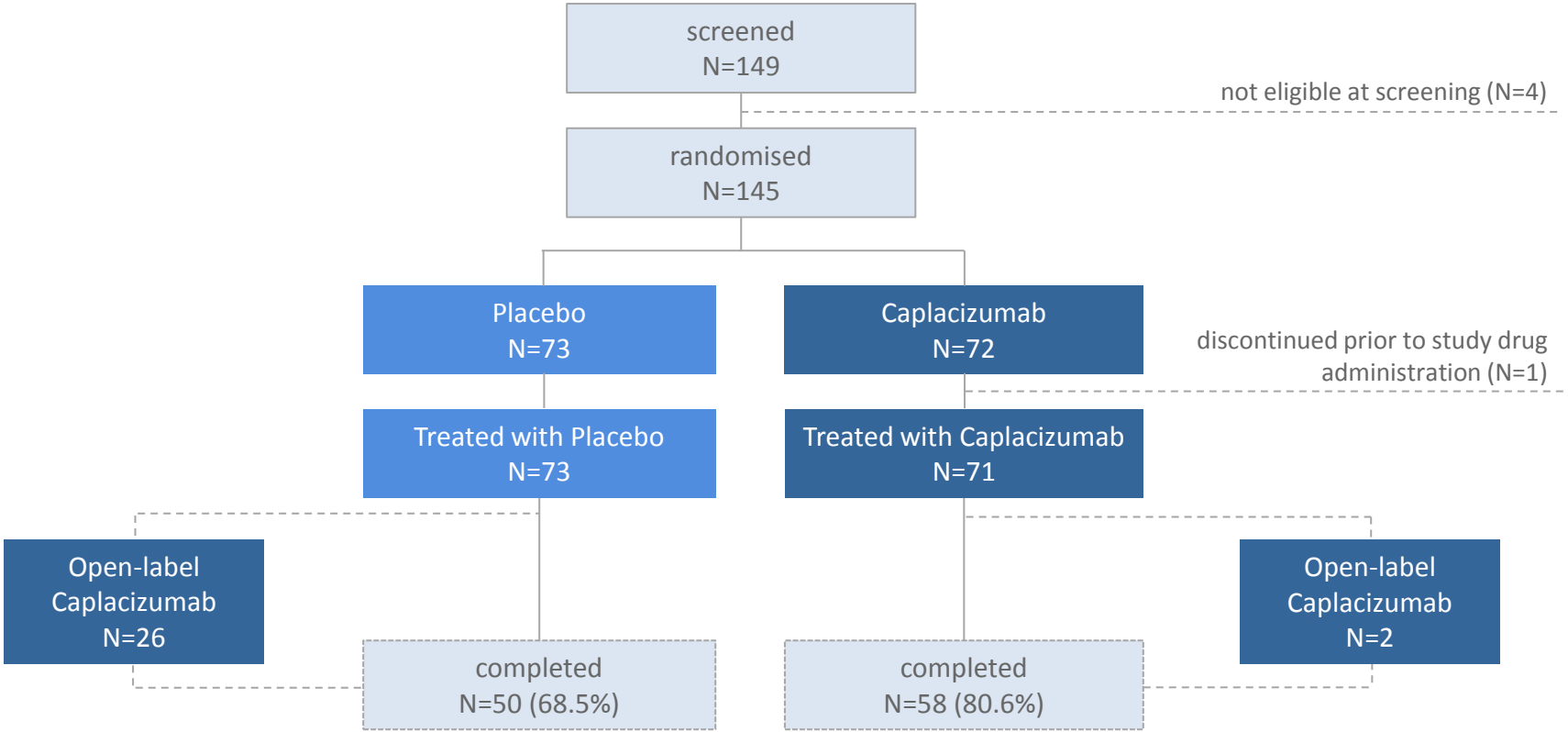
Key study endpoints

- **Primary endpoint:** time to confirmed platelet count response[1]
- **Key secondary endpoints (hierarchically tested)**
  1. aTTP-related death, recurrence of aTTP, or at least one major thromboembolic event during the study drug treatment period
  2. recurrence of aTTP in the overall study period
  3. refractoriness to treatment
  4. time to normalization of 3 organ damage markers
- **Safety**
- **PK/PD and anti drug antibodies[2]**

[1] Platelet count response was defined as initial platelet count ≥ 150×10^9/L with subsequent stop of daily PE within 5 days

[2] Data not yet available

Recruitment flow

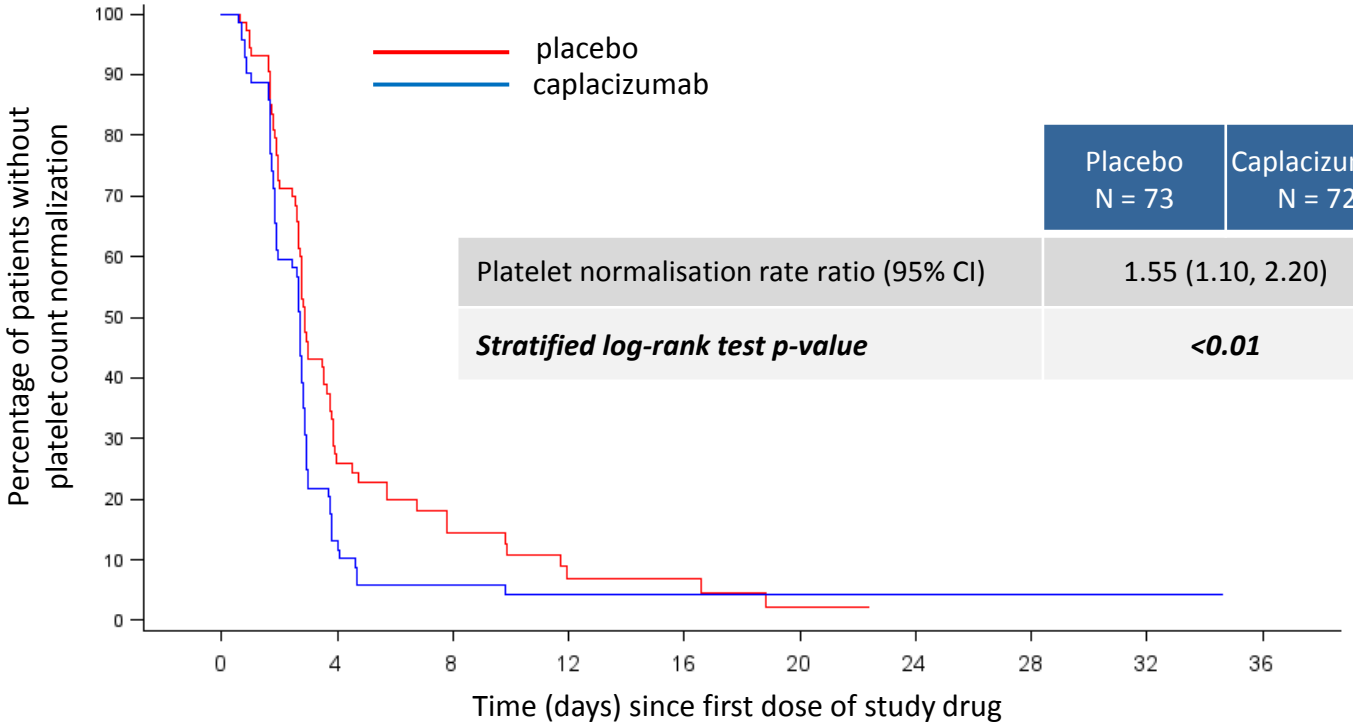


Demographics and baseline disease characteristics

	Placebo N=73	Caplacizumab N=72
Mean age (SD)	47.3 (14.1)	44.9 (13.5)
Females – N (%)	51 (69.9)	49 (68.1)
Baseline platelet count (10^9/L) - mean (SD)	39.1 (29.1)	32.0 (27.2)
Previous aTTP episode(s) – N (%)		
- initial	34 (46.6)	48 (66.7)
- recurrent	39 (53.4)	24 (33.3)
ADAMTS13 activity at baseline – N (%)		
- <10%	65 (90.3)	58 (81.7)
- ≥10%	7 (9.7)	13 (18.3)
Disease severity at baseline – N (%)*		
- Less severe	48 (65.8)	42 (58.3)
- Very severe	25 (34.2)	30 (41.7)

** Very severe was defined as: French severity score ≥3 (cerebral involvement: yes=1 / no=0, LDH: >10xULN=1 / ≤10xULN=0, age: >60 years=2 / >40 and ≤60 years=1 / ≤40 years=0), or severe neurological involvement at baseline, or cardiac involvement (cTnI > 2.5 x upper limit of normal)*

Primary endpoint: time to platelet count response*



	Placebo N = 73	Caplacizumab N = 72
Platelet normalisation rate ratio (95% CI)	1.55 (1.10, 2.20)	
Stratified log-rank test p-value	***<0.01***	

* Platelet count response was defined as initial platelet count ≥ 150×10^9/L with subsequent stop of daily PE within 5 days

First key secondary endpoint

Subjects with aTTP-related death, aTTP recurrence or a major thromboembolic event during the study drug treatment period

Number of subjects (%)	Placebo N=73	Caplacizumab N=72*
Total number of subjects with at least one of the events[1]	**36 (49.3)**	**9 (12.7)**
aTTP-related death[2]	3 (4.1)	0
recurrence (exacerbation) of aTTP[3]	28 (38.4)	3 (4.2)
at least one treatment emergent major thromboembolic event[2]:	6 (8.2)	6 (8.5)
- cerebrovascular accident	*3 (4.1)*	*2 (2.8)*
- myocardial infarction	*1 (1.4)*	*1 (1.4)*
- pulmonary embolism	*0*	*1 (1.4)*
- deep venous thrombosis (spontaneous)	*1 (1.4)*	*0*
- deep venous thrombosis (catheter-associated)	*2 (2.7)*	*3 (4.2)*
p-value	***<0.0001***	

** percentages are based on 71 subjects entering the study drug treatment period; [1] patients could have more than 1 event; [2] adjudication of aTTP-related death and major thromboembolic events by a blinded independent committee; [3] recurrence = recurrent thrombocytopenia after initial recovery of platelet count, requiring re-initiation of daily PEX*

Second key secondary endpoint

Subjects with aTTP recurrence during the overall study period

Number of subjects (%)	Placebo N=73	Caplacizumab N=72*
aTTP recurrence[1]	**28 (38.4)**	**9 (12.7)**
During the study drug treatment period (exacerbations)	28 (38.4)	3 (4.2)
During the follow-up period (relapses)	0	6 (9.1)[2]
p-value	***<0.001***	

** percentages are based on 71 subjects entering the study drug treatment period and 66 subjects in the follow-up period*
[1] recurrence = recurrent thrombocytopenia after initial recovery of platelet count, requiring re-initiation of daily PEX
[2] ADAMTS-13 activity levels were <10% at the end of the study drug treatment period in all of these patients

Third key secondary endpoint

Percentage of subjects with refractory aTTP

- Protocol-specified key secondary endpoint (Benhamou *et al.*, 2015)

Number of subjects (%)	Placebo N=73	Caplacizumab N=72
Refractory aTTP[1]	**3 (4.2)**	**0**
p-value	***0.057***	

[1] refractory TTP = absence of platelet count doubling after 4 days of standard treatment and LDH > ULN

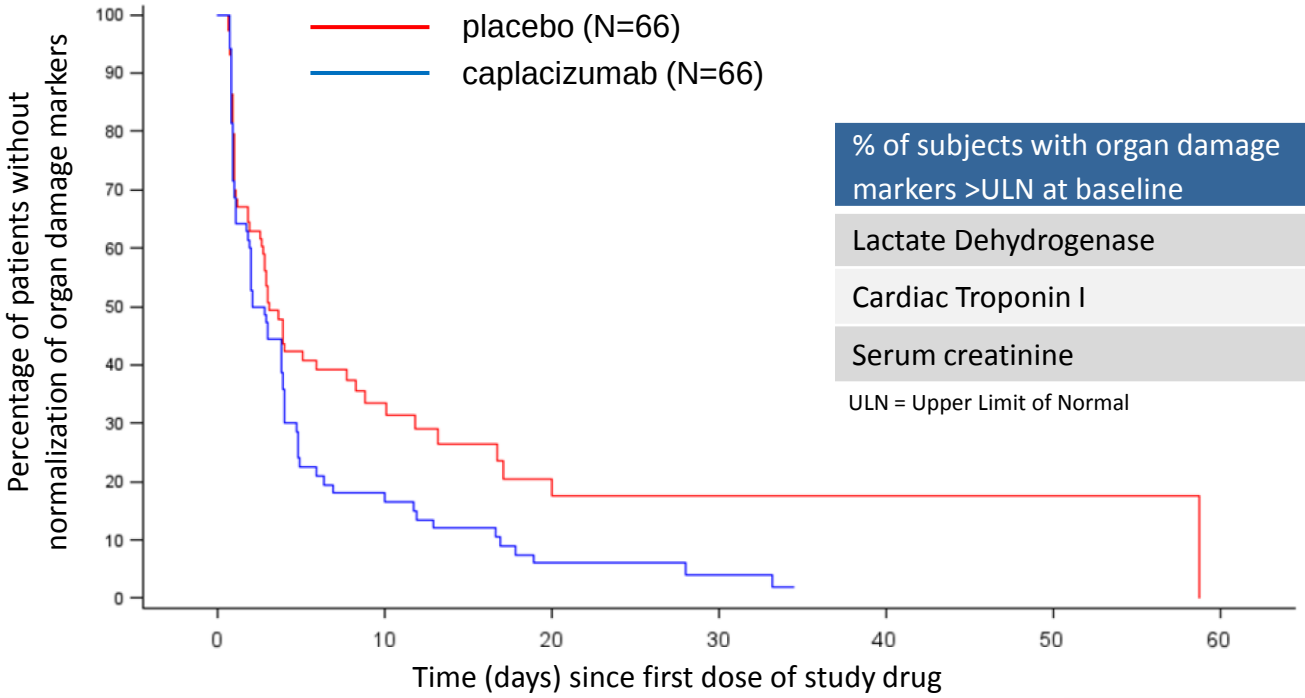
- International TTP working group consensus definition (Scully *et al.*, 2017)

Number of subjects (%)	Placebo N=73	Caplacizumab N=72
Refractory aTTP[2]	**5 (7.0)**	**0**
p-value	***0.018***	

[2] refractory TTP = persistent thrombocyopenia, lack of a sustained platelet count increment or platelet counts of <50 x 10^9 L-1 and a persistently raised LDH level (> 1.5 ULN) despite five plasma exchanges and steroid treatment

Fourth key secondary endpoint

Time to normalization of organ damage markers



% of subjects with organ damage markers >ULN at baseline	All subjects N=145
Lactate Dehydrogenase	87.1%
Cardiac Troponin I	53.8%
Serum creatinine	22.7%

ULN = Upper Limit of Normal

Other secondary endpoints

Plasma exchange parameters, duration of ICU stay and overall hospitalization

Overall study drug treatment period (mean±SE)	Placebo N=73	Caplacizumab N=71	% relative reduction
Number of days of Plasma Exchange	9.4±0.8	5.8±0.5	↓38%
Volume of plasma (L)	35.9±4.2	21.3±1.6	↓41%
Number of days in Intensive Care Unit	9.7±2.1 (n=27)	3.4±0.4 (n=28)	↓65%
Number of days in Hospital	14.4±1.2	9.9±0.7	↓31%

Safety

Overall summary of Treatment-Emergent Adverse Events (TEAEs)

Number of subjects (%) with	Placebo N=73	Caplacizumab N=71
At least one TEAE	71 (97.3)	69 (97.2)
At least one study drug-related TEAE	32 (43.8)	41 (57.7)
At least one TEAE leading to study drug discontinuation	9 (12.3)	5 (7.0)
At least one SAE	39 (53.4)	28 (39.4)
At least one study drug-related SAE	4 (5.5)	10 (14.1)
At least one SAE leading to death	3 (4.1)	1 (1.4)[1]

[1] adverse event occurred during the follow-up period of the study and was assessed by the investigator as not related to study drug treatment

Safety

Bleeding-related TEAEs*

	Placebo - n (%)	Caplacizumab - n (%)
Bleeding-related TEAEs (by SMQ)[1]	**17 (23.3)**	**33 (45.6)**
Epistaxis	1 (1.4)	17 (23.9)
Gingival bleeding	0	8 (11.3)
Bruising	3 (4.1)	5 (7.0)
Hematuria	1 (1.4)	4 (5.6)
Vaginal hemorrhage	1 (1.4)	3 (4.2)
Menorrhagia	1 (1.4)	2 (2.8)
Catheter site hemorrhage	3 (4.1)	2 (2.8)
Injection site bruising	2 (2.7)	2 (2.8)
Hematochezia	0	2 (2.8)
Hematoma	0	2 (2.8)

* Treatment emergent adverse events occurring in at least 2 subjects in either group

[1] Standardized MedDRA Query “Hemorrhage”

Caplacizumab Phase III HERCULES study – Conclusions

Caplacizumab addresses the pathophysiological platelet aggregation that leads to the formation of microthrombi and the resultant mortality and morbidity seen in aTTP

- Faster resolution of an aTTP episode with significantly shorter time to platelet count response
- Clinically relevant reduction in aTTP-related death, exacerbation of aTTP, or a major thromboembolic event
- Prevention of aTTP relapses when treatment is extended until resolution of underlying disease
- Potential to prevent refractory disease and speed normalization of markers of organ damage
- Striking reduction in use of plasma exchange and length of stay in the ICU and hospital
- Safety profile in line with previous study results and mechanism of action

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