

The predictive value of ADAMTS13 activity for treatment monitoring of patients with acquired TTP: data from the Phase II TITAN trial with caplacizumab

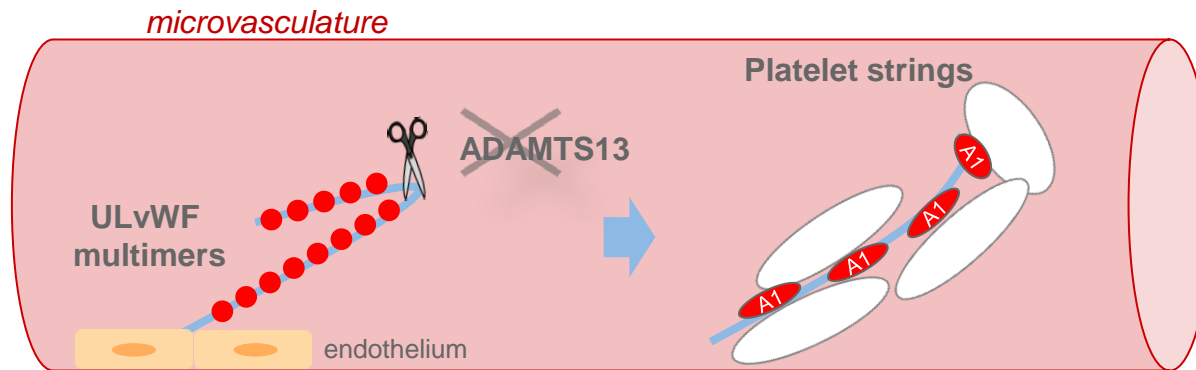
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Filip Callewaert, Hans Ulrichs, Johanna A. Kremer Hovinga, Katelijne De Swert, Dominique Tersago

Acquired thrombotic thrombocytopenic purpura (TTP)

Background

- Acute and life threatening rare disorder of the blood coagulation system
 - annual incidence of 11 cases/million¹
 - 10,000 acute events annually in US and Europe
 - mortality remains high (10-20%)² and ~36% of patients have relapses³
- Mortality and morbidity caused by ultra-large von Willebrand factor-mediated platelet aggregation



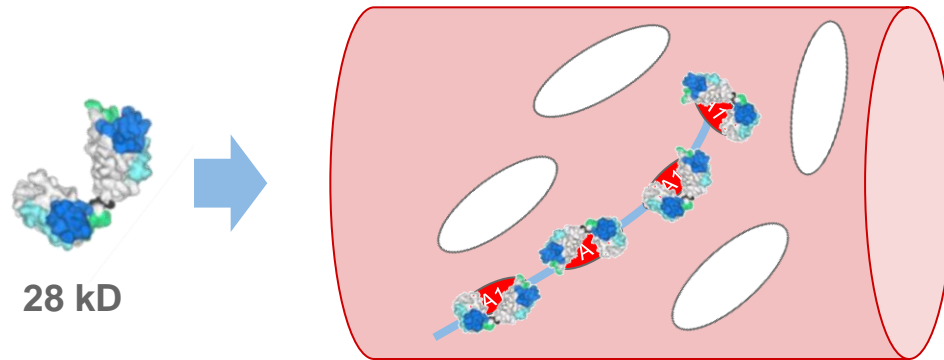
Microvascular thrombosis

- consumes platelets → severe thrombocytopenia
- blocks microvasculature → tissue ischemia with neurological, myocardial, renal signs & symptoms
- leads to red blood cell fragmentation → haemolytic anaemia

¹ George et al, Eur J Haematol 2008; ² Hovinga et al. paper, Blood, 2010; ³ Scully et al, Br J Haematology 2012

Caplacizumab

Mode of action of the anti-vWF Nanobody*

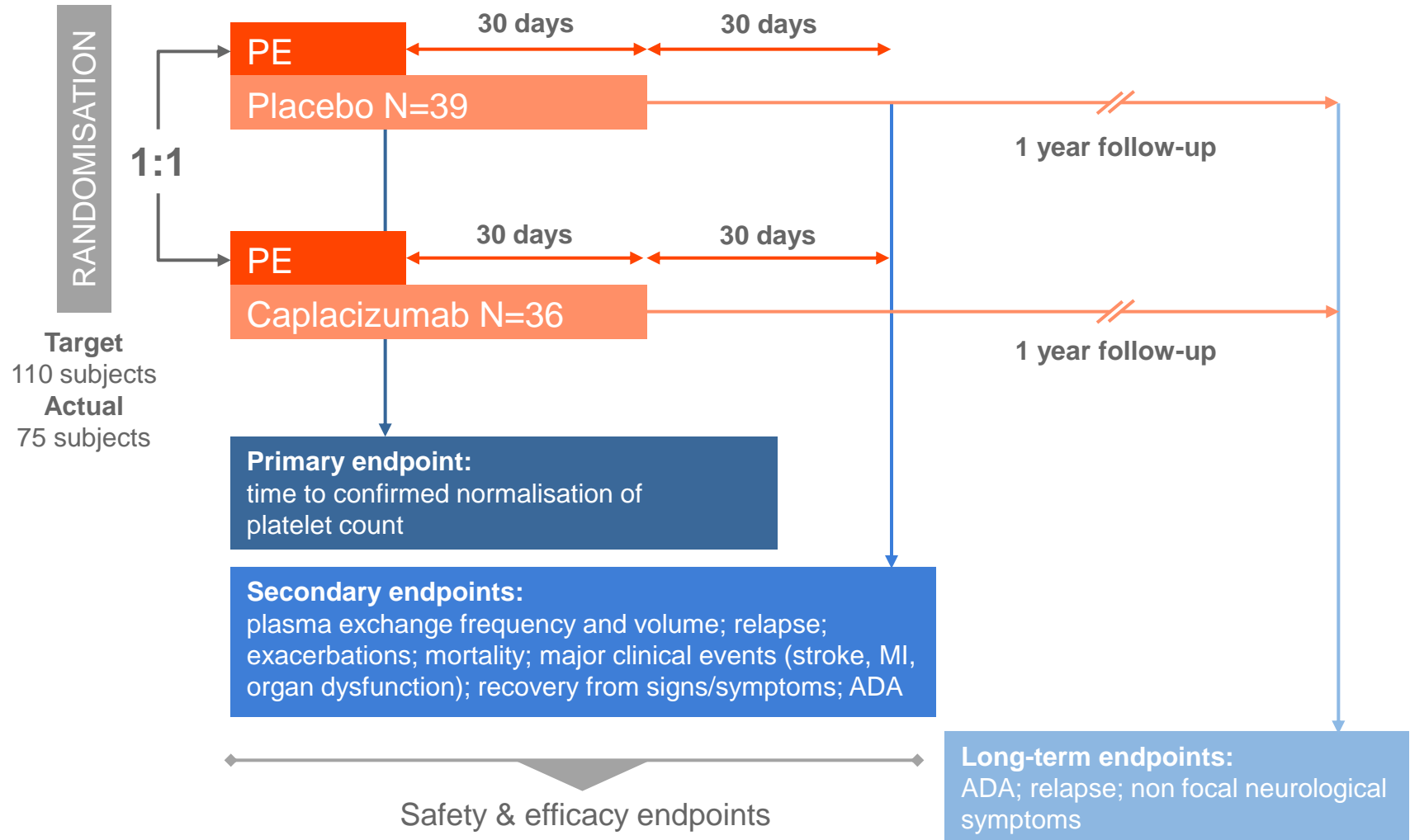


- Caplacizumab binds to A1 domain of vWF
- Immediate inhibition of platelet string formation and consumption of platelets
 - faster normalisation of platelets
 - reduction of tissue damage

* Nanobody® is a biologic derived from heavy chain only antibodies

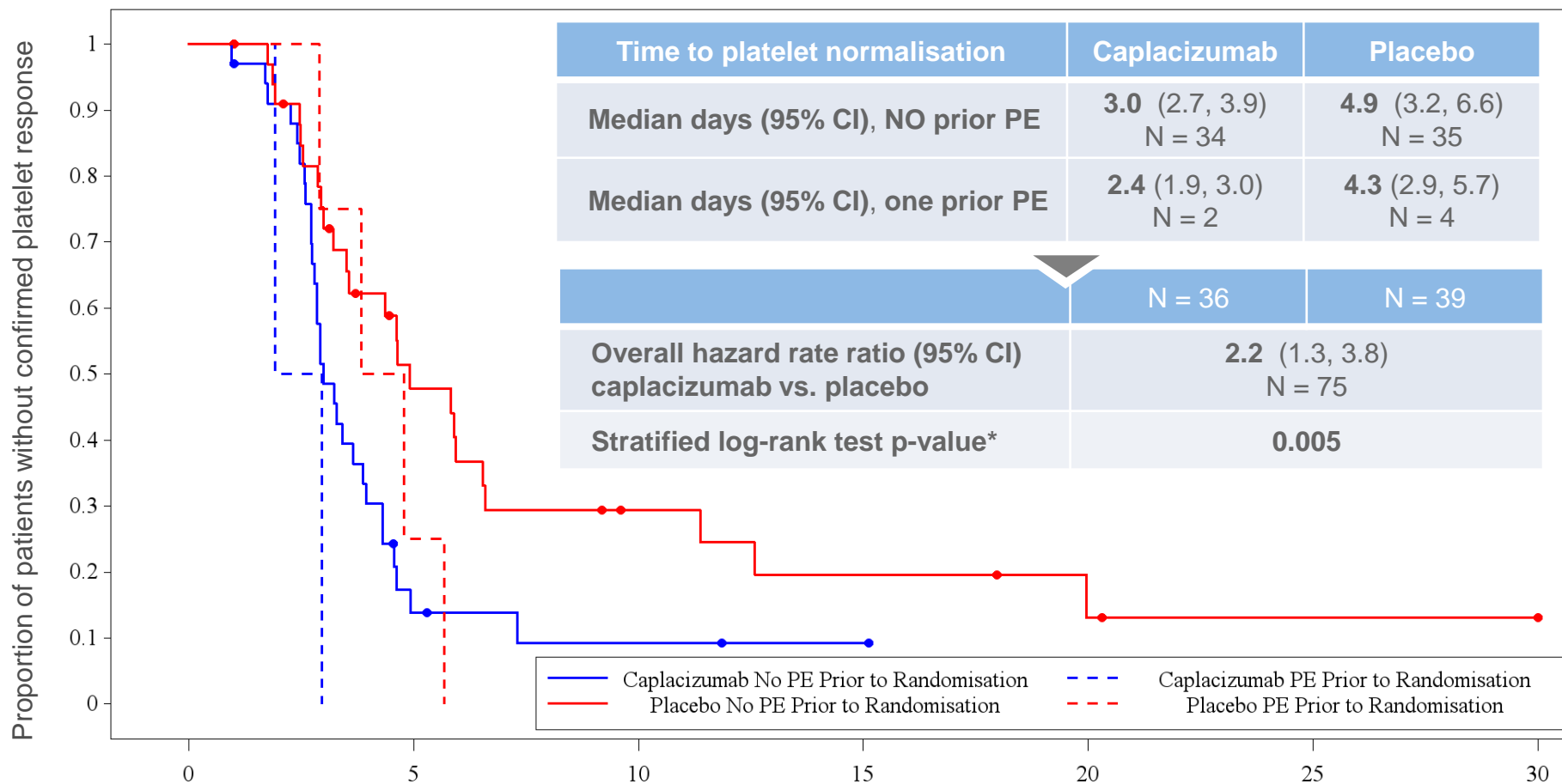
Caplacizumab Phase II TITAN trial

Design and schedule



Caplacizumab Phase II TITAN trial

Primary endpoint – time to platelet normalisation



The group of patients treated with caplacizumab achieved confirmed platelet normalisation at more than twice the rate of the group receiving placebo

Caplacizumab Phase II TITAN trial

Key secondary outcomes and safety profile of caplacizumab

- In the caplacizumab group, fewer patients had exacerbations of TTP, but a higher number of relapses was observed during the follow-up period

Proportion (number) of subjects (ITT population)	Caplacizumab N = 36	Placebo N = 39
Complete remission	81% (29)	46% (18)
Exacerbation	8% (3)	28% (11)
Exacerbation and/or relapse up to 1 month follow-up	28% (10)	28% (11)
Deaths, n	0	2

- Acceptable safety profile (manageable mild bleeding tendency)

Proportion of subjects (safety population)	Caplacizumab N = 35	Placebo N = 37
Subjects with any TEAE	97%	100%
- with bleeding event	54%	38%
Subjects with any TE Serious AEs	57%	51%
- with serious bleeding event	6%	5%

Caplacizumab Phase II TITAN trial

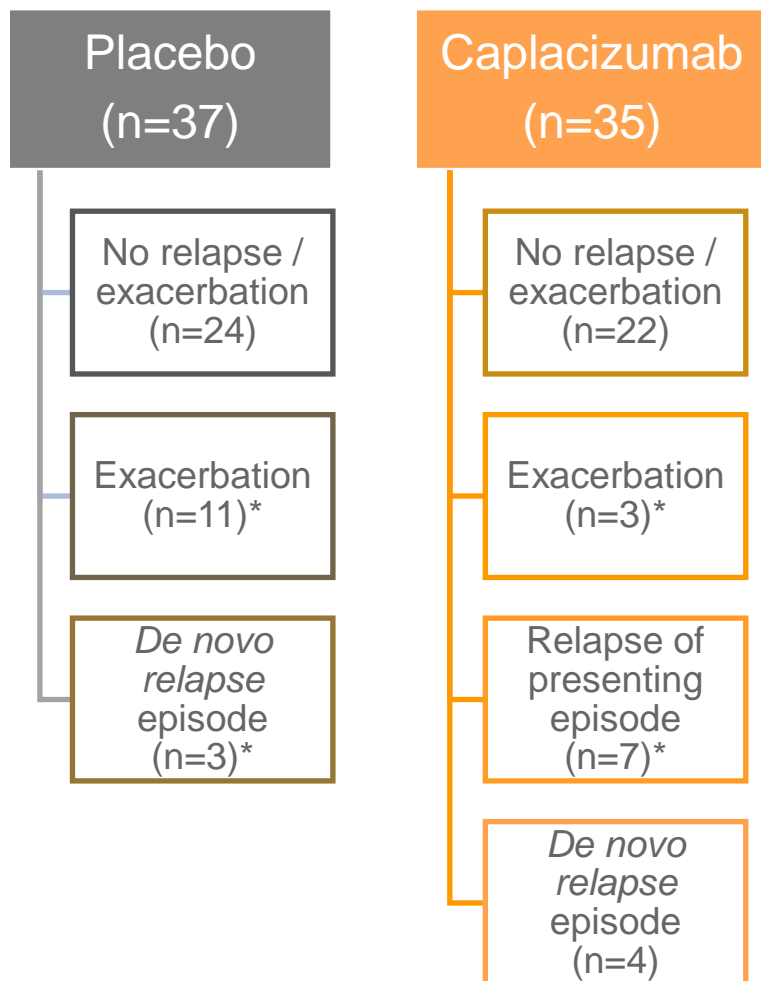
Post-hoc analysis: relapses, exacerbations and ADAMTS13 activity

- Objective
 - Evaluate ADAMTS13 activity as marker for underlying disease activity
 - Evaluate ADAMTS13 activity as marker to guide optimal treatment duration of caplacizumab
- Data interpretation

Biomarker level	
Underlying disease activity	ADAMTS13 activity <10%
No underlying disease activity	ADAMTS13 activity ≥10%
Clinical picture	
Exacerbation	Recurrent disease in the period of 30 days after stop of daily PE
Relapse of presenting episode	Relapse during FU period (>30 days after stop of daily PE) Underlying disease activity linked to the presenting episode
<i>De novo</i> relapse episode	Relapse during FU period (>30 days after stop of daily PE) Presenting episode showed signs of normalisation/resolution; relapse considered as a <i>de novo</i> event

Caplacizumab Phase II TITAN trial

Post-hoc analysis: ADAMTS13 activity



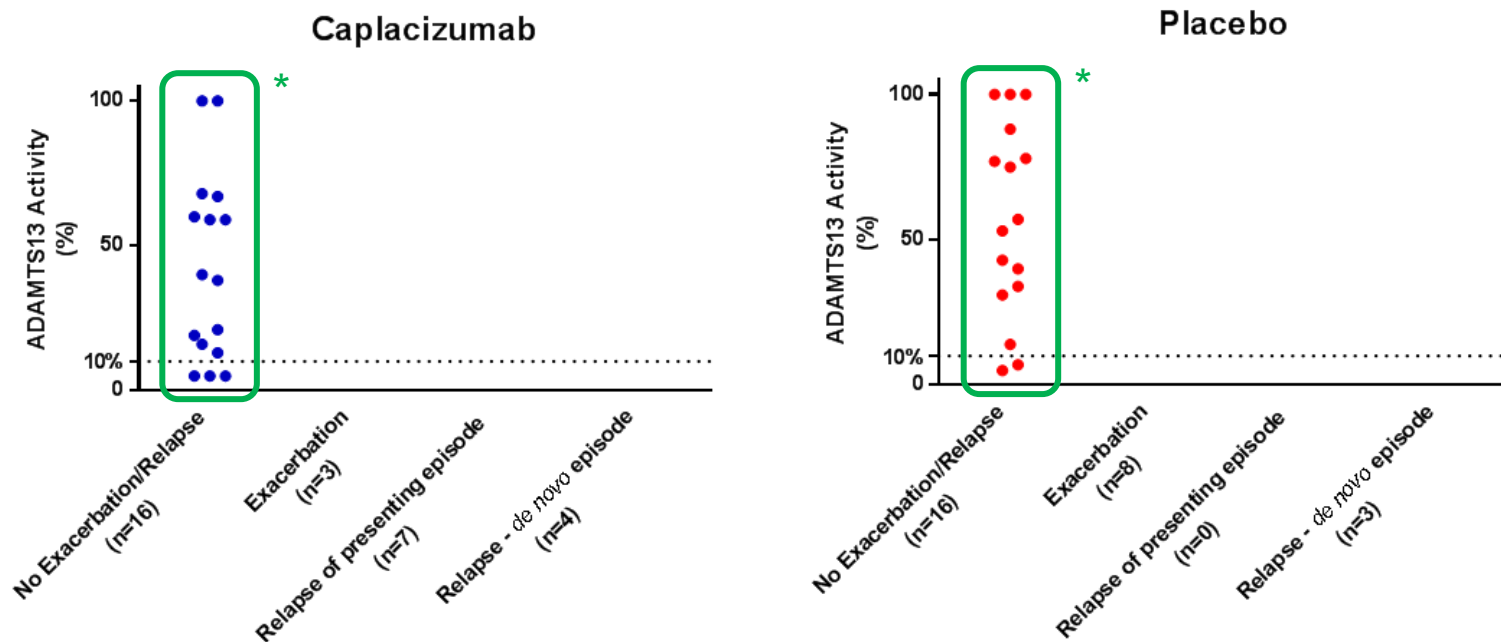
- Exacerbations or relapses were related to the patient's available ADAMTS13 activity data:
 - If a relapse was preceded by continuously low ADAMTS13 (<10%) during treatment, it was considered as relapse of presenting episode
 - If a relapse was preceded by ADAMTS13 activity $\geq 10\%$ during treatment, it was considered as a de novo TTP episode
- Data used for analysis:
 - Value closest to the end of treatment period
 - Value closest to the time of exacerbation
- Patients excluded from analysis
 - Non-ADAMTS13 mediated disease ($\geq 10\%$ at baseline) (n=3)
 - Patients with insufficient data (n=12)

* One patient in each treatment group had both an exacerbation and a relapse, and was counted in both categories

Caplacizumab Phase II TITAN trial

Underlying disease activity based on ADAMTS13 activity

* Data plotted: ADAMTS13 activity closest to treatment stop (range: 2-15 days before treatment stop)



Patients without exacerbations or relapses

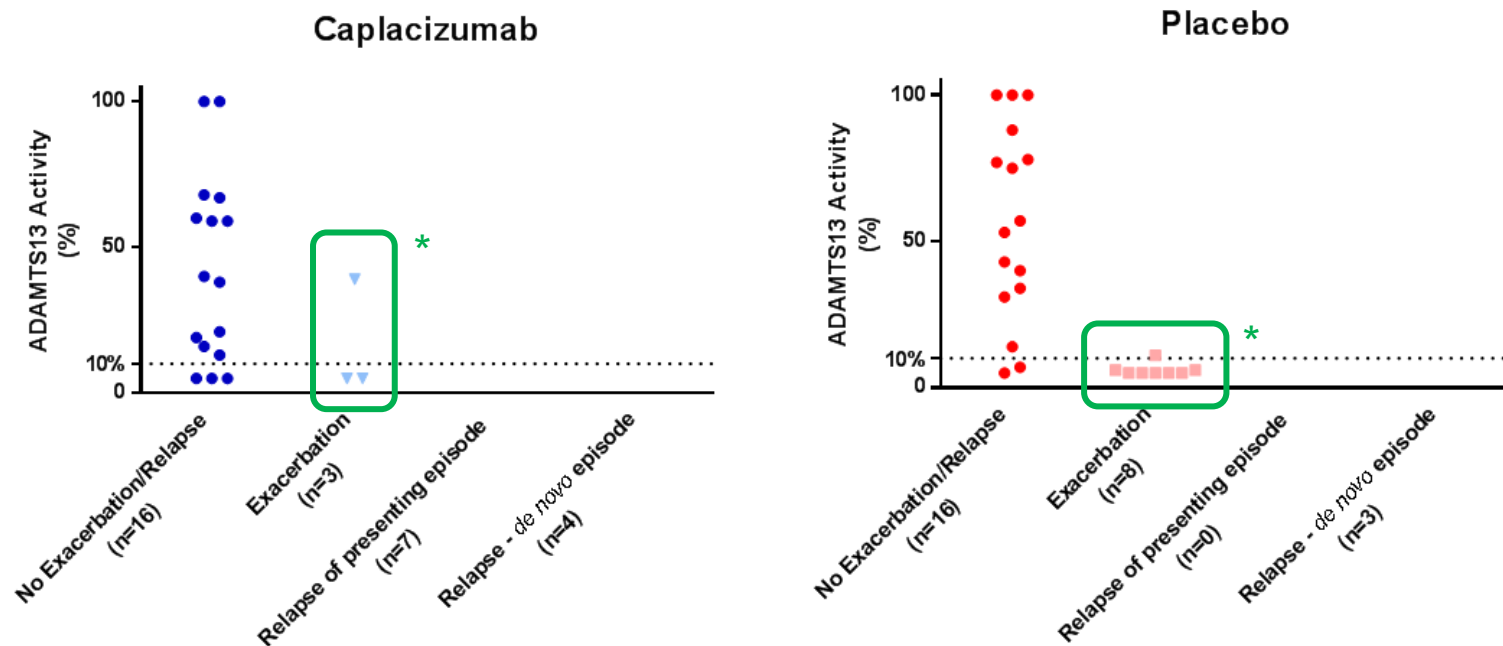
- Caplacizumab: 13/16 (81%) had ADAMTS13 activity values $\geq 10\%$ close to treatment stop
- Placebo: 14/16 (88%) had ADAMTS13 activity values $\geq 10\%$ close to treatment stop

In the majority of patients without exacerbation or relapse, ADAMTS13 activity recovered to levels above 10%, suggesting resolution of the presenting TTP episode

Caplacizumab Phase II TITAN trial

Underlying disease activity based on ADAMTS13 activity

* Data plotted: ADAMTS13 activity closest to exacerbation (range: 0-8 days before exacerbation)



Patients with exacerbations

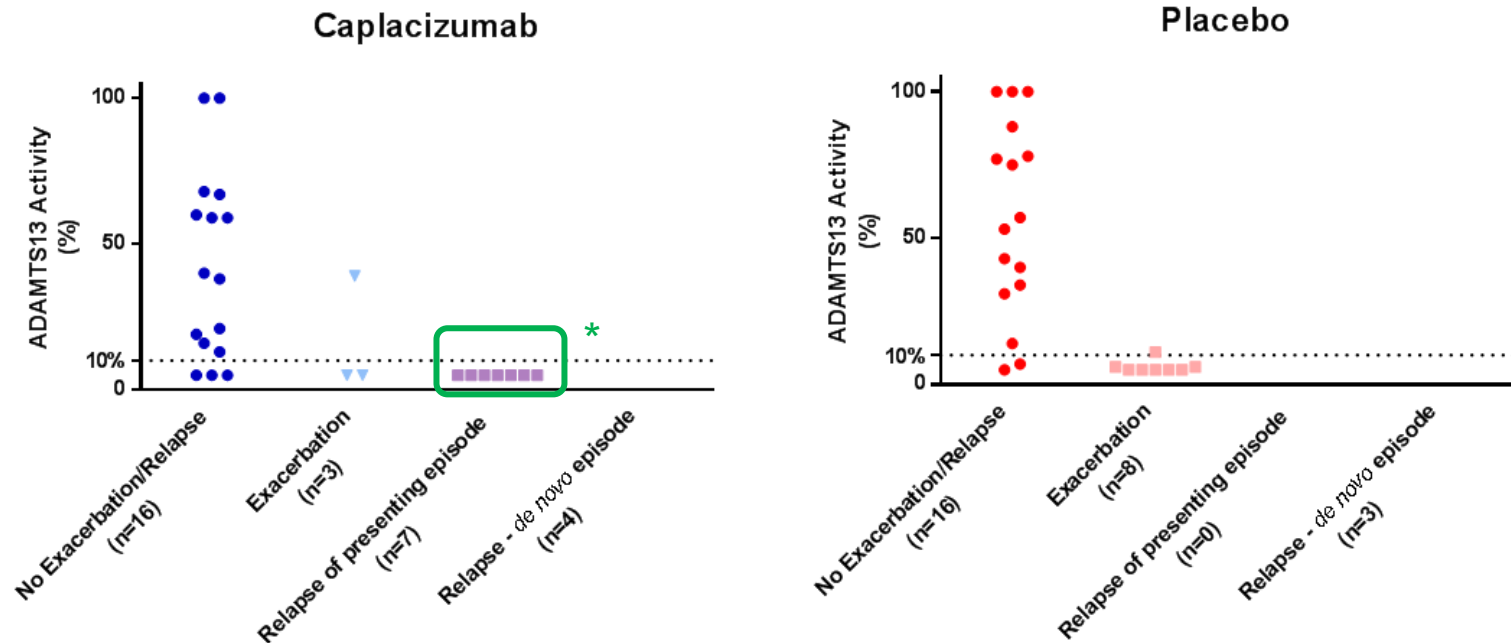
- Caplacizumab: 2/3 (67%) had ADAMTS13 activity <10% around the time of their exacerbation
- Placebo: 7/8 (88%) had ADAMTS13 activity <10% around the time of their exacerbation

In the majority of patients with exacerbations, ADAMTS13 activity was below 10%, suggesting unresolved disease activity leading to exacerbation

Caplacizumab Phase II TITAN trial

Underlying disease activity based on ADAMTS13 activity

* Data plotted: ADAMTS13 activity closest to treatment stop (range: 2-9 days before treatment stop)



Patients with relapses of the presenting TTP episode

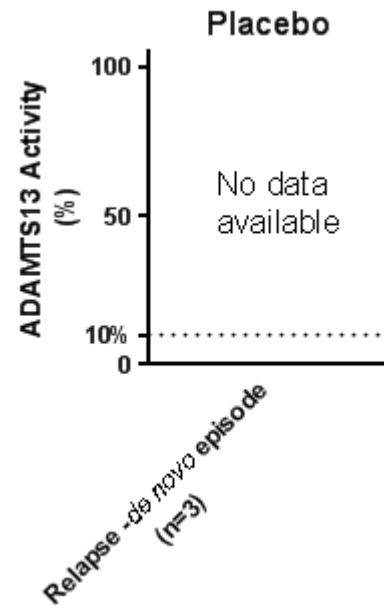
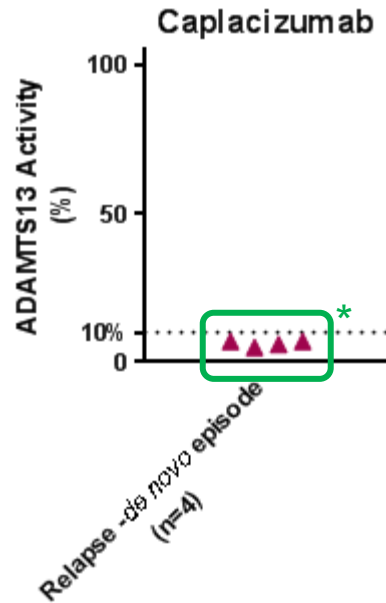
- Caplacizumab: 7/7 (100%) had ADAMTS13 activity values <10% close to treatment stop; relapses occurred within 10 days after treatment stop
- Placebo: N/A – all were 'de novo' relapses

All subjects in the caplacizumab group with relapses that occurred soon after the end of treatment had continuously low ADAMTS13 activity (<10%), indicative of ongoing disease

Caplacizumab Phase II TITAN trial

Underlying disease activity based on ADAMTS13 activity

* Data plotted: ADAMTS13 activity data available around time of relapse (range: 0-1 day before relapse)



Patients with a *de novo* relapse episode

- Caplacizumab: all 4 patients had again ADAMTS13 activity <10% at the time of relapse
- Placebo: no data available around the time of relapse

In the majority of patients with a *de novo* relapse episode, ADAMTS13 activity recovered to levels above 10% near treatment stop, suggesting resolution of the presenting TTP episode; values were low again (<10%) at the time of relapse, indicating a new TTP episode

ADAMTS13 activity as predictive marker

Conclusions

- 30-day treatment period (post PE) with caplacizumab has demonstrated a decrease in the number of exacerbations, but a higher number of relapses was observed during the follow-up period
- TITAN data support the use of ADAMTS13 activity as a predictive marker for recurrences of TTP and its potential for treatment decisions
 - ADAMTS13 activity is able to predict relapses which occur shortly after stopping caplacizumab treatment, which are considered as relapses of the presenting TTP episode (unresolved disease activity)
- Extending the caplacizumab treatment period for those patients at risk for relapse (i.e. with underlying disease activity based on ADAMTS13 activity) may maintain the protective effects of caplacizumab until the underlying disease is adequately treated and resolved
 - Will be further investigated during upcoming Phase III study

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