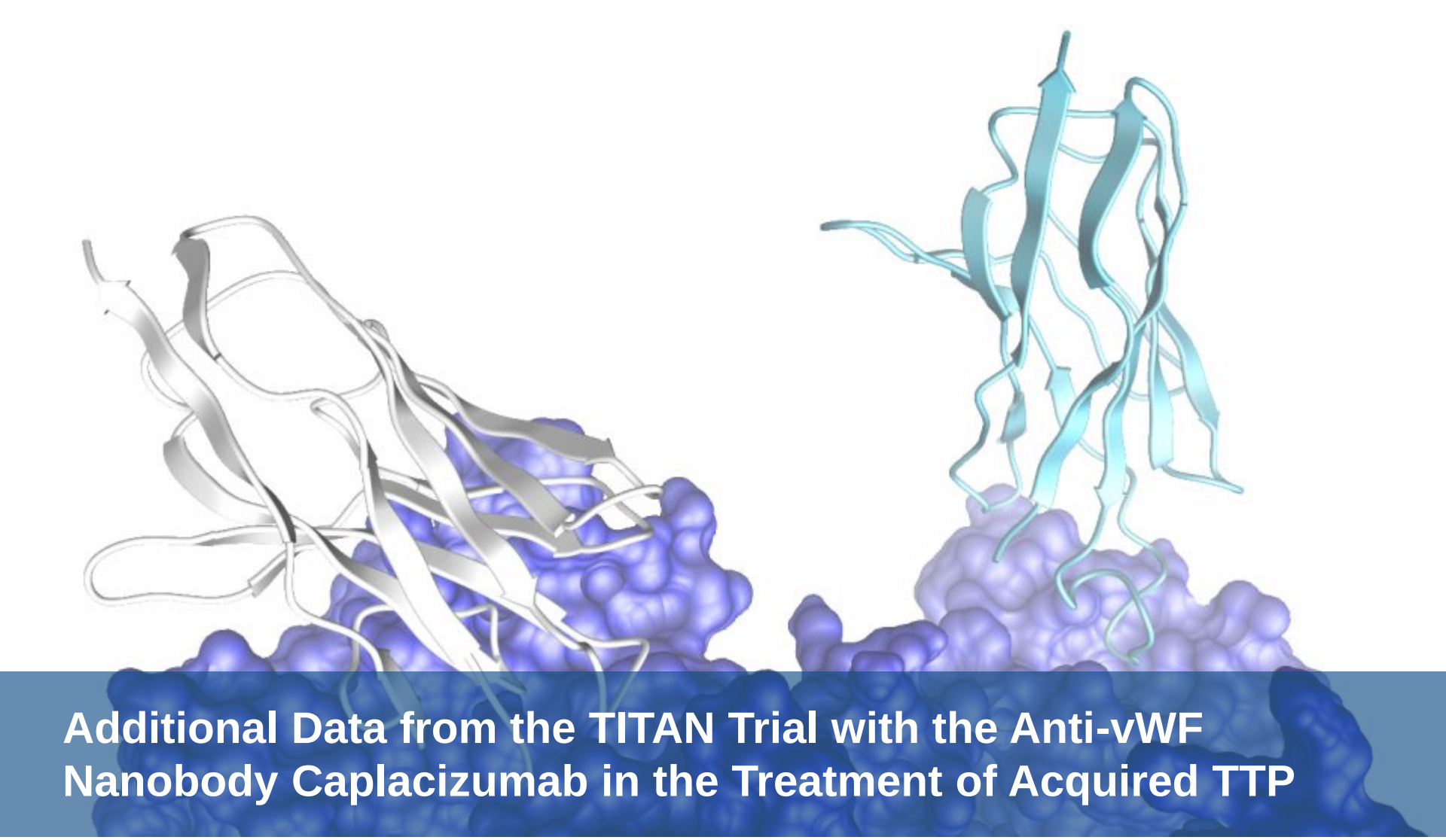


Additional Data from the TITAN Trial with the Anti-vWF Nanobody Caplacizumab in the Treatment of Acquired TTP

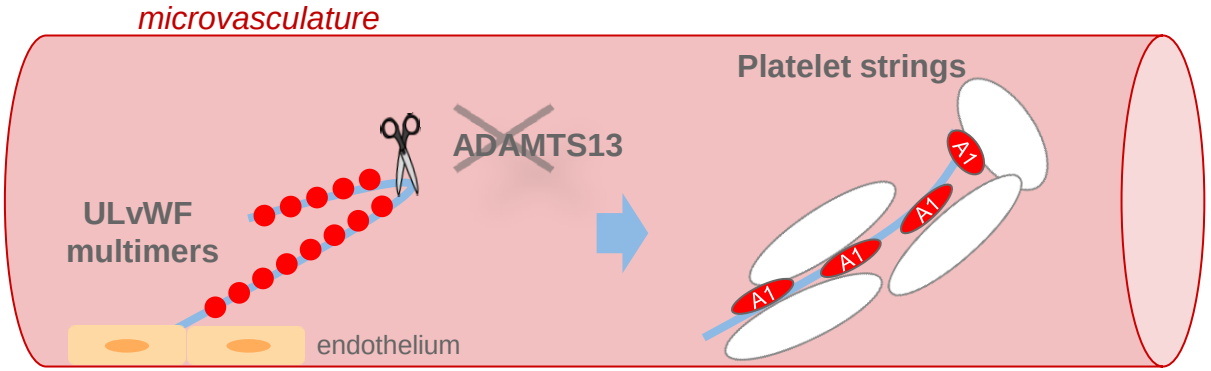
ISTH, Toronto, June 24th 2015

Flora Peyvandi, Marie Scully, Paul Knöbl, Johanna A. Kremer Hovinga, Haifeng Wu, Spero Cataland, Dominique Tersago

Acquired thrombotic thrombocytopenic purpura (TTP)

Background

- Acute and life threatening rare disorder of the blood coagulation system
  - annual incidence of 11 cases/million[1]
  - 10,000 acute events annually in US and Europe
  - mortality remains high (10-20%)[2] and ~36% of patients have relapses[3]
- Mortality and morbidity caused by ultra-large von Willebrand factor-mediated platelet aggregation



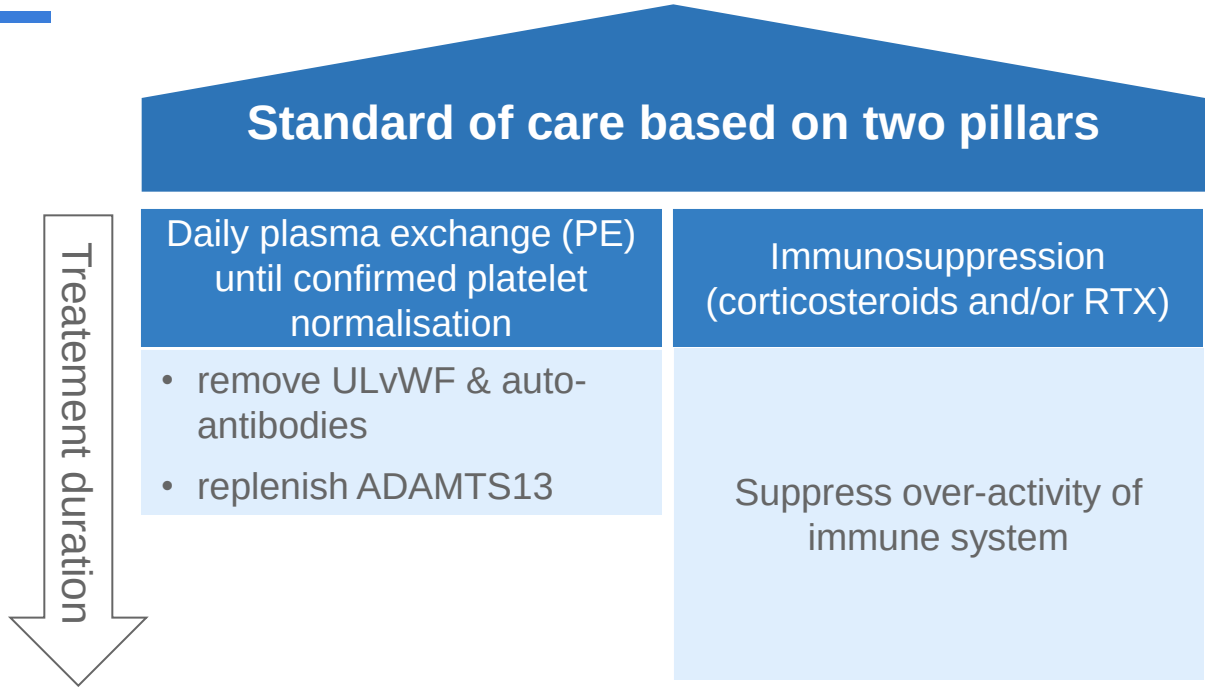
Microvascular thrombosis

- 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

Acquired TTP

Current treatment paradigm

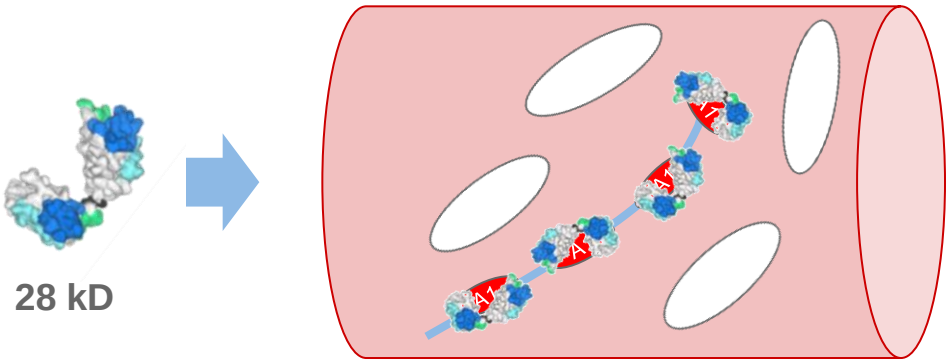


Rationale for new treatment of acquired TTP

- PE takes time, requires special equipment and trained staff
- PE complications (hypersensitivity reactions, infections, central line infection and thrombosis)
- exacerbations after stopping PE ➔ more microvascular thrombosis
- insufficient immunosuppressive treatment, leading to recurrences ➔ more microvascular thrombosis
- significant remaining mortality and morbidity (tissue ischemia)

Caplacizumab

Mode of action of the anti-vWF Nanobody*

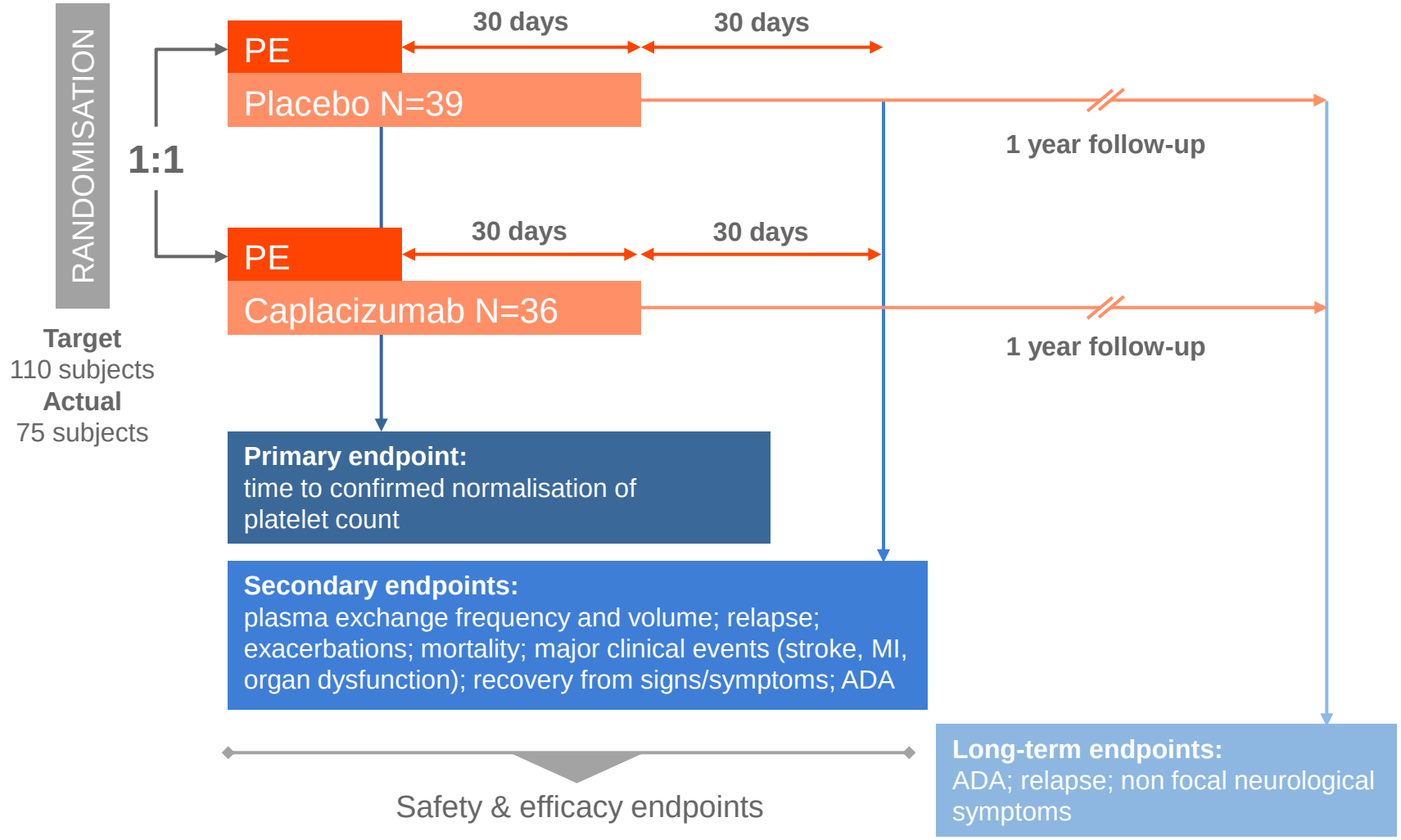


- Caplacizumab binds to A1 domain of vWF
- Immediate inhibition of platelet string formation and consumption of platelets
  - faster normalisation of platelets
  - reduction of tissue damage

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

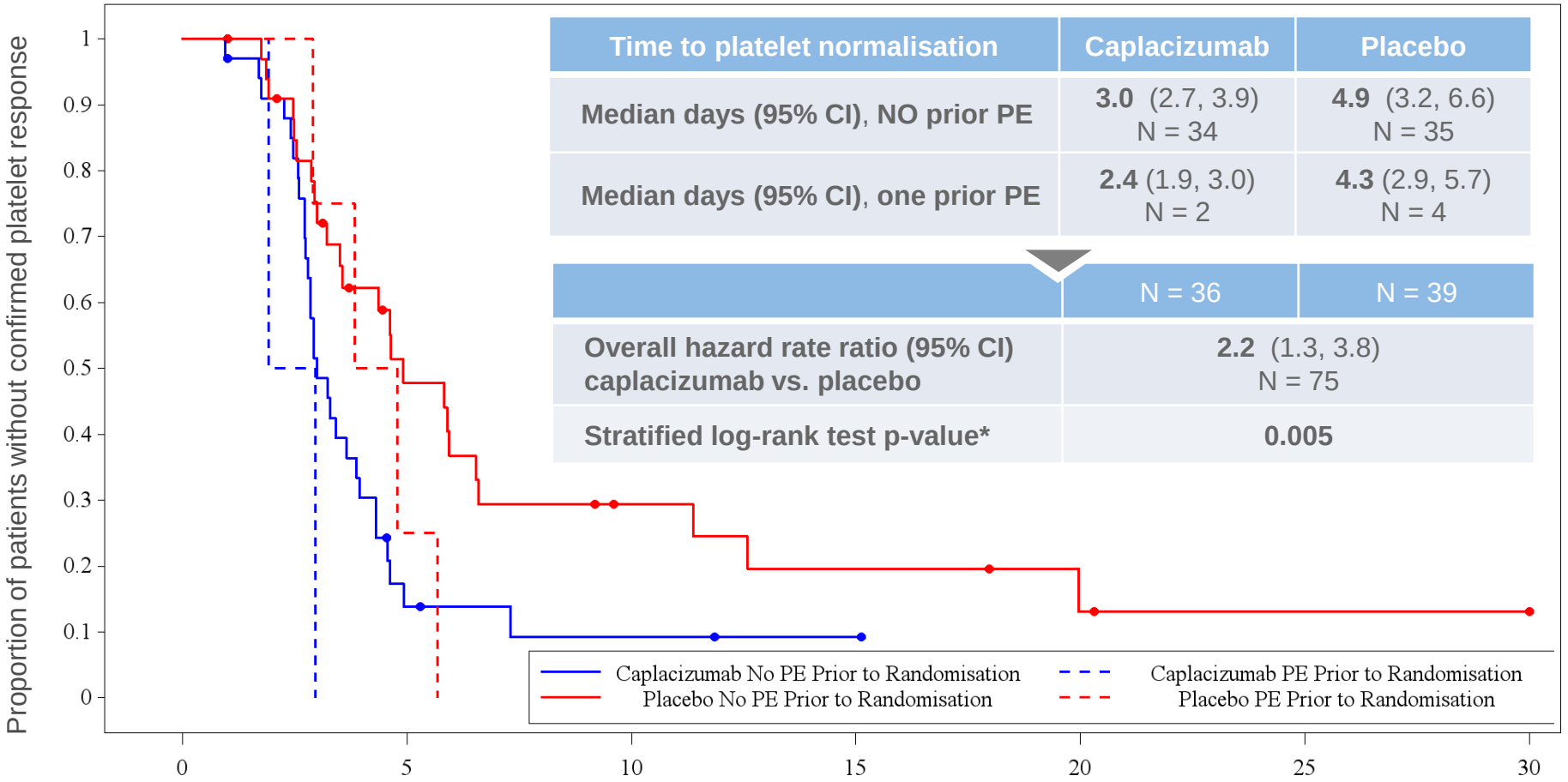
Caplacizumab Phase II TITAN trial

Design and schedule



Caplacizumab Phase II TITAN trial

Primary endpoint – time to platelet normalisation



Time to platelet normalisation	Caplacizumab	Placebo
Median days (95% CI), NO prior PE	**3.0** (2.7, 3.9) N = 34	**4.9** (3.2, 6.6) N = 35
Median days (95% CI), one prior PE	**2.4** (1.9, 3.0) N = 2	**4.3** (2.9, 5.7) N = 4

	N = 36	N = 39
Overall hazard rate ratio (95% CI) caplacizumab vs. placebo	**2.2** (1.3, 3.8) N = 75	
Stratified log-rank test p-value*	**0.005**	

** **log-rank test p-value = 0.013** evaluated time to confirmed platelet response between the 4 groups presented above*

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

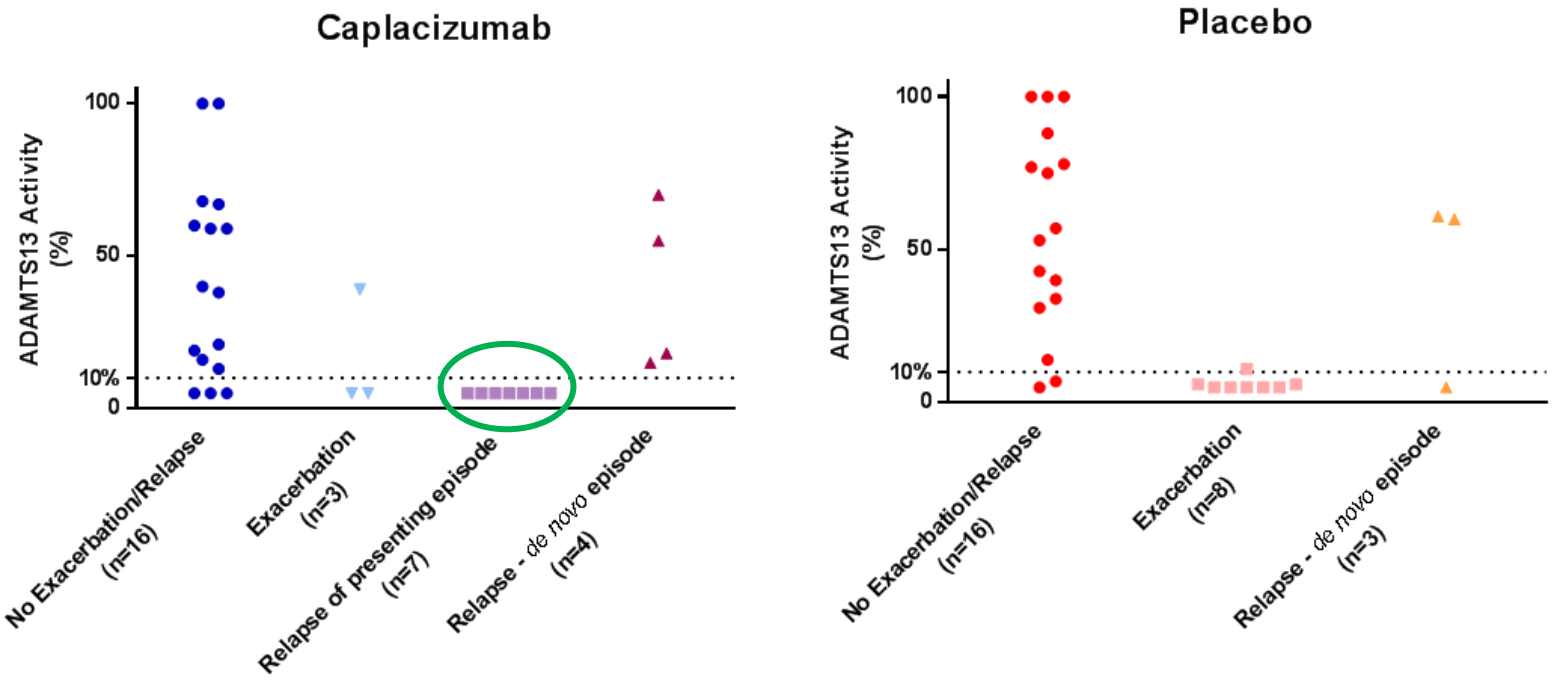
Key secondary endpoints

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

In the caplacizumab treatment group a higher proportion of subjects achieved complete remission and fewer patients had exacerbations of TTP

Caplacizumab Phase II TITAN trial

Underlying disease activity based on ADAMTS13 activity



Data plotted: ADAMTS13 activity data available closest to treatment stop or data close to the day of exacerbation

- 7 patients relapsed within 10 days after stopping caplacizumab
  - All had continuous low ADAMTS13 activity (<10%) during and near treatment stop
  - ➢ Continue caplacizumab treatment in case underlying disease activity is not resolved

Oral presentation **OR363** (Session ADAMTS13; Wed 6/24/2015, 2.30pm, room 705)

Caplacizumab Phase II TITAN trial

Safety profile

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%
Subjects discontinued due to TEAE	8%	0%

- Increased bleeding tendency in caplacizumab treatment group
  - 80% of reported events were mild
  - only 3 subjects required drug treatment; no requirement for vWF/FVIII substitution

Caplacizumab treatment resulted in an increased tendency for mild/moderate bleeding events but which were readily managed

Caplacizumab Phase II TITAN trial

Strong clinical proof of concept

- TITAN trial has demonstrated the therapeutic effect of caplacizumab
  - shorter time to platelet normalisation
  - reduced number of exacerbations during treatment, but a higher number of relapses during the follow-up period
  - acceptable safety profile

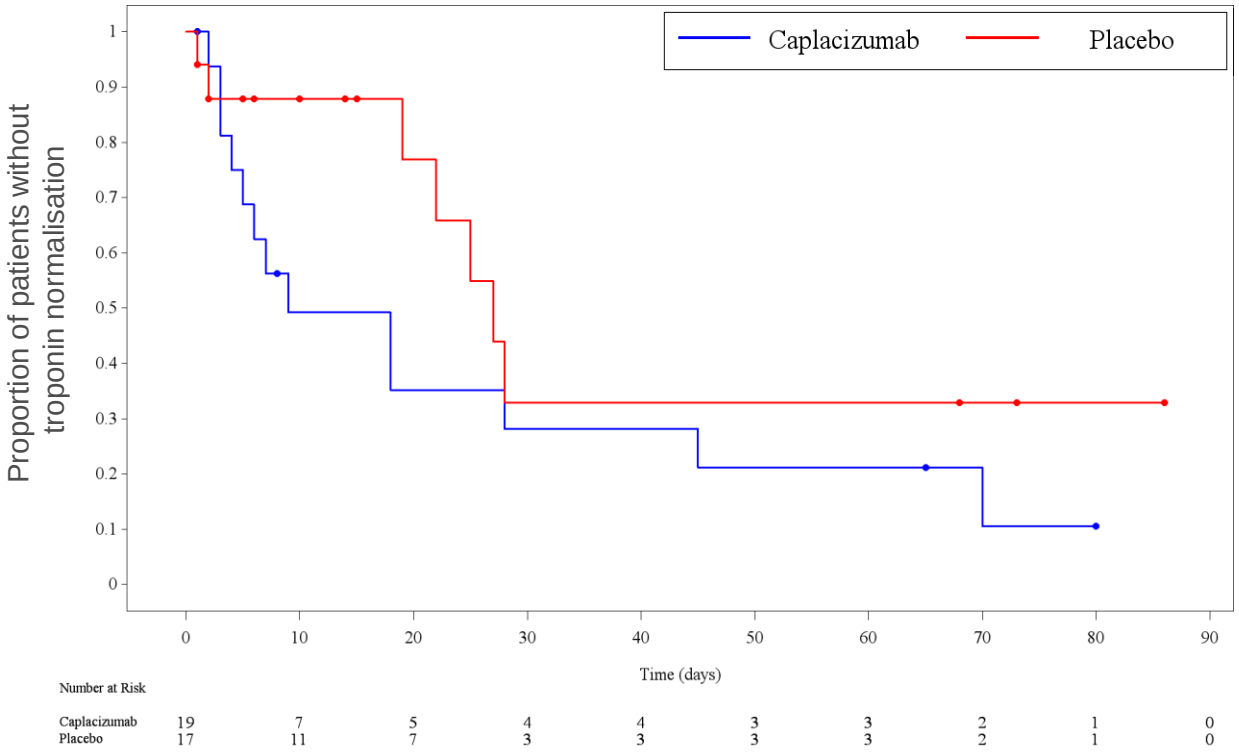
- Additional (post hoc) analysis to understand
  - potential impact on tissue ischemia
  - potential benefit on PE parameters, evaluated during different study periods
  - immunogenicity profile

Caplacizumab Phase II TITAN trial

Cardiac system - faster time to troponin normalisation

Time to Troponin T or Troponin I normalisation*

(patients with elevated troponin levels at baseline)



- More rapid return to normal levels of Troponin T or I in subjects who received caplacizumab
- Median time to response
  - Caplacizumab: 9 days
  - Placebo: 27 days
- Subjects with elevated troponin at baseline
  - Caplacizumab 53%
  - Placebo 46%

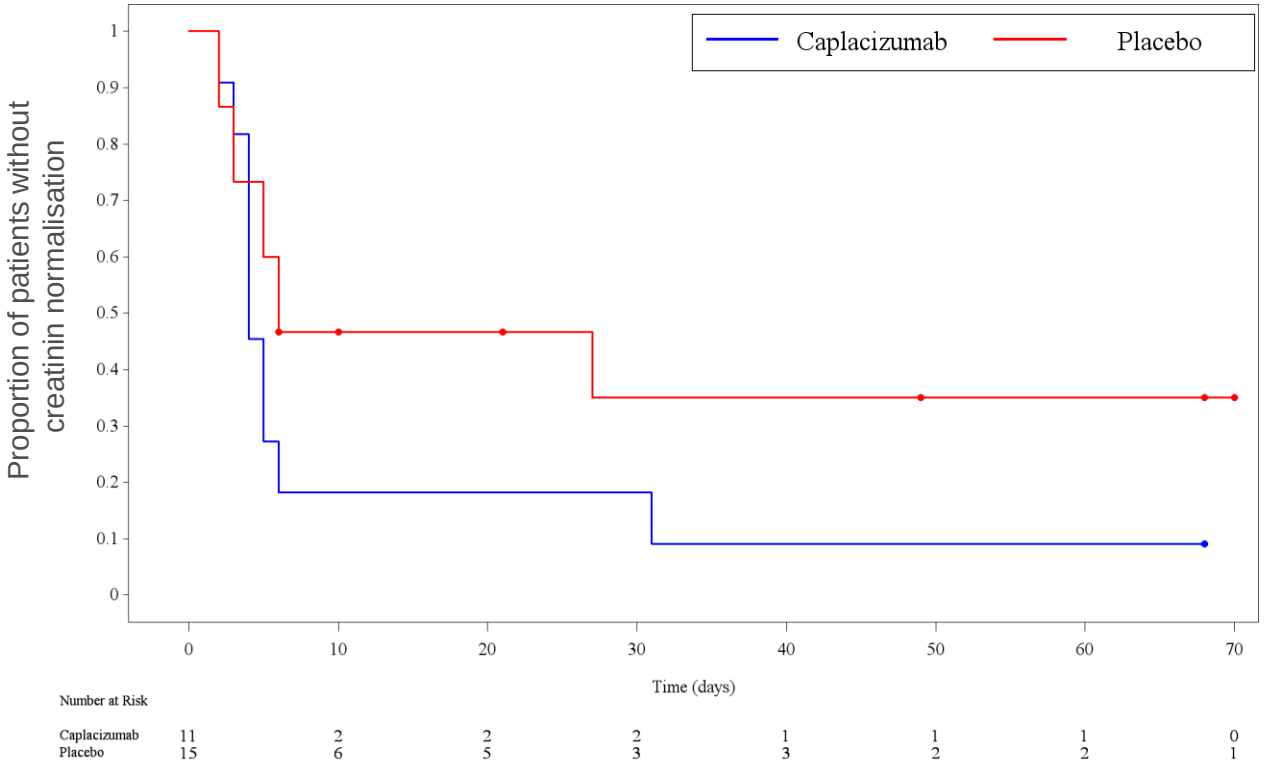
* Possible dilutive effect of PE on troponin (during daily PE period) cannot be excluded

Caplacizumab Phase II TITAN trial

Renal system - faster time to creatinine normalisation

Time to creatinine normalisation*

(patients with elevated creatinine levels at baseline)



- More rapid return to normal levels of creatinine in subjects who received caplacizumab
- Median time to response
  - Caplacizumab: 4 days
  - Placebo: 6 days
- Subjects with elevated creatinine at baseline
  - Caplacizumab 31%
  - Placebo 41%

* Possible dilutive effect of PE on creatinine (during daily PE period) cannot be excluded

Caplacizumab Phase II TITAN trial

Overall tissue damage - LDH

- LDH is a clinically relevant general marker of organ damage

- Number and proportion of subjects in ITT Population with LDH ≤ 2 x ULN
  - relevant difference achieved already on day 2, confirmed on day 3
  - proportions similar as from day 4

Proportion of subjects with LDH ≤ 2 x ULN by study day (ITT population)

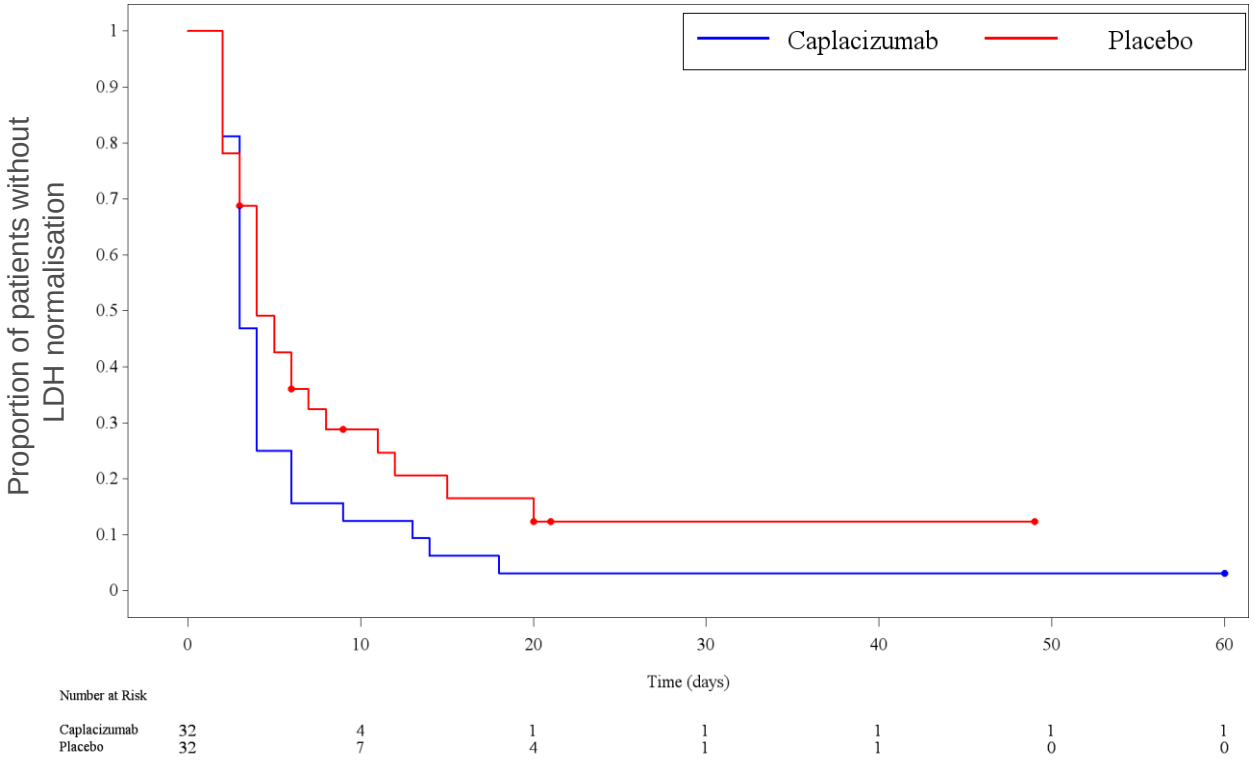
Study Day	ALX-0081 N=36 n (%)	Placebo N=39 n (%)
Baseline	11 (30.6%)	9 (23.1%)
Day 2	28 (77.8%)	20 (51.3%)
Day 3	33 (91.7%)	29 (74.4%)
Day 4	34 (94.4%)	34 (87.2%)
Day 5	34 (94.4%)	34 (87.2%)

Caplacizumab Phase II TITAN trial

Overall tissue damage – faster time to LDH normalisation

Time to LDH normalisation*

(patients with elevated LDH levels at baseline)



- More rapid return to normal levels of LDH in subjects who received caplacizumab
- Median time to response
  - Caplacizumab: 3 days
  - Placebo: 4 days
- Subjects with elevated LDH at baseline
  - Caplacizumab 91%
  - Placebo 87%

* Possible dilutive effect of PE on LDH (during daily PE period) cannot be excluded

Caplacizumab Phase II TITAN trial

Reduction in number of PE days

- Number of PE days for different study periods
  - reduction in number of PE days during daily PE and overall treatment period (including the 30-day post-daily PE period)
  - benefit lost during follow-up period, reflective of higher number of relapses

Study Period		Caplacizumab N=35	Placebo N=37	Total N=72
Daily PE Period on Treatment	n	35	37	72
	Mean	5.9	7.9	6.9
	SD	2.43	6.43	4.99
Overall Treatment Period	n	35	37	72
	Mean	7.7	11.7	9.7
	SD	4.68	8.45	7.12
Overall (Until 1 Month FU)	n	35	37	72
	Mean	10.2	11.7	11.0
	SD	6.64	8.45	7.61

Caplacizumab Phase II TITAN trial

Additional data – immunogenicity

- Anti-drug antibody (ADA) evaluation performed on safety population, during study drug treatment and up to 12 months follow-up
  - 35 caplacizumab treated TTP patients
  - 37 placebo treated TTP patients

- Results

	Treatment emergent ADA
Placebo treated	0/37 (0%)
Caplacizumab treated	3/35 (9%)*

- Interpretation
  - no effect on PK/PD parameters
  - no immunogenicity related AE

* time to first occurrence ranged from 98 to 138 days

Caplacizumab Phase II TITAN trial

Conclusions

- The TITAN study met its primary endpoint in achieving a 39% reduction in time to platelet normalisation
  - supported by a lower number of exacerbations
  - a higher number of relapses was observed during the follow-up period; majority can be linked with unresolved disease activity (ADAMTS13 <10%)
  - generally mild increased bleeding tendency

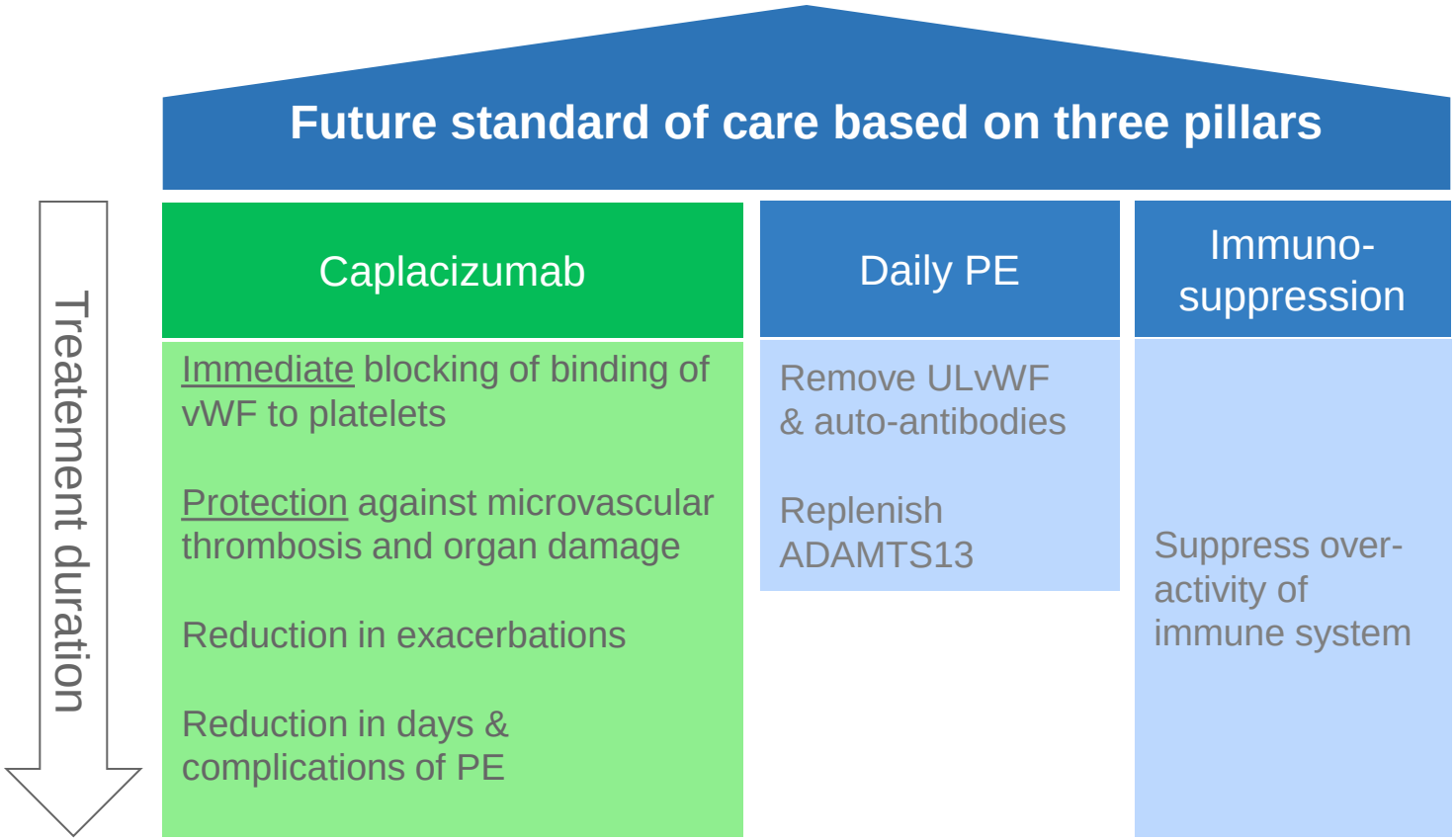
- Exploratory analyses suggest that caplacizumab more rapidly curtails ongoing tissue damage (organ damage biomarkers)

- Further analysis demonstrated that caplacizumab reduces the number of PE days in the treatment of acquired TTP in line with the faster platelet normalisation

- Low number of TE immunogenicity, without impact on PK/PD or safety

Caplacizumab in acquired TTP

Changing the treatment paradigm



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