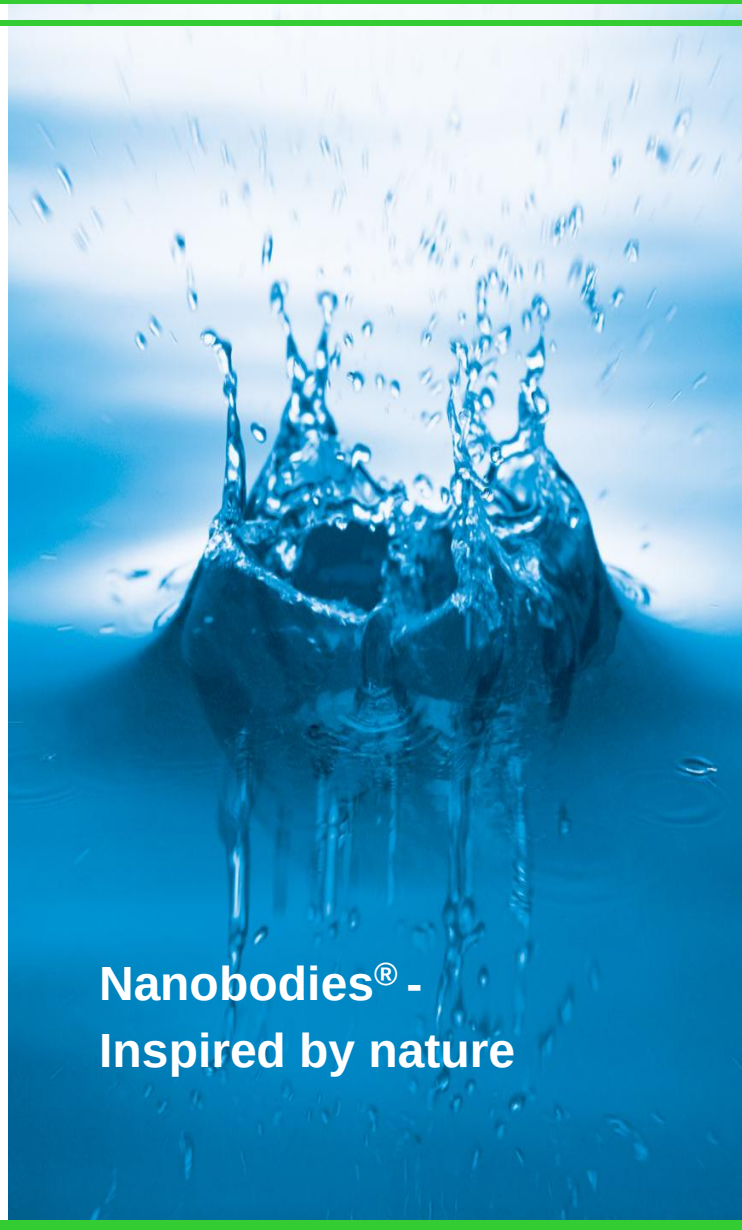
Caplacizumab, anti-vWF Nanobody®, potentially changing the treatment paradigm in TTP: results of the TITAN trial

Selected for “BEST OF ASH”

American Society of Hematology Annual Meeting 2014



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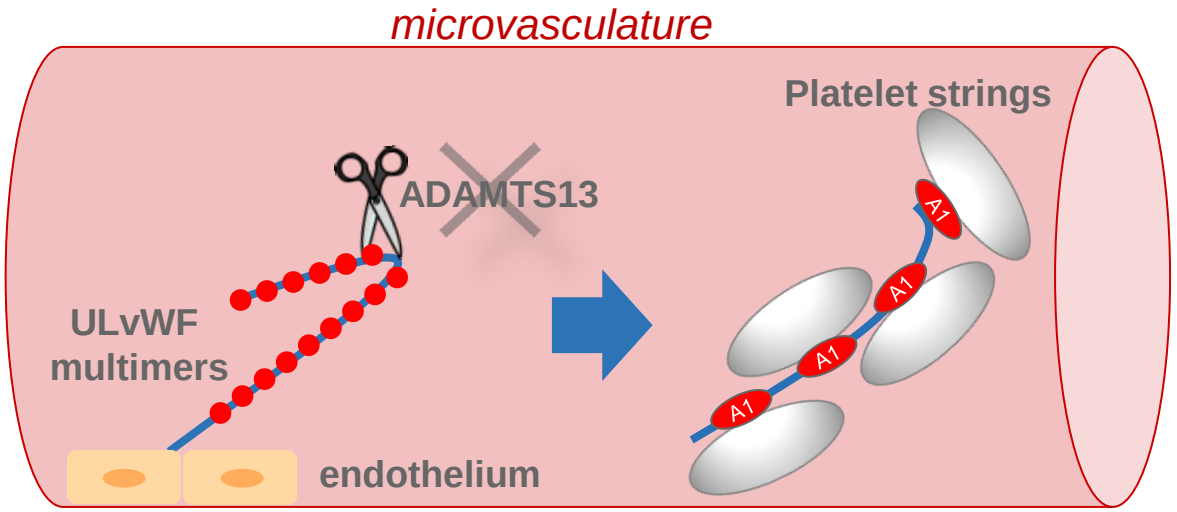
Acquired thrombotic thrombocytopenic purpura (TTP)

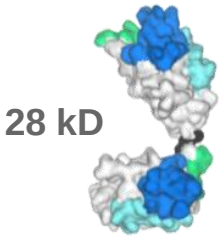
- Rare disease: reported incidence 5 -11 cases per million people per year
- PE (plasma exchange) decreased mortality from 90% to 10-20% today
- Risk of recurrence: 20-30%

Microvascular thrombosis

- consumes platelets ➔ severe thrombocytopenia
- blocks microvasculature ➔ tissue ischemia with neurological, myocardial, renal signs & symptoms
- leads to red blood cell fragmentation ➔ hemolytic anemia

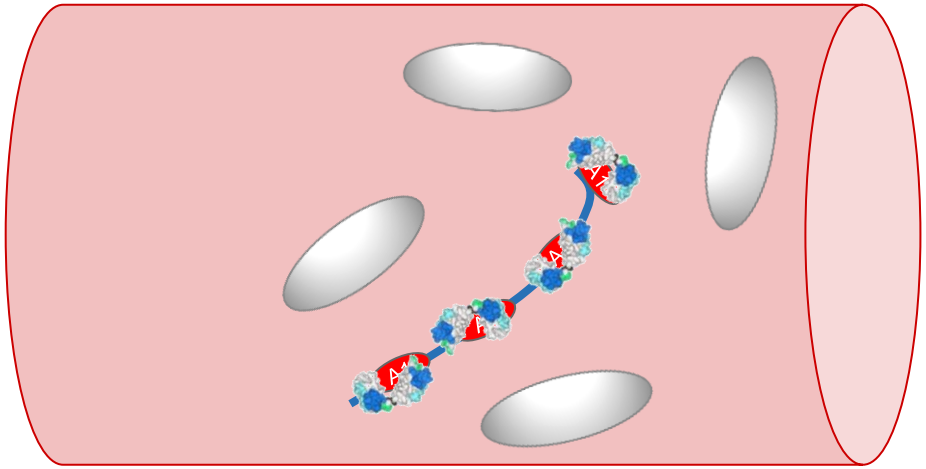


Caplacizumab is an anti-vWF Nanobody

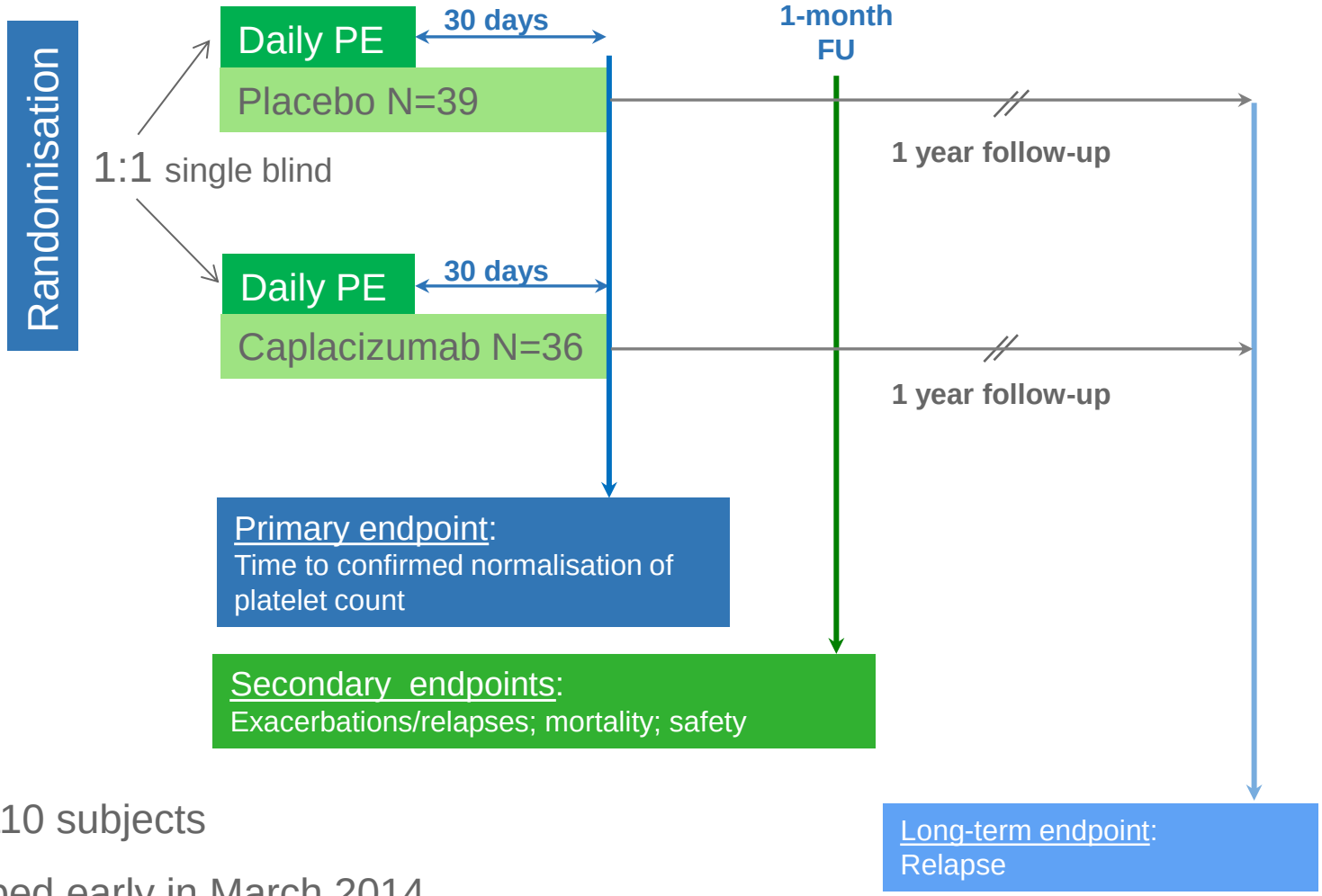


Caplacizumab binds A1 domain of vWF

➔ prevents platelets being consumed in microthrombi with ULvWF



TITAN trial design



Target – 110 subjects

Trial stopped early in March 2014

75 subjects enrolled over 3 years in 32 sites in Europe, US, Israel and Australia

Balanced baseline characteristics

Proportion of subjects		Caplacizumab N = 36	Placebo N= 39
Initial episode		67%	69%
Female gender		67%	51%
ADAMTS13 activity*	< 10%	78%	77%
	≥ 10%	6%	15%
	missing	17%	8%

* ADAMTS13 activity: fluorogenic FRETS-VWF73 method (central lab, Dr. Kremer Hovinga, Bern, Switzerland)

Mean baseline value	Caplacizumab N = 36	Placebo N= 39
Platelets (10^9/L) – mean ± SD	21 (± 18)	28 (± 20)
LDH (U/L) – mean ± SD	1,277 (± 853)	1,270 (± 939)
Age (years) – mean ± SD	41 (± 13)	43 (± 13)

Concomitant treatment for the presenting TTP episode

- Patients with acquired TTP receive as standard of care treatment: daily plasma exchange until platelets normalise and corticosteroids

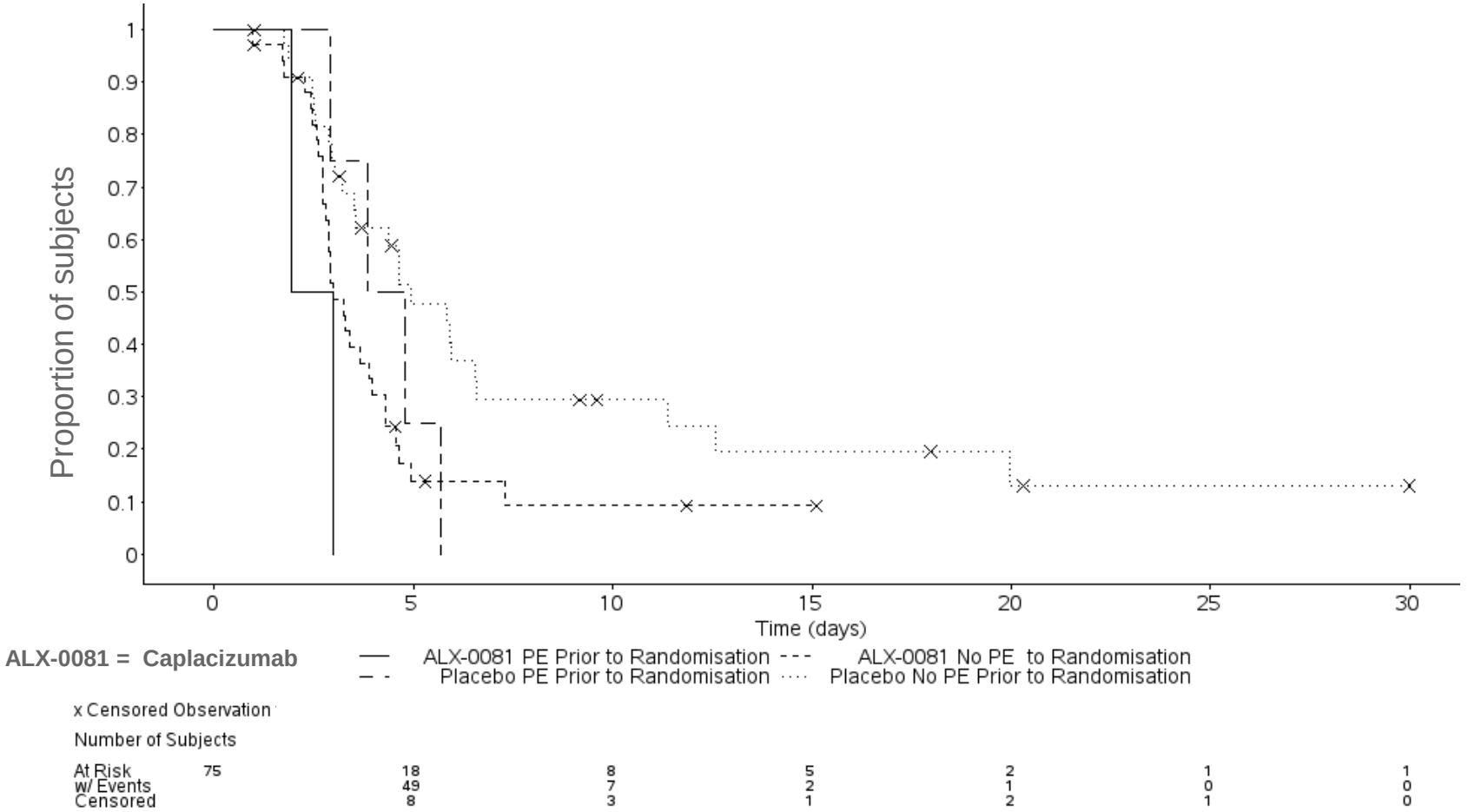
Proportion of subjects	Caplacizumab N = 36	Placebo N = 39
Tapered plasma exchange	31%	28%
Concomitant corticosteroids	89%	92%
Rituximab use during daily PE	6% (1)*	23%(2)*

(1) 0 of 2 subjects had exacerbation or relapse in caplacizumab arm

(2) 3 of 9 subjects had exacerbation in placebo arm (4, 9 and 27 days after rituximab start)

* 2 of 2 subjects in caplacizumab arm and 4 of the 9 subjects in placebo arm were from a single site

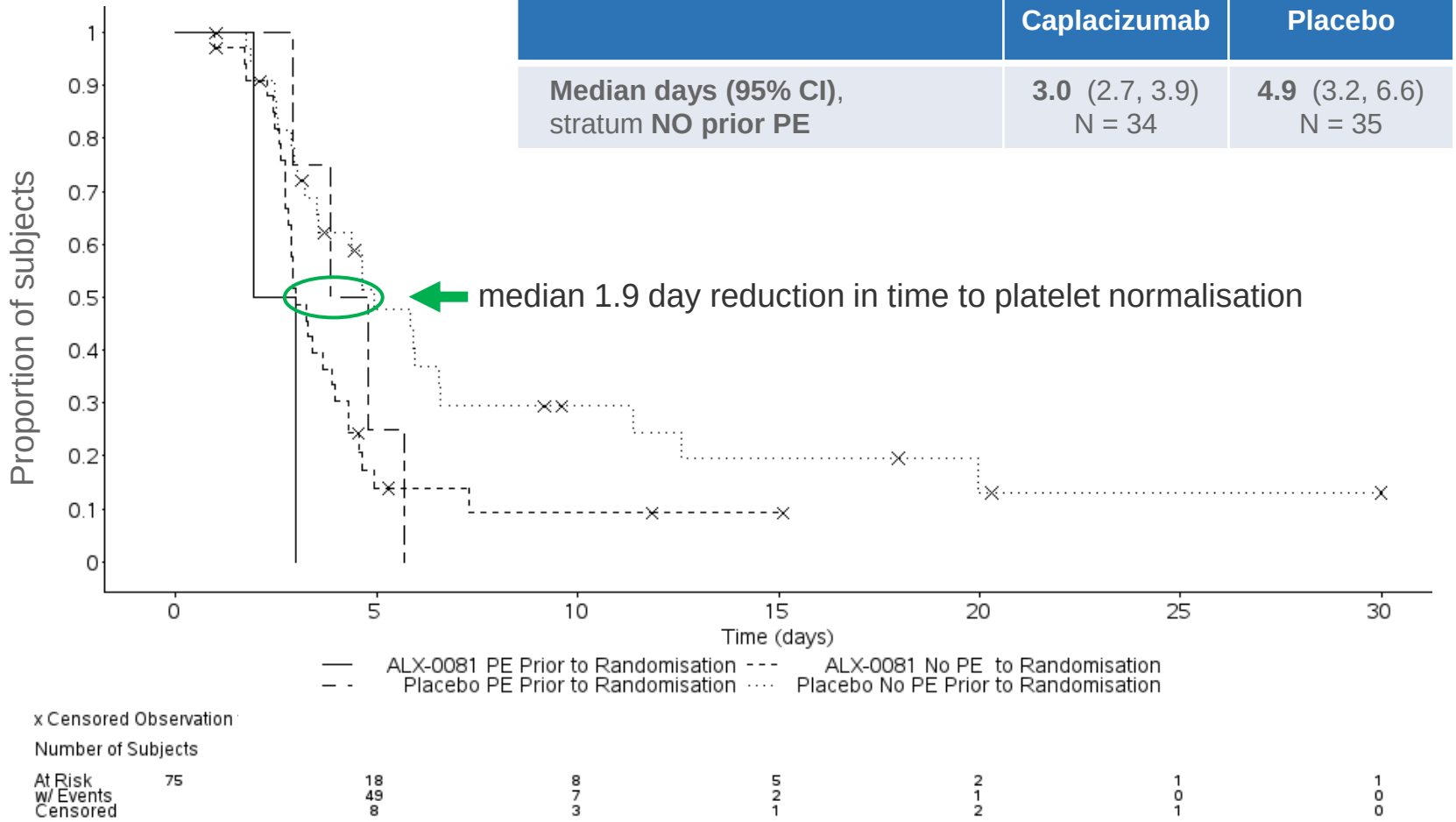
Primary endpoint: Kaplan-Meier curves for time to confirmed platelet normalisation



Stratified analysis for one prior PE Yes (n = 6) or No (n = 69)

Primary endpoint: Kaplan-Meier curves for time to confirmed platelet normalisation

	Caplacizumab	Placebo
Median days (95% CI), stratum **NO prior PE**	**3.0** (2.7, 3.9) N = 34	**4.9** (3.2, 6.6) N = 35



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Primary endpoint: Kaplan-Meier curves for time to confirmed platelet normalisation

	Caplacizumab	Placebo
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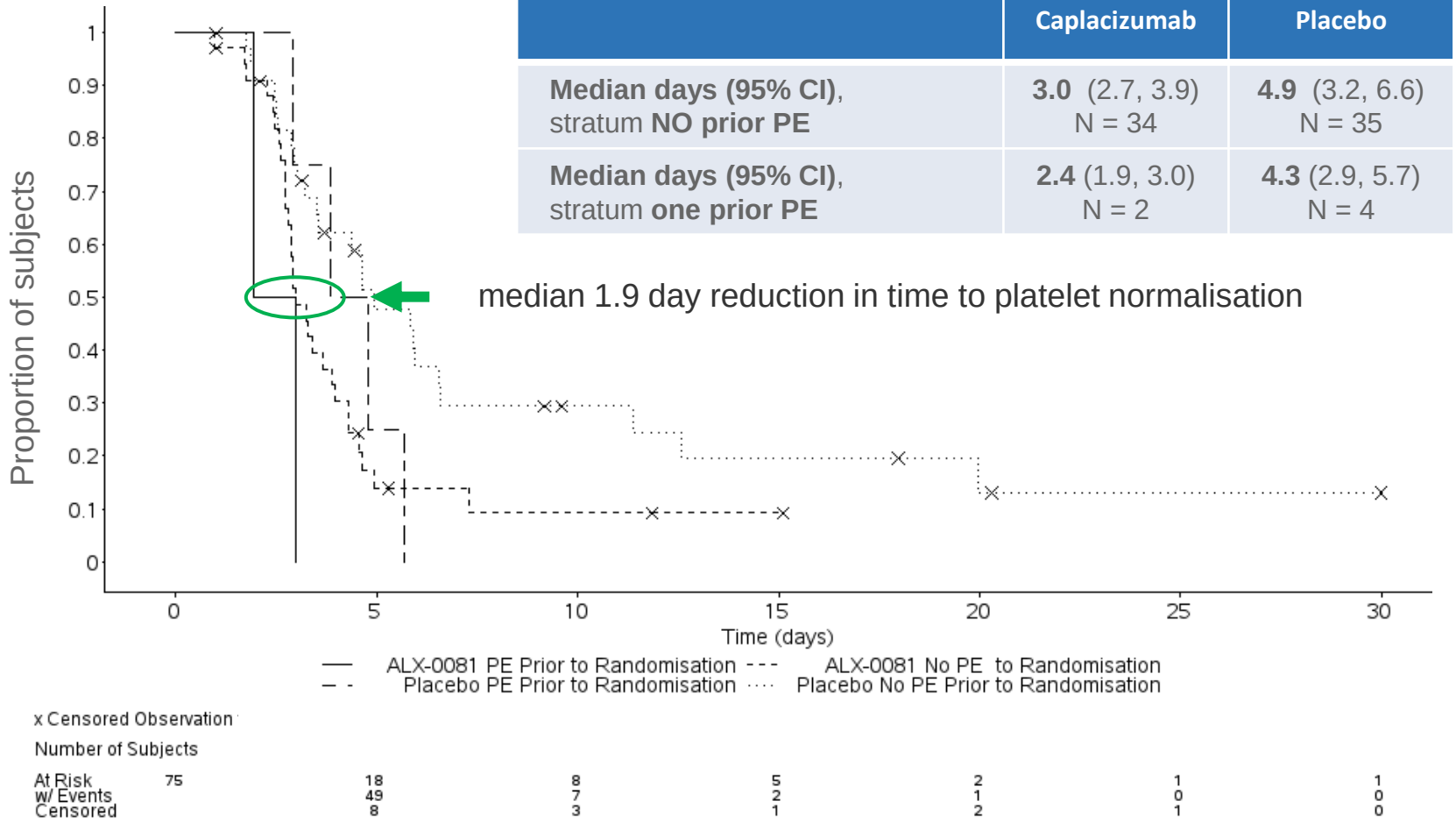
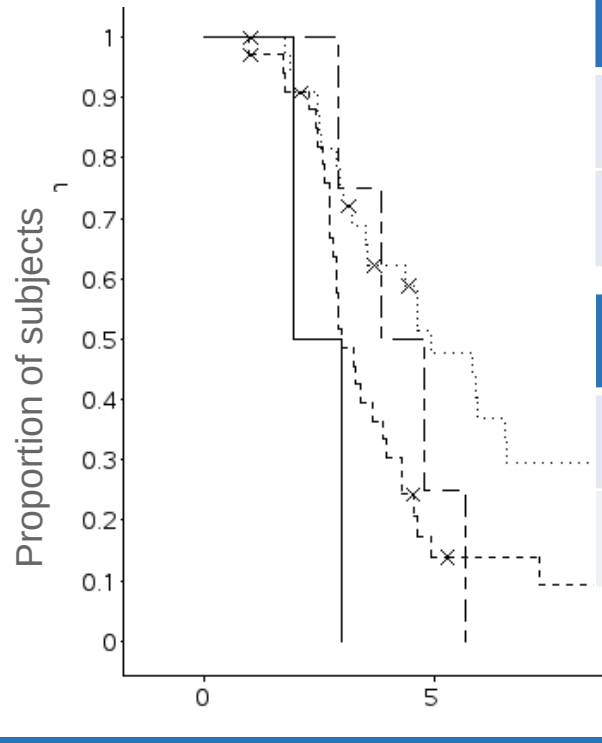
Median days (95% CI), stratum **one prior PE**	**2.4** (1.9, 3.0) N = 2	**4.3** (2.9, 5.7) N = 4



median 1.9 day reduction in time to platelet normalisation

Stratified analysis for one prior PE Yes (n = 6) or No (n = 69)

Primary endpoint: Kaplan-Meier curves for time to confirmed platelet normalisation



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

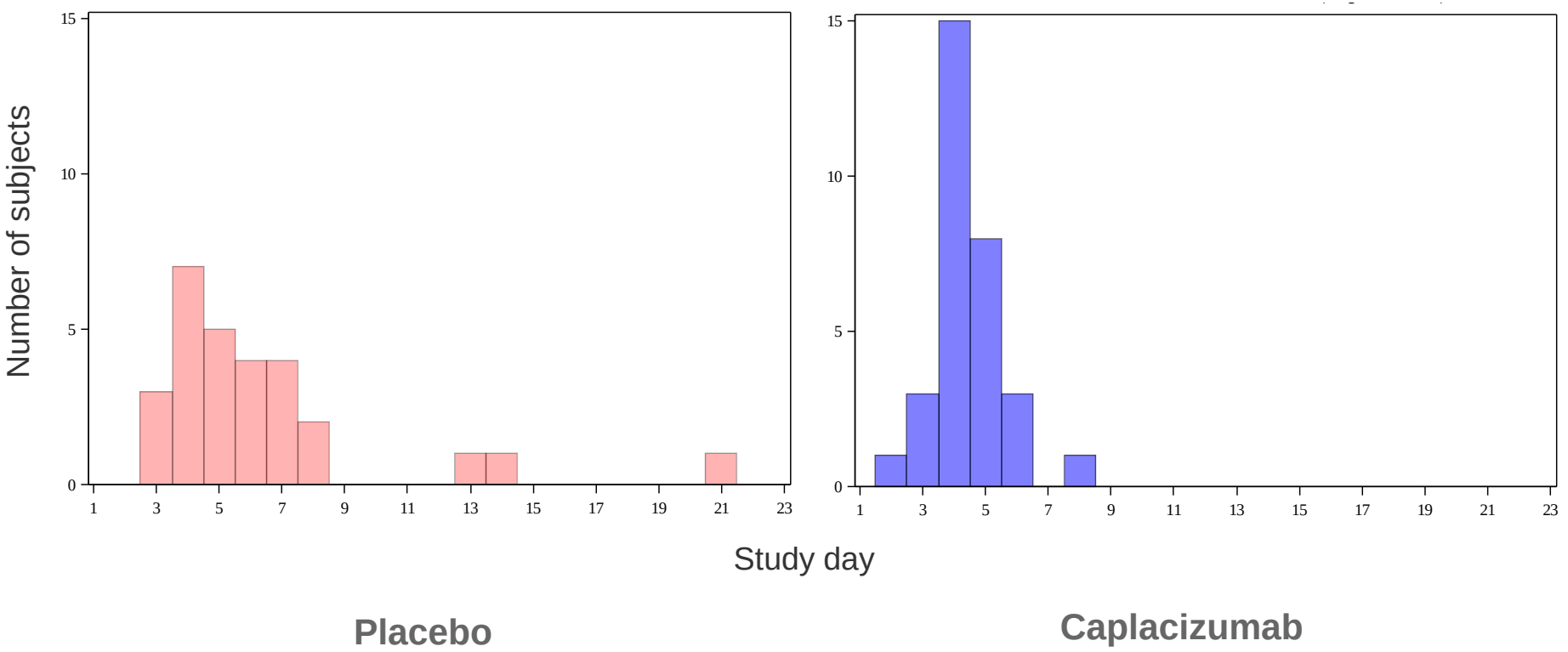
	N = 36	N = 39
Overall hazard rate ratio (95% CI) caplacizumab vs. placebo	**2.2** (1.3, 3.8) N = 75	
Stratified log-rank test p-value	**0.013**	

Patients treated with caplacizumab achieved confirmed platelet normalisation at more than twice the rate of those receiving placebo

Stratified analysis for one prior PE Yes (n = 6) or No (n = 69)

Platelet count normalisation was more rapidly and more consistently attained in caplacizumab arm

Number of subjects with platelet normalisation per day after start of study treatment

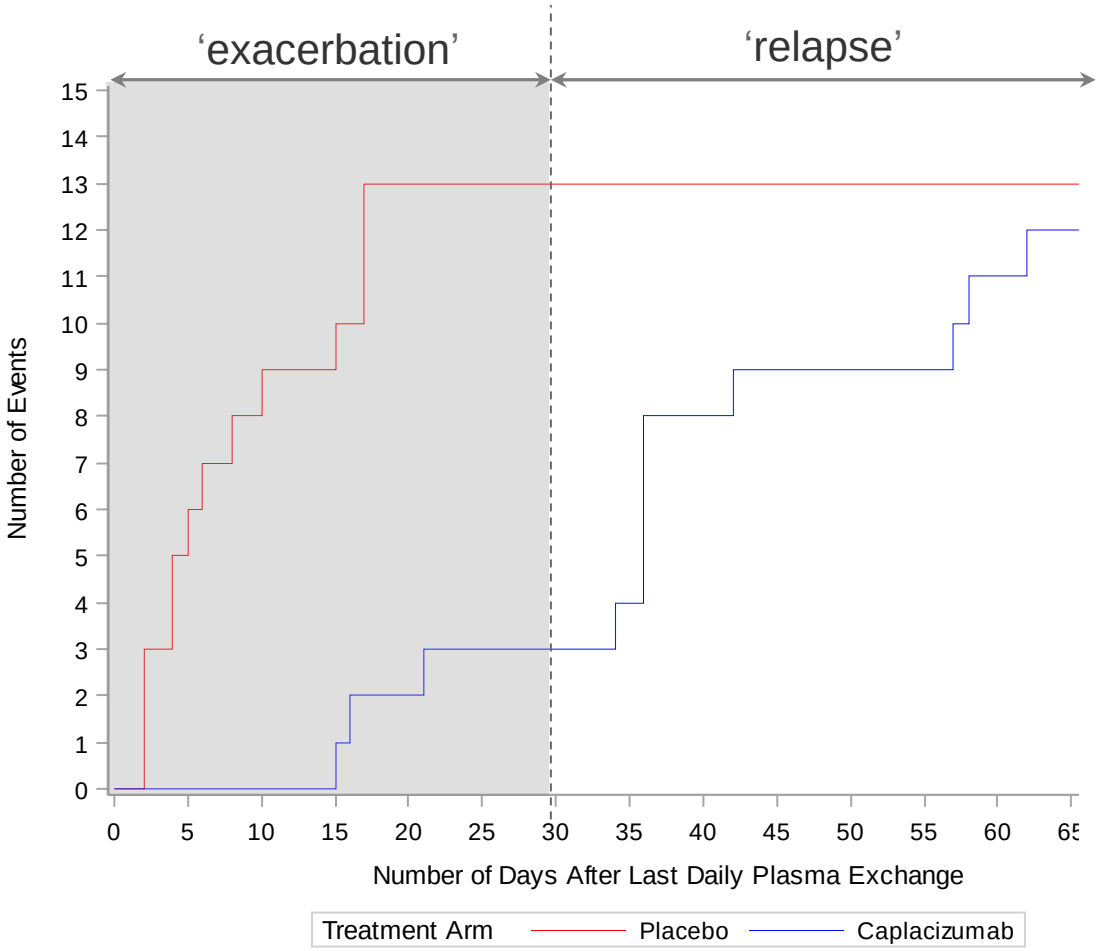


Post hoc analysis

Key secondary endpoints at 1 month follow-up

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

Caplacizumab reduces the number of exacerbations



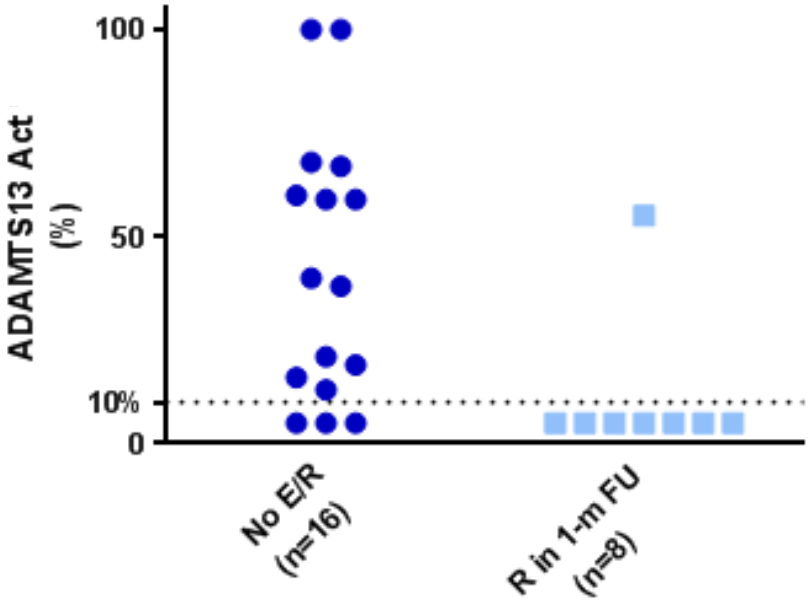
- Demonstrates protective effect of caplacizumab in acute phase of active TTP
- Benefit is seemingly lost in some subjects if caplacizumab is stopped before underlying disease activity is resolved (based on ADAMTS13 activity for this assessment)

Cumulative frequency of exacerbation and relapse events

Post hoc analysis

Continued underlying disease activity: possible explanation for relapses shortly after stopping caplacizumab?

ADAMTS13 activity near end of caplacizumab treatment

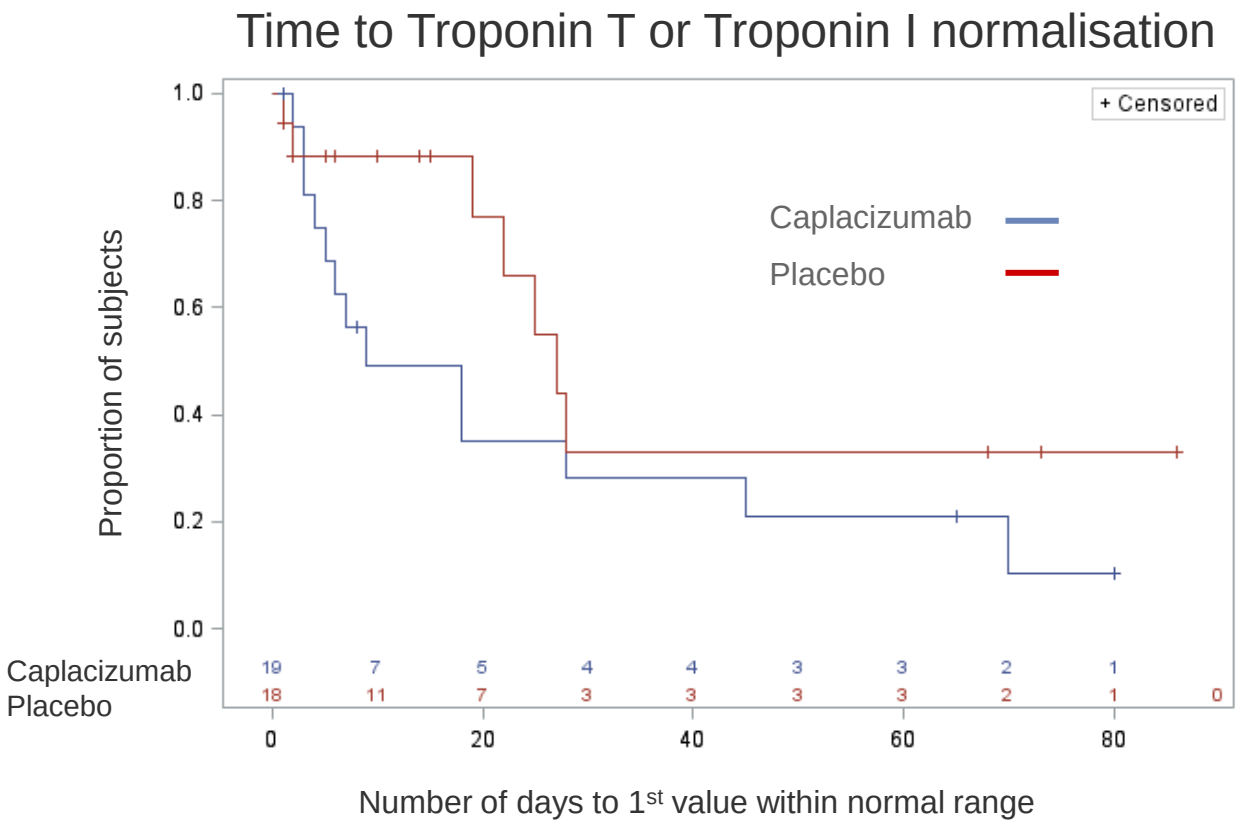


- 8 subjects treated with caplacizumab **with relapse (R)** in **1-m FU period**:
  - **7** had ADAMTS13 activity < 10%
  - **1** had ADAMTS13 activity ≥ 10%
- 22 subjects treated with caplacizumab with **no exacerbation (E) or relapse (R)** in 1-m FU period:
  - **13** had ADAMTS13 activity ≥ 10%
  - **3** had ADAMTS13 activity < 10%
  - 6 excluded due to insufficient data

ADAMTS13 activity <10% indicative of disease activity

Post hoc analysis

Impact of platelet protective effect on biomarkers of organ damage – exploratory analysis



- More rapid return to normal levels of Troponin T or I in subjects who received caplacizumab
- Suggests possibly more rapid resolution of tissue ischemia

Abnormally high Troponin T or I levels at baseline were followed until normalisation

- 53% of caplacizumab treated subjects
- 46% of placebo treated subjects

Post hoc analysis

Safety profile of caplacizumab in TITAN trial

Proportion of subjects	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%

Number of events	Caplacizumab N = 35	Placebo N= 37
Number of TEAEs	574	545
Number of TE Serious AEs	44	36

Increased bleeding tendency in caplacizumab arm

- 80% of reported events were mild
- only 3 subjects required drug treatment (tranexamic acid, methylergonovine)
- no requirement for vWF/FVIII substitution

Summary and conclusions

- TITAN trial has demonstrated the effects of caplacizumab
  - shorter time to platelet normalisation
  - reduced number of exacerbations during treatment
  - acceptable safety profile, with increased tendency for mild/moderate bleeding events which were readily managed

- These data suggest that caplacizumab
  - prevents consumption of platelets, thereby protecting patients from further formation of microvascular thrombi
  - has the potential to become an important new treatment of acquired TTP, in addition to plasma exchange and immunosuppressive therapy, as this remains a challenging disease to treat

Thanks to the Patients and Investigators + site staff who participated in the TITAN trial

Australia
- Bird, R.
- Crispin, P.
- He, S.
- Hsu, D.

Austria
- Knoebl, P.
- Linkesch, W.

Belgium
- Breems, D. A.
- Dierickx, D.
- Efira, A.
- Sonet, A.

Bulgaria
- Peytchev, D.

France
- Chantepie, S.

Germany
- Beutel, G.
- Bommer, M.
- Chemnitz, J.
- Fischereder, M.
- Jörres, A.
- Krämer, B.
- Mühlfeld, A.
- Özcan, F.
- Scharrer, I.

Israel
- Horowitz, N.
- Inbal, A.
- Rund, D.

Italy
- Capalbo, S.F.
- Facchini, L.
- Fianchi, L.
- Giuffrida, G.
- Leone, G.
- Peyvandi, F.

Romania
- Balea, M.
- Vasilica, M.

Spain
- Arbona, C.
- Carmona, M.
- de la Rubia, J.
- Vives, S.

Switzerland
- Angelillo-Scherrer, A.
- Kremer Hovinga Strebel, J.
- Studt, J.D.

United Kingdom
- Austin, S.
- Hunt, B.
- Martlew, V.
- Scully, M.

United States
- Antun, A.
- Blinder, M.
- DeSancho, M.
- Kaplan, R.
- Kessler, C.
- Kiss, J.
- Knovich, M.A
- Lerner, R.
- Metjian, A.
- Refaai, M.
- Rodgers, G.
- Sarode, R.
- Weitz, I.
- Wu, H.

Ablynx

Q&A