Major thromboembolic events and mortality in acquired thrombotic thrombocytopenic purpura: results from the phase 2 study with caplacizumab

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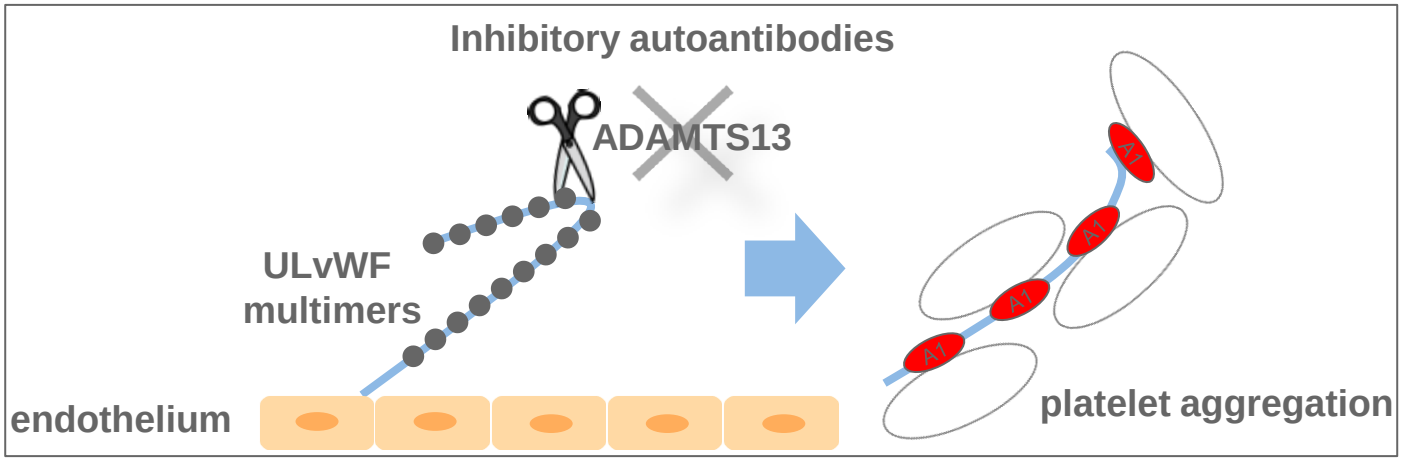
Acquired thrombotic thrombocytopenic purpura (aTTP)



platelet consumption	→	severe thrombocytopenia
red blood cell fragmentation	→	hemolytic anemia
tissue ischemia	→	organ dysfunction (brain, heart, kidneys)
vascular occlusion	→	thromboembolic events (stroke, myocardial infarction, thrombosis)

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Thrombotic complications in aTTP

- Patients with aTTP remain at risk for acute thromboembolic complications until remission is achieved:
  - Nationwide Inpatient Sample (2007-2011):

Table 2. In-hospital complications/comorbidities for platelet consumptive disorders: TTP, HIT, and ITP using all admissions

	TTP N* (%)	HIT N* (%)	ITP N* (%)
Bleeding			
Any documented bleeding†	1451 (13.7)	358 (5.7)	9187 (11.5)
CNS bleed	114 (1.1)	59 (0.9)	791 (1.0)
Gastrointestinal bleeding	520 (4.9)	168 (2.7)	3989 (5.0)
Genitourinary bleeding	909 (8.6)	140 (2.2)	4839 (6.1)
Bleeding with a RBC transfusion during same hospitalization (%)	656 (6.2)	140 (2.2)	2881 (3.6)
Thrombosis			
Any thrombosis (%)‡	425 (4.1)	1150 (20.6)	665 (0.9)
Venous thrombosis (%)	396 (3.8)	986 (17.6)	629 (0.8)
Arterial thrombosis (%)§	35 (0.3)	189 (3.4)	36 (0.1)
AMI (%)	546 (5.1)	449 (7.1)	401 (0.5)
Stroke (%)	557 (5.2)	144 (2.3)	235 (0.3)

Goel et al, Blood 2015

Refractoriness to treatment in aTTP

- registry of the French Reference Center for Thrombotic Microangiopathies:

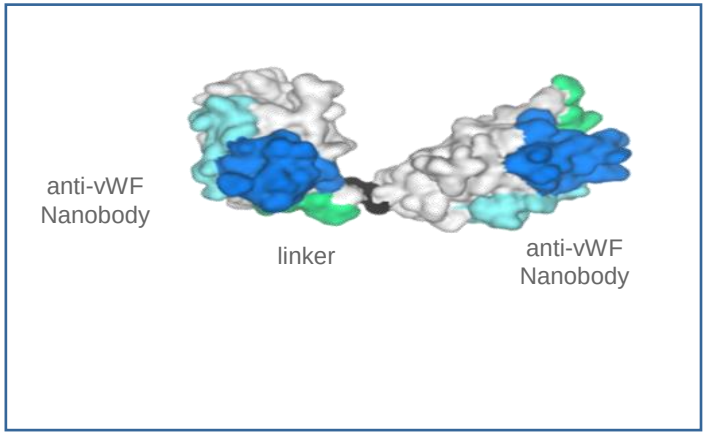
Table 1 Clinical characteristics of patients according to outcome

Parameters	Non-survivors, % ($N = 33$)	Survivors, % ($N = 100$)	Overall population, % ($N = 133$)	P
Age (years)	**54 ± 18**	**46 ± 17**	**48 ± 17**	**0.02**
Female	70 (23)	66 (66)	67 (89)	0.7
Cardiovascular risk factors and pre-existing comorbidities	52 (17)	55 (55)	54 (72)	0.73
Arterial hypertension	24 (8)	20 (20)	21 (28)	0.6
Diabetes	9 (3)	8 (8)	8 (11)	0.84
Past history of ischemic stroke	3 (1)	6 (6)	5 (7)	0.51
Past history of ischemic heart disease	9 (3)	7 (7)	8 (10)	0.69
Clinical cardiac symptoms	12 (4)	15 (15)	14 (19)	0.85
Electrocardiogram findings ($N = 104$)	7.7 (2)	14.1 (11)	12.5 (13)	0.51
Neurologic involvement	82 (27)	64 (64)	68 (91)	0.056
Headache	18 (6)	27 (27)	25 (33)	0.31
Confusion	**27 (9)**	**12 (12)**	**16 (21)**	**0.04**
Seizure	**24 (8)**	**8 (8)**	**12 (16)**	**0.01**
Coma/vigilance disturbances	**30 (10)**	**14 (14)**	**18 (24)**	**0.035**
Focal deficiency	33 (11)	37 (37)	36 (48)	0.7
Hemoglobin level (g dL^{-1})	7.8 ± 2.1	8.1 ± 1.9	8.0 ± 2.0	0.49
Reticulocyte count ($N = 90$)	188 ± 106	191 ± 106	191 ± 106	1
LDH level (× normal) ($N = 124$)	7.5 ± 5.9	5.4 ± 3.0	5.9 ± 3.9	0.11
Platelet count (10^9 L^{-1}) ($N = 132$)	18 ± 23	20 ± 21	20 ± 22	0.13
Serum creatinine (μmol L^{-1})	**158 ± 100**	**115 ± 84**	**125 ± 89**	**0.02**
Estimated glomerular filtration rate (mL min^{-1})	**59 ± 34**	**78 ± 33**	**74 ± 34**	**0.013**
Serum cardiac troponin-I (μg mL^{-1})	**2.2 ± 0.8**	**0.7 ± 0.2**	**1.1 ± 0.3**	**0.002**
Flare-up	100 (3)	63 (63)	64 (66)	0.19
Refractory TTP ($N = 112$)	**50 (8)**	**12 (11)**	**17 (19)**	**0.0009**
ADAMTS-13 inhibitor ($N = 104$)	96 (24)	92 (73)	93 (97)	0.86
Anti-ADAMTS-13 antibodies ($N = 124$)	99 ± 53	88 ± 49	90 ± 50	0.22
Antiplatelet therapy	**12 (4)**	**9 (9)**	**9.7 (13)**	**0.50**

LDH, lactate dehydrogenase; TTP, thrombotic thrombocytopenic purpura. Quantitative values are expressed as mean ± standard deviation. Qualitative values are expressed as percentage (total number). In cases of missing values, the number of patients tested is specified in parentheses in the left column (N). $P < 0.05$ was considered to be statistically significant. Significant values appear in bold.

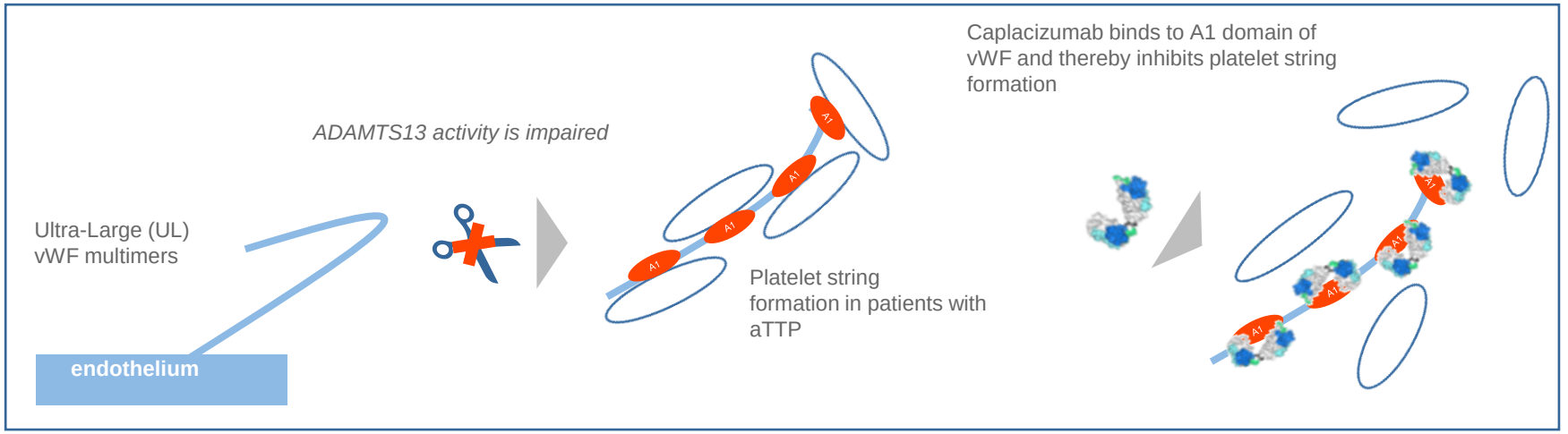
Benhamou et al , J Thromb Haemost. 2015

Caplacizumab mode of action



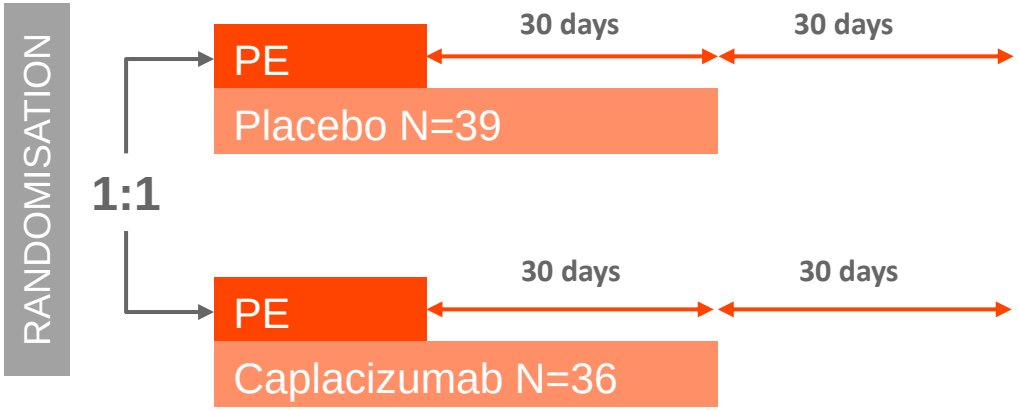
Rapidly stops formation of micro-clots

28 kD bivalent Nanobody
Targets platelet-binding A1 domain of vWF
Produced in *E. coli*



PE: plasma exchange
ULvWF: Ultra-large von Willebrand Factor
ADAMTS13: a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13

TITAN trial with caplacizumab in aTTP



- In conjunction with standard of care[1]:
  - 38 % reduction in time to confirmed platelet count normalization
  - 71 % fewer exacerbations during treatment

- Aim of the post-hoc analyses:
  - assess the impact of treatment with caplacizumab on refractoriness to treatment
  - assess the impact of treatment with caplacizumab on the incidence of major thromboembolic events during the study drug treatment period and the incidence of TTP-related mortality

1) Peyvandi et al, NEJM 2016

Methods

- Refractoriness to treatment:
  - Failure of platelet response after 7 days despite daily PEX treatment[1]
  - Absence of platelet count doubling after 4 days of standard treatment, and LDH>ULN[2]

- Treatment-emergent major thromboembolic adverse events during study drug treatment period:
  - standardized MedDRA Query (SMQ) for ‘embolic and thrombotic events’
  - transient episodes were not considered major thromboembolic events and were, therefore, not included in this analysis

- TTP-related mortality during the study:
  - based on adverse events reporting (relatedness to TTP judged by the Investigator)

1) Sayani et al, Blood, 2015
2) Soucemarianadin et al, European Journal of Haematology, 2015

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Refractoriness to treatment

	Caplacizumab (N=35)	Placebo (N=37)
Refractoriness to treatment, n (%)[3]		
Failure of platelet response after 7 days despite daily PE treatment[1]	2 (5.7%)	8 (21.6%)*
Absence of platelet count doubling after 4 days of standard treatment, and LDH>ULN[2]	0 (0)	4 (10.8%)

* 2 patients in the placebo group who discontinued the study prematurely (before 7 days) without reaching the platelet count criteria (i.e. platelet count <150x10^9/l) were counted as refractory to treatment

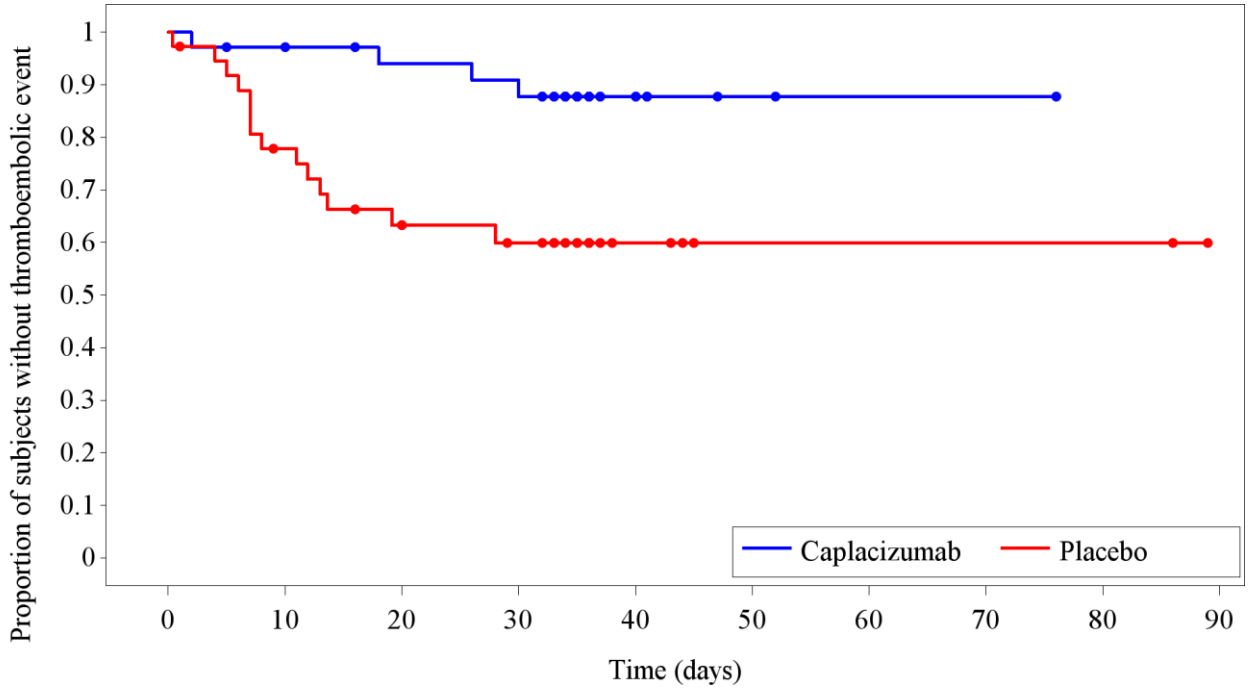
1) Sayani et al, Blood, 2015
2) Soucemarianadin et al, European Journal of Haematology, 2015
3) Peyvandi, NEJM 2016

Major thromboembolic events during the treatment period and overall TTP-related mortality

	Caplacizumab (N=35)		Placebo (N=37)	
	Events, n	Subjects, n (%)	Events, n	Subjects, n (%)
Embolic and thrombotic events (SMQ)				
Acute myocardial infarction	0	0	2	2 (5.4%)
Deep vein thrombosis	0	0	1	1 (2.7%)
Venous thrombosis	0	0	1	1 (2.7%)
Pulmonary embolism	1	1 (2.9%)	1	1 (2.7%)
Ischemic stroke	0	0	1	1 (2.7%)
Hemorrhagic stroke	0	0	1	1 (2.7%)
Thrombotic thrombocytopenic purpura [1]	3 [2]	3 (8.6%) [2]	13	11 (29.7%)
TTP-related mortality				
Deaths related to TTP	0	0	2	2 (5.4%)
TOTAL	**4**	**4 (11.4%) [3], #**	**22**	**16 (43.2%) [3], #**

[1] this preferred term consisted of recurrences of TTP during the treatment period, defined in the protocol as exacerbations of TTP
[2] one AE reported as 'Thrombocytopenia' was not considered in this analysis, as this event was reported as part of the presenting disease
[3] a subject may have experienced more than one event
Nominal p=0.006

Kaplan-Meier plot of major thromboembolic events during the study drug treatment period

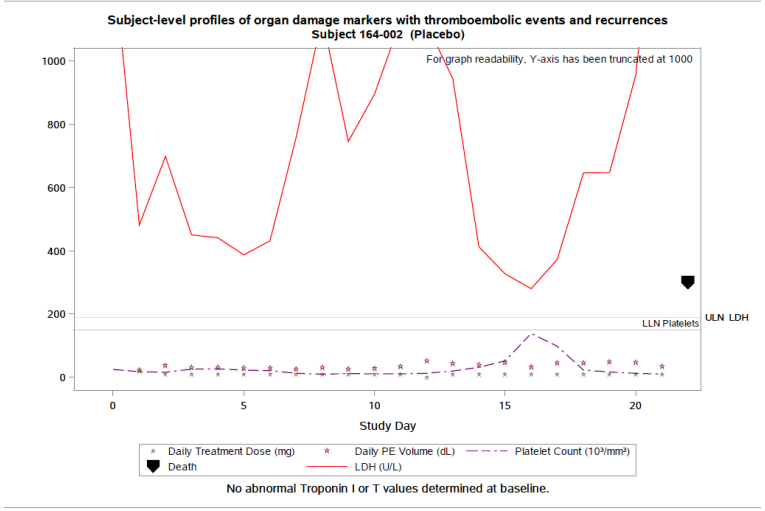


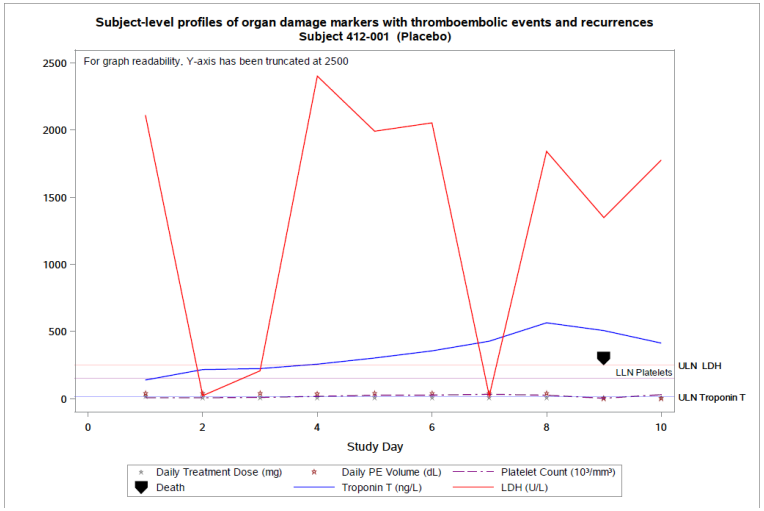
Days from first dose of study drug
Censored observations are represented by a dot; any subject still at risk at the end of the treatment period is censored at the end of the treatment period

- Thromboembolic events are acute complications of aTTP

TTP-related mortality: the importance of refractoriness

- Individual patient profiles indicate absence of platelet response despite daily PE treatment





- Both deaths (both in the placebo group) in the TITAN study were in subjects refractory to treatment

- No deaths were reported in the caplacizumab treated group

Summary and conclusions

- These post-hoc analyses of the TITAN trial dataset have demonstrated that :
  - a lower proportion of subjects treated with caplacizumab became refractory to treatment
  - a lower proportion of subjects treated with caplacizumab experienced one or more major thromboembolic events, or died, as compared to placebo
- These data suggest that treatment with caplacizumab:
  - may have the potential to reduce the major morbidity and mortality associated with acquired TTP
- A phase III confirmatory study is ongoing and includes a prospectively defined assessment of these clinically meaningful endpoints

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