POST-SAN DIEGO 2023
Novità dal Meeting della Società Americana di Ematologia

Novità dal Meeting
della Società Americana
di Ematologia
Verona, 15-16-17 Febbraio 2024

Disclosures
Monica Carpenedo

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Sanofi					X		

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Thrombotic MicroAngiopathies (TMA) @ASH 2023

Education Session, Presidential Symposium, Ham-Wasserman Lecture, abstracts

- Labor & Delivery: DIC, HELLP, Pre-eclampsia
- aHUS,TTP: how to distinguish and what to do
- Consumptive Coagulopathy in the ICU

- Complement and Innate immunity
  - Intracellular Complement and Adoptive Immunity
  - Targeting Complement to Treat Hematological diseases

- Thrombocytopenia due to platelet activation: HIT and beyond
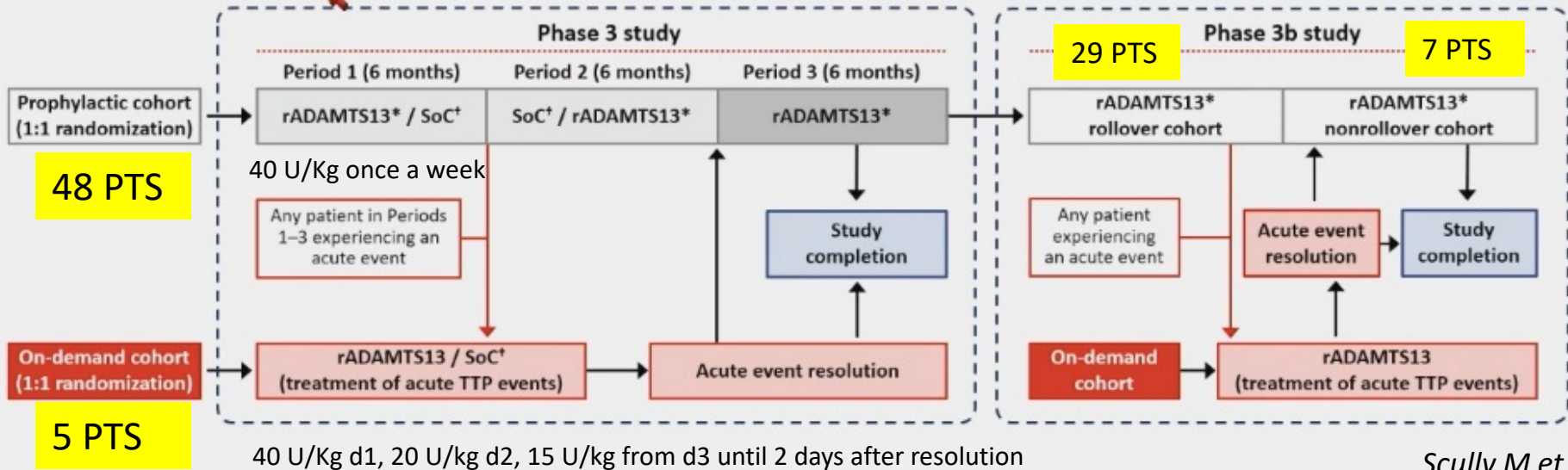
Congenital TTP
Acquired TTP

Recombinant ADAMTS13 for the Treatment of Acute TTP Events in Patients with Congenital Thrombotic Thrombocytopenic Purpura: Results from the Phase 3 Randomized, Controlled, Crossover Study and the Phase 3b Continuation Study

Marie Scully, Thomas L. Ortel, Ziqiang Yu, Maria Waliullah, Pinghai Zhang, Munjal Patel, Parth Patwari, Bjorn Mellgard, Linda T. Wang

cTTP: ulra rare disorder caused by an inherited deficiency of ADAMTS13 (5% of all TTP)

Phase 3 pivotal study: a prospective, randomized, controlled, open-label, multicenter, 2-period crossover study
Phase 3b study: a prospective, open-label, multicenter, continuation study

Interim analysis cutoff date: August 12, 2022

Phase 3 study

Period 1 (6 months)	Period 2 (6 months)	Period 3 (6 months)
rADAMTS13* / SoC†	SoC† / rADAMTS13*	rADAMTS13*

40 U/Kg once a week

29 PTS   7 PTS

Phase 3b study

rADAMTS13* rollover cohort — rADAMTS13* nonrollover cohort

48 PTS

Prophylactic cohort (1:1 randomization)

Any patient in Periods 1–3 experiencing an acute event

Study completion

5 PTS

On-demand cohort (1:1 randomization)

rADAMTS13 / SoC† (treatment of acute TTP events)

Acute event resolution

Any patient experiencing an acute event

Acute event resolution

Study completion

On-demand cohort

rADAMTS13 (treatment of acute TTP events)

40 U/Kg d1, 20 U/kg d2, 15 U/kg from d3 until 2 days after resolution

Scully M et al

*40 IU/kg Q1W or Q2W. †SoC dose and treatment regimen determined by the treating physician; SoC treatment could include fresh frozen plasma, solvent/detergent-treated plasma, or factor VIII/von Willebrand factor concentrates. ADAMTS13, a disintegrin and metalloproteinase with thrombospondin motifs 13; Q1W, once every week; Q2W, once every 2 weeks; rADAMTS13, recombinant ADAMTS13; SoC, standard of care; TTP, thrombotic thrombocytopenic purpura.
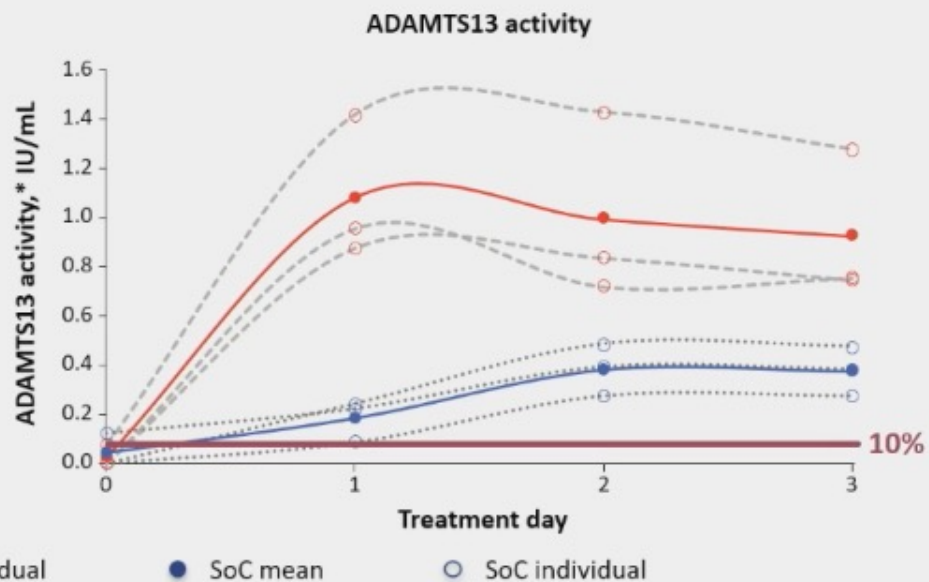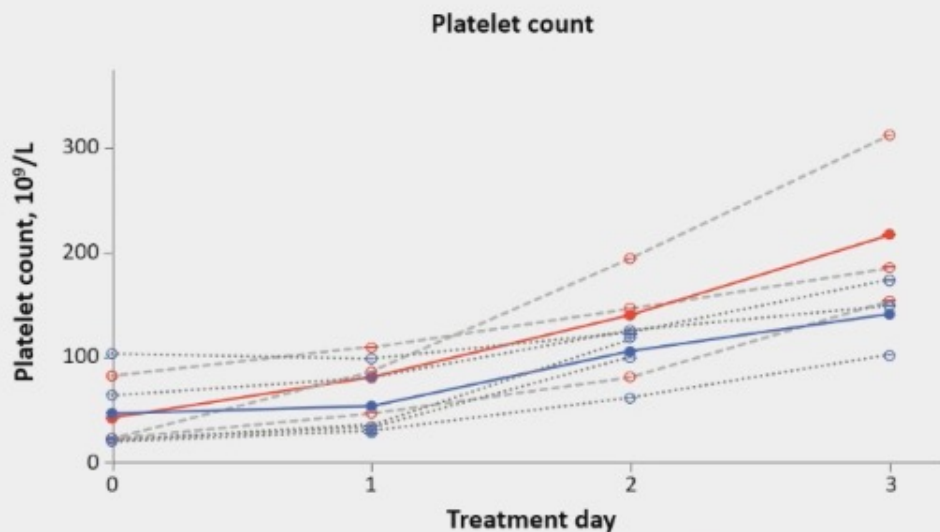
No acute events occurred while patients were receiving rADAMTS13 prophylaxis
8 suspected acute TTP events were treated in 7 patients

Treated with rADAMTS13 (3 events)　　　　　　　　　　　Treated with SoC (5 events)

Platelet counts and ADAMTS13 activity during the first 3 days of treatment for a suspected acute TTP event

Over the first 3 treatment days, the mean platelet count increased more than ~5-fold with rADAMTS13 and ~3-fold with SoC; Treatment with rADAMTS13 resulted in a rapid increase in ADAMTS13 activity levels to normal range
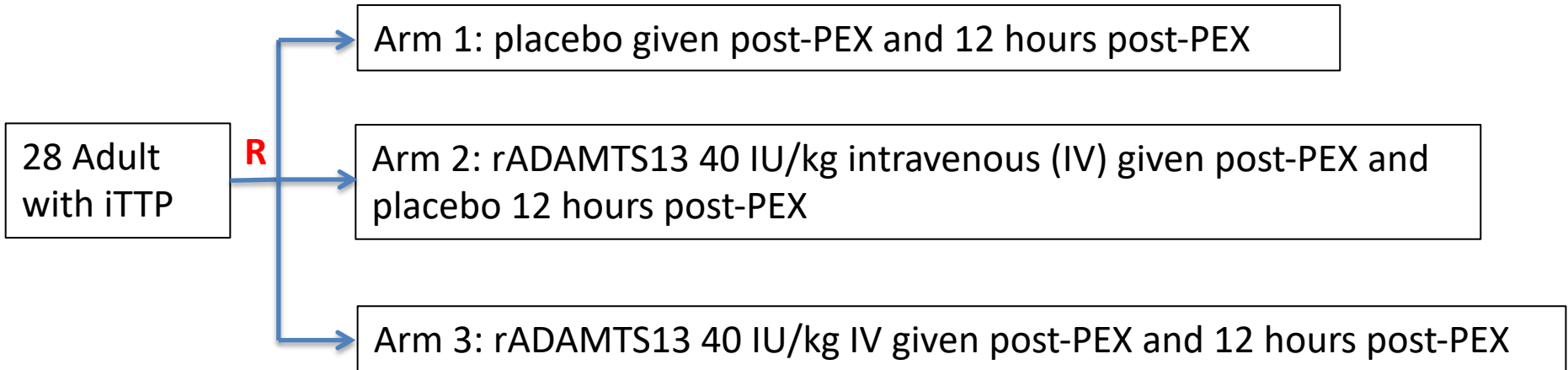

Platelet count

ADAMTS13 activity

● rADAMTS13 mean　　○ rADAMTS13 individual　　● SoC mean　　○ SoC individual

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Conclusions

✓ No serious TEAEs related to rADAMTS13 were reported (nausea, feeling hot, thrombocytosis)

✓ No neutralizing antibodies against ADAMTS13 were observed

✓ All 3 acute TTP events treated with rADAMTS13 resolved promptly with the treatment protocol

✓ The resolution of acute TTP events and an improvement in platelet count in patients with cTTP following treatment with rADAMTS13 was closely related to higher ADAMTS13 activity exposure

S305 PHASE 2 RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND, MULTICENTER STUDY OF RECOMBINANT ADAMTS13 IN PATIENTS WITH IMMUNE-MEDIATED THROMBOTIC THROMBOCYTOPENIC PURPURA

28 Adult with iTTP

R

Arm 1: placebo given post-PEX and 12 hours post-PEX

Arm 2: rADAMTS13 40 IU/kg intravenous (IV) given post-PEX and placebo 12 hours post-PEX

Arm 3: rADAMTS13 40 IU/kg IV given post-PEX and 12 hours post-PEX

Patients received treatment until clinical remission (platelet normalization [≥150 ×10^9/L] and lactate dehydrogenase levels <2 × upper limit of normal for ≥48 hours following initial platelet normalization

Scully M et al, EHA Frankfurt June 2024

Primary endpoints: ADAMTS13 activity levels and PK/PD relationships.

Secondary endpoints: incidence of treatment emergent adverse events (TEAEs), serious TEAEs, and changes in antibody levels

Arm 1 — Arm 2 — Arm 3 — Normal ADAMTS13 plasma activity

* Time of plasma exchange

Scully M et al
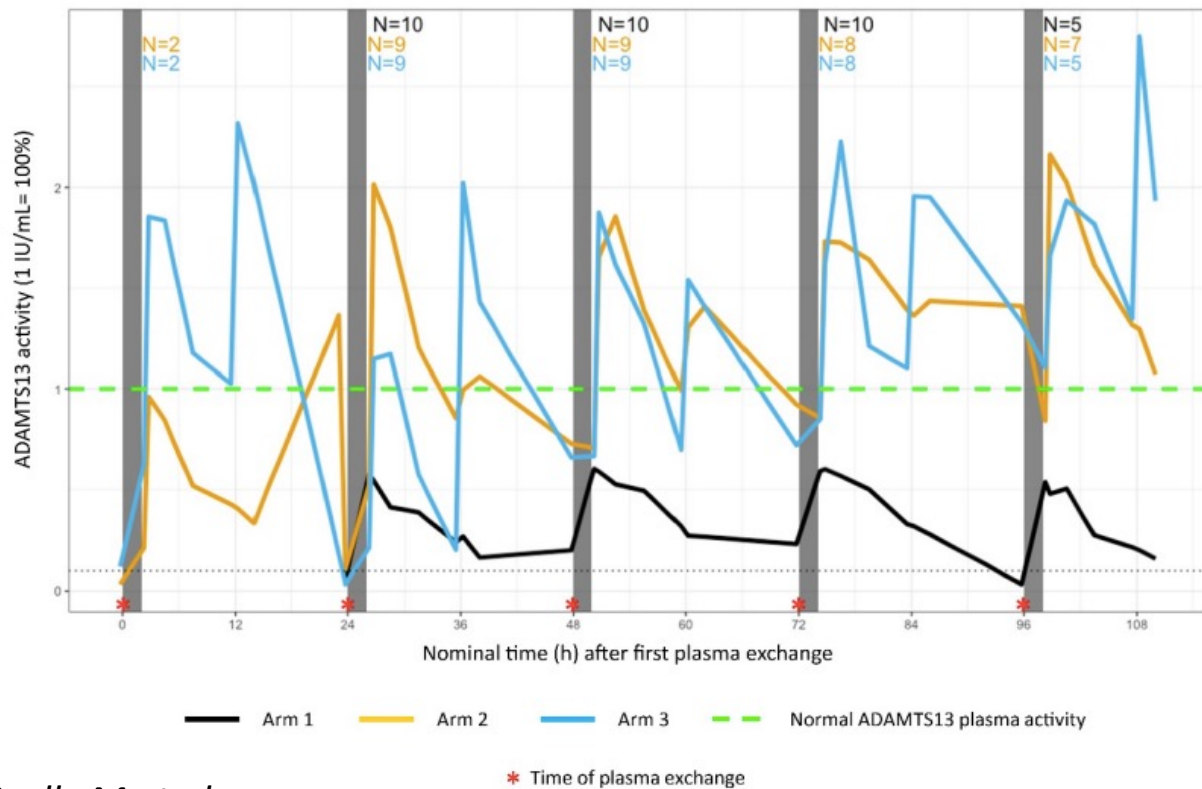
Higher plasma ADAMTS13 activity exposures were achieved in Arm 2 vs Arm 1 (up to **5.4-fold higher geometric mean [**GM] for maximum concentration [Cmax] and Arm 3 vs Arm 1 (up to **11.7-fold higher GM** for Cmax

Serious TEAEs:
- 6 in arm 1
- 2 in arm 2
- 3 in arm 3

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FDA U.S. FOOD & DRUG
ADMINISTRATION

← Home / News & Events / FDA Newsroom / Press Announcements / FDA Approves First Treatment for Patients with Rare Inherited Blood Clotting Disorder

FDA NEWS RELEASE

FDA Approves First Treatment for Patients with Rare Inherited Blood Clotting Disorder

November 2024

rADAMTS13 approved as prophylactic or on-demand enzyme replacement therapy for adult and pediatric patients with congenital thrombocytopenic purpura (cTTP)

Estimating the Population-Based Prevalence of Congenital Thrombotic Thrombocytopenic Purpura Using Large-Scale Sequencing Data

Omid Seidizadeh, Andrea Cairo, Ilaria Mancini, Pasquale Agosti, Frits Rosendaal, Flora Peyvandi

- cTTP: ulra rare disorder caused by an inherited deficiency of ADAMTS13 (5% of alla TTP)
- Most estimates suggest a **prevalence of 0.5 to 2 cases** per million population

AIM

- To establish the **worldwide and within-population prevalence of cTTP** in the general population using the genome Aggregation Database (gnomAD)

- To explore the worldwide **mutational burden of** *ADAMTS13*

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METHOD

gnomAD
genome aggregation database

- ADAMT13 variants were obtained from the gnomAD (v2.11)
- gnomAD: 125,748 exomes and 15,708 genomes from unrelated individuals
- Individuals with severe pediatric disease and their first degree relatives are excluded

- Results were compared to the Human Gene Mutation Database (HGMD), Leiden Open Variation Database (LOVD v 3.0), Clin Var and literature
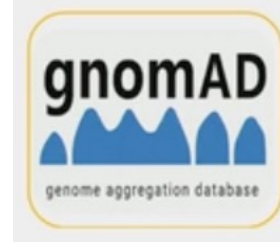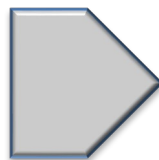
2212 ADAMTS13 variants were found in gnomAD

992: frameshifts, nonsense, splicing variants (-8/+8)

250 variants predicted pathogenetic by *in silico* or already reported to be associated with cTTP

167 | Novel
83 | Reported
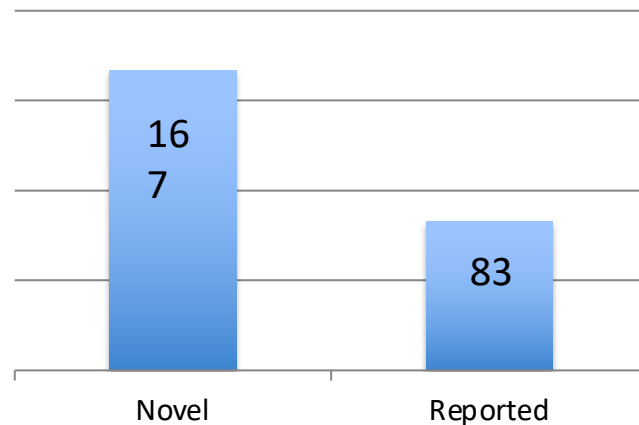
ESTIMATED GLOBAL PREVALENCE OF cTTP USING ONLY THE REPORTED VARIANTS (n = 83)

Population	Total Number Of Alleles	Total Number Of affected alleles	Collective Frequency Of Variants	Prevalence in 10^6 Individuals (recessively inherited)	Prevalence in 100 Individuals (Carrier)
All	282912	1159	0.004	17	0.8
African/African American	24974	62	0.002	6	0.5
Latino/Admixed American	35440	134	0.004	14	0.7
Ashkenazi Jewish	10370	8	0.001	0.6	0.2
East Asian	19954	42	0.002	4	0.4
Finnish	25124	129	0.005	26	1.0
European (not Finnish)	129206	710	0.005	30	1.1
South Asian	30616	49	0.002	3	0.3
Other ethnicities	7228	25	0.003	12	0.7

NUMBER OF ALLELES AFFECTED BY REPORTED AND NOVEL VARIANTS

Population	Total number of affected alleles	Total number of affected alleles by reported variants	Total number of affected alleles by novel variants	% of affected alleles by novel variants
All	2166	1159	1007	46.5
Africans/African Americans	633	62	571	90.2
Latino/Admixed American	278	134	144	51.8
Ashkenazi Jewish	18	8	10	55.6
East Asians	86	42	44	51.2
Finnish	140	129	11	7.9
Europeans (not Finnish)	857	710	147	17.2
South Asians	114	49	65	57.0
Other ethnicities	40	25	15	37.5

*p.Pro341Leu

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Conclusions

- We estimated the worldwide and within-population prevalence of cTTP using 141,456 genome and exomes sequencing data from gnomAD

- We provided a global mutational landscape of *ADAMTS13* by identifying **167 novel variants** and creating and evidence-based **dataset of 250 known pathogenetic variants**

- Based on this population-based genetic epidemiology study, the prevalence of cTTP is substantially higher than previously suggested

- Probably a large number of cTTP patients are underdiagnosed

Persistent ADAMTS13 Inhibitor May Lead to Delayed ADAMTS13 Recovery in Japanese Patients with Caplacizumab-Treated Immune-Mediated Thrombotic Thrombocytopenic Purpura

Kenki Saito, Kazuya Sakai, Masayuki Kubo, Hidekazu Azumi, Atsushi Hamamura, Shinichi Ochi, Shinya Kobayashi, Hideo Yagi, Masanori Matsumoto

- A UK group recently reported that delayed normalization of ADAMTS13 activity was seen in acute iTTP patients receiving caplacizumab *(Prasannan et al, Blood 2023)*

- However there has been no evaluation of the temporale changes in anti ADAMTS13 IgG levels nor of ADAMTS 13 functional inhibitors in the acute phase

- Therefore **we analyzed the temporal changes of ADAMTS13 activity** and its i**nhibitor** in acute iTTP cases before and after introduction of caplacizumab

- Primary iTTP patients diagnosed from January 2019 –July 2023; once a week or more ADAMTS13 monitoring for ADAMTS13 activity and inhibitor during acute phase

- **Capla treatment group** vs **non Capla** treatment group

Demographic and biochemical data of enrolled patients

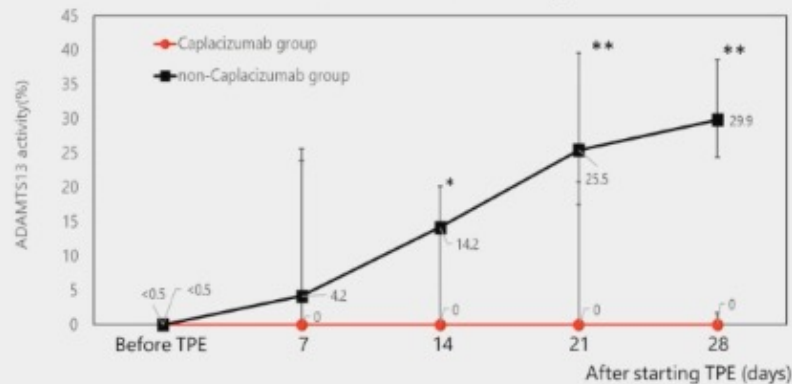|	Caplacizumab group (n=14)	Non-Caplacizumab group (n=16)	P value
Follow-up period, days	55.0 (49.3-72.8)	44 (23.3-61.3)	0.197
Age, y	71 (62.8-80.0)	66.5 (52.0-84.3)	0.983
Female sex, n/n total (%)	6/14 (42.9%)	9/16 (56.3%)	0.715
initial episode, n/n total (%)	13/14 (92.9%)	15/16 (93.8%)	1
Hemoglobin, initial, g/dL	8.1 (7.5-9.1)	7.9 (6.7-10.0)	0.901
Platelet, initial, $\times 10^9$/L	1.1 (0.8-1.2)	1.1 (0.7-1.3)	0.754
Lactate dehydrogenase, initial, IU/L	1086 (931-1282)	1038 (857-1272)	0.854
Serum creatinine, initial, mg/dL	1.01 (0.68-1.51)	1.15 (0.82-1.39)	0.739
Total Bilirubin, initial, mg/dL	3.9 (2.6-4.8)	3.1 (2.5-4.2)	0.394
Neuropsychiatric symptoms, n/n total (%)	11/14 (78.6%)	9/16 (56.3%)	0.26
ADAMTS13 activity <0.5%, initial- n/n total (%)	14/14 (100%)	16/16 (100%)	-
ADAMTS13 antigen (%)	<1.5 (<1.5-6.2)	<1.5 (<1.5-3.7)	0.077
ADAMTS13 inhibitor, initial, BU/mL	8.0 (4.6-12.7)	3.3 (1.2-6.4)	**0.058**
Anti ADAMTS13 IgG antibody level, initial, U/mL	100.7 (59.6-215.9)	65.1 (24.6-76.0)	0.43
Plasma BAFF level, initial, pg/mL	861.1 (685.3-1228.4)	824.2 (704.9-1075)	0.697

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Verona, 15-16-17 Febbraio 2024

Treatement administered to the enrolled patients

	Caplacizumab group (n=14)	Non-Caplacizumab group (n=16)	P value
TPE, n/n total (%)	14/14 (100%)	16/16 (100%)	-
Number of TPE treatment, n	**8 (7-8.8)**	**15 (8-20)**	**0.025**
Date of final TPE, d	**8 (7-16.5)**	**22 (9-27.3)**	**0.049**
Glucocorticoids, n/n total (%)	14/14 (100%)	16/16 (100%)	-
Rituximab, n/n total (%)	11/14 (78.6%)	13/16 (81.4%)	1
Time from 1st TPE to 1st rituximab dose, d	12 (4.5-15.5)	10 (7-13)	0.954
Duration of caplacizumab treatment, d	49 (39.5-59.5)		-

Changes in ADAMTS13-related parameters

ADAMTS13 activity

ADAMTS13 antigen
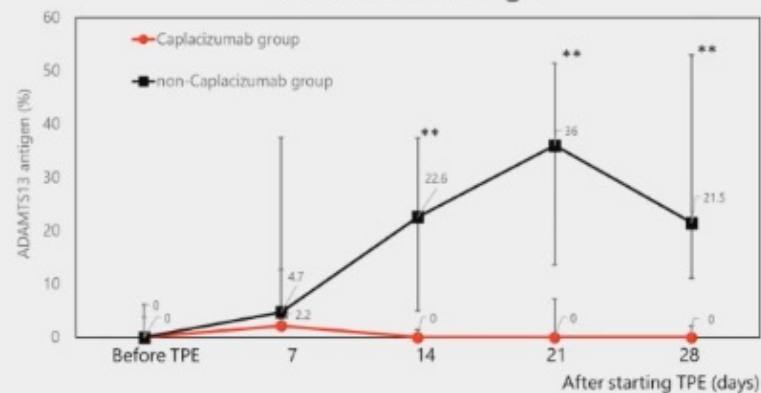
Anti-ADAMTS13 inhibitor
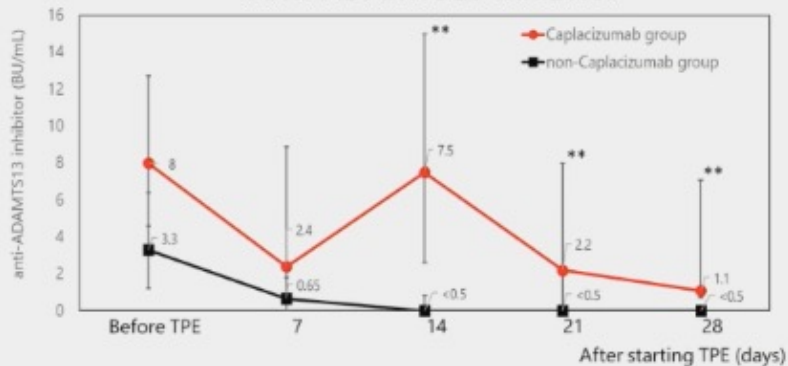
Anti-ADAMTS13 IgG
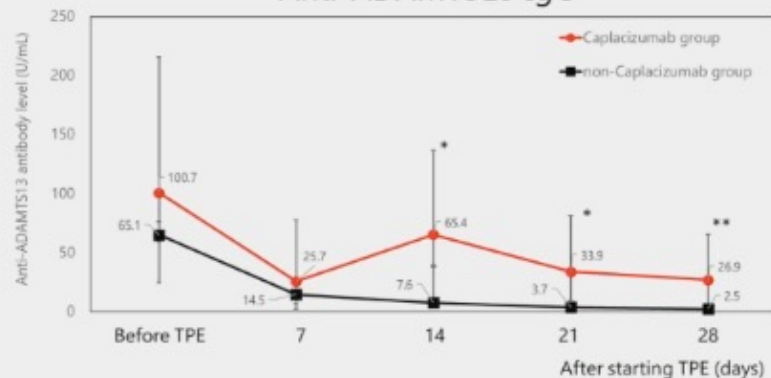
The median **ADAMTS13 activity and antigen levels** on day14, 21, and 28 were significantly **lower** in the caplacizumab group.

The median **anti-ADAMTS13 inhibitor and IgG levels** on day14, 21, and 28 were significantly **higher** in the caplacizumab group.

Recovery of ADAMTS13 activity and platelet counts

	Capla group (n=14)	Non Capla group (n= 16)	P value
Time from 1° TPE to ADAMTS13 activity > 10%, d	43 (31.0-55.0)	23 (14.5-33.3)	**0,014**
Time from 1° TPE to ADAMTS13 activity > 20%, d	52 (33.0-55.0)	25 (20.5-43.5)	0.134
Time after last TPE to ADAMTS13 activity > 10%, d	35 (11.3-41.3)	2 (2.0-3.0)	**<0.001**
Time after last TPE to ADAMTS13 activity > 20%, d	38.5 (17.5-48.5)	11.0 (3.0-18.8)	0.008
Time to achieve plt count > 100 x 10^9/L, d	5 (4.0-5.0)	8.5 (5.8-15)	**< 0.001**

In the caplacizumab group, iTTP patients experienced:
- A delayed recovery of ADAMTS13 avtivity
- Faster normalization of platelet count

ADAMTS13 RECOVERY IN ACUTE THROMBOTIC THROMBOCYTOPENIC PURPURA AFTER CAPLACIZUMAB THERAPY. THE SPANISH REGISTRY

ADAMTS13 Recovery After Caplacizumab Therapy in Immune-Mediated Thrombotic Thrombocytopenic Purpura (iTTP)

Context of Research

- Caplacizumab prevents VWF-platelet interaction and is approved for the treatment of iTTP

- Delayed normalization of ADAMTS13 activity has been recently reported in a proportion of iTTP patients treated with the caplacizumab

Patients and Methods

- Retrospective analysis of 113 iTTP episodes in 108 patients from the Spanish Registry of Thrombocytopenic Purpura:

  - 75 episodes treated with caplacizumab

 - 38 episodes without caplacizumab

Main Findings

No difference was observed in time to ADAMTS13 recovery (≥20%) from the start of plasma exchange (PEX) according to caplacizumab use

Log-rank P = .860

Capla (n = 74)
No capla (n = 36)
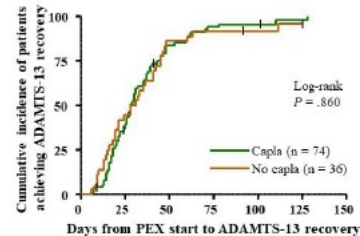
A longer time to ADAMTS13 recovery from PEX end was observed in patients starting caplacizumab ≤3 days from PEX
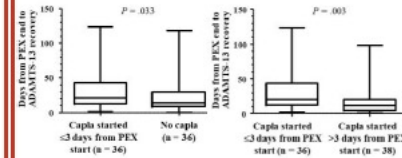
Early caplacizumab was associated with a shorter time on PEX treatment
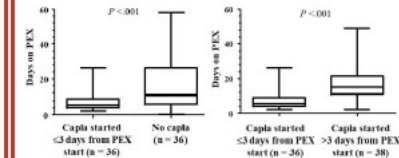
Conclusions: In this retrospective analysis of 108 patients with iTTP, the use of caplacizumab was not associated with delayed normalization of ADAMTS13 activity.

Blood

Mingot-Castellano M.E. et al. Blood 2024

Comparing the Impact of Rituximab Dosing on Longitudinal ADAMTS13 Parameters in TTP
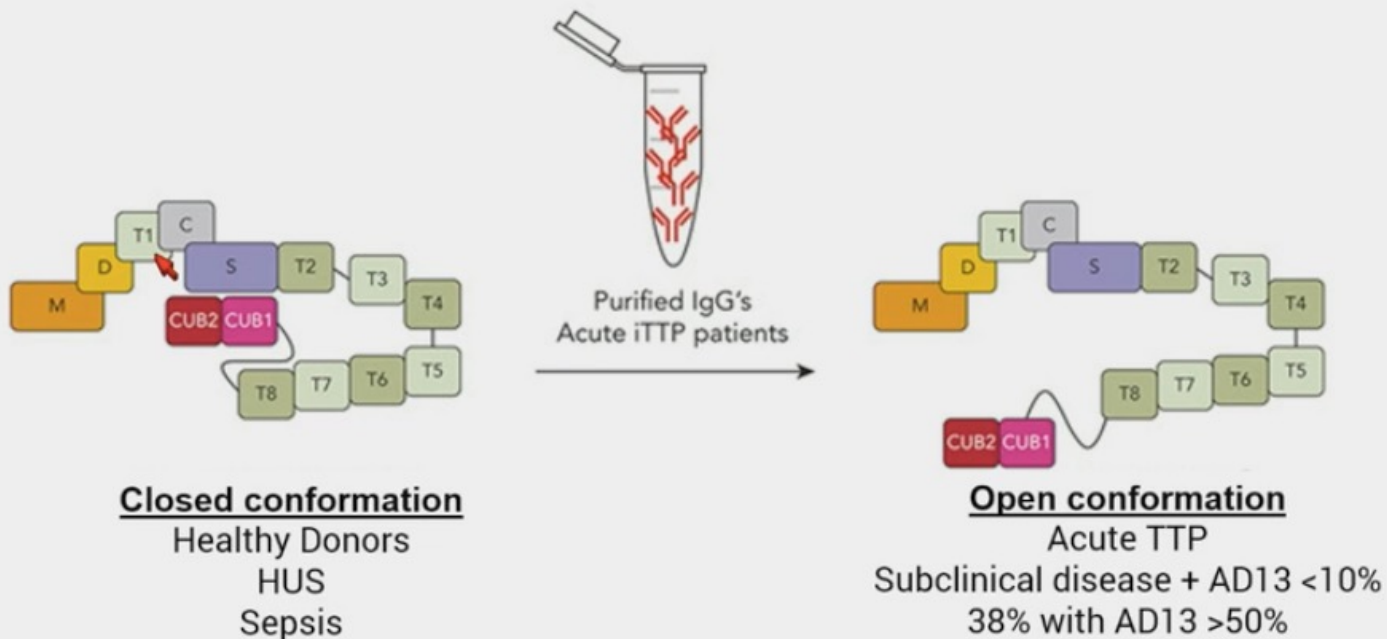
Maryam Subhan, Nithya Prasannan, Bertina Dragunaite, Karen Vanhoorelbeke, Marie Scully, Mari Thomas

Background and aim

- It is widely accepted practice to use rituximab to prevent a clinical and AD13 TTP relapse.

- However, the dosing regimens used vary across treating centres.

- The Elective Rituximab in TTP (ERTTP) study is an ongoing UK-based randomised control trial comparing low dose rituximab (4 doses of 200mg weekly) to standard dose rituximab (4 doses of $375mg/m^2$ weekly) in AD13 relapses. (REC: 17/LO/1055)

- We examined longitudinal ADAMTS13 conformation to investigate the effect of rituximab dose in a a subset of patient episodes: those enrolled at UCLH, comprising 32 of all 69 episodes.
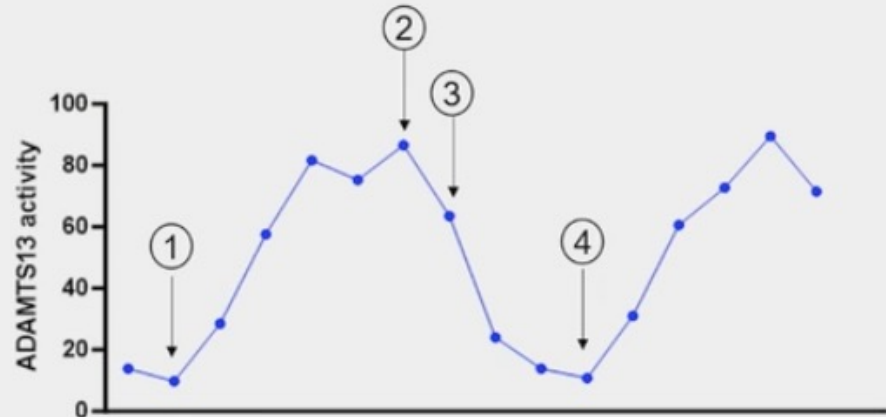
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ADAMTS13 conformation

Closed conformation
Healthy Donors
HUS
Sepsis

Purified IgG's
Acute iTTP patients

Open conformation
Acute TTP
Subclinical disease + AD13 <10%
38% with AD13 >50%

Roose et al (2018). J Thromb Haemost., Roose et al (2020) Blood.

Method

ADAMTS13 activity was measured **from commencement of rituximab** on Day 1, 8, 15 & 22, month 1, 3, 6 and then 6 monthly **until retreatment**.

ADAMTS13 conformation was analysed in 32 episodes (with 24 patients) with 1C4 ELISA and ADAMTS13 antigen ELISA at a minimum of 4 different timepoints:
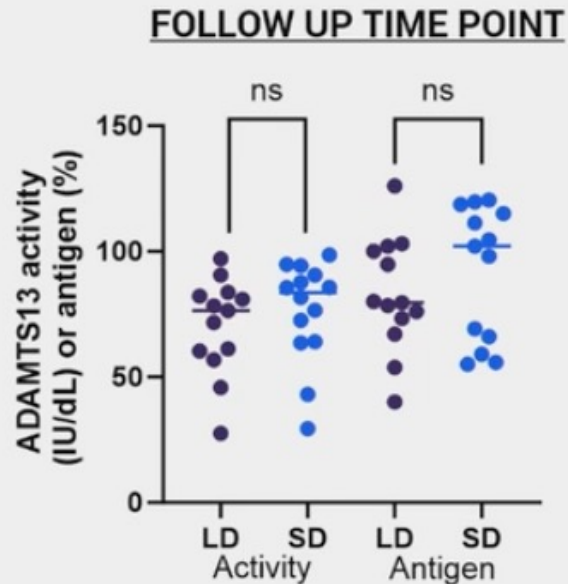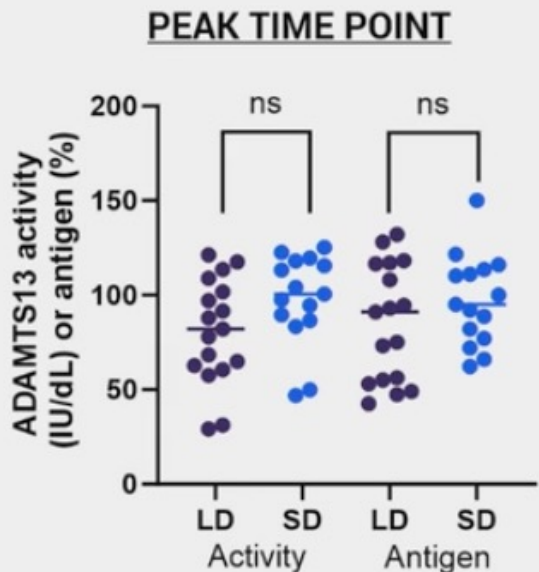
1. ADAMTS13 activity <15IU/dL or %

2. Peak ADAMTS13 activity

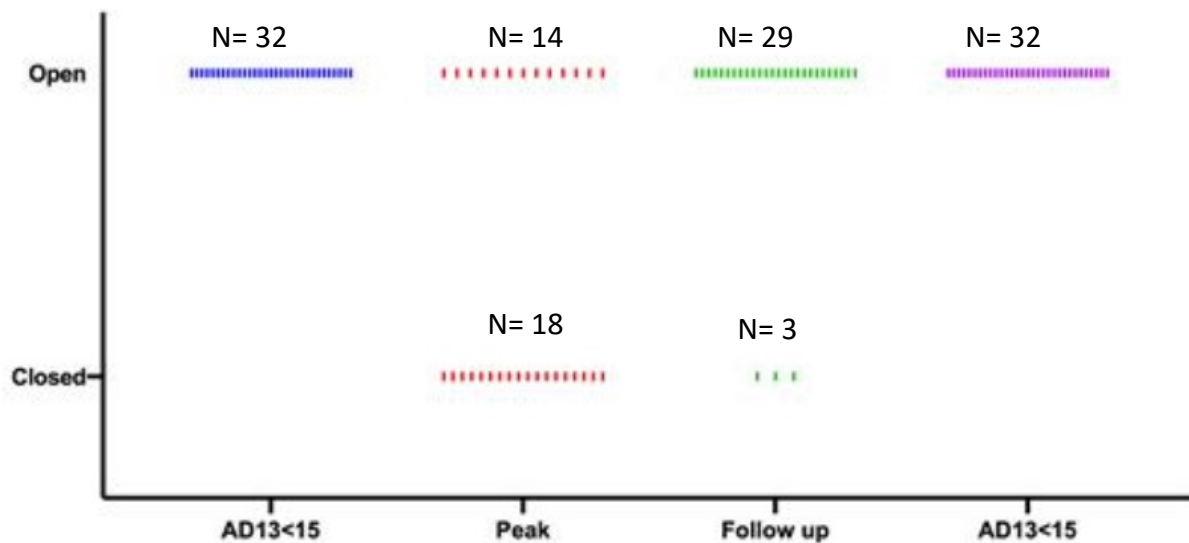3. Follow-up sample after peak

4. Subsequent ADAMTS13 relapse

AD13 Activity & Antigen at Peak & F/U

N=32

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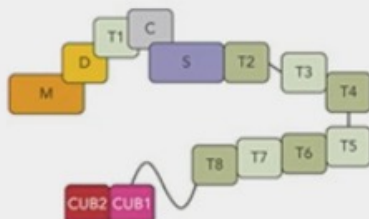di Ematologia

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ADAMTS13 Conformation at Timepoints of Interest

ADAMTS13 for each of 32 episodes tested at the four time points: initial ADAMTS13 relapse, peak of response, interim follow up , next relapse
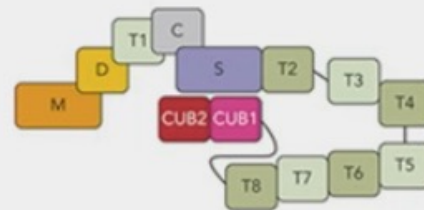
I. *Open at PEAK*

Median AD13 63.8%

II. *Closed at PEAK*

Median AD13 106.5%

AD13 conformation at peak related more to AD13 activity than rituximab dose received.

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311. DISORDERS OF PLATELET NUMBER OR FUNCTION | NOVEMBER 13, 2019

Disruption of ADAMTS13-Autoantibody Complexes with an ADAMTS13 Spacer Domain As a Potential Therapeutic Strategy for Immune Thrombotic Thrombocytopenic Purpura

Konstantine Halkidis, MD PhD, X. Long

Check for update

Blood (2019) 134 (Supplement_1)

https://doi.org/10.1182/blood-201

ADAMTS-13 conformation influences autoimmune recognition in immune thrombotic thrombocytopenic purpura

Mary I. Underwood[1] | Mari R. Thomas[2] | Marie A. Scully[2] | James T. B. Crawley[1]

J Thromb Haem 2023

Open ADAMTS-13 conformation index predicts earlier relapse in immune-mediated thrombotic thrombocytopenic purpura

Laure De Waele[1] | Kazuya Sakai[1,2] | Ilaria Mancini[3] | György Sinkovits[4] |

J Thromb Haem 2023

PHASE II STUDY OF DANAZOL WITH PLASMA EXCHANGE AND CORTICOSTEROIDS FOR THE TREATMENT OF THROMBOTIC THROMBOCYTOPENIC PURPURA

V. TORRI[1,2], M. FRIEDMAN[3,4], I. SHAPIRA[5], A. PATEL[1,6,7,8], J. YOE[1], V. SHAH[9], T. MIRZOYEV[1], M. MACHUCA[5] and M. VARMA[1]

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3. Pathology/Blood Bank, Mount Sinai West and Mount Sinai Morningside, New York, NY; 4. NYU Langone Hospital-Long Island, Mineola, NY;
5. Hematology-Oncology, Mount Sinai Beth Israel, New York, NY; 6. RWJ Barnabas Health-Jersey City Medical Center, Jersey City, NJ;
7. St. George's University School of Medicine, St. George's, Grenada; 8. New York Institute of Technology, New York, NY;
9. Pathology/Blood Bank, Mount Sinai Beth Israel, New York, NY

EG: daily PE, prednisone 1 mg/kg, and danazol 600 mg; tapering of steroid and danazol

HC: PE with or without steroid (patients treated from 2000 to 2007)

	Experimental Group (n= 9)	Historical Control Group (n=20)	P value
Average N of PEX	14.8	16.1	>0.05
Average time to remission (days)	11.4	11	>0.05
Average lenght of stay (days)	27.3	24.9	>0.05

	Experimental Group	Historical Control Group
N relapse	1	6
N patients with relapses	1	4
Time to relapse (months)- median range	43	28.5 (2.5-97)

Accrual target: 16 patients to detect a 40% decrease in the n of PE's with 80% power and a level of significance of 0.05: The study was terminated in 2018 due to low accrual

Management of Immune Thrombotic Thrombocytopenic Purpura without Therapeutic Plasma Exchange: Analysis of Efficacy and Safety Data

Lucas Kühne, Paul Knoebl, Kathrin Eller, Ingrid Pabinger, Paul T. Brinkkoetter, Linus A. Voelker

Retrospective study:

42 iTTP pts, with increase in plt count after 1° Capla (TPE free cohort)
vs
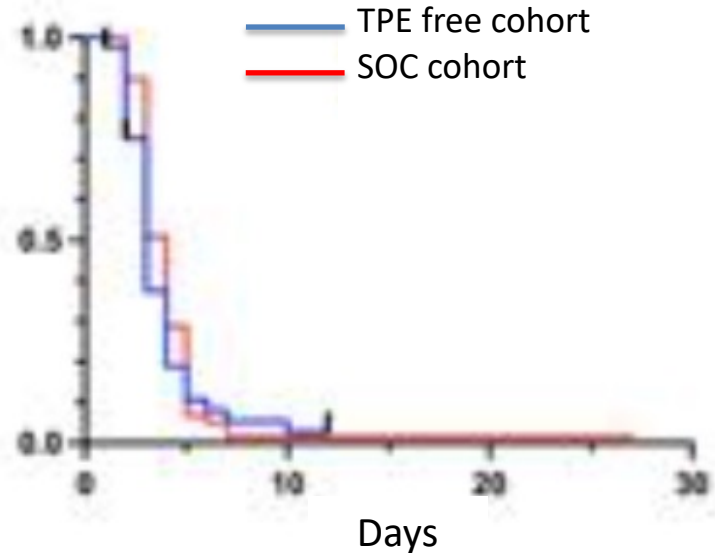59 iTTP pts receiving Capla + TPE + IS (SOC cohort)

median time to platelet count normalization
- ✓ **3 and 4 days; P = 0.31**

no significant differences in clinical response, exacerbations, refractoriness, or iTTP-related deaths

TEAE: 26.2 vs 25.4

No, at risk

	0	5	10	15	20	25	30
TPE-free cohort	42	7	2	0	0	0	0
SOC cohort	59	17	1	1	1	1	0

SUMMARY

- rADAMTS13 as first targeted replacement treatment in cTTP
- Suggestions and evidence of underestimated number of cTTP
- New insights in ADAMTS13 conformation changes during treatment of iTTP
- New (?) treatment option to reduce relapse risk of iTTP
- Treatment of iTTP without PEX…(?!)

San Diego, December 2023 -----→ and again in December 2024.. .