POST-NEW ORLEANS 2022
Novità dal Meeting della Società Americana di Ematologia

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Thrombotic MicroAngiopathies (TMA) @ASH 2022

Scientific Sessions, abstracts

Is it time to change TTP first line?

- **Caplacizumab without PEX in iTTP**
- Setting future clinical trial thresholds in iTTP

About TTP patients in remission/risk of relapse

- **Bortezomib in r/r TTP**
- **Silent Cerebral Infarction in TTP remission**
- **ADAMTS13 Activity level and risk of relapse**

aHUS and TMA HSCT-related

- **Trial with Masp2 inhibitor in pediatric patients and TA-TMA**
- Characteristics and triggering events in aHUS

Paroxysmal Nocturnal Hemoglobinuria (PNH) @ASH 2022

Late breaking abstract session

Oral monotherapy with iptacopan, a proximal Complement Inhibitor of Factor B, has superior efficacy to intravenous terminal complement inhibition with standard of care eculizumab or ravulizumab

Oral session (Chair: Bruno Fattizzo & C)

- **Vemircopan** (ALXN2050) monotherapy in PNH: interim Data from a phase 2 Open label proof of concept study
- Results from the First phase 3 **crovalimab** (C5 inhibitor) Study COMMODORE 3: Efficacy and safety in complement naive patients with PNH

A Phase 3 Study to Evaluate the Efficacy and Safety of Caplacizumab Without First-line Theraeutic Plasma Exchange in Adults With Immune-mediated Thrombotic Thrombocytopenic Purpura

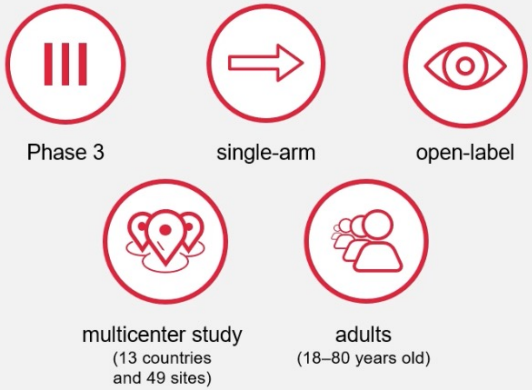
Unmet need:

While TPE is considered a mainstay of iTTP treatment, it is burdensome and associated with complications[4–6]

Although reports from real-world clinical practice suggest the efficacy of TPE-free regimens in iTTP,[7–10] the use of caplacizumal without TPE has not been evaluated in a clinical trial setting

Aim: To evaluate the efficacy and safety of caplacizumab in combination with IST without first-line TPE in adults with iTTP

MAYARI (NCT05468320) is a:



Interventions:

- All participants will begin caplacizumab and corticosteroid therapy immediately after clinical diagnosis
- Anti-CD20 antibody therapy can be initiated after confirmation of iTTP diagnosis (ADAMTS13 activity <10%)
- If, after initiation of caplacizumab therapy, baseline ADAMTS13 activity level is found to be 10%–20%, the investigator may use their clinical judgment to decide whether to continue caplacizumab. If ADAMTS13 level is found to be >20%, caplacizumab should be discontinued
- Caplacizumab treatment will be continued until sustained ADAMTS13 activity level of ≥50% at 2 consecutive visits after platelet count normalization or 12 weeks
- Participants will not receive TPE as first-line therapy
- TPE may be started after 24 hours for lack of adequate response per prespecified criteria or clinical deterioration at any time

Sriya Gunawardena et al

Statistical approach:
Approximately 61 participants will be enrolled to ensure that 55 participants with ADAMTS13 activity <10% at baseline are available for analysis of the primary endpoint. With the sample size of 55, assuming the true responder rate[a] is 70%, the lower bound of 95% CI would be 58%

Adults (18–80 years old) with a clinical diagnosis of initial or recurrent iTTP (ADAMTS13 activity <10%) if they have:

- Thrombocytopenia (platelet count <100×10^9/L)
- Microangiopathic hemolytic anemia
- French thrombotic microangiopathy score of:
  - 1 (either platelet count ≤30×10^9/L or serum creatinine <2.26 mg/dL)

OR

  - 2 (platelet count ≤30×10^9/L and serum creatinine <2.26 mg/dL)

Participants will be recruited from sites able to obtain baseline ADAMTS13 activity results within 48 hours

- Other known causes of thrombocytopenia
- Serum creatinine >2.26 mg/dL if platelet count is >30×10^9/L
- Congenital TTP (known at time of study entry)
- Severe neurological or cardiac disease
- Clinically significant active bleeding or known co-morbidities associated with high risk of bleeding (excluding thrombocytopenia)
- Inherited or acquired coagulation disorders
- Participants requiring or expected to require invasive procedures immediately
- Ongoing use of chronic anticoagulant or antiplatelet therapy

Study Outcomes

1. **Primary endpoint:** Proportion of participants achieving remission without requiring TPE during overall study period
2. Proportion of participants achieving remission during the overall study period
3. Proportion of participants requiring TPE during the on-treatment period
4. Proportion of participants achieving a clinical response during the on-treatment period
5. Time to initial platelet count response (≥150×10^9/L sustained for ≥2 days)
6. Proportion of participants with iTTP-related exacerbation or death during the on-treatment period and overall study period
7. Refractoriness[b] during the on-treatment period
8. Overall mortality during the overall study period
9. Safety and tolerability during the treatment-emergent period
10. Patient-reported clinical outcomes

Definition of remission:
Sustained clinical response[a] with either (a) no TPE and no anti-VWF therapy for ≥30 days (clinical remission) or (b) with attainment of ADAMTS13 activity level ≥50% at 2 consecutive visits (complete ADAMTS13 remission), whichever occurs first

Revised outcome definitions from the International Working Group for iTTP will be utilized[1]

This novel study will define the efficacy and safety of caplacizumab + IST without first-line TPE in adults with iTTP

This regimen would avert the risks for substantial complications associated with TPE and represents a paradigm shift in the frontline management of iTTP

Bortezomib In Relapsed/Refractory Autoimmune-mediated Thrombotic Thrombocytopenic Purpura: A Single-center Retrospective Study And Systematic Review

Nicholas C.J. Lee, MD,[1,2] Sean Yates, MD,[3] Siayareh Rambally, MD,[4] Ravi Sarode, MD,[3,4] Ibrahim F. Ibrahim, MD,[4] Yu-Min Shen, MD,[4] Sandra Hofmann, MD, PhD,[4] and Natalie R. Bavli, MD[4]

[1]Department of Internal Medicine; [2]Pediatrics; [3]Division of Transfusion Medicine and Hemostasis, Department of Pathology; [4]Division of Hematology, Department of Internal Medicine; University of Texas Southwestern, Dallas, TX

AIM:

- To report our institutional experience with bortezomib for iTTP, increasing the number of reported cases by over 25%
- Describe the first cohort of patients previously treated with caplacizumab and for ADAMTS13 relapse1-3
- Perform a systematic literature review to describe patterns of care and response to therapy

Retrospective Study

- Included all iTTP patients treated with bortezomib at University of Texas Southwestern and Parkland Health and Hospital System from 1/1/2013 to 11/1/2022
- Definitions per International Working Group Guidelines

Systematic Review

- PRISMA guideline-adherent, querying MEDLINE, Embase, and Web of Science

UTSW COHORT

- Eight patients treated with bortezomib
- Three patients with secondary iTTP
- Treatment indication for relapse (n=5) or refractory iTTP (n=3)
- All patients were treated with plasma exchange, corticosteroids, and rituximab
- Additional therapies included caplacizumab (38%) and cyclosporine (13%)
- Six patients (75%) had a response to bortezomib therapy
- Of the patients with a response to bortezomib therapy, one patient had a clinical relapse at 5 months
- One patient had a side effect (decreasing pulmonary function)

	Total (n=32)
Age, y, median (IQR)	45 (29-54)
Sex	
Male	8 (25)
Female	24 (75)
Previous TTP episodes, # (IQR)	0 (0-2)
Previous TTP therapies, # (IQR)	3.5 (3-4)
Previous TTP Therapies	
PLEX	31 (97)
Corticosteroids	32 (100)
Rituximab	31 (97)
Cyclophosphamide	6 (19)
Intravenous immunoglobulin	5 (16)
N-acetylcysteine	5 (16)
Caplacizumab	3 (9)
Vincristine	2 (6)
Mycophenolate mofetil	2 (6)
Cyclosporine	2 (6)
Splenectomy	1 (3)
Bortezomib indication	
Refractory	24 (75)
Recurrent	0 (0)
Refractory & recurrent	3 (9)
Biochemical Relapse	5 (16)
Bortezomib dose (n = 29)	
1.3mg/m^2	15 (52)
1 mg/m^2	14 (48)
Bortezomib administration, initial (n=22)	
Subcutaneous	15 (68)
Intravenous	7 (32)
Bortezomib response, initial	
Complete response	22 (69)
Partial response	1 (3)
No response	6 (19)
PLEX wean	2 (6)
Decreased inhibitor	1 (3)
Bortezomib rechallenge (n=4)	
Complete response	4 (100)
Partial response	0 (0)
No response	0 (0)
Relapse after bortezomib (n=23)	
No relapse	20 (87)
Relapse	3 (13)
Time to relapse after bortezomib, months, median (range)	7 (5-20)

189 articles screened

Patient and Disease Characteristics

- Median age of 45
- 75% female patients
- Bortezomib is generally used in an initial iTTP presentation

Pre-bortezomib therapy data

- Median of 3.5 therapies attempted prior to bortezomib administration
  - All patients except 2 received PLEX, corticosteroids, and rituximab (one was a Jehovah's witness)
- Indication most often for refractory (67%) or recurrent & refractory disease (19%)

. Overall response 78%

- Adverse events occurred in 14% of patients

CONCLUSIONS

- Bortezomib is a promising therapy in relapsed and refractory iTTP
- 85% of patients with a clinical response to bortezomib remained in remission with a median follow-up of 18 months
- The majority of bortezomib administration is for refractory cases (86%)
- In ADAMTS13 relapse, the complete response rate was 60% (3/5 in our cohort)
- Re-challenge with bortezomib and increasing the cumulative total dose may be a reasonable strategy, as all patients re-challenged had a complete response (4/4)
- Further randomized controlled trials needed to discern the utility of bortezomib in relapse and refractory iTTP

Silent Cerebral Infarction during iTTP Remission – Prevalence, Predictors and Impact on Cognition

iTTP survivors experience major adverse neurocognitive sequelae

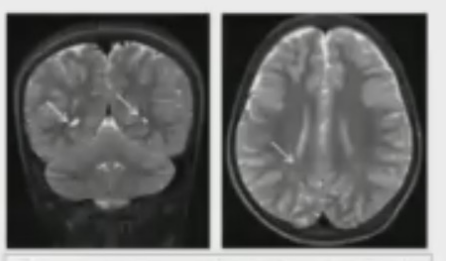
- 5-fold increased risk of stroke in clinical remission
- Persistent difficulties with memory and concentration
- Possible causes of cognitive impairment in iTTP:
  - ✓ Ischemic events during acute iTTP events
  - ✓ Associated with depression, which is common in iTTP (50-80%)
  - ✓ Silent cerebral infarction (SCI) during clinical remission

Jia Yu (S.Chaturvedi) et al, John Hopkins Medicine

Silent cerebral infarction (SCI)

SCI are ischemic lesions on brain MRI without overt neurological deficits attributable to the location of the lesion

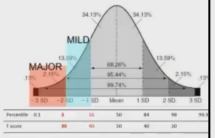
- SCI are reported in sickle cell disease and older adults (increase with age)
- In these population, SCI are associated with:
  - ✓ Cognitive impairment
  - ✓ Future stroke



NeST (**Ne**urological **S**equelae of **T**TP) Study

Cognitive testing using the NIH ToolBox Cognition Battery

NIH Toolbox Cognition battery		
CONSTRUCT	MEASURE	
Executive function	Dimensional Change Card Sort	Fluid cognition composite
Attention	Flanker Inhibitory Control Attention Test	
Episodic memory	Picture Sequence Memory Test	
Working memory	List Sorting Working Memory Test	
Processing speed	Pattern Comparison Test	
	Oral symbol Digit Test	
Immediate Recall	Auditory Verbal Learning Test	
Language	Picture Vocabulary Test	Crystallized cognition composite
	Oral Reading Recognition	



- Fully corrected T-scores (adjusted for age, sex, race, parental education)

Brain assessment of SCI

SCI defined as:

- T2 and FLAIR hyperintense infarct like lesion
- ≥ 3 mm in two dimensions
- Without any neurological anbnormally explained by locatio of the lesion

Panel of 3 neuroradiologists

- Blinded review of each MRI by 2 neuroradiologists
- Third observer served as a tie breaker in case of disagreement

2020-2022

Immune TTP
- Age > 18 years
- Clinical remission

STUDY VISIT 1
- Neuro exam (NIHSS)
- NIH ToolBox Cognitive Battery
- Brain MRI
- Beck depression inventory II (BDI-II)

STUDY VISIT 2 and 3
- Neuro exam (NIHSS)
- NIH ToolBox Cognitive Battery
- Brain MRI
- Beck depression inventory II (BDI-II)

Continued follow up in TTP registry

Baseline — Year 1 — Year 2

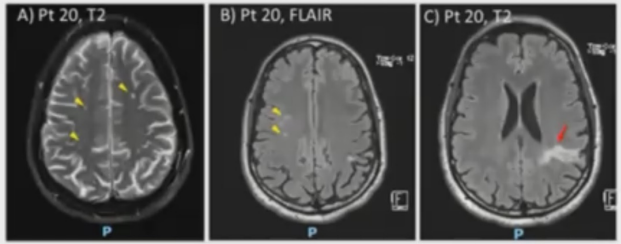
QUESTIONS (visit 1)
- What is the prevalence of SCI in iTTP?
- Is SCI associated with cognitive impairment?

QUESTIONS (visit 2 and 3)
- What is the incidence of new SCI in remission?
- Is SCI a risk factor for future stroke?

SCI is present in 50% of iTTP survivors

42 enrolled, 36 completed MRI*

SCI present in **50%**



In A and B, T2 and FLAIR imaging show hyperintense SCI lesions (yellow arrowheads). Panel C shows an old infarct on T2 sequence in the same patient 5 years prior. The SCI are new since previous imaging.

*2 excluded due to metal shrapnel or implants, 2 declined due to anxiety and claustrophobia, and another 2 could not complete the MRI due to claustrophobia

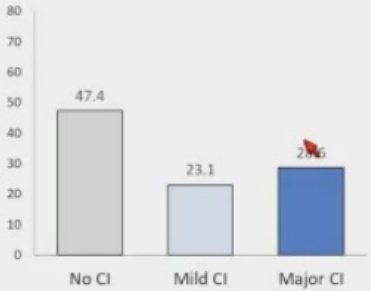
Predictors of SCI

Variable	Odds ratio	95% CI	P
Age	**1.09**	**1.01 - 1.16**	**0.021**
History of stroke	**10.69**	**1.34 - 85.43**	**0.025**
Number of iTTP episodes	1.27	0.74 - 2.17	0.380
Hypertension	0.54	0.09 - 3.36	0.510
Black race (vs. White)	18.5	0.77 - 445.61	0.072
Other race (vs. White)	70.10	0.66 - 7465.39	0.074

Logistic regression model

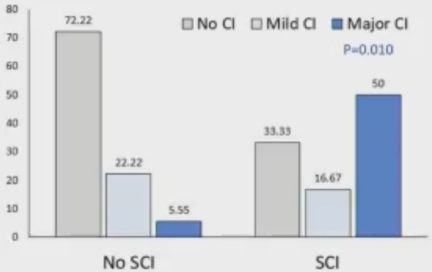
Prevalence of cognitive impairment

52.3% had CI on ≥ 1 test



Most common deficits observed		
Test		Domain
Dimensional change card sort	38.1%	Executive function
Flanker inhibitory control and attention	26.2%	Executive function, attention
Pattern comparison test	23.8%	Processing speed

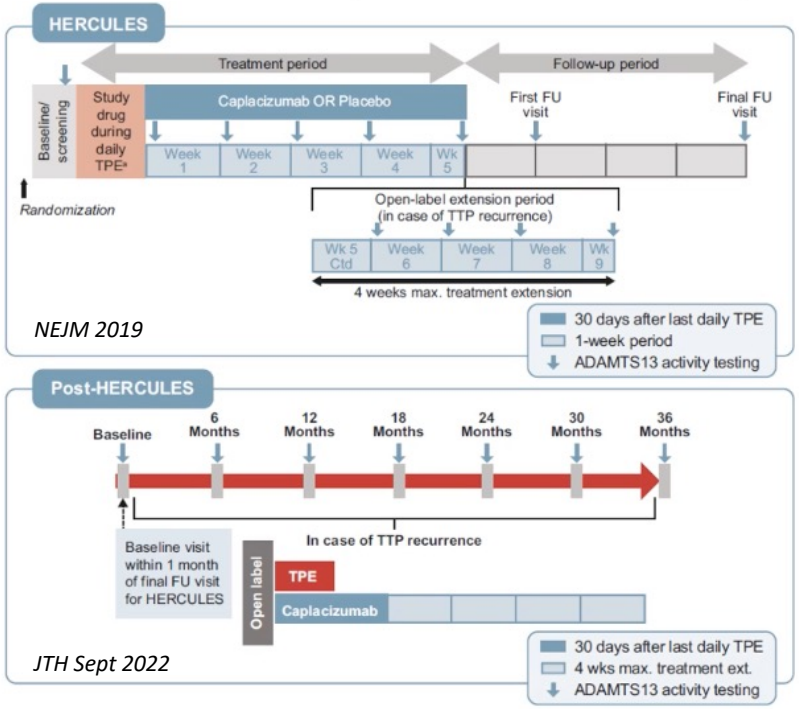
SCI is associated with cognitive impairment



Variable	OR (95% CI)	P
Any cognitive impairment		
Silent cerebral infarction	10.5 (1.45 – 76.63	0.020
History of stroke	0.49 (0.06 – 4.19)	0.523
BDI-II score	1.12 (1.01 – 1.25)	0.034
Major cognitive impairment		
Silent cerebral infarction	7.98 (1.11 – 57.27)	0.039
History of stroke	0.33 (0.04 – 2.93)	0.325
BDI-II score	1.03 (0.95 – 1.12)	0.425

The Role of ADAMTS13 Activity Levels on Disease Exacerbation or Relapse in Patients With Immune-Mediated Thrombotic Thrombocytopenic Purpura: Post Hoc Analysis of the Phase 3 HERCULES and Post-HERCULES Studies

Johanna A. Kremer Hovinga,[1,a] Javier de la Rubia,[2] Katerina Pavenski,[3] Ara Metjian,[4] Paul Knöbl,[5] Flora Peyvandi,[6,7] Spero Cataland,[8] Paul Coppo,[9] Umer Khan,[10] Laurel A. Menapace,[11] Ana Paula Marques,[12] Sriya G



Study Design

- This post hoc analysis included all patients from HERCULES who received at least 1 dose of caplacizumab or placebo (mITT population) and were followed until the end of HERCULES or post-HERCULES
- ADAMTS13 activity levels were determined at baseline, weekly during the treatment period starting with the first day after end of TPE, and twice during follow-up
- A threshold of <10% ADAMTS13 activity was not part of the inclusion criteria in HERCULES
- Risk of events, including exacerbations and relapses, was assessed according to ADAMTS13 activity at baseline or end of HERCULES study drug treatment[b]

Definitions

- iTTP events were defined based on adverse event codes of "thrombotic thrombocytopenic purpura"
- **HERCULES:** exacerbations were defined as recurrences during the double-blind treatment period post-TPE, and relapses as recurrences after the double-blind treatment period
- **Post-HERCULES:** exacerbations were defined as recurrences occurring ≤30 days after end of study treatment, and relapses occurring >30 days after end of study treatment

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; Ctd, continued; exchange; TTP, thrombotic thrombocytopenic purpura; wk, week.
[a]TPE treatment period was of variable duration. [b]Cox proportional hazard models were performed to evaluate risk of event.

FU, follow-up; iTTP, immune-mediated thrombotic thrombocytopenic purpura; mITT, modified intention-to-treat; TPE, therapeutic plasma

The objective of this study was to evaluate ADAMTS13 activity as a potential biomarker of exacerbation or relapse risk using post hoc analyses of integrated data from the HERCULES and post-HERCULES studies

Subsequent iTTP Events According to ADAMTS13 Activity at End of HERCULES Study Drug Treatment Period

ADAMTS13 level at end of HERCULES study drug treatment, pooled across treatment groups and studies[a]				
	Exacerbation		Relapse	
	Yes	No	Yes	No
Proportion of people with event				
n (%)	29 (20.7)	111 (79.3)	15 (10.7)	125 (89.3)
ADAMTS13 activity at end of treatment				
Median	5.0	60.8	2.5	51.7
(min, max)	(1.0, 77.0)	(1.0, 119.0)	(1.0, 90.4)	(1.0, 119.0)
P-value[b]	<0.0001		0.0150	
Distribution, n (%)[c]				
<10%	21 (72.4)	26 (23.4)	10 (66.7)	37 (29.6)
≥10% and <20%	1 (3.5)	5 (4.5)	0	6 (4.8)
≥20%	7 (24.1)	75 (67.6)	5 (33.3)	77 (61.6)
P-value[d]	<0.0001		0.0421	
<50%	26 (89.7)	43 (38.7)	11 (73.3)	58 (46.4)
≥50%	3 (10.3)	63 (56.8)	4 (26.7)	62 (49.6)
P-value[d]	<0.0001		0.0992	

- In the HERCULES mITT population, 140/144 patients had follow-up data after end of HERCULES study drug treatment
- Of these patients, 39 (27.9%) had events in HERCULES or post-HERCULES after end of treatment
  - Median ADAMTS13 activity was lower in those who experienced an exacerbation or relapse compared with those who did not ($P<0.05$)

- The proportion of patients with an ADAMTS13 activity <10% or <20% at end of treatment was greater among those with an exacerbation or relapse versus those without ($P<0.05$)
- The proportion of patients with an ADAMTS13 activity <50% at end of treatment was greater among those with an exacerbation versus those without ($P<0.0001$)

Regardless of the treatment received (caplacizumab or placebo), lower ADAMTS13 activity levels at end of treatment were associated with a higher risk of an event in the HERCULES and post-HERCULES studies

Trial in Progress: An Open-Label, Multi-Center Phase 2 Study Evaluating Efficacy and Safety of the MASP-2 Inhibitor Narsoplimab in Pediatric Patients with High-Risk Hematopoietic Stem Cell Transplant-Associated Thrombotic Microangiopathy (HSCT-TMA)

BACKGROUND

- HSCT-TMA (also known as TA-TMA) is a potentially life-threatening complication associated with multi-organ injury and significant morbidity and mortality[1,2]
- In the HSCT setting, endothelial injury triggers activation of the lectin pathway of complement and in turn the coagulation cascade, together leading to TMA[1]
- Narsoplimab (OMS721) inhibits MASP-2, the effector enzyme of the lectin pathway and an activator of the coagulation cascade[1,3]
- Narsoplimab was previously evaluated for safety and efficacy in adults with high-risk HSCT-TMA in an open-label pivotal trial (NCT02222545)[3]

OBJECTIVE: The purpose of this Phase 2 study is to evaluate the safety, efficacy, pharmacokinetics, pharmacodynamics, and immunogenicity of narsoplimab in high-risk pediatric-aged patients with TMA following HSCT

MASP 2: Mannan binding lectin-associated serine protease-2

Pullman W et al

METHODS: Key Inclusion and Exclusion Criteria

Key Inclusion and Exclusion Criteria

Inclusion Criteria

- Age ≥28 days to <18 years
- alloHSCT recipient (treatment of non-malignant or malignant disease)
  - All donor cell sources permitted:
    - Matched, mismatched, haploidentical
    - Related, unrelated
    - Bone marrow, peripheral blood stem cells, and umbilical cord blood
- High-risk HSCT-TMA diagnosis
- Met ≥1 HSCT-TMA high-risk criterion

Exclusion Criteria

- Prior treatments with eculizumab, ravulizumab, or defibrotide within 3 months
- STEC-HUS
- ADAMTS13 activity <10%
- Severe, uncontrolled systemic bacterial or fungal infection requiring antimicrobial therapy
- Malignant hypertension
- Abnormal liver function (ALT or AST >5× ULN)

High-risk HSCT-TMA Diagnosis Definition

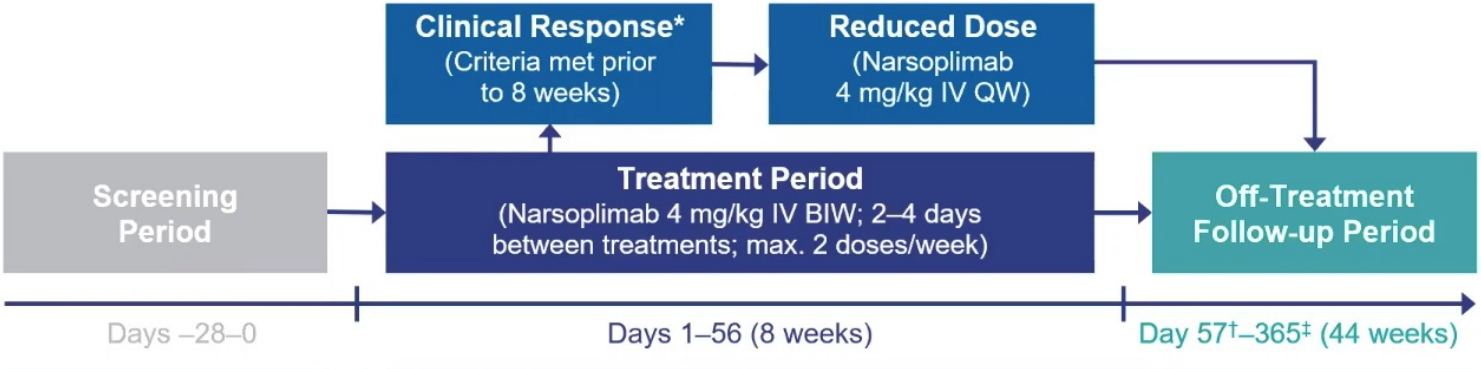
Criteria	Definition
Platelet count	<50,000/μL or a ≥50% decrease in platelet count from the highest value obtained following transplant
and at least one of the following:	
Evidence of microangiopathic hemolysis	• Presence of schistocytes (per high-power field) • Serum LDH (>ULN) • Haptoglobin (<LLN)

High-risk HSCT-TMA Criteria

Criteria	Definition
1. HSCT-TMA persistence	≥2 weeks following modification of CNI or sirolimus
or	
2. Evidence of ≥1 one of the following:	• Spot P/C >2 mg/mg • Serum creatinine >1.5× pre-TMA level • Biopsy-proven GI TMA • TMA-related neurological abnormality • Pericardial or pleural effusion* • Pulmonary hypertension* • Grade III or Grade IV GVHD† • Elevated serum C5b-9 >244 ng/mL

*Without alternative explanation; †Or at risk of Grade III or Grade IV GVHD if immunosuppression was to be modified.
alloHSCT, allogeneic HSCT; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CNI, calcineurin inhibitor; GI, gastrointestinal; GVHD, graft-versus-host disease; LDH, lactate dehydrogenase; LLN, lower limit of normal; P/C, protein/creatinine; STEC-HUS, Shiga toxin-producing *Escherichia coli* hemolytic uremic syndrome; ULN, upper limit of normal.

METHODS: Trial Design



The planned recruitment is at least 18 pediatric patients (distributed across the age range)

Primary Endpoint:
- 100-day survival from date of high-risk HSCT-TMA diagnosis

Secondary Endpoints:
- Safety
- 52-week survival
- Overall survival
- ADA response
- Clinical response rate*
- Narsoplimab PK
- Lectin pathway activity (C4d deposition)

*Clinical response is defined as improvement in laboratory TMA markers and clinical benefit; †Patients ending treatment early who agree to remain in the study will enter into follow-up; ‡Patients who withdraw from the study prior to completion, either during a treatment or a follow-up visit, will have assessments for the last follow-up visit, if possible.
ADA, anti-drug antibody; BIW, twice weekly; IV, intravenous; PK, pharmacokinetics; QW, once weekly.

METHODS: Definition of Clinical Response in Pediatric HSCT-TMA Patients

Improvement in TMA Laboratory Markers

LDH
<1.5× ULN

+

Platelet count

Baseline ≤20 × 10^9/L:
Triple baseline and absolute count >30 × 10^9/L and no platelet transfusions for 2 days

Baseline >20 × 10^9/L:
Increase by ≥50% and absolute count >75 × 10^9/L and no platelet transfusions for 2 days

and

Improvement in Clinical Status in at Least One Organ

Blood

Freedom from transfusions for at least 4 weeks

Kidney

Reduction of creatinine >40%
or
Creatinine below the upper limit of normal and reduction of creatinine >20%
or
Discontinuation of renal replacement therapy

Pulmonary

Extubation and discontinuation of ventilator support
or
Discontinuation of non-invasive mechanical ventilation

Neurologic

Improvement in reversible or stabilization of irreversible neurological conditions

GI

Improvement assessed using GI measures in the MAGIC criteria

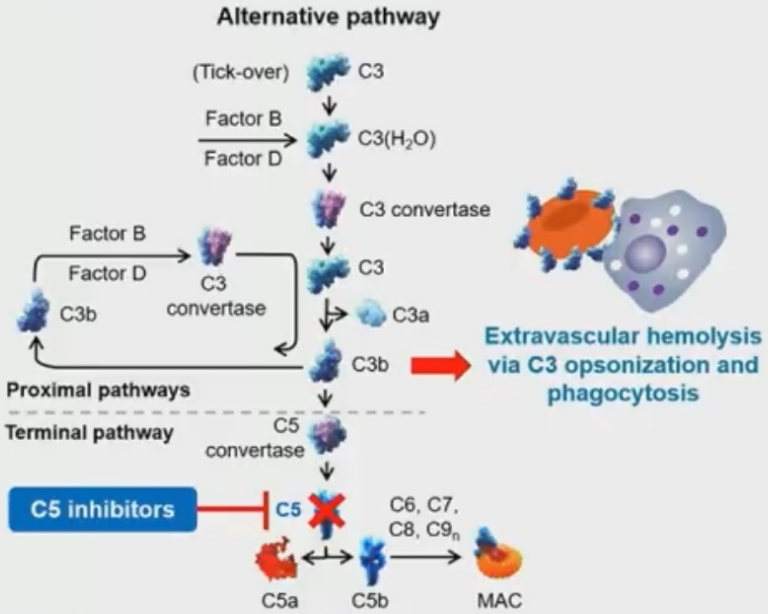
MAGIC, Mount Sinai Acute GVHD International Consortium.

CONCLUSIONS

- Following the favorable results obtained in a pivotal Phase 2 study in adults with HSCT-TMA, further evaluation of narsoplimab in pediatric patients with high-risk HSCT-TMA is warranted
- This is the first clinical trial evaluating the efficacy and safety of narsoplimab in high-risk pediatric patients with HSCT-TMA

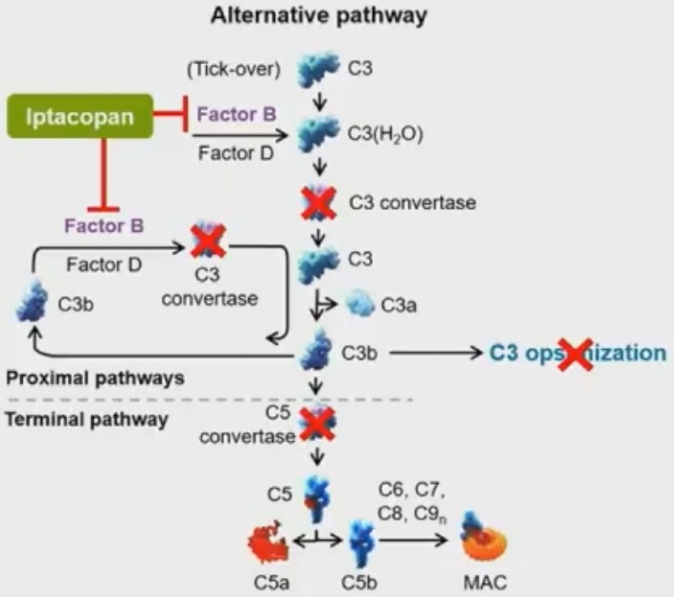
PNH

Oral monotherapy with iptacopan, a proximal complement inhibitor of factor B, has superior efficacy to intravenous terminal complement inhibition with standard of care eculizumab or ravulizumab and favorable safety in patients with paroxysmal nocturnal hemoglobinuria and residual anemia: Results from the randomized, active-comparator-controlled, open-label, multicenter, Phase III APPLY-PNH study



- PNH is a **rare, chronic hematological disorder** characterized by intravascular hemolysis, thrombophilia and bone marrow failure[1,2]
- PNH is caused by a somatic mutation in the *PIGA* gene, resulting in a lack of the GPI-anchored complement-regulating proteins **CD55** and **CD59**, leading to **intravascular hemolysis**[1,2]
- Targeting the **terminal complement pathway** at C5 with **SoC eculizumab and ravulizumab** controls intravascular hemolysis, reduces thrombosis and improves overall survival[3–9]
- **Up to two-thirds** of patients have clinically meaningful residual anemia, largely because of emerging **extravascular hemolysis**; consequently, some patients are **transfusion dependent**[1,10]

Iptacopan is a first-in-class, oral, selective factor B inhibitor that targets the complement system proximally via the alternative pathway[1]



Iptacopan binds to the **active site** of factor B, **inhibiting** the activity of **C3 convertase**[1]

- Iptacopan **controlled intra- and extravascular hemolysis** in 10 patients with a suboptimal response to eculizumab, leading to **transfusion independence** and an **improved quality of life**[2]

THE LANCET
Haematology

Addition of iptacopan, an oral factor B inhibitor, to eculizumab in patients with paroxysmal nocturnal haemoglobinuria and active haemolysis: an open-label, single-arm, phase 2, proof-of-concept trial

Antonio M Risitano, Alexander Röth, Juliette Soret, Camilla Frieri, Flore Sicre de Fontbrune, Luana Marano, Ferras Alashkar, Lina Benajiba, Serena Marotta, Izabela Rozenberg, Julie Milojevic, Peter End, Prasanna K Nidamarthy, Guido Jungo, Régis Peffault de Latour

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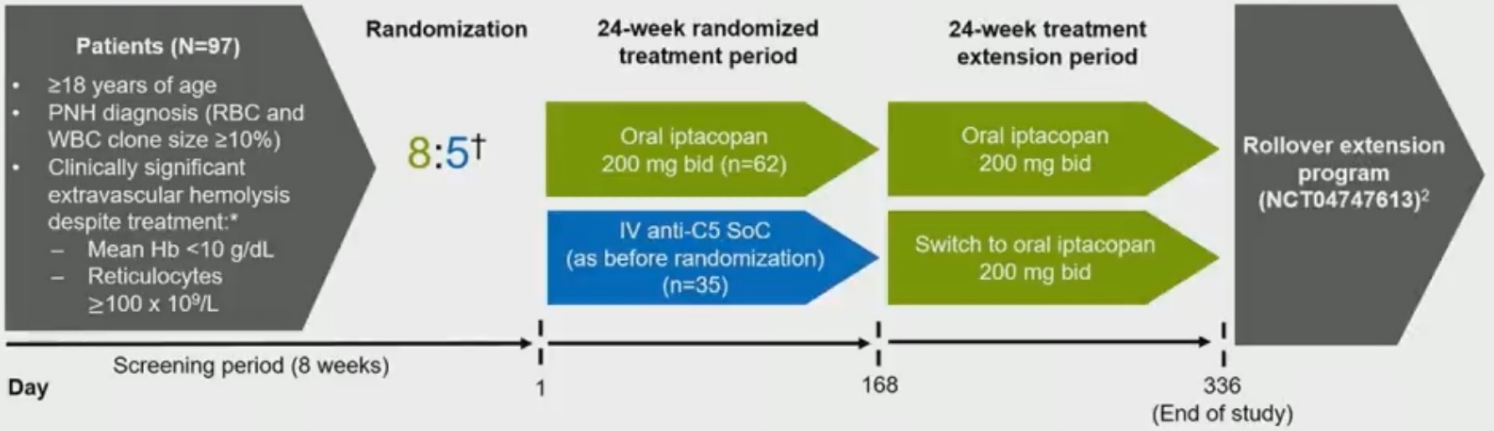
1. Schubart A *et al. Proc Natl Acad Sci USA* 2019;116:7926–31; 2. Risitano AM *et al. Lancet Haematol* 2021;8:e344–54

Oral presented at the 64th ASH Annual Meeting, held in person in New Orleans, LA, USA and virtually on 10–13 December 2022

APPLY-PNH is an open-label, randomized, multicenter, Phase III trial investigating iptacopan monotherapy in PNH patients with residual anemia despite SoC therapy (NCT04558918)[1]



*With a stable regimen of eculizumab or ravulizumab for at least 6 months preceding randomization; †Stratified by prior anti-C5 treatment and RBC transfusions in the preceding 6 months
bid, twice daily; Hb, hemoglobin; IV, intravenous; RBC, red blood cell; WBC, white blood cell

1. ClinicalTrials.gov. NCT04558918. Available at: https://clinicaltrials.gov/ct2/show/NCT04558918 (accessed November 2022);
2. ClinicalTrials.gov. NCT04747613. Available at: https://clinicaltrials.gov/ct2/show/NCT04747613 (accessed November 2022)

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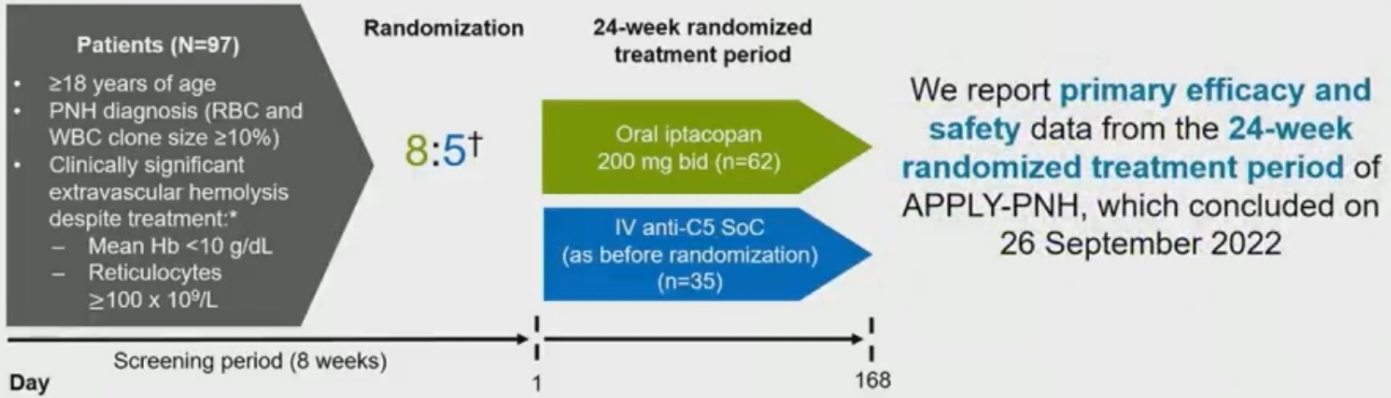

We report **primary efficacy and safety** data from the **24-week randomized treatment period** of APPLY-PNH, which concluded on 26 September 2022

*With a stable regimen of eculizumab or ravulizumab for at least 6 months preceding randomization; †Stratified by prior anti-C5 treatment and RBC transfusions in the preceding 6 months
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APPLY-PNH is a superiority trial with two primary endpoints

Primary

- Hematological response defined as an **increase from baseline in Hb of ≥2 g/dL* in the absence of RBC transfusions†**
- Hematological response defined as **Hb ≥12 g/dL* in the absence of RBC transfusions†**

Secondary

- **Transfusion avoidance†**
- **Change from baseline:***
  - Hb levels‡
  - FACIT-Fatigue scores
  - Absolute reticulocyte count
  - LDH levels
- Occurrences of **clinical breakthrough hemolysis** and **MAVEs§**
- Safety§

*Assessed between Days 126 and 168; †Between Days 14 and 168 and neither meeting the criteria for administration of an RBC transfusion nor receiving an RBC transfusion between Days 14 and 168; ‡Excluding values within 30 days of RBC transfusion; §Throughout the study
The overall study Type I error rate was controlled at the one-sided 2.5% level. All presented *P* values are two-sided and unadjusted
FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase; MAVE, major adverse vascular event
1. Bretz F *et al. Stat Med* 2009;28:586–604; 2. Bretz F *et al. Stat Med* 2011;30:1489–501

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Demographics and disease characteristics at baseline were generally balanced between arms

	Iptacopan 200 mg bid N=62	Anti-C5 SoC N=35	Overall N=97
Mean age, years (SD)	51.7 (16.9)	49.8 (16.7)	51.0 (16.8)
Female, n (%)	43 (69.4)	24 (68.6)	67 (69.1)
Time since diagnosis, years (SD)	11.9 (9.8)	13.6 (10.9)	12.5 (10.2)
Anti-C5 SoC			
Eculizumab,* n (%)	40 (64.5)	23 (65.7)	63 (64.9)
Ravulizumab,* n (%)	22 (35.5)	12 (34.3)	34 (35.1)
Mean duration, years (SD)	3.8 (3.5)	4.2 (3.9)	4.0 (3.6)
Received RBC transfusions,* n (%)	35 (56.5)	21 (60.0)	56 (57.7)
Mean baseline Hb, g/dL (SD) [range]	8.9 (0.7) [6.8–10.0]	8.9 (0.9) [6.2–9.9]	8.9 (0.8) [6.2–10.0]
Mean baseline LDH, U/L (SD) [range]	269.1 (70.1) [150–539]	272.7 (84.8) [133–562]	270.4 (75.3) [133–562]
Baseline LDH >1.5 x ULN, n (%)	4 (6.5)	3 (8.6)	7 (7.2)
Mean baseline absolute reticulocyte count, 10^9/L (SD) [range]	193.2 (83.6) [51–563]	190.6 (80.9) [90–412]	192.3 (82.3) [51–563]

*In the 6 months prior to randomization
SD, standard deviation; ULN, upper limit of normal

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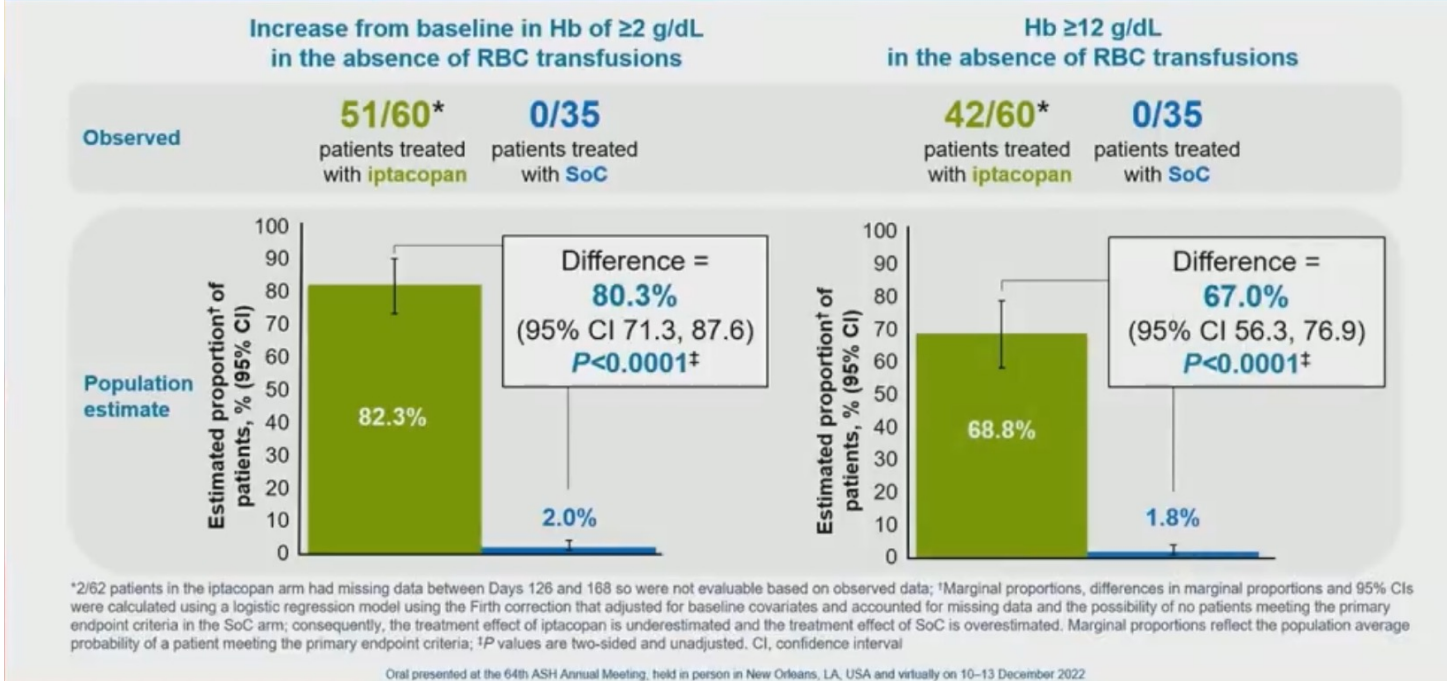
Iptacopan monotherapy was superior to SoC for both primary endpoints



*2/62 patients in the iptacopan arm had missing data between Days 126 and 168 so were not evaluable based on observed data; †Marginal proportions, differences in marginal proportions and 95% CIs were calculated using a logistic regression model using the Firth correction that adjusted for baseline covariates and accounted for missing data and the possibility of no patients meeting the primary endpoint criteria in the SoC arm; consequently, the treatment effect of iptacopan is underestimated and the treatment effect of SoC is overestimated. Marginal proportions reflect the population average probability of a patient meeting the primary endpoint criteria; ‡*P* values are two-sided and unadjusted. CI, confidence interval

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Iptacopan monotherapy was superior to SoC for transfusion avoidance

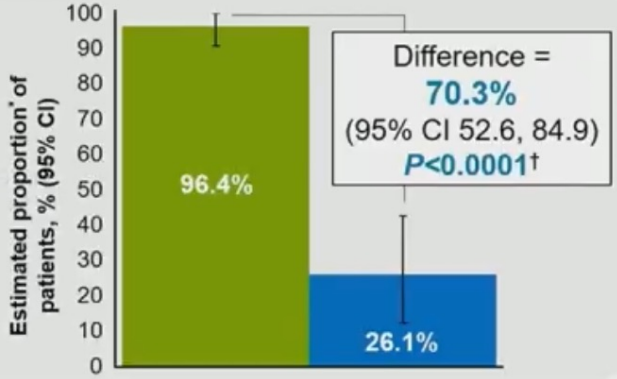
Transfusion avoidance

Observed

60/62 patients treated with **iptacopan**

14/35 patients treated with **SoC**

Population estimate



A ***post hoc* sensitivity analysis** using a different approach for handling missing data confirmed the significance of the pre-specified analysis:

- **96.7%** (95% CI 91.3, 100.0)
- **38.9%** (95% CI 23.1, 55.8)
- Difference = **57.8%** (95% CI 39.8, 74.2) ***P*<0.0001†**

*Marginal proportions, differences in marginal proportions and 95% CIs were calculated using a logistic regression model that adjusted for baseline covariates and accounted for missing data. Marginal proportions reflect the population average probability of a patient meeting the endpoint criteria; †*P* values are two-sided and unadjusted

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Secondary efficacy end points and safety

Iptacopan monotherapy was **superior** to SoC **at reducing ARC** from baseline, demonstrating **control of extravascular hemolysis**

Adjusted mean difference in change from baseline* in **ARC**:

–116.26 x 10^9/L

(95% CI –132.17, –100.36)

***P*<0.0001**[†,‡]

Iptacopan monotherapy **maintained LDH levels** upon switching from SoC, indicating **control of intravascular hemolysis**

Adjusted mean ratio to baseline* in log-transformed **LDH level**:

0.96 [95% CI 0.90, 1.03] versus **0.98** [0.89, 1.07]

(not significantly different[§])

Iptacopan monotherapy was **superior** to SoC for annualized rate of **breakthrough hemolysis**[¶]

Patients with at least one event:[‡]

2/62 versus **6/35**

Annualized rate ratio = **0.10**
(95% CI 0.02, 0.61)

***P*=0.0118**[†,§]

Safety

- Any TEAE: **82.3%** versus **80.3%**
- Headache (**16.1%** vs **2.9%**) and diarrhea (**14.5%** vs **5.7%**) were more commonly reported with iptacopan
- COVID-19 (**8.1%** vs **25.7%**) and breakthrough hemolysis (**3.2%** vs **17.1%**) were more commonly reported with SoC
- Serious TEAEs: **9.7%** versus **13.4%**
- No serious infections caused by encapsulated bacteria
- No patients discontinued study treatment because of TEAEs
- No deaths

Only **one MAVE** in the study

- **Transient ischemic attack** in the iptacopan arm
- Considered **unrelated to iptacopan**
- Patient had concomitant **sick sinus syndrome** and is **continuing to receive iptacopan**

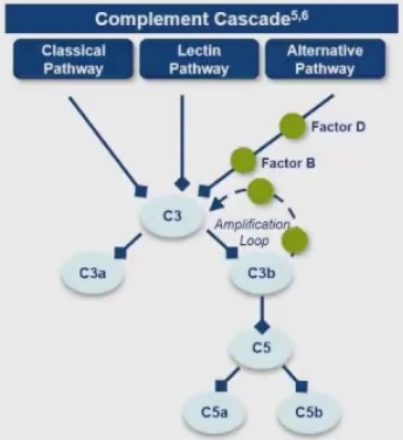
Vemircopan (ALXN2050) Monotherapy in Paroxysmal Nocturnal Hemoglobinuria: Interim Data From a Phase 2 Open-Label Proof-of-Concept Study

Browett P,Kulasekararaj AG, Notaro R, Ogawa M, Risitano A, Yu J, Lee JW

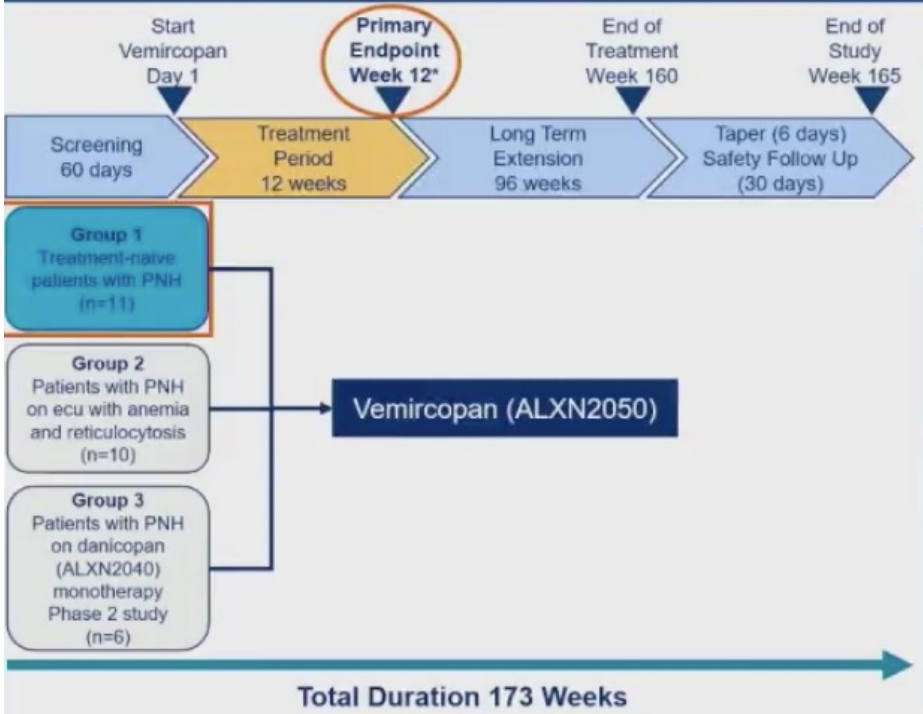
- **Second-in-class oral Factor D inhibitor, vemircopan (ALXN2050), has the same mechanism of action as danicopan**
- **Vemircopan demonstrates increased potency and binding affinity for Factor D and is being developed as monotherapy for PNH**
  - Vemircopan achieves rapid, complete, and sustained AP inhibition with BID oral administration[1]

BACKGROUND
ROLE OF FACTOR D

- **Factor D inhibitors block the complement AP[1] and may inhibit IVH while preventing EVH**
- **Factor D is an attractive target with lower plasma concentration compared to C3 and Factor B[2]**
  - The oral factor D inhibitor danicopan (ALXN2040) showed efficacy as an add-on treatment to the C5 inhibitor eculizumab[3]
  - There was unfavorable PK/PD blockade of FD in some patients when treated with danicopan as a monotherapy[4]



PHASE 2 STUDY DESIGN (NCT04170023)



Patient Population

- **PNH patients ≥18 years**
- **Group 1 (naive):**
  - Hgb <10.5 g/dL
  - ARC ≥100 x 10^9/L
  - LDH ≥1.5 x ULN

Dosing

- **Vemircopan 120 mg BID**
- **Dose can be escalated to 180 mg BID if:**
  - Hgb has not increased ≥1 g/dL by Week 4 relative to baseline or
  - Patient received blood transfusion or
  - LDH >1.5 x ULN by Day 14 in 2 consecutive assessments

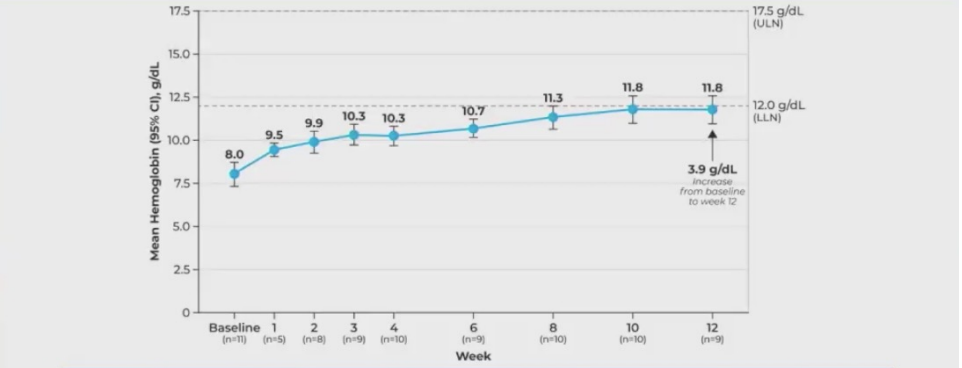
Efficacy Measures

- **Primary: Change from baseline in Hgb at week 12**
- **Key secondary endpoints**
  - Transfusion avoidance
  - Change from baseline in LDH and ARC
  - Change from baseline in FACIT-Fatigue

*12-week data based on a data cutoff of 30 April 2022.
ARC, absolute reticulocyte count; **BID**, twice daily; **ecu**, eculizumab; **FACIT-Fatigue,** Functional Assessment of Chronic Illness Therapy – Fatigue; **Hgb**, hemoglobin; **LDH**, lactate dehydrogenase; **PNH,** paroxysmal nocturnal hemoglobinuria; **ULN**, upper limit of normal.

N= 11

PRIMARY ENDPOINT: VEMIRCOPAN TREATMENT RESULTED IN AN INCREASE IN MEAN HEMOGLOBIN FROM BASELINE TO WEEK 12



During the 12 weeks of treatment, 8 of the 9 participants (89%) avoided blood transfusion*
In weeks 2–26, all patients avoided blood transfusion

Change from baseline is calculated in the same number of patients at week 12.
*1 patient taking a 120-mg dose received blood transfusion on day 2 due to low hemoglobin of 5.1 g/dL.
LLN, lower limit of normal; **ULN**, upper limit of normal.

Data cutoff date: April 30, 2022

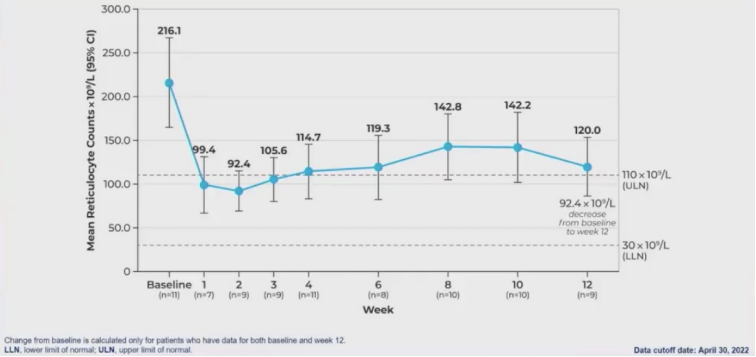
VEMIRCOPAN TREATMENT LED TO DECREASE IN MEAN LDH FROM BASELINE TO WEEK 12

LDH reduction maintained over 12 weeks follow-up, indicating rapid and sustained control of IVH

Change from baseline is calculated only for patients who have data for both baseline and week 12.
IVH, intravascular hemolysis; **LDH**, lactate dehydrogenase; **ULN**, upper limit of normal.

Data cutoff date: April 30, 2022

VEMIRCOPAN TREATMENT LED TO DECREASE IN MEAN RETICULOCYTE COUNT FROM BASELINE TO WEEK 12



Change from baseline is calculated only for patients who have data for both baseline and week 12.
LLN, lower limit of normal; **ULN**, upper limit of normal.

Data cutoff date: April 30, 2022

In this interim analysis of treatment-naive participants with PNH, vemircopan monotherapy controlled IVH (demonstrated by reduction in LDH to <1.5xULN)

Vemircopan monotherapy prevented clinically significant EVH (demonstrated by 3.9 g/dL increase in Hgb level and ARC reduction) in the treatment-naive participants

Participants were less fatigued, as reflected by an improvement of 13.3 in the FACIT-Fatigue score

Vemircopan was well tolerated with no new safety signals identified during the 12-week evaluation period

CONCLUSIONI

- TMA:
  - In studio un nuovo paradigma di trattamento della fase acuta di TTP almeno in pazienti con presentazione meno grave
  - Maggiore attenzione verso i pazienti in remissione, per studiare e limitare gli esiti a distanza, per identificare i pazienti ad alto rischio di relapse e trattare più efficacemente i refrattari/recidivati
  - Nuova potenziale terapia nelle HSCT-TMA

- EPN:
  - nuove molecole per nuovi target della cascata del complemento per ottimizzare il controllo dell'emolisi intra ed extravascolare

GRAZIE PER
L’ATTENZIONE

“There is always light behind the clouds”