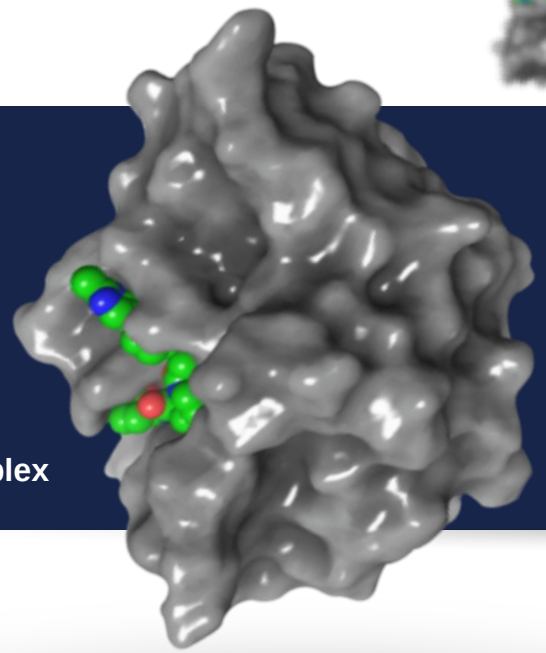

ACH-4471:
Factor D Complex

Danicopan (ACH-4471) in Untreated Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH)

Phase 2, Open-label, Proof of Concept Study of the Oral, Small Molecule Factor D Inhibitor

Abstract: S864
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Disclosures

- **Advisory Board**
  - Merck, Janssen, Roche, AbbVie
- **Associate Editor**
  - Internal Medicine Journal
- **Research Funding to Auckland City Hospital**
  - Roche, Beigene, Amgen

This trial is sponsored by Achillion Pharmaceuticals Inc. and includes an investigational medication.

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Paroxysmal Nocturnal Hemoglobinuria (PNH)

Dysregulation of the Alternative Pathway

Rare, acquired, blood disorder

- Reported prevalence approximately **16 per million people**[1]

Red blood cells lacking complement regulatory proteins CD55 and CD59, leads to intra- and extra-vascular hemolysis[2]

Disease Manifestations

- Hemolytic anemia
- Hemoglobinuria
- Fatigue
- Thrombosis
- Smooth muscle dysfunction
  - Abdominal pain
  - Dysphagia
  - Erectile dysfunction
- Dyspnea
- Chronic kidney disease
- Pulmonary hypertension

[1]Szer and Hill et al, *Clin Hematol Oncol* 2012. [2]Brodsky et al, *Blood* 2014

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Rationale for pursuing additional mechanisms of action beyond C5 inhibition for treating PNH

- ✓ **PNH, an Alternative Pathway (AP) mediated disease**[1]
  - A selective therapy that allows the Classical (CP) and Lectin Pathways (LP) to remain intact:
    - Allows for bactericidal killing of encapsulated organisms in the presence of adequate titers[2,3]
- ✓ **A mechanism controlling both intravascular and extravascular hemolysis**[4]
  - A substantial number of patients not achieving optimal response to C5 inhibition is likely due to extravascular hemolysis [5,6,7]
- ✓ **Options for patients**
  - Need for a non-injectable therapy

[1] Parker CJ. *Hematology*. 2008:93-103.
[2] Granoff , Kim H, Topaz N, et al. Haematol.2018.209692; Doi:10.3324/haematol.2018.209692.
[3] Konar M an Granoff D. Blood. 2017; doi: https://doi.org/10.1182/blood-2017-05-781450
[4] Arason GJ, Jorgensen GH, Ludviksson BR. Scand J Immunol. 2010 May;71(5):317-28.
[5] McKinley et al, ASH Dec 2017. Abst. 3471.
[6] Hillmen et al. *Br J Haematol.* 2013; 162: 62–73.
[7] Loschi et al. *Am J Hematol*. 2016; 91:366–370.

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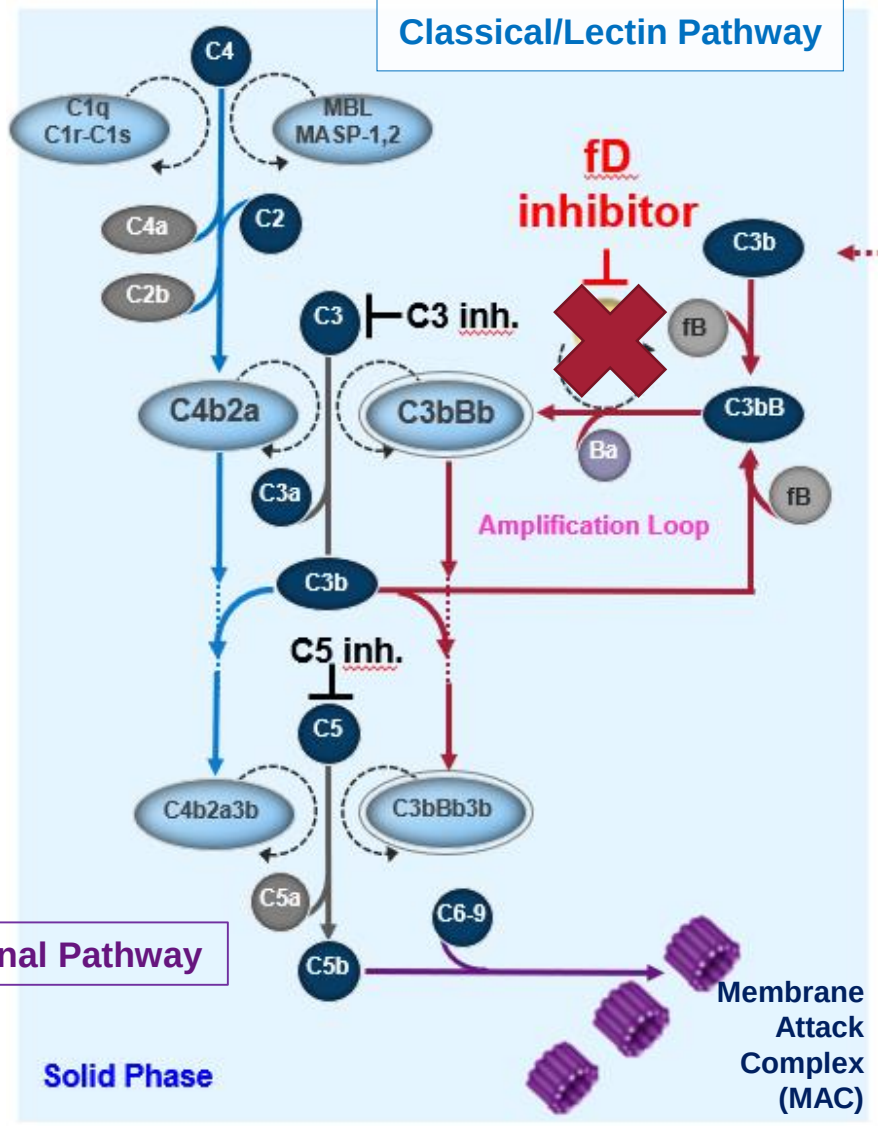
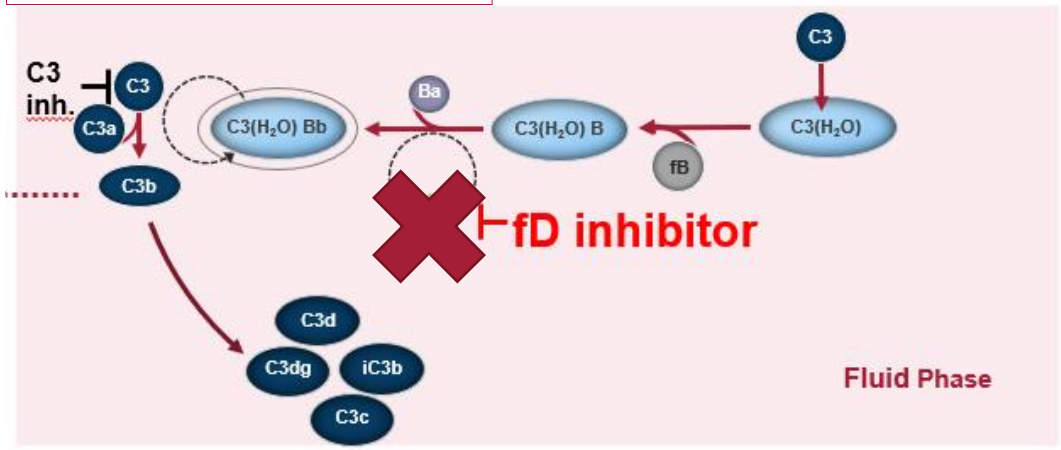
Factor D (fD): Mechanistic Rationale
A Critical Point within the Alternative Pathway





- **fD: rate-limiting enzyme/critical control point of the AP with an extremely low plasma concentration (~2 µg/mL)** [1, 2]
- **AP inhibition blocks the amplification loop: inhibiting up to 80% of the downstream complement cascade**[1]
- **Dysregulated AP involved in the pathogenesis of multiple disorders**[3]

Target Factor D (fD)

- **Danicopan fD inhibitor: small molecule with oral bioavailability**

[1]Harboe M, Ulvund G, Vien K et al. The quantitative role of alternative pathway amplification in classical pathway induced terminal complement activation. Clin Exp Immunol. 2004;138:439-446.
[2]Konar M an Granoff D. Eculizumab blocks vaccine-induced opsonophagocytic killing of meningococci by whole blood from immunized adults. Blood. 2017; doi: https://doi.org/10.1182/blood-2017-05-781450
[3]Thurman JM, Holers VM..J Immunol. 2006 Feb 1;176(3):1305-10

Danicopan: Study in Untreated PNH Patients

Study Design: Phase 2, Open-label, Multi-Center, Multi-Dose

OBJECTIVES

1° Reduction in LDH from baseline at Day 28

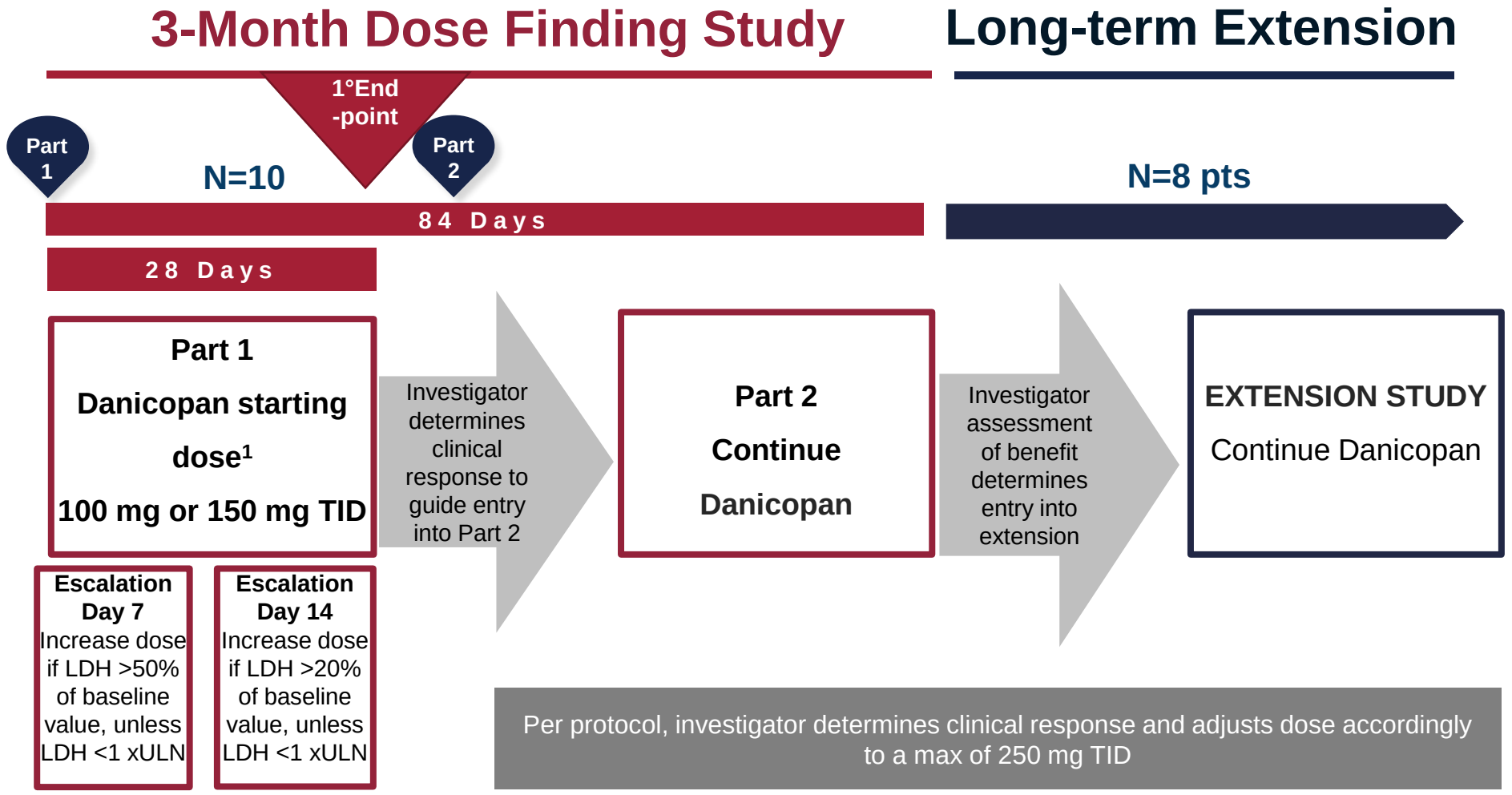
2° Improvements in Hgb and Safety

KEY INCLUSION CRITERIA

- Patients ≥ 18 y/o
- Anemia (Hgb <12 g/dL)
- LDH >1.5X ULN
- PNH clone size > 10% (Type III RBCs and/or granulocytes)

KEY EXCLUSION CRITERIA

- History of organ/stem cell/marrow transplant
- Eculizumab <75 days before study



Hgb: hemoglobin, LDH: lactose dehydrogenase, ULN: upper limit of normal, RBC: red blood cell, TID: three times daily

[1]Per protocol, the starting dose was increased to 150 mg after the enrollment of the first 2 patients

Danicopan: Study in Untreated PNH Patients
Patient Enrollment/Disposition

Countries:
Italy
New Zealand
South Korea
United Kingdom

11 screened

1 screen failure due to elevated LFTs and creatinine

10 dosed

8 completed study

8 entered long term extension

2 discontinued study

1- withdrew due to personal reasons not related to safety (Day 40)

1- withdrew due to serious adverse event (Day 51)

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Danicopan: Study in Untreated PNH Patients Baseline Demographics

Sex, n (%)	**N=10**
Female	5 (50)
Male	5 (50)
Race, n (%)	**N= 10**
White	7 (70)
Asian	1 (10)
South Asian Indian	1 (1)
Native Hawaiian/Pacific Islander	1 (1)
Age, years	**N=10**
Mean	35.9
Range	17[1]-63

[1] Patient considered adult at 17 in country of enrollment

Danicopan: Study in Untreated PNH Patients Baseline Disease Characteristics

Disease history	**N=10**	
Aplastic Anemia and PNH	2	
PNH	8	
PNH duration, years	**N=10**	
Mean	5.7	
Range	3 months-14 years	
LDH (xULN)	**N= 10**	
Mean	5.67	
Range	1.63-8.55	
Hemoglobin (mg/dL)	**N=10**	
Mean	9.8	
Range	6.9-12.0	
RBC transfusions in 52 weeks prior to screening	**N=4**	
	Instances	**Units**
Total	21	38
RBC transfusions in 12 weeks prior to screening	**N=2**	
	Instances	**Units**
Total	6	12

Danicopan: Study in Untreated PNH Patients Dosing

Protocol Starting Dose Danicopan N=10	Maximum Dose Achieved in Study N=10	Current Dose in Extension Study N=8
100 mg TID, n=2 →	175 mg TID, n=2 →	200 mg TID, n=1 250 mg TID, n=1
150 mg TID, n=8 →	150 mg TID, n=2 175 mg TID, n=2 200 mg TID, n=4 →	150 mg TID, n=2 175 mg TID, n=2 200 mg TID, n=2

Per protocol, the starting dose was increased to 150 mg after the enrollment of the first 2 patients

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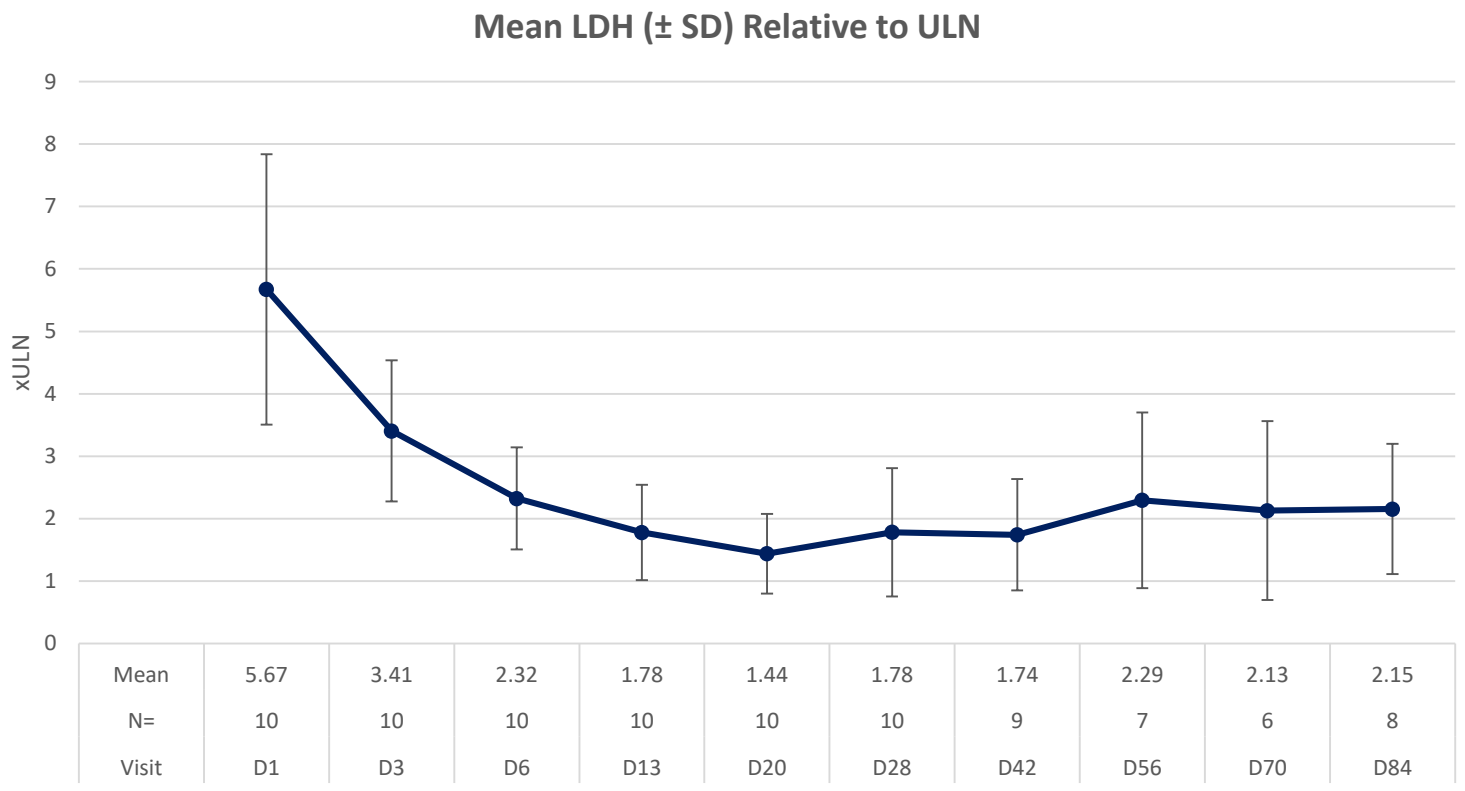
Danicopan: Study in Untreated PNH Patients
LDH Reduction Over Time



Mean	5.67	3.41	2.32	1.78	1.44	1.78	1.74	2.29	2.13	2.15
N=	10	10	10	10	10	10	9	7	6	8
Visit	D1	D3	D6	D13	D20	D28	D42	D56	D70	D84

Note: one sample at Day 56 and two samples at Day 70 were not obtained

Primary Endpoint: Change in LDH compared to baseline at day 28

Baseline: mean LDH= 5.7x ULN

Day 28: mean LDH= 1.8x ULN

Day 84: mean LDH= 2.2x ULN

Note: Baseline for n=8 who completed the study was 5.6

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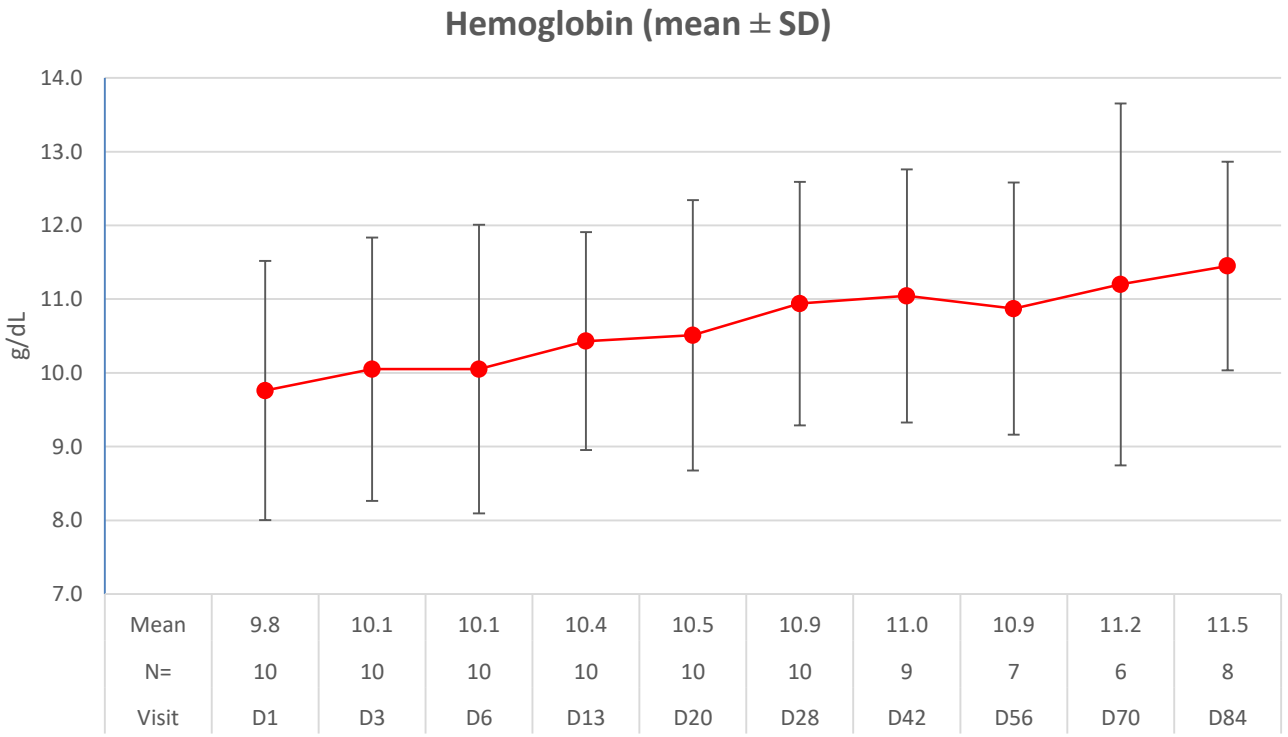
Danicopan: Study in Untreated PNH Patients
Rise in Hgb at Day 28 and through Day 84



Note: one sample at Day 56 and two samples at Day 70 were not obtained

Baseline: mean 9.8 g/dL

Day 28: mean Hgb increased by 1.1 g/dL

Day 84: mean Hgb increased by 1.7 g/dL

Note: Baseline for n=8 who completed the study was 9.7. There was a mean 1.8 g/dL increase in Hgb in these 8 patients.

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Danicopan: Study in Untreated PNH Patients Additional Parameters of Interest

Lab Parameters	Baseline N=10 Mean (Range)	Day 28 N=10 Mean (Range)	Day 84 N=8 Mean (Range)
Reticulocytes (10^9/L)	154 (45-249)	70 (38-109)	81 (45-130)
Total Bilirubin (mg/dL)	1.31 (0.41 – 2.40)	0.63 (0.23- 1.04)	0.59 (0.41-1.05)
PNH Clone (Type III erythrocytes) (%)	32 (11-78)	44 (31-82)	56 (36-92)
Quality of Life Assessment			
FACIT-Fatigue[1]	34 (20-49)	43 (23-52)	47 (31-52)

[1]Derived scores are based on the FACIT Fatigue Scale V4. Score range 0-52. A score of less than 30 indicates severe fatigue. The higher the score, the better the quality of life.

Transfusions

RBC transfusions in 12 weeks prior to screening	N=2	
	Instances	Units
Total	6	12

RBC transfusions during trial	N=2	
	Instances	Units
Total	4	9

Transfusions During the Trial

- 3 of the 4 instances (7 units total) occurred in one patient with aplastic anemia who had continued needs for transfusions during the study
- 1 of the 4 instances (2 units total) occurred in separate patient who was transfused during breakthrough hemolysis in the setting of a viral infection

Danicopan: Study in Untreated PNH Patients
Treatment Emergent Adverse Events

Treatment Emergent Adverse Events (TEAE), N=10	
Number of Patients Reporting a TEAE	9
Number of Total Reported TEAEs	33
Most Commonly Reported TEAEs by MedDRA Preferred Term [1,2]	
Headache	4
Upper Respiratory Tract Infection	4
Back Pain	2
Hemolysis	2
Hemoglobinuria	2

[1]Reported by greater than 10% of patients.
[2]MedDRA- Medical Dictionary for Regulatory Activities- standardized international medical terminology

- 91% of events were mild/moderate in severity
- 79% of events were determined to be unrelated to study drug
- One patient experienced a serious adverse event that consisted of the following: elevated ALT (G3), elevated AST (G4), and breakthrough hemolysis (G3). Patient discontinued study drug and event resolved. Event was considered possibly related to study drug.

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Danicopan: Study in Untreated PNH Patients Summary

- Proof of concept in PNH has been demonstrated with Danicopan (ACH-4471) a novel, oral, small molecule inhibitor of fD
- Danicopan monotherapy resulted in meaningful reductions in LDH, increases in hemoglobin and quality of life, as shown by the FACIT Fatigue scores
- Inhibiting fD was able to prevent MAC-mediated intravascular hemolysis in the absence of terminal pathway blockade
- Extension study is ongoing; two patients treated as long as 2 years
- Further efficacy is expected with next-generation, oral fD inhibitor (ACH-5228)
  - ~ 3x potency vs. danicopan
  - Twice daily administration allows for maintenance of >90% AP inhibition

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Danicopan: Study in Untreated PNH Patients Thank You

Thank you to the participants, the sites and the following investigators for their contributions:

Presenter/Investigator

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Investigators

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  - Azienda Ospedaliera Universitaria Careggi; Instituto per lo Studio, la Prevenzione e la Rete Oncologica, Firenze, Italy
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  - Universita Federico II di Napoli, Napoli, Italy

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