Novartis Investor Relations

Iptacopan ASH Update

Investor Presentation
December 13, 2022

NOVARTIS | Reimagining Medicine

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Participants

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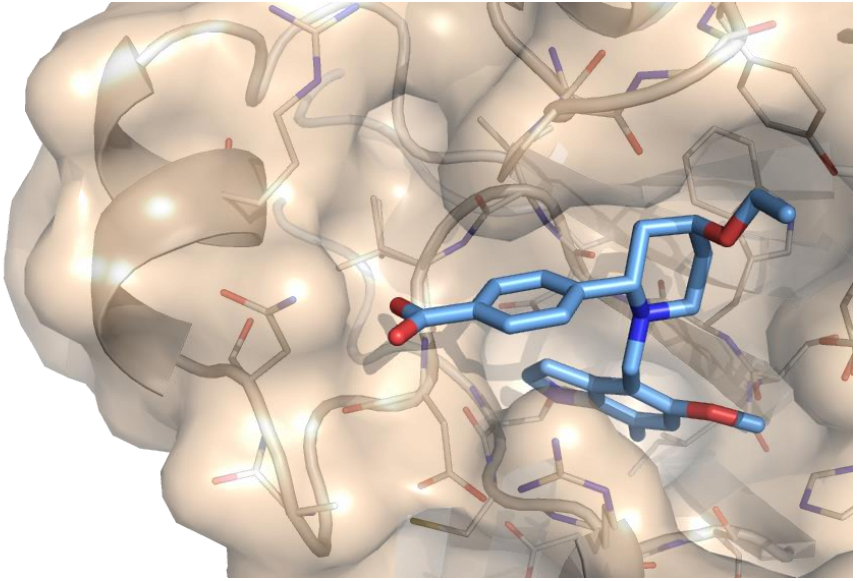
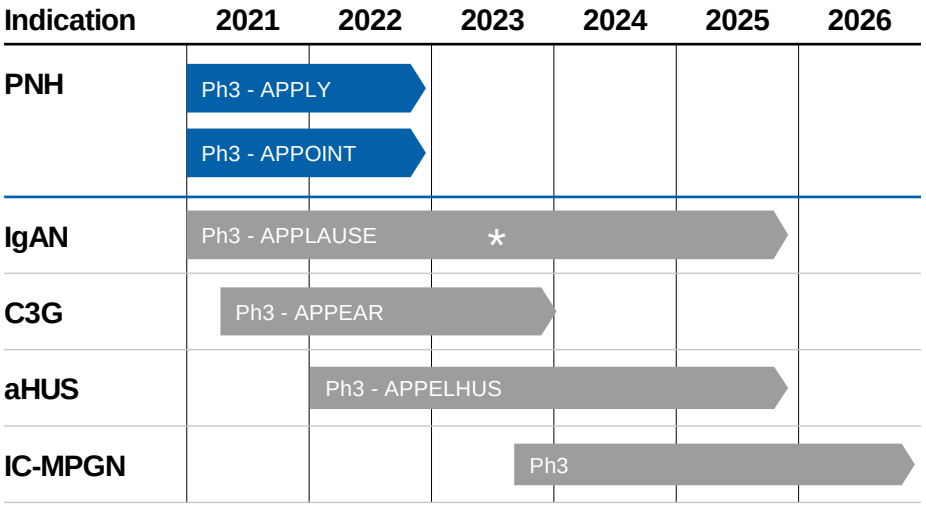
Iptacopan is a first-in-class, oral, selective factor B inhibitor of the alternative complement pathway

- Dysregulation of the complement pathway is associated with a range of rare hematologic and renal diseases
- As a selective factor B inhibitor, iptacopan targets the complement system proximally via the alternative pathway, leaving classical and lectin pathway signaling intact
- Discovered in-house at NIBR



Opportunity to redefine care in multiple complement-driven conditions



Phase 3 studies initiated or planned; additional indications are being explored

Market potential

Indication	US prevalence thousands
Hematology	
PNH	<10
Nephrology	
IgAN	~46-55[1]
C3G	<10
aHUS	<10
IC-MPGN	<10

PNH = paroxysmal nocturnal hemoglobinuria IgAN = IgA nephropathy C3G = C3 glomerulopathy aHUS = atypical hemolytic uremic syndrome IC-MPGN = immune complex membranoproliferative glomerulonephritis
* 9 months readout may support US submission for accelerated approval 1. Estimated number of patients at high risk of progression with proteinuria > 1g/day (~25-30%)

Two positive Ph3 studies in PNH are the first pivotal readouts for iptacopan

Study	APPLY-PNH ☑	APPOINT-PNH ☑
Patient type	PNH patients with **residual anemia despite anti-C5**	PNH patients **naive to complement inhibitor therapy**
Intervention	Iptacopan vs. anti-C5 antibody	Iptacopan, single-arm study

Significant unmet need remains in PNH despite current standard of care anti-C5 therapy

PNH prevalence 10-20 cases/million = ~6k patients in the US[1]

63%

of patients treated with a terminal complement inhibitor showed signs of ongoing **hemolysis**[2]

~1/3

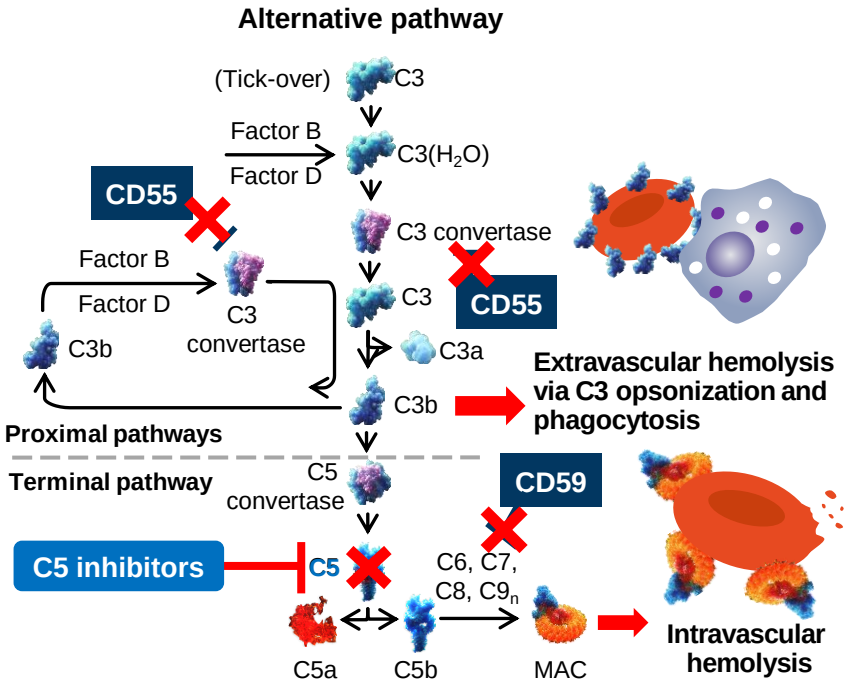
of patients reported having ≥1 RBC **transfusion** despite treatment with terminal complement inhibitors[3,4]

>75%

of patients treated with terminal complement inhibitors reported **fatigue** symptoms[3]

1. Cançado RD, 2021 and Jalbert JJ, 2019, Mon Pere N, 2018. 2. Risitano AM et al. Blood. 2009;113(17):4094-4100. 3. Dingli D et al. Ann Hematol. 2022;101(2):251-263.
4. Kulasekararaj AG et al. Eur J Haematol. 2022;109(3):205-214. doi:10.1111/ejh.13783.

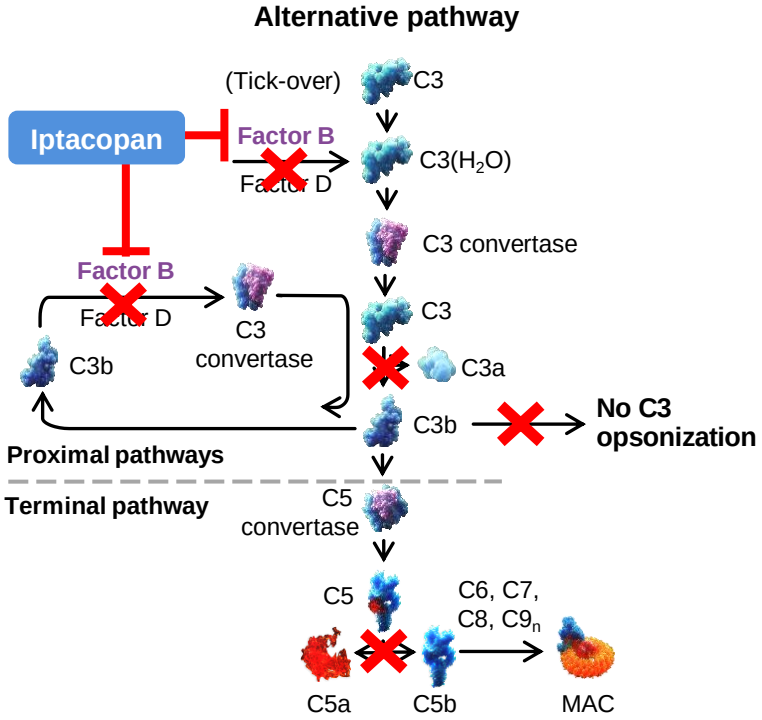
Complement regulation in PNH is impaired[1,2]



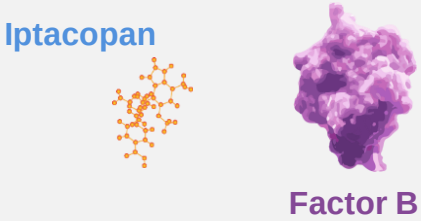
- PNH is a **rare, chronic hematological disorder** characterized by intravascular hemolysis (IVH), thrombophilia and bone marrow failure[1,2]
- Caused by an acquired mutation in hematopoietic stem cells, which results in a lack of complement-regulatory proteins, leading to IVH
- Targeting the **terminal complement pathway** at C5 can address IVH, reduce thrombosis and improve overall survival[3–9]
- However, **up to 2/3** of patients have clinically meaningful residual anemia, largely because of emerging **extravascular hemolysis**[1,10]

C = complement component; CD = cluster of differentiation; GPI = glycosylphosphatidylinositol; MAC = membrane attack complex; PNH = paroxysmal nocturnal hemoglobinuria; SoC = standard of care.
1. Risitano AM et al. Front Immunol 2019;10:1157. 2. Risitano AM, Peffault de Latour R. Br J Haematol 2022;196:288–303. 3. Hillmen P et al. N Engl J Med 2006;355:1233–43. 4. Kelly RJ et al. Blood 2011;117:6786–92. 5. Brodsky RA et al. Blood 2008;111:1840–7. 6. Hillmen P et al. Blood 2007;110:4123–8. 7. Loschi M et al. Am J Hematol 2016; 91:266–70. 8. Kulasekararaj AG et al. Blood 2019;133:540–9. 9. Lee JW et al. Blood 2019;133:530–9. 10. Risitano AM et al. Blood 2009;113:4094–100

Iptacopan, a first-in-class, oral, selective factor B inhibitor, 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 sub-optimal response to eculizumab, leading to **transfusion independence** and an **improved quality of life**[2]

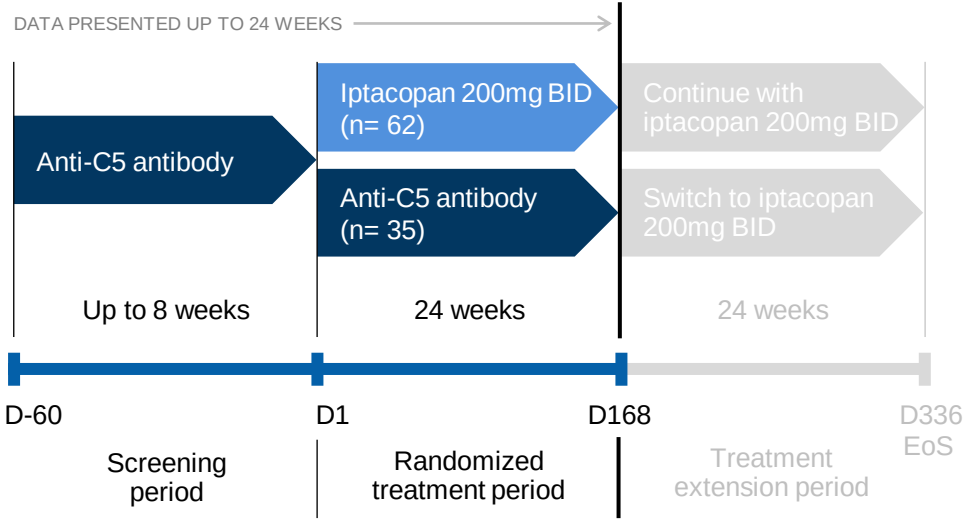
THE LANCET Haematology

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

Material from The Lancet Haematology is used with permission. 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.

APPLY-PNH is a randomized Ph3 trial investigating iptacopan monotherapy in PNH patients with residual anemia despite SoC

Study design



Population (n = 97)

Adult PNH patients with residual anemia (Hb < 10g/dL) on a stable regimen of anti-C5 therapy 6 months prior to randomization

Primary endpoints

- ☑ Superiority for proportion of patients achieving increase in Hb ≥ 2g/dL from baseline in the absence of RBC transfusion
- ☑ Superiority for proportion of patients achieving Hb ≥ 12g/dL in the absence of RBC transfusion

PNH = Paroxysmal Nocturnal Hemoglobinuria Hb = Hemoglobin RBC = Red Blood Cell BID = twice a day EoS = End of Study

Iptacopan was superior to SoC for both primary endpoints; majority of iptacopan patients achieved more normal Hb levels vs. 0 on SoC

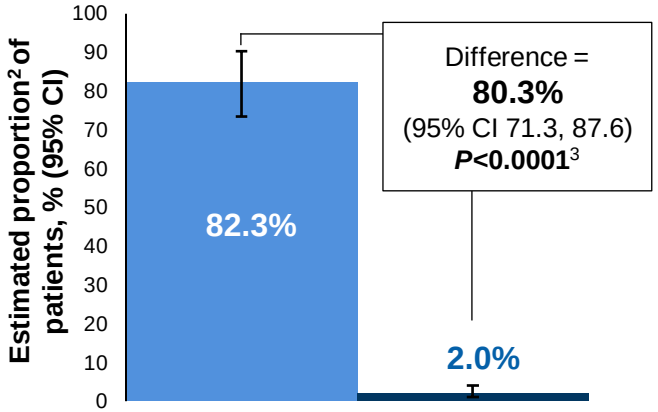
Increase from baseline in Hb of ≥ 2 g/dL
in the absence of RBC transfusions

Observed

51/60[1]
patients treated with **iptacopan**

0/35
patients treated with **SoC**

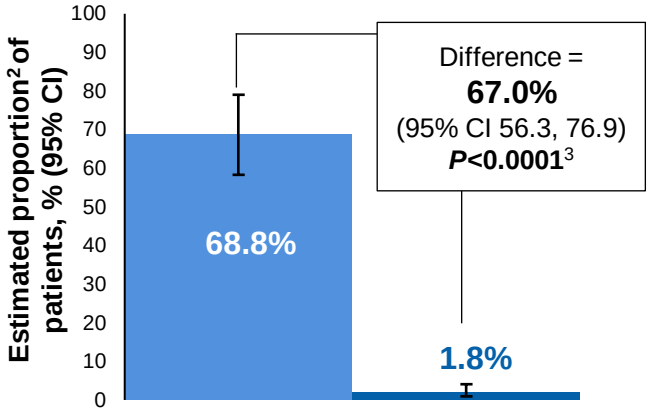
Population estimate



Hb ≥ 12 g/dL
in the absence of RBC transfusions

42/60[1]
patients treated with **iptacopan**

0/35
patients treated with **SoC**



1. 2/62 patients in the iptacopan arm had missing data between Days 126 and 168 so were not evaluable based on observed data. 2. 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. 3. P values are two-sided and unadjusted. CI, confidence interval

Iptacopan monotherapy was superior to SoC for transfusion avoidance

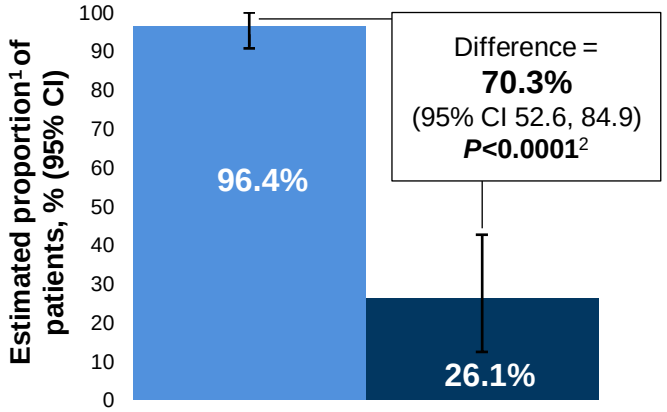
Transfusion avoidance

Observed

60/62 patients treated with **iptacopan**

14/35 patients treated with **SoC**

Population estimate



Of the patients treated with anti-C5 therapy who received transfusions, they received on average **more than double the number of transfusions** vs. the few patients on iptacopan

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)

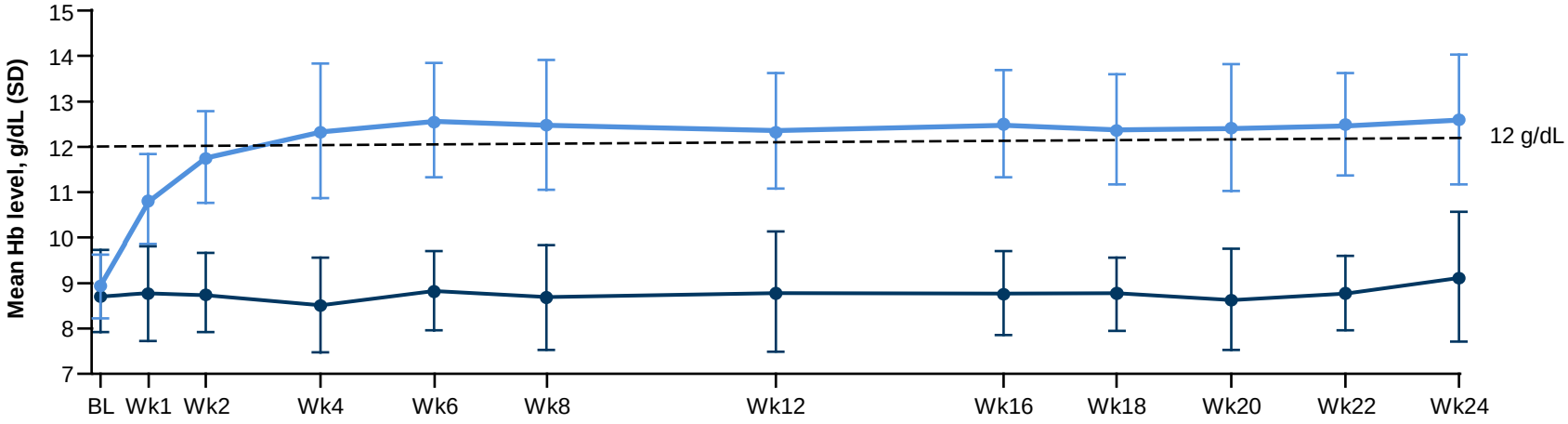
38.9% (95% CI 23.1, 55.8)

Difference = **57.8%** (95% CI 39.8, 74.2), **P<0.0001[2]**

1. 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. 2. *P* values are two-sided and unadjusted

Iptacopan monotherapy was superior to SoC at increasing Hb level from baseline

Mean Hb (SD) over time during the 24-week randomized treatment period[3]



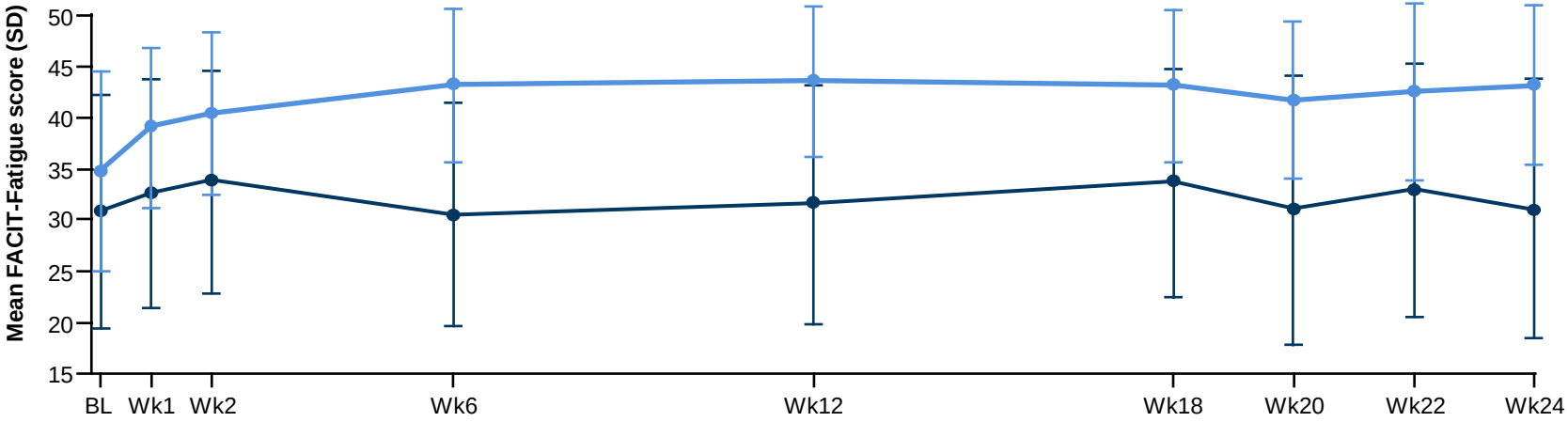
Patients with available data	Study visit											
	BL	Wk1	Wk2	Wk4	Wk6	Wk8	Wk12	Wk16	Wk18	Wk20	Wk22	Wk24
Iptacopan	62	61	59	60	59	59	60	59	59	59	57	61
Anti-C5 SoC	35	29	27	32	32	31	33	28	34	32	32	34

Adjusted mean Hb change from baseline[1] (95% CI) was +3.59 (3.32, 3.86) g/dL for iptacopan vs −0.04 (−0.42, 0.35) g/dL for SoC, with a difference of +3.63 (3.18, 4.08) g/dL (P<0.0001[2]).

1. Between Days 126 and 168 (excluding values within 30 days of RBC transfusion). 2. A repeated measures model, adjusting for covariates including baseline Hb, was used for comparisons between the treatment arms. P value is two-sided and unadjusted. 3. Includes post-transfusion data. 2/62 patients in the iptacopan arm and 21/35 patients in the SoC arm had RBC transfusions between Days 14 and 168. BL = baseline Wk = week

Iptacopan monotherapy was superior to SoC at reducing patient-reported fatigue from baseline

Mean FACIT-Fatigue score (SD) during the 24-week randomized treatment period



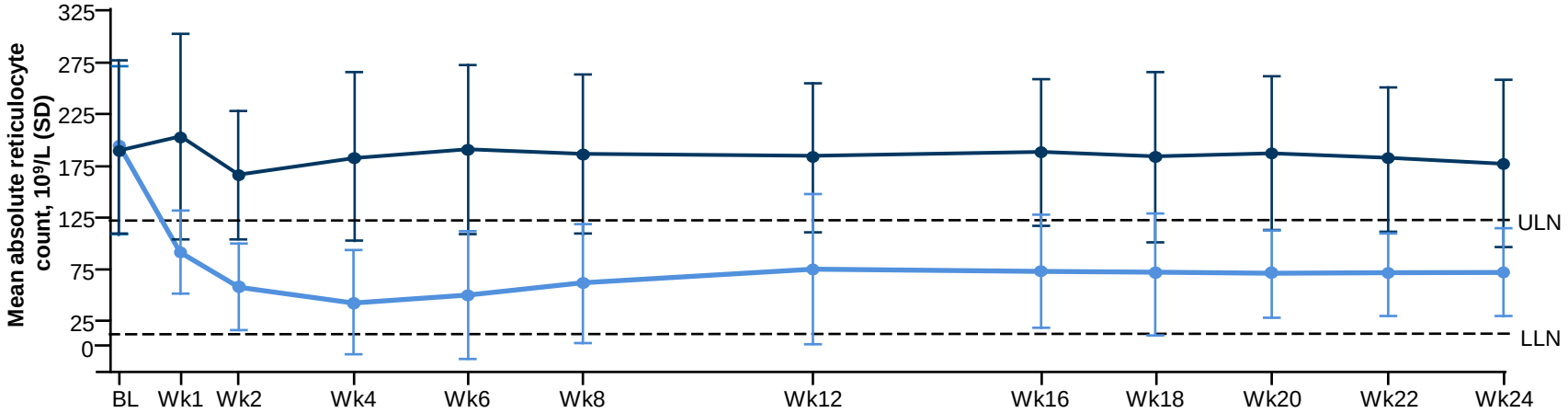
Patients with available data	Study visit							
Iptacopan	62	60	57	61	57	58	59	56	60
Anti-C5 SoC	33	27	28	32	29	29	28	28	30

Adjusted mean change from baseline[1] in FACIT-Fatigue score (95% CI) was +8.59 (6.72, 10.47) for iptacopan vs +0.31 (−2.20, 2.81) for SoC, with a difference of +8.29 (5.28, 11.29) (P<0.0001[2])

1. Between Days 126 and 168. 2. A repeated measures model, adjusting for covariates including baseline FACIT-Fatigue score, was used for comparisons between the treatment arms. P value is two-sided and unadjusted.

Iptacopan monotherapy was superior to SoC at reducing absolute reticulocyte count from baseline

Mean absolute reticulocyte count (SD) during the 24-week randomized treatment period



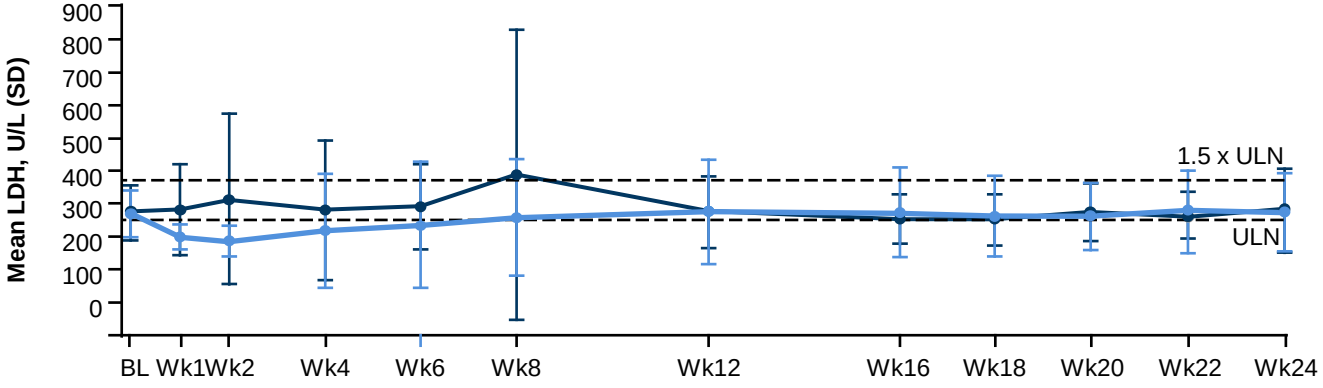
Patients with available data	Study visit											
	BL	Wk1	Wk2	Wk4	Wk6	Wk8	Wk12	Wk16	Wk18	Wk20	Wk22	Wk24
Iptacopan	62	61	58	60	59	59	60	56	59	56	56	58
Anti-C5 SoC	35	28	27	32	31	31	33	27	34	32	32	34

Adjusted mean change from baseline[1] in absolute reticulocyte count (95% CI) was −115.89 (−126.49, −105.30) x 10^9/L for iptacopan vs +0.37 (−13.03, 13.77) x 10^9/L for SoC, with a difference of −116.26 (−132.17, −100.36) x 10^9/L (P<0.0001[2]).

1. Between Days 126 and 168. 2. A repeated measures model, adjusting for covariates including baseline absolute reticulocyte count, was used for comparisons between the treatment arms. P value is two-sided and unadjusted.
LLN = lower limit of normal ULN = upper limit of normal

There was no significant difference between iptacopan monotherapy and SoC for change from baseline in LDH level

Mean LDH level (SD) during the 24-week randomized treatment period



Patients with available data	Study visit											
	BL	Wk1	Wk2	Wk4	Wk6	Wk8	Wk12	Wk16	Wk18	Wk20	Wk22	Wk24
Iptacopan	62	61	61	61	62	62	62	61	59	59	57	61
Anti-C5 SoC	35	28	28	34	34	34	34	34	35	33	32	35

- As expected, with all patients having been treated with anti-C5s prior to entering the study, IVH was well controlled and LDH levels < 1.5x ULN in the vast majority of patients
- No difference in LDH levels shows that **iptacopan maintains IVH control**

Adjusted geometric mean ratio to baseline[1] in log-transformed LDH (95% CI) was 0.96 (0.90, 1.03) for iptacopan vs 0.98 (0.89, 1.07) for SoC, equating to a reduction of 1.15% (95% CI −10.18, 11.32) with iptacopan vs SoC (P=0.8345[2]).

1. Between Days 126 and 168. 2. A repeated measures model, adjusting for covariates including baseline LDH, was used for comparisons between the treatment arms. P value is two-sided and unadjusted. ULN = upper limit of normal

Iptacopan monotherapy was superior to SoC for annualized rate of clinical breakthrough hemolysis[1]

	Arm	n/N[2]	Adjusted annual rate, % (95% CI)	Rate ratio (95% CI)[3]	P value[3]
Rate of clinical breakthrough hemolysis[1]	Iptacopan	2/62	0.07 (0.02, 0.31)	0.10 (0.02, 0.61)	0.0118
	Anti-C5 SoC	6/35	0.67 (0.26, 1.72)		

- Rate ratio of 0.10 means **10-fold lower rate of annualized clinical breakthrough hemolysis**

1. Events that met the protocol-specified criteria for clinical breakthrough hemolysis. All hemolytic events were also reported as TEAEs, even if they did not meet the criteria for clinical breakthrough hemolysis. 2. n=number of patients with at least one event, N=overall number of patients. 3. A negative binomial model was used for the comparison between treatment arms. *P* value is two-sided and unadjusted. TEAE = treatment-emergent adverse event.

There was no significant difference between iptacopan monotherapy and SoC for the annualized rate of MAVEs

	Arm	n/N[1]	Adjusted annual rate, % (95% CI)	Rate ratio (95% CI)[2]	P value[2]
Rate of MAVEs	Iptacopan	1/62	0.03 (0.00, 0.25)	Not estimable	0.3173
	Anti-C5 SoC	0/35	0		

- Serious TEAE of **transient ischemic attack**, considered by the investigator to be **unrelated to iptacopan**
- The patient had a concomitant serious TEAE of sick sinus syndrome and is **continuing** to receive **iptacopan** treatment

MAVE = major adverse vascular event 1. n=number of patients with at least one event, N=overall number of patients. 2. A negative binomial model was used for the comparison between treatment arms. *P* value is two-sided and unadjusted.
TEAE = treatment-emergent adverse event.

Iptacopan monotherapy was well tolerated and had a favorable safety profile

Most common TEAEs (≥4 patients in either arm)[1]

n (%)	Iptacopan 200mg bid N=62	Anti-C5 SoC N=35
Any TEAE	**51 (82.3)**	**28 (80.0)**
Mild / Moderate / Severe, %	**32.3 / 45.2 / 4.8**	**37.1 / 34.3 / 8.6**
Headache	10 (16.1)	1 (2.9)
Diarrhea	9 (14.5)	2 (5.7)
Nasopharyngitis	7 (11.3)	2 (5.7)
Nausea	6 (9.7)	1 (2.9)
COVID-19	5 (8.1)	9 (25.7)
Urinary tract infection	5 (8.1)	1 (2.9)
Arthralgia	5 (8.1)	1 (2.9)
Abdominal pain	4 (6.5)	1 (2.9)
Increased blood LDH	4 (6.5)	3 (8.6)
Dizziness	4 (6.5)	0
Breakthrough hemolysis	2 (3.2)	6 (17.1)

No deaths

No discontinuations due to TEAEs

Serious TEAEs:
9.7% vs **14.3%**

Hemolysis serious TEAEs:
Iptacopan: None

SoC: Breakthrough hemolysis (n=1) and extravascular hemolysis (n=1)

No serious infections caused by encapsulated bacteria

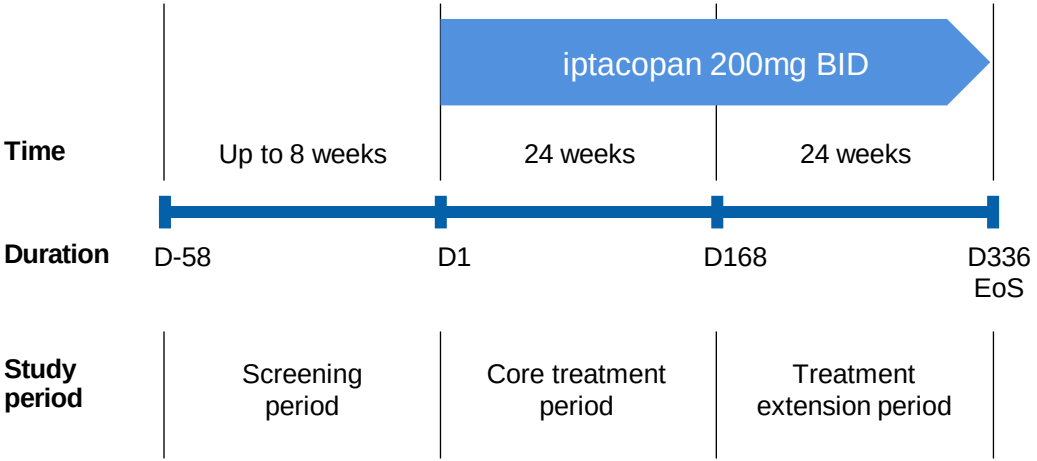
TEAE = treatment-emergent adverse event 1. Organized by descending frequency in the iptacopan arm

Two positive Ph3 studies in PNH first pivotal readouts for iptacopan

Study	APPLY-PNH ☑	APPOINT-PNH ☑
Patient type	PNH patients with **residual anemia despite anti-C5**	PNH patients **naive to complement inhibitor therapy**
Intervention	Iptacopan vs. anti-C5 antibody	Iptacopan, single-arm study

APPOINT-PNH study is a single-arm Ph3 trial investigating iptacopan monotherapy in treatment-naive patients with PNH

Study design



Population (n = 40)

Adult PNH patients with hemolysis (LDH > 1.5x ULN) and anemia (Hb < 10g/dL) naive to complement inhibitor therapy

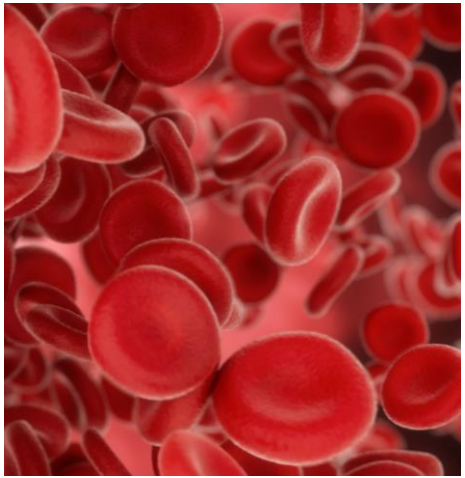
Primary endpoint

☑ Proportion of patients achieving a sustained increase in Hb of ≥ 2g/dL, in the absence of transfusions

BID = twice a day EoS = End of Study ULN = upper limit of normal

Iptacopan monotherapy achieved clinically meaningful increases in hemoglobin levels in treatment-naive patients with PNH

- **APPOINT-PNH met primary endpoint** of proportion of patients achieving a sustained increase in Hb of ≥ 2g/dL, in the absence of transfusions, at 24 weeks
- **Safety profile consistent** with previously reported data
- **Data to be presented** at upcoming medical meeting



As a potent, selective factor B inhibitor, iptacopan has the potential to be practice-changing, the new standard of care in PNH

Addresses both intravascular and extravascular hemolysis

Superior in PNH patients with residual anemia despite prior anti-C5 treatment (APPLY)

- Normalized hemoglobin levels
- Reduced need for transfusions
- Reduced patient-reported fatigue
- Favorable safety with no serious breakthrough hemolysis

Clinically meaningful Hb increases in treatment-naive patients (APPOINT)

- Safety profile consistent with APPLY-PNH

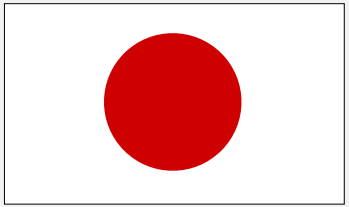
Significant QoL benefits as the first oral monotherapy

Global regulatory filings starting in H1 2023

Selected iptacopan PNH submissions

FDA submission
expected H1 2023

EMA submission
expected H1 2023



PMDA submission
expected H2 2023

China FDA submission
expected H2 2023

Orphan Drug Designation
FDA Apr. 2020, EMA Jul. 2020

Breakthrough Therapy Designation
FDA Dec. 2020

Participants

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Renal & Metabolism Development

Reshema Kemps-Polanco

Executive Vice President,
Oncology US

The path to PNH diagnosis and treatment involves many steps and can take months to years

Delays in diagnosis and treatment of PNH

- Up to 3 years to diagnose PNH (avg. 7-9 months)
- Median age at disease onset 36 years[1]
- Common symptoms (e.g., fatigue, hemoglobinuria) can have multiple causes
- "Watch & Wait" for disease progression before treatment is initiated
- Patients still experiencing symptoms and may be receiving transfusions

Increase urgency to intervene earlier

Limited options available for treatment

- Until 2021, only anti-C5's available for treatment
- 4-6 weeks to determine if treatment is working
- Some patients unwilling to commit to regular infusions

More choice in first line and switch

Need to make treatment for life manageable

- Regular monitoring with stable patients every 3 months but unstable patients as often as weekly
- "Good enough" patient outcomes accepted
- Managed by hematologists

Unburden patients from infusions and expect more from treatments

1. 5. Schrezenmeier H et al. Ann Hematol. 2020;99(7):1505-1514. Source: Patient journey market research 2022

Opportunity to redefine PNH treatment paradigm

~6k
Prevalent[1]
PNH patients in US

Treated with complement inhibitor[3]
30%

- Current market ~USD 2bn WW (USD 1bn US)[4]
- **Of C5-treated patients, ~80% have Hb < 12g/dL**[5]
  - Still experiencing symptoms
  - Managing life around infusion schedule
  - Some still receiving transfusions

Displace Anti-C5

Untreated
70%

- Varying views of when treatment should be started
- Heterogeneous presentation of symptoms
- Some unwilling to commit to regular infusions
- Some still receiving transfusions

Potentially increase treatment rate

~400
Incident[2]
PNH patients/year in US

Start appropriate patients on iptacopan

1. Prevalence: 12-18 per million individuals in the US (Jalbert JJ, 2019, Mon Pere N, 2018). 2. Incidence: 1.0-1.5 per million individuals (Hill A, 2017). 3. Treated with anti-C5 or anti-C3 4. Based on C5i therapies only
5. Debureaux PE et al. Bone Marrow Transplant 2021;56:2600–2 Source: Patient journey market research 2022

Significant experience in non-malignant hematology and rare disease provides strong foundation for launch

Track record of execution in rare hematology / oncology conditions

- **Promacta** market leadership in SAA (ultra-rare) and ITP (rare) based on deep understanding of **HCP insights** and **patient needs / motivations**; also an **oral option** in originally infusion-driven market
- Building on rare disease playbook from **Vijoice** and **Afinitor TSC** launches, including early and critical focus on **patient engagement and advocacy**

Existing relationships with PNH treaters

- **~2.5k** hematologists / oncologists seeing PNH patients
- Rare disease, but treated and managed not just by experts in large centers, but also community HCPs
- Strong existing customer **relationships with majority of PNH treaters**
- **Top medical experts** engaged in either clinical studies or advisory capacity
- **Account profiling underway** to identify individual success levers

Launch readiness to support rare disease success is on track

Patient engagement and activation

- Relationships built with key patient advocacy groups
- Focus on educating PNH patients on available therapies and activating them to seek treatment that's right for their life

Disease state education

- Launched PNH disease education campaign at ASH 2022 to raise awareness of high burden of disease and unmet need
- Ongoing digital engagement

Patient support services

- Detailed mapping of patient journey to minimize friction for new and switch patients
- Leveraging experience in Rare Disease, Oncology and MS to ensure best practice

Comprehensive evidence generation

- Ph3 program covering broad spectrum of PNH patients: treatment naïve (APPOINT) and switch (APPLY)
- Patient registries with key stakeholder organizations

Field medical and field sales teams already in place

On track to launch a potential new standard-of-care in PNH

1

Iptacopan could be practice-changing:

- ☑ Superior efficacy to anti-C5 therapy
- ☑ Significant QoL benefits
- ☑ Oral option in infusion market
- ☑ Potential new standard of care

2

On track with launch readiness:

- ☑ Playbook for rare disease launches
- ☑ Existing relationships with PNH HCPs
- ☑ Disease education campaign launched
- ☑ Medical and sales teams in place

Q&A

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Appendix

Iptacopan has the potential to become the new SoC in a well established and growing global PNH market

PNH complement inhibitors market size is estimated at **~USD 2bn**[1]

PNH market is expected to grow at **7.6% CAGR** over the next 10 years in the 7 major markets[2] driven by new entrants and increased penetration of complement inhibitors[3]

Current total C5 inhibitor sales in PNH roughly **evenly split between US and ex-US**[1]

Significant opportunities ex-US, including China, where until recently there were no complement inhibitors available

1. Evaluate Pharma Dec 2022. 2. 7 Major Markets: US, Germany, France, UK, Italy, Spain and Japan. 3. Delveinsights PNH market report 2022.