Oral iptacopan monotherapy increases paroxysmal nocturnal hemoglobinuria (PNH) red blood cell clone size via control of intra- and extravascular hemolysis in anti-C5-treated PNH patients with anemia


1 AORN Moscati, Avellino, Italy; 2 University of Naples Federico II, Naples, Italy; 3 West German Cancer Center, University Hospital Essen, University Duisburg-Essen, Essen, Germany; 4 King’s College Hospital NHS, London, UK; 5 National Institute for Health and Care Research and Wellcome King’s Research Facility, London, UK; 6 King’s College, London, UK; 7 Hospital A Beneficência Portuguesa, São Paulo, Brazil; 8 Osaka University Graduate School of Medicine, Suita, Japan; 9 Duke University School of Medicine, Durham, NC, USA; 10 UOC Oncematologia, AULSS7 Pademontana, Bassiano del Grappa (VI), Vicenza, Italy; 11 St James’s University Hospital, Leeds, UK; 12 Radboud University Medical Center, Nijmegen, Netherlands; 13 University of Ulm, Ulm, Germany; 14 German Red Cross Blood Transfusion Service Baden-Württemberg-Hessen and University Hospital Ulm, Ulm, Germany; 15 Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milan, Italy; 16 ABC Medical School, Santo André, Brazil; 17 University Hospital RWTH Aachen, Aachen, Germany; 18 Medical Center Hamburg-Eppendorf, Hamburg, Germany; 19 Toulouse University Hospital Center, Toulouse-Oncopole University Cancer Institute, Toulouse, France; 20 University of Torino, Turin, Italy; 21 Hospital Clinic de Barcelona, Barcelona, Spain; 22 Huällen Tzu Chi Hospital, Hualien, Taiwan; 23 Kyoto University, Kyoto, Japan; 24 Medical College of Georgia, Augusta, GA, USA; 25 Eussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA; 26 Azienda Ospedaliera Universitaria Careggi, Firenze, Italy; 27 Istituto per lo Studio, la Prevenzione e la Rete Oncologica, Firenze, Italy; 28 City of Hope Medical Center, Duarte, CA, USA; 29 Eiblandklinikum Riesa, Riesa, Germany; 30 CHU Lille, Université de Lille, Lille, France; 31 Japanese Red Cross Society Suwa Hospital, Suwa, Japan; 32 French Référence Center for Aplastic Anemia and Paroxysmal Nocturnal Hemoglobinuria, Paris, France; 33 Novartis Pharma AG, Basel, Switzerland; 34 Novartis Healthcare Private Limited, Hyderabad, India; 35 Novartis Pharmaceuticals UK Limited, London, UK; 36 Novartis Institutes for BioMedical Research, Basel, Switzerland; 37 Assistance Publique Hôpitaux de Paris, Université Paris Cité, Paris, France

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Oral presented at the European Hematology Association 2023 congress, held in Frankfurt, Germany and virtually on 8–11 June 2023
## Disclosures

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<tr>
<th>Company</th>
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Complement regulation in PNH is impaired\textsuperscript{1,2}

- PNH is a \textbf{rare, chronic hematological disorder} characterized by intravascular hemolysis, thrombophilia and bone marrow failure\textsuperscript{1,2}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{complement_regulation_pnh}
\caption{Complement regulation in PNH}
\end{figure}

C, complement component; CD, cluster of differentiation; GPI, glycosylphosphatidylinositol; MAC, membrane attack complex; PNH, paroxysmal nocturnal hemoglobinuria


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Complement regulation in PNH is impaired\textsuperscript{1,2}

- PNH is a rare, chronic hematological disorder characterized by intravascular hemolysis, thrombophilia and bone marrow failure\textsuperscript{1,2}

- PNH is caused by a somatic mutation in the \textit{PIGA} gene, resulting in a lack of the GPI-anchored complement-regulating proteins \textit{CD55} and \textit{CD59}, leading to intravascular hemolysis\textsuperscript{1,2}

C, complement component; CD, cluster of differentiation; GPI, glycosylphosphatidylinositol; MAC, membrane attack complex; PNH, paroxysmal nocturnal hemoglobinuria


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- Targeting the \textbf{terminal complement pathway} at C5 with \textbf{eculizumab} and \textbf{ravulizumab} controls intravascular hemolysis, reduces thrombosis and improves overall survival\textsuperscript{3–9}

---

### C5 Inhibitors

- \textbf{C5 inhibitors}

- C, complement component; CD, cluster of differentiation; GPI, glycosylphosphatidylinositol; MAC, membrane attack complex; PNH, paroxysmal nocturnal hemoglobinuria


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Complement regulation in PNH is impaired\(^1,\!\!^2\)

**Alternative pathway**

\[ \text{C3b convertase} \]

\[ \text{C3a, C3b} \]

**Proximal pathways**

\[ \text{Factor B} \]

\[ \text{Factor D} \]

**Terminal pathway**

\[ \text{C5 convertase} \]

\[ \text{C5a, C5b, MAC} \]

- **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 *eculizumab* and *ravulizumab* controls intravascular hemolysis, reduces thrombosis and improves overall survival\(^3\!–\!9\).

- **Up to two-thirds** of patients have clinically meaningful persistent anemia, largely because of emerging **extravascular hemolysis**; consequently, some patients are **transfusion dependent**\(^1,\!\!^10\).

---

C, complement component; CD, cluster of differentiation; GPI, glycosylphosphatidylinositol; MAC, membrane attack complex; PNH, paroxysmal nocturnal hemoglobinuria


Oral presented at the European Hematology Association 2023 congress, held in Frankfurt, Germany and virtually on 8–11 June 2023
Iptacopan is a first-in-class, oral, selective factor B inhibitor that targets the complement system proximally via the alternative pathway\(^1\)

**Alternative pathway**

1. **Factor B**
2. **Factor D**
3. **C3 convertase**
4. **C3(H\(_2\)O)**
5. **C3 convertase**
6. **C5 convertase**
7. **C3b**
8. **C5b**
9. **C5a**
10. **C5b**
11. **C6, C7, C8, C9\(_n\)**
12. **MAC**

Iptacopan binds to the **active site** of factor B, inhibiting the activity of **C3 convertase**\(^1\)

**Proximal pathways**

**Terminal pathway**

---

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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**\(^2\)

---

Material from *The Lancet Haematology* is used with permission

Oral presented at the European Hematology Association 2023 congress, held in Frankfurt, Germany and virtually on 8–11 June 2023
APPLY-PNH is an open-label, randomized, multicenter, Phase III trial investigating iptacopan monotherapy in PNH patients with residual anemia despite anti-C5 therapy (NCT04558918)^1

Randomization

Patients (N=97)
- ≥18 years of age
- PNH diagnosis (RBC and WBC clone size ≥10%)
- Mean Hb <10 g/dL
- Stable anti-C5 regimen* for ≥6 months preceding randomization

8:5†

24-week randomized treatment period

Oral iptacopan 200 mg bid (n=62)

IV anti-C5 (as before randomization) (n=35)

24-week treatment extension period

Oral iptacopan 200 mg bid

Switch to oral iptacopan 200 mg bid

Rollover extension program (NCT04747613)^2

Day

Screening period (8 weeks)

1

168

336

(End of study)

*Eculizumab or ravulizumab; †Stratified by prior anti-C5 treatment and RBC transfusions in the preceding 6 months

1. ClinicalTrials.gov. NCT04558918. Available at: https://clinicaltrials.gov/ct2/show/NCT04558918 (accessed June 2023);
APPLY-PNH is an open-label, randomized, multicenter, Phase III trial investigating iptacopan monotherapy in PNH patients with residual anemia despite anti-C5 therapy (NCT04558918)\(^1\)

- Patients (N=97)
  - ≥18 years of age
  - PNH diagnosis (RBC and WBC clone size ≥10%)
  - Mean Hb <10 g/dL
  - Stable anti-C5 regimen* for ≥6 months preceding randomization

Randomization: 8:5\(^+\) 24-week randomized treatment period

Day 1

Screening period (8 weeks)

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

- Oral iptacopan 200 mg bid (n=62)
- IV anti-C5 (as before randomization) (n=35)

*Eculizumab or ravulizumab; \(^+\)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 June 2023);
**APPLY-PNH is a superiority trial with two primary endpoints**

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
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</thead>
<tbody>
<tr>
<td>• Hematological response defined as an <strong>increase from baseline in Hb of ≥2 g/dL</strong> in the absence of RBC transfusions†&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>• Transfusion avoidance†&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
<tr>
<td>• Hematological response defined as <strong>Hb ≥12 g/dL</strong> in the absence of RBC transfusions†</td>
<td>• Change from baseline:*&lt;br&gt;– Hb levels‡&lt;br&gt;– FACIT-Fatigue scores&lt;br&gt;– Absolute reticulocyte count&lt;br&gt;– LDH levels</td>
</tr>
</tbody>
</table>

<sup>*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</sup>

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

### APPLY-PNH is a superiority trial with two primary endpoints

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
<th>Exploratory</th>
</tr>
</thead>
</table>
| • Hematological response defined as an increase from baseline in Hb of ≥2 g/dL* in the absence of RBC transfusions† | • Transfusion avoidance†  
  • Change from baseline:*  
  – Hb levels‡  
  – FACIT-Fatigue scores  
  – Absolute reticulocyte count  
  – LDH levels  
  • Occurrences of clinical breakthrough hemolysis and MAVEs§  
  • Safety§ | • Total PNH RBC (type II + type III PNH RBCs) and WBC clone size‖  
• C3 fragment deposition (type II + type III PNH RBCs that were C3d+)‖ |
| • Hematological response defined as Hb ≥12 g/dL* in the absence of RBC transfusions† | | |

- A multiple testing procedure adjusting for multiplicity was used to determine superiority\(^1,2\)

---

*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; †Assessed by flow cytometry

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

### Demographics and disease characteristics at baseline were generally balanced between arms

<table>
<thead>
<tr>
<th></th>
<th>Iptacopan 200 mg bid (N=62)</th>
<th>Anti-C5 (N=35)</th>
<th>Overall (N=97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>51.7 (16.9)</td>
<td>49.8 (16.7)</td>
<td>51.0 (16.8)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>43 (69.4)</td>
<td>24 (68.6)</td>
<td>67 (69.1)</td>
</tr>
<tr>
<td>Time since diagnosis, years (SD)</td>
<td>11.9 (9.8)</td>
<td>13.6 (10.9)</td>
<td>12.5 (10.2)</td>
</tr>
<tr>
<td>Anti-C5 therapy</td>
<td></td>
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</tr>
<tr>
<td>Eculizumab,(*) n (%)</td>
<td>40 (64.5)</td>
<td>23 (65.7)</td>
<td>63 (64.9)</td>
</tr>
<tr>
<td>Ravulizumab,(*) n (%)</td>
<td>22 (35.5)</td>
<td>12 (34.3)</td>
<td>34 (35.1)</td>
</tr>
<tr>
<td>Mean duration, years (SD)</td>
<td>3.8 (3.5)</td>
<td>4.2 (3.9)</td>
<td>4.0 (3.6)</td>
</tr>
<tr>
<td>Received RBC transfusions,(*) n (%)</td>
<td>35 (56.5)</td>
<td>21 (60.0)</td>
<td>56 (57.7)</td>
</tr>
<tr>
<td>Mean baseline Hb, g/dL (SD) [range]</td>
<td>8.9 (0.7) [6.8–10.0]</td>
<td>8.9 (0.9) [6.2–9.9]</td>
<td>8.9 (0.8) [6.2–10.0]</td>
</tr>
<tr>
<td>Mean baseline LDH, U/L (SD) [range]</td>
<td>269.1 (70.1) [150–539]</td>
<td>272.7 (84.8) [133–562]</td>
<td>270.4 (75.3) [133–562]</td>
</tr>
<tr>
<td>Baseline LDH &gt;1.5 x ULN, n (%)</td>
<td>4 (6.5)</td>
<td>3 (8.6)</td>
<td>7 (7.2)</td>
</tr>
<tr>
<td>Mean baseline absolute reticulocyte count, (10^9)/L (SD) [range]</td>
<td>193.2 (83.6) [51–563]</td>
<td>190.6 (80.9) [90–412]</td>
<td>192.3 (82.3) [51–563]</td>
</tr>
<tr>
<td>Mean total PNH RBC(†) clone size, % (SD) [range]</td>
<td>64.6 (27.5) [10.6–99.9]</td>
<td>57.4 (29.7) [9.8–99.4]</td>
<td>62.0 (28.4) [9.8–99.9]</td>
</tr>
<tr>
<td>Mean C3d+ PNH RBCs,(†) (SD) [range]</td>
<td>19.2 (16.1) [0.0–71.8]</td>
<td>17.5 (12.2) [1.8–51.2]</td>
<td>18.6 (14.8) [0.0–71.8]</td>
</tr>
</tbody>
</table>

\*In the 6 months prior to randomization; \(†\)Type II + type III PNH RBCs
SD, standard deviation; ULN, upper limit of normal
Iptacopan monotherapy was superior to anti-C5 for both primary endpoints

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

<table>
<thead>
<tr>
<th>Observed</th>
<th>51/60* patients treated with iptacopan</th>
<th>0/35 patients treated with anti-C5</th>
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</table>

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

<table>
<thead>
<tr>
<th>Observed</th>
<th>42/60* patients treated with iptacopan</th>
<th>0/35 patients treated with anti-C5</th>
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</thead>
</table>

*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 anti-C5 arm; consequently, the treatment effect of iptacopan is underestimated and the treatment effect of anti-C5 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

Oral presented at the European Hematology Association 2023 congress, held in Frankfurt, Germany and virtually on 8–11 June 2023
Iptacopan monotherapy was superior to anti-C5 at increasing Hb level from baseline

- Adjusted mean Hb change from baseline* (95% CI) was +3.59 (3.32, 3.86) g/dL for iptacopan vs −0.04 (−0.42, 0.35) g/dL for anti-C5, with a difference of +3.63 (3.18, 4.08) g/dL (\(P<0.0001\)†)

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

- Between Days 126 and 168 (excluding values within 30 days of RBC transfusion); †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; ‡Includes post-transfusion data. 2/62 patients in the iptacopan arm and 21/35 patients in the anti-C5 arm had RBC transfusions between Days 14 and 168. BL, baseline; Wk, week

<table>
<thead>
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<th>Patients with available data</th>
<th>Week</th>
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<tr>
<td><strong>Iptacopan</strong></td>
<td>62</td>
</tr>
<tr>
<td><strong>Anti-C5</strong></td>
<td>35</td>
</tr>
</tbody>
</table>

Oral presented at the European Hematology Association 2023 congress, held in Frankfurt, Germany and virtually on 8–11 June 2023
Iptacopan monotherapy was superior to anti-C5 for transfusion avoidance

Transfusion avoidance

**Observed**

- **60/62** patients treated with **iptacopan**
- **14/35** patients treated with **anti-C5**

*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.

**Population estimate**

- **96.4%** (95% CI 52.6, 84.9)
- **26.1%**

**Difference = 70.3%**

P < 0.0001†

Oral presented at the European Hematology Association 2023 congress, held in Frankfurt, Germany and virtually on 8–11 June 2023.
Iptacopan monotherapy was superior to anti-C5 at reducing patient-reported fatigue from baseline

- Adjusted mean change from baseline* in FACIT-Fatigue score (95% CI) was **+8.59 (6.72, 10.47) for iptacopan** vs **+0.31 (−2.20, 2.81)** for anti-C5, with a difference of **+8.29 (5.28, 11.29) (P<0.0001†)**

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

*Between Days 126 and 168; †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

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Mean score in healthy general US population

Mean score 43.6

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<table>
<thead>
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<th>Patients with available data</th>
<th>Week</th>
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</thead>
<tbody>
<tr>
<td><strong>Iptacopan</strong> 62 60 57</td>
<td>57</td>
</tr>
<tr>
<td>Anti-C5 33 29 28</td>
<td>29</td>
</tr>
</tbody>
</table>

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Oral presented at the European Hematology Association 2023 congress, held in Frankfurt, Germany and virtually on 8–11 June 2023
Iptacopan monotherapy was superior to anti-C5 at reducing absolute reticulocyte count from baseline

- Adjusted mean change from baseline* in absolute reticulocyte count (95% CI) was 
  $-115.89 \ (-126.49, -105.30) \times 10^9/L$ for iptacopan vs $+0.37 \ (-13.03, 13.77) \times 10^9/L$ for anti-C5, with a difference of 
  $-116.26 \ (-132.17, -100.36) \times 10^9/L$ ($P<0.0001$†)

*Between Days 126 and 168; †A repeated measures model, adjusting for covariates including baseline absolute reticulocyte count, was used for comparisons between the treatment arms.

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

 Patients with available data

<table>
<thead>
<tr>
<th></th>
<th>Iptacopan</th>
<th>Anti-C5</th>
</tr>
</thead>
<tbody>
<tr>
<td>62</td>
<td>61</td>
<td>58</td>
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<tr>
<td>60</td>
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<td>56</td>
<td>59</td>
</tr>
<tr>
<td>33</td>
<td>56</td>
<td>56</td>
</tr>
</tbody>
</table>

Week

| 60 | 56 | 59 | 56 | 56 | 58 |
| 33 | 27 | 34 | 32 | 32 | 34 |
Increases in total PNH RBC clone size were observed in the iptacopan arm by week 4

- In the **iptacopan** arm, mean total PNH RBC* clone size increased from **64.6% at baseline** to **93.2% at Week 24**; the increase in mean total PNH RBC* clone size **between baseline and Week 24 was 28.6%†**
- In the **anti-C5** arm, mean total PNH RBC clone size* through Week 24 remained **similar to baseline**

![Graph showing mean total PNH RBC* clone size (SD) during the 24-week randomized treatment period](image)

<table>
<thead>
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<th>Patients with available total PNH RBC* clone size data</th>
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<td></td>
<td>60</td>
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<tr>
<td></td>
<td>33</td>
</tr>
</tbody>
</table>

*Type II + type III PNH RBCs; †Among the 60 iptacopan-treated patients who had available data at baseline and Week 24
With iptacopan monotherapy, the mean percentage of total PNH RBCs became similar in size to PNH WBCs

- **Monocyte clone size** data were similar to those for granulocyte clone size throughout the 24-week treatment period.

### Mean total PNH RBC* and granulocyte clone size (SD) during the 24-week randomized treatment period

**Patients with available total PNH RBC* (granulocyte) clone size data**

<table>
<thead>
<tr>
<th><strong>Week</strong></th>
<th><strong>Iptacopan</strong></th>
<th><strong>Anti-C5</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>62 (60)</td>
<td>35 (35)</td>
</tr>
<tr>
<td>4</td>
<td>57 (56)</td>
<td>28 (27)</td>
</tr>
<tr>
<td>8</td>
<td>57 (55)</td>
<td>32 (31)</td>
</tr>
<tr>
<td>16</td>
<td>56 (45)</td>
<td>28 (26)</td>
</tr>
<tr>
<td>20</td>
<td>53 (41)</td>
<td>32 (29)</td>
</tr>
<tr>
<td>24</td>
<td>60 (50)</td>
<td>33 (26)</td>
</tr>
</tbody>
</table>

*Type II + type III PNH RBCs
C3 fragment deposition became negligible in the iptacopan arm by Week 16

- In the **iptacopan** arm, the mean percentage of C3d+ PNH RBCs* decreased from **19.2% at baseline** to **0.3% at Week 24**; the **reduction** in mean percentage of C3d+ PNH RBCs* **between baseline and Week 24** was **19.2%†**
- In the **anti-C5** arm, C3 fragment deposition through Week 24 remained **similar to baseline**

**Mean C3d+ PNH RBCs** (SD) during the 24-week randomized treatment period

<table>
<thead>
<tr>
<th>Patients with available data</th>
<th>Iptacopan</th>
<th>Anti-C5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week</td>
<td>59</td>
<td>34</td>
</tr>
<tr>
<td>Baseline</td>
<td>55</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>52</td>
<td>31</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>43</td>
<td>28</td>
</tr>
<tr>
<td>20</td>
<td>38</td>
<td>31</td>
</tr>
<tr>
<td>24</td>
<td>47</td>
<td>31</td>
</tr>
</tbody>
</table>

*Type II + type III PNH RBCs that were C3d+; †Among the 47 iptacopan-treated patients who had available data at baseline and Week 24

Oral presented at the European Hematology Association 2023 congress, held in Frankfurt, Germany and virtually on 8–11 June 2023
There was no significant difference between iptacopan monotherapy and anti-C5 for change from baseline in LDH level

- Adjusted geometric mean ratio to baseline* in log-transformed LDH (95% CI) was 0.96 (0.90, 1.03) for iptacopan vs 0.98 (0.89, 1.07) for anti-C5, equating to a reduction of 1.15% (95% CI −10.18, 11.32) with iptacopan vs anti-C5 (*P=0.8345†)

*Between Days 126 and 168; †A repeated measures model, adjusting for covariates including log-transformed baseline LDH, was used for comparisons between the treatment arms. *P value is two-sided and unadjusted
Iptacopan monotherapy was superior to anti-C5 for annualized rate of clinical breakthrough hemolysis*

<table>
<thead>
<tr>
<th>Rate of clinical breakthrough hemolysis*</th>
<th>Arm</th>
<th>n/N†</th>
<th>Adjusted annual rate, % (95% CI)</th>
<th>Rate ratio (95% CI)‡</th>
<th>P value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Iptacopan</td>
<td>2/62</td>
<td>0.07 (0.02, 0.31)</td>
<td>0.10 (0.02, 0.61)</td>
<td>0.0118</td>
</tr>
<tr>
<td></td>
<td>Anti-C5</td>
<td>6/35</td>
<td>0.67 (0.26, 1.72)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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; †n=number of patients with at least one event, N=overall number of patients; ‡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 anti-C5 for the annualized rate of MAVEs

<table>
<thead>
<tr>
<th>Rate of MAVEs</th>
<th>Arm</th>
<th>n/N*</th>
<th>Adjusted annual rate, % (95% CI)</th>
<th>Rate ratio (95% CI)†</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Iptacopan</td>
<td>1/62</td>
<td>0.03 (0.00, 0.25)</td>
<td>Not estimable</td>
<td>0.3173</td>
</tr>
<tr>
<td></td>
<td>Anti-C5</td>
<td>0/35</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- 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

*n=number of patients with at least one event, N=overall number of patients; †A Poisson model was used for the comparison between treatment arms. P value is two-sided and unadjusted*
Iptacopan monotherapy was well tolerated and had a favorable safety profile

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Iptacopan 200 mg bid N=62</th>
<th>Anti-C5 N=35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAE</td>
<td>51 (82.3)</td>
<td>28 (80.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>10 (16.1)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (14.5)</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>7 (11.3)</td>
<td>2 (5.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (9.7)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>COVID-19</td>
<td>5 (8.1)</td>
<td>9 (25.7)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>5 (8.1)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5 (8.1)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4 (6.5)</td>
<td>1 (2.9)</td>
</tr>
<tr>
<td>Increased blood LDH</td>
<td>4 (6.5)</td>
<td>3 (8.6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (6.5)</td>
<td>0</td>
</tr>
<tr>
<td>Breakthrough hemolysis</td>
<td>2 (3.2)</td>
<td>6 (17.1)</td>
</tr>
</tbody>
</table>

*Organized by descending frequency in the iptacopan arm

- **Hemolysis serious TEAEs:**
  - **Anti-C5**: breakthrough hemolysis (n=1) and extravascular hemolysis (n=1)
  - **Iptacopan**: none
- **No serious infections** caused by *Neisseria meningitidis*, *Streptococcus pneumoniae* or *Haemophilus influenzae*
- **No patients discontinued** study treatment, except one because of pregnancy (iptacopan)
- **No deaths**
Conclusions

- **Oral iptacopan monotherapy** was **superior** to anti-C5 treatment at **improving Hb levels without** the need for **RBC transfusions**.

- Iptacopan monotherapy was **superior** to anti-C5 treatment for **transfusion avoidance** and **patient-reported fatigue**.

- **C3 fragment deposition became negligible** with iptacopan monotherapy, which, along with improved absolute reticulocyte counts, indicate the **resolution of extravascular hemolysis**.

- Iptacopan monotherapy led to an **increase in** **PNH RBC clone size to >90% of the total RBC population** by Week 24, indicating **increased survival** of these cells and thus **comprehensive control of hemolysis**.

- Iptacopan monotherapy was well tolerated, with a **favorable safety profile** and **no serious breakthrough hemolysis**.

- **Iptacopan monotherapy** may represent a **practice-changing, oral, outpatient treatment**, which may become a **preferred treatment option** for patients with hemolytic PNH who have an **inadequate response** to **IV anti-C5 therapy**.
Acknowledgments

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  - **Republic of Korea**: Samsung Medical Center
  - **Spain**: CHUS, Santiago de Compostela; Hospital Clinic of Barcelona; University Hospital Donostia
  - **Taiwan**: Hualien Tzu Chi Hospital; National Taiwan University Hospital
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