PF1297

# Pharmacodynamic Effect of Nipocalimab in Warm Autoimmune Hemolytic Anemia (wAIHA) and Correlation With Clinical Improvement

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## Background

- Warm autoimmune hemolytic anemia (wAIHA) is a rare, potentially life-threatening disease characterized by mainly immunoglobulin G (IgG) autoantibody–mediated destruction of healthy red blood cells (RBCs)[1-3]
- The neonatal Fc receptor (FcRn) extends the half-life of IgG antibodies by recycling IgG that would otherwise undergo lysosomal degradation[4,5]
- Nipocalimab is a fully human monoclonal antibody that binds the FcRn with high specificity and affinity, blocking the IgG-recycling pathway and lowering total IgG (including pathogenic IgG autoantibodies) without impacting other key humoral and cellular immune functions[6-8]
- In the double-blind (DB) ENERGY study of participants with wAIHA (NCT04119050), nipocalimab demonstrated improvements in hemoglobin (Hgb) response and fatigue that were maintained over 24 weeks, with no new safety signals

## Objective

**To characterize the pharmacodynamic (PD) effect of nipocalimab on total IgG, pathogenic anti-RBC IgG autoantibodies, and to evaluate correlations with changes in Hgb and hemolytic markers during the DB period of the ENERGY study**

## Methods

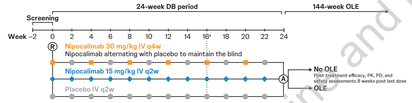
### Study Design

- The phase 2/3, multicenter, randomized, placebo-controlled ENERGY study enrolled adults with wAIHA (Hgb <10 g/dL, laboratory evidence of hemolysis, and direct antiglobulin test with positive IgG with or without C3d) who had received ≥1 prior therapy and consented to participate
- Participants were randomized (1:1:1) to receive nipocalimab 30 mg/kg intravenous (IV) every 4 weeks (q4w), nipocalimab 15 mg/kg IV every 2 weeks (q2w), or placebo IV q2w during the 24-week DB period of the study (**Figure 1**)

### Biomarker Sample Analyses

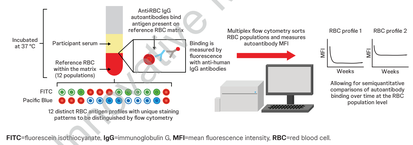
- Total IgG, Hgb, bilirubin levels, and reticulocyte counts were measured at Medpace Reference Laboratories during the DB period
- Pathogenic anti-RBC IgG autoantibody levels were determined in a subset of participants from the ENERGY study during the DB period, where samples were available and local regulation was permitted
  - All samples from participants who received a rescue blood transfusion and/or IV immunoglobulins before Week 16 were excluded from analyses
  - Participants who received a rescue blood transfusion and/or IV immunoglobulins after Week 16 had all data points after the rescue treatment excluded
- Pathogenic anti-RBC IgG levels were evaluated at Sanquin Diagnostiek B.V. using a semiquantitative, multiplex flow cytometry–based assay to measure binding of anti-RBC IgG to 12 reference RBC populations at 37 °C (representing warm autoantibodies pathogenic in wAIHA; **Figure 2**)
- The median percent change values across all reference RBC types that had positive antibody binding at baseline were used to represent the overall percent change in pathogenic anti-RBC IgG
- Percent changes in total and anti-RBC IgG levels were presented with the last observation carried forward (LOCF). Spearman correlations of change in total and anti-RBC IgG levels with changes in Hgb and hemolytic markers (ie, reticulocyte counts, indirect bilirubin) were determined

**FIGURE 1: Study design schematic**




**A**=assignment, **DB**=double-blind, **Hgb**=hemoglobin, **IV**=intravenous, **OLE**=open-label extension, **PD**=pharmacodynamics, **PK**=pharmacokinetics, **q2w**=every 2 weeks, **q4w**=every 4 weeks, **R**=randomization, **W**=Week.
[a]Participants who met failure criteria (ie, failure to demonstrate ↑ g/dL Hgb increase and presence of symptoms) at or after W16 were allowed early escape to the OLE.

**FIGURE 2: A semiquantitative, multiplex flow cytometry–based assay to measure serum anti-RBC IgG levels**




**FITC**=fluorescein isothiocyanate, **IgG**=immunoglobulin G, **MFI**=mean fluorescence intensity, **RBC**=red blood cell.

## Key Takeaways

- **Nipocalimab rapidly and persistently reduced total and pathogenic IgG in wAIHA, consistent with its mechanism of action as an FcRn blocker**
- **Reduction in anti-RBC IgG correlated with improvement in Hgb and hemolysis markers, providing potential mechanistic support for the clinical effectiveness of nipocalimab in wAIHA**
- **Altogether, these findings support FcRn blockade as a mechanism-based therapeutic approach in wAIHA**

## Results

### Demographics and Clinical Characteristics

- Disposition of 118 participants in the ENERGY study was based on participant consent, local regulations, and sample availabilities; the following analyses had:
  - Total IgG (N = 114): 38, 37, and 39 participants for nipocalimab 30 mg/kg IV q4w, 15 mg/kg IV q2w, and placebo, respectively
  - Anti-RBC IgG (N = 89): 30, 31, and 28 participants for nipocalimab 30 mg/kg IV q4w, 15 mg/kg IV q2w, and placebo, respectively
- Baseline clinical characteristics for participants in the PD analysis sets were similar (**Table 1**)

**TABLE 1: Baseline demographic and clinical characteristics**

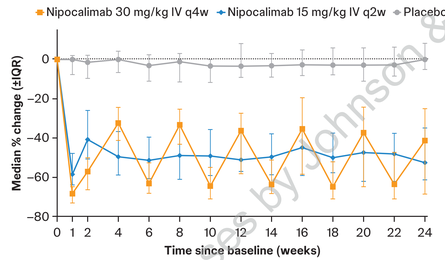
| | Total IgG analysis (N = 114) | Anti-RBC IgG analysis (N = 89) |
|---|---|---|
| **Female,** n (%) | 63 (55) | 49 (55) |
| **Age in years,** mean (SD) | 57 (17) | 57 (17) |
| **Primary wAIHA,** n (%) | 99 (87) | 80 (90) |
| **Months from initial wAIHA diagnosis,** median (IQR) | 31 (19-70) | 30 (19-66) |
| **Hematologic characteristics,** mean (SD) | | |
| Total IgG, g/L | 10.5 (4.9) | 10.6 (5.1) |
| Indirect bilirubin, µmol/L | 40 (32) | 40 (33) |
| Hgb, g/dL | 8.9 (1.3) | 9.1 (1.2) |
| Reticulocytes, cells/µL | 259 (132) | 255 (130) |

**Hgb**=hemoglobin, **IgG**=immunoglobulin G, **IQR**=interquartile range, **RBC**=red blood cell, **SD**=standard deviation, **wAIHA**=warm autoimmune hemolytic anemia.

### Total IgG Levels

- Rapid and persistent reduction in total IgG was observed from Week 1 through Week 24 in the nipocalimab groups compared with placebo (**Figure 3**)
- For the 30 mg/kg IV q4w regimen, alternating peaks and nadirs in total IgG were observed due to q4w dosing with a q2w sampling schedule
- The median overall reduction from baseline in total IgG was:
  - Week 1: 69% and 60% for nipocalimab 30 mg/kg IV q4w and 15 mg/kg IV q2w, respectively
  - Week 24: 33% and 53% for nipocalimab 30 mg/kg IV q4w and 15 mg/kg IV q2w, respectively

**FIGURE 3: Total IgG levels over time**



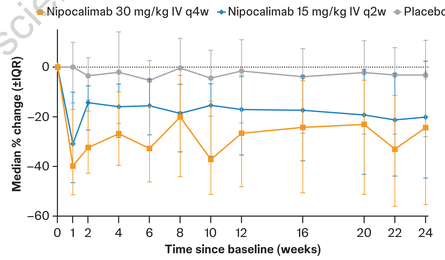

| Participants | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nipocalimab 30 mg/kg IV q4w | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 38 |
| Nipocalimab 15 mg/kg IV q2w | 37 | 37 | 37 | 37 | 37 | 37 | 37 | 37 | 37 | 37 | 37 | 37 | 37 | 37 |
| Placebo | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 39 | 38 | 38 | 38 | 38 |

**IgG**=immunoglobulin G, **IQR**=interquartile range, **IV**=intravenous, **q2w**=every 2 weeks, **q4w**=every 4 weeks.

### Pathogenic Anti-RBC IgG Autoantibody Levels

- Rapid and persistent reduction in pathogenic anti-RBC IgG autoantibodies was observed in nipocalimab treatment groups (**Figure 4**), with consistent trends across the 12 reference RBC types
- The median overall reduction in anti-RBC IgG was:
  - Week 1: 41% and 35% for nipocalimab 30 mg/kg IV q4w and 15 mg/kg IV q2w, respectively
  - Week 24: 23% and 16% for nipocalimab 30 mg/kg IV q4w and 15 mg/kg IV q2w, respectively
- No appreciable reduction was observed with placebo over 24 weeks

**FIGURE 4: Summary plot of anti-RBC IgG over time**



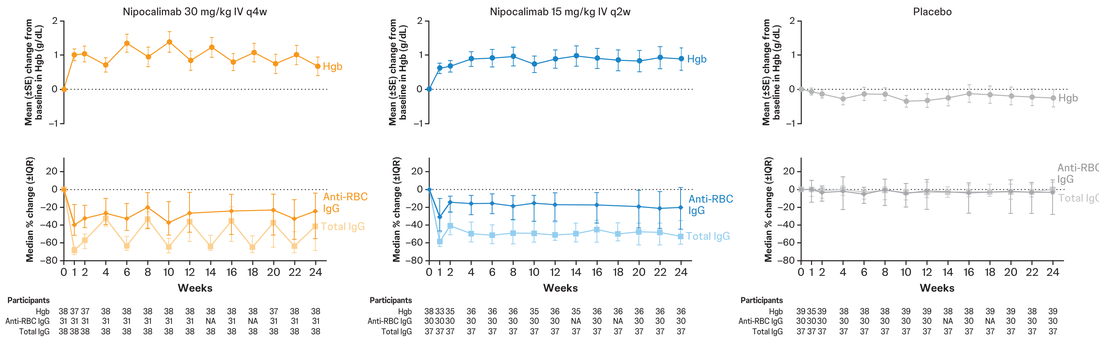

| Participants | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nipocalimab 30 mg/kg IV q4w | 31 | 31 | 31 | 31 | 31 | 31 | 31 | 31 | 31 | 31 | 31 | 31 | 31 | 31 |
| Nipocalimab 15 mg/kg IV q2w | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| Placebo | 28 | 28 | 28 | 28 | 28 | 28 | 28 | 28 | 28 | 28 | 28 | 28 | 28 | 28 |

**IgG**=immunoglobulin G, **IQR**=interquartile range, **IV**=intravenous, **q2w**=every 2 weeks, **q4w**=every 4 weeks, **RBC**=red blood cell.

### Correlations Between Changes in Hematologic Levels and Changes in Pathogenic Anti-RBC IgG Autoantibodies

- In nipocalimab-treated participants, concordant changes for Hgb and PD biomarkers in opposite directions were observed. This was more apparent in the 30 mg/kg IV q4w group, which had alternating peaks and nadirs in total IgG (**Figure 5**)
- In all participants included in the analysis, pathogenic anti-RBC IgG reduction correlated with improvement in Hgb ($R$ = −0.33, $P$ <0.0001) as well as improvement in hemolytic markers, such as reticulocyte counts ($R$ = 0.31, $P$ <0.0001) and indirect bilirubin levels ($R$ = 0.24, $P$ <0.0001; **Figure 6**)
- A similar and more modest correlation was observed between total IgG reduction and Hgb improvement ($R$ = −0.22, $P$ <0.0001; data not shown)

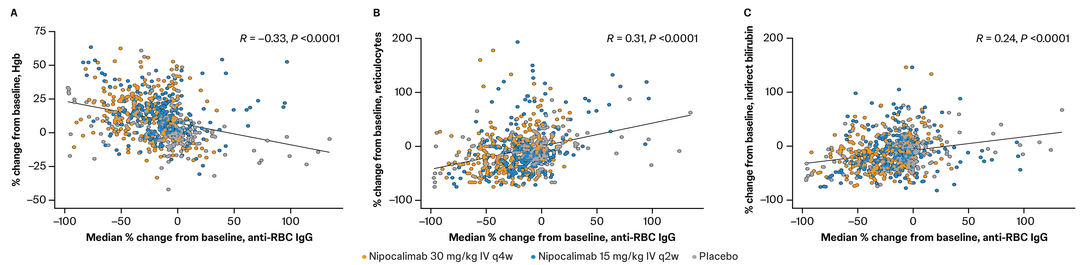
**FIGURE 5: Concordance between Hgb improvement and reductions in total IgG and pathogenic anti-RBC IgG autoantibodies**




| Participants | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hgb | 38 | 37 | 37 | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 37 | 38 | 38 | |
| Anti-RBC IgG | 31 | 31 | 31 | 31 | 31 | 31 | NA | 31 | NA | 31 | 31 | 31 | | |
| Total IgG | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 38 | 38 | | |
| Hgb | 38 | 33 | 35 | 36 | 36 | 36 | 35 | 36 | 35 | 36 | 36 | 36 | 36 | |
| Anti-RBC IgG | 30 | 30 | 30 | 30 | 30 | 30 | NA | 30 | NA | 30 | NA | 30 | 30 | |
| Total IgG | 37 | 37 | 37 | 37 | 37 | 37 | 37 | 37 | 37 | 37 | 37 | 37 | 37 | |
| Hgb | 39 | 35 | 39 | 38 | 38 | 38 | 39 | 39 | 38 | 38 | 39 | 39 | 38 | 39 |
| Anti-RBC IgG | 30 | 30 | 30 | 30 | 30 | 30 | NA | 30 | NA | 30 | 30 | 30 | 30 | 30 |
| Total IgG | 37 | 37 | 37 | 37 | 37 | 37 | 37 | 37 | 37 | 37 | 37 | 37 | 37 | 37 |

**Hgb**=hemoglobin, **IgG**=immunoglobulin G, **IQR**=interquartile range, **IV**=intravenous, **NA**=not available, **q2w**=every 2 weeks, **q4w**=every 4 weeks, **RBC**=red blood cell, **SE**=standard error.

**FIGURE 6: Spearman correlation analysis of percent change from baseline: (A) Hgb, (B) reticulocyte counts, and (C) indirect bilirubin versus percent change from baseline in anti-RBC IgG autoantibodies during the DB period**




**DB**=double-blind, **Hgb**=hemoglobin, **IgG**=immunoglobulin G, **q2w**=every 2 weeks, **q4w**=every 4 weeks, **RBC**=red blood cell.



**PRESENTED AT:** The 31st European Hematology Association (EHA) Congress; 11-14 June 2026; Stockholm, Sweden. **REFERENCES: 1.** Barcellini W, et al. *Blood.* 2014;124(19):2930-2936. **2.** Berentsen S, Barcellini W. *N Engl J Med.* 2021;385(15):1407-1419. **3.** Cherif H, et al. *Eur J Haematol.* 2025;114(1):129-138. **4.** Pyzik M, et al. *Nat Rev Immunol.* 2023;23(7):415-432. **5.** Seth NP, et al. *MAbs.* 2025;17(1):2461191. **6.** Ling LE, et al. *Clin Pharmacol Ther.* 2019;105(4):1031-1039. **7.** Noaiseh G, et al. *Lancet.* 2025;406(10518):2435-2448. **8.** Antozzi C, et al. *Neurology.* 2024;102(2):e207937. **ACKNOWLEDGMENTS:** This research was sponsored by Johnson & Johnson. Writing and editorial assistance were provided by Sarah M Ferrigno, PhD, of Lumanity Communications Inc., and were funded by Johnson & Johnson. **DISCLOSURES: BF** received honoraria for service on a consultancy/advisory board from Alexion, Johnson & Johnson, Novartis, Recordati, Roche, and Sobi. **IM** received research funding from Alexion, Annexon, Bioverativ, Incyte, Kezar, Novartis, Principia, Rigel, and Sanofi; and served in a consulting role for Alexion, Alpine/Vertex, Apellis, Janssen, Novartis, Sanofi, and Recordati. **YU** received honoraria from Alexion, Chugai, Incyte, Kaken, Nippon Shinyaku, Novartis, Recordati, Sanofi, and Sobi; received consultancy fees from Alexion, Asahi Kasei, Chugai, Janssen, Johnson & Johnson, Novartis, Ono Pharmaceutical, Recordati, Sanofi, and Sobi; received research funding from Chugai; and serves as an editor for the *International Journal of Hematology.* **JMIV** received research support from BeOne and AbbVie/Genmab; received consultancy fees from Sanofi and Janssen; and received speaker fees from BMS, BeOne, Sanofi, and Amgen (all paid to the institute). **EM**, **VL**, **KB**, **LEL**, **CS**, **KS**, **CAC**, **SG**, and **MTdS** are employees of and may hold stock/stock options in Johnson & Johnson. **EvdA** and **KF** have no conflicts to disclose.