Assessment of Nipocalimab Effects on Fatigue in Warm Autoimmune Hemolytic Anemia: Results From the Double-Blind Phase 2/3 ENERGY Trial

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Key Takeaways

- **Nipocalimab demonstrated a benefit in durable hemoglobin response as well as improvements in debilitating fatigue**
- **A greater proportion of patients on nipocalimab 30 mg/kg q4w reported fatigue improvement through Week 24, with improvements observed as early as Week 2**
- **Patients on nipocalimab reported improvement on FACIT-Fatigue experience and impact subscales**
- **A greater number of nipocalimab-treated patients met or exceeded the FACIT-Fatigue meaningful change threshold (6-points or more) compared with placebo**
- **FACIT-Fatigue scores showed low to moderate correlation with hemoglobin across the study and at Week 24**

Background

- Warm autoimmune hemolytic anemia (wAIHA) is a life-threatening, relapsing-remitting disease characterized by autoantibody-mediated premature destruction of red blood cells (RBCs)[1-3]
- Fatigue is the primary patient-reported symptom of wAIHA, and is identified as the most debilitating symptom by patients, requiring frequent rest during the day and limiting their capacity to function[4,5]
  - Additional symptoms include dizziness, weakness, and shortness of breath
  - wAIHA symptoms impact nearly all domains of health-related quality of life (HRQoL), including daily activities, work, social life, and emotional well-being
  - Patients report frustration, anxiety, and fear as consequences of not knowing then they might experience a relapse
- Nipocalimab is an immunoselective neonatal Fc receptor (FcRn) blocker that reduces circulating immunoglobulin G (IgG) levels, including pathogenic autoantibodies, while preserving immune function[6-10]
  - In wAIHA, nipocalimab lowers anti-RBC pathogenic antibodies and has the potential of decreasing hemolysis and increasing hemoglobin[11]

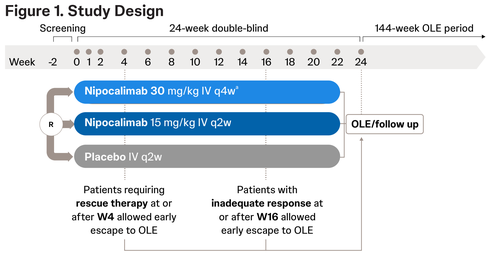
Objectives

- To assess the impact of intravenous nipocalimab on fatigue in patients with wAIHA using data from the ENERGY trial

Methods

- ENERGY (NCT04119050) is a multicenter, randomized, double-blind, placebo-controlled, phase 2/3 study evaluating safety and efficacy of nipocalimab vs placebo in patients with wAIHA (**Figure 1**)

Figure 1. Study Design



Statistical significance determined based on equal-weight approach to control the family-wise type I error rate. [a]Nipocalimab 30 mg/kg IV at W0 and q4w through W20 and placebo IV at W2 and q4w through W22.
***C3d**=complement component 3d, **DAT**=direct antiglobulin test, **FACIT-Fatigue**=Functional Assessment of Chronic Illness Therapy-Fatigue, **Hgb**=hemoglobin, **IgG**=immunoglobulin G, **IV**=intravenous, **OLE**=open-label extension, **q2w**=every 2 weeks, **q4w**=every 4 weeks, **R**=randomization, **W**=week, **wAIHA**=warm autoimmune hemolytic anemia.*

Participants
- ≥18 years of age
- Primary or secondary wAIHA (for ≥3 months)
- Current or previous treatment
- Hgb <10 g/dL
- Positive DAT (IgG or IgG+C3d)
- Evidence of hemolysis

Primary Endpoint: Durable Hemoglobin Response
- Hgb ≥10 g/dL **AND**
- Hgb increase ≥2 g/dL from baseline **AND**
- For 3 consecutive visits (≥28 days) **AND**
- Starting by Week 16 **AND**
- Without rescue therapy or dose modification of ongoing stable background treatment for wAIHA, including any increase in oral corticosteroids

Key Secondary Endpoints
- Improvement in FACIT-Fatigue[12] (Week 24)
- Corticosteroid dose reduction (Week 24)

FACIT-Fatigue
- Thirteen items scored on a 5-point Likert scale from 0 to 4
  - Total score range: 0 (worst fatigue) to 52 (no fatigue)
- Contains experience (feeling of fatigue; 5 items) and impact (daily functioning; 8 items) subscales
- 7-day recall period
- Meaningful change threshold (MCT) for an individual patient-level improvement on FACIT-Fatigue total score established as 6-points

Results

Baseline characteristics

- Baseline characteristics were consistent with the wAIHA patient population (**Table 1**)

Table 1. Baseline characteristics

Baseline characteristics	Nipocalimab 30 mg/kg q4w (n=38)	Nipocalimab 15 mg/kg q2w (n=38)	Placebo (n=39)
Mean age (range), years	56.1 (24–79)	53.1 (18–80)	59.9 (24–86)
Female (%)	55	58	51
Primary wAIHA[a] (%)	92	87	82
Median (IQR) time since diagnosis, months	32 (20–60)	44 (21–81)	23 (17–71)
Mean (SD) baseline hemoglobin, g/dL	9.2 (1.4)	8.6 (1.3)	9.0 (1.4)
Mean (SD) FACIT-Fatigue score	34.5 (10.7)	35.0 (10.5)	31.1 (12.2)
Current treatments for wAIHA (%)			
Any concomitant CS	74	87	77
IST or CS at >20 mg/day of prednisone or equivalent[a]	45	39	46
Prior treatments for wAIHA (%)			
Prior rituximab use	42	55	49
Prior transfusions	58	58	59
Prior splenectomy	3	16	10

[a]Stratification factors (primary or versus secondary wAIHA; screening hemoglobin ≤8.5 g/dL or versus >8.5 g/dL; no treatment or corticosteroids at dose ≤20 mg/day of prednisone or equivalent with no immunosuppressants vs immunosuppressants or corticosteroids at >20 mg/day of prednisone or equivalent or no such treatment).
***CS**=corticosteroids, **FACIT-Fatigue**=Functional Assessment of Chronic Illness Therapy-Fatigue, **IQR**=interquartile range, **IST**=immunosuppressive therapy, **q2w**=every 2 weeks, **q4w**=every 4 weeks, **SD**=standard deviation, **wAIHA**=warm autoimmune hemolytic anemia.*

Safety

- Safety findings were consistent with the known safety profile of nipocalimab and the known clinical risks associated with wAIHA (**Table 2**)

Table 2. Summary of treatment-emergent adverse events with nipocalimab versus placebo in wAIHA patients

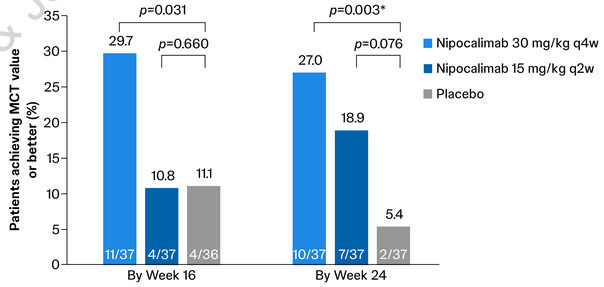
AE, n (%)	Nipocalimab 30 mg/kg q4w (n=38)	Nipocalimab 15 mg/kg q2w (n=38)	Placebo (n=39)
TEAEs	35 (92.1)	30 (81.1)	35 (89.7)
SAEs	8 (21.1)	6 (16.2)	14 (35.9)
AEs leading to discontinuation	2 (5.3)	5 (13.5)	1 (2.6)
AEs of interest			
Grade ≥3 infections	2 (5.3)	3 (8.1)	5 (12.8)
Adjudicated MACE	0	2 (5.4)	0
Adjudicated DVT and/or PE	1 (2.6)	0	0
Hypoalbuminemia (albumin <20 g/L)	0	0	0
Death	0	2 (5.4)	0

***AE**=adverse event, **DVT**=deep vein thrombosis, **MACE**=major adverse cardiovascular event, **PE**=pulmonary embolism, **q2w**=every 2 weeks, **q4w**=every 4 weeks, **SAE**=serious AE, **TEAE**=treatment-emergent AE.*

Achievement of MCT for FACIT-Fatigue

- A greater proportion of patients on nipocalimab 30 mg/kg q4w met or exceeded the MCT (6-point improvement) for FACIT-Fatigue (**Figure 4**)

Figure 4. Patients achieving MCT value of 6-point improvement or better for FACIT-Fatigue

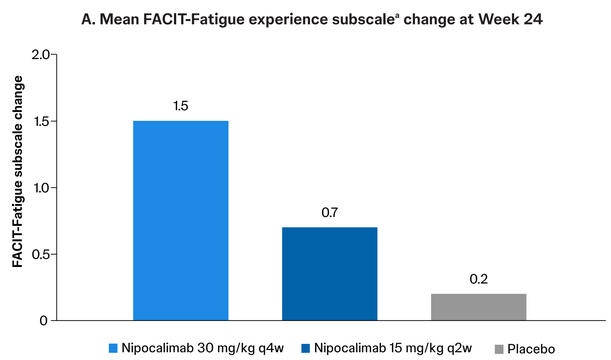


P value based on a Stratified Cochran-Mantel-Haenszel test with wAIHA disease classification (primary or vs secondary wAIHA), screening hemoglobin value (≤8.5 g/dL vs >8.5 g/dL), and concurrent treatment for wAIHA (no treatment or corticosteroids at dose ≤20 mg/day of prednisone or equivalent with no immunosuppressants vs immunosuppressants or corticosteroids at >20 mg/day of prednisone or equivalent) as stratification factors. If the Mantel Fleiss criterion was not satisfied, then a Fisher's exact test was performed.
**One-sided p<0.02499 vs placebo considered nominally significant.*
***FACIT-Fatigue**=Functional Assessment of Chronic Illness Therapy-Fatigue, **MCT**=meaningful change threshold, **q2w**=every 2 weeks, **q4w**=every 4 weeks, **wAIHA**=warm autoimmune hemolytic anemia.*

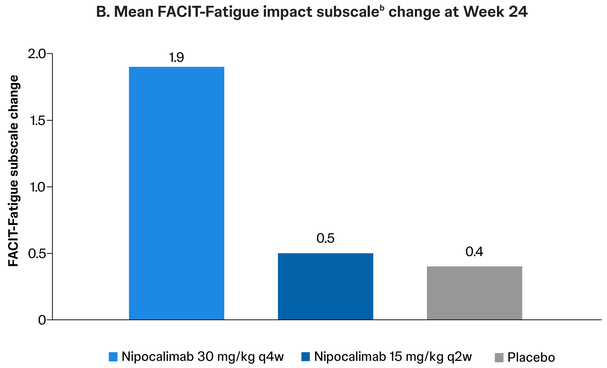
Mean FACIT-Fatigue subscales change at Week 24

- FACIT-Fatigue subscales evaluating feeling of fatigue and impact on daily functioning showed improvement with nipocalimab 30 mg/kg q4w (**Figure 6**)

Figure 6. FACIT-Fatigue subscales change at Week 24



[a]Experience subscale includes 5 items.

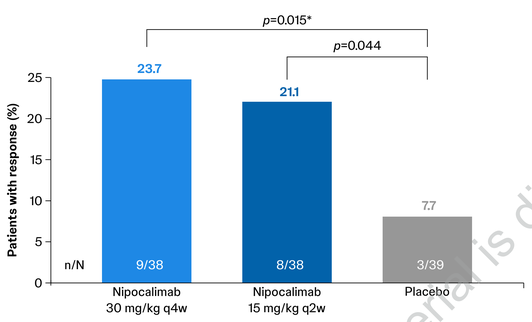


[b]Impact subscale includes 8 items.
***FACIT-Fatigue**=Functional Assessment of Chronic Illness Therapy-Fatigue, **q2w**=every 2 weeks, **q4w**=every 4 weeks.*

Primary endpoint: durable hemoglobin response

- Nipocalimab 30 mg/kg q4w significantly improved durable hemoglobin response versus placebo (p=0.015; **Figure 2**)

Figure 2. Durable hemoglobin response with nipocalimab versus placebo

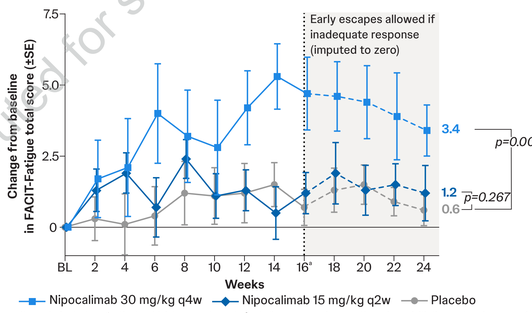


*Composite analysis strategy (patients with intercurrent events [including any use of rescue therapies or initiation or dose increase of protocol-specified standard-of-care background therapy] were considered to be nonresponders). P values based on equal-weight approach to control the family-wise type I error rate with a 1-sided α=0.02499 using a Cochran-Mantel-Haenszel test. *One-sided p<0.02499 vs placebo considered significant.*
***q2w**=every 2 weeks, **q4w**=every 4 weeks.*

Key secondary endpoint: change in FACIT-Fatigue total score from baseline

- Nipocalimab 30 mg/kg delivered rapid improvements in fatigue at Week 2, which was maintained through Week 24 (**Figure 3**)

Figure 3. Change in FACIT-Fatigue total score from baseline through Week 24

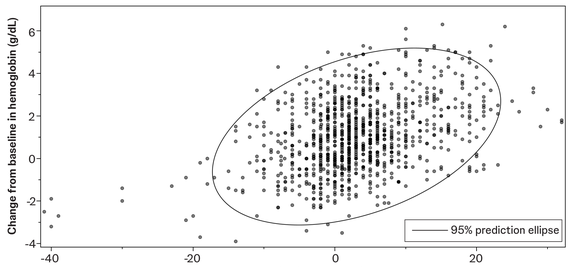


*Composite analysis strategy (patients with intercurrent events [including any use of rescue therapies or initiation or dose increase of protocol-specified standard-of-care background therapy] were considered to be nonresponders). P values based on equal-weight approach to control the family-wise type I error rate. *One-sided p<0.02499 vs placebo considered nominally significant, based on an equal-weight approach to control the family-wise type I error rate. [c]Participants meeting failure criteria (ie, presence of symptoms and failure to demonstrate ≥1 g/dL hemoglobin increase) at or after Week 16 were, at the investigator's discretion, allowed discontinuation of double-blinded treatment and early escape to the OLE.*
***BL**=baseline, **FACIT-Fatigue**=Functional Assessment of Chronic Illness Therapy-Fatigue, **OLE**=open-label extension, **q2w**=every 2 weeks, **q4w**=every 4 weeks, **SE**=standard error.*

Change in FACIT-Fatigue total score vs change in hemoglobin

- Changes in FACIT-Fatigue total score showed low to moderate correlation with changes in hemoglobin (**Figure 5**)
- Correlation with all treatment groups combined:
  - Across all time points (repeated measures correlation): r=0.4353
  - At Week 24: r=0.3331

Figure 5. Change in FACIT-Fatigue total score vs change in hemoglobin across all time points post-baseline



Based on 1020 observations; p<0.0001. The correlation coefficient is calculated using all visits and treatments together, therefore one patient contributes multiple pairs of data. A mixed model approach proposed by Hamlett, Ryan, and Wolfinger[13] was used because it fully specifies the correlation structure within a subject's repeated measurements using both the within-subject as well as between subject variation.
***FACIT-Fatigue**=Functional Assessment of Chronic Illness Therapy-Fatigue.*

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