Assessment of Pharmacokinetic and Pharmacodynamic Drug-Drug Interactions with Nipocalimab and Relevance to Patients with Rheumatic Diseases

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Key Takeaways

- **Co-administration of nipocalimab with fremanezumab or etanercept decreased pharmacokinetic exposure of treatments across Phase 1 studies**
- **There was no impact of fremanezumab, etanercept or hydroxychloroquine on pharmacokinetic exposure of nipocalimab**
- **Although healthy participants were enrolled, these findings may help inform patients with auto-immune diseases given nipocalimab in combination with other monoclonal antibodies, IgG-based Fc-fusion proteins, as well as those taking (hydroxy) chloroquine**

Background

The neonatal Fc receptor (FcRn) interacts with the fragment crystallizable (Fc) portion of immunoglobulin G (IgG) and extends IgG half-life by preventing its lysosomal degradation[1]

Nipocalimab, is in clinical development as a treatment for auto-immune diseases. It selectively binds the IgG binding site on the FcRn receptor, thereby blocking FcRn recycling. This could potentially increase the clearance of IgG and interfere with the pharmacokinetics (PK) of co-administered IgG- and Fc-based therapeutic proteins, leading to potential drug-drug interactions[2]

Nipocalimab may increase the clearance of **fremanezumab**, a prototypical monoclonal antibody with a long half-life, or **etanercept**, an Fc fusion protein[3,4]

Hydroxychloroquine, an immunosuppressive therapy used in the treatment of rheumatology diseases, may raise lysosomal pH and reduce the IgG lowering effect of nipocalimab through a pharmacodynamic (PD)-based interaction[5]

Objectives

To assess the drug-drug interaction between nipocalimab and fremanezumab or etanercept for PK-based interactions, and between nipocalimab and hydroxychloroquine for PD-based interactions in healthy subjects in 2 Phase 1 clinical studies

Methods

In a Phase 1 study, fremanezumab was administered alone as a single dose on Day 1, co-administered with nipocalimab on Day 1, or off-set administered on Day 1 followed by nipocalimab on Day 15 (Figure 1)

- Primary endpoint was to evaluate the effect of nipocalimab co-administration on fremanezumab PK in healthy participants
- Secondary endpoints were to characterize the adverse events of nipocalimab after co-administration of fremanezumab

In a 2-part Phase 1 study, the potential PK interaction of nipocalimab on etanercept (part 1) or hydroxychloroquine on nipocalimab (part 2) was assessed in healthy participants (Figure 2)

- Primary endpoint for part 1 was to evaluate the effect of nipocalimab on the PK of etanercept
- Primary endpoint for part 2 was to characterize the effect of hydroxychloroquine on IgG reduction and the PK profile of nipocalimab after co-administration

FIGURE 1. Study design of an open-label, parallel, 3-way, drug interaction study to investigate the effect of nipocalimab or off-set administration on the PK of fremanezumab in healthy participants

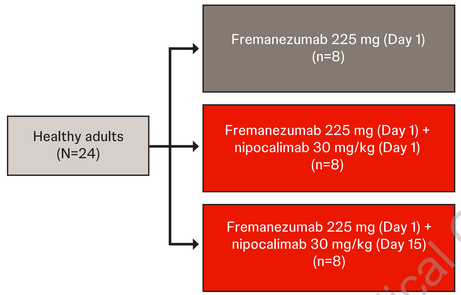
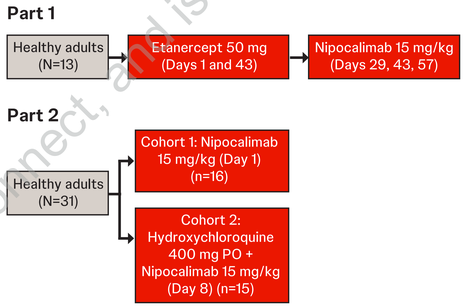


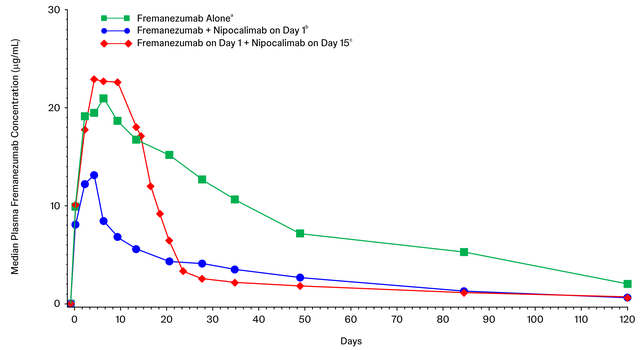
FIGURE 2. Study design of a drug-drug interaction study to investigate the effect of nipocalimab administration on the PK of etanercept (Part 1) or hydroxychloroquine on the PK and PD of nipocalimab (Part 2) in healthy participants



Results

Co- and offset-administration of nipocalimab with fremanezumab greatly reduced the exposure of fremanezumab compared with fremanezumab alone

- When co-administered with nipocalimab, **maximum concentration (C_{max}) and exposure ($AUC_{0\text{-}inf}$) of fremanezumab decreased by 42% and 66%, respectively, compared with fremanezumab alone**
- When nipocalimab was administered 14 days after fremanezumab (offset), **the exposure of fremanezumab decreased by 54% but the C_{max} remained unchanged compared with fremanezumab alone**



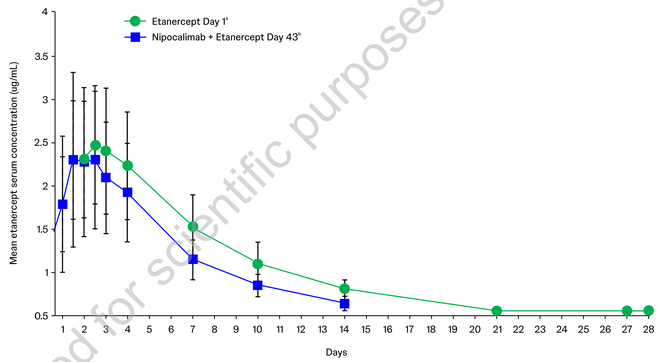
Treatment comparison	Parameter	Treatment Geometric LSMs: Test (n)	Reference (n)	Ratio of Geometric Mean, % (90% CI)
Fremanezumab + nipocalimab together (Test)[b] vs fremanezumab alone (Reference)[a]	C_{max} (µg/mL)	13.1 (8)	22.7 (8)	57.7 (44.1-75.6)
	$AUC_{0\text{-}last}$ (µg*d/mL)	352 (8)	1013 (8)	34.7 (28.7-42.1)
	$AUC_{0\text{-}inf}$ (µg*d/mL)	386 (8)	1125 (8)	34.4 (28.1-42.0)
Fremanezumab on D1 + nipocalimab on D15 (Test)[c] vs fremanezumab alone (Reference)[a]	C_{max} (µg/mL)	24.5 (8)	22.7 (8)	108 (82.6-142)
	$AUC_{0\text{-}last}$ (µg*d/mL)	483 (7)	1013 (8)	47.7 (39.1-58.2)
	$AUC_{0\text{-}inf}$ (µg*d/mL)	517 (7)	1125 (8)	46.0 (37.4-56.6)

[a]Fremanezumab alone: 225 mg fremanezumab subcutaneous injection at Hour 0 on Day 1. [b]Co-administration of fremanezumab + nipocalimab: 225 mg fremanezumab subcutaneous injection co-administered with 30 mg/kg nipocalimab IV infusion over 30 minutes starting at Hour 0 on Day 1. [c]Offset treatment of fremanezumab + nipocalimab: 225 mg fremanezumab subcutaneous injection at Hour 0 on Day 1, and 30 mg/kg nipocalimab IV infusion over 30 minutes starting at Hour 0 on Day 15. $AUC_{0\text{-}inf}$, Area under the curve from time 0 to infinite time; $AUC_{0\text{-}last}$, Area under the curve from time 0 to last measurable concentration; CI, confidence interval; LSM, least squares of the mean.

- Treatment-emergent adverse events were **transient, mild or moderate in severity, resolved without medication, and were considered unrelated to study treatment**
- **No adverse events of special interest** or related to vital signs, electrocardiogram, or clinical laboratory parameters were reported
- 2 patients **discontinued treatment in the offset group, but this was not considered treatment-related**

Co-administration of nipocalimab with etanercept reduced etanercept concentration and exposure compared with etanercept alone

- When co-administered with nipocalimab, **C_{max} and AUC of etanercept decreased by 9% and 28%, respectively** when compared with participants who received etanercept alone



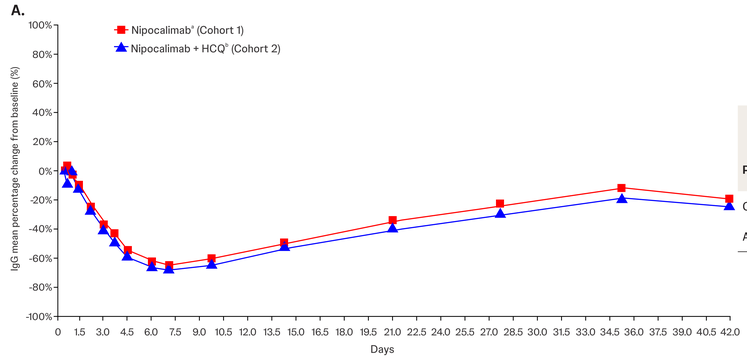
Treatment comparison	Parameter	Treatment Geometric LSMs: Test (n)[b]	Reference (n)	Ratio of Geometric Mean, % (90% CI)
Nipocalimab + etanercept together (Test)[b] vs etanercept (Reference)[a]	C_{max} (µg/mL)	2.0 (13)	2.2 (13)	91.4 (74.4-112.2)
	$AUC_{0\text{-}last}$ (µg*d/mL)	11.0 (13)	15.5 (13)	71.2 (60.7-83.6)
	$AUC_{0\text{-}inf}$ (µg*d/mL)	12.8 (11)	17.7 (11)	72.1 (62.5-83.2)

[a]Etanercept Day 1 (reference): on Day 1, participants were administered a single subcutaneous dose of 50 mg etanercept.
[b]Nipocalimab + Etanercept participants were administered a single subcutaneous dose of 50 mg etanercept on Days 1 and 43. Participants were administered nipocalimab as a single intravenous dose of 15 mg/kg on Days 29, 43 and 57.

Co-administration of hydroxychloroquine with nipocalimab did not impact IgG levels and had no impact on the pharmacokinetic profile of nipocalimab compared with administration of nipocalimab alone

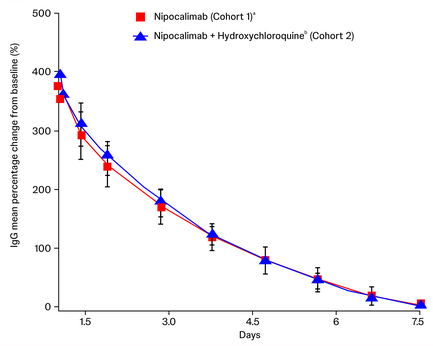
- IgG profiles **of nipocalimab were comparable when nipocalimab was administered with or without hydroxychloroquine** (**Figure A**)
- PK profile of nipocalimab **was similar with or without co-administration with hydroxychloroquine** (**Figure B**)

A.



Parameter	Treatment (reference)[a] Geometric LSMs (n)	Treatment (test)[b] Geometric LSMs (n)
C_{max} (µg/mL)	65.1 (16)	69.3 (15)
$AUC_{0\text{-}last}$ (µg*d/mL)	1401 (16)	1677 (15)

B.



Pharmacokinetic Parameter	Nipocalimab alone[a]	Nipocalimab + hydroxychloroquine[b]
Mean (SD) C_{max} (µg/mL)	382 (45.0) [n=16]	401 (47.1) [n=15]
Mean (SD) $AUC_{0\text{-}inf}$ (µg*d/mL)	920 (231) [n=12]	884 (117) [n=8]

[a]Nipocalimab (Reference): On Day 1, participants were administered a single dose of 15 mg/kg of nipocalimab as an IV infusion.
[b]Nipocalimab + Hydroxychloroquine (Test): On Day 8, participants were administered a single oral dose of 400 mg hydroxychloroquine followed immediately by a single dose of 15 mg/kg of nipocalimab as an IV infusion.

PRESENTED AT: European Alliance of Associations for Rheumatology (EULAR); June 11-14, 2025; Barcelona, Spain. **REFERENCES: 1.** Pyzik M, et al. *Front Immunol.* 2019;10:1540. **2.** Ling LE, et al. *Clin Pharmacol Ther.* 2019;105(4):1031-1039. **3.** Bei D, et al. Poster presented at American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM). Sep 21-24, 2022. **4.** Zhou J, et al. Poster presented at American College of Clinical Pharmacology (ACCP). Sep 25-27, 2022. **5.** Schrezenmeier E and Dorner T. *Nat Rev Rheumatol.* 2020;16(3):155-166. **DISCLOSURES:** Jia Zhou, An Vermeulen, Weirong Wang, and Jocelyn H. Leu are employees and/or stockholders of Johnson & Johnson. Di Bei was an employee of Johnson & Johnson at the time that this work was completed. She is now an employee of Otsuka.