Insights Into Nipocalimab-Neonatal Fragment Crystallizable Receptor Structure (FcRn), Binding Affinity, and Inhibition of Immunoglobulin G Recycling: Comparison With Efgartigimod

Scan the QR code.
The QR code is intended to provide scientific information for individual reference, and the information should not be altered or reproduced in any way.

Nilufer Seth[1], Rui Xu[2], Brian Stoveken[3], Matthew DuPrie[3], Samuel Sihapong[2], Traymon Beavers[3], Leona E. Ling[1], Maria Ait-Tihyaty[4], John J. Sheehan[5], Tuan Vu[6]

[1]Johnson & Johnson, Cambridge, MA, USA; [2]Johnson & Johnson, San Diego, CA, USA; [3]Johnson & Johnson, Spring House, PA, USA; [4]Johnson & Johnson, Raritan, NJ, USA; [5]Johnson & Johnson, Titusville, NJ, USA; [6]University of South Florida, Florida, USA

**Presented by Dr. Sheng Gao*

Introduction

- Nipocalimab is a fully human, aglycosylated monoclonal antibody with high affinity and specificity for neonatal fragment crystallizable receptor (FcRn) with a dissociation constant (K_D) of ≤31.7 pM at pH 6.0, and K_D ≤57.8 pM at pH 7.4.[1]
- Nipocalimab blocks the binding of immunoglobulin G (IgG) to FcRn, thereby inhibiting FcRn-mediated recycling of IgG and reducing circulating IgG levels, including pathogenic IgG.[1]
- Nipocalimab demonstrated a dose-dependent, pharmacokinetic-pharmacodynamic-receptor occupancy relationship resulting in rapid and sustained reductions in IgG, aligning with clinical response observed in patients with gMG.[1]
- Nipocalimab is being studied in several autoantibody and alloantibody diseases and has been approved by the U.S. Food and Drug Administration for use in anti-acetylcholine receptor antibodies (AChR) and anti-muscle-specific kinase (MuSk) antibody-positive patients (adults and adolescents aged ≥12 years) with generalized myasthenia gravis (gMG).[2]
- Efgartigimod is the Fc portion of an IgG1 antibody engineered for affinity to FcRn and is another FcRn inhibitor approved for gMG treatment.[3]

Objective

- **To compare the FcRn blockers, nipocalimab vs efgartigimod, with respect to their structural interactions with FcRn, binding affinities to FcRn, and potency of inhibition of IgG recycling in human aortic endothelial cells (HAECs).**

Methods

- Nipocalimab binding epitopes on FcRn were determined using X-ray crystallography (PDB ID: 9MI6).
- Efgartigimod-FcRn complex structure was downloaded from the Protein Data Bank (PDB ID: 7Q15).
- Binding affinities were determined using surface plasmon resonance.
- Imaging pulse-chase and IgG recycling assays were performed using HAECs which endogenously express FcRn.

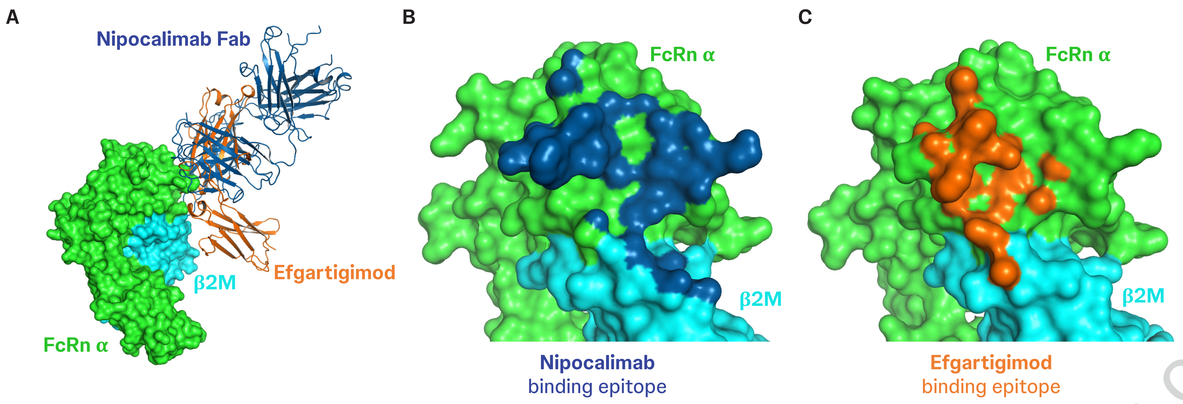
Key Takeaways

- **There were differences between nipocalimab and efgartigimod with respect to their binding epitopes, binding affinities, and inhibition of IgG recycling.**
- **Nipocalimab demonstrated:**
  - **30% larger binding interface with FcRn than efgartigimod.**
  - **Over 500-fold higher binding affinity at pH 6.0 and over 3,500-fold higher binding affinity at neutral pH versus efgartigimod**
  - **A longer intracellular residence time upto 18 hrs, consistent with its expected site of action (endosomal pathway) at lower doses than efgartigimod.**
  - **A ~300-fold greater in vitro inhibition of IgG recycling when compared to efgartigimod.**

Results

Nipocalimab has a 30% larger binding interface with FcRn compared with efgartigimod

Figure 1: Nipocalimab has a larger binding interface with FcRn (1017.5 Å²) compared with efgartigimod (651.3 Å²)



Structural overlay of nipocalimab and efgartigimod bound FcRn suggests that both molecules target the Fc binding site of FcRn (**Figure 1A**). But Nipocalimab binding footprint on FcRn (**Figure 1B**) is larger than that of efgartigimod (**Figure 1C**) (1017.5 Å² vs 651.3 Å²).

Nipocalimab has over 500-fold greater binding affinity to FcRn at pH 6.0 and over 3,500-fold greater binding to FcRn at neutral pH compared with efgartigimod

Table 1: SPR Binding Affinity (K_D) at (endosomal) pH 6.0

	n	k_a (M^{-1} s^{-1})	k_d (s^{-1})	K_D (pM)
Nipocalimab	20	2.05E+06	5.25E-05	≤32
Efgartigimod	4	8.52E+05	1.33E-02	16,100 (10,820–21,380)

Table 2: SPR Binding Affinity (K_D) at (cell surface) pH 7.4

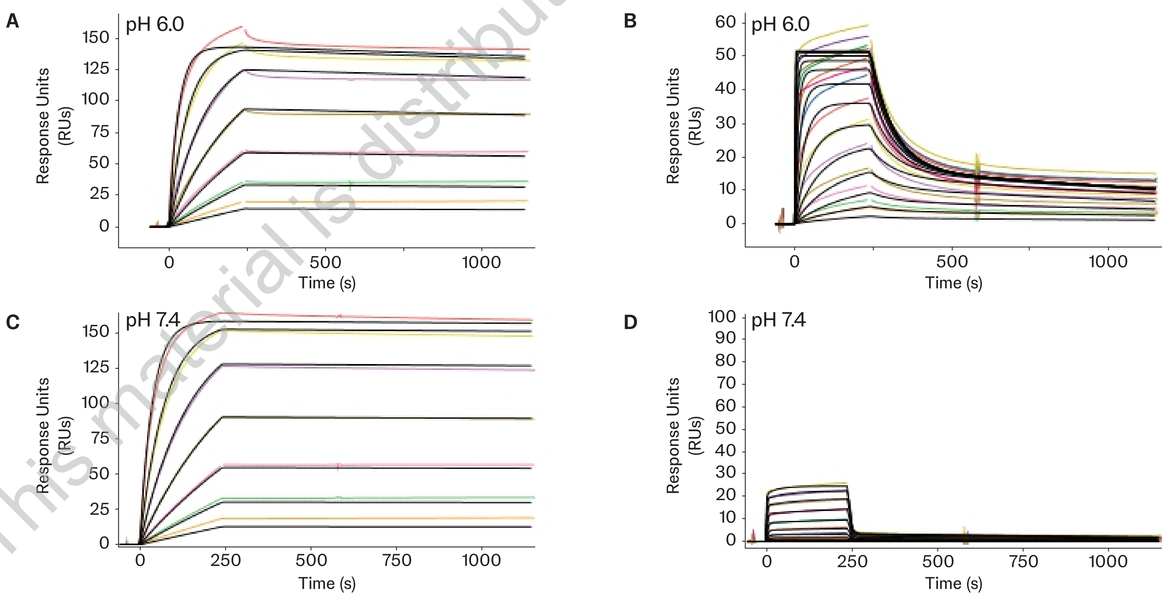
	n	k_a (M^{-1} s^{-1})	k_d (s^{-1})	K_D (pM)
Nipocalimab	22	1.28E+06	7.42E-05	≤58
Efgartigimod	4	8.26E+05	1.72E-01	208,000 (188,600-227,400)

- A large number of nipocalimab K_D values exceeded the limit of quantitation in this surface plasmon resonance (SPR) method, therefore the affinity reported is an upper limit.
- Efgartigimod binding data was modeled using a heterogenous-ligand binding model, to account for observed negative cooperativity in FcRn binding. Reported here is the dominant affinity interaction for efgartigimod (**Figure 2**).

Figure 2: SPR sensograms showing binding of niopcalimab or efgartigimod to FcRn at pH 6.0 and pH 7.4

Nipocalimab exhibits pH independent binding: high picomolar affinity to FcRn at both endosomal pH and neutral (cell surface) pH

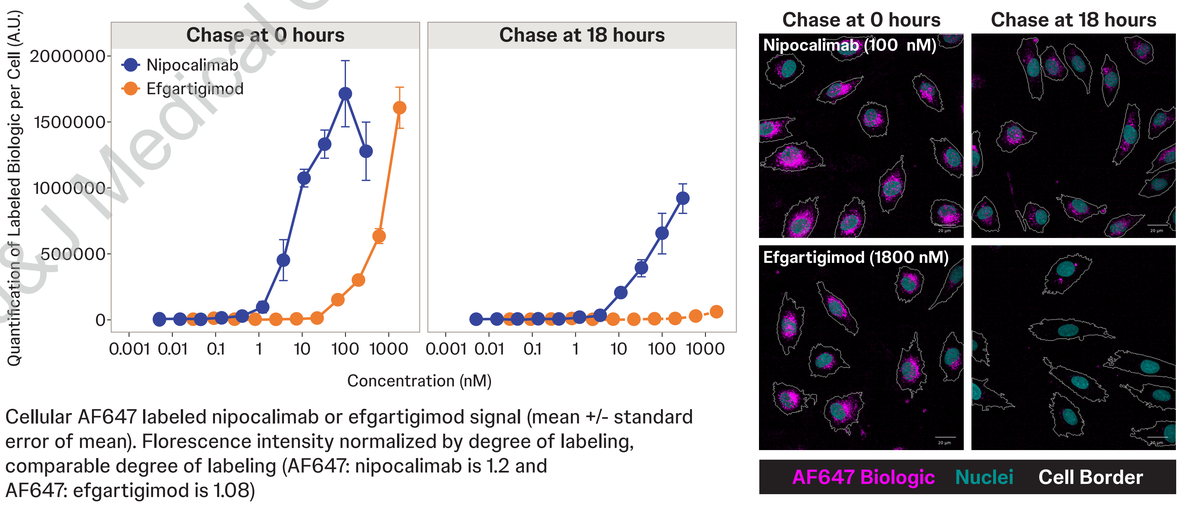
Efgartigimod exhibits pH dependent binding: low nanomolar affinity to FcRn at endosomal pH and 13-fold lower affinity at neutral (cell surface) pH



k_a=association rate constant, **k_d**=dissociation rate constant, **K_D**=Equilibrium dissociation constant; affinity of ligand/analyte binding, **n**=number of replicates, **M**=mole, **s**=second, **pM**=picomolar, **SPR**=surface plasmon resonance.

Nipocalimab exhibits longer intracellular residence time at lower doses versus efgartigimod

Figure 3: Pulse-Chase in HAECs



Cellular AF647 labeled nipocalimab or efgartigimod signal (mean +/- standard error of mean). Florescence intensity normalized by degree of labeling, comparable degree of labeling (AF647: nipocalimab is 1.2 and AF647: efgartigimod is 1.08)

HAECs expressing endogenous levels of FcRn were pulsed with different concentrations of Alexa Fluor 647–labeled nipocalimab or efgartigimod, for 1 hour and subsequently washed and chased for 0 or 18 hours. Cells were imaged using an Opera Phenix spinning disk confocal and analyzed in SImA.

100 nM of AF647 labeled nipocalimab and 1800 nM of AF647 efgartigimod were used for the pulse, cells were washed and imaged at 0 and 18 hours.

Nipocalimab demonstrated ~300-fold greater potency in inhibiting IgG recycling in a cell-based assay compared with efgartigimod

Figure 4: IgG recycling assays in HAECs

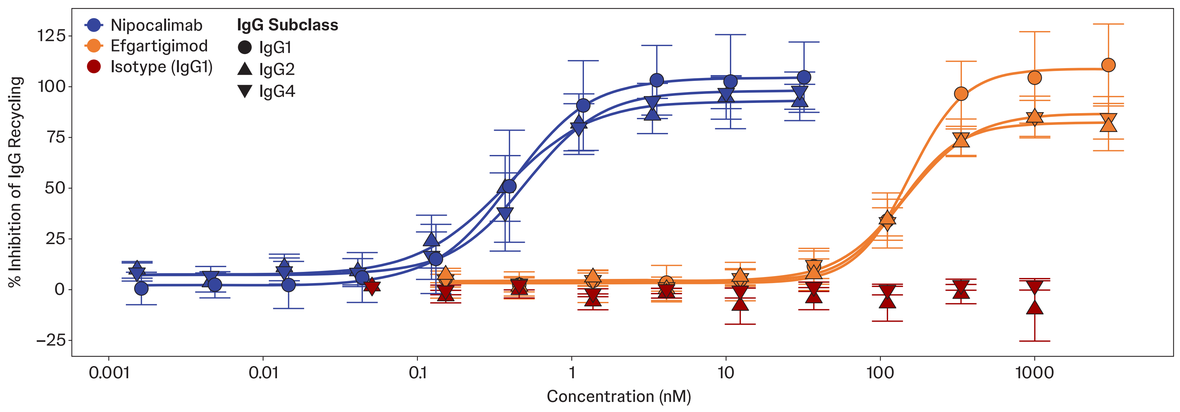


Table 3: IC_{50s} of nipocalimab and efgartigimod for inhibition of IgG subtypes

IgG	IgG1 (IC_{50})	IgG2 (IC_{50})	IgG4 (IC_{50})
Nipocalimab	0.41 nM	0.36 nM	0.51 nM
Efgartigimod	155 nM	136 nM	146 nM

- Concentration-response curves showing nipocalimab and efgartigimod potency against IgG subclasses IgG1, IgG2, and IgG4. Error bars represent standard deviation.
- IgG3 data was not generated due to lower binding affinity to FcRn, and poor cellular assay signals.

FcRn=neonatal fragment crystallizable receptor, **IC**=Inhibitory concentration, **IgG**=Immunoglobulin G, **nM**=nanomolar.

- Nipocalimab demonstrated 378-fold greater potency in inhibiting IgG1 and IgG2 recycling compared with efgartigimod.
- Nipocalimab demonstrated 286-fold greater potency in inhibiting IgG4 recycling compared with efgartigimod.

This material is distributed for scientific purposes on J&J Medical Connect, and is not for promotional use

PRESENTED AT: American Association of Neuromuscular & Electrodiagnostic Medicine (AANEM) 2025; San Francisco, CA, USA; Oct 29–Nov 1, 2025. **REFERENCES: 1.** Seth NP et al., *mAbs* 2025;17(1):2461191. **2.** Carlo A et al., *Lancet Neurol* 2025;24(2):105–116. **3.** argenx. FDA approves new treatment for myasthenia gravis [media release]. 17 Dec 2021. https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-myasthenia-gravis **ACKNOWLEDGMENTS:** The authors thank the participants and investigators for their participation in the study. Priyanka Bannikoppa, PhD and Divya Narayan (SIRO Medical Writing Pvt Ltd, India) and Doyel Mitra, PhD (Johnson & Johnson) provided editorial assistance. Amit Kavle (SIRO Medical Writing Pvt Ltd, India) provided graphic designing assistance for this poster. This study was sponsored by Johnson & Johnson. **DISCLOSURES: Nilufer Seth, Rui Xu, Brian Stoveken, Matthew DuPrie, Samuel Sihapong, Traymon Beavers, Leona E. Ling, Maria Ait-Tihyaty,** and **John J. Sheehan:** Employee of Johnson & Johnson and may hold stocks or stock options in Johnson & Johnson. **Tuan Vu:** MG-related research or grant support: Alexion/AstraZeneca Rare Disease, Amgen, argenx, Cartesians, COUR, Dianthus, Johnson & Johnson, Immunovant, NMD Pharma, Regeneron, and UCB; consultant &/or speaker bureau: Alexion, argenx, CSL Behring, Amgen, Johnson & Johnson, ImmunAbs, and Dianthus. **Maria Ait-Tihyaty:** Was an employee of Johnson & Johnson at the time of study and is currently employed at Dianthus Therapeutics. This study was sponsored by Johnson & Johnson.