Population Pharmacokinetics and Pharmacodynamics Modeling of Nipocalimab in Adolescents Aged 12 to Less Than 18 Years with Generalized Myasthenia Gravis

Yupeng Ren, PhD[1], Yaowei Zhu, PhD[2]*, Navin Goyal, PhD[2], Juan Jose Perez Ruixo, PhD[3], Ruben Faelens, PhD[3]

[1]Clinical Pharmacology and Pharmacometrics, Johnson & Johnson, Shanghai, China; [2]Clinical Pharmacology and Pharmacometrics, Johnson & Johnson, Spring House, PA, USA; [3]Clinical Pharmacology and Pharmacometrics, Johnson & Johnson, Beerse, Belgium

**Presenting author*

Key Takeaways

- **The adult PK-IgG model adapted for adolescents characterized the observed PK and PD profiles in adolescents with gMG.**
- **The similar model-predicted PK and PD profiles between adolescents and adults demonstrated that the dose regimen for adults (30 mg/kg intravenous [IV] followed by 15 mg/kg IV every-2-weeks) is also appropriate for adolescents with gMG.**

Background

- Nipocalimab is a fully human immunoglobulin G1 (IgG1) monoclonal antibody that binds with high affinity and blocks IgG-binding site on endogenous neonatal Fc receptor (FcRn).[1]
- Nipocalimab demonstrated sustained disease control when added to standard-of-care therapy in a phase 3 study in adults with generalized myasthenia gravis (gMG) who are positive for anti-acetylcholine receptor, anti-muscle-specific tyrosine kinase, or anti-low-density lipoprotein receptor-related protein 4 antibodies.[2]
- The pathophysiology of MG is similar between adult and pediatric patients.[3-6]
- In this regard, an ongoing, open-label phase 2/3 study (vibrance-MG) is evaluating the pharmacokinetics (PK) and pharmacodynamics (PD), safety and efficacy of nipocalimab in adolescents and children (≥2 to ≤12 years) with gMG.[7]

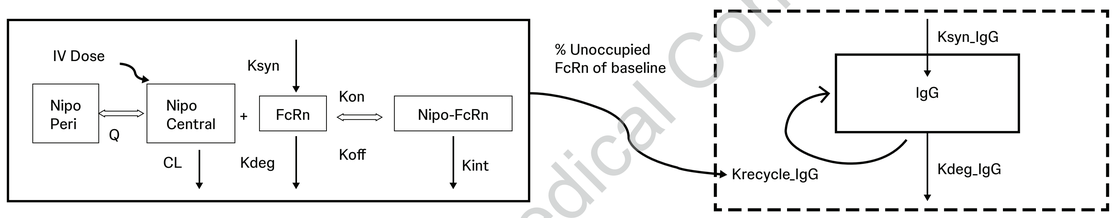
Objective

- **To confirm if the dose regimen for adult patients is also appropriate for adolescents with gMG.**

Methods

- Serum nipocalimab concentrations from 7 adolescents with gMG and total IgG serum profiles from 5 of the 7 adolescents were obtained in the vibrance-MG Study.
- The 7 adolescents with a body weight of 30.9 kg and above received the same dose regimen as the adults in the Phase 3 study (30 mg/kg intravenous followed by 15 mg/kg IV every-2-weeks).
- A previously developed PK-IgG model for adult patients with gMG was adapted to account for expected age- and body weight-related differences in the adolescent gMG population, impacting baseline FcRn abundance (**Figure 1**).

Figure 1: PK/RO/IgG Model Schematic for Nipocalimab IV Dosing[4]



- An external evaluation on the adapted model for adolescents was performed.
- The individual PK and PD parameters for adolescent patients were compared with the corresponding results for adult patients in the phase-3 study (Vivacity-MG3).

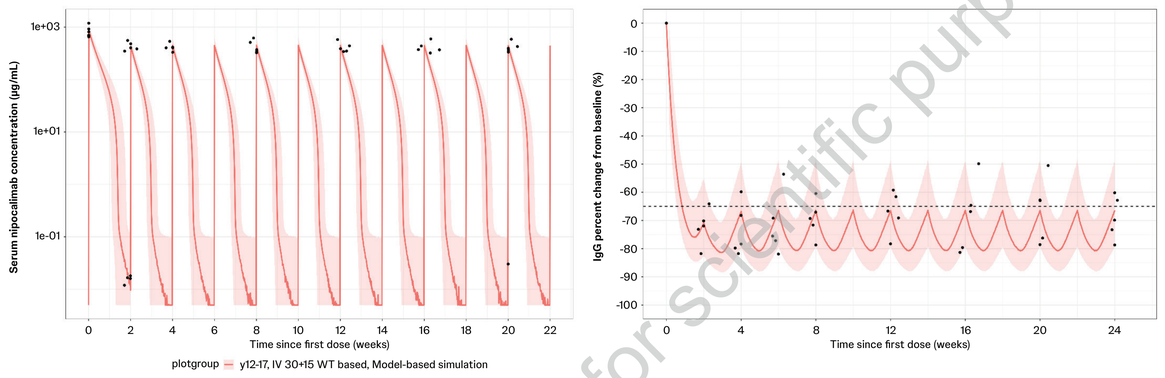
gMG=Generalized myasthenia gravis; **FcRn**=neonatal Fc receptor; **IgG**=Immunoglobulin G; **IV**=Intravenous; **PD**=Pharmacodynamic; **PK**=Pharmacokinetic; **RO**=Receptor occupancy

Results

External evaluation of the simulation-based model

- External evaluation demonstrated that the adapted model for adolescents could adequately capture both the central tendency and the variability of the observed PK and PD (total IgG percent change from baseline) data in adolescents (**Figure 2**).

Figure 2: Simulation-based Model Evaluation of Serum Nipocalimab Concentrations Over Time and Total IgG Percent Change From Baseline Using the Adapted Population PK-IgG Model for Adolescents

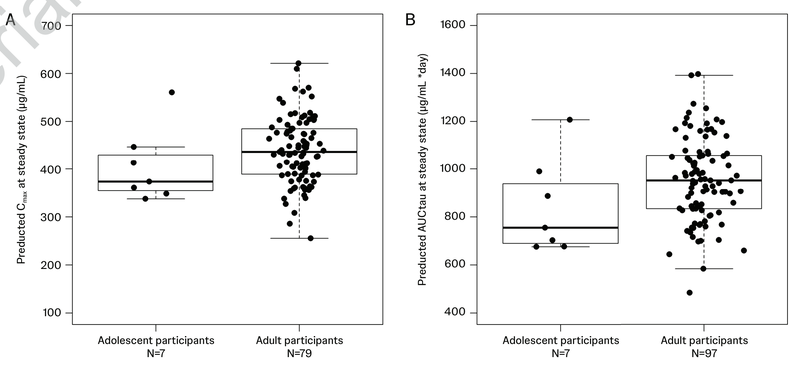


gMG=Generalized myasthenia gravis; **IgG**=Immunoglobulin G; **PD**=Pharmacodynamic; **PK**=Pharmacokinetic

Model-prediction of PK and PD between adolescent and adult gMG populations

- The model-predicted PK (maximum concentration and area under the curve [AUC_{tau}]) and PD (percent change from baseline in pre-dose, average, and nadir total serum IgG) metrics were consistent between adolescent and adult gMG populations (**Figure 3 & 4**).

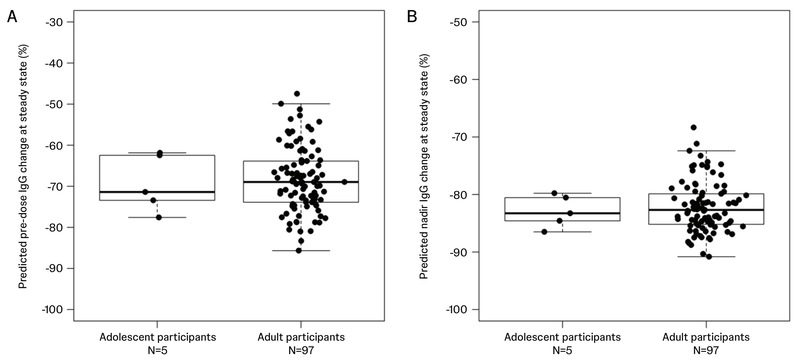
Figure 3: Comparison of Model-predicted Steady-state Predose (A) and Nadir (B) Total IgG Percent Change From Baseline Between Adolescents in vibrance-MG study and Adults in Vivacity-MG3 study



gMG=Generalized myasthenia gravis; **IgG**=Immunoglobulin G; **PD**=Pharmacodynamic; **PK**=Pharmacokinetic

Model-prediction of PK and PD between adolescent and adult gMG populations

Figure 4: Comparison of Model-predicted Steady-state C_{max} (A) and AUC_{tau} (B) of Serum Nipocalimab Concentrations Between Adolescents in vibrance-MG study and Adults in Vivacity-MG3 study



gMG=Generalized myasthenia gravis; **IgG**=Immunoglobulin G; **PD**=Pharmacodynamic; **PK**=Pharmacokinetic

Predicted PK and IgG exposure metrics

Table 1: Summary of Predicted PK and IgG Exposure Metrics Between Adolescents in vibrance-MG study and Adults in Vivacity-MG3 study

Parameter Mean (SD) Median [Range]	Description	Adolescents (N=7[a])	Adults (N=97)
$C_{max, ss}$ (µg/mL)	Maximum concentration at steady state	406 (78.1) 374 [338, 560]	439 (68.5) 436 [255, 621]
$AUC_{tau, ss}$ (µg/mL*day)	Area under the curve during a dosing interval period at steady state	842 (199) 755 [676, 1210]	956 (173) 954 [484, 1400]
$IgG_{nadir, ss}$ (%)	Nadir total serum IgG reduction from baseline at steady state	−82.9 (2.79) −83.3 [−86.5, −79.8]	−82.2 (4.36) −82.7 [−90.8, −68.4]
$IgG_{average, ss}$ (%)	Average total serum IgG reduction from baseline at steady state	−77.6 (4.51) −78.5 [−82.8, −72.7]	−76.9 (5.80) −77.3 [−88.8, −62.1]
$IgG_{predose, ss}$ (%)	Predose total serum IgG reduction from baseline at steady state	−69.4 (6.93) −71.4 [−77.6, −61.9]	−68.5 (7.87) −69.0 [−85.7, −47.5]

$AUC_{0\text{-}2W}$=area under the curve over 2 weeks after initial dose; **$AUC_{tau,ss}$**=area under the curve over a dosing interval at steady state; **C_{max}**=maximum serum nipocalimab concentration; **$C_{max,ss}$**=maximum serum nipocalimab concentration at steady state; **IgG**=total serum immunoglobin G; **N**=number of participants; **PK**=pharmacokinetics; **SD**=standard deviation.
[a]For IgG parameters, the number of adolescents is 5.

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