

Predicting Clinical Efficacy Endpoints of a Nipocalimab Phase 3 Study with a Population PKPD Model Developed with Data from a Phase 2 Study in Generalized Myasthenia Gravis

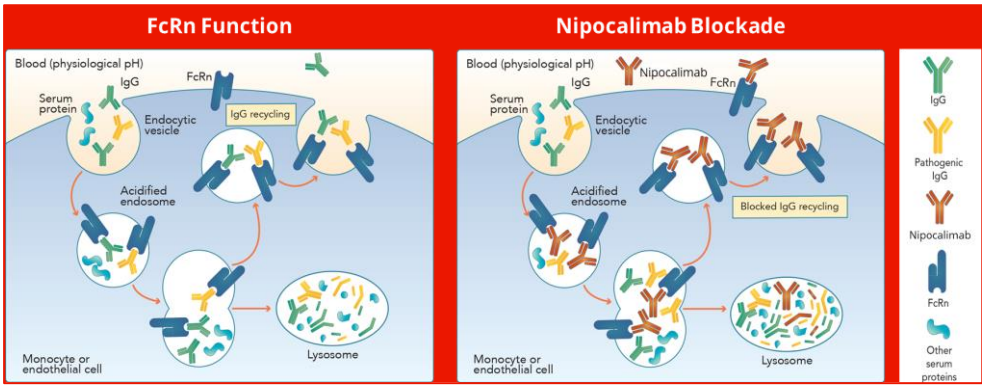
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Background

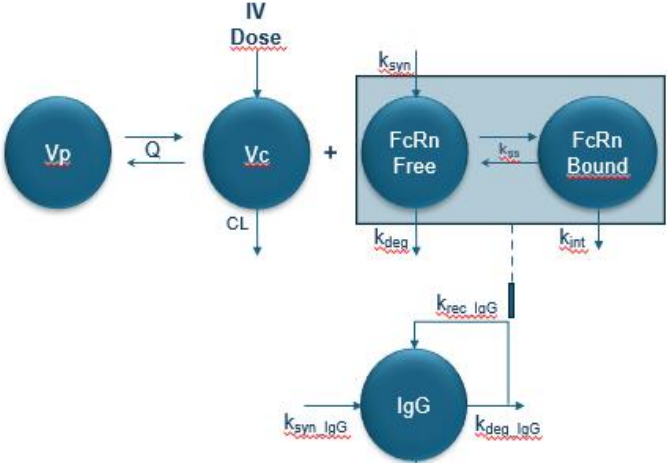
Generalized myasthenia gravis (gMG) is a rare, chronic, neuromuscular disease caused by pathogenic autoantibodies that impair or prevent muscle contraction. Circulating autoantibodies targeting the acetylcholine receptor (AChR) are present in 85% of cases, the muscle-specific tyrosine kinase (MuSK) in 7-8% of cases, while 7% to 8% of patients have neither anti-AChR nor anti-MuSK antibodies (“seronegative” gMG).

Nipocalimab is a fully human immunoglobulin G (IgG) 1 monoclonal antibody (mAb) that binds to FcRn with high affinity and blocks binding of endogenous IgG to FcRn, inhibiting IgG recycling, decreasing IgG half-life, and thus rapidly reducing the circulating levels of IgG, including pathogenic IgG autoantibodies. Nipocalimab demonstrated efficacy, favorable safety and tolerability, and dose-dependent IgG reduction in a Phase 2 study [1], and in the pivotal Phase 3 study [2] in patients with gMG.



Model

A comprehensive semi-mechanistic population model was developed integrating the nipocalimab serum concentrations, FcRn occupancy and IgG reduction data from Ph1 clinical studies in healthy participants and Phase 2 study, accounting for the relationship between total serum IgG reduction and MG-ADL scores reduction in patients with gMG. The model fit the Phase 1/Phase 2 data well.



Key Question

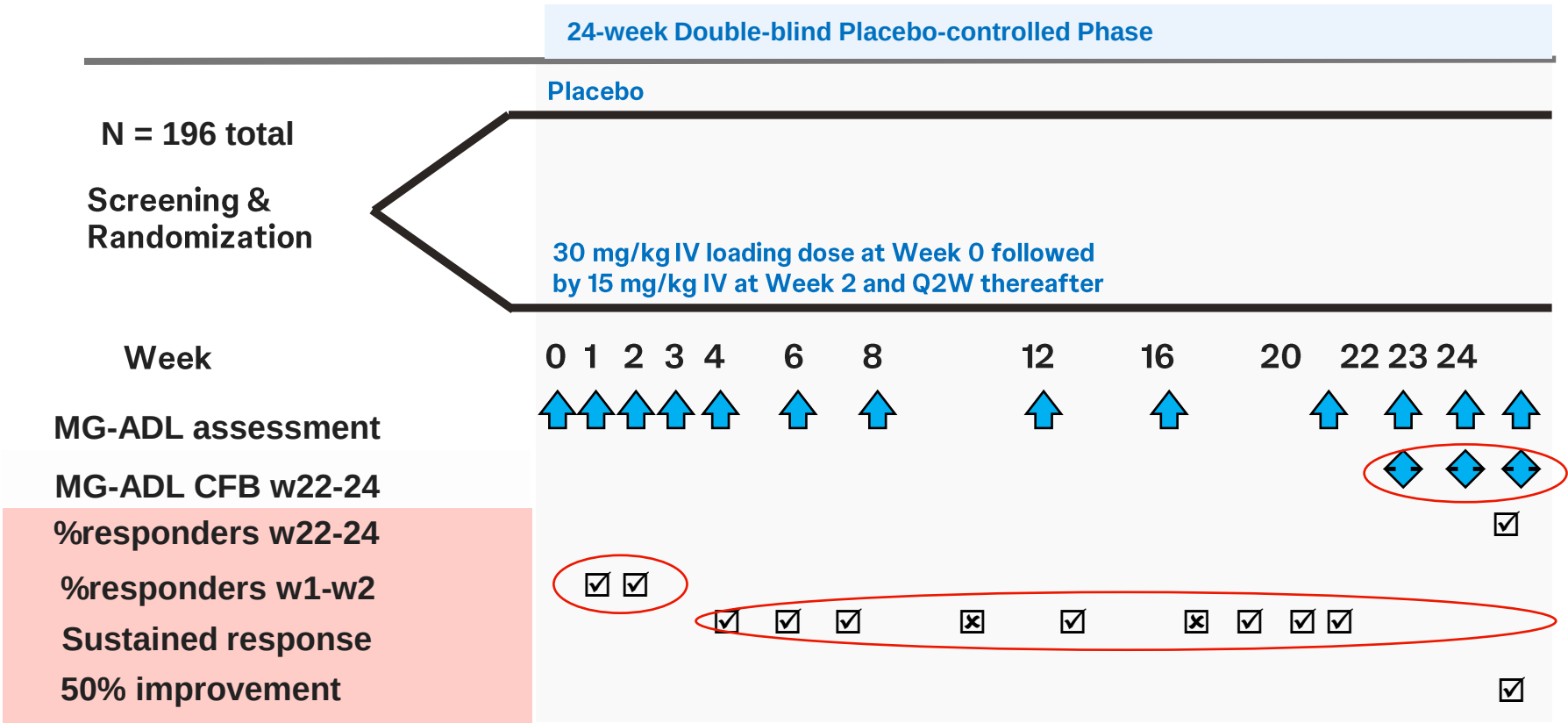
The model predicted a dose of 15mg/kg q2w to be safe and efficacious. This dose was previously unstudied in patients.

In hindsight, did the model predict the Ph3 study well?

Methods

- Simulate 2,000 virtual Phase 3 studies with N=196 patients (1:1 placebo:treatment)
- Derive individual MG-ADL model predictions (with residual error)
- For each virtual clinical study, calculate endpoints (single number per trial).
- Derive median and 95% CI across studies.
- For true Phase 3 data [2], calculate endpoints in the same manner.
- Compare simulated endpoints to true endpoints

Phase 3 study design / endpoints



Results

Endpoint	Placebo		Nipocalimab		Difference	
	Predicted	Observed	Predicted	Observed	Predicted	Observed
MG-ADL CFB w22-24	-2.86 (-1.87 to -3.88)	-3.22	-4.86 (-3.96 to -5.76)	-4.98	-2.01 (-0.67 to -3.35)	-1.75
%responders w22-24	58.1 (46.8 to 71.0)	66.1	76.8 (66.7 to 85.5)	82.6	18.0 (1.2 to 32.9)	16.5
%responders w1-2	54.8 (42.5 to 65.8)	56.2	79.2 (70.1 to 88.3)	62.3	25.4 (10.0 to 39.4)	6.2
Sustained response	30.1 (20.5 to 39.7)	34.2	52.6 (42.1 to 63.2)	60.5	22.6 (9.0 to 37.1)	26.3
50% improvement	35.5 (24.2 to 46.8)	32.3	52.2 (40.6 to 63.8)	56.5	17.8 (0.1 to 33.5)	24.3

Conclusion

- The model-based simulated endpoints aligned with 4 out of 5 observed endpoints in the Phase 3 study
- These results underscore the potential of pharmacometric approaches as a tool for optimizing dosing regimens and guiding clinical study design

[1]: Antozzi, Carlo, et al. "Safety and efficacy of nipocalimab in patients with generalized myasthenia gravis: results from the randomized phase 2 vivacity-MG study." *Neurology* 102.2 (2024): e207937.
[2]: Antozzi, Carlo, et al. "Safety and efficacy of nipocalimab in adults with generalised myasthenia gravis (Vivacity-MG3): a phase 3, randomised, double-blind, placebo-controlled study." *The Lancet Neurology* 24.2 (2025): 105-116.