Safety and efficacy of nipocalimab in adults with generalised myasthenia gravis (Vivacity-MG3): a phase 3, randomised, double-blind, placebo-controlled study

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Summary

Background Given burdensome side-effects and long latency for efficacy with conventional agents, there is a continued need for generalised myasthenia gravis treatments that are safe and provide consistently sustained, long-term disease control. Nipocalimab, a neonatal Fc receptor blocker, was associated with dose-dependent reductions in total IgG and anti-acetylcholine receptor (AChR) antibodies and clinically meaningful improvements in the Myasthenia Gravis Activities of Daily Living (MG-ADL) scale in patients with generalised myasthenia gravis in a phase 2 study. We aimed to assess the safety and efficacy of nipocalimab in a phase 3 study.

Methods Vivacity-MG3 was a phase 3, randomised, double-blind, placebo-controlled, phase 3 study conducted at 81 outpatient centres with expertise in myasthenia gravis in 17 countries in Asia–Pacific, Europe, and North America. Adults (aged ≥18 years) with generalised myasthenia gravis inadequately controlled with standard-of-care therapy (MG-ADL score ≥6) were randomly assigned (1:1) to either nipocalimab (30 mg/kg loading dose then 15 mg/kg every 2 weeks for maintenance dosing) or placebo infusions every 2 weeks, added to standard-of-care therapy in both groups, for 24 weeks. Randomisation was stratified by antibody status, day 1 MG-ADL total score, and region. The sponsor, investigators, clinical raters, and participants were masked to treatment assignment. The primary endpoint was the difference between nipocalimab and placebo based on least-squares mean change from baseline in MG-ADL total score averaged over weeks 22, 23, and 24 in the intention-to-treat population of patients who were antibody-positive (for AChR, anti-muscle-specific tyrosine kinase [MuSK], or anti-low-density lipoprotein receptor-related protein 4 [LRP4]). Adverse events were assessed in patients who received at least one dose of study drug. This study is registered at ClinicalTrials.gov, NCT04951622; the double-blind phase is completed and an open-label extension phase is ongoing.

Findings Between July 15, 2021, and Nov 17, 2023, 199 patients were enrolled, and 196 patients received study drug (98 in the nipocalimab group and 98 in the placebo group); of these, 153 (77 in the nipocalimab group and 76 in the placebo group) were antibody-positive. The least-squares mean change in MG-ADL score from baseline to weeks 22, 23, and 24 was –4·70 (SE 0·329) in the nipocalimab group versus –3·25 (0·335) in the placebo group (difference –1·45 [95% CI –2·38 to –0·52]; p=0·0024). The incidence of adverse events was similar between groups (82 [84%] of 98 in both the nipocalimab and placebo groups), including infections (42 [43%] of 98 in the nipocalimab group and placebo group) and headache (14 [14%] of 98 in the nipocalimab group and 17 [17%] of 98 in the placebo group). Serious adverse events were reported for nine (9%) of 98 patients in the nipocalimab group and 14 (14%) of 98 patients in the placebo group, three of which had a fatal outcome (nipocalimab: myasthenic crisis; placebo: cardiac arrest and myocardial infarction).

Interpretation Results from the completed double-blind phase of Vivacity-MG3 support the role of nipocalimab, added to standard-of-care therapies, as a safe treatment for sustained disease control over 6 months for a broad population of patients with generalised myasthenia gravis who are antibody-positive. The ongoing open-label extension phase should provide longer term sustained safety and efficacy data with nipocalimab.

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Introduction

Generalised myasthenia gravis is a chronic autoimmune disease associated with functional impairment, which is characterised by fluctuating, fatigable muscle weakness. Approximately 95% of patients with generalised myasthenia gravis are antibody-positive (85% anti-acetylcholine receptor [AChR]-positive, about 8% anti-muscle-specific tyrosine kinase [MuSK]-positive, and

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See **Comment** page 88

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See **Online** for appendix

Research in context

Evidence before this study

We searched for "randomized clinical trials" in PubMed between 1983 and Oct 1, 2024, using several similar iterations of the terms "FcRn blocker" and "generalized myasthenia gravis", with no language restriction. We identified three studies. Conventional treatments used in generalised myasthenia gravis (oral corticosteroids and immunosuppressants) are associated with burdensome side-effects and long latency before showing clinical effects. Complement inhibitors have safety limitations and are approved only for patients who are antibody-positive for acetylcholine receptor (AChR). Recently approved neonatal Fc receptor (FcRn) blockers are an emerging therapeutic strategy that use as-needed cyclic dosing; however, this dosing approach requires patients to experience symptom worsening before seeking another cycle of treatment, creating uncertainty on how to optimally determine the timing of the next treatment cycle. There remains an unmet need for fast-acting, safe treatments for a broader group of patients with generalised myasthenia gravis who are antibody-positive that selectively address the underlying antibody pathology of the disease and provide consistently sustained, uninterrupted disease control.

Added value of this study

Nipocalimab constitutes a fully human, high-affinity, and high-specificity monoclonal antibody that blocks FcRn to lower circulating IgG. Results of a previous phase 2, dose-ranging study of nipocalimab in generalised myasthenia gravis correlated clinical outcomes to sustained pharmacodynamic effects in generalised myasthenia gravis. Nipocalimab, with its consistent fixed dosing and targeted at a broad antibody-positive study cohort, could provide an alternative approach to current therapies, selectively addressing the underlying IgG antibody pathology of myasthenia gravis and potentially providing rapid and consistently sustained, uninterrupted disease control with a good safety profile.

Implications of all the available evidence

In Vivacity-MG3, consistently dosed nipocalimab therapy rapidly lowered circulating IgG, including myasthenia gravis pathogenic antibodies, with sustained effect on antibody concentrations over 6 months. This reduction resulted in clinically meaningful, sustained improvement in patients' symptoms up to 6 months. These results increase confidence in FcRn blockade as a rapid, safe, and effective treatment approach for generalised myasthenia gravis. The Vivacity-MG3 results extend the literature from previous studies of FcRn blockers by showing the safety and sustained effectiveness of consistently dosed nipocalimab over 6 months in a broader range of patients with generalised myasthenia gravis than in previous studies of FcRn blockers.

about 1–2% anti-low-density lipoprotein receptor-related protein 4 [LRP4]-positive).[1] These IgG antibodies mediate disruption of cholinergic transmission at the neuromuscular junction. The burden of illness in generalised myasthenia gravis, including medications, outpatient visits, hospital admissions, and intensive care treatment, is substantial and higher than that of many other chronic neurological diseases.[2]

Long-standing therapies for generalised myasthenia gravis include acetylcholinesterase inhibitors (which ameliorate the neuromuscular transmission defect), broad-spectrum immunosuppressants (eg, glucocorticoids, rituximab, and azathioprine), and immunomodulators (intravenous immunoglobulin). Subtherapeutic effects or an incomplete response and side-effects can limit long-term use of these therapies, underscoring the need for better tolerated as well as more effective treatment options.[3–5] Complement protein C5 inhibition represents a relatively new treatment option,[6–8] but the increased risk of serious meningococcal infections, the need for several immunisations, and efficacy restricted to patients who are AChR antibody-positive pose limitations.[9,10] An emerging treatment strategy for IgG antibody-mediated diseases like generalised myasthenia gravis is inhibition of neonatal fragment crystallisable (Fc) receptor (FcRn), which blocks the recycling of IgG.[11–13] An Fc fragment (efgartigimod, intravenous and subcutaneous infusion) and a humanised monoclonal antibody targeting FcRn (rozanolixizumab, subcutaneous infusion) have been approved for treatment of generalised myasthenia gravis with as-needed dosing;[14,15] however, as-needed dosing can require patients to experience symptom-worsening before seeking another cycle of treatment,[14,15] creating uncertainty on how to optimally determine the timing of the next treatment cycle.[16]

Nipocalimab is a fully human monoclonal antibody that binds to FcRn with high affinity and specificity, which results in IgG reduction while not affecting other immunoglobulin classes or humoral or cellular immune function.[11,17] The aglycosylated and effectorless design of nipocalimab prevents immune effector functions, such as complement-dependent cytotoxic effects and antibody-dependent cell-mediated cytotoxic effects.[3,11,18] In a first-in-human phase 1 study in healthy volunteers, nipocalimab was well tolerated and demonstrated rapid and substantial (about 85%) reduction of IgG from baseline.[11] In a phase 2 generalised myasthenia gravis study, nipocalimab produced rapid and dose-dependent reductions in total IgG (69% at 1 week after first ≥30 mg/kg dose [minimal observed, which translates to 77% simulated maximum]), and dose-dependent reductions in anti-AChR antibodies were also observed. These declines in total IgG and antibody concentrations were associated with clinically meaningful improvements

in the Myasthenia Gravis Activities of Daily Living (MG-ADL) scale and other efficacy endpoints.[19]

The phase 3 Vivacity-MG3 study was designed to assess the safety and efficacy of nipocalimab, compared with placebo, in patients with antibody-positive generalised myasthenia gravis who had an inadequate response to stable standard-of-care therapy. Safety and efficacy results (primary and key secondary efficacy endpoints, and specific other secondary endpoints [IgG concentration, minimum symptom expression] that help contextualise and contrast results with those of other FcRn blockers) from the double-blind phase of the Vivacity-MG3 phase 3 study are reported herein; other secondary endpoints and results from the ongoing open-label phase will be reported after completion of the open-label study.

Methods

Study design

Vivacity-MG3 is a double-blind, randomised, placebo-controlled, multicentre, phase 3 study, with an ongoing open-label extension phase. Patients were enrolled at 81 sites in 17 countries (Australia, Belgium, Canada, China, Czechia, Denmark, France, Germany, Italy, Japan, Mexico, Poland, South Korea, Spain, Sweden, Taiwan, and the USA) in Asia–Pacific, Europe, and North America. An institutional review board or independent ethics committee at each study site approved the final study protocol and amendments (first approval number SSU00151113). The study was conducted in accordance with the protocol, ethical principles that originated in the Declaration of Helsinki, and current guidelines on Good Clinical Practices.

All individuals voluntarily provided written informed consent before enrolment. An independent Data Monitoring Committee is monitoring safety data on an ongoing basis; an Event Adjudication Committee (members masked to treatment assignment) monitored for major adverse cardiovascular events.

Patients

Eligible study patients were adults (≥18 years of age) with symptoms of generalised myasthenia gravis categorised as Myasthenia Gravis Foundation of America class IIa or IIb to class IVa or IVb at screening. Eligibility criteria also required patients to have suboptimal response (defined as MG-ADL score of ≥6 at screening and baseline) to their current, stable standard-of-care therapy for generalised myasthenia gravis (ie, stable dose of acetylcholinesterase inhibitor for ≥2 weeks before screening; stable dose and regimen of glucocorticosteroid for ≥4 weeks before baseline; or stable dose and regimen of immunosuppressant [ie, azathioprine, mycophenolate mofetil or mycophenolic acid, methotrexate, ciclosporin, tacrolimus, or cyclophosphamide] for ≥6 months, and a stable dose for ≥3 months before baseline). Individuals who had received rituximab in the 6 months before first study drug dose, intravenous immunoglobulin, plasmapheresis, or immunoadsorption therapy within 6 weeks before first dose, or current treatment with a complement protein C5 inhibitor or FcRn blocker were excluded. The full list of the inclusion and exclusion criteria is presented in the protocol (appendix p 13).

Randomisation and masking

Patients were centrally randomised in a 1:1 ratio to study drug using an interactive web response system. Randomisation was balanced by using randomly permuted blocks of four and was stratified by antibody status (antibody-positive or antibody-negative), day 1 MG-ADL total score (≤9 or >9), and region (east Asia, USA, rest of world).

An unmasked site pharmacist prepared the study drug for infusion in an area that was not accessible to the masked site staff. After preparation, opaque sleeves were placed over the intravenous infusion container and a dispensing label with blinded study drug information was then applied. The sponsor, investigators, clinical raters, and study participants were masked to treatment assignment.

Procedures

Patients were assessed for study eligibility during a 4-week screening phase, which was followed by a 24-week double-blind treatment phase (appendix p 3). Nipocalimab (30 mg/kg initial dose followed by 15 mg/kg) or placebo (normal saline) was administered by intravenous infusion at study sites every 2 weeks. This dosing regimen was selected on the basis of modelling and simulation using the phase 2 trial data.[19] Because nipocalimab or placebo was administered as an add-on treatment to background standard-of-care therapies, all subsequent occurrences of nipocalimab or placebo should be understood to indicate nipocalimab plus standard-of-care therapy, or placebo plus standard-of-care therapy. Dose modification of nipocalimab was not allowed. Patients continued their background, stable standard-of-care myasthenia gravis therapies, with no changes permitted during the double-blind phase. Those who completed the double-blind phase had the option to continue receiving nipocalimab in an open-label extension phase. Patients who experienced clinical deterioration requiring rescue therapy were discontinued from the double-blind phase and could enter into the open-label phase after completion of rescue treatment with either intravenous immunoglobulin or plasmapheresis.

Blood samples were collected for measurement of pharmacodynamic effects, including serum concentrations of total IgG, IgG subclasses (IgG1, IgG2, IgG3, and IgG4), and IgA, IgM, and IgE. Serum concentrations of pathogenic anti-AChR and anti-MuSK antibodies were analysed by radioimmunoprecipitation assay at LabCorp (Burlington, NC, USA). Serum concentration of anti-LRP4

was determined by cell-based immunofluorescence assay from Athena Diagnostics at Quest (Marlborough, MA, USA). In China, the following tests were used at a local LabCorp location: an anti-AChR and anti-MuSK ELISA and, for anti-LRP4, a locally available cell-based indirect immunofluorescence assay. Standard safety assessments (ie, haematology, serum chemistry, urinalysis, physical examination, vital signs, and electrocardiogram), and adverse events were monitored throughout the study.

Outcomes

The primary efficacy endpoint was the difference between nipocalimab and placebo groups in the least-squares mean change from baseline in MG-ADL total score averaged over weeks 22, 23, and 24 in patients with seropositive generalised myasthenia gravis. From a clinical standpoint, the rationale for averaging over weeks 22, 23, and 24 was to demonstrate sustained efficacy over the last 2 weeks (ie, the last dosing interval of treatment, given the variable nature of myasthenia gravis, whereby the disease can severely fluctuate from week to week). Averaging ensures that efficacy is not based on a single timepoint, which might not accurately reflect a consistent treatment effect.

The key secondary endpoints, analysed in a hierarchical order (described in Statistical analysis below) in patients who were antibody-positive, were the differences between nipocalimab and placebo in the following: average change from baseline in Quantitative Myasthenia Gravis (QMG) score over weeks 22 and 24; percentage of patients with at

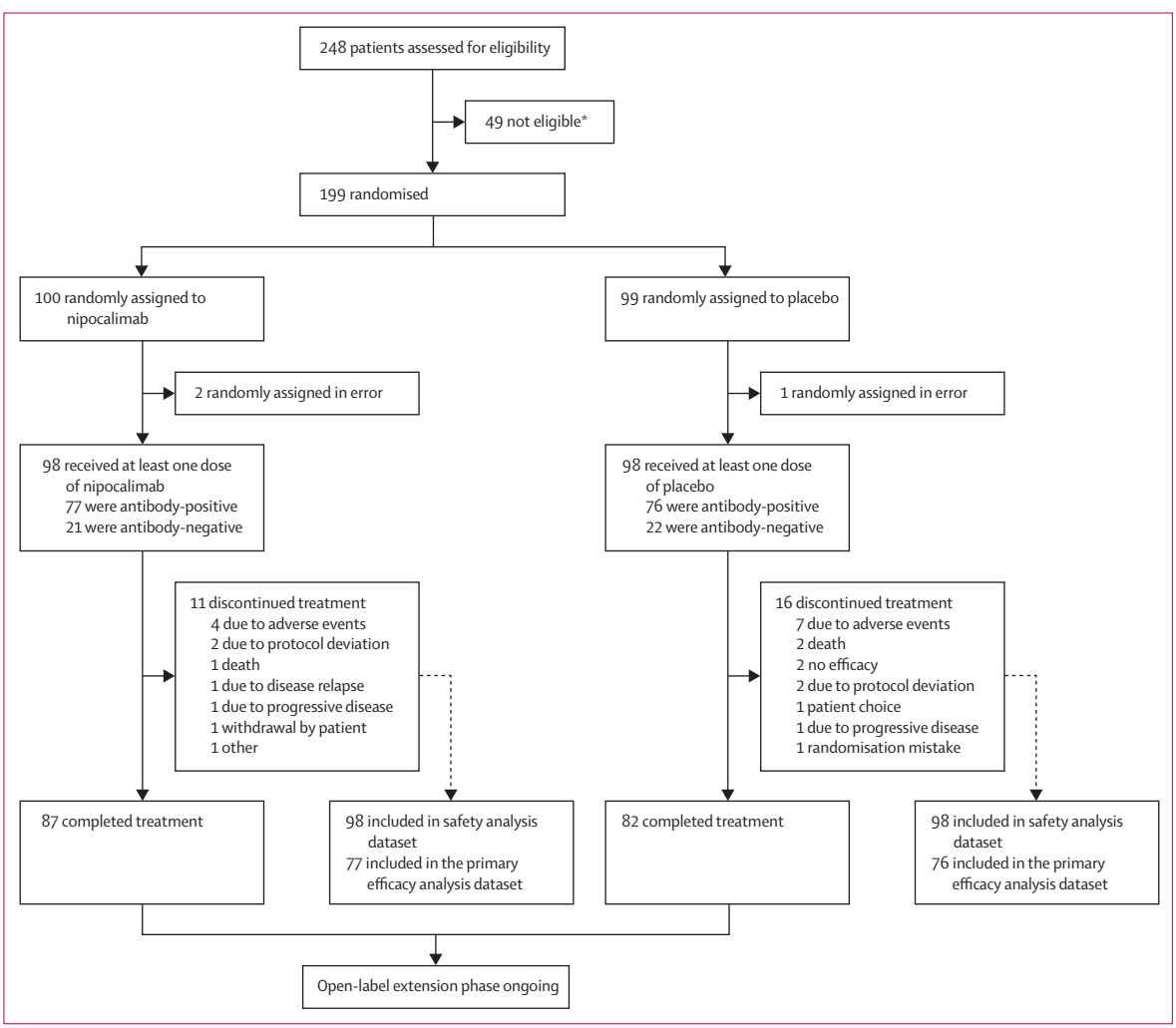

Figure 1: **Trial profile**
The primary efficacy analysis dataset included all randomly assigned patients who received at least one dose (partial or complete) of study drug in the double-blind phase and were antibody-positive for a generalised myasthenia gravis-related pathogenic antibody (antibodies to acetylcholine receptor, anti-muscle-specific tyrosine kinase, or anti-lipoprotein-related protein receptor 4), confirmed before randomisation. The safety analysis dataset included all randomly assigned patients who received at least one dose (partial or complete) of either study drug in the double-blind phase (including both antibody-positive and antibody-negative patients). The three patients randomly assigned in error were never dosed. One patient who discontinued treatment due to a randomisation mistake did not meet the eligibility criteria. *49 patients did not meet one or more of the study inclusion or exclusion criteria.

least a 2-point improvement in average MG-ADL total score (a 2-point improvement best predicts clinical improvement at the individual patient level)[20] over weeks 22, 23, and 24 compared with baseline; percentage of patients with at least a 2-point improvement in MG-ADL total score at week 1, week 2, or week 1 and 2 compared with baseline; percentage of patients with at least a 2-point improvement in MG-ADL total score at weeks 4–24 compared with baseline, with up to two non-consecutive excursions allowed between weeks 6 through 23; and percentage of patients with at least a 50% improvement in MG-ADL over weeks 22, 23, and 24 compared to baseline.

Other secondary endpoints reported here are: the percentage of patients who were antibody-positive who reached minimal symptom expression (defined as MG-ADL total score of 0 or 1) at any time during the double-blind phase; and the percentage of patients maintaining minimal symptom expression at 75% of all timepoints through the double-blind phase. The remaining predefined secondary endpoints will be reported after completion of the open-label extension study.

Safety outcomes were treatment-emergent adverse events, change from baseline in haematology and chemistry indices, vital signs, and electrocardiogram. Pharmacodynamic outcomes were percent change from baseline in myasthenia gravis-specific antibody and total and subclass IgG concentrations.

Statistical analysis

The study was designed to have at least 90% power with a two-sided type-1 error of 5% to detect a standardised effect size of at least 0·57, assuming a dropout rate of 20% at week 24 and using a mixed-effect model for repeated measures (MMRM). A standardised effect size of 0·57 was based on estimates of between-group differences (≥1·7) and SDs (approximately 3) from clinical trial simulations of the MG-ADL total score. On the basis of these considerations, a sample size of at least 150 eligible patients who were antibody-positive was planned, 75 in each treatment group.[21,22] Unrelated to the sample size calculation, approximately 40 individuals who were antibody-negative (20 per treatment group) were to be enrolled and randomly assigned to study drug to ascertain the efficacy of nipocalimab in this group with high unmet need. The sample size of 75 patients who are antibody-positive per treatment group also provided at least 90% power to detect a standardised effect size of at least 0·57 for the QMG key secondary endpoint.

Safety analyses were done on a dataset that included all randomly assigned patients who received at least one dose (partial or complete) of either nipocalimab or placebo in the double-blind phase. Efficacy analyses were done on a primary efficacy analysis dataset that included patients from the safety analysis dataset who were antibody-positive for a generalised myasthenia gravis-related pathogenic antibody (anti-AChR, anti-MuSK, or anti-LRP4), confirmed before randomisation.

Statistical analyses were done using SAS version 9.04, and R version 4.2.1. Analyses of the primary efficacy endpoint and the five key secondary efficacy endpoints were tested at a two-sided significance level of 0·05. A fixed-sequence approach was applied to control type-1 error across the primary and key secondary endpoints.

The primary efficacy endpoint was analysed using MMRM, with weekly change from baseline as the dependent variable; factors for study intervention group, antibody status (antibody-positive [for AChR or MuSK] or antibody-negative [for AChR and MuSK], as randomised), region, week, and study intervention group-by-week interaction; and baseline MG-ADL total score as a covariate. MMRM analyses were done on observed data; however, observations collected after

	Nipocalimab + standard of care (N=77)	Placebo + standard of care (N=76)
Age, years		
Mean (SD)	52·5 (15·66)	52·3 (16·37)
Range	20–81	20–81
≥65 years old	18 (23%)	19 (25%)
Sex*		
Male	27 (35%)	34 (45%)
Female	50 (65%)	42 (55%)
Race*		
White	49 (64%)	47 (62%)
Asian	24 (31%)	25 (33%)
Black or African American	1 (1%)	1 (1%)
American Indian or Alaska Native	1 (1%)	0
Not reported	2 (3%)	3 (4%)
Duration of myasthenia gravis, years	6·9 (7·44)	8·9 (8·13)
Baseline MG-ADL total score	9·4 (2·73)	9·0 (1·97)
Baseline QMG total score	15·1 (4·78)	15·7 (4·92)
MGFA class		
I	1† (1%)	0
IIa	7 (9%)	10 (13%)
IIb	11 (14%)	10 (13%)
IIIa	34 (44%)	29 (38%)
IIIb	17 (22%)	15 (20%)
IVa	3 (4%)	10 (13%)
IVb	4 (5%)	2 (3%)
Antibody-positive at screening		
AChR	63 (82%)	71 (93%)
MuSK	12 (16%)	4 (5%)
LRP4	2 (3%)	1 (1%)
Standard-of-care therapy		
Anticholinesterase inhibitors	64 (83%)	66 (87%)
Steroids	47 (61%)	54 (71%)
Non-steroidal immunosuppressive therapy	41 (53%)	41 (54%)

Data are n (%) or mean (SD), unless otherwise stated. AChR=acetylcholine receptor. LRP4=lipoprotein-related protein receptor 4. MG-ADL=Myasthenia Gravis-Activities of Daily Living. MGFA=Myasthenia Gravis Foundation of America. MuSK=muscle-specific tyrosine kinase. QMG=Quantitative Myasthenia Gravis. *According to patient self-report. †Patient had MGFA class IIa at screening and MG-ADL of 8 at both screening and baseline.

Table 1: **Patient demographics and baseline characteristics (primary efficacy analysis dataset)**

treatment discontinuation or change in standard-of-care therapy were deemed missing in the primary analysis. No imputation was done for missing observations. The between-group difference of the average change over weeks 22, 23, and 24 was tested with an F-test of the linear contrast that averaged the change from baseline over the timepoints. Tipping point sensitivity analyses were done to evaluate the missing-at-random assumption inherent in the MMRM analysis of the primary endpoint (appendix p 4).

If the primary efficacy endpoint met statistical significance at the 5% two-sided α level, the five key secondary efficacy endpoints were to be analysed in hierarchical order, according to a fixed-sequence approach. Key secondary endpoints were considered statistically significant (two-sided 0·05 level) only if the endpoint was individually significant and previous endpoints in the hierarchy were significant. The key secondary endpoint based on QMG score was analysed using the same MMRM model as for the primary endpoint. For each of the MG-ADL key secondary endpoints, the percentage of patients who were responders according to the endpoint criteria was analysed by Cochran-Mantel-Haenszel tests controlling for the baseline MG-ADL total score randomisation strata (≥9 or <9), antibody status, and region. Between-group differences in proportions and 95% Wald CIs (on the basis of the normal approximation) were calculated. Non-response was assumed at timepoints with missing assessments or timepoints following treatment discontinuation or change in standard of care.

Analysis by antibody subgroup (AChR antibody-positive; MuSK antibody-positive; LRP4 antibody-positive; antibody-negative) was done on the MG-ADL primary endpoint, with antibody subgroup added as a main effect to the MMRM model and study intervention-by-antibody subgroup and study intervention-by-time point-by-antibody subgroup interaction terms also added. The between-group difference of the average change from baseline over weeks 22, 23, and 24 and its 95% CI were estimated from the MMRM for each antibody subgroup. The same analysis was also done for the QMG total score (first key secondary endpoint). Other efficacy endpoints, pharmacodynamics, and safety outcomes were summarised in a descriptive manner.

The study is registered at ClinicalTrials.gov (NCT04951622) and EudraCT (2020-005732-29).

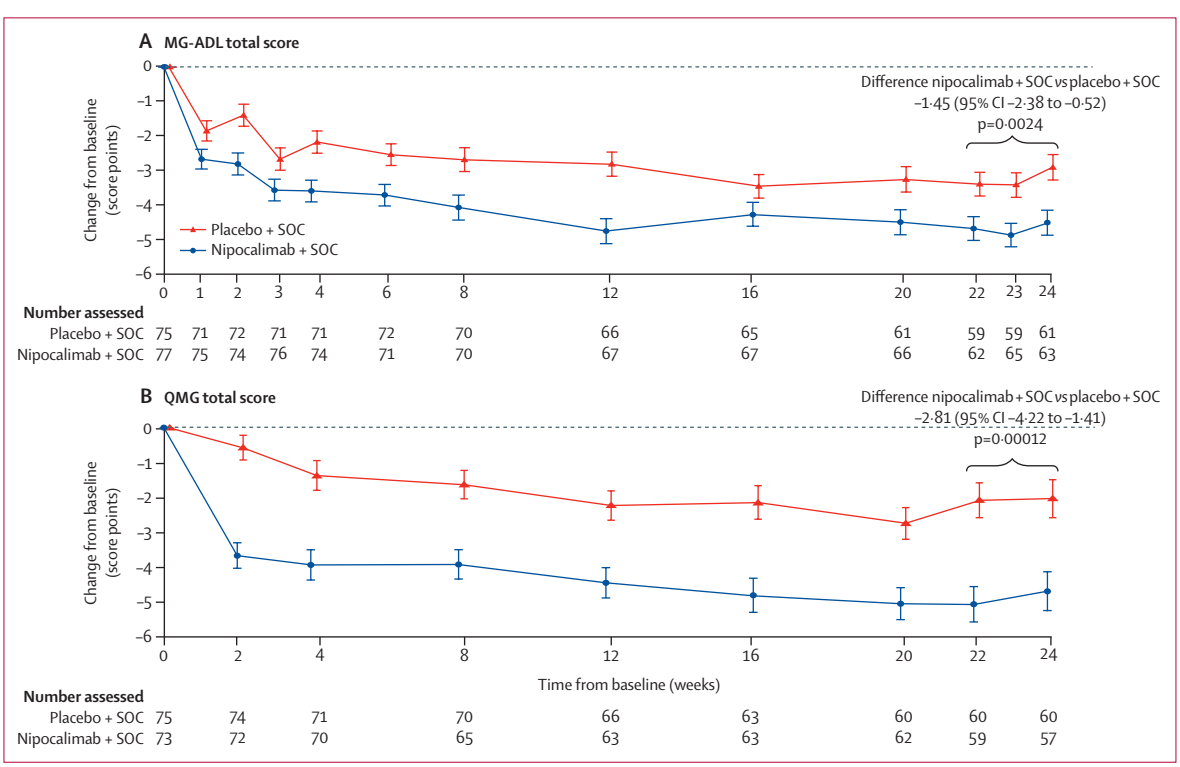

Figure 2: **MG-ADL and QMG least-squares mean change from baseline (SE) over 24 weeks**
Symbols represent least squares mean at each timepoint and error bars represent the SE. A significantly greater average reduction from baseline in MG-ADL total score was observed over weeks 22, 23, and 24 for the nipocalimab group (least squares mean change −4·70 [SE 0·329]) than for the placebo group (−3·25 [0·335]), with least-squares mean difference from placebo of −1·45 (95% CI −2·38 to −0·52, p=0·0024). A significantly greater average reduction from baseline in QMG total score was observed over weeks 22 and 24 for the nipocalimab group (least-squares mean change −4·86 [SE 0·504]) than for the placebo group (−2·05 [0·499]) with least-squares mean difference from placebo of −2·81 (95% CI −4·22 to −1·41; p=0·00012). MG-ADL total score ranges from 0 to 24; a higher score indicates greater symptom severity. QMG total score ranges from 0 to 39; a higher score indicates greater symptom severity. Negative change in score indicates improvement. MG-ADL=Myasthenia Gravis-Activities of Daily Living. QMG=Quantitative Myasthenia Gravis. SE=standard error. SOC=standard of care.

Role of the funding source
The funder of the study had a role in study design, patient recruitment, data collection, data analysis, data interpretation, writing of the study report and manuscript, and the decision to submit the manuscript for publication.

Results

Between July 15, 2021, and Nov 17, 2023, 199 patients were enrolled and randomly assigned, of whom 196 (98 in each treatment group) received at least one dose of study drug and were included in the safety analysis dataset (figure 1). A major protocol deviation was noted for 20 patients in the nipocalimab group and 28 patients in the placebo group; the majority were either addressed by prespecified statistical methods described in the statistical analysis plan or were missed safety assessments that did not affect the overall safety of the participants. The primary efficacy analysis dataset comprised 153 randomly assigned and treated patients who were antibody-positive (77 in the nipocalimab group and 76 in the placebo group). Among the patients who were antibody-positive, 134 (88%) were antibody-positive for AChR, 16 (11%) for MuSK, and three (2%) for LRP4 (table 1). Most patients completed 24 weeks of double-blind treatment (figure 1).

Demographic and baseline clinical characteristics of antibody-positive patients (table 1) are representative of the generalised myasthenia gravis population. Mean MG-ADL of 9·2 (SD 2·38) and mean QMG score of 15·4 (SD 4·85) are consistent with considerable disease burden at baseline, even though more than 97% in each treatment group (nipocalimab 75 [97%] of 77; placebo 76 [100%] of 76) were on stable background standard-of-care therapy, including anticholinesterase inhibitors (nipocalimab 64 [83%] of 77; placebo 66 [87%] of 76), steroids (nipocalimab 47 [61%] of 77; placebo 54 [71%] of 76), and non-steroidal immunosuppressive therapies (nipocalimab 41 [53%] of 77; placebo 41 [54%] of 76). 31 (40%) of 77 patients in the nipocalimab group and 30 (39%) of 76 patients in the placebo group were taking both a steroid and a non-steroidal immunosuppressant; 18 (23%) and 11 (15%) patients in the respective treatment groups were taking acetylcholinesterase inhibitors as their only treatment. Approximately a quarter of patients (nipocalimab 26 [27%] of 98; placebo 24 [24%] of 98) used a lipid-lowering agent during the double-blind phase, most started before study enrolment. More than half of patients had a history of cardiovascular disease (nipocalimab 55 [56%] of 98; placebo 58 [59%] of 98).

A significantly greater reduction from baseline in MG-ADL total score was observed over weeks 22, 23, and 24 (primary efficacy endpoint) for the nipocalimab group (least-squares mean change –4·70 [SE 0·329]) than for the placebo group (–3·25 [0·335]), with a difference between groups of –1·45 (95% CI –2·38 to –0·52; p=0·0024; figure 2; appendix p 6). The estimated treatment difference for nipocalimab versus placebo in male patients was –2·39 (95% CI –3·87 to –0·91) and in female patients was –0·86 [–2·06 to 0·34). A statistically significantly greater reduction from baseline in QMG total score was also observed over weeks 22 and 24 (first key secondary endpoint) for the nipocalimab group (least squares mean change –4·86 [SE 0·504]) compared with the placebo group (least squares mean change –2·05 [0·499]), with a difference between groups of –2·81 (95% CI –4·22 to –1·41; p=0·00012; figure 2; appendix p 6).

A statistically significant treatment effect, favouring nipocalimab, was observed for the key secondary responder endpoint of percentage of patients with at least a 2 point improvement in average MG-ADL total score over weeks 22, 23, and 24 (between-group difference 16·2% [95% CI 0·9 to 31·5]; p=0·021; figure 3). The between-group difference for the third key secondary endpoint of

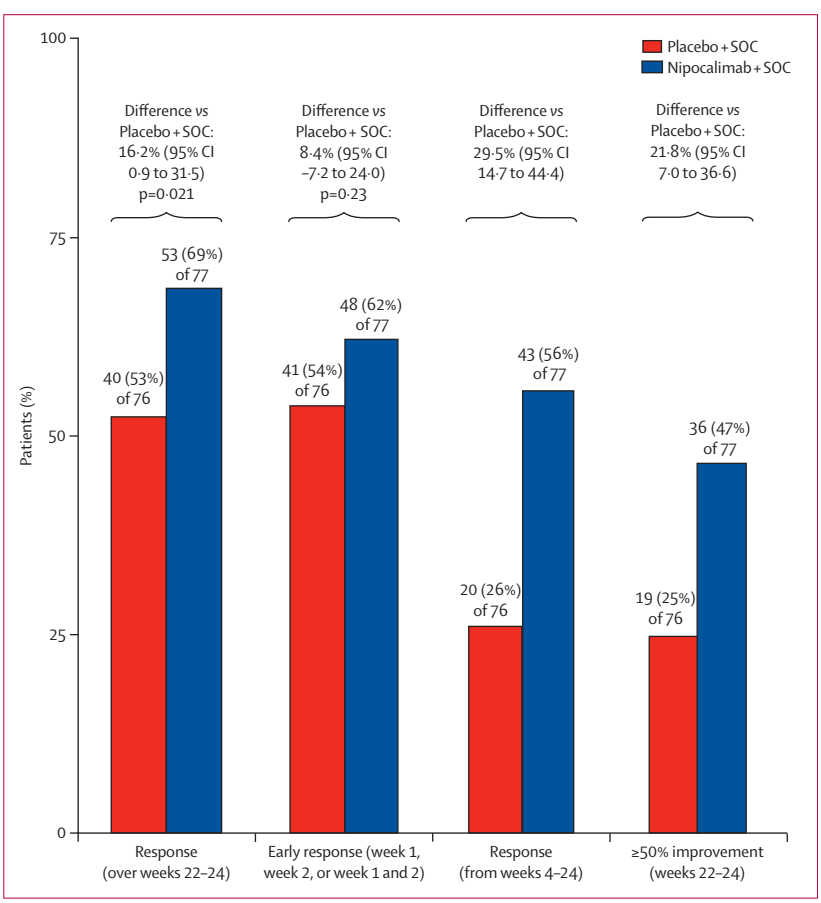

Figure 3: **MG-ADL responder endpoints**
Improvements of at least 2 points (response) and at least 50% are based on average improvement over weeks 22, 23, and 24. Early response is at least a 2-point improvement at week 1, week 2, or week 1 and 2. Response from weeks 4 to 24 is at least a 2-point improvement from week 4 to week 24 with up to two non-consecutive excursions from week 6 to week 23. p values from the Cochran-Mantel-Haenszel test controlling for baseline MG-ADL total score (<9 or ≥9), antibody status, and region. The p values were not reported for response (from weeks 4–24) or at least 50% improvement (weeks 22–24) because the preceding comparison in the hierarchy (ie, early response [week 1, week 2, or week 1 and 2] was not statistically significant at a two-sided α of 0·05). MG-ADL=Myasthenia Gravis-Activities of Daily Living. SOC=standard of care.

early response, defined as response at week 1, week 2, or week 1 and week 2, was not statistically significant (between-group difference 8·4% [95% CI –7·2 to 24·0]; p=0·23; figure 3). Given that the between-group difference for the third key secondary endpoint was not statistically significant, the two subsequent key secondary endpoints could not be formally tested according to the predefined testing sequence. Estimates for these endpoints showed a higher percentage of patients had a response from weeks 4 to 24 in the nipocalimab group than in the placebo group, and a higher percentage of patients showed at least 50% symptom improvement in the nipocalimab group compared with the placebo group (figure 3). Approximately a third of patients (24 [31%] of 77) treated with nipocalimab reached the predefined other secondary endpoint of minimal symptom expression at any time during the double-blind phase, compared with ten (13%) of 76 patients treated with placebo. Further, eight (10%) of 77 patients treated with nipocalimab reached minimal symptom expression at at least 75% of all timepoints during the double-blind phase, compared with one (1%) of 76 patients treated with placebo. Patients treated with nipocalimab reached numerically higher levels of improvement (up to ≥8 points in MG-ADL and up to ≥9 points in QMG) at predefined visit weeks, compared with patients treated with placebo (appendix p 7).

Nipocalimab demonstrated rapid and sustained lowering of IgG (figure 4). The median predose (minimal) total IgG reduction from baseline after the loading dose was –74·6% (IQR –79·4 to –68·7) at week 2 and –68·8% (–75·3 to –62·2) at week 24. A significant reduction in each IgG subclass is shown in the appendix (p 8); AChR antibody and MuSK antibody concentrations also showed reductions over the 6-month double-blind phase. No changes in total IgM, IgA, or IgE were observed.

Both the AChR antibody-positive and MuSK antibody-positive cohorts showed improvement in MG-ADL, consistent with the overall results in the nipocalimab group. No statistical difference in MG-ADL average change from baseline over weeks 22, 23, and 24 was observed between the treatment groups in the antibody-negative population (appendix p 9). Two of three patients who were anti-LRP4-positive had assessments up to week 24; both patients, one in the nipocalimab group and one in the placebo group, showed a reduction in MG-ADL at week 24. Anti-LRP4 antibodies are of the IgG1 and IgG2 subclasses, and both patients treated with nipocalimab who were anti-LRP4 positive showed rapid and sustained reductions in total IgG and in IgG1 and IgG2 subclasses during the double-blind phase up to week 24, compared with the single patient who was anti-LRP4 positive and received placebo (appendix p 10).

The overall incidence of adverse events was similar between the nipocalimab and placebo groups (table 2). Investigators characterised most adverse events reported for patients treated with nipocalimab as mild or moderate. Of note, no difference between treatment groups was observed on the basis of incidences of infusion-related reactions, infections, and severe infections or infections that required intravenous anti-infective or operative or invasive intervention (table 2). 11 (11%) of 98 patients receiving nipocalimab and none receiving placebo developed peripheral oedema; all patients at the time of oedema had albumin concentrations within normal limits (33–49 g/L for individuals aged 18–69 years, 33–46 g/L for those aged

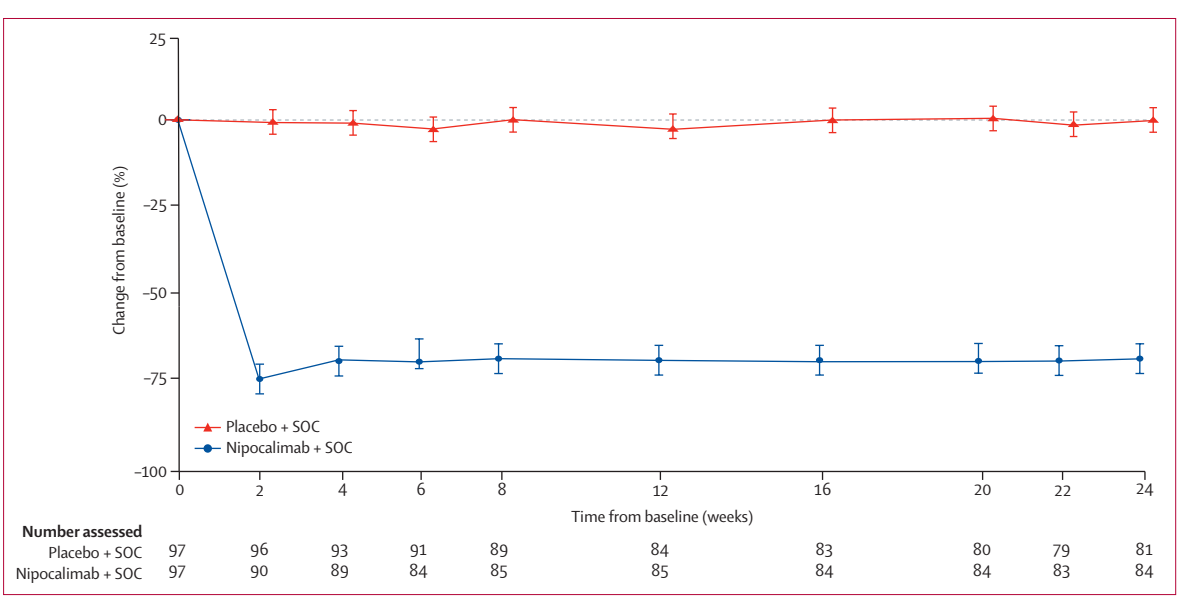

Figure 4: **Median (IQR) percent change from baseline IgG in the double-blind phase**
Symbols represent the median and error bars the IQR. SOC=standard of care.

70–80 years, and 30–46 g/L for those aged >80 years). Five (5%) of 98 patients receiving nipocalimab reported urinary tract infection compared with two (2%) of 98 receiving placebo. 12 patients in each treatment group experienced worsening myasthenia gravis. One patient receiving nipocalimab compared with two patients receiving placebo experienced a myasthenic crisis, and five receiving nipocalimab compared with seven receiving placebo required rescue medication.

The percentage of participants with one or more serious adverse events was lower in the nipocalimab group compared with the placebo group (appendix p 11). Three serious adverse events had a fatal outcome: one in the nipocalimab group (myasthenic crisis) and two in the placebo group (cardiac arrest and myocardial infarction); none of the deaths was considered to be related to the study treatment by the investigator. No adjudicated major adverse cardiovascular events were reported in the nipocalimab group, versus three in the placebo group (two fatal events of sudden cardiac death and one non-fatal event of unstable angina).

Five (5%) of 98 patients in the nipocalimab group discontinued treatment because of adverse events: two due to worsening myasthenia gravis, one due to thrombocytopenia (the patient had a history of thrombocytopenia attributed by the investigator to ongoing azathioprine treatment), one due to urticaria, and one due to fatal serious adverse event of myasthenic crisis. Seven (7%) of 98 patients in the placebo group discontinued treatment because of serious adverse events: two because of worsening myasthenia gravis, one because of appendicitis, one because of fatal cardiac arrest, one because of a liver disorder, one because of fatal myocardial infarction, and one because of cerebral haemorrhage, COVID-19, femur fracture, myasthenia gravis crisis, and sepsis.

Increases in fasting total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were observed in the nipocalimab group (appendix p 12). At week 24, mean percent change from baseline was 7·8% (SD 16·86) for total cholesterol, 7·0% (20·87) for HDL, and 8·3% (23·12) for LDL in the nipocalimab group, and was –4·1% (12·30) for total cholesterol, –1·6% (13·84) for HDL, and –3·0% (18·56) for LDL in the placebo group. Given the concomitant increase in total cholesterol and HDL, the mean total cholesterol:HDL ratio in the nipocalimab group remained lower than 4 throughout the 24-week double-blind phase and similar to placebo at 24 weeks (nipocalimab 3·6 [1·36], placebo 3·5 [1·21]).

No clinically meaningful changes were reported in vital signs, electrocardiogram recordings, or other clinical laboratory evaluations (including leukocytes), and no liver abnormalities met Hy's law criteria. There was a mild decrease of albumin in the nipocalimab group (mean percent change from baseline in albumin was –7·2% [SD 5·37] with nipocalimab and –2·1% [7·08] with placebo at week 24); however, all albumin values stayed within the normal laboratory reference range.

	Nipocalimab plus standard of care (N=98)	Placebo plus standard of care (N=98)
Any adverse event	82 (84%)	82 (84%)
Related adverse event*	28 (29%)	28 (29%)
Any serious adverse event	9 (9%)	14 (14%)
Related serious adverse event	1 (1%)	1 (1%)
Adverse event leading to permanent discontinuation of study drug	5 (5%)	7 (7%)
Any infection	42 (43%)	42 (43%)
Severe infection or infection requiring invasive treatment	3 (3%)	4 (4%)
Infusion-related reactions	10 (10%)	11 (11%)
Most frequently reported adverse events†		
COVID-19-associated adverse events	15 (15%)	12 (12%)
Headache	14 (14%)	17 (17%)
Muscle spasms	12 (12%)	3 (3%)
Myasthenia gravis	12 (12%)	12 (12%)
Peripheral oedema	11 (11%)	0

Adverse events are listed in decreasing order on the basis of incidence in the nipocalimab group and in alphabetical order for events with the same incidence. *Per investigator assessment. †≥10% in nipocalimab group.

Table 2: **Treatment-emergent adverse events in the double-blind phase**

Discussion

In the Vivacity-MG3 study, nipocalimab showed clinically meaningful and sustained efficacy over 6 months in a broad cohort of patients with antibody-positive (anti-AChR-positive, anti-MuSK-positive, or anti-LRP4-positive) generalised myasthenia gravis, in both the primary, clinician-assessed and patient-reported outcome (MG-ADL) and the key secondary, clinician-assessed outcome (QMG). Statistically significant effects in both patient-reported and clinician-reported outcomes support the clinically meaningful benefits of nipocalimab in generalised myasthenia gravis. More patients in the nipocalimab group than in the placebo group also achieved MG-ADL responder status at both weeks 1 and 2. A key secondary endpoint assessed the sustainability of therapeutic effect; approximately two times more patients in the nipocalimab group than in the placebo group reached MG-ADL responder status by week 4, with response sustained through the end of the 6-month double-blind phase.

The Vivacity-MG3 study is one of the largest and the longest randomised controlled studies of generalised myasthenia gravis treatment with a molecularly unique FcRn blocker, which provides placebo-controlled data on the safety and sustained efficacy of consistent dosing every 2 weeks, removing the uncertainty of dose timing and possibly avoiding fluctuations of clinical benefit associated with deterioration-based dosing. The most obvious difference in the results of Vivacity-MG3 compared with the equivalent trials of efgartigimod and

rozanolixzumab[14,15] is the uninterrupted sustained treatment efficacy in a broader group of patients who are antibody-positive. The antibody-positive study cohort (88% positive for AChR antibodies, 10% for MuSK antibodies, and 2% for LRP4 antibodies) is representative of the general myasthenia gravis patient population. In addition, these results show nipocalimab was well tolerated among patients. IgG lowering was rapid and substantial (–75% at week 2) and sustained over 6 months (minimum steady-state predose reduction of around 70%), with no evidence of diminishing pharmacodynamic effect. Consistent with these findings, patients treated with nipocalimab showed numerically greater treatment differences for MG-ADL and QMG compared with placebo as early as week 1, and the magnitude of separation from placebo achieved at week 2 was generally maintained and similar to the separation seen at week 24 (figure 2). Nipocalimab also reduced IgG subclass concentrations; anti-AChR and anti-MuSK antibodies followed a similar pattern in patients who were antibody-positive. The magnitude of lowering for both IgG was generally associated with greater improvement in symptoms, suggesting a correlation between the reduction of IgG and clinical improvement in generalised myasthenia gravis.

The Vivacity-MG3 study enrolled a relatively large cohort of patients who were triple-antibody-negative (negative for antibodies to AChR, MuSK, and LRP4) and clinically diagnosed with generalised myasthenia gravis on the basis of investigator clinical examination or electrophysiological studies. Subgroup analysis did not differentiate nipocalimab from placebo in the patients who were antibody-negative. No FcRn blocker treatment has shown efficacy in a controlled study in antibody-negative patients,[14,15] which might include a heterogeneous cohort with poorly understood pathophysiology. As some patients might benefit, the role of FcRn blocking in triple-antibody negative myasthenia gravis needs further investigation.

Existing treatments for generalised myasthenia gravis are associated with short-term and long-term adverse effects that can limit their use.[14,15] By contrast to the phase 3 trials of the other FcRn blockers, Vivacity-MG3 did not restrict enrolment on the basis of IgG thresholds at screening or set a minimum requirement for the proportion of non-ocular generalised myasthenia gravis symptoms. In the phase 1 and phase 2 studies, dose-dependent reductions in serum IgG concentrations associated with nipocalimab treatment were observed and no obvious effects on the frequency, severity, or type of infections were noted in comparison to the placebo-treated group. To ensure patient safety, patients with known or suspected clinical immunodeficiency syndromes were excluded, and severe infections or those requiring intravenous antibiotics or invasive interventions were classified as an adverse event of special interest, but an IgG threshold was not set as an exclusion criterion. Coupled with inclusion of patients who were anti-LRP4-positive, the Vivacity-MG3 study, thus, rigorously assesses the safety and efficacy of nipocalimab in a cohort that reflects the anticipated treatment-eligible cohort and for the longest placebo-controlled duration to date.

Nipocalimab was well tolerated during Vivacity-MG3, with most adverse events characterised as mild or moderate. Of note, there was no difference in overall incidence of infections between the nipocalimab and placebo groups. Headache was also reported at a similar incidence in both treatment groups. No serious or severe infusion reactions were observed in either group. The incidence of peripheral oedema was higher with nipocalimab than with placebo. Oedema might be associated with low albumin; however, all patients at the time of oedema had albumin concentrations within normal limits. The higher incidence of muscle spasms with nipocalimab compared with placebo could potentially be due to improved neuromuscular signalling, similar mechanistically to muscle spasms seen with use of cholinergic agents in the setting of efficient immunomodulation.[23] None of the adverse events of peripheral oedema or muscle spasms was serious, severe, or led to study discontinuations.

Elevations in total cholesterol and LDL have been reported with drugs in the FcRn blocker class.[24] Mild increases from baseline in LDL and HDL were observed with nipocalimab at week 24; none of these increases led to study discontinuation. The ratio of mean total cholesterol to HDL remained stable (<4); low total cholesterol-to-HDL ratios are potentially suggestive of limited effect on cardiovascular risk status.[25] The mechanism of elevation in total cholesterol, LDL, and HDL is not well understood and could be due to decreases in serum albumin. Albumin has been reported as a regulator of cholesterol transport,[26] and reduction of albumin might result in elevation of blood lipids, as has been reported with primary hypoalbuminaemia;[27] further investigation is needed.

The placebo effect observed in the pivotal phase 3 study was larger than that reported in other published studies in myasthenia gravis. Augmentation of placebo effect because of expectation bias has been observed to modulate clinical outcomes in other therapeutic areas such as chronic pain management[28] and depression.[29] Similarly, expectation bias was also observed in myasthenia gravis trials, in which the MG-ADL response rate in the placebo group increased over time with approvals within the C5 inhibitor class; for example, a 3-point or greater placebo response rate of 40% was observed in the REGAIN trial[6] (eculizumab) concluding in 2016, and 53% in the RAISE trial (zilucoplan) concluding in 2021.[7] It is possible, therefore, that expectation bias could partly account for the magnitude of placebo effect in the phase 3 study of nipocalimab, given that two FcRn blockers (efgartigimod and

rozanolixizumab) were approved for generalised myasthenia gravis during its conduct. Notably, nipocalimab demonstrated statistically significant changes over placebo and clinically meaningful improvement across several endpoints through the 6-month clinical trial. More patients receiving nipocalimab reached the established clinically meaningful improvement of at least 2 points for MG-ADL and at least 3 points for QMG, and approximately a third of patients improved from a baseline mean MG-ADL score of 9·4 (SD 2·73) to reach minimal symptom expression at any time during the study.

There are some limitations to our study. Despite a concerted global effort to ensure enrolment of a representative population, the percentage of enrolled Black patients was low (1%); however, the Vivacity-MG3 population was more diverse than recent myasthenia gravis studies,[7,14,15] and no evidence at this time indicates that response to nipocalimab varies with race. Only three patients who were LRP4 antibody-positive were enrolled; however, this prevalence is consistent with the low prevalence of this rare antibody, and reductions in IgG1 and IgG2 antibody subclasses (which make up LRP4 antibodies) were seen with nipocalimab treatment. Nipocalimab was administered as an add-on treatment to standard-of-care therapies, so all findings should be interpreted within this context. The completion of the open-label extension phase of this study will further inform how well treatment effect is maintained with nipocalimab and provide longer term safety data.

In conclusion, in the Vivacity-MG3 study, nipocalimab demonstrated sustained efficacy and a favourable safety profile over 6 months, in a broad range of patients with generalised myasthenia gravis.

Contributors

SR, KK, PS, EY, YZ, and HS designed the study. CA, TV, RJN, CF, VB, JDB, HY, EM, J-SP, MG, MS, TS, SH, KS, and YS enrolled patients. SR developed the original draft of the manuscript. KK did the statistical analysis. SR, KK, PS, EY, CA, and TV have directly accessed and verified the underlying data reported in the manuscript. All authors contributed to the review and editing of the manuscript and supported in the interpretation of the data. All authors met the ICMJE criteria and all those who fulfilled those criteria are listed as authors. Authors had full access to all of the data, were involved in writing or revising the manuscript, and had final responsibility for the decision to submit for publication.

Declaration of interests

SR, EY, PS, KK, YZ, JJS, and HS are employees of Janssen Research & Development or Janssen Global Services (Johnson & Johnson companies) and might hold stock or stock options in Johnson & Johnson. CA received funding for travel, meeting attendance, and advisory board participation from Alexion, Momenta, Sanofi, argenx, UCB, and Janssen Pharmaceuticals. TV has received research or grant support related to myasthenia gravis from Alexion and AstraZeneca Rare Disease, Amgen, argenx, Cartesians, COUR, Dianthus, Immunovant, Johnson & Johnson, NMD Pharma, Regeneron, and UCB. TV serves as a consultant or on speaker bureaus for Alexion and AstraZeneca Rare Disease, Amgen, argenx, CSL Behring, Dianthus, Johnson & Johnson, and Takeda. RJN has received research support from Alexion, AstraZeneca Rare Disease, argenx, Genentech, Grifols, Immunovant, Momenta Pharmaceuticals (now Janssen), the Myasthenia Gravis Foundation of America, the National Institutes of Health (National Institute of Neurological Disorders and Stroke and National Institute of Allergy and Infectious Diseases), Ra Pharmaceuticals (now UCB), and Viela Bio (Horizon Therapeutics, now Amgen), and has served as consultant or advisor for Alexion, AstraZeneca Rare Disease, argenx, Cour Pharmaceuticals, Immunovant, Momenta Pharmaceuticals (now Janssen), Ra Pharmaceuticals (now UCB), and Viela Bio (Horizon Therapeutics, now Amgen). CF has served as a consultant or advisor for Argenx, Momenta and Janssen, the Muscular Dystrophy Association, and UCB. VB has received research support from AZ-Alexion, Grifols, CSL, UCB, argenx, Takeda, Octapharma, Akcea, Momenta (Johnson & Johnson), Immunovant, Ionis, and Viela. JDB has served on an advisory board for Argenx, Alexion Pharmaceuticals, CSL, UCB Pharma, Janssen Pharmaceuticals, and Sanofi Genzyme. TS has received honoraria for attendance at advisory boards from Argenx, Alnylam, Pfizer, and UCB. SH has received speakers´ honoraria from Alexion, Argenx, UCB, Grifols, Roche, and Janssen and honoraria for attendance at advisory boards from Alexion, Argenx, and Roche. SH is member of the medical advisory board of the German Myasthenia Society, DMG. HY, EM, J-SP, MG, MS, KS, and YS report no competing interests.

Data sharing

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through the Yale Open Data Access Project site at http://yoda.yale.edu.

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References

1 Meriggioli MN, Sanders DB. Muscle autoantibodies in myasthenia gravis: beyond diagnosis? *Expert Rev Clin Immunol* 2012; **8:** 427–38.
2 Guptill JT, Sharma BK, Marano A, et al. Estimated cost of treating myasthenia gravis in an insured US population. *Muscle Nerve* 2012; **45:** 363–66.
3 Gable KL, Guptill JT. Antagonism of the neonatal Fc receptor as an emerging treatment for myasthenia gravis. *Front Immunol* 2019; **10:** 3052.
4 Nguyen-Cao TM, Gelinas D, Griffin R, Mondou E. Myasthenia gravis: Historical achievements and the "golden age" of clinical trials. *J Neurol Sci* 2019; **406:** 116428.
5 Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: Executive summary. *Neurology* 2016; **87:** 419–25.
6 Howard JF, Utsugisawa K, Benatar M, et al. Safety and efficacy of eculizumab in anti-acetylcholine receptor antibody positive refractory generalised myasthenia gravis (REGAIN): a phase 3, randomised, double-blind, placebo-controlled, multicentre study. *Lancet Neurol* 2017; **16:** 976–86.
7 Howard JF Jr, Bresch S, Genge A, et al; RAISE Study Team. Safety and efficacy of zilucoplan in patients with generalised myasthenia gravis (RAISE): a randomised, double-blind, placebo-controlled, phase 3 study. *Lancet Neurol* 2023; **22:** 395–406.
8 Vu T, Meisel A, Mantegazza R, et al. Terminal complement inhibitor ravulizumab in generalized myasthenia gravis. *NEJM Evid* 2022; **1:** EVIDoa2100066.
9 SOLIRIS (eculizumab) injection, for intravenous use. Prescribing Information. 2024, Alexion Pharmaceuticals, Inc. https://alexion.com/Documents/Soliris_USPI.pdf (accessed July 30, 2024).
10 ZILBRYSQ (zilucoplan) injection, for subcutaneous use. Prescribing Information. 2023, UCB, Inc. https://www.ucb-usa.com/zilbrysq-prescribing-information.pdf (accessed July 30, 2024).
11 Ling LE, Hillson JL, Tiessen RG, et al. M281, an anti-FcRn antibody: pharmacodynamics, pharmacokinetics, and safety across the full range of IgG reduction in a first-in-human study. *Clin Pharmacol Ther* 2019; **105:** 1031–39.

12 Liu L, Garcia AM, Santoro H, et al. Amelioration of experimental autoimmune myasthenia gravis in rats by neonatal FcR blockade. *J Immunol* 2007; **178:** 5390–98.

13 Roopenian DC, Akilesh S. FcRn: the neonatal Fc receptor comes of age. *Nat Rev Immunol* 2007; **7:** 715–25.

14 Howard JF Jr, Bril V, Vu T, et al. Safety, efficacy, and tolerability of efgartigimod in patients with generalised myasthenia gravis (ADAPT): a multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol* 2021; **20:** 526–36.

15 Bril V, Drużdż A, Grosskreutz J, et al; MG0003 study team. Safety and efficacy of rozanolixizumab in patients with generalised myasthenia gravis (MycarinG): a randomised, double-blind, placebo-controlled, adaptive phase 3 study. *Lancet Neurol* 2023; **22:** 383–94. Erratum in: *Lancet Neurol* 2023; **22:** e11.

16 Singer M, Khella S, Bird S, et al. Single institution experience with efgartigimod in patients with myasthenia gravis: Patient selection, dosing schedules, treatment response, and adverse events. *Muscle Nerve* 2024; **69:** 87–92.

17 Nelke C, Spatola M, Schroeter CB, et al. Neonatal Fc Receptor-targeted therapies in neurology. *Neurotherapeutics* 2022; **19:** 729–40.

18 Wang X, Mathieu M, Brezski RJ. IgG Fc engineering to modulate antibody effector functions. *Protein Cell* 2018; **9:** 63–73.

19 Antozzi C, Guptill J, Bril V, et al; Vivacity-MG Phase 2 Study Group. Safety and efficacy of nipocalimab in patients with generalized myasthenia gravis: results from the randomized phase 2 Vivacity-MG Study. *Neurology* 2024; **102:** e207937.

20 Muppidi S, Wolfe GI, Conaway M, Burns TM, MG Composite And MG QOL15 Study Group. MG-ADL: still a relevant outcome measure. *Muscle Nerve* 2011; **44:** 727–31.

21 Donohue MC. Power and sample size calculations for longitudinal data. R package version 1.0-21. 2020. Available from: https://github.com/mcdonohue/longpower (accessed July 30, 2024).

22 Lu K, Luo X, Chen PY. Sample size estimation for repeated measures analysis in randomized clinical trials with missing data. *Int J Biostat* 2008; **4:** 1.

23 Masuda M, Utsumi H, Tanaka S, et al. Treatment of myasthenia gravis with high-dose cholinesterase inhibitors and calcineurin inhibitors caused spontaneous muscle cramps in patients. *Clin Neuropharmacol* 2018; **41:** 164–170.

24 Ward ES, Gelinas D, Dreesen E, et al. Clinical significance of serum albumin and implications of FcRn inhibitor treatment in IgG-mediated autoimmune disorders. *Front Immunol* 2022; **13:** 892534.

25 Mortensen MB, Nordestgaard BG. Elevated LDL cholesterol and increased risk of myocardial infarction and atherosclerotic cardiovascular disease in individuals aged 70-100 years: a contemporary primary prevention cohort. *Lancet* 2020; **396:** 1644–52.

26 Sankaranarayanan S, de la Llera-Moya M, Drazul-Schrader D, et al. Serum albumin acts as a shuttle to enhance cholesterol efflux from cells. *J Lipid Res* 2013; **54:** 671–76.

27 Del Ben M, Angelico F, Loffredo L, Violi F. Treatment of a patient with congenital analbuminemia with atorvastatin and albumin infusion. *World J Clin Cases* 2013; **1:** 44–48.

28 Perfitt JS, Plunkett N, Jones S. Placebo effect in the management of chronic pain. *BJA Educ* 2020; **20:** 382–7.

29 Khan A, Mar KF, Brown WA. Consistently modest antidepressant effects in clinical trials: the role of regulatory requirements. *Psychopharmacol Bull* 2021; **51:** 79–108.