NIHR | Innovation Observatory

Newcastle University

# Health Technology Briefing
# November 2023

## Nipocalimab for Generalised Myasthenia Gravis

| Company/Developer | Janssen-Cilag Ltd |
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☒ New Active Substance ☐ Significant Licence Extension (SLE)

| NIHRIO ID: 28008 | NICE ID: Not available | UKPS ID: 663713 |
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## Licensing and Market Availability Plans

Currently in phase 2/3 clinical development.

## Summary

Nipocalimab is currently in clinical development for the treatment of adults with generalised myasthenia gravis (gMG). gMG is a rare, long-term autoimmune disorder that leads to muscle weakness and tiredness, which can be seriously debilitating and life-threatening, affecting eye alignment, swallowing, speech, mobility and respiratory function. These symptoms can significantly impair independence and quality of life. gMG is caused by the body's immune system wrongly launching an attack against the neuromuscular junction — the place where nerve cells communicate with muscle cells. This attack is largely driven by self-reactive antibodies, also known as autoantibodies, and more specifically, by immunoglobulin G (IgG) autoantibodies. Current treatments have long-term side effects, which can be intolerable for patients, and can take several months to become effective.

Nipocalimab, administered intravenously, is a therapeutic antibody that is designed to block the IgG binding site on the neonatal Fc receptor (FcRn), which is a protein that normally helps to prevent IgG antibodies circulating in the bloodstream from being degraded. By blocking IgG binding to FcRn, nipocalimab aims to increase the rate at which IgG autoantibodies are degraded, thereby reducing their levels in the bloodstream and easing gMG severity. If licensed nipocalimab would offer a new treatment option for gMG.

## Proposed Indication

Treatment of generalised myasthenia gravis (gMG) in adult patients.[1]

# Technology

## Description

Nipocalimab (JNJ-80202135, M281) is a fully human, aglycosylated immunoglobulin (Ig)G1 monoclonal antibody (mAb) designed to selectively bind, saturate, and block the IgG binding site on the endogenous neonatal Fc receptor (FcRn).[1,2] FcRn, is expressed in endothelial cells and is responsible for recycling IgG into the circulation and for the relatively long half-life of IgG antibodies compared to other immunoglobulins. , By blocking IgG binding to FcRn, nipocalimab aims to increase the rate at which IgG autoantibodies are degraded, thereby reducing their levels in the bloodstream and easing gMG severity.[2,3]

Nipocalimab is currently in phase 2/3 development (NCT03772587, NCT04951622) for the treatment of adults with gMG. In the phase 3 clinical trial (NCT04951622), nipocalimab will be administered as an intravenous infusion once every 2 weeks for 24 weeks.[1,4,5]

## Key Innovation

Current treatments for gMG can include immune-suppressants and anticholinesterases.[6] However, many of these treatments are associated with long-term side-effects, which can be intolerable for patients, as well as taking several months to become effective.[7,8] Nipocalimab specifically binds to the IgG binding site on FcRn blocking the binding of the IgG to the FcRn.[9] Nipocalimab has high specificity, minimising off-target effects.[10,11] If licensed, Nipocalimab will offer a new treatment option to adults with gMG.

## Regulatory & Development Status

Nipocalimab does not currently have marketing authorisation in the EU/UK for any indication.

Nipocalimab is currently in phase 3 clinical development for the following indications:[12]

- Children with gMG
- Chronic Inflammatory Demyelinating Polyneuropathy
- In pregnancies at risk of severe hemolytic disease of the fetus and newborn
- Warm autoimmune hemolytic anemia

As well as multiple other phase 2 indications including:[13]

- Chronic Inflammatory Demyelinating Polyneuropathy
- Active Rheumatoid Arthritis
- Active Idiopathic Inflammatory Myopathies
- Warm Autoimmune Hemolytic Anemia
- Active Systemic Lupus Erythematous
- Active Lupus Nephritis
- Primary Sjogren's Syndrome

Nipocalimab has an orphan drug in the USA in 2021 for myasthenia gravis.[14]

# Patient Group

## Disease Area and Clinical Need

gMG develops in adults due to a defect in the immune system.[15] Complement is a part of the immune system and normally helps to protect against certain types of infections. However, in people with gMG, complement is activated by antibodies, which trigger complement to damage the area where the nerves and muscles meet., meaning that muscles are not able to contract as well as usual.[16] It most commonly affects the muscles that control the eyes and eyelids, facial expressions, chewing, swallowing and speaking. But it can affect most parts of the body.[17] The most common symptoms of gMG are drooping eyelids, double vision, difficulty in making facial expressions, problems with chewing and swallowing, slurred speech, weak arms, legs or neck, and shortness of breath and, occasionally, serious breathing difficulties.[17,18] Symptoms can become more severe with tiredness and can be triggered by factors such as stress, infections and certain medicines in some people.[18] Most individuals with gMG have no family history of the condition.[19]

In the UK, gMG affects about 15 in every 100,000 people.[20] Although it can affect people of any age, gMG typically starts in women under 40 and men over 60.[17] In England (2022-23), there were 5,515 finished consultant episodes (FCE) for MG (ICD-10=G70.0) leading to 4,272 admissions, 2,708 day cases and 115,720 FCE bed days.[21]

## Recommended Treatment Options

There is currently no treatment option recommended by NICE for gMG.
The following pharmacological treatment options are currently used to treat gMG.[6]

- Prednisolone is given as immunosuppressant therapy
- Azathioprine can be started at the same time as a corticosteroid
- Ciclosporin, methotrexate or mycophenolate mofetil can be used in patients who are unresponsive or intolerant to other treatments
- Anticholinesterases (neostigmine and pyridostigmine bromide) as an adjunct to immunosuppressant therapy

In addition, surgery may be undertaken to remove the thymus gland, a gland in the chest linked to MG; this can improve symptoms in some people with an unusually large thymus.[17]

## Clinical Trial Information

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| Trial | NCT04951622, EudraCT2020-005732-29, Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Nipocalimab Administered to Adults With Generalized Myasthenia Gravis.<br>**Phase 3:** Recruiting<br>**Locations:** US, Australia, Canada and 9 EU countries<br>**Primary completion date:** November 2023 |
| Trial Design | Randomised, Parallel assignment, Triple masked |
| Population | N=198 (estimated). Adults aged 18+ with diagnosis of myasthenia gravis with genialized muscle weakness meeting. |
| Intervention(s) | Nipocalimab Intravenously administered once every 2 weeks for up to 24 weeks |
| Comparator(s) | Matched Placebo Intravenously administered once every 2 weeks for up to 24 weeks |
| Outcome(s) | Primary outcome measures: |

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| | • Average change from baseline in Myasthenia Gravis - activities of daily living (MG-ADL) score [ Time frame: baseline up to week 24]<br>See trial record for full list of outcome measures |
| Results (efficacy) | - |
| Results (safety) | - |
| **Clinical Trial Information** | |
| Trial | NCT03772587, EudraCT2018-002247-28, A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Efficacy, Pharmacokinetics and Pharmacodynamics of M281 Administered to Adults With Generalized Myasthenia Gravis<br>**Phase 2:** Complete<br>**Locations:** UK, US, Canada and 5 EU countries<br>**Primary completion date:** June 2020 |
| Trial Design | Randomized, Parallel Assignment, Quadruple masked |
| Population | N=68 (actual). Adults aged 18+ with documented history of generalized myasthenia gravis. |
| Intervention(s) | Nipocalimab (Intravenously administered):<br>Group 1: 5 mg/kg every 4 weeks<br>Group 2: 30 mg/kg every 4 weeks<br>Group 3: 60 mg/kg, single dose on day 1<br>Group 4: 60 mg/kg every 2 weeks |
| Comparator(s) | Matched placebo (Intravenously administered) |
| Outcome(s) | Primary outcome measures:<br>• Number of participants with adverse events (AE) [Time frame: up to day 113]<br>• Change from baseline in the total Myasthenia Gravis - activities of daily living (MG-ADL) score at day 57 [Time frame: baseline; day 57]<br>See trial record for full list of outcome measures |
| Results (efficacy) | There was a change in total myasthenia gravis, as measured by the mean (SD) score, for all patients with gMG group 1 = -2.5 (2.4), group 2 = -3.9 (3.0), group 3 = -1.5 (2.8), group 4 = -3.9 (3.7). This is compared to a mean change of -1.8 (3.2) in the placebo group.[5] |
| Results (safety) | 11 of 14 patients in the placebo group experienced an AE. 12 of 14 experienced an AE in experimental group 1. 9 of 13 experienced an AE in experimental group 2. 12 of 13 experienced an AE in experimental group 3. 12 of 14 experienced an AE in experimental group 4. Serious AEs were experienced by 2 of 14 of the placebo group. In the experimental groups, only group 2 had 1 serious AE, while the others had zero.[5] |
| **Clinical Trial Information** | |

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| Trial | NCT03896295, EudraCT2018-003618-41, An Open-label Extension Study of MOM-M281-004 to Evaluate the Safety, Tolerability, and Efficacy of M281 Administered to Patients With Generalized Myasthenia Gravis.<br>**Phase 2:** Terminated (Study was originally halted due to the COVID-19 pandemic. The study was later terminated prematurely as the participants will have the option to enter into an open-label extension portion of a planned future study. It was not due to safety concerns.)<br>**Locations:** UK, US, Canada and 5 EU countries |
| Trial Design | Single group assignment, open label. |
| Population | N=37 (actual). Adults aged 18+ with a documented history of gGM. |
| Intervention(s) | Group 1: participants who received placebo in MOM-M281-004 study received intravenous nipocalimab, 30 mg/kg every 4 weeks.<br>Group 2: participants who received nipocalimab in MOM-M281-004 received intravenous nipocalimab, 30 mg/kg every 4 weeks. |
| Comparator(s) | No matched placebo |
| Outcome(s) | Primary outcome measures:<br>• Number of participants with adverse events [Time frame: Up to approximately 1 year]<br>See trial record for full list of outcome measures. |
| Results (efficacy) | - |
| Results (safety) | Treatment emergent AEs occurred in 22 of 37 patients (4 of 7 in group 1 and 18 of 30 in group 2). Serious AEs occurred in 5 of 37 patients (1 of 7 in group 1 and 4 of 30 in group 2).[4] |

## Estimated Cost

The cost of Nipocalimab is not yet known.

## Relevant Guidance

### NICE Guidance

- NICE technology appraisal in development. Zilucoplan for treating antibody positive generalised myasthenia gravis (GID-TA11096). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Rozanolixizumab for treating antibody-positive generalised myasthenia gravis (GID-TA10994). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Efgartigimod for treating generalised myasthenia gravis (GID-TA10986). Expected October 2023.
- NICE technology appraisal in development. Ravulizumab for treating generalised myasthenia gravis (GID-TA10987). Expected July 2023.

### NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Rituximab bio-similar for the treatment of myasthenia gravis (adults). 170084P. September 2018.

- NHS England. 2014/15 NHS Standard Contract for Neuromuscular Operational Delivery Network Specification. D04/ODN/a.
- NHS England. 2013/14 NHS Standard Contract for Neurosciences: Specialised Neurology (Adult). D04/S/a.
- NHS England. 2013/14 NHS Standard Contract for Diagnostic Service for Rare Neuromuscular Disorders (All ages). D04/S(HSS)/a.

### Other Guidance

- Narayanaswami, P., Sanders D. B., Wolfe G., Benatar M., Cea G., Evoli A., et al. International Consensus Guidance for Management of Myasthenia Gravis. Neurology. 2021.[22]
- Sanders D. B., Wolfe G. I., Benatar M., Evoli A., Gilhus N. E., Illa I., et al. International consensus guidance for management of myasthenia gravis: Executive summary. 2016.[23]
- Sussman J, Farrugia ME, Maddison P, Hill M, Hilton-Jones D. Myasthenia gravis: Association of British Neurologists' management guidelines. 2015.[24]

## Additional Information

## References

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