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Antigen-specific immune therapy (CNP-106) for treatment of generalised myasthenia gravis: rationale and design of first-in-human randomised controlled trial

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ABSTRACT

Introduction Myasthenia gravis (MG) is a T cell-dependent B cell-mediated autoimmune disease with pathogenic antibodies directed against components of the acetylcholine receptor (AChR). Current therapies do not address the root cause of the disease (autoimmune recognition of AChR) and are associated with possible serious side effects. Therefore, new therapeutic options targeting antigen-specific autoimmunity are needed. COUR nanoparticle (CNP-106) is an antigen-specific immune tolerance therapy directed to the AChR to stop the pathogenic driver of MG. Data from experimental models suggest the potential benefit of CNP-106 to patients by reprogramming the immune system to AChR and stopping the progression of the disease. The aim of this study is to determine the safety and preliminary efficacy of CNP-106 in AChR antibody-positive generalised MG subjects.

Methods and analysis The outlined study is a multicentre Phase 1b/2a double-blind, randomised, placebo-controlled trial with an enrolment target of 54 AChR antibody-positive generalised MG subjects. The primary endpoint is safety and tolerability. Exploratory and secondary endpoints include disease-specific clinical scores, measures of quality of life and activities of daily living, antigen-specific T cells and AChR antibodies. Trial enrolment is anticipated to start in 2024.

Ethics and dissemination The trial has ethical approval from the Central Institutional Review Boards and has clinical trial authorisation from the Food and Drug Administration. Trial results will be communicated to participants, presented at national and international meetings and published in peer-reviewed journals.

Trial registration number NCT06106672.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Myasthenia gravis (MG) is characterised by autoimmune dysfunction in neuromuscular transmission due to anti-acetylcholine receptor (AChR) antibodies produced by B cells which are regulated by T cells. Clinical trials to date have focused on the downstream effects of various treatments without incorporating endpoints that assess these central autoimmune processes responsible for disease burden.

WHAT THIS STUDY ADDS

⇒ The COUR nanoparticle-106 trial described here is the first randomised controlled trial of an antigen-specific immune tolerising therapy in subjects with AChR antibody-positive generalised MG. The trial describes mechanistic outcome measures using antigen-specific T-cell readouts to assess the immunological benefit of treatment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This proof-of-concept study with a small patient population aims to inform design in future registration trials. Furthermore, this study design incorporates the novel antigen-specific immune endpoints involved in the autoimmune mechanisms driving MG disease progression.

INTRODUCTION

Myasthenia gravis (MG) has an incidence of 4.1–30 cases per million person-years and a prevalence of 150–200 per million adults worldwide.[1] In MG, activation of T cells and B cells specific to the acetylcholine receptor (AChR) results in antibody-related impairment of AChR signalling at the neuromuscular junction (NMJ). Patients with MG experience fatigable weakness of the ocular muscles (ptosis, diplopia), bulbar muscles (dysphagia, dysphonia, dysarthria, chewing difficulty) and limb muscles[2] resulting in lower mental and physical health-related quality of life relative to the general population.[3] The burden of disease includes its impact on economic, social and emotional well-being.[4]

Common treatment approaches to MG include steroids and immunosuppressive therapies. Pyridostigmine, a cholinesterase

inhibitor, is the recommended initial treatment especially if symptoms are mild. That said, many patients will inevitably require corticosteroids or broad-acting immunosuppressants (ie, azathioprine, mycophenolate mofetil). Current therapies are associated with possible significant side effects including gastrointestinal upset, increased risk of infection and liver damage along with weight gain, elevated blood sugars, bone loss and Cushing syndrome as with chronic steroid use.[5] Plasma exchange (PLEX) and intravenous immunoglobulin (IVIg) are typically considered short-term therapies and used for myasthenic crisis or exacerbation.[6] Patients may also undergo thymectomy to help reduce medication use and disease severity but this is not curative.[7] Complement inhibitors (ie, eculizumab) or neonatal FC receptor inhibitors (ie, efgartigimod) which target downstream immunopathology are Food and Drug Administration (FDA)-approved for the treatment of AChR antibody-positive generalised MG. Currently available new agents require frequent/chronic intravenous or subcutaneous dosing and increase the risk of infection.[8–10] There are no proven therapies that target the root cause of MG, antigen-specific T cell-dependent B cell-mediated autoimmunity leading to postsynaptic NMJ destruction via pathogenic antibodies. Induction of immune tolerance remains the holy grail for the treatment of autoimmune disorders.

As such, COUR nanoparticle (CNP-106 nanoparticles, encapsulating the major immunogenic T cell and B cell epitopes mapped in AChRα[11 12] and AChRε[13–15] (COUR Pharmaceuticals Development, Skokie, Illinois, USA) maybe a therapeutic option to treat MG by tolerising to disease-specific autoantigens including the major immunogenic region recognised by human anti-AChRα antibodies.

CNP-106 nanoparticles are immunomodulatory and achieve efficacy by reprogramming the immune system to the encapsulated antigen (figure 1). In brief, after intravenous administration, CNP-106 particles are taken up by marginal zone macrophages in the spleen, macrophages in the liver and the reticuloendothelial system/mononuclear phagocyte system (RES/MPS). The putative mechanism of action depends on the uptake of particles by antigen-presenting cells (APCs), particularly splenic marginal zone macrophages and liver APCs expressing scavenger receptors such as the macrophage receptor with collagenous structure in a fashion similar to the clearance of apoptotic debris.[16] Presentation to autoreactive T cells results in them becoming anergic or antigen-specific T regulatory cells (Tregs). The antigen-specific Tregs are CD25 and Foxp3-positive T cells and have the standard characteristics of regulating the autoreactive immune response.

The CNP particle design was first introduced into human clinical studies under product name CNP-101, also known as TIMP-GLIA and TAK-101.[17] After infusion of CNP-101 encapsulating gliadin proteins, the particles distribute to the RES/MPS and gliadin proteins are phagocytosed by APCs inducing immune tolerance to gluten in coeliac disease (CD) subjects. Safe human intravenous administration of this initial platform particle CNP-101 was demonstrated in Phase 1 and 2a clinical trials. CNP-101 was well tolerated and abrogated gluten antigen-specific T cell activation in CD subjects suggesting that

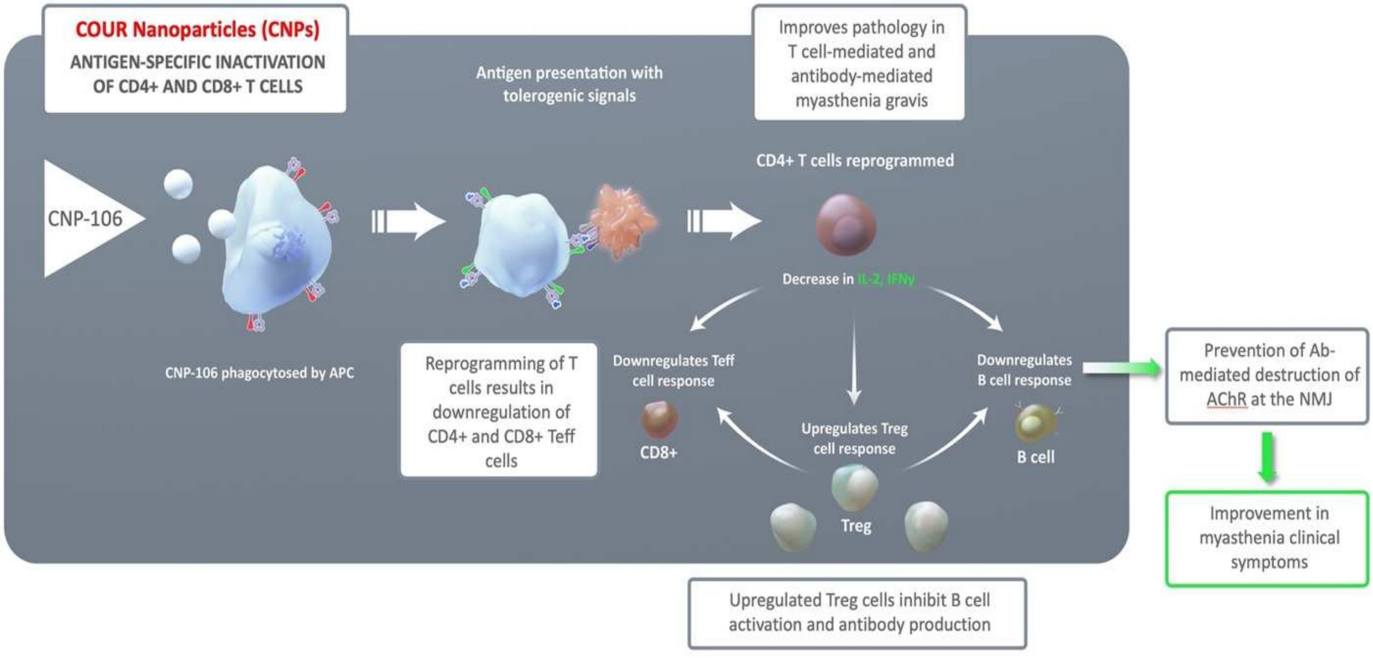

Figure 1 Mechanism of action for COUR nanoparticle (CNP-106) encapsulating seven AChRα and AChRε peptides (CNP-106). Ab, antibody; AChR, acetylcholine receptor; APC, antigen-presenting cell; IFNγ, interferon gamma; IL-2, interleukin 2; NMJ, neuromuscular junction; Treg, T regulatory cell.

antigen-specific tolerance was induced and representing a novel approach translatable to other immune-mediated diseases.[17]

Preliminary animal data from our group in an experimental autoimmune MG mouse model suggests that CNP-106 is safe and induces tolerance to autoreactive T cells leading to improvement in muscle function. Here, we describe the rationale and design of the first-in-human (FIH) double-blind, randomised, placebo-controlled clinical trial of CNP-106 in adults with generalised MG. This trial is unique as it represents the first investigation of antigen-specific immunotherapy for autoimmune MG.

STUDY OBJECTIVES

Primary objective

To assess the safety and tolerability of CNP-106 treatment in generalised MG subjects.

Secondary and exploratory objectives

To assess the pharmacodynamic (PD) and clinical efficacy of CNP-106 in generalised MG subjects.

METHODS/DESIGN

This study is a Phase 1b/2a FIH clinical trial to assess the safety, tolerability, PDs and preliminary efficacy of multiple ascending doses of CNP-106. The total duration of the clinical study is 222 days (42 days for screening and 180 study days). Once the study is complete, all subjects will have the opportunity to roll over into a long-term follow-up study.

Subjects ages 18–75 with generalised AChR antibody-positive MG will be screened up to 42 days (±7 days) prior to enrolment into the study. If subjects are currently on a standard of care therapy, they will remain on their current standard of care therapy during the course of the study at the discretion of the investigator.

Screening will be completed per the Schedule of Events (SOE) (figure 2). Subjects who meet all inclusion and no exclusion criteria after completing the screening visit will be enrolled in the studybox 1.

Subjects will be randomised on day 1 into the current dose cohort in a 2:1 ratio to receive two separate administrations of intravenous CNP-106 or placebo on day 1 and day 8. Investigational product (IP) will be administered by intravenous infusion over approximately 3–4 hours using a graduated rate of infusion. Subjects will undergo medical observation in the clinic for acute adverse events (AEs) for 4 hours following infusion on day 1 and day 8.

In the postdosing period, subjects will return to the clinic for safety labs, PD measurements, MG activities of daily living score (MG-ADL), MG quality of life 15 revision (MG-QOL-15r), quantitative MG score (QMG) and MG composite score (MGC) assessments, assessment of AEs and medication changes per the SOE (figure 2).

= IP administration
X = Key readouts

	Screen	Dosing Period		Post-Dosing Follow-Up Period				
Day(s)	-42	1	8	15	60	90[a]	120	180
Primary Endpoints								
AEs/SAEs, Labs	X	X	X	X	X	X	X	X
Secondary Endpoints								
Antigen-specific CD4+ and CD8+ T cells	X	X		X	X	X	X	X
Activated antigen-specific CD4+ and CD8+ T cells	X	X		X	X	X	X	X
Exploratory Endpoints								
MG-ADL	X	X	X	X	X	X	X	X
QMG	X	X	X	X	X	X	X	X
MG-QOL-15r	X	X	X	X	X	X	X	X
MGC	X	X	X	X	X	X	X	X
Healthcare Utilization	X				X			X
AChR Ab levels	X	X		X	X	X	X	X
MuSK Ab levels	X	X		X	X	X	X	X

[a] A third dose will be administered only to the subjects randomized to receive three doses of IP.

Figure 2 Schedule of Events. Ab, antibody; AChR, acetylcholine receptor; AEs, adverse events; IP, intraperitoneal; MG-ADL, myasthenia gravis-activities of daily living; MGC, myasthenia gravis composite; MG-QOL-15r, myasthenia gravis quality of life 15 revision; MuSK, muscle-specific kinase; QMG, quantitative myasthenia gravis; SAEs, severe adverse events.

Box 1 Key inclusion and exclusion criteria

Key inclusion criteria

⇒ Subjects who are willing and able to provide Institutional Review Board approved written informed consent and privacy language as per national regulations.
⇒ Men and non-pregnant women, ages 18–75 years inclusive.
⇒ Subjects with Myasthenia Gravis Foundation of America (MGFA) Clinical Classification Class III–IV disease for cohort 1 followed by MGFA Class II–IV disease for subsequent cohorts after data monitoring committee review.
⇒ Subjects positive for anti-acetylcholine receptor antibodies by radioimmunoassay (Mayo Clinic).
⇒ Subjects with MG-activities of daily living (MG-ADL) Score ≥6 at screening and baseline visit with ≥ 50% of the score derived from non-ocular symptoms.
⇒ Subjects with quantitative MG (QMG) Score ≥11 at screening and baseline visit.

Key exclusion criteria

⇒ Subjects with MGFA classification I or V disease.
⇒ Subjects with MG-ADL Score <6 at screen or subjects with MG-ADL Score ≥6 at screen with <50% of the score derived from non-ocular symptoms.
⇒ Subjects with QMG Score <11 at screen.
⇒ Subjects who have used the following medications:
  ⇒ Tacrolimus within six months prior to the first dosing;
  ⇒ Methotrexate within five half-lives or 90 days after the last dose, whichever is longer);
  ⇒ Anti-neonatal FC receptor inhibitors (eg, efgartigimod) within five half-lives for 90 days after the last dose, whichever is longer;
  ⇒ C5 complement inhibitors (eg, eculizumab) within five half-lives or 90 days after the last dose, whichever is longer;
  ⇒ Inclusion of subjects on other immunomodulatory drugs will be at the discretion of the medical monitor and study site investigator.
⇒ Subjects who have used immunoglobulins were given subcutaneous or intravenous (SCIg or IVIg) or plasmapheresis/plasma exchange within four weeks before screening.
⇒ Subjects who have had thymectomy or any other thymic surgery performed within 12 months prior to screening.
⇒ Subjects with untreated thymic malignancy, carcinoma or thymoma.
⇒ Subjects with a history of or currently active immune disorders other than MG (including autoimmune disease) unless the condition, after discussion with the medical monitor and study site investigator, has been deemed to be acceptable for the subject's participation in this study.
⇒ Subjects with a history of or current active diseases other than MG requiring immunosuppressive drugs (including azathioprine, prednisone, prednisolone, budesonide, cyclosporine, tacrolimus, methotrexate or mycophenolate mofetil) unless the condition, after discussion with the medical monitor and site investigator, has been deemed to be acceptable for the subject's participation in this study.

At the end of the study, subjects will return to the clinic for collection of safety labs, PD measurements, MG-ADL, MG-QOL-15r, QMG and MGC assessments and final assessment of AEs and medication changes.

The adaptive study design includes escalation and expansion phases (figure 3). The escalation phase is planned to enrol up to three cohorts (approximately six subjects per cohort) at multiple dose levels. The planned dose levels are as follows:

Cohort 1: 150 mg.
Cohort 2: 350 mg.
Cohort 3: Additional dose level as recommended by the data monitoring committee (DMC).

Dosing of subjects within cohort 1 will be separated by at least 7 days. After all subjects in a dose cohort have completed the day 15 office visit (7 days post-second dose), the DMC will be convened to review all available safety data. At this time, the DMC will determine whether additional enrolment is needed or it is acceptable to proceed to the next dose cohort. The DMC will also recommend if the 7 day stagger interval should continue.

Approximately 30 subjects in the expansion phase will be randomised 2:1 to receive a placebo or a safe and tolerable dose level of CNP-106 identified in the escalation phase. An additional cohort of six subjects will be randomised to receive a third dose of CNP-106 on day 90. One or more dose levels of CNP-106 may be explored in the expansion phase.

ELIGIBILITY CRITERIA

Key inclusion and exclusion criteria for the clinical study are listed in box 1.

INTERVENTION

Subjects will be randomised 2:1 to receive either CNP-106 (150 mg, 350 mg or a DMC-selected dose) or placebo (200 mL 0.9% sodium chloride) on day 1 and day 8. Subjects in the expansion phase randomised to the three-dose cohort will receive either CNP-106 or placebo on day 1, day 8 and day 90.

EXPERIMENTAL INTERVENTION/PLACEBO

The experimental intervention used in the clinical trial is CNP-106 which is given intravenously as a 200 mL infusion. Subjects randomised to receive placebo will receive a control infusion of normal saline. The CNP-106/placebo infusion will be administered in a double-blinded manner.

CONCOMITANT MEDICATIONS

All medications taken at least once in the 3 months before screening throughout the study duration will be recorded in the electronic case report form (eCRF). Subjects on any medication for the treatment of MG (eg, corticosteroids, pyridostigmine, rituximab) at the time of study enrolment must agree not to increase their dosage for the study duration. Any change to dosage requires review by the medical monitor and approval by the site investigator.

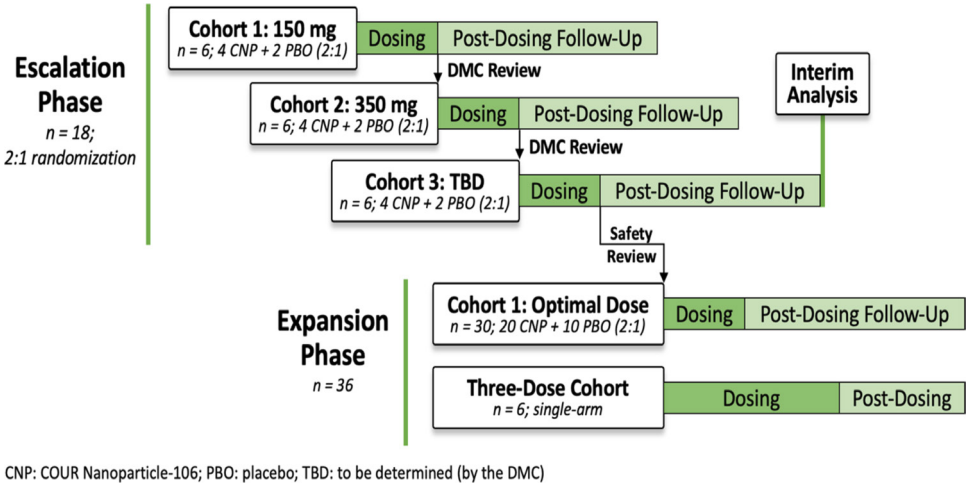

Figure 3 Clinical study design schematic. DMC, data monitoring committee.

RANDOMISATION AND BLINDING

Randomisation will be conducted by a third-party vendor web-based system at a 2:1 ratio. The treatment assignment will be kept blinded from the subjects, study assessors and study investigators until study completion. The randomisation system will generate a randomisation number for each subject that links to their corresponding treatment assignment. Only unblinded pharmacists and the study sponsor's unblinded representative will have access to the unblinded treatment assignments.

STUDY PROCEDURES AND OUTCOME MEASURES

The SOE is outlined in figure 2.

Safety assessments

The primary outcome measure is safety. General safety assessments will include physical examinations, vital signs (temperature, blood pressure, heart rate and respiratory rate), ECG and monitoring for AEs and severe adverse events (SAEs). Laboratory safety endpoints will include coagulation, chemistry, serology, serum cytokines, complement, tryptase, haematology, urinalysis and metabolites. Chemokines and tryptase will be assessed at the time of any infusion reaction.

Clinical outcome assessments

The severity and burden of the disease will be assessed using the following MG-specific outcome measures: MG-ADL, MGC, MG-QOL-15r and QMG. Table 1 details the scoring system, validation and clinical meaningfulness of each score change.

Healthcare resource utilisation

Baseline healthcare resource utilisation will be captured and reported as hospital and rescue therapy use within 1 year previous to the study start. Healthcare resource utilisation will be reported as MG exacerbation rate requiring rescue therapy with IVIg/PLEX throughout the course of the study.

Antigen-specific T cell biology

Quantification and phenotyping of total and antigen-specific T cell populations will be assessed using a 30-colour flow cytometry panel developed at Benaroya Research Institute.[18] Changes in antigen-specific CD4+T effector, antigen-specific CD8+T effector and antigen-specific CD4+Treg populations and activation markers will be reported and compared between CNP-106 treated and placebo-treated subjects. Serum samples will be collected according to the SOE (figure 2).

Antibodies

AChR (binding antibody) and muscle-specific kinase (MuSK) antibodies will be measured by radioimmunoassay in a Clinical Laboratory Improvement Amendments certified central lab under Title 21 of the Code of Federal Regulations (CFR) compliant conditions. Serum samples will be collected according to the SOE (figure 2).

Table 1 Clinical outcome measures

Outcome measure	Items	Total score range	Patient-reported versus physician-reported	Minimum score improvement associated with meaningful clinical benefit
MG-ADL[13 14]	8	0–24	Patient	2
MGC[15 16]	10	0–50	Patient and physician	3
MG-QOL-15r[17 18]	15	0–60	Patient	Not established
QMG[19]	13	0–39	Physician	2.6

For all measures, higher scores indicate a greater impact of MG on functional activities and burden of disease.
MG, myasthenia gravis; MG-ADL, MG activities of daily living; MGC, MG composite; MG-QOL-15r, MG quality of life 15 revision; QMG, quantitative MG.

DATA ANALYSIS

Sample size calculation

The study is not powered to detect significant changes in PD and clinical outcomes but data trending will be used to inform future registrational trials.

Analysis of outcome measures

The analysis will be based on the intention to treat.

Primary outcome

Safety and tolerability of CNP-106 will be measured by the frequency of treatment-related AEs and SAEs between CNP-106 treated and placebo-treated groups.

Exploratory outcomes

Exploratory endpoints will be assessed on day 60, 90 and 180. The mean change from baseline to endpoint between CNP-106 and placebo treatment groups will be analysed using analysis of variance. The change in MG clinical scores (MG-ADL, MGC, QMG, MG-QOL-15r), changes in antibodies (anti-AChR and anti-MuSK antibodies) and change in T cells will be reported. An interim analysis will be performed after all subjects in the escalation phase have reached day 180. A final analysis will be performed when all participants have completed the study procedures.

Premature discontinuation from IP

A subject may be prematurely discontinued from IP dosing for any of the following reasons:

- Safety including AEs or the development of clinically significant laboratory abnormalities. The subject must be followed clinically until the event is resolved or deemed stable;
- Pregnancy (either female subjects or pregnant partners of male subjects);
- Subject wishes to withdraw consent for reasons other than an AE;
- Subject non-compliance or unwillingness to comply with the procedures required by the protocol;
- Investigator discretion;
- Sponsor request.

Efforts will be made to follow all subjects who discontinue IP for any reason. Such follow-up will include all relevant evaluations for safety including clinical assessments and collection of laboratory study results as set out in this protocol.

DATA MONITORING, QUALITY CONTROL AND QUALITY ASSURANCE

Data collection

All subjects will be assigned a unique study identifier. Data entry, processing and retention will be performed in accordance with US regulations (21 CFR part 312.62).

Discontinuation rules

The study will be paused (enrolment and treatment of subjects) if there is one AE of Grade≥2 that persists for more than 2 weeks or if there is an unanticipated AE of≥Grade 3 (CTCAE, most current version) that occurs within 4 hours of IP administration. This pause will allow the DMC to conduct an investigation and provide advice and recommendations regarding study stopping or protocol revisions.

Monitoring, quality control and quality assurance

This study will be managed by COUR Pharmaceuticals who will provide support to the clinical sites and training through site initiation visits and routine monitoring visits.

Data monitoring committee

An independent DMC will be commissioned to review ongoing safety data for this study.

Study monitoring

Site visits will be conducted by an authorised sponsor representative who will inspect eCRFs at regular intervals throughout the study, to verify adherence to the protocol and completeness, consistency and accuracy of the data being entered.

RECORDING AND REPORTING AES AND SAES

AEs will be reported in a manner consistent with the FDA Guidance for Industry and Investigators.[19]

AEs and SAEs

All AE and SAE reporting and treatment will be performed according to the study protocol and in accordance with regulatory guidance.

Dissemination

All data and discoveries arising out of the study, patentable or non-patentable, shall be the sole property of the sponsor. The sponsor reserves the right to prior review of any publication or presentation of information related to the study.

DISCUSSION

MG is a chronic autoimmune condition with a high burden of disease that negatively impacts functional activities and the quality of life of patients. Current standard treatments rely on chronic immunosuppression and are associated with a number of possible serious side effects including increased risk of infection. Despite recent advances and targeted strategies, there remains a significant unmet medical need with this rare disease and an opportunity for novel therapeutics to positively impact individuals with MG.

The ideal therapeutic approach to MG may be antigen-specific tolerance against AChR to stop autoimmune recognition of AChR. In preliminary preclinical studies, CNP-106 reprogrammed pathogenic T cells, leading to AChR tolerance and improvement in myasthenia clinical symptoms. Treatment with CNP-106 has the potential to prevent immune-mediated destruction of the

NMJ, stopping further progression of muscle weakness and abrogating active disease. CNP-106 treatment has the potential to arrest disease allowing for recovery and repair at the motor endplate resulting in restoration of normal function and muscle strength.

CNP-106 is the only therapeutic targeting the pathological driver in autoimmune MG. Unlike any comparator, CNP-106 specifically targets APCs, reprogramming the immune system, with the potential to offer permanent relief from symptoms without chronic dosing requirement. The potential safety risks associated with CNP-106 are low as CNP-106 specifically modulates disease-relevant cell types.

The goal of this Phase 1b/2a FIH study of CNP-106 in MG is to gather safety and preliminary efficacy data and will specifically assess:

1. Immunological PD efficacy by a decrease in antigen-specific T cell activation;
2. Clinical benefit by improvement in MG-specific outcomes.

Findings from the FIH study will not be powered to detect significant clinical changes between treatment groups but will provide critical data to inform future phase clinical trial design. As the clinical development programme for CNP-106 progresses, the plan will be to expand on these safety and efficacy endpoints in larger, randomised, controlled studies and to further investigate meaningful clinical endpoints for patients with MG.

In summary, this study is the first of its kind exploring the safety and efficacy of a novel antigen-specific therapy in MG. CNP-106 has the potential to induce tolerance to AChR and improve myasthenia clinical symptoms without the need for broad immunosuppression or chronic dosing. The results of this study will pave the way for a new class of therapeutics targeting multiple arms of the dysregulated immune response leading to improvement in clinical disease and immune tolerance.

Contributors SGB and AE conceptualised the study. SGB, DM and MF wrote the study protocol. RJN contributed clinical input to the overall protocol concept and design. All authors wrote, edited and approved the manuscript. MF and RJN are the guarantors.

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Competing interests RJN is contracted as a clinical consultant of COUR Pharmaceuticals. All other authors are employees of COUR.

Patient consent for publication Not applicable.

Ethics approval The trial has approval from an independent central institutional review board, specifically WCG (IRBInstitutional Review Board tracking ID is 20235448).

Provenance and peer review Not commissioned; externally peer reviewed.

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