nature medicine

Article

https://doi.org/10.1038/s41591-025-04171-y

BCMA-directed mRNA CAR T cell therapy for myasthenia gravis: a randomized, double-blind, placebo-controlled phase 2b trial

Received: 27 October 2025

Accepted: 9 December 2025

Published online: 09 January 2026

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Myasthenia gravis (MG) is driven by the secretion of autoantibodies from pathogenic B cell maturation antigen (BCMA)-expressing plasma cells. In this phase 2b randomized, controlled, double-blind trial, we evaluated Descartes-08, an autologous BCMA-directed mRNA chimeric antigen receptor T cell therapy, in patients with generalized MG (gMG). Patients ($n = 26$) were randomly allocated to receive once-weekly intravenous infusions of Descartes-08 ($n = 15$) or placebo ($n = 11$) over 6 weeks. The primary endpoint was a ≥5-point improvement in the MG Composite (MGC) score at month 3. Secondary endpoints included the mean change from baseline in MGC, MG Activities of Daily Living (MG-ADL) and Quantitative MG (QMG) scores by month 12. At month 3, the proportion of patients achieving a ≥5-point improvement in the MGC score was significantly higher for those treated with Descartes-08 compared to placebo in the overall population (66.7% ($n = 10/15$) versus 27.3% ($n = 3/11$), $P = 0.0472$) and in a subpopulation of those positive for autoantibodies to the acetylcholine receptor (63.6% ($n = 7/11$) versus 12.5% ($n = 1/8$), $P = 0.0258$). For patients treated with Descartes-08, the changes from baseline in mean MGC, MG-ADL and QMG scores at month 4 were −7.1, −5.5 and −4.8, respectively, with 83.0% of patients achieving a sustained and clinically meaningful response at month 12. Notably, 33.0% of patients achieved minimum symptom expression (MSE) (MG-ADL score ≤1) by month 6, which was sustained through month 12. Among biologic-naive patients, 55.60% achieved MSE by month 6, which was maintained through month 12 without additional treatment. Descartes-08 was generally safe and well tolerated. Infusion-related reactions were the most common adverse events reported (Descartes-08, 80.0% ($n = 16/20$); placebo, 56.3% ($n = 9/16$)). In summary, a single course of six once-weekly infusions of Descartes-08 was well tolerated and resulted in sustained clinically meaningful responses among patients with gMG. ClinicalTrials.gov identifier: NCT04146051.

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Myasthenia gravis (MG) is an antibody-mediated autoimmune condition that causes damage to the postsynaptic membrane at the neuromuscular junction, affecting neurotransmission from motor neurons to skeletal muscle[1]. MG is typically characterized by chronic weakness and muscle fatigue that worsens with exertion[2–4]. While most patients initially present with ocular disturbances, including ptosis or diplopia[1], symptoms often evolve within 2 years of onset, affecting limb, respiratory and bulbar function—termed generalized MG (gMG)[2]. gMG is further classified according to the presence of pathogenic autoantibodies that target discrete components of the neuromuscular junction milieu, including the acetylcholine receptor (AChR), low-density lipoprotein receptor-related protein 4 (LRP4) and muscle-specific tyrosine kinase (MuSK)[5]. Up to 85% of patients with gMG are positive for autoantibodies to AChR[5], which leads to impairments in AChR function, downstream activation of the complement cascade and destruction of the postsynaptic membrane architecture[1,5]. The secretion of AChR autoantibodies is primarily driven by pathogenic B cell maturation antigen (BCMA)-expressing plasmablasts and long-lived plasma cells[6], and recent studies have suggested that BCMA may be an attractive therapeutic target in gMG[7–9].

Conventional treatments for gMG include chronic broad immunosuppression with corticosteroids and nonsteroidal immunosuppressive therapy; however, these are often insufficient for complete symptom control and can result in considerable toxicity due to off-target effects[10]. Additionally, despite recent advances in targeted biologic treatments for gMG, such as anti-CD19/CD20 monoclonal antibodies, complement inhibitors and neonatal fragment crystallizable receptor (FcRn) antagonists[11–15], many patients continue to experience incomplete disease control. This necessitates chronic immunosuppressive treatment to maintain symptom improvement, which affects infection risk, daily activities, functional status and quality of life[4,11–13,16,17].

Chimeric antigen receptor (CAR) T cell therapy, particularly BCMA-directed CAR T cell therapy, has become one of the mainstays in the treatment of B cell-derived hematologic malignancies. While conventional BCMA-directed CAR T cell therapies—which rely on integrating lentiviral or gamma-retroviral vectors to encode the CAR—involve lymphodepletion chemotherapy that requires intensive postinfusion monitoring, with the potential for acute and delayed toxicity[18–20], nonintegrating BCMA-directed CAR T cell therapies may circumvent this toxicity due to the lack of requirement for chemotherapy. Additionally, a nonintegrating CAR T cell therapeutic approach that directly targets the BCMA-expressing plasmablasts and long-lived plasma cells driving autoantibody secretion and neuromuscular junction destruction in patients with gMG has the potential to provide a tolerable and effective treatment strategy to optimize patient outcomes.

Descartes-08 is an autologous BCMA-directed CAR T cell therapy that uses mRNA instead of an integrating viral vector to encode the CAR protein. This feature results in transient targeting and a well-defined pharmacokinetic profile without the risk of unchecked proliferation[21]. In an open-label, multicenter, phase 1b/2a trial of Descartes-08 in gMG (MG-001 parts 1 and 2), patients who received six once-weekly doses without preconditioning chemotherapy in an outpatient setting experienced a robust improvement in gMG symptom severity, as measured by several standardized scales[7]. The improvements persisted through 12 months of follow-up and were not associated with severe toxicity[22]. Here, we report the efficacy and safety of Descartes-08 for the treatment of gMG in a phase 2b, randomized, double-blind, placebo-controlled trial (MG-001 part 3).

Results

Participant characteristics

In this phase 2b, double-blind, placebo-controlled trial, eligible patients with gMG who tested negative for autoantibodies to MuSK were randomized 1:1 to receive six once-weekly intravenous infusions of Descartes-08 or placebo. The study included a 12-month follow-up period to assess the efficacy of treatment using the MG Composite (MGC), MG Activities of Daily Living (MG-ADL) and Quantitative MG (QMG) scores. On January 8, 2024, after the enrollment of 44 participants and before the unblinding of data and database lock, the steering committee of the trial, in consensus with the study monitoring committee, decided to implement a change in the primary outcome: from the MG-ADL score to the MGC score (previously a secondary outcome). The original primary outcome (MG-ADL score) was changed to a secondary outcome. This decision was made based on the recommendations of the 2000 MG Foundation of America (MGFA) Task Force[23], with plans to use the MGC score as the primary outcome in a subsequent phase 3 trial. Consequently, the primary endpoint for this phase 2b study was a ≥5-point improvement in the MGC score at month 3. The secondary endpoints were the mean change from baseline in MGC, MG-ADL, QMG and MG-Quality of Life 15-revised (MG-QoL-15r) scores by month 12. Safety outcomes were considered a separate endpoint.

A total of 50 participants were screened for eligibility in this study (MG-001 part 3) between November 10, 2022, and January 15, 2024 (Fig. 1). Of those, 45 participants met the inclusion criteria and underwent a single leukapheresis with a median of six doses produced (range, four to six doses). In accordance with the protocol, 9 of the 45 participants (20.0%) were not randomized; they received Descartes-08 under an open-label protocol because they failed to meet the therapeutic dose requirements for treatment, as fewer than six doses were manufactured (results to be reported separately). Thirty-six participants were deemed eligible and randomized to receive Descartes-08 ($n = 20$) or placebo ($n = 16$), comprising the safety population. Twenty-six participants were enrolled in an academic institution and had at least one postinfusion follow-up available, and they comprised the primary efficacy population. Of these, 19 (73.1%) were AChR autoantibody-positive, 1 (3.8%) was LRP4 autoantibody-positive and 6 (23.1%) were triple seronegative. Participants who tested positive for MuSK autoantibodies were excluded from the study.

Participant characteristics were generally balanced between treatment groups upon randomization to either the Descartes-08 group or the placebo group (Table 1). Notably, two participants with MGFA class IIa MG were enrolled in the placebo group, whereas no participants with MGFA class IIa MG were enrolled in the Descartes-08 group. Only one participant (enrolled in the Descartes-08 group) had MGFA class IVa MG. Overall, 11 (73.3%) participants in the Descartes-08 group and 8 (72.7%) participants in the placebo group had MGFA class III or IV MG.

There were differences in concomitant medication use between treatment groups (Table 1). The proportion of participants reporting concomitant use of nonsteroidal immunosuppressants was lower in the Descartes-08 group than in the placebo group ($n = 6$, 40.0% versus $n = 8$, 73.0%). Conversely, the number of participants reporting the use of concomitant complement inhibitors and orally administered corticosteroids was higher for the Descartes-08 group than the placebo group (complement inhibitors: $n = 4$, 26.7% versus $n = 1$, 9.1%; orally administered corticosteroids: $n = 9$, 60.0% versus $n = 4$, 36.4%). The median daily dose of concomitant prednisone equivalent was 20 mg (range, 5–25 mg) in the Descartes-08 group and 10 mg (range, 6–20 mg) in the placebo group, with no changes in dosing allowed before month 6. Almost half of the participants in the Descartes-08 group ($n = 7/15$, 40.0%) and 6 of 11 (54.5%) participants in the placebo group received prior or ongoing complement inhibitors, and a third of participants in both groups received an FcRn inhibitor as prior treatment for their MG, indicating the refractory nature of the disease in a large proportion of study participants.

Primary outcome

At month 3, there were significantly more MGC responders (≥5-point score reduction) in the Descartes-08 group compared to the placebo group in the overall population (66.7% versus 27.3%, $P = 0.0472$; Table 2).

https://doi.org/10.1038/s41591-025-04171-y

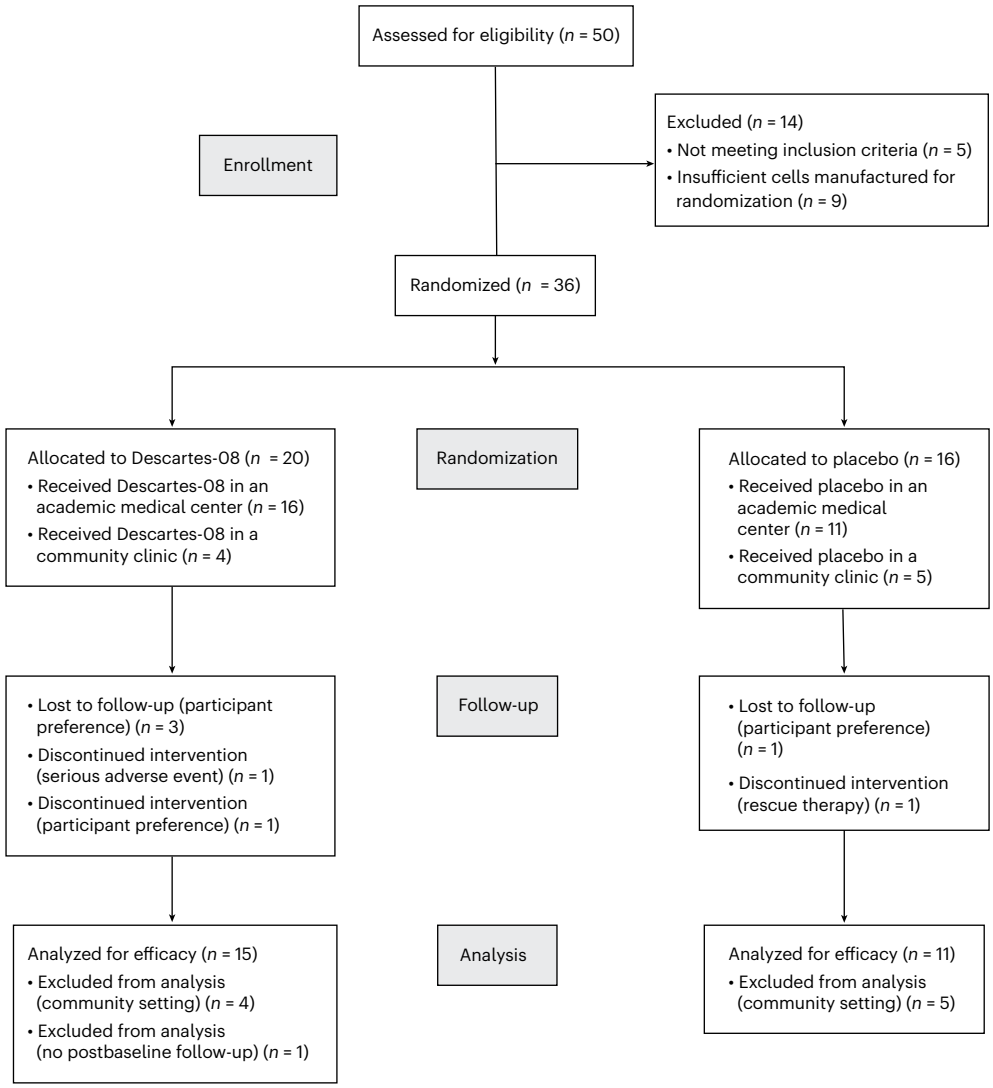

Fig. 1 | CONSORT diagram for the MG-001 part 3 study. The numbers of participants who were assessed, enrolled, randomized, treated and included in analyses are shown.

The mean (s.d.) change from baseline in the MGC score at month 3 was −5.0 (6.67) for the Descartes-08 group and −2.3 (7.73) for the placebo group. Similar results were observed for the participants comprising the AChR autoantibody-positive population, with significantly more MGC responders in the Descartes-08 group than in the placebo group (63.6% versus 12.5%, $P = 0.025815$; Extended Data Table 1). The mean (s.d.) change from baseline in the MGC score at month 3 for those who were AChR autoantibody-positive was −5.0 (5.62) for the Descartes-08 group and 0.1 (4.85) for those treated with placebo.

Key secondary outcomes

At month 3, the Descartes-08 group demonstrated substantially greater numerical and clinically meaningful reductions compared to the placebo group in the mean MG-ADL score (4.1 versus 1.6), QMG score (−3.9 versus −1.5) and MG-QoL-15r score (−5.7 versus −3.7) (Fig. 2). Responses deepened further during the follow-up for those in the Descartes-08 group, with the mean (s.d.) MG-ADL score reduction reaching −5.5 (1.1) at month 4 (day 113), which was maintained at month 12 (mean (s.d.) score, −4.8 (1.4)). QMG score reductions also continued throughout the follow-up period in the Descartes-08 group, reaching maximum improvement at month 12 (mean (s.d.) score, −6.0 (2.1)). Minimum symptom expression (MSE), defined as an MG-ADL score of ≤1, was achieved by 33.3% ($n = 4/12$) of participants in the Descartes-08 group who reached month 6 of follow-up, and all individuals maintained this status through month 12. Of those achieving MSE, two participants were AChR autoantibody-positive and two were triple seronegative. One participant in the placebo group who was triple seronegative achieved MSE status.

Similar trends in MG severity reduction from baseline were observed in patients treated with Descartes-08 who were AChR autoantibody-positive. Minimum improvements in MGC and MG-ADL scores were higher for the Descartes-08 group than the placebo group at month 3 (Fig. 3), with 81.8% versus 37.5% of participants achieving a minimum of a 3-point improvement in the MGC score and 63.6% versus 25.0% of participants achieving a minimum of a 3-point reduction in the MG-ADL score. There was a significant and clinically meaningful reduction in the mean (s.d.) MG-ADL score at month 3 for the Descartes-08 group compared to the placebo group (−3.4 (2.84) versus 0.6 (2.93), $P = 0.0409$) (Extended Data Fig. 1). This reduction in the MG-ADL score was maintained up to month 12 for those in the Descartes-08 group.

In a prespecified analysis stratifying participants by disease onset, 80.0% ($n = 4/5$) of those treated with Descartes-08 who had early-onset MG, defined as the development of symptoms before the age of 50 years, were MGC responders at month 3, compared to 20.0% ($n = 1/5$) in

https://doi.org/10.1038/s41591-025-04171-y

Table 1 | Participant demographics and characteristics at baseline

Characteristics		Descartes-08 (*n*=15)	Placebo (*n*=11)	Total (*n*=26)
Mean age, years (s.d.)		56.7 (16.39)	59.0 (13.96)	57.7 (15.16)
Sex, *n* (%)	Female	10 (66.7)	6 (54.5)	16 (61.5)
	Male	5 (33.3)	5 (45.5)	10 (38.5)
Mean weight, kg (s.d.)		93.83 (20.001)	105.37 (27.496)	98.71 (23.669)
Ethnicity, *n* (%)	White, non-Hispanic	13 (86.7)	11 (100.0)	24 (92.3)
	Other	2 (13.3)	0	2 (7.7)
MGFA class at screening, *n* (%)	IIa	0	2 (18.2)	2 (7.7)
	IIb	4 (26.7)	1 (9.1)	5 (19.2)
	IIIa	2 (13.3)	5 (45.5)	7 (26.9)
	IIIb	8 (53.3)	3 (27.3)	11 (42.3)
	IVa	1 (6.7)	0	1 (3.8)
	IVb	0	0	0
Median age at disease onset, years (range)		55 (16–76)	51 (25–71)	53 (16–76)
Median duration of disease, years (range)		5.5 (2–23)	10 (4–26)	6 (2–26)
MG antibody status, *n* (%)	Anti-AChR	11 (73.3)	8 (72.7)	19 (73.1)
	Anti-LRP4	1 (6.7)	0	1 (3.8)
	Triple seronegative	3 (20.0)	3 (27.3)	6 (23.1)
Mean score (s.d.)	QMG	17.3 (7.31)	14.7 (4.03)	16.2 (6.17)
	MG-ADL	10.5 (3.20)	9.8 (2.79)	10.2 (3.00)
	MGC	16.4 (6.39)	15.7 (3.95)	16.1 (5.41)
	MG-QoL-15r	19.1 (7.62)	17.7 (4.73)	18.5 (6.48)
Previous MG therapies (standard of care), *n* (%)	Pyridostigmine	9 (60.0)	9 (81.8)	18 (69.2)
	Prednisone	7 (46.7)	5 (45.5)	12 (46.2)
	Other immunosuppressants	7 (46.7)	9 (81.8)	16 (61.5)
	Complement inhibitor	3 (20.0)	5 (45.5)	8 (30.8)
	FcRn inhibitor	5 (33.3)	4 (36.4)	9 (34.6)
Previous intravenous infusion of immunoglobulin, *n* (%)		11 (73.3)	9 (81.8)	20 (76.9)
Previous plasma exchange, *n* (%)		3 (20.0)	6 (54.5)	9 (34.6)
Diagnosis of thymoma, *n* (%)		1 (6.7)	4 (36.4)	5 (19.2)
Previous thymectomy, *n* (%)		4 (26.7)	6 (54.5)	10 (38.5)
Previous MG crisis requiring intubation, *n* (%)		2 (13.3)	0	2 (7.7)
Ongoing MG therapy, *n* (%)	Pyridostigmine	11 (73.3)	7 (63.6)	18 (69.2)
	Prednisone	9 (60.0)	4 (36.4)	13 (50.0)
	Azathioprine	3 (20.0)	2 (18.2)	5 (19.2)
	Mycophenolate mofetil	3 (20.0)	6 (54.5)	9 (34.6)
	Complement inhibitor	4 (26.7)	1 (9.1)	5 (19.2)
No. of concomitant MG therapies, median (range)		2 (1–4)	2 (1–5)	2 (1–5)

the placebo group (Extended Data Table 2). Reductions in MG severity were generally consistent between participants with early-onset MG and those with late-onset MG who were treated with Descartes-08.

Tapering of the prednisone dose was allowed at the investigators' discretion after the month 6 visit. After a median follow-up of 12 months, the median daily dose of orally administered prednisone equivalent in the Descartes-08 group was 9 mg (range, 2.5–20 mg), compared to 20 mg (range, 5–25 mg) at baseline—a 55.0% decrease. As there was no tapering allowed before month 6, the median dose in the placebo group remained unchanged throughout the follow-up at 10 mg (range, 6–20 mg). None of the participants randomized to Descartes-08 required escalation in MG therapies for the duration of the study, including intravenous infusion of immunoglobulin or plasma exchange. All 11 participants in the placebo group received Descartes-08 under an open-label protocol after the primary endpoint assessment at month 3, and treatment outcomes will be reported separately.

Safety

Adverse event (AE) rates were similar between groups, with 17 of 20 (85.0%) participants in the Descartes-08 group and 13 of 16 (81.3%) participants in the placebo group reporting at least one AE during the study (Table 3). Most AEs were mild or moderate (Common Terminology Criteria for AEs (CTCAE) grades 1–2). Among 20 participants in the safety population randomized to Descartes-08 and 16 participants randomized to placebo, 5 (25.0%) and 2 (12.5%), respectively, experienced a grade 3 AE. In the Descartes-08 group, grade 3 AEs included a vasovagal reaction, a bacterial infection, fever, a herpes simplex virus (HSV) reactivation and a thromboembolic event (thrombosis of a central

https://doi.org/10.1038/s41591-025-04171-y

Table 2 | Mean change from baseline in MGC, MG-ADL and QMG scores at month 3

MG Clinical Outcomes		Descartes-08 (*n*=15)	Placebo (*n*=11)
MGC score	Baseline, mean (s.d.)	16.4 (6.39)	15.7 (3.95)
	Month 3, mean (s.d.)	11.4 (8.57)	13.5 (8.48)
	Change from baseline at month 3, mean (s.d.)	−5.0 (6.67)	−2.3 (7.73)
	Responder (≥5-point reduction), *n* (%)	10 (66.7)	3 (27.3)
	Difference in proportions (95% CI)	0.39 (0.01–0.77)	
	P value	0.0472	
MG-ADL score	Baseline, mean (s.d.)	10.5 (3.20)	9.8 (2.79)
	Month 3, mean (s.d.)	6.4 (4.31)	8.2 (3.82)
	Change from baseline at month 3, mean (s.d.)	−4.1 (3.38)	−1.6 (4.06)
QMG score	Baseline, mean (s.d.)	17.3 (7.3)	14.7 (4.03)
	Month 3, mean (s.d.)	13.4 (7.53)	13.2 (5.12)
	Change from baseline at month 3, mean (s.d.)	−3.9 (4.37)	−1.5 (4.27)

Statistical significance was determined using a two-sided two-independent-sample proportion test. CI, confidence interval.

venous port placed several years before enrollment). Meanwhile, grade 3 AEs reported in the placebo group included disease exacerbation and urinary tract infection. Of these, only the case of fever was deemed possibly treatment-related.

There were no grade 4 or 5 (death) events in either group for the duration of the study (Table 3). Five serious AEs (SAEs) occurred in the Descartes-08 group (25.0%), while three SAEs occurred in the placebo group (18.8%). Of these, three in the Descartes-08 group and one in the placebo group occurred after the first infusion: one each of an infusion-related reaction (IRR), syncope, HSV reactivation and hip fracture. Of the three SAEs occurring after the first infusion in the Descartes-08 group, one (HSV reactivation) took place in an academic medical center, while two were reported in a community clinic. The only SAE deemed to be related to treatment was a grade 3 IRR manifesting as a fever of 40 °C, which started within 12 h of the fifth infusion and resolved within 48 h without the administration of tocilizumab or steroids. Due to the rapid onset and resolution of the severe fever without intervention, and in the absence of a concomitant increase in inflammatory markers commonly associated with cytokine release syndrome (CRS), this event was deemed to be an acute IRR.

Generally, IRRs manifested as an acute onset of headache, nausea, fever, chills, arthralgia and myalgia within 8 h of infusion. In all but one case (the above-mentioned grade 3 IRR), IRRs were managed in an outpatient setting and resolved within 24 h without tocilizumab or steroid administration. For participants reporting headaches and nausea in all or most of the six infusions, additional premedication with ondansetron was warranted. Fevers, chills and myalgias typically occurred after doses two through five for participants who experienced these AEs, with four of six grade 2 fevers (39–40 °C) occurring after the second and third infusions. There were no notable differences in demographics or disease characteristics among participants randomized to Descartes-08 who developed a fever. However, those who developed a fever may have been more likely to respond and experience more pronounced symptom improvement, as measured by the MG-ADL score, than those who did not (Extended Data Table 3).

Infection rates were similar between the treatment groups, with more upper respiratory infections reported in the placebo group than in the Descartes-08 group (25.0% versus 15.0%), while more HSV reactivations were reported in the Descartes-08 group compared to the placebo group (15.0% versus 0%) (Table 3). Notably, all HSV reactivations occurred in patients with a prior history of labial herpes who were on concomitant azathioprine. There was no difference in total circulating B cell levels between the Descartes-08 and placebo groups, and there were no cases of hypogammaglobulinemia. Serum levels of vaccine titers were similar between the two groups at month 3 and were maintained through month 12 in the Descartes-08 group. While there was no difference between the groups in AChR autoantibody levels at month 3, an exploratory assay of all autoreactive antibodies showed a significant difference in the change at month 3 between Descartes-08 and placebo (*Nature Medicine* companion paper[24]).

Broad inflammatory cytokines in the circulation, including interferon-γ (IFNγ) and tumor necrosis factor (TNF), did not appreciably change throughout the study and did not differ between the Descartes-08 and placebo groups (Extended Data Table 4). Despite this, the levels of several important cytokines associated with MG and autoimmunity—including interleukin-6 (IL-6), IL-24, chemokine (C–C motif) ligand 19 (CCL19) and artemin—decreased at month 3 when comparing patients receiving Descartes-08 and those receiving placebo (*Nature Medicine* companion paper[24]).

Post hoc analyses

A post hoc analysis was conducted to evaluate the magnitude of response to Descartes-08 in participants who were biologic-naive and those with prior biologic exposure. Participants with no prior exposure to complement inhibitors, FcRn inhibitors or CD19/CD20-targeting monoclonal antibodies (biologic-naive) demonstrated an improved response to Descartes-08 compared to those with prior biologic exposure, with 55.6% ($n = 5/9$) of participants achieving MSE by month 6, which was maintained through month 12. Additionally, the biologic-naive group had a greater proportion of MGC responders at month 3 compared to the group with prior biologic exposure (88.9% versus 33.3%). There were also notable reductions in MG severity scores from baseline to month 3 for the biologic-naive group versus those with prior biologic exposure (mean (s.d.) score: MGC −7.7 (5.24) versus 1.0 (6.96); MG-ADL −5.2 (3.27) versus −2.5 (3.08); QMG −5.0 (3.84) versus −2.2 (4.92)), with scores further improved by month 12 (MGC −11.0 (4.0), MG-ADL −7.1 (1.9), QMG −9.4 (2.6)) (Extended Data Table 5 and Extended Data Fig. 2). Notably, 100.0% of biologic-naive participants maintained at least a clinically meaningful response at month 12.

A second post hoc analysis was conducted to assess cell dose infusion and MGC response. Overall, the mean cell dose per infusion was similar among those treated with Descartes-08, irrespective of whether they achieved a response or not (Extended Data Table 6).

Discussion

In this randomized phase 2b trial, six once-weekly doses of a BCMA-directed mRNA cell therapy (Descartes-08), administered in an outpatient setting, were generally well tolerated and led to significantly

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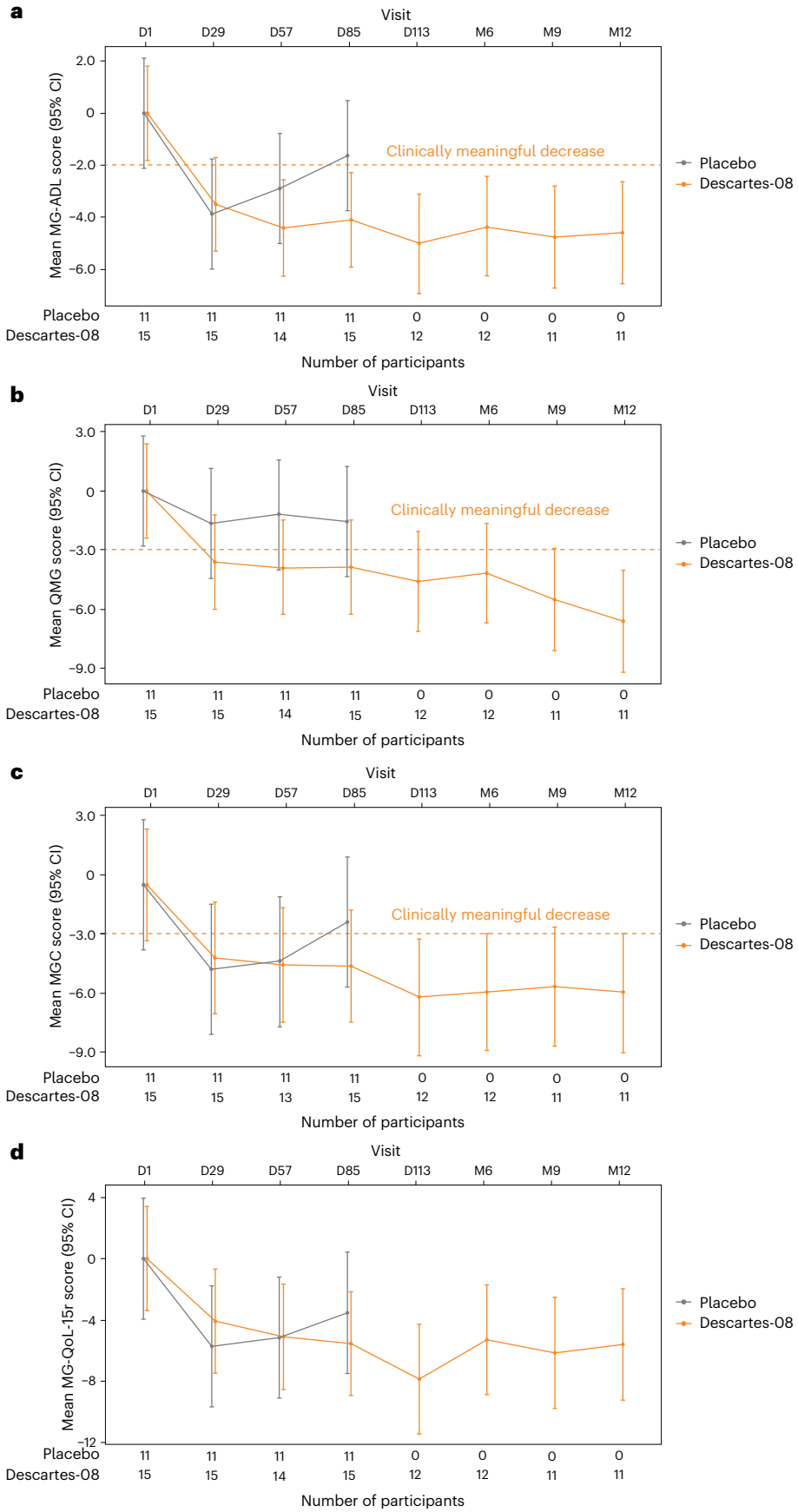

Fig. 2 | Change from baseline in disease severity scores over the study period. Mean (95% CI) change from baseline over 3 months for placebo and over 12 months for Descartes-08 in MG-ADL (**a**), QMG (**b**), MGC (**c**) and MG-QoL-15r (**d**) scores. Direction of improvement is indicated by decreasing scores. Horizontal dotted line represents the threshold for a clinically meaningful decrease. D, day; M, month.

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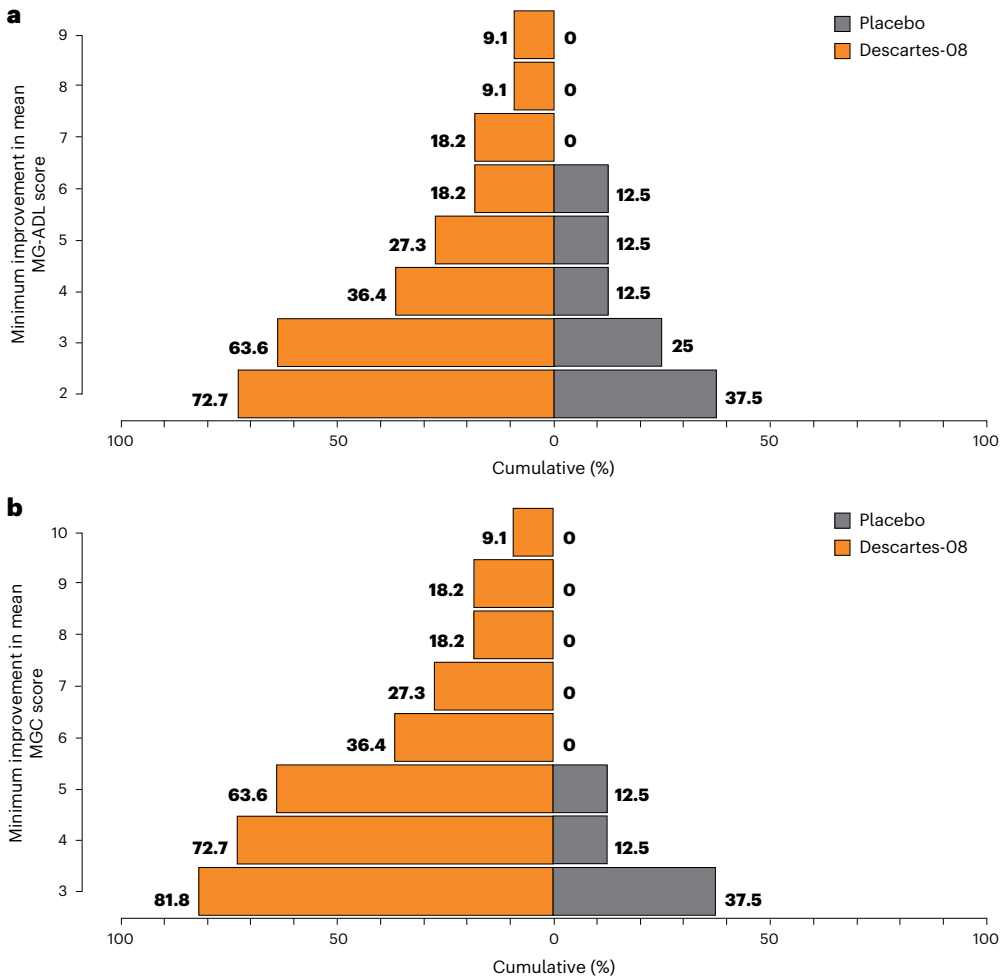

Fig. 3 | Minimum point improvement in disease severity scores in patients with AChR antibody-positive MG. Minimum improvement at month 3 in mean MG-ADL (a) and MGC (b) scores in patients with AChR antibody-positive MG treated with either Descartes-08 or placebo. Values represent the percentage of participants in each treatment group achieving minimum point improvement.

higher rates of clinical response compared to placebo—as measured by a ≥5-point reduction in the MGC score—in patients with gMG. AE rates were comparable between the Descartes-08 and placebo groups. AEs were mostly mild or moderate in severity, with IRRs being the most commonly reported AEs. All clinical outcome measures showed greater improvement in the Descartes-08 group compared with the placebo group, including patient-reported outcomes as measured by the MG-ADL score, objective improvements in patient strength as measured by the QMG score and the combination of the two measured by the MGC score. Notably, a third of all participants and more than half of those who were biologic-naive achieved MSE, which was maintained through 12 months of follow-up, all while decreasing the median dose of background corticosteroids by 55.0%. The results of this trial indicate that a valuable new treatment opportunity in gMG—a brief course of treatment leading to at least a year-long benefit—may be achievable.

There has been increased interest in CAR T cell therapy for autoimmune diseases, primarily through the direct transfer of approaches originally developed for the treatment of refractory malignancies[25,26]. MG is one of several conditions in which conventional CAR T cell therapy, generated through stable transduction with viral vectors and directed toward CD19, has shown promising early results, including durable drug-free remissions attributed to an 'immune reset', with expected AEs including grade 1–2 CRS, immune effector cell-associated neurotoxicity syndrome (ICANS), severe hematologic toxicity and transient immunosupression[27–29]. Descartes-08 is different in two important ways: it uses mRNA instead of a viral vector and targets BCMA instead of CD19. The first property, the use of mRNA, is thought to obviate the need for lymphodepletion chemotherapy because this transient engineering makes the need for extensive proliferation less relevant. As a result, this study was performed in the outpatient setting without preconditioning and with abbreviated postinfusion monitoring[7,22,30]. Lack of access is a commonly identified downside of engineered cell therapies, including CAR T cell therapies[31,32]. An improved safety profile enabled the use of Descartes-08 in community clinics that are not typically considered appropriate for cell therapy administration. By including these sites in this phase 2b trial, we have demonstrated the feasibility of administering mRNA cell therapy to a wider population of patients. However, barriers to biologic therapy accessibility remain, as seen in the recently approved treatments for gMG[33].

In a phase 1/2a study, all seven participants with gMG who received six once-weekly doses of Descartes-08 as initial treatment showed notable improvements in MG scores, and three achieved MSE[7]. Of the seven participants, two experienced a worsening of their condition 12 months after the initial treatment, and another participant worsened at 18 months. All three received an additional 6-week course of Descartes-08 and had the same or better response compared to the initial treatment[22]. In this phase 2b trial, the initial response rate was lower, with 10 of 15 participants (66.7%) achieving at least a 5-point improvement in the MGC score; however, all responses were maintained through 12 months, and 80.0% of participants had at least a clinically meaningful

https://doi.org/10.1038/s41591-025-04171-y

Table 3 | Treatment-emergent AEs from day 1 to month 3 for Descartes-08 and placebo

Events	Descartes-08 (*n*=20)	Placebo (*n*=16)
Any AE	17 (85.0)	13 (81.3)
SAE	5 (25.0)	3 (18.8)
Any AE leading to discontinuation of study drug	1 (5.0)	1 (6.3)
Any infection	8 (40.0)	6 (37.5)
Upper respiratory infection	3 (15.0)	4 (25.0)
HSV reactivation	3 (15.0)	0
COVID-19 infection	1 (5.0)	1 (6.3)
Catheter-related infection	1 (5.0)	0
Urinary tract infection	0	1 (6.3)
Any IRR	16 (80.0)	9 (56.3)
Headache	10 (50.0)	7 (43.8)
Nausea	9 (45.0)	4 (25.0)
Fever	11 (55.0)	1 (6.3)
Chills	12 (60.0)	0
Myalgia	7 (35.0)	0
Other common AEs		
Fatigue	7 (35.0)	1 (6.3)
Limb swelling	2 (10.0)	2 (12.5)
Diarrhea	3 (15.0)	1 (6.3)

Data are presented as *n* (%). COVID-19, coronavirus disease 2019.

response 1 year after treatment, highlighting the durability of the effect. Notably, the 5-point improvement cutoff is higher than the 3-point decrease in the MGC score considered to be clinically meaningful. This threshold was chosen to account for the higher-than-expected baseline MGC score compared to the scores observed in the MGC validation set[34]. Similar trends in MGC response were observed between the overall cohort and the AChR autoantibody-positive population. Together, these results confirm that, while anti-AChR antibody status is useful in classifying disease, its relevance as a marker to track progression or response to treatment is limited[35,36], including in the deep and durable clinical responses to Descartes-08 that we observed here when targeting BCMA-positive cells.

There was a notable difference in response between participants who had prior treatment with—and poor response to—complement and FcRn inhibitors and those who were biologic-naive. This may represent a true difference in biology due to a yet-to-be-determined mechanism, an artifact of a small sample size or a reflection of more treatment-refractory disease. However, it is notable that, even in the cohort of patients who were nonresponders to biologics, a proportion achieved a clinically meaningful improvement in the MGC score after Descartes-08, in contrast to those who were randomized to placebo.

There were several notable placebo responses during the early follow-up in the overall cohort. Although these responses were waning by the primary endpoint assessment at month 3, they led to a lack of statistical significance in the study's secondary outcomes of efficacy. The most pronounced improvements in MG severity scales in the placebo group—including one case of MSE—were observed in participants with triple seronegative MG, consistent with larger placebo-controlled studies that included this cohort of patients[13,17]. Moreover, a transient effect of leukapheresis cannot be excluded, particularly as therapeutic plasma exchange is a common treatment option for refractory MG[37]. Intriguingly, our *Nature Medicine* companion paper[24] outlines changes in several correlative biomarkers after apheresis in both the placebo and Descartes-08 groups. This potential effect underscores the importance of placebo-controlled studies to fully appreciate the impact of any intervention under investigation, including autologous cell therapy.

All current gMG treatments, including the most recently introduced complement inhibitors, FcRn inhibitors and CD19/20-targeting monoclonal antibodies, rely on broad or targeted immunosuppression that is directly tied to their mechanism of action and pharmacodynamic activity[38]. Acute and chronic toxicities of the older generation of immunosuppressants are burdensome for patients with MG and can impose substantial disruption on patients' daily activities[39]. The newer agents carry different but known risks, including increased susceptibility to meningococcal infections, which require prior immunization for use of complement inhibitors[40,41], while a higher risk of vaccine failure and worse outcomes during viral infections are associated with broad B cell-depleting therapies[42,43]. While FcRn inhibitors have not been associated with similar acute immunosuppression and have not shown an increased risk of infection compared to placebo across trials in different indications[44], postmarketing analyses continue to highlight the risk of infection as a concern[45,46]. In line with observations from the phase 1b/2a portion of the study, Descartes-08 was not associated with B cell depletion or hypogammaglobulinemia (a universal toxicity of conventional BCMA-targeting CAR T cell therapies)[47,48]. This may be a consequence of more targeted destruction and modulation of bone marrow-resident BCMA-high plasma cells, which contribute to the autoreactome but do not produce the bulk of circulating immunoglobulin. Notably, most immunoglobulin-producing BCMA-positive plasma cells reside in the connective tissues of the gastrointestinal tract and the lungs[49], and the majority of circulating immunoglobulin G (IgG) is recycled rather than newly produced[50]. As Descartes-08 does not affect IgG recycling, and the administered dose—combined with the lack of chemotherapy—is not sufficient to penetrate the connective tissues that are not usual pathways of lymphocyte trafficking, it may not result in even transient hypogammaglobulinemia. Instead, Descartes-08 produced distinct on-target immune effects—reducing BCMA-positive plasma cells and activated plasmacytoid dendritic cells, modulating T cell and cytokine activity, and reshaping autoantibody and transcriptional profiles—indicating a precise, transient immune reset without broad immunosuppression or major AEs, as discussed in our *Nature Medicine* companion paper[24].

Use of mRNA in place of a viral vector is thought to minimize or even eliminate the risk of CRS and ICANS, the two toxicities most commonly associated with CAR T cell therapy[51]. In our study, most participants randomized to Descartes-08 developed postinfusion fevers for approximately half of the administered infusions, which could be interpreted as grade 1 CRS[52]. However, several properties of the observed fevers do not support this interpretation. As noted in the original observations, the acute onset of high fevers is expected to lead, in the case of true CRS, to other associated symptoms (such as refractory hypotension and hypoxia) without the rapid administration of IL-6-directed therapy or steroids[51–53]. An elevation of IL-2, IL-6 and TNF levels by orders of magnitude above baseline would also be expected, which we did not observe with Descartes-08 treatment[53–56]. In fact, treatment with Descartes-08 significantly reduced the levels of important disease-associated cytokines (that is, IL-6) compared to placebo. Therefore, the IRRs may represent the initial engagement and activation of CAR T cells that do not lead to a self-sustained cytokine release, owing to the transient, nonreplicating nature of mRNA and the dilution of the CAR among the proliferating T cells[21,30]. An additional host immune response against the murine CAR construct may also contribute to the observed effect and has been reported in an older generation of mRNA CAR T cell therapies for malignancies[57]. However, successful retreatment 12–18 months after the initial dosing argues against this hypothesis[22].

There are several important limitations to note. First, although randomized and placebo-controlled, this was a phase 2 study with a

limited sample size and modest power (80%) to detect differences in the primary outcome, making any comparisons in secondary outcomes purely descriptive. Numerical differences between treatment group scores did not meet the hierarchical threshold for formal testing and were, therefore, not analyzed for statistical significance. Consequently, while these are important preliminary data supporting the efficacy of Descartes-08, formal statistical comparisons are required to further aid in interpretation. In combination with the heterogeneous population enrolled, in terms of both gMG antibody type and prior treatment history, the small sample size also severely limits any inferences that can be made about the subgroups. Second, due to the small sample size, there was an imbalance in several disease characteristics, such as disease duration and the rate of thymoma, both of which were higher in the placebo group. This is an important consideration, as these factors can be associated with both better and worse outcomes for different treatments[58–60]. Third, although a minority of participants (23.1%) were triple seronegative, this was still an overrepresentation compared to the general population, significantly affecting the magnitude of the early response observed in the placebo group. Fourth, disease-specific antibodies were surveyed using radioimmunoassay in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, which, although in line with standard clinical practice, may be insufficiently sensitive to the changes in antibody subtype, mode of activity and epitope being targeted[61–63]. Fifth, the protocol mandated keeping the dose of prednisone stable until the month 6 visit (limiting the time available for dose de-escalation to 6 months) and did not allow any changes in the dose of nonsteroidal immunosuppressants. While ensuring that these medications would not confound the comparison between the active and placebo groups, this plan may not have fully surveyed the potential of Descartes-08 to obviate the need for any background therapy, thereby making the achievement of drug-free remission during the study impossible. Finally, although the study team was blinded, the IRRs—specifically fevers, chills and myalgias—were more common in the Descartes-08 group and may have affected the assessment of gMG severity scales. However, the required training and certification should have mitigated this factor.

As the discussion above highlights, autoimmune diseases create unique opportunities and challenges for cell therapy. This is notable considering that all currently approved CAR T cell therapies are for hematologic cancers. In particular, the risk tolerance and acceptable patient burden in cancer are higher than those in autoimmune diseases, owing to differences in disease severity, urgency, median survival and disease duration. For example, inpatient treatment, lymphodepletion, therapy-related toxicities and the risk of secondary malignancies are acceptable in patients with cancer receiving existing CAR T cell options, but they may be less tolerable for patients with autoimmune diseases. As another example, patients with cancer qualifying for CAR T cell therapy generally have a poor prognosis without this treatment. Moreover, in almost all cases, they receive only a single treatment round. Conversely, autoimmune diseases are generally not fatal—although many are associated with comorbidities—and have treatment and management horizons that span decades. Thus, the ability to redose patients infrequently if a relapse occurs may be an important therapeutic feature in this area relative to oncology.

Treatment horizon and safety are just two hurdles that new technologies must address to achieve accessibility in offering CAR T cell therapies to patients with autoimmune diseases. As we show here, using RNA to target BCMA-positive cell populations results in mechanistic changes that are associated with safe, effective and lasting therapeutic effects without the need for inpatient administration or preconditioning. Other emerging therapies could also contribute to improved accessibility in complementary ways. For example, new delivery technologies such as viral vectors and lipid nanoparticles are now being clinically tested for in vivo CAR T cell therapy[64]. In these approaches, nucleic acid payloads encoding the CAR are infused into patients in a nanoparticulate format[64,65]. Thus, if successful, in vivo CAR formulations are off-the-shelf and do not need to be manufactured uniquely for each patient. This would further reduce manufacturing and administration hurdles and improve accessibility. However, these technologies are only now entering clinical testing and will need to achieve transfection of T cells in vivo with sufficient numbers and potency for efficacy. Likewise, considerations of immunogenicity and durability will be important, particularly when considering the possibility of antidrug antibodies if redosing is required. These examples are not mutually exclusive. Coupling in vivo delivery technologies with clinically derisked RNA payloads could lead to synergies in the design of future therapies.

To conclude, the magnitude of the clinical effect observed in this study highlights that a short course of mRNA CAR T cell therapy to be disease-modifying and to achieve major and long-lasting improvements in gMG symptoms while decreasing the need for background immunosuppressive therapy. The observed safety profile broadens the reach of cell therapy beyond patients with severe and refractory symptoms to a younger population with more moderate disease. A phase 1b/2a study is underway for children and adolescents with juvenile dermatomyositis and other autoimmune conditions (HELIOS, NCT07089121). In gMG, a confirmatory phase 3 trial is enrolling patients with anti-AChR antibody-positive disease (AURORA, NCT06799247).

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-025-04171-y.

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Methods

Oversight

The MG-001 part 3 trial was performed in accordance with the principles of the Declaration of Helsinki and the International Council for Harmonization E6 guidelines for Good Clinical Practice. The trial was approved by regulatory authorities in each country (USA, Canada and Türkiye), the central and local institutional review boards in the USA (Western Institutional Review Board-Copernicus Group, WCG IRB, Puyallup, WA), and the ethics committee at each site in other countries (the research ethics boards at the University of Toronto and the University of Alberta, as well as the ethics committee at Istanbul University). Oversight of the study was provided by an independent study monitoring committee comprising a neurologist, a hematologist specializing in cell therapy and a statistician. The committee met at least annually to review the safety data. All participants provided written informed consent before any study-related activities.

Trial design

MG-001 part 3 was a phase 2b, randomized, double-blind, placebo-controlled trial of Descartes-08 in patients with MGFA class II–IV gMG, conducted in academic medical centers and community neurology clinics in North America and Türkiye (ClinicalTrials.gov identifier: NCT04146051). All eligible participants underwent leukapheresis and had a Descartes-08 lot and an acellular placebo lot manufactured under Good Manufacturing Practice conditions. Participants were then randomly assigned in a 1:1 ratio to receive intravenous treatment with Descartes-08 or placebo, administered once weekly for 6 weeks as an intravenous infusion over 20 min. The placebo was matched to Descartes-08 in appearance and supplied in identical containers. Randomization was performed centrally using a computer-generated permuted-block scheme without stratification. Block sizes were varied and concealed from site personnel to maintain unpredictability in allocation. The randomization list was accessible only to the unblinded pharmacy or designated unblinded study staff responsible for preparing the study infusions; investigators, participants, outcome assessors and all other study personnel remained blinded to the treatment assignment throughout the trial. The random allocation sequence was generated by the study statistician and implemented centrally at the autologous lot manufacturing stage by sponsor staff who were otherwise uninvolved in the study conduct. The dose of Descartes-08 was 52.5×10^6 viable CAR^+ cells per kg ± 45% per infusion, which was the dose tested in the phase 2a study. Participants who underwent apheresis but did not have the minimum number of cells to reach the required dose were not randomized; they received Descartes-08 under an open-label protocol and were not included in this analysis. Diphenhydramine (or an equivalent) and acetaminophen were administered 30 min before each infusion as premedications. Blinding of study personnel, clinic staff and participants during infusion was maintained using opaque coverings for the infusion bag and tubing, which were identical between Descartes-08 and placebo. Participants were observed for 1 h after each infusion.

Blinded follow-up occurred at 2 weeks (month 2) and 6 weeks (month 3) after the last infusion. Participants who demonstrated a ≥3-point worsening of the MG-ADL score from baseline or showed signs of an impending myasthenic crisis could receive rescue therapy, which, for those randomized to placebo, included Descartes-08.

Both the study teams and participants were blinded to the treatment assignment through the month 3 visit. After the primary endpoint assessment at month 3, participants randomized to placebo had the option to cross over to Descartes-08, which was administered under an open-label protocol. All participants were followed up for 12 months.

Part 3 was added to the MG-001 study protocol in amendment v3.0 (August 1, 2022). Major amendments include v3.2 (October 17, 2023), which increased the enrollment cap to 50; v3.3 (January 8, 2024), which specified a 5-point reduction in the MGC score at month 3 as the primary endpoint; and v4.2 (June 19, 2024), which defined the primary efficacy population and outlined the use of the estimand framework for intercurrent events.

Participants

All participants were required to meet the following inclusion criteria: ≥18 years of age; a diagnosis of gMG, defined as MGFA clinical class III or IV (part 1; dose escalation) or class II–IV (parts 2–4) at the time of screening; use of concomitant immunosuppressive drugs deemed necessary by the investigator; daily dose of corticosteroids of ≤40 mg per day of prednisone equivalent, with a stable dose for a minimum of 4 weeks before the baseline visit; for the seropositive cohort only: MG-specific antibody titer must be above the reference laboratory's upper limit of normal and documented within 10 years of screening (patients who were MuSK or LRP4 autoantibody-positive were allowed to be enrolled in parts 1 and 2 only and were not eligible for this trial); for the seronegative cohort only: unequivocal response to cholinesterase inhibitors and abnormal repetitive nerve stimulation or increased jitter (participants must not have another neuromuscular disease that may cause increased jitter and must have a negative congenital myasthenic syndrome panel); participants must be willing to return for all study visits; participants must be able to provide written informed consent; women of reproductive potential must agree to use highly effective birth control from screening through 14 days after the last dose of Descartes-08 (women of childbearing potential are defined as women who have reached menarche and who have not been postmenopausal for at least 24 consecutive months; that is, have had menses within the preceding 24 months or have not undergone a sterilization procedure, such as hysterectomy, tubal ligation or bilateral oophorectomy); and participants must have an MG-ADL total score of ≥6.

Individuals who met any of the following criteria were excluded from participation in this study: major chronic illness that was not well managed at the time of study entry and, in the opinion of the investigator, may increase the risk to the patient; intravenous infusion of immunoglobulin or plasma exchange within 4 weeks before the baseline (day 1) visit; treatment with rituximab or ocrelizumab within 12 months before the baseline (first infusion) visit; treatment with calcineurin inhibitors (for example, tacrolimus, cyclosporine, cyclophosphamide), FcRn antagonists and/or other biologics within 3 weeks before the planned leukapheresis and within 8 weeks before the baseline (first infusion) visit; initiation of eculizumab treatment within 8 weeks before the baseline (first infusion) visit (patients who had been receiving eculizumab for more than 8 weeks and met other criteria for enrollment were eligible for treatment on the trial); sexually active female patients of childbearing age who were pregnant based on a serum pregnancy test, lactating or not using an acceptable birth control method (combined estrogen and progestogen-containing hormonal contraception associated with inhibition of ovulation (oral, intravaginal or transdermal); progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable or implantable); an intrauterine device; an intrauterine hormone-releasing system; bilateral tubal occlusion; and a vasectomized partner). Male patients were to agree to effective contraception (for example, condoms (male or female) with or without a spermicidal agent, a diaphragm or cervical cap with spermicide, or an intrauterine device) from screening through 14 days after the last dose of Descartes-08. True heterosexual sexual abstinence was considered an acceptable form of contraception. Periodic abstinence and withdrawal were not considered acceptable methods of contraception. Other exclusion criteria: abnormal prothrombin time/international normalized ratio or partial thromboplastin time increased by >1.5-fold or the patient is on anticoagulation therapy (except in cases of elevated partial thromboplastin time with documented lupus anticoagulant, in patients who had been on stable doses of anticoagulation therapy for more than 6 months following a venous thromboembolism diagnosis, or in patients on stable doses of anticoagulation therapy for at least 8 weeks after an atrial fibrillation diagnosis; these conditions will not be exclusionary unless, in the investigator's opinion, they make

participation in the study unsafe); absolute neutrophil count <1,000 cells per microliter; hemoglobin <8.0 g dl^{-1}; platelets <50,000 cells per mm^3; alanine transaminase and/or aspartate transaminase levels more than three times above upper limit of normal; creatinine clearance less than 30 ml min^{-1}; history of primary immunodeficiency or organ or allogeneic bone marrow transplant; seronegativity for hepatitis B surface antigen; seronegativity for hepatitis C antibody (if a hepatitis C antibody test is positive, patients must be tested for the presence of viremia by reverse transcription followed by PCR and must be negative for hepatitis C virus RNA); history of positive human immunodeficiency virus (HIV) or positive HIV at screening; active tuberculosis or a positive QuantiFERON test at screening; any other laboratory abnormality that, in the opinion of the investigator, may jeopardize the individual's ability to participate in the study; any active significant cardiac or pulmonary disease (patients with asthma and chronic obstructive pulmonary disease controlled with inhaled medications were allowed); a history of malignancy that required treatment in the past 3 years, except for successfully treated squamous cell and/or basal cell carcinoma of the skin and/or breast or colon cancer that was surgically removed and did not require adjuvant chemotherapy or radiotherapy; treatment with any investigational agent within 2 weeks of screening or five half-lives of the investigational drug (whichever is longer); receipt of a live vaccination within 4 weeks before baseline (day 1) or intent to receive live vaccination during the study (mRNA-based vaccines such as those against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are not considered live; likewise, the Janssen COVID-19 vaccine is not live); a history of significant recurrent infections or any active infection that may interfere with the patient's participation in the study in the opinion of the investigator; and any known psychiatric illness that may interfere with the patient's participation in the study in the opinion of the investigator.

Permitted concomitant medications for gMG included pyridostigmine, corticosteroids (equivalent to ≤40 mg of prednisone per day), azathioprine, mycophenolate mofetil and complement inhibitors, provided the dose was stable for at least 8 weeks before the first infusion. No dosing changes were allowed for concomitant MG-specific medications during the study, other than corticosteroids. The dose of corticosteroids was not permitted to be increased, but it could be tapered at the site investigator's discretion after month 6.

Randomization and blinding

Following the successful manufacturing of the autologous product, participants enrolled in part 3 were randomized 1:1 to receive either Descartes-08 or placebo. Randomization was performed centrally using a computer-generated permuted-block scheme without stratification (Mathematica v13.0, Wolfram Research). Block sizes were varied and concealed from site personnel to maintain unpredictability in allocation. The randomization list was accessible only to the unblinded pharmacy or designated unblinded study staff responsible for preparing the study infusions; investigators, participants, outcome assessors and all other study personnel remained blinded to the treatment assignment throughout the trial. The lack of stratification by site, combined with the small sample size and a higher-than-anticipated rate of enrolled participants not being randomized, likely led to unequal allocation between the active group and the placebo group.

Participants, study team members and all sponsor staff involved in the treatment or clinical evaluation of the patients, as well as in the review or analysis of data, were blinded to the treatment assignment until after the primary endpoint assessment. The bag and tubing containing the final infusion product were covered with an opaque, light-protective cover to ensure the blinding of participants and study team members.

Endpoints

The primary endpoint was the proportion of participants who demonstrated a ≥5-point decrease in the MGC score at month 3 compared to baseline. The MGC scale is a ten-item, 60-point weighted instrument composed of both patient-reported and provider-assessed items, which are themselves components of two other scales (MG-ADL and QMG). MGC was recommended by the 2000 MGFA Task Force for MG trials[34]. A 3-point change in the MGC score is considered clinically meaningful.

Secondary efficacy endpoints were the mean change from baseline in MGC, MG-ADL, QMG and MG-QoL-15r scores at each postinfusion visit (months 2, 3, 4, 6, 9 and 12), as well as the proportion of participants with ≥2–8-point improvements in MG-ADL, QMG and MGC scores at each postinfusion visit. The MG-ADL scale is an eight-item, 24-point, patient-reported instrument that assesses the effects of gMG on daily functioning[65]. A 2-point change is considered clinically meaningful. The QMG scale is a standardized, 39-point scoring system consisting of 13 provider-assessed items, which include hand-grip strength and forced vital capacity[66]. A 3-point change is considered clinically meaningful. The MG-QoL-15r scale is a 15-item, 30-point quality-of-life, patient-reported instrument with no consensus on what constitutes a clinically meaningful change[67].

Safety endpoints included the occurrence of AEs and SAEs from the time of apheresis through month 12, as well as laboratory values and vital signs. AEs were coded using CTCAE version 5.0. Serum samples collected during noninfusion visits (screening day, day 57, day 85) and preinfusion visits (day 1, day 29) were analyzed using the Meso Scale Discovery platform, in addition to serum immunoglobulin, vaccine titer and anti-AChR antibody testing in a CLIA-compliant laboratory. Cytokines were analyzed using the following panels: S-PLEX Proinflammatory Panel 1 (IFNγ, IL-10, IL-1β, IL-6, TNF), V-PLEX Proinflammatory Panel 1 (IL-8), V-PLEX Chemokine Gen B Panel 1 (MCP-1) and V-PLEX Cytokine Panel 1 (GM-CSF), all from Meso Scale Discovery.

Statistical analysis

We estimated that 15 participants per treatment group would provide 80% power to detect a difference of 47% in responders between Descartes-08 and placebo. Calculations assumed 87% responders in the Descartes-08 group and 40% responders in the placebo group, based on a two-sample proportion test for independent samples to detect a difference in proportions at the 0.05 (nondirectional) level of significance. The effect size estimate was based on the results of the phase 1b/2a study of Descartes-08 in gMG and historical placebo controls, and it was verified using Monte Carlo analyses of 100,000 trials to estimate the mean proportion of responders and the s.d. expected in the placebo group for a range of cutoff values (2–8 points) across all four scores (MG-ADL, MGC, QMG and MG-QoL-15r). To account for screen failures and missed randomization due to insufficient cells manufactured, we enrolled up to 50 participants.

Primary efficacy analyses were performed on a modified intention-to-treat (mITT) population, comprising all participants enrolled at an academic medical center who had at least one postbaseline follow-up. Baseline demographics and safety endpoints (that is, type and frequency of AEs) were analyzed in all enrolled participants using descriptive statistics. Categorical variables were expressed as percentages, while continuous variables were presented as means and s.d. values or medians and ranges for variables with a skewed distribution (including those with a mean-to-s.d. ratio of <2).

The primary endpoint—the response status at month 3 (day 85), in which responders were defined as those who had a reduction of 5 points or more in their MGC total score compared to baseline—was analyzed using a two-independent-sample proportion test at a two-sided 5% significance level; a Wald chi-squared test was used to determine whether there was a significant association between the treatment group and the response status. The primary estimand defined the population of interest as the mITT population, which included all participants who had at least one postbaseline follow-up measurement. Participants who required rescue medication before day 85 had their MGC scores set to missing; these were imputed using baseline observation carried

forward, with the response status set to nonresponder. All other missing data were imputed using multiple imputation, assuming data were missing at random. This was not required for the participants in the mITT population, as the data were complete.

The percentage of responders in each treatment group, along with the difference in proportions between the treatment arms with the corresponding Wald 95% CI, was reported. Missing data were imputed using a fully conditional specification method, which included sex, age, race, treatment group and baseline scores. A total of 50 complete datasets were generated. PROC MI and PROC MIANALYZE were used to conduct multiple imputation and combine the results. Subgroup analyses were carried out to determine whether there was a difference in the response between participants who were anti-AChR antibody-positive and those who were anti-AChR antibody-negative, between those with early- and late-onset disease, between those with and without prior exposure to complement and FcRn inhibitors, and between those who did and did not develop a fever. Differences in the proportions of responders were determined within each treatment group. The difference in the proportion of responders was assessed, and the Wald chi-squared test for association between response status and subgroup was performed separately within each treatment group.

Statistical analyses were conducted using SAS (version 9.2 or higher) and Mathematica (version 11.0 or higher), where applicable.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Access to anonymized trial-level data (analysis datasets) and/or the study protocol will be provided upon request to qualified researchers conducting independent, rigorous research, after the review and approval of a research proposal and statistical analysis plan, as well as the execution of a data sharing agreement. Data requests can be submitted at any time and will be responded to within 30 business days of submission. The data will be accessible for 12 months. Requests can be submitted to trials@cartesiantx.com.

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Acknowledgements

This work was supported by Cartesian Therapeutics, which provided the study product and was involved in the design, execution and analysis of the study. M. Kurtoglu and C.M.J. were supported by the National Institute of Neurological Disorders and Stroke/National Institutes of Health grants 1R44NS115426-01A1 and 1R44NS137943-01. We acknowledge G. Wolfe, S. A. Ali, M. Mete and A. Nickless. We also thank M. Barra of Barra Hersey LLC and E. Rybak of Cartesian Therapeutics for editorial support, as well as L. Graham of Ogilvy Health for medical writing assistance.

Author contributions

The sponsor, Cartesian Therapeutics, in collaboration with the investigators, designed the trial and gathered, analyzed and interpreted the data. T.V., H.D., M.D.M., T.M. and J.F.H. wrote the first draft of the manuscript without professional medical writing assistance. All other authors (M.R., S.S., T.R., B.M., M.P., G. Small, C.K., M.V., A.P., G. Sahagian, M.H.F., A.S., C.B.-T., Z.S., K.G., M.A.B., H.K., R.N.R., R.R.F., C.A.S., M. Kalayoglu, M. Kurtoglu, M.S., M.D., and C.M.J.) contributed to the conduct of the study as investigators, participated in data collection and interpretation, and reviewed and approved the final version of the manuscript. The sponsor provided funding for editorial and journal submission assistance only. All the authors provided critical reviews, contributed to subsequent drafts and approved the submission of the manuscript for publication. The authors vouch for the accuracy and completeness of the data and the fidelity of the trial to the protocol. All the authors signed a confidentiality disclosure agreement with the sponsor.

Competing interests

H.K., R.N.R., R.R.F., C.A.S., M. Kurtoglu, M. Kalayoglu, M.S., C.M.J. and M.D.M. are employees of and/or hold equity in Cartesian Therapeutics. C.M.J. is appointed as a professor at the University of Maryland and as a Research Health Scientist at the VA Maryland Health Care System. The views in this paper do not reflect the views of the state of Maryland or the US government. C.M.J. is a founder of Nodal Therapeutics and Patch Bio and holds equity positions with Nodal Therapeutics, Patch Bio, Aletira Therapeutics and Barinthus Biotherapeutics. C.B.-T. has served as a member of the advisory board for argenx, Alexion, UCB, Janssen and NMD Pharma. She has been a consultant for argenx, Janssen, Novartis and UCB. She has received research support from the US Department of Defense, Muscular Dystrophy Canada and MGNet. She is the primary developer of the Myasthenia Gravis Impairment Index (MGII) and may receive royalties. T.V. is a site principal investigator at the University of South Florida for myasthenia gravis clinical trials sponsored by Alexion/AstraZeneca, argenx, Amgen, Cartesians, COUR, Dianthus, EMD Serono, Johnson & Johnson, Immunovant, NMD Pharma, Regeneron and UCB. T.V. received speaking and/or consulting honoraria related to myasthenia gravis from Alexion, Amgen, argenx, Dianthus and Johnson & Johnson. T.M. has received research funding from the Muscular Dystrophy Association and the National Institutes for Health (R01AR074457, UM1TR004927, R21AR082649, UO1NS139215 and f T32AR083870). T.M. has received research funding from the following sponsors: Alexion, Amicus, AnnJi, Argenx, Aro Bio, Ask Bio, Audentes (now Astellas Gene Therapy), Cabaletta, Cartesian Therapeutics, Fate Therapeutics, ML-Bio, Momenta, NKarta, Ra Pharmaceuticals, Sanofi, Spark Therapeutics and Valerion. T.M. has served as a consultant for Alexion, Amicus, AnnJi, Argenx, Aro Bio, Arvinas, Ask Bio, Astellas Gene Therapeutics, AvroBio, BioCryst, Cabaletta, Creyon, Dyne, Fate Therapeutics, Horizon Therapeutics, Immunovant, Maze Therapeutics, Merck, Poseida, Regeneron, Shionogi, Momenta (now Janssen), Sanofi, UCB and Variant Bio. T.M. serves on the medical advisory board for the Myositis Association and the Neuromuscular Disease Foundation. He serves on the data safety monitoring board for Acceleron, Applied Therapeutics (Chair), Avidity, Sarepta, Sirolimus in IBM trial (Chair) and the NI. J.F.H. discloses research funding (paid to his institution) from Ad Scientiam, Alexion AstraZeneca Rare Disease, argenx, Cartesian Therapeutics, Centers for Disease Control and Prevention, Merck EMD Serono, MGFA, Muscular Dystrophy Association, NIH, NMD Pharma and UCB Bioscience; honoraria/consulting fees from AcademicCME, Alexion AstraZeneca Rare Disease, Amgen, argenx, Biohaven Ltd, Cartesian Therapeutics, CheckRare CME, CoreEvitas, Curie.bio, H. Lundbeck A/S, Japan Tobacco Company, Merck EMB Serono, NMD Pharma, Novartis Pharma, PeerView CME, Physicians' Education Resource (PER) CME, PlatformQ CME, Regeneron Pharmaceuticals, Seismic Therapeutics, TG Therapeutics, Toleranzia AB and UCB Pharma. H.D. has served as a speaker and consultant for Alexion/AstraZeneca and UCB. K.G. received speaking honoraria (remotely) for Alexion /AstraZebeca and Argenx, consulting honoraria for Alexion/AstraZeneca, Amgen, Novartis and UCB. She also served as a DSMB member for Cabaletta and Cour. C.K. served as a consultant and/or on an advisory board for Acceleron, Alpine, Alexion/AstraZeneca, Alnylam, Amgen, Amicus, Annexon, Applied Therapeutics, Argenx, Catalyst, Corino, Biogen, CSL Behring, Genentech, Immunovant,

Intellia, Ionis, J&J, Medison, Neuroderm, Novo Nordisk, Nuvig, Octapharma, Pfizer, Sanofi, UCB, Takeda, Vertex and Zai Lab. S.S. served as a speaker and/or consultant for UCB, Argenx and Astra Zeneca. G. Sahagian has received funding as an Investigator for clinical trials sponsored by Argenx, Sanofi, Lilly, Biogen, Cartesian, Immunovant, NMD Pharma, Regeneron and UCB. He received speaking and/or consulting honoraria from Alexion/AstraZeneca, Amgen, Argenx, Biogen, Cartesian and Immunovant. M.D received consultancy fees, payment or honoraria for lectures, presentations, manuscript writing or educational events, and participated on a Data Safety Monitoring Board or Advisory Board for Abcuro, Amicus, Annexon, ArgenX, Astellas, Cabaletta Bio, Catalyst, Covance/Labcorp/Fortrea, CSL-Behring, Creyon Bio, Inc., Dianthus, EMD Serono/Merck, Horizon, Ig Society, Inc, Janssen, Medlink, Nuvig, Octapharma, Sanofi Genzyme, Shire Takeda and TACT/Treat NMD and Vertex. M.M.D. has received grants or from Abcuro, Alexion/ AstraZeneca, Alnylam Pharmaceuticals, Amicus, ArgenX, Biosensics, Bristol-Myers Squibb, Cabaletta Bio, Catalyst, CSL-Behring, EMD Serono, FDA/OOPD, GlaxoSmithKline, Genentech, Grifols, Horizon Immnunovant, Mitsubishi Tanabe Pharma, MDA, NIH, Nkarta, Novartis, Octapharma, Orphazyme, Priovant, Ra Pharma/UCB Biopharma, Sanofi Genzyme, Sarepta Therapeutics, Shire Takeda, Spark Therapeutics and The Myositis Association. M.D. received royalty for manuscript writing from Wolters Kluwer Health/UpToDate and from Elsevier and for discovery relating to health care from Zevra Therapeutics. Z.S. has served as member of the advisory boards or Site Principal Investigator for clinical trials sponsored by Argenx, Alexion/AstraZeneca, UCB, Janssen, CSL Behring, Takeda, Regeneron, Immunovant, Novartis and Pfizer. The other authors declare no competing interests.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-025-04171-y.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41591-025-04171-y.

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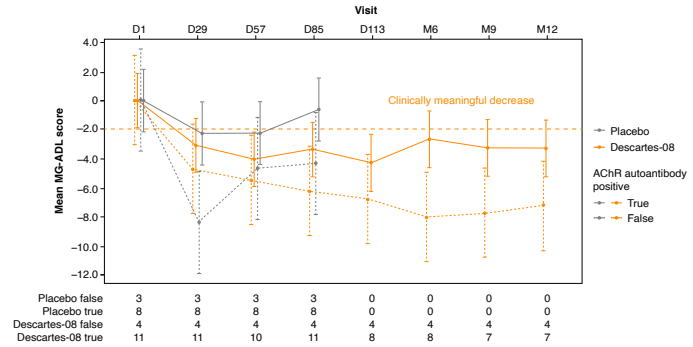
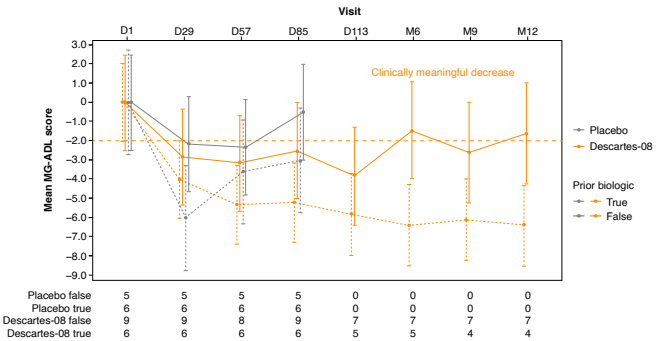
Peer review information *Nature Medicine* thanks Jialiang Li and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Primary Handling Editor: Saheli Sadanand, in collaboration with the *Nature Medicine* team.

https://doi.org/10.1038/s41591-025-04171-y



Extended Data Fig. 1 | Change in MG-ADL score for AChR autoantibody-positive and -negative participants. Mean (95% CI) change from baseline in MG-ADL score over 3 months for placebo and over 12 months for Descartes-08 in AChR autoantibody-positive and -negative participants. Orange dashed line represents the threshold for a clinically meaningful reduction in MG-ADL score. AChR, acetylcholine receptor; CI, confidence interval; MG-ADL, Myasthenia Gravis Activities of Daily Living.

https://doi.org/10.1038/s41591-025-04171-y



Extended Data Fig. 2 | Change in MG-ADL score for biologic-naïve and biologic-exposed participants. Mean (95% CI) change from baseline in MG-ADL score over 3 months for placebo and over 12 months for Descartes-08 in biologic naïve and biologic-exposed participants. Biologic-exposed participants were non-responders to prior FcRn or complement inhibitor treatment. Orange dashed line represents the threshold for a clinically meaningful reduction in MG-ADL score. CI, confidence interval; FcRn, fragment crystallizable (neonatal); MG-ADL, Myasthenia Gravis Activities of Daily Living.

https://doi.org/10.1038/s41591-025-04171-y

Extended Data Table 1 | Demographics, characteristics at baseline, and outcomes of participants randomized to Descartes-08 who were AChR autoantibody-positive and those who were AChR autoantibody-negative in the primary efficacy (mITT) population

		Descartes-08		Placebo	
		AChR autoantibody-positive (*n* = 11)	AChR autoantibody-negative (*n* = 4)	AChR autoantibody-positive (*n* = 8)	AChR autoantibody-negative (*n* = 3)
Mean age, years (SD)		57.7 (18.25)	54.0 (11.40)	57.5 (15.6)	63.0 (9.54)
Sex, *n* (%)	Female	6 (54.5)	4 (100.0)	4 (50.0)	2 (66.7)
	Male	5 (45.5)	0	4 (50.0)	1 (33.3)
Mean weight, kg (SD)		93.71 (19.054)	94.18 (25.522)	111.10 (24.528)	90.10 (34.546)
Ethnicity, *n* (%)	White, non-Hispanic	9 (81.8)	4 (100.0)	8 (100.0)	3 (100.0)
	Other	2 (18.2)	0	0	0
MGFA class at screening, *n* (%)	IIa	0	0	1 (12.5)	2 (66.7)
	IIb	4 (36.4)	0	0	0
	IIIa	2 (18.2)	0	5 (62.5)	0
	IIIb	4 (36.4)	4 (100.0)	2 (25.0)	1 (33.3)
	IVa	1 (9.1)	0	0	0
	IVb	0	0	0	0
Median age at disease onset, years (range)		57 (16–76)	43 (27–55)	53 (25–71)	49 (28–60)
Median duration of disease, years (range)		4 (2–14)	10 (5–23)	8 (4–11)	23 (5–26)
MG antibody status, *n* (%)	Anti-AChR	11 (100.0)	0	8 (100.0)	0
	Anti-LRP4	0	1 (25.0)	0	0
	Triple seronegative	0	3 (75.0)	0	3 (100.0)
Previous MG therapies (standard of care), *n* (%)	Pyridostigmine	6 (54.5)	3 (75.0)	7 (87.5)	2 (66.7)
	Prednisone	5 (45.5)	2 (50.0)	4 (50.0)	1 (33.3)
	Other immunosuppressants	4 (36.4)	3 (75.0)	7 (87.5)	2 (66.7)
	Complement inhibitor	2 (18.2)	1 (25.0)	5 (62.5)	0
	FcRn inhibitor	5 (45.5)	0	4 (50.0)	0
Previous intravenous immunoglobulin, *n* (%)		8 (72.7)	3 (75.0)	8 (100.0)	1 (33.3)
Previous plasma exchange, *n* (%)		1 (9.1)	2 (50.0)	5 (62.5)	1 (33.3)
Diagnosis of thymoma, *n* (%)		1 (9.1)	0	4 (50.0)	0
Previous thymectomy, *n* (%)		3 (27.3)	1 (25.0)	6 (75.0)	0
Previous MG crisis requiring intubation, *n* (%)		2 (18.2)	0	0	0
MG ongoing therapy, *n* (%)	Pyridostigmine	8 (72.7)	3 (75.0)	5 (62.5)	2 (66.7)
	Prednisone	6 (54.5)	3 (75.0)	3 (37.5)	1 (33.3)
	Azathioprine	3 (27.3)	0	1 (12.5)	1 (33.3)
	Mycophenolate mofetil	0 (100.0)	3 (75.0)	5 (62.5)	1 (33.3)
	Complement inhibitor	3 (27.3)	1 (25.0)	0	1 (33.3)
Number concomitant MG therapies at baseline, median (range)		2 (1–3)	2.5 (1–4)	2.25 (1–5)	2 (1–3)
MGC score	Baseline, mean (SD)	15.8 (6.00)	18.0 (8.12)	14.63 (4.07)	18.7 (1.53)
	Month 3, mean (SD)	10.8 (7.61)	13.0 (12.0)	14.8 (7.76)	10.0 (11.13)
	Change from baseline at month 3, mean (SD)	-5.0 (5.62)	-5.0 (10.10)	0.1 (4.85)	-8.7 (11.5)
	Responder (≥5-point reduction), *n* (%)	7 (63.6)	3 (75.0)	1 (12.5)	2 (66.7)
MG-ADL score	Baseline, mean (SD)	9.7 (3.20)	12.8 (2.22)	9.6 (3.25)	10.3 (1.15)
	Month, 3 mean (SD)	6.4 (4.23)	6.5 (5.20)	9.0 (3.16)	6.0 (5.29)
	Change from baseline at month 3, mean (SD)	-3.4 (2.84)	-6.3 (4.27)	-0.6 (2.92)	-4.3 (6.11)
QMG score	Baseline, mean (SD)	16.5 (6.90)	19.5 (9.04)	14.4 (4.47)	15.7 (3.06)
	Month 3, mean (SD)	12.8 (6.91)	15.0 (10.0)	14.5 (4.93)	9.7 (4.51)
	Change from baseline at month 3, mean (SD)	-3.6 (3.91)	-4.5 (6.14)	0.1 (3.00)	-6.0 (4.36)

AChR, acetylcholine receptor; FcRn, fragment crystallizable (neonatal); LRP4, lipoprotein receptor-related protein 4; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis Composite; MGFA, Myasthenia Gravis Foundation of America; mITT, modified intention-to-treat; QMG, Quantitative Myasthenia Gravis; SD standard deviation.

https://doi.org/10.1038/s41591-025-04171-y

Extended Data Table 2 | Demographics, characteristics at baseline, and outcomes of participants randomized to Descartes-08 or placebo with early- and late-onset disease in the primary efficacy (mITT) population

		Descartes-08		Placebo	
		Early onset (*n* = 5)	Late onset (*n* = 10)	Early onset (*n* = 5)	Late onset (*n* = 6)
Mean age, years (SD)		40.8 (18.03)	64.7 (7.86)	50 (15.6)	66.5 (6.92)
Sex, *n* (%)	Female	5 (100.0)	5 (50.0)	4 (80.0)	2 (33.3)
	Male	0	5 (50.0)	1 (20.0)	4 (66.7)
Mean weight, kg (SD)		91.22 (28.469)	95.14 (16.012)	92.79 (34.903)	115.85 (15.732)
Ethnicity, *n* (%)	White, non-Hispanic	3 (60.0)	10 (100.0)	5 (100.0)	6 (100.0)
	Other	2 (40.0)	0	0	0
MGFA class at screening, *n* (%)	IIa	0	0	1 (20.0)	1 (16.7)
	IIb	4 (80.0)	4 (40.0)	0	1 (16.7)
	IIIa	0	2 (20.0)	2 (40.0)	3 (50.0)
	IIIb	0	4 (40.0)	2 (40.0)	1 (16.7)
	IVa	1 (20.0)	0	0	0
	IVb	0	0	0	0
Median age at disease onset, years (range)		27 (16–48)	58.5 (50–76)	30 (25–49)	58 (51–71)
Median duration of disease, years (range)		10 (2–23)	4 (2–14)	10 (5–26)	5.5 (4–11)
MG antibody status, *n* (%)	Anti-AChR	2 (40.0)	9 (90.0)	3 (60.0)	4 (66.7)
	Anti-LRP4	1 (20.0)	0	0	0
	Triple seronegative	2 (40.0)	1 (10.0)	2 (40.0)	1 (16.7)
Previous MG therapies (standard of care), *n* (%)	Pyridostigmine	4 (80.0)	5 (50.0)	3 (60.0)	6 (100.0)
	Prednisone	3 (60.0)	4 (40.0)	2 (40.0)	3 (50.0)
	Other immunosuppressants	4 (80.0)	3 (30.0)	3 (60.0)	6 (100.0)
	Complement inhibitor	1 (20.0)	2 (20.0)	1 (20.0)	4 (66.7)
	FcRn inhibitor	0	5 (50.0)	1 (20.0)	3 (50.0)
Previous intravenous immunoglobulin, *n* (%)		4 (80.0)	7 (70.0)	4 (80.0)	5 (83.3)
Previous plasma exchange, *n* (%)		2 (40.0)	1 (10.0)	2 (40.0)	4 (66.7)
Diagnosis of thymoma, *n* (%)		0	1 (10.0)	2 (40.0)	2 (33.3)
Previous thymectomy, *n* (%)		2 (40.0)	2 (20.0)	3 (60.0)	3 (50.0)
Previous MG crisis requiring intubation, *n* (%)		1 (20.0)	1 (10.0)	0	0
MG ongoing therapy, *n* (%)	Pyridostigmine	3 (60.0)	8 (80.0)	5 (100.0)	2 (33.35)
	Prednisone	3 (60.0)	6 (60.0)	1 (20.0)	3 (50.0)
	Azathioprine	0	3 (30.0)	0 (100.0)	2 (33.3)
	Mycophenolate mofetil	0	0	4 (80.0)	2 (33.3)
	Complement inhibitor	2 (40.0)	2 (20.0)	0	1 (16.7)
Number concomitant MG therapies at baseline, median (range)		2 (1–4)	2 (1–3)	2 (1–3)	2 (1–5)
MGC score	Baseline, mean (SD)	19.4 (6.58)	14.9 (6.06)	17.4 (2.70)	14.3 (4.50)
	Month 3, mean (SD)	9.9 (8.08)	14.4 (9.66)	18.4 (8.14)	13.3 (6.77)
	Change from baseline at month 3, mean (SD)	-5.0 (8.69))	-5.0 (5.96	1.0 (7.18)	-5.0 (7.67)
	Responder (≥5-point reduction), *n* (%)	4 (80.0)	6 (60.0)	1 (20.0)	2 (33.3)
MG-ADL score	Baseline, mean (SD)	11.0 (3.32)	10.3 (3.30)	11.2 (3.11)	8.67 (2.07)
	Month 3, mean (SD)	7.2 (4.09)	6.0 (4.57)	9.4 (2.61)	7.2 (4.58)
	Change from baseline at month 3, mean (SD)	-3.8 (3.96)	-4.3 (3.27)	-1.8 (2.95)	-1.5 (5.09)
QMG score	Baseline, mean (SD)	21.8 (6.30)	15.0 (6.96)	17.0 (3.39)	12.8 (3.71)
	Month 3, mean (SD)	11.9 (6.74)	16.4 (8.91)	14.8 (3.63)	11.8 (6.08)
	Change from baseline at month 3, mean (SD)	-5.4 (4.72)	-3.1 (4.23)	-2.2 (4.09)	-1.0 (4.73)

AChR, acetylcholine receptor; FcRn, fragment crystallizable (neonatal); LRP4, lipoprotein receptor-related protein 4; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis Composite; MGFA, Myasthenia Gravis Foundation of America; mITT, modified intention-to-treat; QMG, Quantitative Myasthenia Gravis; SD standard deviation.

https://doi.org/10.1038/s41591-025-04171-y

Extended Data Table 3 | Demographics, characteristics at baseline, and outcomes of participants randomized to Descartes-08 who did and did not develop a fever in the primary efficacy (mITT) population

		Descartes-08	
		Fever (*n* = 10)	No fever (*n* = 5)
Mean age, years (SD)		51.9 (17.73)	66.4 (7.60)
Sex, *n* (%)	Female	8 (80.0)	2 (40.0)
	Male	2 (20.0)	3 (60.0)
Mean weight, kg (SD)		89.07 (20.469)	103.36 (16.951)
Ethnicity, *n* (%)	White, non-Hispanic	8 (80.0)	5 (100.0)
	Other	2 (20.0)	0
MGFA class at screening, *n* (%)	IIa	0	0
	IIb	2 (20.0)	2 (40.0)
	IIIa	0	2 (40.0)
	IIIb	7 (70.0)	1 (20.0)
	IVa	1 (10.0)	0
	IVb	0	0
Median age at disease onset, years (range)		49 (16–70)	60 (50–76)
Median duration of disease, years (range)		6 (2–23)	4 (3–14)
MG antibody status, *n* (%)	Anti-AChR	6 (60.0)	5 (100.0)
	Anti-LRP4	1 (10.0)	0
	Triple seronegative	3 (30.0)	0
Previous MG therapies (standard of care), *n* (%)	Pyridostigmine	7 (70.0)	2 (40.0)
	Prednisone	3 (30.0)	4 (80.0)
	Other immunosuppressants	4 (40.0)	3 (60.0)
	Complement inhibitor	1 (10.0)	2 (40.0)
	FcRn inhibitor	2 (20.0)	3 (60.0)
Previous intravenous immunoglobulin, *n* (%)		7 (70.0)	4 (80.0)
Previous plasma exchange, *n* (%)		2 (20.0)	1 (20.0)
Diagnosis of thymoma, *n* (%)		0	1 (20.0)
Previous thymectomy, *n* (%)		2 (20.0)	2 (40.0)
Previous MG crisis requiring intubation, *n* (%)		2 (20.0)	0
MG ongoing therapy, *n* (%)	Pyridostigmine	8 (80.0)	3 (60.0)
	Prednisone	7 (70.0)	2 (40.0)
	Azathioprine	2 (20.0)	1 (20.0)
	Mycophenolate mofetil	3 (30.0)	0
	Complement inhibitor	2 (20.0)	2 (40.0)
Number concomitant MG therapies at baseline, median (range)		2.5 (1–4)	2 (1–2)
Prednisone daily equivalent dose at baseline, median (range)		5.7 (5–70)	12.5 (5–20)
MGC score	Baseline, mean (SD)	17.9 (6.28)	13.4 (6.11)
	Month 3, mean (SD)	11.5 (8.82)	11.2 (9.04)
	Change from baseline at month 3, mean (SD)	-6.4 (6.96)	-2.2 (5.63)
	Responder (≥5-point reduction), *n* (%)	8 (80.0)	2 (40.0)
MG-ADL score	Baseline, mean (SD)	10.5 (2.83)	10.6 (4.22)
	Month 3, mean (SD)	5.7 (3.89)	7.8 (5.22)
	Change from baseline at month 3, mean (SD)	-4.8 (3.49)	-2.8 (3.03)
QMG score	Baseline, mean (SD)	18.4 (8.25)	15.0 (4.95)
	Month 3, mean (SD)	14.4 (8.71)	11.4 (4.51)
	Change from baseline at month 3, mean (SD)	-4.0 (4.11)	-3.6 (5.37)

AChR, acetylcholine receptor; FcRn, fragment crystallizable (neonatal); LRP4, lipoprotein receptor-related protein 4; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis Composite; MGFA, Myasthenia Gravis Foundation of America; mITT, modified intention-to-treat; QMG, Quantitative Myasthenia Gravis; SD standard deviation.

https://doi.org/10.1038/s41591-025-04171-y

Extended Data Table 4 | Serum cytokine levels from baseline to month 3

Median (range)		Screen	Day 1	Day 29	Month 2	Month 3
n	Active	14	18	19	18	18
	Placebo	15	16	16	15	15
IFN-γ (fg/mL)	Active	317 (179–2058)	593.5 (135–1645)	590.5 (22.65–3521)	657.75 (203.5–31609)	562.5 (270–5221)
	Placebo	389 (95.9–4146)	587.5 (224–16672)	567.25 (227.5–21749)	491.5 (164–1011.5)	503 (187–2940.5)
IL-10 (fg/mL)	Active	1089.5 (528.5–3886.5)	1001.75 (349.5–3645)	956.5 (422.5–3342.5)	1111.5 (607.5–67470.5)	1252 (622.5–10977)
	Placebo	1086.5 (363–22568)	950.75 (<340–3187.5)	1047.25 (<340–3191)	1261 (344–3052)	1044 (370.5–2019)
IL-1β (fg/mL)	Active	<327 (<327–394.5)	<327 (<327–476.5)	<327 (<327–591)	<327 (<327–108271.5)	<327 (<327–16546)
	Placebo	<327 (<327–<327)	<327 (<327–<327)	<327 (<327–378.5)	<327 (<327–583)	<327 (<327–<327)
IL-6 (fg/mL)	Active	3026 (743–10444)	3127.25 (1195.5–32437)	3335.5 (706.5–18934)	2572.5 (1008–12081.5)	3225.25 (1390–20627)
	Placebo	2239 (1139.5–5862)	3453.75 (1237–26118.5)	2900 (824.5–>32800)	2318 (944.5–>32800)	3099 (887.5–26641)
TNF-α (fg/mL)	Active	869.5 (427.5–2399)	899.75 (380.5–2172)	866.5 (323.5–2317)	959.25 (430.5–>54850)	1187.25 (518–11029.5)
	Placebo	844.5 (520.5–1465)	847 (550–1236)	981.5 (659.5–1539.5)	957.5 (649.5–1168)	971 (567–1475.5)
MCP-1 (pg/mL)	Active	340 (147–512)	318.75 (114.5–582.5)	309 (126–660.5)	323.75 (153–687.5)	337.5 (176.5–625)
	Placebo	313.5 (128–429)	335.5 (116–746)	333.25 (92.2–784)	305 (144–516.5)	302 (116.5–520)
GM-CSF (pg/mL)	Active	<1.68 (<1.68–<1.68)	<1.68 (<1.68–<1.68)	<1.68 (<1.68–<1.68)	<1.68 (<1.68–16.9)	<1.68 (<1.68–<1.68)
	Placebo	<1.68 (<1.68–<1.68)	<1.68 (<1.68–<1.68)	<1.68 (<1.68–<1.68)	<1.68 (<1.68–<1.68)	<1.68 (<1.68–<1.68)
IL-8 (pg/mL)	Active	10.75 (3.79–22.8)	11.4 (5.535–83.15)	10.3 (3.605–118)	11.025 (4.695–238)	12.1 (6.095–75.05)
	Placebo	12.3 (5.205–49.45)	13.95 (4.1–71.9)	14.25 (3.88–193.5)	10.95 (7.815–235.5)	12.55 (6.55–209)

Serum cytokine levels were measured from baseline to Month 3 using Meso Scale Discovery (MSD) testing services. GM-CSF, granulocyte-macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; MCP, monocyte chemoattractant protin-1; TNF, tumor necrosis factor.

https://doi.org/10.1038/s41591-025-04171-y

Extended Data Table 5 | Demographics, characteristics at baseline, and outcomes of participants randomized to Descartes-08 or placebo with and without prior exposure to complement and FcRn inhibitors in the primary efficacy (mITT) population

		Descartes-08		Placebo	
		Prior biologics (*n* = 6)	No prior biologics (*n* = 9)	Prior biologics (*n* = 6)	No prior biologics (*n* = 5)
Mean age, years (SD)		65.7 (9.37)	50.8 (17.76)	58.0 (12.76)	60.2 (16.75)
Sex, *n* (%)	Female	4 (66.7)	6 (33.3)	4 (66.7)	2 (40.0)
	Male	2 (66.7)	3 (33.3)	2 (33.3)	3 (60.0)
Mean weight, kg (SD)		102.30 (18.882)	88.19 (19.689)	103.30 (20.328)	107.86 (36.868)
Ethnicity, *n* (%)	White, non-Hispanic	6 (77.8)	7 (88.9)	6 (100.0)	5 (100.0)
	Other	0 (22.2)	2 (11.1)	0	0
MGFA class at screening, *n* (%)	IIa	0	0	1 (16.7)	2 (40.0)
	IIb	1 (33.3)	3 (33.3)	0	0
	IIIa	2 (55.6)	0	3 (50.0)	2 (40.0)
	IIIb	3 (11.1)	5 (55.6)	2 (33.3)	1 (20.0)
	IVa	0	1 (11.1)	0	0
	IVb	0	0	0	0
Median age at disease onset, years (range)		55 (48–76)	55 (16–70)	53 (25–66)	49 (28–71)
Median duration of disease, years (range)		6.5 (3–14)	4.5 (2–23)	8.3 (4–11)	6 (5–26)
MG antibody status, *n* (%)	Anti-AChR	5 (83.3)	6 (66.7)	6 (100.0)	2 (40.0)
	Anti-LRP4	1 (16.7)	0	0	0
	Triple seronegative	0	3 (33.3)	0	3 (60.0)
Previous MG therapies (standard of care), *n* (%)	Pyridostigmine	5 (83.3)	4 (44.4)	5 (83.3)	4 (80.0)
	Prednisone	4 (66.7)	3 (38.9)	4 (66.7)	1 (20.0)
	Other immunosuppressants	3 (50.0)	4 (44.4)	5 (83.3)	4 (80.0)
	Complement inhibitor	3 (50.0)	0	5 (83.3)	0
	FcRn inhibitor	5 (83.3)	0	4 (66.7)	0
Previous intravenous immunoglobulin, *n* (%)		3 (50.0)	8 (88.9)	6 (100.0)	2 (40.0)
Previous plasma exchange, *n* (%)		1 (16.7)	2 (33.3)	3 (50.0)	3 (60.0)
Diagnosis of thymoma, *n* (%)		1 (16.7)	0	3 (50.0)	1 (20.0)
Previous thymectomy, *n* (%)		1 (16.7)	3 (33.3)	5 (83.3)	1 (20.0)
Previous MG crisis requiring intubation, *n* (%)		0	2 (22.2)	0	0
MG ongoing therapy, *n* (%)	Pyridostigmine	4 (66.7)	7 (77.8)	4 (66.7)	3 (60.0)
	Prednisone	4 (66.7)	5 (55.6)	3 (50.0)	1 (20.0)
	Azathioprine	0	3 (33.3)	0	2 (40.0)
	Mycophenolate mofetil	1 (16.7)	2 (22.2)	4 (66.7)	2 (40.0)
	Complement inhibitor	3 (50.0)	1 (11.1)	0	1 (20.0)
Number concomitant MG therapies at baseline, median (range)		2 (1–4)	2 (1–3)	2 (1–5)	1.8 (1–3)
MGC score	Baseline, mean (SD)	16.0 (7.10)	16.7 (6.30)	16.0 (3.41)	15.4 (4.93)
	Month 3, mean (SD)	15.0 (11.87)	9.0 (4.92)	16.7 (7.76)	9.6 (8.39)
	Change from baseline at month 3, mean (SD)	-1.0 (6.96)	-7.7 (5.24)	0.7 (5.54)	-5.8 (9.09)
	Responder (≥5-point reduction), *n* (%)	2 (33.3)	8 (88.9)	1 (16.7)	2 (40.0)
MG-ADL score	Baseline, mean (SD)	10.8 (4.31)	10.3 (2.5)	10.5 (3.27)	9.0 (2.12)
	Month 3, mean (SD)	8.3 (2.62)	5.1 (2.62)	10.0 (3.03)	6.0 (3.74)
	Change from baseline at month 3, mean (SD)	-2.5 (3.08)	-5.2 (3.27)	-0.5 (3.39)	-3.0 (4.74)
QMG score	Baseline, mean (SD)	16.0 (5.72)	18.1 (8.43)	14.8 (5.04)	14.6 (2.97)
	Month 3, mean (SD)	13.8 (6.43)	13.1 (8.56)	15.3 (5.39)	10.6 (3.71)
	Change from baseline at month 3 mean (SD)	-2.2 (4.92)	-5.0 (3.84)	0.5 (3.45)	-4.0 (4.12)

AChR, acetylcholine receptor; FcRn, fragment crystallizable (neonatal); LRP4, lipoprotein receptor-related protein 4; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis Activities of Daily Living; MGC, Myasthenia Gravis Composite; MGFA, Myasthenia Gravis Foundation of America; mITT, modified intention-to-treat; QMG, Quantitative Myasthenia Gravis; SD standard deviation.

https://doi.org/10.1038/s41591-025-04171-y

Extended Data Table 6 | Manufactured Descartes-08 dose

	Descartes-08	Placebo	Total
mITT population, *n*	15	11	26
Mean cells/kg (SD), per infusion	42.31×10^6 (15.77)	35.54×10^6 (13.04)	39.45×10^6 (14.80)
Median cells/kg (range), per infusion	40.84 (16.58–85.58)	32,24 (13.41–58.25)	37.28 (13.41–85.58)
Mean cells (SD), total dose	22.95×10^9 (7.35)	21.08×10^9 (5.89)	22.16×10^9 (6.71)
Median cells (range), total dose	22.62 (10.02–42.48)	20.58 (10.38–34.14)	22.02 (10.02–42.48)
Safety population, *n*	20	16	36
Mean cells/kg (SD), per infusion	41.80×10^6 (15.39)	41.89×10^6 (15.71)	41.82×10^6 (15.30)
Median cells/kg (range), per infusion	39.96 (16.58–85.58)	37.28 (13.41–66.72)	38.22 (13.41–85.58)
Mean cells (SD), total dose	23.26×10^9 (6.69)	22.19×10^9 (6.38)	22.79×10^9 (6.48)
Median cells (range), total dose	22.8 (10.02–42.48)	21.3 (10.38–35.1)	22.08 (10.02–42.48)
MGC responders at month 3, *n*	10	-	-
Mean cells/kg (SD), per infusion	44.29×10^6 (17.82)	-	-
Median cells/kg (range), per infusion	43.55 (16.58–85.58)	-	-
Mean cells (SD), total dose	22.55×10^9 (5.43)	-	-
Median cells (range), total dose	23.16 (10.02–28.44)	-	-
MGC non-responders at month 3, *n*	5	-	-
Mean cells/kg (SD), per infusion	37.75×10^6 (11.11)	-	-
Median cells/kg (range), per infusion	33.25 (25.62–53.64)	-	-
Mean cells (SD), total dose	24.15×10^9 (8.77)	-	-
Median cells (range), total dose	22.32 (14.22–42.48)	-	-

MGC, Myasthenia Gravis Composite; mITT, modified intention-to-treat; SD, standard deviation.

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Last updated by author(s): 10/27/2025

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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Study data was collected and managed using Castor EDC.
Data analysis	Statistical analyses were done using SAS, version 9.2 or higher, and Mathematica, version 11.0 or higher, where applicable.

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- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

Access to anonymized trial-level data (analysis datasets) and/or the Study Protocol will be provided by request from qualified researchers performing independent, rigorous research, after review and approval of a research proposal and statistical analysis plan and execution of a data sharing agreement. Data requests can be submitted at any time and will be responded to within 30 business days of submission. The data will be accessible for 12 months. Requests can be submitted to trials@cartesiantx.com.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Demographic data is presented in Table 1 Participant Demographics and Characteristics at Baseline. Participant-level data is available upon request according to the Data Availability statements.
Reporting on race, ethnicity, or other socially relevant groupings	Demographic data is presented in Table 1 Participant Demographics and Characteristics at Baseline. Participant-level data is available upon request according to the Data Availability statements.
Population characteristics	Demographic data is presented in Table 1 Participant Demographics and Characteristics at Baseline. Participant-level data is available upon request according to the Data Availability statements.
Recruitment	Fifty participants were screened between November 10, 2022 and January 15, 2024 in academic medical centers and community neurology clinics in North America. Thirty-six participants were determined to be eligible and randomized to receive Descartes-08 or placebo.
Ethics oversight	The trial was approved by regulatory authorities in each country and the central (Western Institutional Review Board-Copernicus Group, WCG IRB, Pyallup, WA 98374, USA) and local institutional review boards in the United States and the ethics committee at each site in other countries.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	15 participants per treatment group was estimated to provide 80% power to detect a difference of 47% in responders between Descartes-08 and placebo. Calculations assumed 87% of responders in the Descartes-08 group and 40% of responders in the placebo group and were based on a two-sample proportions test for independent samples to detect a difference in proportions at the 0.05 (non-directional) level of significance.
Data exclusions	The primary efficacy analyses were performed on a modified intention-to-treat (mTT) population, comprising of all participants enrolled at an academic medical center who have at least one post-baseline follow-up.
Replication	Not applicable for randomized trial.
Randomization	Following leukapheresis, subjects were then randomly assigned in a 1:1 ratio using permuted block randomization without stratification to receive intravenous Descartes-08 or placebo.
Blinding	Study teams and participants were blinded to the assignment through the Month 3 visit.

Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	*Briefly describe the study type including whether data are quantitative, qualitative, or mixed-methods (e.g. qualitative cross-sectional, quantitative experimental, mixed-methods case study).*
Research sample	*State the research sample (e.g. Harvard university undergraduates, villagers in rural India) and provide relevant demographic information (e.g. age, sex) and indicate whether the sample is representative. Provide a rationale for the study sample chosen. For studies involving existing datasets, please describe the dataset and source.*
Sampling strategy	*Describe the sampling procedure (e.g. random, snowball, stratified, convenience). Describe the statistical methods that were used to predetermine sample size OR if no sample-size calculation was performed, describe how sample sizes were chosen and provide a rationale for why these sample sizes are sufficient. For qualitative data, please indicate whether data saturation was considered, and what criteria were used to decide that no further sampling was needed.*

Data collection	*Provide details about the data collection procedure, including the instruments or devices used to record the data (e.g. pen and paper, computer, eye tracker, video or audio equipment) whether anyone was present besides the participant(s) and the researcher, and whether the researcher was blind to experimental condition and/or the study hypothesis during data collection.*
Timing	*Indicate the start and stop dates of data collection. If there is a gap between collection periods, state the dates for each sample cohort.*
Data exclusions	*If no data were excluded from the analyses, state so OR if data were excluded, provide the exact number of exclusions and the rationale behind them, indicating whether exclusion criteria were pre-established.*
Non-participation	*State how many participants dropped out/declined participation and the reason(s) given OR provide response rate OR state that no participants dropped out/declined participation.*
Randomization	*If participants were not allocated into experimental groups, state so OR describe how participants were allocated to groups, and if allocation was not random, describe how covariates were controlled.*

Ecological, evolutionary & environmental sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	*Briefly describe the study. For quantitative data include treatment factors and interactions, design structure (e.g. factorial, nested, hierarchical), nature and number of experimental units and replicates.*
Research sample	*Describe the research sample (e.g. a group of tagged Passer domesticus, all Stenocereus thurberi within Organ Pipe Cactus National Monument), and provide a rationale for the sample choice. When relevant, describe the organism taxa, source, sex, age range and any manipulations. State what population the sample is meant to represent when applicable. For studies involving existing datasets, describe the data and its source.*
Sampling strategy	*Note the sampling procedure. Describe the statistical methods that were used to predetermine sample size OR if no sample-size calculation was performed, describe how sample sizes were chosen and provide a rationale for why these sample sizes are sufficient.*
Data collection	*Describe the data collection procedure, including who recorded the data and how.*
Timing and spatial scale	*Indicate the start and stop dates of data collection, noting the frequency and periodicity of sampling and providing a rationale for these choices. If there is a gap between collection periods, state the dates for each sample cohort. Specify the spatial scale from which the data are taken*
Data exclusions	*If no data were excluded from the analyses, state so OR if data were excluded, describe the exclusions and the rationale behind them, indicating whether exclusion criteria were pre-established.*
Reproducibility	*Describe the measures taken to verify the reproducibility of experimental findings. For each experiment, note whether any attempts to repeat the experiment failed OR state that all attempts to repeat the experiment were successful.*
Randomization	*Describe how samples/organisms/participants were allocated into groups. If allocation was not random, describe how covariates were controlled. If this is not relevant to your study, explain why.*
Blinding	*Describe the extent of blinding used during data acquisition and analysis. If blinding was not possible, describe why OR explain why blinding was not relevant to your study.*

Did the study involve field work? ☐ Yes ☐ No

Field work, collection and transport

Field conditions	*Describe the study conditions for field work, providing relevant parameters (e.g. temperature, rainfall).*
Location	*State the location of the sampling or experiment, providing relevant parameters (e.g. latitude and longitude, elevation, water depth).*
Access & import/export	*Describe the efforts you have made to access habitats and to collect and import/export your samples in a responsible manner and in compliance with local, national and international laws, noting any permits that were obtained (give the name of the issuing authority, the date of issue, and any identifying information).*
Disturbance	*Describe any disturbance caused by the study and how it was minimized.*

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used: A list of antibodies used through the study is provided in the Supplementary Information of the companion manuscript.

Validation: Product release data including flow cytometry were generated using validated methods described in the companion manuscript.

Eukaryotic cell lines

Policy information about cell lines and Sex and Gender in Research

Cell line source(s): MM.1S (Cat # CRL-2974) cell lines were obtained from ATCC.

Authentication: MM1S-GFP cell lines were authenticated by short tandem repeat profiling.

Mycoplasma contamination: MM1S-GFP cell lines were tested and found negative for mycoplasma.

Commonly misidentified lines (See ICLAC register): No commonly misidentified cell lines were used.

Palaeontology and Archaeology

Specimen provenance: *Provide provenance information for specimens and describe permits that were obtained for the work (including the name of the issuing authority, the date of issue, and any identifying information). Permits should encompass collection and, where applicable, export.*

Specimen deposition: *Indicate where the specimens have been deposited to permit free access by other researchers.*

Dating methods: *If new dates are provided, describe how they were obtained (e.g. collection, storage, sample pretreatment and measurement), where they were obtained (i.e. lab name), the calibration program and the protocol for quality assurance OR state that no new dates are provided.*

☐ Tick this box to confirm that the raw and calibrated dates are available in the paper or in Supplementary Information.

Ethics oversight: *Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.*

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Animals and other research organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research, and Sex and Gender in Research

Laboratory animals: NSG mice (NOD.Cg-PrkdcSCIDIl2rgTM1wJ1/SzJ), aged 6–8 weeks, from The Jackson Laboratory and housed in a specific pathogen–free facility at Noble Life Sciences in this study

Wild animals: No wild animals were used in this study.

Reporting on sex: Preclinical pharmacology study was performed using female mice.

Field-collected samples: No field-collected samples were obtained or analyzed for the study

Ethics oversight	All animal experimental protocols were approved and monitored by Noble Life Sciences Institutional Animal Care and Use committee and were under the care of a licensed veterinarian and OLAW assurance.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	NCT04146051
Study protocol	The Study Protocol is available to qualified researchers as indicated in the Data Availability Statement. Information on the phase IIb clinical study is publicly available on clinicaltrials.gov according to clinicaltrials.gov policy (NCT04146051).
Data collection	Information on the phase IIb clinical study is publicly available on clinicaltrials.gov according to clinicaltrials.gov policy (NCT04146051). Additional information on Data collection is provided in this study's companion article and available as per conditions of the Data Availability Statements of this and the companion article.
Outcomes	The primary efficacy endpoint was the proportion of participants who experienced a 5 point or greater decrease in the myasthenia gravis composite (MGC) score at month 3 compared to baseline. Secondary efficacy endpoints were the mean change from baseline in MGC, myasthenia gravis activities of daily living (MG-ADL), quantitative MG (QMG), and MG-Quality of Life 15-revised (MG-QoL-15r) at each post-infusion visit (months 2, 3, 4, 6, 9, and 12), as well as proportion of participants with greater than or equal to 2-8 point improvements in the MG-ADL, QMG, and MGC at each post-infusion visit.

Dual use research of concern

Policy information about dual use research of concern

Hazards

Could the accidental, deliberate or reckless misuse of agents or technologies generated in the work, or the application of information presented in the manuscript, pose a threat to:

No	Yes	
☐	☐	Public health
☐	☐	National security
☐	☐	Crops and/or livestock
☐	☐	Ecosystems
☐	☐	Any other significant area

Experiments of concern

Does the work involve any of these experiments of concern:

No	Yes	
☐	☐	Demonstrate how to render a vaccine ineffective
☐	☐	Confer resistance to therapeutically useful antibiotics or antiviral agents
☐	☐	Enhance the virulence of a pathogen or render a nonpathogen virulent
☐	☐	Increase transmissibility of a pathogen
☐	☐	Alter the host range of a pathogen
☐	☐	Enable evasion of diagnostic/detection modalities
☐	☐	Enable the weaponization of a biological agent or toxin
☐	☐	Any other potentially harmful combination of experiments and agents

Plants

Seed stocks	No plants or seed stocks were used in this study.
Novel plant genotypes	No plants or seed stocks were used in this study.
Authentication	No plants or seed stocks were used in this study.

ChIP-seq

Data deposition

☐ Confirm that both raw and final processed data have been deposited in a public database such as GEO.

☐ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links *May remain private before publication.*	*For "Initial submission" or "Revised version" documents, provide reviewer access links. For your "Final submission" document, provide a link to the deposited data.*
Files in database submission	*Provide a list of all files available in the database submission.*
Genome browser session (e.g. UCSC)	*Provide a link to an anonymized genome browser session for "Initial submission" and "Revised version" documents only, to enable peer review. Write "no longer applicable" for "Final submission" documents.*

Methodology

Replicates	*Describe the experimental replicates, specifying number, type and replicate agreement.*
Sequencing depth	*Describe the sequencing depth for each experiment, providing the total number of reads, uniquely mapped reads, length of reads and whether they were paired- or single-end.*
Antibodies	*Describe the antibodies used for the ChIP-seq experiments; as applicable, provide supplier name, catalog number, clone name, and lot number.*
Peak calling parameters	*Specify the command line program and parameters used for read mapping and peak calling, including the ChIP, control and index files used.*
Data quality	*Describe the methods used to ensure data quality in full detail, including how many peaks are at FDR 5% and above 5-fold enrichment.*
Software	*Describe the software used to collect and analyze the ChIP-seq data. For custom code that has been deposited into a community repository, provide accession details.*

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	Detachment of cells with TrypLE (ThermoFisher) to form cell suspension, Incubation with fluorescently-labelled antibodies and washing prior to analysis
Instrument	Guava EasyCyte 12HT and Agilent NovoCyte 3000
Software	GuavaSoft Version 3.3, NovoExpress 1.6.1, FlowJo 10.8.1

Cell population abundance	Cell population abundance evaluation is described in the methods and Supplementary Information
Gating strategy	Gating strategies are provided in the methods and Supplementary Information

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.

Magnetic resonance imaging

Experimental design

Design type	*Indicate task or resting state; event-related or block design.*
Design specifications	*Specify the number of blocks, trials or experimental units per session and/or subject, and specify the length of each trial or block (if trials are blocked) and interval between trials.*
Behavioral performance measures	*State number and/or type of variables recorded (e.g. correct button press, response time) and what statistics were used to establish that the subjects were performing the task as expected (e.g. mean, range, and/or standard deviation across subjects).*

Acquisition

Imaging type(s)	*Specify: functional, structural, diffusion, perfusion.*
Field strength	*Specify in Tesla*
Sequence & imaging parameters	*Specify the pulse sequence type (gradient echo, spin echo, etc.), imaging type (EPI, spiral, etc.), field of view, matrix size, slice thickness, orientation and TE/TR/flip angle.*
Area of acquisition	*State whether a whole brain scan was used OR define the area of acquisition, describing how the region was determined.*

Diffusion MRI ☐ Used ☐ Not used

Preprocessing

Preprocessing software	*Provide detail on software version and revision number and on specific parameters (model/functions, brain extraction, segmentation, smoothing kernel size, etc.).*
Normalization	*If data were normalized/standardized, describe the approach(es): specify linear or non-linear and define image types used for transformation OR indicate that data were not normalized and explain rationale for lack of normalization.*
Normalization template	*Describe the template used for normalization/transformation, specifying subject space or group standardized space (e.g. original Talairach, MNI305, ICBM152) OR indicate that the data were not normalized.*
Noise and artifact removal	*Describe your procedure(s) for artifact and structured noise removal, specifying motion parameters, tissue signals and physiological signals (heart rate, respiration).*
Volume censoring	*Define your software and/or method and criteria for volume censoring, and state the extent of such censoring.*

Statistical modeling & inference

Model type and settings	*Specify type (mass univariate, multivariate, RSA, predictive, etc.) and describe essential details of the model at the first and second levels (e.g. fixed, random or mixed effects; drift or auto-correlation).*
Effect(s) tested	*Define precise effect in terms of the task or stimulus conditions instead of psychological concepts and indicate whether ANOVA or factorial designs were used.*

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference (See Eklund et al. 2016)	*Specify voxel-wise or cluster-wise and report all relevant parameters for cluster-wise methods.*
Correction	*Describe the type of correction and how it is obtained for multiple comparisons (e.g. FWE, FDR, permutation or Monte Carlo).*

Models & analysis

n/a	Involved in the study
☐	☐ Functional and/or effective connectivity
☐	☐ Graph analysis
☐	☐ Multivariate modeling or predictive analysis

Functional and/or effective connectivity

Report the measures of dependence used and the model details (e.g. Pearson correlation, partial correlation, mutual information).

Graph analysis

Report the dependent variable and connectivity measure, specifying weighted graph or binarized graph, subject- or group-level, and the global and/or node summaries used (e.g. clustering coefficient, efficiency, etc.).

Multivariate modeling and predictive analysis

Specify independent variables, features extraction and dimension reduction, model, training and evaluation metrics.