Twelve-Month Follow-Up of Patients With Generalized Myasthenia Gravis Receiving BCMA-Directed mRNA Cell Therapy

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Abstract

We report the 12-month follow-up results of a phase 2 clinical of Descartes-08 (NCT04146051), BCMA-directed RNA chimeric antigen receptor T-cell (rCAR-T) therapy for myasthenia gravis (MG) given as an outpatient treatment without lymphodepletion. In the Phase 2a part of the study, all 7 participants who received six weekly infusions of Descartes-08 exhibited clinically meaningful improvement in common MG severity scales (MG Composite, MG Activities of Daily Living, Quantitative MG scores, and Quality of Life 15-revised) at Month 3. At Month 9 follow-up, all participants continued to experience marked clinical improvements. Five out of seven participants maintained clinical improvement at Month 12. Of the two participants who experienced loss of clinical effect at Month 12 and were eligible for retreatment, one was retreated and had rapid improvement in clinical scores with minimal symptom expression which was ongoing at Month 6 of follow-up. All three participants with detectable anti-acetylcholine receptor (AChR) antibody levels at baseline experienced autoantibody reductions by Month 6, which deepened further by Month 9, and were maintained at Month 12. These data support continued development of Descartes-08 in myasthenia gravis and other autoantibody-associated autoimmune disorders.

We recently reported on the safety and preliminary clinical activity of Descartes-08, an mRNA-engineered chimeric antigen receptor (rCAR) T-cell therapy, in patients with generalized myasthenia gravis (gMG) (NCT04146051).[1] Descartes-08 is administered in the outpatient setting, does not require lymphodepleting chemotherapy, and targets B-cell Maturation Antigen (BCMA) expressed on long-lived plasma cells (LLPCs) and plasmacytoid dendritic cells (pDCs).[2] In the Phase 2a part of the study, all 7 participants (4 acetylcholine receptor [AChR]+, 2 muscle-specific kinase [MuSK]+, 1 seronegative, by history) who received six weekly infusions of Descartes-08 exhibited clinically meaningful improvement in common MG severity scales at Month 3. Three of the 7 participants achieved minimal symptom expression (MSE)[3]. Two were intravenous immunoglobulin (IVIG) infusion-dependent and one was plasmapheresis-dependent for years prior to treatment, and maintained responses without further IVIG or plasmapheresis. Here, we report the results of the final per-protocol one year follow-up.

Clinical trial design, objectives, outcome measures, laboratory and data analysis methods, and demographic characteristics were previously described.[1] Descartes-08 maintained a favorable safety profile, with no new product-related adverse events reported during the 12-month follow-up period. At Month 9 follow-up, approximately 7 months after the last infusion and without new or increased MG-directed drugs, all participants continued to experience substantial clinical responses as measured by the MG Activities of Daily Living Score[4] (mean change -6.3 [95% CI -3·5 to -9.1], **Figure 1A**), MG Composite Score[5] (-16·6 [-13·4 to -19·5, **Figure 1B**), Quantitative MG scores[6] (-8·4 [-5·2 to -11·6], **Figure 1C**), and Quality of Life 15-revised score[7] (-12 [-8 to -16], **Figure s1**). At Month 12, 5 of the 7 participants maintained clinically meaningful improvement, including one with MSE. Two participants had worsening disease at Month 12 and became eligible for retreatment. One opted for retreatment, which led to a rapid decrease in MG-specific clinical scores and MSE. The MSE is ongoing at Month 6 of retreatment follow-up (**Figure 1D**).

Three of the 4 participants with a history of anti-AChR antibody had detectable levels at baseline, and all three showed reductions in antibody levels by Month 6 (-17%, -44%, and -65%). These reductions continued at Month 9 (-35%, -100% [undetectable], and -70%), and persisted at Month 12 (-33%, -44% and -65% reductions, **Figure 1E**). The participant whose anti-AChR antibody was undetectable at Month 9 and -44% at Month 12 also had worsening disease from Month 9 to Month 12 but did not opt for retreatment. Five of the 7 participants had circulating anti-meningococcal antibodies at baseline, all from prior vaccination. As we previously reported, there was a small but detectable decrease in these antibodies at Month 3.[1] The reduction deepened by Month 9 (-48% [-25% to -75%]) and stabilized by Month 12 to lower but still protective levels (-48% [-35% to -69%], **Figure s2**), following a similar pattern to the anti-AChR antibody reduction. In contrast, there was no appreciable decrease in total immunoglobulin levels (**Figure s3**), including total IgG levels at Month 3 (-21% [-56% to +14]).

In summary, we observed continued clinical improvement and autoantibody reductions after BCMA-directed rCAR-T treatment that persisted through the one-year follow-up period. A patient with clinical relapse at Month 12 again achieved MSE after redosing. The favorable safety profile of this mRNA CAR-T treatment is in contrast to DNA-based CAR-T treatments, which require lymphodepletion chemotherapy with potential hematologic toxicities and oncogenic risk from genomic integration of CAR DNA. DNA-based CAR-T therapy also targets a much broader population of non-pathogenic CD19-positive cells, which can cause unnecessary immunosuppression.[8] Therapies targeting BCMA, but not CD19 or CD20, have advantageous effects on patients' autoantibody signatures.[9] Our observations suggest that using rCAR-T therapy to target BCMA-positive cells—including LLPCs—can result in durable depletion of autoantibodies and clinically meaningful improvement in MG severity scores without severe toxicity, agammaglobulinemia, or increased risk of infection. These data support continued development of Descartes-08 in myasthenia gravis and other autoantibody-associated autoimmune disorders.

Contributors statement

All authors had full access to the study design information, reviewed, edited, and provided final approval of the manuscript content, and had final responsibility for the decision to submit for publication. Study design: MK, MDM, TM. Investigation and data collection: NC, GS, MHF, TV, JFH, TM. Data analysis: MDM, CAS. Data verification: MK, JFH. Data interpretation: CAS, CJ, MK, MDM, TV, TM, JFH. Writing — original draft: MDM.

Declaration of interests

G Sahagian has received research support from Cartesian Therapeutic, Inc., Immunovant, and argenx paid to his institution; consulting fees from UCB pharma and Immunovant; honoraria from argenx and Alexion, and travel support from argenx and Immunovant; he also has unpaid positions at MGFCA and AANEM. M Feinberg has received honoraria as a consultant or advisory board member from argenx. CM Jewell has an equity position in Barinthus Biotherapeutics. CM Jewell, M Kurtoglu, and MD Miljkovic are employees of and have ownership interest in Cartesian Therapeutics, Inc. CM Jewell is appointed as an employee of the University of Maryland and VA Maryland Health Care System. The views in this paper do not reflect the views of the state of Maryland or the US Government. MD Miljkovic is appointed as an employee of the University of Maryland Baltimore County. The views in this paper do not reflect the views of the state of Maryland. T Vu is the USF Site Principal Investigator for MG clinical trials sponsored by Alexion/AstraZeneca, argenx, Ra/UCB, Horizon/Viela Bio, Janssen/Momenta, Immunovant, Regeneron, Dianthus, and Cartesian Therapeutics, and receives speaking and/or consulting honoraria relating to MG from Alexion, argenx, and UCB. T Mozaffar has received research support (paid to his institution) from Alexion Pharmaceuticals, Inc, Amicus, Annji, argenx, Astellas Gene Therapy, Cartesian Therapeutics, ML Bio, Sanofi, Spark Therapeutics, UCB and Valerion; consulting fees from Alexion Pharmaceuticals, Inc, Amicus, Annji, argenx, Audentes/Astellas Gene Therapy, Horizon Therapeutics, Maze Therapeutics, Momenta, Sanofi and UCB; support for attending meetings and/or travel from Sanofi; participation on a DSMB or an advisory board from Srepta, Applied Therapeutics, and the National Institutes of Health. JF Howard, Jr. has received research support (paid to his institution) from Alexion AstraZeneca Rare Disease, argenx, Cartesian Therapeutics, the Centers for Disease Control and Prevention, Myasthenia Gravis Foundation of America, Muscular Dystrophy Association, National Institutes of Health (including the National Institute of Neurological Disorders and Stroke and the National Institute of Arthritis and Musculoskeletal and Skin Diseases), Patient-Centered Outcomes Research Institute, Ra Pharmaceuticals Inc (now UCB), and Takeda Pharmaceuticals; honoraria from Alexion AstraZeneca Rare Disease, argenx, Biologix Pharma, Immunovant, Inc, Merck EMB Serono, NMD Pharma, Novartis Pharma, Ra Pharmaceuticals Inc (now UCB), Regeneron Pharmaceuticals Inc, Sanofi US, Viela Bio/ Horizon Therapeutics plc, Inc (now Amgen) and Zai Labs; he has also received nonfinancial support from Alexion Pharmaceuticals, Inc, argenx BV, Ra Pharmaceuticals Inc (now UCB), Toleranzia AB and Zai Labs. All other authors declare no competing interests.

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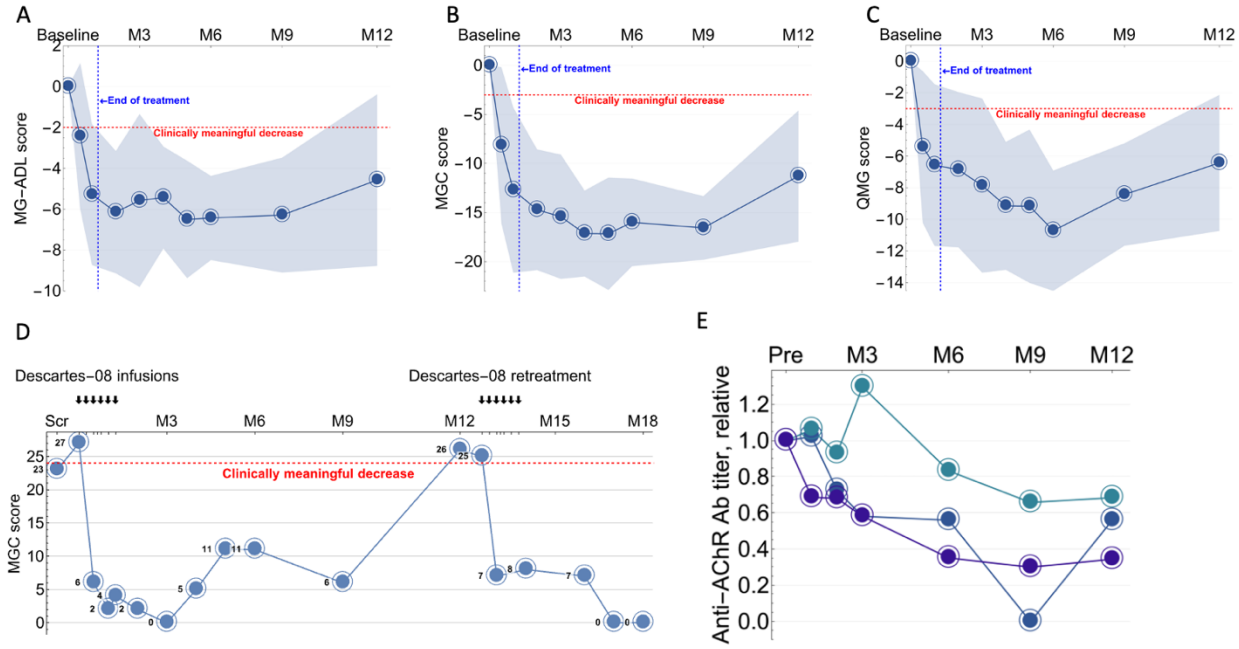
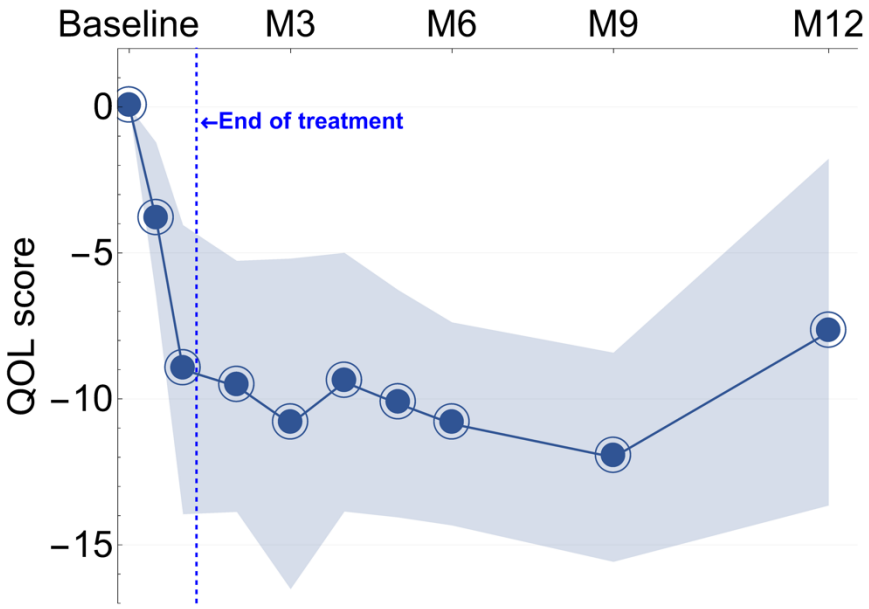
Tables and figures

Figure 1. Changes in disease severity scores and serum autoantibody levels.



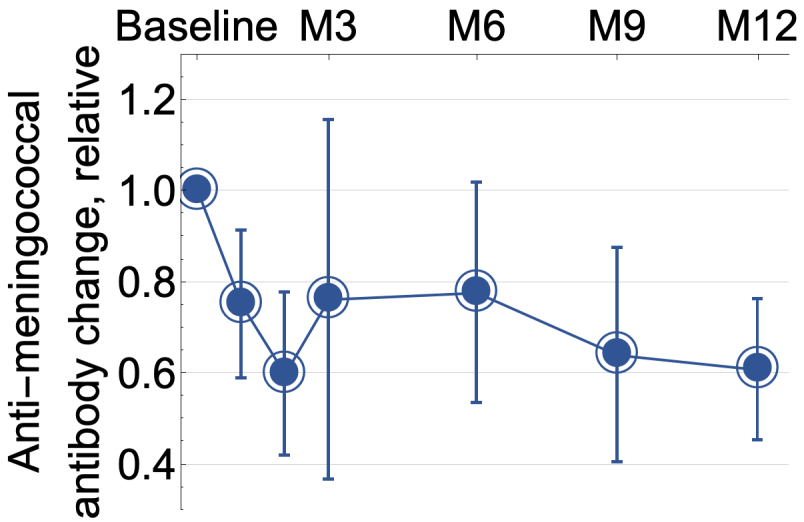
A–C: Mean change from Baseline (line) and 95% CI (bands) in Myasthenia Gravis Activities of Daily Living Score (MG-ADL, **A**), Quantitative Myasthenia Gravis Score (QMG, **B**)**,** Myasthenia Gravis Composite Score (MGC, **C**) during 12 months of follow-up for MG-001 participants who received six once-weekly doses (n=7). **D:** Change from Baseline in MGC Score after initial dosing and retreatment in a participant experiencing relapse at Month 12. **E:** Relative change in serum anti-acetylcholine receptor antibody levels in the three participants with detectable antibodies at baseline. Each line represents one patient.

Figure s1. Mean change from baseline in Myasthenia Gravis Quality-of-Life Revised Scale (MG-QoL-15r) score.



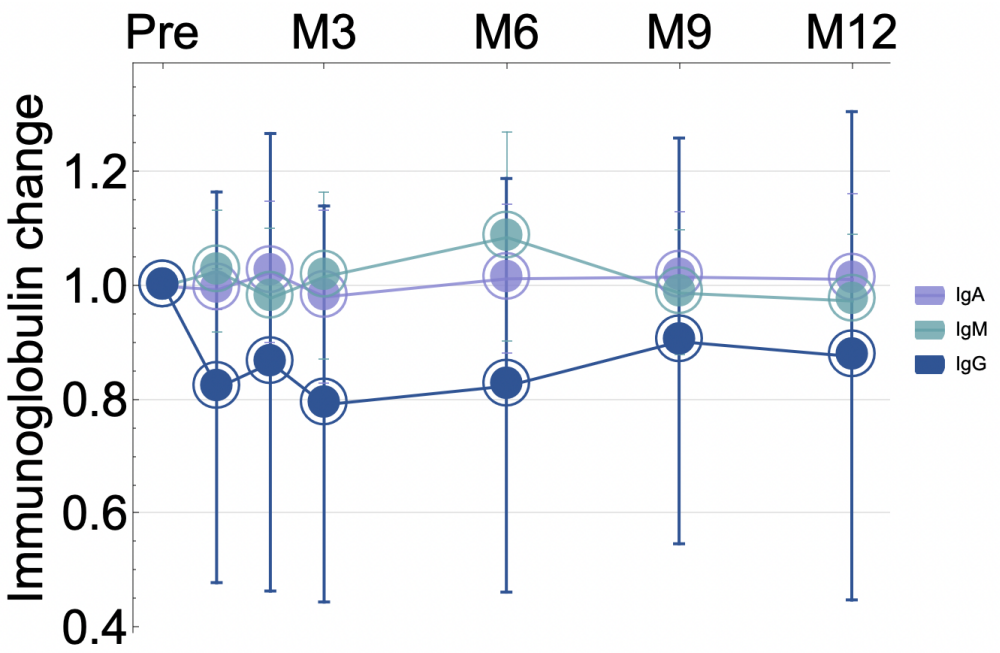
Band represents 95% CI.

Figure s2. Relative change from baseline in anti-meningococcal antibody titers (all serogroups).



Error bars represent 95% CI.

Figure s3. Relative change from baseline in total immunoglobulin levels.



Error bars represent 95% CI.