THE LANCET
Neurology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Granit V, Benatar M, Kurtoglu M, et al. Safety and clinical activity of autologous RNA chimeric antigen receptor T-cell therapy in myasthenia gravis (MG-001): a prospective, multicentre, open-label, non-randomised phase 1b/2a study. *Lancet Neurol* 2023; **22:** 578–90.

Safety and Efficacy of Autologous RNA Chimeric Antigen Receptor T-cell (rCAR-T) Therapy in Myasthenia Gravis: a prospective, multicenter, open-label, non-randomised phase 1b/2a study

Supplementary Appendix

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Figure s1. Potency of Descartes-08 lots from patients with MG as measured by interferon-γ release assay after co-culture with BCMA-positive MM1S cells compared to potency of three healthy volunteer lots. Horizontal bars represent median.

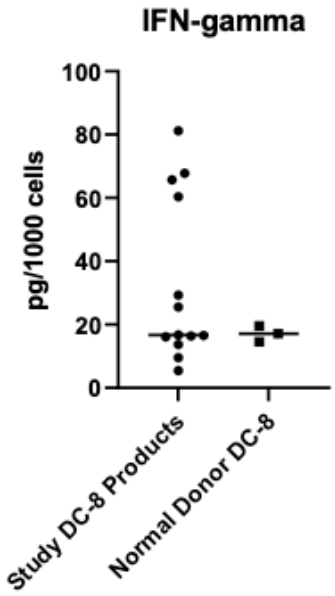

Figure s2. Change from baseline in MG ADL, QMG, MGC, and MG-QoL15r over 6 months for 3 participants in Part-1. Lines represent changes for individual patients. Arrows represent Descartes-08 infusions at Dose Level 1 (the smallest arrow), 2 (middle arrow) and 3 (the largest arrow).

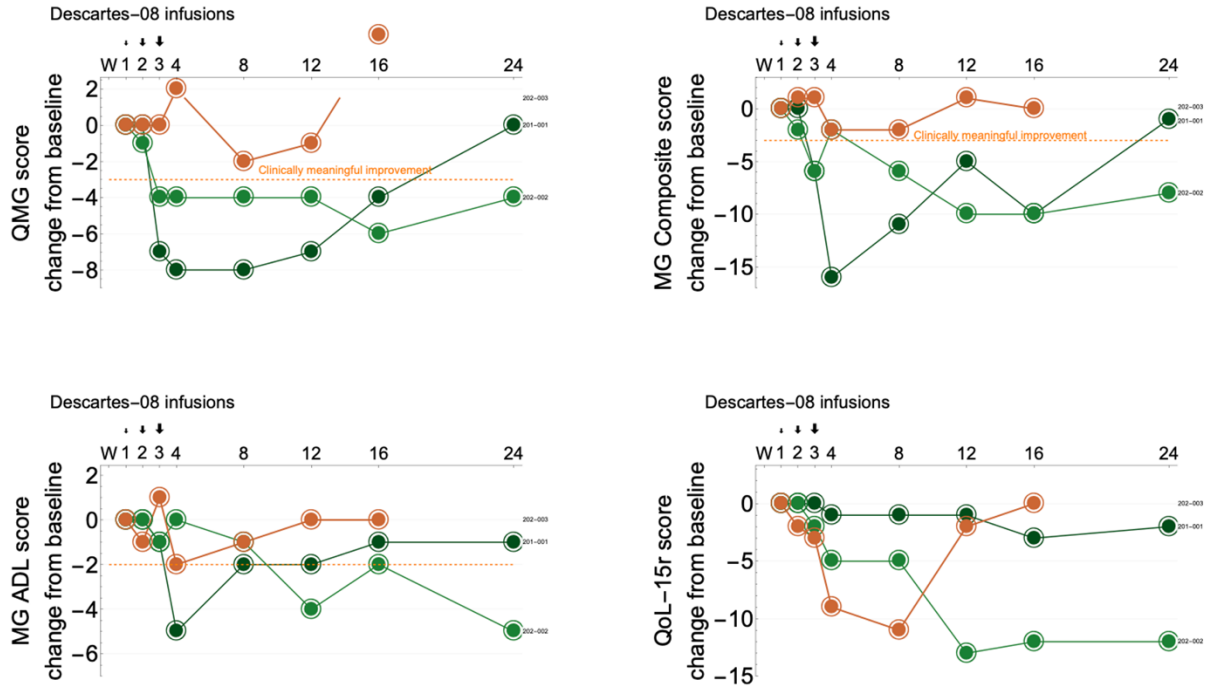

Figure s3. **Additional exploratory analyses**. **A:** Pharmacokinetic analysis of MG-001 participants by quantitative reverse transcriptase polymerase chain reaction (qRT-PCR) for CAR mRNA at screening (Scr), Day 1 pre-infusion (D1 pre) and 1 hour post-infusion (D1 1h), Week 5 pre-infusion (W5 pre) and 1 hour post-infusion (W5 1h), Week 8 (W8), and Week 12 (W12). Gray horizontal bars represent the median. Orange boxes represent the 25th to 75th percentile. Vertical bars represent the full range. **B:** Representative scatter plot of differential abundance of TCR clonotypes from Screening to Week 1 pre-treatment (left) and Screening to Week 20 (right) for a seronegative participant enrolled to Arm 2. Orange points represent rearrangements significantly more abundant in the second (y-axis) sample; Teal points are significantly more abundant in the first (x-axis) sample. Points on one of the axes were not detected in the other sample. **C:** Differential TCR clonotype abundance between screening and Day 57/85 in 6 participants enrolled to Arm 1 (Patients C and E) or Arm 2 (Patients A, B, D, F).

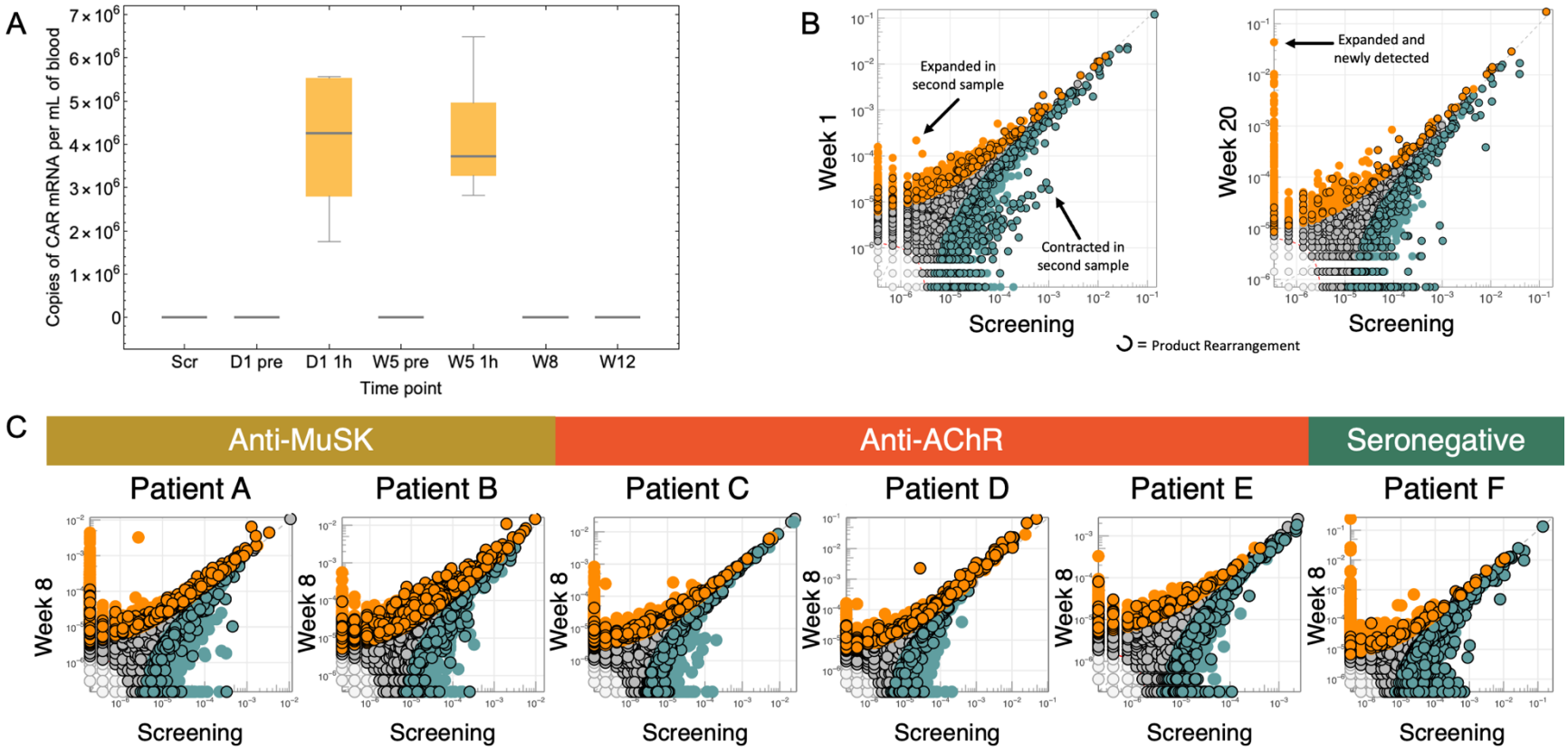

Table s1. Baseline characteristics and study interventions of individual participants

No.	Age	Sex	Weight (kg)	Ab	MGFA Class	Age at onset	MG duration	Baseline MG severity scores				Ongoing/ most recent treatment	Part/ Arm	Actual dose per infusion (CAR+ cells/kg, × 10^6)	Number of infusions	Total infused CAR+ cells (× 10^9)	MG PISA**	
								QMG	MGC	MG ADL	QoL 15r						Best	Last
1	63	M	112.7	AChR	IIIa	58	5	18	27	13	26	Pyr, Pred, MMF	Part-1	Varied	3	6.87	I	I
2	69	F	71.3	AChR	IIIa	44	25	11	15	6	20	Pred, MMF	Part-1	Varied	3	6.38	I	I
3	38	F	64.8	AChR	IIIa	25	13	14	16	7	24	Pyr, Pred	Part-1	Varied	3	6.26	I	I
4	70	F	71.3	AChR	IIIa	44	26	8	13	6	12	IVIg	Arm-3	56.2	6	18.77	U	U
5	38	F	85.2	Other	IIIb	25	13	11	25	9	18	IVIg	Arm-2	37	6	18.9	I	I
6	52	F	110.0	AChR	IIa	36	16	16	27	13	26	Pyr, Aza	Arm-2	22.7*	6	11.34	I	I
7	50	F	81.5	AChR	IIIa	26	23	23	26	12	22	IVIg, MMF, Pyr, Aza	Arm-2	63.1	6	30.85	I	I
8	66	M	88.0	Other	IIa	57	10	19	23	8	14	Pyr, Pred	Arm-2	30.0	6	15.62	I	I
9	19	F	72.5	AchR	Ivb	15	4	19	30	14	26	Pyr, IVIg	Arm-1	74.7	6	33.12	I	I
10	39	F	63.3	AchR	IIIa	25	14	17	23	11	23	Pyr, Pred	Arm-1	70.8	6	26.89	I	I
11	40	F	44.8	Other	IIIb	14	27	12	12	6	15	Pyr, Pred	Arm-2	58.8	6	15.80	U	U
12	83	M	101.1	AchR	IIIb	79	4	13	22	13	18	Pyr, Pred	Arm-2	24.9*	6	16.47	I	I
13	70	M	100.5	AChR	IIIb	54	15	16	21	7	9	Pyr, Pred	Arm-1	32.2	3	9.65	U	U
14	38	F	115.2	AChR	IIIa	17	21	16	25	13	20	Pyr, Pred	Arm 2	28.6*	6	17.14	I	I

* Actual dose lower than planned for Dose Level 3 (28.875–76.125 × 10^6 CAR+ cells/kg per infusion)

** I: Improved; U: Unchanged

Table s2. Immunophenotype of Descartes-08 lots in MG-001 Part-2 participants.

Lot*	Viability (%)	CD8+ (%)	CD3+CD56- (%)	Perforin+ (%)	Helios+ (%)	CD57 (%)	PD1 (%)
04	76.0	99.5	NA	97.66	37.65	4.92	10.46
03	80.5	96.9	91.1	97.94	4.02	54.19	12.56
05	80.7	97.8	72.3	97.45	7.37	42.66	15.71
10	82.1	99.6	85.6	93.54	39.64	2.97	12.46
13	87.4	99.7	73.2	92.69	36.12	7.81	16.66
17	84.4	98.3	64.2	92.7	5.33	18.02	19.03
21	87.9	95.5	67.4	93.09	10.24	53	9.09
27	78.2	99.4	90.8	87.92	6.14	18.63	19.74
23	79.2	99.4	78.8	90.31	4.63	22.68	24.54
25	81.7	98.9	80.9	89.97	8.83	31.59	18.84
29	78.2	99.3	NA	90.0	2.13	3.36	2.54
16	80.8	95.5	62.5	81.56	18.4	14.83	10.86

* One lot was manufactured but not infused for a patient with a qualifying MG-ADL score (≥6) at screening, but whose score was <6 at the time of planned infusion.

Table s3. Serum cytokine levels before and during treatment for all participants, and serum tryptase level of participants who developed urticarial rash.

Median cytokine concentration pg/mL (range)	Screen (n=10)	Day 1* (n=10)	Day 29* (n=9)	Day 57 (n=10)	Day 85 (n=5)	Fever (n=4)	Rash** (n=1)	Normal Range ‡
CXCL10	315.1 (125.5 - 593.1)	308.9 (219.7 - 447.7)	354.0 (208.7 - 403.4)	200.3 (37.5 - 508.7)	148.8 (140.7 - 798.4)	3108.6 (1615.2 - 12626)	NA	36.4-248.9
CCL2	358.4 (89.6 - 536.9)	390.6 (57 - 750)	318 (50.4 - 611)	254.2 (36.3 - 532.1)	216.1 (49.9 - 289.6)	1200.2 (573 - 5914.6)	NA	56.5-281.1
IFNγ	153 (<6.1 - 1026.2)	149.2 (<6.1 - 563.4)	30 (<6.1 - 161.8)	60.1 (<6.1 - 520.7)	<6.0 (<6.0 - 306.4)	103.7 (30.1 - 1459.5)	<4.2	<LOD-93.4
TGFβ	88.7 (<56.7 - 1298.9)	98.1 (<56.7 - 515.2)	<18.6 (<18.6 - 359.9)	43 (<18.6 - 411.5)	<18.6 (<18.6 - 178.9)	<114.9 (<114.9 - 129.9)	NA	<LOD-208.5
IL-6	115 (<6.7 - 771.8)	117 (<6.7 - 629.7)	26.9 (<6.7 - 283.3)	24.8 (<6.7 - 542.1)	<6.7 (<6.7 - 142.4)	47.8 (<28.1 - 208.3)	<2.0	<LOD-53.8
IL-10	18.2 (<3.4 - 184)	21.7 (<3.4 - 125.7)	5.9 (<3.4 - 60.5)	7.3 (2.7 - 68.1)	2.7 (2.7 - 30.5)	39.2 (24 - 50.9)	4.2	<LOD-24.1
CXCL8 (IL-8)	36.1 (1.9 - 100.8)	27.2 (3.4 - 67.1)	8.9 (<1.2 - 53.8)	12 (<1.2 - 43.9)	3.9 (<1.2 - 38.9)	25.8 (9.8 - 175.3)	<3.0	<LOD-208.5
IL-17A	93.2 (<1.5 - 208.5)	58.2 (<1.5 - 206.4)	6.7 (<1.5 - 203.3)	33.5 (<1.5 - 317.2)	2.2 (<1.5 - 77)	20.1 (11.2 - 223.1)	<1.4	<LOD-667.0
IL-1β	28.3 (<6.5 - 663.4)	30.2 (<6.5 - 200.8)	<6.5 (<6.5 - 82.6)	23.2 (<6.5 - 131.2)	14.4 (<6.5 - 65)	18.6 (<15.0 - 34.5)	<6.5	<LOD-125.8
TNFα	84.9 (<2.2 - 402.5)	72.3 (<2.2 - 266.7)	41.5 (<2.2 - 176.3)	50.3 (<2.2 - 358)	16.5 (2.3 - 352.6)	13.9 (10.7 - 106.3)	4.0	<LOD-50.0
IL-12p70	13 (<4.4 - 174.3)	13.2 (<2.7 - 126.1)	<3.4 (<3.4 - 55.5)	7.2 (<3.4 - 95.8)	<3.4 (<3.4 - 28)	9.9 (5.7 - 54.3)	<1.9	<LOD-15.8
IL-4	126.5 (<6.1 - 538)	55.7 (<6.1 - 519.3)	45.1 (<6.1 - 503.5)	34.2 (<6.1 - 564.6)	13.1 (<8.3 - 547.3)	<13.6 (<13.6 - 564)	<2.2	<LOD-833.7
IL-2	33.6 (<2.0 - 109.1)	19.2 (<2.0 - 62.1)	11.9 (<2.0 - 63)	7.0 (<2.0 - 84.9)	6.4 (3 - 88.1)	<4.3 (<4.3 - 61.8)	<2.1	<LOD-115.9
Tryptase (mcg/L)	NA	NA	NA	NA	NA	NA	8.3	<110 †

* Samples obtained prior to scheduled infusion ** Cytokine panel performed by ARUP Laboratories in a CLIA-certified laboratory

† from CLIA / Quest range. ‡ from Biolegend normal range. NA – not evaluated.

Table s4. Semi-quantitative cell cluster assay of the first five participants enrolled to Arm 1 or Arm 2 of Part-2. Units represent a visual score on a scale 0–4; the threshold for positivity is 1. ACHRe: epsilon subunit of the acetylcholine receptor; ACHRg: gamma subunit of the acetylcholine receptor; MUSK: muscle-specific kinase; LRP4: low-density lipoprotein receptor-related protein 4.

ID	MG type	Time point	ACHRe	ACHRg	MUSK	LRP4
1	AChR+	Screening	0	0	0	0
		Day 29	0	0	0	0
		Day 57	0	0	0	0
2	Seronegative	Screening	0	0	0	0
		Day 29	0	0	0	0
		Day 57	0	0	0	0
3	AChR+	Screening	1.5	3	0	0
		Day 29	1.5	3	0	0
		Day 57	2	3	0	0
4	AChR+	Screening	0.5	3.5	0	0
		Day 29	0	3	0	0
		Day 57	0	4	0	0
5	MuSK	Screening	0	0	3	0
		Day 22	0	0	3.5	0
		Day 36	0	0	3	0

Table s5. Summary of key changes to protocol MG-001

Date	Version	Description	Enrollment			
			Part 1	Part 2 Arm 1	Part 2 Arm 2	Part 2 Arm 3
4/21/2019	1.5	Original IRB-approved protocol	0	0	0	0
7/26/2019	1.6	Single-center to multi-center study	0	0	0	0
9/20/2019	1.7	Clarified daily study procedures	1	0	0	0
1/23/2020	1.8	Part 1 revised to include intra-patient dose escalation; Part 2 revised to allow enrollment of patients with MGFA Class II–IV.	0	0	0	0
2/19/2020	1.9	Minor clarifications to study procedures	1	0	0	0
4/5/2021	2.0	Part 2 revised to: allow enrollment of patients with anti-LRP4 antibody in addition to AChR and MuSK; explore different administration schedules (twice-weekly, weekly, monthly); reduce the intensity of post-infusion monitoring (from 4 hours to 1 hour post-infusion).	1	0	0	1
9/15/2021	2.1	Part 2 Arm 2 revised to include a cohort of seronegative patients.	0	0	0	0
12/22/2021	2.2	Eligibility revised to include patients receiving eculizumab after publication of open-label extension data; other minor clarifications to study procedures.	0	3	7	0

CLINICAL STUDY PROTOCOL

AUTOLOGOUS T-CELLS EXPRESSING A CHIMERIC ANTIGEN RECEPTOR DIRECTED TO B-CELL MATURATION ANTIGEN (BCMA) IN PATIENTS WITH GENERALIZED MYASTHENIA GRAVIS (MG)

Protocol number:	MG-001
IND number:	18964
Product name:	Descartes-08
Principal Investigator:	Volkan Granit, MD Assistant Prof, Clin. Neurology U. Miami School of Medicine
Sponsor:	Cartesian Therapeutics, Inc.
Address:	704 Quince Orchard Rd, Suite 210A Gaithersburg, MD 20878
Phone:	+1-301-348-8698
Website:	www.cartesiantherapeutics.com
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Study Product:	**Descartes-08**
Original Protocol Date:	07-MAR-2019
Current Protocol Version:	2.2
Current Protocol Date:	22-DEC -2021

SPONSOR SIGNATURE PAGE

Company/Sponsor signatory

Date

Milos Miljkovic, MD, MSc
Cartesian Therapeutics, Inc.
704 Quince Orchard Road
Gaithersburg, MD 20878
Tel 301-348-6898

INVESTIGATOR'S AGREEMENT

I have received and read the investigator's brochure for Descartes-08. I have read the protocol and agree to conduct the study as outlined and in conformance with Good Clinical Practices (GCPs) and applicable regulatory requirements. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Printed Name of Investigator

Signature of Investigator

Date

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ABBREVIATIONS AND DICTIONARY OF TERMS

AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartyl aminotransferase
AUC	Area Under the (time-concentration) Curve
BCMA	B-Cell Maturation Antigen
BSC	Biological Safety Cabinet
CAR	Chimeric Antigen Receptor
CBC	Complete blood count
CK	Creatine Kinase
CMC	Chemistry, Manufacturing, and Controls
CNS	Central Nervous System
CrCl	Creatinine Clearance
CRS	Cytokine Release Syndrome
CSF	Cerebrospinal fluid
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMF	Drug Master File
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
GLP	Good Laboratory Practice
GMG	Generalized Myasthenia Gravis
GMP	Good Manufacturing Practice
HAMA	Human anti-mouse antibody
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard Ratio
ICE	Immune Effector Cell-Associated Encephalopathy
IFN-λ	Interferon-gamma
Ig	Immunoglobulin
IL	Interleukin
IND	Investigational New Drug (application)
IV	Intravenous(ly)
MG	Myasthenia Gravis
MG ADL	Myasthenia Gravis Activities of Daily Living
MG MMT	Myasthenia Gravis Manual Muscle Testing
MG QoL 15R	Myasthenia Gravis Quality of Life
MM	Multiple Myeloma

MTD	Maximal Tolerated Dose
MusK	Muscle specific tyrosine kinase
MRSD	Maximum Recommended Starting Dose
MSSD	Maximum Safe Starting Dose
nAchR	Nicotinic Acetylcholine Receptor
NCI	National Cancer Institute
NGS	Next Generation Sequencing
NOAEL	No Observed Adverse Effect Level
NSAID	Non-steroidal anti-inflammatory drug
PI	Principal Investigator
PK	Pharmacokinetic
QMG	Quantitative Myasthenia Gravis
SAE	Serious Adverse Event
SEM	Standard Error of the Mean
SM	Starting Materials
SUSAR	Serious Unexpected Adverse Reaction
TK	Toxicokinetic(s)
TNF α	Tumor-necrosis factor alpha

PROTOCOL SYNOPSIS

Title: Autologous T-cells Expressing a Chimeric Antigen Receptor Directed to B-Cell Maturation Antigen (BCMA) in patients with Generalized Myasthenia Gravis (GMG).

Study Description: This is a Phase Ib/IIa dose-escalation study to evaluate the safety, tolerability and preliminary efficacy of autologous T-cells expressing a chimeric antigen receptor (CAR) directed to B-Cell maturation antigen (BCMA) in patients with GMG. The cell product will be referred to as "Descartes-08". This study has two parts, **Part 1 and Part 2**. In **Part 1**, Descartes-08 will be administered to each patient at 3 increasing Dose Levels to establish MTD. In **Part 2,** up to 15 additional patients with autoantibody-positive GMG (Seropositive Cohort) and up to 5 patients with seronegative GMG (Seronegative Cohort) will be enrolled to further characterize the safety of MTD. In Arms 1 to 3, each patient will receive up to 6 doses of Descartes-08 at a safe Dose Level reached in Part 1 following one of the three administration schedules: Arm 1- twice a week x 3 weeks to the Seropositive Cohort; Arm 2- once a week x 6 weeks to Seronegative and Seropositive Cohorts; Arm 3- once a month x 6 months to the Seropositive Cohort. The protocol contains specific rules to determine what Dose Level is safe.

Objectives: **The primary objective** is to assess the safety, tolerability, and manufacturing feasibility of Descartes-08 in patients with GMG. Part 1 of the study follows an intra-patient dose escalation design, where Descartes-08 will be dose-escalated within each of 3 to 6 patients; the patients will also be staggered at least 21 days apart. In Part 2, patients will receive up to 6 doses of Descartes-08 at a dose established as safe and tolerable in Part 1; each dose will be administered in 3 different schedules in seropositive patients and in a weekly schedule to seronegative patients to assess the safety and tolerability of a multiple (repeated) dosing schedule up to 1 year.

The secondary objectives are to:

1. Determine the change from baseline over a period of 24 weeks in the titer of myasthenia gravis-specific autoantibodies in seropositive patients and the 4 Immunoglobulin types in all patients (IgG, IgM, IgA, IgE) following multiple infusions of Descartes-08 administered in 3 different schedules;
2. Quantify the clinical effect of Descartes-08 in all patients using standard clinical assessment scales (Quantitative Myasthenia Gravis (QMG), Myasthenia Gravis Quality of Life (MG QoL 15R), Myasthenia Gravis Activities of Daily Living (MG ADL), MG

Composite, MGFA Class and MG Post Intervention Status (MG PIS) over a period of 1 year.

The exploratory objectives are to:

1. Evaluate the presence, frequency and titer of anti-mouse human antibody (HAMA) following single or multiple infusions of Descartes-08;
2. Assess standard pharmacokinetic parameters of Descartes-08 in blood following single or multiple infusions by a validated qPCR assay to the CAR construct; and
3. Evaluate biomarkers of safety and efficacy (i.e., serum cytokine levels, serum inflammatory markers, plasma BCMA levels, vaccination titers (any vaccination, i.e. tetanus, meningococcus, etc. within the past 3 years is accepted) and Ig subtypes) following single or multiple infusions of Descartes-08.

Endpoints:

The primary endpoint is the Maximum Tolerated Dose (MTD) defined as the Dose Level at which no more than one patient has shown Dose-Limiting Toxicity (DLT) after Part 1 of the study is completed. "Completed" means that 3 patients completed the study without a DLT; or 6 patients completed the study with no more than 1 DLT. If the number of cells required for a target Dose Level cannot be manufactured for at least 3 patients, then the highest achievable (and safe) dose level will be determined as Maximum Feasible Dose (MFD).

The secondary endpoints are:

1. The proportion of patients achieving a ≥2-point change from Baseline up to Year 1 in the MG Activities of Daily Living (MG-ADL) score and Quantitative Myasthenia Gravis (QMG) score.
2. The proportion of patients achieving a ≥3-point change from Baseline up to Year 1 in the MG Composite (MGC) score.
3. The mean change from Baseline up to Year 1 in the MG-ADL, QMG, MG-QoL15R, and MGC scores.
4. The proportion of patients achieving ≥50% reduction from Baseline up to Year 1 in myasthenia-specific autoantibody titers in seropositive patients.
5. The optimal Descartes-08 administration schedule that can achieve ≥50% reduction in autoantibody titers for at least 8 weeks in seropositive patients.

Exploratory endpoints are: 1) percent change of all immunoglobulin subtypes as a function of dose and length of treatment; 2) the proportion of patients

	who have a clinically meaningful benefit from single versus multiple doses of Descartes-08.
Study Population:	Up to 18 adult patients with Myasthenia Gravis Foundation of America (MGFA) Grade III or IV (Part 1; Dose escalation) or Grade II-IV (Part 2; expansion phase) MG in whom immunosuppression therapy is clinically indicated in the judgement of the treating neurologist.
Phase:	Ib/IIa
Study Site:	Multi-center
Study Intervention:	Patients will undergo leukapheresis as per institution guidelines and product will be shipped to the Sponsor's laboratory for isolation and processing of T-cells under Good Manufacturing Practice (GMP). The frozen final product (Descartes-08) will be shipped to the clinical site where it will be thawed and intravenously administered. In Part 1, The following doses of anti-BCMA CAR-T cells are planned: • Dose 1: 3.5 x 10^6 CAR+ cells/kg • Dose 2: 17.5 x 10^6 CAR+ cells/kg • Dose 3: 52.5 x 10^6 CAR+ cells/kg In Part 2, the maximum safe and tolerable dose achieved in Part 1 will be administered over the course of 3 weeks (Arm 1), 6 weeks (Arm 2), or 6 months (Arm 3).
Study Duration:	18 months
Participant Duration:	30 Weeks (Part 1), 1 year (Part 2)
Abbreviated Eligibility Criteria	**Inclusion Criteria** are: 1. Patient must be at least 18 years of age. 2. Patient must have GMG, defined as MGFA clinical classification grades 3 or 4 (Part 1; dose escalation) or grades 2-4 (Part 2; expansion phase) at the time of screening. 3. Concomitant immunosuppressive drugs must be deemed necessary by the investigator. 4. If a patient is using corticosteroids, the daily dose should not exceed 40 mg/day of prednisone equivalent. The dose must be stable for a minimum of 4 weeks prior to baseline (Day 1) visit. 5. Seropositive Cohort only: Acetylcholine receptor autoantibody (anti-nAChR) titer or Muscle specific tyrosine kinase autoantibody (anti-MuSK) or Low-density lipoprotein receptor-related protein 4 autoantibody (anti-LRP4) or anti-AChR cluster antibody must be above

the reference laboratory upper normal limit (UNL) and documented within the past 10 years of screening.

6. Seronegative Cohort only: Unequivocal response to cholinesterase inhibitors AND abnormal repetitive nerve stimulation or increased jitter (must not have another neuromuscular disease, which may cause increase jitter).
7. Patient must be willing to return for all study visits.
8. Patient must be able to give written informed consent.
9. Women of reproductive potential must agree to use highly effective birth control from screening through 14 days post last dose of Descartes-08. (See Section 1.1 for cell infusion days and Section 5.1 for definition of reproductive potential).
10. MG-Activities of Daily Living (MG-ADL) total score ≥ 6.

Exclusion Criteria are:

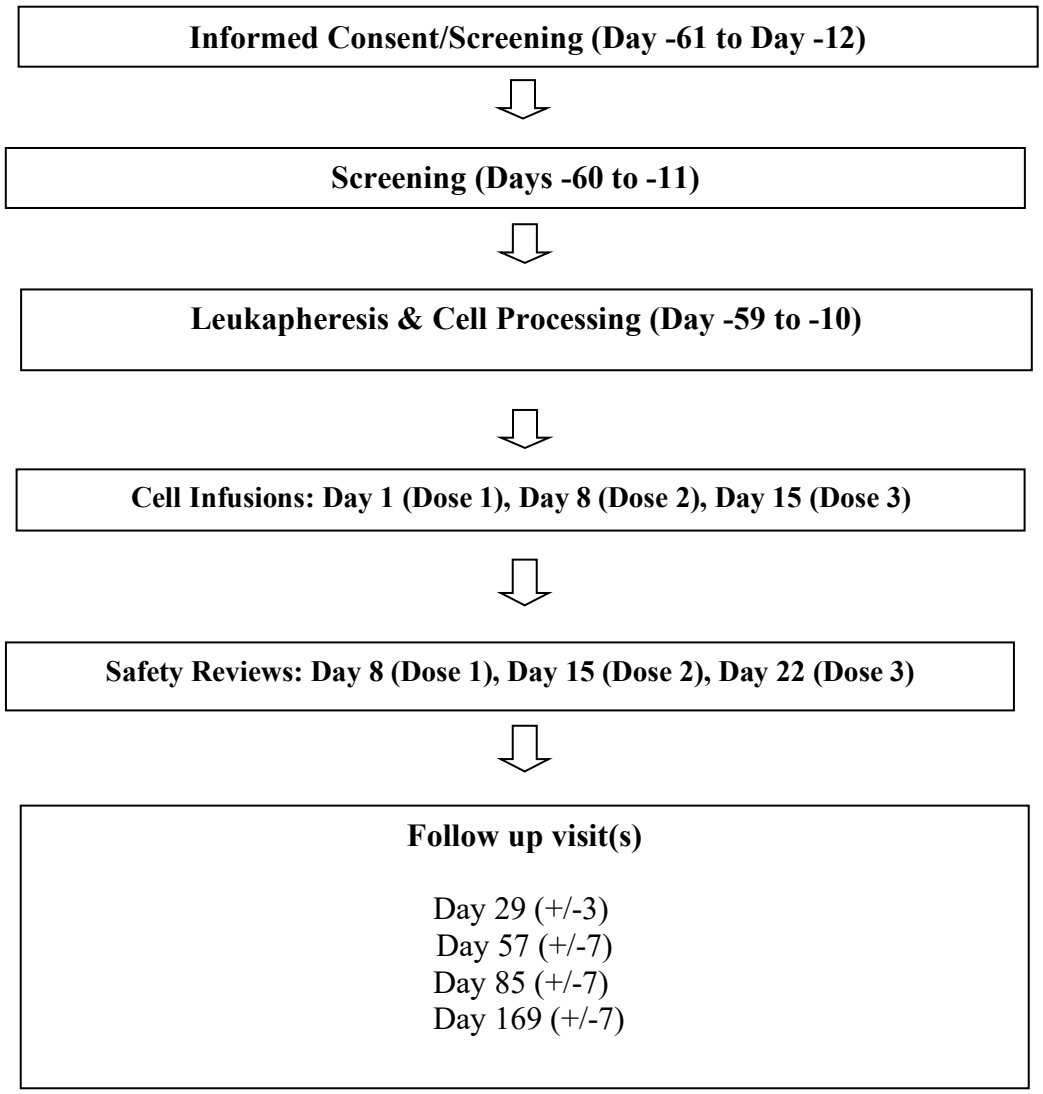
1. Major chronic illness that is not well managed at the time of study entry and in the opinion of the investigator may increase the risk to the patient.
2. Patient is pregnant or lactating.
3. Treatment with IVIg or plasma exchange within 4 weeks prior to the baseline (Day 1) visit.
4. Treatment with rituximab/ocreluzimab or calcineurin inhibitors, e.g., tacrolimus, cyclosporine or cyclophosphamide or Neonatal Fc receptor antagonists, e.g. efgartigimod. Wash-out periods for these agents are 3 weeks before planned leukapheresis and 8 weeks prior to baseline (first infusion) visit.
5. Patient has started treatment with a Complement 5a (C5a) inhibitor, e.g. eculizumab, within 8 weeks of baseline (first infusion) visit. (NOTE: patients who have been receiving a C5a inhibitor for more than 8 weeks and meet other criteria for enrollment are eligible for treatment).
6. Abnormal PT/INR or PTT increased > 1.5-fold at screening or patient is on anticoagulation therapy.
7. ANC < 1000 cells/microliter, Hemoglobin: < 8.0 g/dL, Platelets: < 50,000/mm at screening
8. ALT or AST > 3x above normal, or Creatinine Clearance < 30 mL/min at screening
9. History of primary immunodeficiency, organ, or allogeneic bone marrow transplant.
10. Active Hepatitis B or Hepatitis C, history of positive HIV or positive HIV at screening, active tuberculosis or positive quantiferon test at screening.
11. Any active significant cardiac or pulmonary disease. Note: Patients with asthma and COPD controlled with inhaled medications are allowed.

12. Treatment with any investigational agent within 4 weeks of screening or 5 half-lives of the investigational drug (whichever is longer).
13. Receipt of a live vaccination within 4 weeks prior to baseline (Day 1) visit or intent to receive live vaccination prior to the end of the study (Note: mRNA-based vaccines such as those against SARS-CoV-2 are NOT considered live).
14. History of malignancy that required treatment in the past 3 years except for successfully-treated squamous cell and/or basal cell carcinoma or breast or early colon cancer that is removed and did not require adjuvant chemotherapy or radiotherapy.
15. History of significant recurrent infections or any active infection at screening visit.
16. Any known psychiatric illness that may interfere with the patient's participation in the study in the opinion of the investigator.

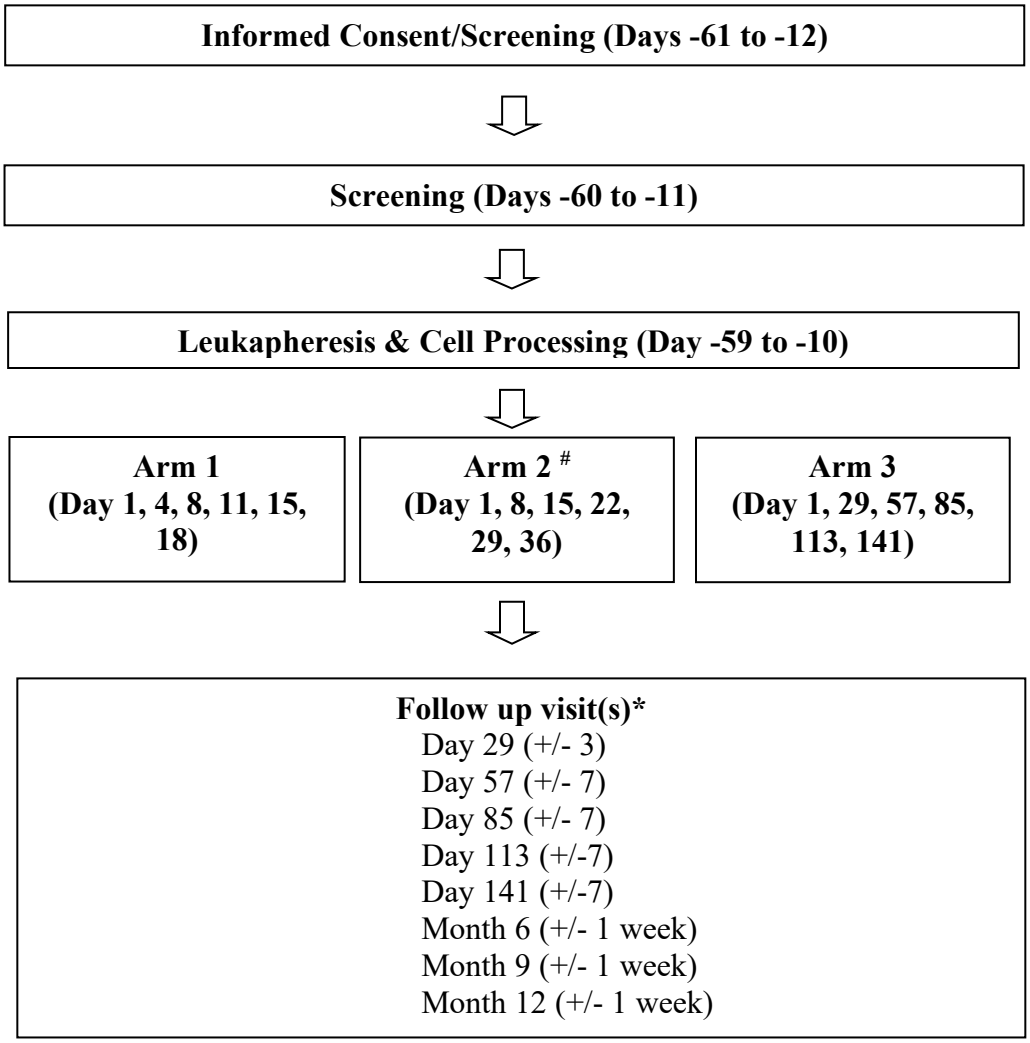
1 STUDY OVERVIEW

1.1 SCHEMA

Part 1



Part 2



* In Arm 2, Day 29 is also a cell infusion day. In Arm 3, Days 29, 57, 85, 113, and 141 are also cell infusion days.

Arm 2 has 2 cohorts: Seropositive and Seronegative

1.2 SCHEDULE OF ACTIVITIES (SOA)

Part 1

Procedures	Screening Visit 1 Day -61 to -12	Screening Visit 2 Day -60 to -11	Study Visit 1 Day -59 to-10	Study Visit 2 Day 1 - Baseline	Study Visit 3[n] Day 8+/- 1	Study Visit 4[n] Day 15+/- 1	Study Visit 5 Day 22+/- 3	Study Visit 6 Day 29+/- 3	Study Visit 7 Day 57 +/-7	Study Visit 8 Day 85 +/- 7	Study Visit 9 Month 6 +/- 1 week
Informed consent	X										
Demographics	X										
Medical history	X										
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
Medication Diary[a]				X	X	X	X	X	X	X	X
Assessment of Veins for Leukapheresis		X									
Leukapheresis			X								
CAR T-Cell Infusion				X	X						
Body Temperature monitoring				X[i]	X[i]	X[i]					
ICE Scale[b]				X	X	X					
Full Physical examination	X			X	X	X	X	X	X	X	X
Vital signs (+ pulse oximetry)	X	X	X	X	X	X	X	X	X	X	X
QMG		X		X	X	X	X	X	X	X	X
MG QoL-15R	X			X	X	X	X	X	X	X	X
MG ADL	X			X	X	X	X	X	X	X	X
MG Composite		X[m]		X	X	X	X	X	X	X	X
MGFA Class		X		X	X	X	X	X	X	X	X
MGFA PIS				X	X	X	X	X	X	X	X
PT/INR, PTT	X										
CBC with differential	X		X[j]	X	X	X	X				X
Serum chemistry [c]	X			X	X	X	X				X
Urinalysis	X			X	X	X	X				X
CRP, Ferritin	X			X	X	X					
Pregnancy test	X[d]			X[k]	X[k]	X[k]	X				

Procedures	Screening Visit 1 Day -61 to -12	Screening Visit 2 Day -60 to -11	Study Visit 1 Day -59 to-10	Study Visit 2 Day 1 - Baseline	Study Visit 3[n] Day 8+/- 1	Study Visit 4[n] Day 15+/- 1	Study Visit 5 Day 22+/- 3	Study Visit 6 Day 29+/- 3	Study Visit 7 Day 57 +/-7	Study Visit 8 Day 85 +/- 7	Study Visit 9 Month 6 +/- 1 week
HIV, Hep B/C, quantiferon	X										
Echocardiogram [e] X											
Lymphocyte subset [f]	X										
Blood samples for exploratory analyses and PK [g]	X			X	X	X	X	X	X	X	X
Immunoglobulins + HAMA [h]	X			X	X	X	X	X	X	X	X
EKG	X			X[l]	X[l]	X[l]	X				X
AE review and evaluation[n]		X	X	X	X	X	X	X	X	X	

a. Patients will record daily use of corticosteroids or approved ISTs starting on the first day of cell infusion. The diary will be reviewed at each visit Starting on Day 8
b. ICE score will be assessed per Section 6. using the requisition form shown in Appendix A.
c. Serum Chemistry includes Glucose, Ca, Mg, Phos, ALP, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, Uric Acid, Cr, ALT, AST, LDH, Amylase.
d. Blood test, only in child-bearing women.
e. If not performed within the past 3 months.
f. Lymphocyte subset includes absolute number and percentages of CD19+, CD4+, CD8+, CD3+, CD16/CD56+ cells in peripheral blood.
g. For details of blood collection see Section 7.4.
h. IgG, IgM, IgA, IgE, and HAMA. For HAMA see Section 7.4 for blood collection details.
i. For the first 22 days, patients will take body temperature every day once in the morning and once in the evening at least 6 hours apart.
j. CBC with differential will be done pre and post leukapheresis.
k. Urine pregnancy test should be performed to rule out pregnancy prior to cell infusion.
l. EKG to be collected before administration of CAR T-cells.
m. MG ADL from Screening Visit 1 can be used to calculate this score unless it was performed more than 12 days from screen visit 1.
n. If a patient experiences Grade 2 AE probably or definitely related to Descartes-08 in previous Dose Level, then they will be admitted for 3 days for inpatient monitoring. See Section 6 for details.

Part 2 *Arm 1*

	Screening Visit 1 Day -61 to Day -12	Screening Day 2 Day -60 to -11	Study Visit 1 Day -59 to -10	Study Visit 2 Day 1- Baseline	Study Visit 3 Day 4	Study Visit 4 Day 8	Study Visit 5 Day 11	Study Visit 6 Day 15	Study Visit 7 Day 18	Study Visit 8 Day 29 +/- 3	Study Visit 9 Day 57 +/-7	Study Visit 10 Day 85 +/- 7	Study Visit 11 Day 113 +/- 7	Study Visit 12 Day 141 +/-7	Study Visit 13 Month 6[j]	Study Visit 14 Month 9[j]	Study Visit 15 Month 12[j]
Informed consent	X																
Demographics	X																
Medical history	X																
Concomitant Medications	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medication Diary[a]				X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of Veins for Leukapheresis		X															
Leukapheresis			X[g]														
CAR T-Cell Infusion[i]				X	X	X	X	X	X								
Full physical examination	X			X		X		X		X	X	X	X	X	X	X	X
Vital signs (with pulse ox)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
QMG		X		X				X		X	X	X	X	X	X	X	X
MG QoL 15R	X			X				X		X	X	X	X	X	X	X	X
MG ADL	X			X				X		X	X	X	X	X	X	X	X
MG COMPOSITE		X		X				X		X	X	X	X	X	X	X	X
MGFA Class		X		X				X		X	X	X	X	X	X	X	X
MGFA Post Intervention Status								X		X	X	X	X	X	X	X	X
PT/INR, PTT	X																
CBC with differential	X			X		X		X									

	Screening Visit 1 Day -61 to Day -12	Screening Day 2 Day -60 to -11	Study Visit 1 Day -59 to -10	Study Visit 2 Day 1- Baseline	Study Visit 3 Day 4	Study Visit 4 Day 8	Study Visit 5 Day 11	Study Visit 6 Day 15	Study Visit 7 Day 18	Study Visit 8 Day 29 +/- 3	Study Visit 9 Day 57 +/-7	Study Visit 10 Day 85 +/- 7	Study Visit 11 Day 113 +/- 7	Study Visit 12 Day 141 +/-7	Study Visit 13 Month 6[i]	Study Visit 14 Month 9[i]	Study Visit 15 Month 12[i]
Serum chemistry[b]	X			X		X		X									
Urinalysis	X			X		X		X									
CRP, Ferritin	X																
Pregnancy test	X[c]			X[h]	X[h]	X[h]	X[h]	X[h]	X[h]								
HIV, Hep B/C, quantiferon	X																
Lymphocyte subset[d]	X																
Blood samples for exploratory analyses[e]	X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Immunoglobulins+ HAMA[f]	X					X		X		X	X	X	X	X	X	X	X
Adverse event review and evaluation		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. Patients will record daily use of corticosteroids or approved ISTs. The diary will be reviewed at each visit Starting on Day 4

b. Serum Chemistry includes Glucose, Ca, Mg, Phos, ALP, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, Uric Acid, Cr, ALT, AST, LDH, Amylase.

c. Blood test, only in child-bearing women.

d. Lymphocyte subset includes absolute number and percentages of CD19+, CD4+, CD8+, CD3+, CD16/CD56+ cells in peripheral blood.

e. For details of blood collection see Section 7.4.

f. IgG, IgM, IgA, IgE, and HAMA. For HAMA see Section 7.4 for blood collection details.

g. Assessments before and after leukapheresis will be performed per institutional policy.

h. Urine pregnancy test should be performed to rule our pregnancy prior to cell infusion.

i. Descartes-08 infusion in Arm 1 is on Days 1,4, 8, 11, 15, 18; Arm 2 on Days 1, 8, 15, 22, 29, 36; Arm 3 on Days 1, 29, 57, 85, 113, 141.

j. Visits can be scheduled +/- 2 weeks of target visit date.

Part 2 *Arm 2*

	Screening Visit 1 Day -61 to Day -12	Screening Day 2 Day -60 to -11	Study Visit 1 Day -59 to -10	Study Visit 2 Day 1- Baseline	Study Visit 3 Day 8	Study Visit 4 Day 15	Study Visit 5 Day 22	Study Visit 6 Day 29 +/- 3	Study Visit 7 Day 36 +/- 3	Study Visit 8 Day 57 +/-7	Study Visit 9 Day 85 +/- 7	Study Visit 10 Day 113 +/- 7	Study Visit 11 Day 141 +/-7	Study Visit 12 Month 6[j]	Study Visit 13 Month 9[j]	Study Visit 14 Month 12[j]
Informed consent	X															
Demographics	X															
Medical history	X															
Concomitant Medications	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Medication Diary[a]				X	X	X	X	X	X	X	X	X	X	X	X	X
Assessment of Veins for Leukapheresis		X														
Leukapheresis			X[g]													
CAR T-Cell Infusion[i]				X	X	X	X	X	X							
Full physical examination	X			X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (with pulse ox)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
QMG		X		X		X		X		X	X	X	X	X	X	X
MG QoL 15R	X			X		X		X		X	X	X	X	X	X	X
MG ADL	X			X		X		X		X	X	X	X	X	X	X
MG COMPOSITE		X		X		X		X		X	X	X	X	X	X	X
MGFA Class		X		X		X		X		X	X	X	X	X	X	X
MGFA Post Intervention Status						X		X		X	X	X	X	X	X	X
PT/INR, PTT	X															

	Screening Visit 1 Day -61 to Day -12	Screening Day 2 Day -60 to -11	Study Visit 1 Day -59 to -10	Study Visit 2 Day 1 - Baseline	Study Visit 3 Day 8	Study Visit 4 Day 15	Study Visit 5 Day 22	Study Visit 6 Day 29 +/- 3	Study Visit 7 Day 36 +/- 3	Study Visit 8 Day 57 +/-7	Study Visit 9 Day 85 +/- 7	Study Visit 10 Day 113 +/- 7	Study Visit 11 Day 141 +/-7	Study Visit 12 Month 6[i]	Study Visit 13 Month 9[i]	Study Visit 14 Month 12[i]
CBC with differential	X			X	X	X	X	X	X							
Serum chemistry[b]	X			X	X	X	X	X	X							
Urinalysis	X			X	X	X	X	X	X							
CRP, Ferritin	X															
Pregnancy test	X[c]			X[h]	X[h]	X[h]	X[h]	X[h]	X[h]							
HIV, Hep B/C, quantiferon	X															
Lymphocyte subset[d]	X															
Blood samples for exploratory analyses[e]	X			X	X	X	X	X	X	X	X	X	X	X	X	X
Immunoglobulins + HAMA[f]	X				X	X		X		X	X	X	X	X	X	X
Adverse event review and evaluation		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. Patients will record daily use of corticosteroids or approved ISTs. The diary will be reviewed at each visit Starting on Day 4
b. Serum Chemistry includes Glucose, Ca, Mg, Phos, ALP, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, Uric Acid, Cr, ALT, AST, LDH, Amylase.
c. Blood test, only in child-bearing women.
d. Lymphocyte subset includes absolute number and percentages of CD19+, CD4+, CD8+, CD3+, CD16/CD56+ cells in peripheral blood.
e. For details of blood collection see Section 7.4.
f. IgG, IgM, IgA, IgE, and HAMA. For HAMA see Section 7.4 for blood collection details.
g. Assessments before and after leukapheresis will be performed per institutional policy..
h. Urine pregnancy test should be performed to rule our pregnancy prior to cell infusion.
i. Descartes-08 infusion in Arm 1 is on Days 1,4, 8, 11, 15, 18; Arm 2 on Days 1, 8, 15, 22, 29, 36; Arm 3 on Days 1, 29, 57, 85, 113, 141.
j. Visits can be scheduled +/- 2 weeks of target visit date.

Part 2 *Arm 3*

	Screening Visit 1 Day -61 to Day -12	Screening Day 2 Day -60 to -11	Study Visit 1 Day -59 to -10	Study Visit 2 Day 1- Baseline	Study Visit 3 Day 29 +/- 3	Study Visit 4 Day 57 +/-7	Study Visit 5 Day 85 +/- 7	Study Visit 6 Day 113 +/- 7	Study Visit 7 Day 141 +/-7	Study Visit 8 Month 6[j]	Study Visit 9 Month 9[j]	Study Visit 10 Month 12[j]
Informed consent	X											
Demographics	X											
Medical history	X											
Concomitant Medications	X	X		X	X	X	X	X	X	X	X	X
Medication Diary[a]				X	X	X	X	X	X	X	X	X
Assessment of Veins for Leukapheresis		X										
Leukapheresis			X[g]									
CAR T-Cell Infusion[i]				X	X	X	X	X	X			
Full physical examination	X			X	X	X	X	X	X	X	X	X
Vital signs (with pulse ox)	X	X		X	X	X	X	X	X	X	X	X
QMG		X		X	X	X	X	X	X	X	X	X
MG QoL 15R	X			X	X	X	X	X	X	X	X	X
MG ADL	X			X	X	X	X	X	X	X	X	X
MG COMPOSITE		X		X	X	X	X	X	X	X	X	X
MGFA Class		X		X	X	X	X	X	X	X	X	X
MGFA Post Intervention Status					X	X	X	X	X	X	X	X
PT/INR, PTT	X											
CBC with differential	X			X	X	X	X	X	X			
Serum chemistry[b]	X			X	X	X	X	X	X			

	Screening Visit 1 Day -61 to Day -12	Screening Day 2 Day -60 to -11	Study Visit 1 Day -59 to -10	Study Visit 2 Day 1- Baseline	Study Visit 3 Day 29 +/- 3	Study Visit 4 Day 57 +/-7	Study Visit 5 Day 85 +/- 7	Study Visit 6 Day 113 +/- 7	Study Visit 7 Day 141 +/-7	Study Visit 8 Month 6[j]	Study Visit 9 Month 9[j]	Study Visit 10 Month 12[j]
Urinalysis	X			X	X	X	X	X	X			
CRP, Ferritin	X											
Pregnancy test	X[c]			X[h]	X[h]	X[h]	X[h]	X[h]	X[h]			
HIV, Hep B/C, quantiferon	X											
Lymphocyte subset[e]	X											
Blood samples for exploratory analyses[e]	X			X	X	X	X	X	X	X	X	X
Immunoglobulins + HAMA[f]	X				X	X	X	X	X	X	X	X
Adverse event review and evaluation		X	X	X	X	X	X	X	X	X	X	X

a. Patients will record daily use of corticosteroids or approved ISTs. The diary will be reviewed at each visit Starting on Day 4
b. Serum Chemistry includes Glucose, Ca, Mg, Phos, ALP, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, Uric Acid, Cr, ALT, AST, LDH, Amylase.
c. Blood test, only in child-bearing women.
d. Lymphocyte subset includes absolute number and percentages of CD19+, CD4+, CD8+, CD3+, CD16/CD56+ cells in peripheral blood.
e. For details of blood collection see Section 7.4.
f. IgG, IgM, IgA, IgE, and HAMA. For HAMA see Section 7.4 for blood collection details.
g. Assessments before and after leukapheresis will be performed per institutional policy.
h. Urine pregnancy test should be performed to rule our pregnancy prior to cell infusion.
i. Descartes-08 infusion in Arm 1 is on Days 1,4, 8, 11, 15, 18; Arm 2 on Days 1, 8, 15, 22, 29, 36; Arm 3 on Days 1, 29, 57, 85, 113, 141.
j. Visits can be scheduled +/- 2 weeks of target visit date.

2 INTRODUCTION AND RATIONALE

2.1 MYASTHENIA GRAVIS

Autoimmune myasthenia gravis (MG) is a disorder of neuromuscular transmission caused by pathogenic autoantibodies that target critical components of the nicotinic acetylcholine receptor (nAChR) or other proteins supporting the receptor's function.[1] Current treatment strategies typically utilize drugs such as prednisone with broad mechanism(s) of action and significant off-target side effects that limit their utility.[2] In addition, about 10% of MG patients do not adequately respond to treatment with currently available drugs and require high-dose prednisone, azathioprine, and mycophenolate mofetil, among others.[3] Patients treated with these medications often have unacceptable side-effects, benefit only from very high doses, and become dependent on repeated rescue therapies such as intravenous immunoglobulin or plasma exchange, requiring frequent hospitalizations. Thus, MG therapies with better efficacy and tolerability are critically needed. Moreover, since shorter-acting therapies such as prednisone are typically associated with more side effects, there is a pressing need for immunomodulatory therapies with a quick onset of action and a more favorable safety profile.

2.1.1 RATIONALE FOR TARGETING B-CELL MATURATION ANTIGEN EXPRESSING CELLS IN MYASTHENIA GRAVIS

Autoimmune MG is the prototypic antibody-mediated disease[1,4], with 85% of GMG and ~40% of ocular MG having disease mediated by high-affinity nAChR or anti- muscle-specific tyrosine kinase (MuSK) antibodies. Of the remaining patients, approximately 30% have low-affinity nAChR or MuSK antibodies requiring high sensitivity radioimmuno and cell-based assays, 7-10% have antibodies that target LRP4, Agrin, or titin, while two thirds are still deemed "seronegative".[5] However, clinical responses seen in these patients after treatment with eculizumab point to as of yet unknown antibodies as mediators of the disease even in seronegative MG.[6] The antibody-driven nature of the disease strongly supports a central role for B-cells and/or plasma cells in the disease process, and has prompted recent efforts to deplete B-cells as a therapeutic approach in MG.[7] Most notable among these is the recent trial of the anti-CD20 monoclonal antibody rituximab in nAChR-antibody-positive GMG. The disappointing results of this trial may reflect the fact that plasma cells and mature plasmablasts – the B-cell-lineage subtypes that are primarily responsible from antibody production - do not express CD20 and are therefore not targeted by rituximab.[4] Our approach, by contrast, is to target B-Cell Maturation antigen (BCMA), also known as CD269 or Tumor Necrosis Factor receptor superfamily member 17 (TNFRSF17), a cell surface protein that is exclusively expressed by only antibody producing B-cells, which are short-lived plasmablasts and long-lived mature plasma cells.[8,9] Elimination of BCMA-expressing cells should reduce the total immunoglobulin pool, lead to a reduction or elimination of all types of autoantibodies that drive MG pathophysiology, and result in clinical benefit. Importantly, BCMA is not expressed on naïve B-cells and most memory B-cells, and therefore targeting this antigen is unlikely to disrupt B-cell homeostasis.[8] These characteristics potentially make BCMA an ideal target in the treatment of MG.

2.1.2 CAR T-CELL TECHNOLOGY

The chimeric antigen receptor (CAR) is a synthetic cell membrane-bound protein with an extracellular antigen-binding domain and an intracellular signaling domain.[10] T-cells engineered to express CAR protein (CAR T-cells) recognize the target cell antigen via the extracellular domain and upon binding become activated through the intracellular domain. An activated CAR T-cell kills the target cell directly. Initial studies testing autologous CAR T-cell therapies have yielded impressive responses in some B-cell malignancies (e.g., ~90% complete response rate in several clinical trials through targeting CD19 in B-cell acute lymphoblastic leukemia) [10].

2.1.3 EXPERIENCE WITH ANTI-BCMA CAR T-CELL CONSTRUCT

The rationale for targeting BCMA positive plasma cells in MG discussed in Section 2.1.1.

BCMA-targeting CAR-T cell therapies have been developed to treat multiple myeloma (MM). The first anti-BCMA CAR construct was developed at NCI[9]. Preclinical studies showed that permanently modified adenovirally- transduced anti-BCMA CAR T-cells produced large amounts of IFN-γ after overnight culture with BCMA-expressing cell lines BCMA-K562 and RPMI8226. Furthermore, when one dose of anti-BCMA CAR T-cells was administered to immunodeficient mice implanted with the human myeloma cell line RPMI8226, tumor eradication was evident in 10/10 animals. Following these remarkable preclinical results, a Phase I dose-escalation trial was initiated at NCI. The trial enrolled MM patients who had relapsed or remained refractory after 3 or more lines of therapy.[11] In the dose-escalation phase, twelve patients were enrolled. Three patients at the two highest dose levels ($3x10^6$ cells/kg and $9x10^6$ cells/kg) achieved significant responses despite their highly- resistant disease. The $9x10^6$ cells/kg dose level was expanded to 16 total patients.[12] Fifteen out of 16 patients achieved very good partial response or better that were durable demonstrating the potency of anti-BCMA CAR T-cells in eliminating BCMA-positive myeloma cells. Based on this unprecedented clinical success of anti-BCMA CAR-T therapy in multiple myeloma, several companies launched clinical trials to test various methods to modify autologous T-cells to express anti-BCMA CAR permanently.

2.2 KNOWN TOXICITIES OF CAR T-CELL THERAPIES

Cytokine-release syndrome (CRS) and neurotoxicity are the most common toxicities that occur after permanently modified CAR T-cell therapy in malignancies.

Cytokine release syndrome: In the recent American Society of Blood and Marrow Transplant (ASBMT) consensus meeting, CRS was defined as “a supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leak (hypoxia) and end-organ dysfunction.”[13] Upon binding of the CAR protein to its target antigen, T-cells become activated and secrete several cytokines that initiate a systemic inflammatory cascade that drives the proliferation and further activation. When T-cells express CAR permanently, this vicious cycle of antigen binding and cytokine secretion drives uncontrolled activation and proliferation of T-cells, resulting in excess cytokines in blood, and leads to a heightened systemic inflammatory response. At first, patients experience malaise, myalgias, and fevers. In more severe cases, these flu-like symptoms are

accompanied by hypotension and hypoxia. Mild forms usually start within 2-3 days and end within 3 weeks while more severe grades are seen earlier, i.e., within 1 day to end within the first 2 weeks.[14] The life-threatening manifestation of CRS is based on cardiac decompensation. The exact mechanism of cardiac decompensation is not clear but appears to be reminiscent of cardiac decompensation that occurs in high-stress conditions like sepsis.[15] Other potentially life-threatening manifestations of CRS are adult respiratory distress syndrome, neurologic toxicity, renal failure, hepatic failure, and disseminated intravascular coagulation. Evidence indicates that IL-6 plays a central role in CRS, and therefore, blockade of IL-6 receptor by tocilizumab is a widely-used treatment to manage severe CRS. Patients refractory to tocilizumab are typically treated with high-dose steroids with the caveat that steroids' lymphotoxic effects may dampen the anti-tumor activity of infused CAR-T-cells.

Several grading systems were developed for CAR T-cell-related CRS with significant differences among them in the criteria for especially Grade 2 vs. Grade 3 toxicity. These grading systems were recently reviewed by 49 experts in an American Society of Blood, and Marrow Transplant (ASBMT) consensus panel and the CRS grading system is shown Table 1 was published as the recommended scale. This protocol will use the ASBMT CRS grading system[13].

Table 1. ASBMT CAR T-cell Related CRS Grading

Grade 1	Grade 2	Grade 3	Grade 4
Fever with or without constitutional symptoms	Fever with hypotension responding to fluids; AND/OR* hypoxia responding to $\leq$ 6L/min nasal cannula	Fever with hypotension managed with one pressor (with or without vasopressin); AND/OR*hypoxia requiring > 6L/min nasal cannula, facemask, nonbreather mask or Venturi mask	Fever with hypotension requiring multiple vasopressors (excluding vasopressin); AND/OR* requiring positive pressure, i.e., CPAP, BiPAP, intubation and mechanical ventilation)

*The score is driven by the most severe event

Neurotoxicity: Neurotoxicity is usually manifested as tremors, varying degrees of encephalopathy and, in severe cases, seizures and increased intracranial pressure.[16,17] Mild forms may be difficult to diagnose because in most cases, neurological symptoms accompany CRS and resolve as the inflammatory state resolves. In rare cases, sudden-onset cerebral edema has been reported which manifests as seizures or severe cognitive impairment and rarely can be fatal.[18] The mechanism of neurotoxicity is not entirely clear but has similarities to the pathophysiology of CRS; for example, the onset of symptoms correlates with cytokine elevations as a result of CAR T-cell activity. Therefore, the delineation between these two adverse events of CAR T-cell treatment can be challenging. Furthermore, CRS itself can cause cognitive impairment, in addition to other neurological symptoms, further complicating the diagnosis. The mechanistic links between systemic inflammation due to CAR T-cell anti-tumor activity and neurotoxicity remain elusive but seem to involve break-down of the blood-brain-barrier. A recent study investigating CAR T-cell-associated neurotoxicity in non-human primates found that an increase in a select number of cytokines in conjunction with an increased number of both CAR and non-CAR expressing T-cells in CSF are two major factors underlying this toxicity.[19] However, the study concluded that these

immune cells infiltrate the brain parenchyma through a complex interplay of various factors, not a single causative factor. Interestingly, CAR T-cell related neurotoxicity in the absence of CRS has been noted in 15-25% of patients[20-31] with anti-CD19 CAR T-cell trials but was observed in much less frequency in anti-BCMA CAR T-cell trials[12,32,33] suggesting that the mechanism of toxicity may be related to the target antigen rather than CAR T-cell activity in general.

Management of neurotoxicity is usually supportive since this adverse event, like CRS, is usually self-limiting and resolves spontaneously within days to weeks.[34,35] On the other hand, in rare cases, when symptoms do not resolve or if the severity of the toxicity is life-threatening, then treatment is mandated, which is guided by the severity of the neurotoxicity. In the recent publication by ASBMT, CAR T-cell-related neurotoxicity grading in clinical trials was also standardized (See Table 2) and will be used for this clinical protocol as well. Assessment of Immune Effector-Cell Associated Encephalopathy (ICE) score is shown in Appendix 1.

Table 2. ASBMT CAR T-cell Related Neurotoxicity Grading

Grade 1	Grade 2	Grade 3	Grade 4
ICE score: 7-9; awakens spontaneously	ICE score: 3-6; AND/OR* Awakens to voice	ICE[aa] score 0-2; awakens only to tactile stimulus; AND/OR* any clinical seizure focal or generalized that resolves rapidly or non-convulsive seizures on EEG that resolve with intervention; AND/OR focal/local edema on neuroimaging	ICE score:0; Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, stupor or coma; AND/OR* life-threatening prolonged seizure (> 5min); AND/OR* repetitive clinical or electrical seizures without return to baseline in between; AND/OR* deep focal motor weakness such as hemiparesis or paraparesis; AND/OR* diffuse cerebral edema on neuroimaging; AND/OR* decerebrate or decorticate posturing; AND/OR*Cranial Nerve VI palsy; AND/OR* Papilledema; AND/OR* Cushing's triad

*The score is driven by the most severe event; [aa] ICE: Immune Effector-Cell Associated Encephalopathy (ICE) score

2.2.1 RATIONALE FOR USING T-CELLS WITH CONTROLLED CAR EXPRESSION

Descartes-08 is an autologous T-cell product transiently expressing a CAR directed against BCMA. Compared to the prevailing CAR T-cell technology, which uses viral DNA transduction (gene transfer), Descartes-08 uses mRNA transfection to create T-cells that only transiently express CAR protein. Descartes-08 is, therefore, a cell therapy, but not gene therapy. In theory, this should limit uncontrolled expansion and proliferation of circulating CAR T-cells and concomitant toxicities such as CRS and neurotoxicity. The use of mRNA-transfected CAR T-cells is also expected to confer dose-linear pharmacokinetics, that is, the number of circulating CAR T-cells should remain proportional to the number of cells infused. This benefit, which cannot be obtained from DNA-transduced CAR T-cells, should provide for more precise dose selection, prevent uncontrolled proliferation, and allow for direct killing of target cells leading to Descartes-

08 cells waning off their CAR expression to undetectable levels over time. [redacted]

Descartes-08 binds BCMA protein and demonstrates robust activation and BCMA-specific, dose- and time-dependent killing of primary patient MM cells and cell lines, even those resistant to immunomodulatory imides (IMiDs). The cytotoxic activity of Descartes-08 is super-stoichiometric, i.e., one Descartes-08 cell can kill more than one MM cell. *In vivo,* nonclinical studies demonstrate a dose-dependent inhibition of tumor growth in a disseminated model of MM.

Cartesian expects to see enhanced clinical benefits of this approach for the treatment of an unmet medical need in MM and autoimmune diseases with reduced adverse effects.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The two well-established risks of CAR T-cell treatment are CRS and neurotoxicity, which are reviewed in Section 2.2.

Descartes-08 is expected to be well tolerated because 1) Descartes-08 expresses CAR transiently, limiting CAR T-cell reactivity with predictable pharmacokinetics; and 2) compared to patients with MM, autoimmune MG patients have substantially fewer plasma cells (i.e., target cells), and reduced target load correlates with lower risk of CRS.[17] Finally, the patients treated at this trial will receive doses of Descartes-08 that are already tested in a sicker patient population, i.e. relapsed refractory multiple myeloma, further reducing the risk of patients enrolled into this trial.

2.3.2 PREFACE TO VERSION 2.0

After treatment of 32 patients with relapsed refractory myeloma and 3 patients with gMG, no SAEs, CRS or neurotoxicity have been seen in patients administered single doses up to $90x10^6$ Descartes-08 cells/kg and cumulative doses up to $300x10^6$ Descartes-08 cells/kg. The dose for Part 2 is $52.5x10^6$ cells/kg per infusion, which was well-tolerated by patients with gMG when given as a single dose. The optimal Descartes-08 administration schedule will be evaluated by testing three different administration schedules. [redacted]

2.3.3 PREFACE TO VERSION 2.1

After treatment of 3 patients with MG and 32 with RRMM, Descartes-08 continues to demonstrate an excellent safety profile. After establishing the highest feasible and safe dose, a Seronegative Cohort was added to Part 2 to further assess effects of Descartes-08 in the full gMG population.

3 OBJECTIVES

The primary objective is to assess the safety, tolerability, and manufacturing feasibility of Descartes-08 in patients with GMG who may also be taking prednisone and other immunosuppressive agents. In Part 1, up to three ascending doses of Descartes-08 will be administered to each of 3 to 6 patients; the patients will be staggered at least 21 days apart and will complete a safety review between each dose. In Part 2, patients will receive up to 6 doses in three different schedules depending on the arm they were enrolled into and will be monitored for up to 1 year to assess the safety and tolerability of a repeated dosing schedule.

The secondary objectives are to:

1. Determine the change from baseline over a period of 24 weeks in the titer of myasthenia specific autoantibody titers, e.g. nicotinic acetylcholine receptor autoantibody (anti-nAChR) or muscle-specific tyrosine kinase autoantibody (anti-MusK or anti-Low-Density-Lipoprotein-Related-Protein4 (anti-LRP4) or anti-AChR cluster antibody and the 4 Immunoglobulin types (IgG, IgM, IgA, IgE) following single or multiple infusions of Descartes-08 in MG auto-antibody seropositive patients;
2. Quantify the clinical effect of single or multiple infusions of Descartes-08 on patients by standard clinical assessment scales (MG-ADL, QMG, MG QoL 15R, MG PIS, MG Composite) over a period of 24 weeks in MG auto-antibody seropositive and seronegative patients together and separately.

The exploratory objectives are to:

1. Evaluate the presence, frequency and titer of anti-mouse human antibody (HAMA) following single or multiple infusions of Descartes-08;
2. Assess standard pharmacokinetic parameters of Descartes-08 in blood following single or multiple infusions by a validated qPCR assay to the CAR construct; and
3. Evaluate biomarkers of safety and efficacy (i.e., serum cytokine levels, serum inflammatory markers, plasma BCMA levels, vaccination (within the past 3 years) titers, and IgG subtypes) following single or multiple infusions of Descartes-08. Patient sera will be assayed for markers of activity including serum BCMA levels, CAR T-cell number in the peripheral blood and a panel of serum cytokines that will at least include IFNγ, IL-6, soluble gp130, soluble IL-6R, TNFα, IL-2, and IL-10. Additional biomarkers and cytokines will be added to the panel based on literature reviews.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is an open-label, multi-center, Phase Ib/IIa study to evaluate the safety and tolerability of Descartes-08, autologous T-cells expressing a CAR directed to BCMA in patients with autoantibody-positive generalized MG. In Part 1, each of 3 patients will receive one dose of Descartes-08 at Dose Level 1; then following observation and satisfactory safety review, one dose of Descartes-08 at Dose Level 2; then finally, following observation and satisfactory safety review, one dose of Descartes-08 at Dose Level 3 (Table 3). These patients will be staggered at least 21 days apart. See Section 4.4 for more detailed dose-escalation rules and means to define the Maximum Tolerated Dose (MTD). In brief, Part 1 will use the following algorithm:

a. If no Descartes-08-related Dose-Limiting Toxicity (DLT) is observed in the first 3 patients, enrollment in Part 1 will be complete, and the MTD will be Dose Level 3. If a patient is withdrawn from Part 1 for reasons other than safety, one or more additional patients must be enrolled to provide 3 completers.

b. If exactly 1 DLT is observed in the first 3 patients, Part 1 will enroll 3 more patients, for a total of 6.

c. At any point that 2 DLTs have been observed, dose escalation will be capped at the Dose Level below which either of the 2 DLTs occurred. For example, if 2 DLTs occur at Dose Level 3, dose escalation will be capped at Dose Level 2. But if DLTs occur at Dose Level 2 and Dose Level 3, dose escalation will be capped at Dose Level 1.

d. In cases where a DLT was observed in Part 1, the MTD will be defined as the highest Dose Level at which *all* patients in Part 1 were dosed for which only 1 DLT was observed. Stated in another way: a safe dose must show a DLT rate of 0 in the first 3 patients, or 1 in all 6 patients of Part 1. A dose that causes, or is above a dose that causes, 2 DLTs will not be deemed safe.

Part 2 of the study will commence once the MTD or Maximum Feasible Dose (MFD) is determined in Part 1. Part 2 of the study will enroll up to 15 additional patients, each of whom can be enrolled into one of 3 treatment arms. Arms are designed based on duration of Descartes-08 activity (max. activity in first 2-3 days which wanes over by Day 7. See Investigator Brochure) and Immunoglobulin G (21 days).

In ***Arm 1,*** Descartes-08 activity will be administered twice a week for 3 weeks to maintain maximal Descartes-08 activity during at least one IgG half-life. A single cohort of 4-5 seropositive patients will be treated in this arm.

In ***Arm 2***, Descartes-08 is administered once a week for at least two IgG half-lives. Two cohorts will be treated in this arm: a Seropositive Cohort (4-5 patients), and a Seronegative Cohort (4-5 patients). Please see Section 5.1 (Inclusion Criteria) for details on cohort eligibility.

In ***Arm 3***, Descartes-08 is administered once in 4 weeks for intermittent Descartes-08 activity over the course of 6 months. A single cohort of 4-5 seropositive patients will be treated in this arm.

Patients screened for Part 2 will be assigned to one of the three Arms at time of enrollment per PI discretion and after Sponsor approval. Regardless of the Arm, each infusion will be dosed up to the MTD ($52.5x10^6$ cells/kg) determined in Part 1.

4.2 JUSTIFICATION FOR DOSE AND SCHEDULE

In Part 1, patients will be treated with dosing schedules outlined in Table 3.

Table 3. Definition of Dose Levels

Dose Level	Dose of Descartes-08*
Level 1	$3.5x10^6$ CAR+ cells/kg
Level 2	$17.5x10^6$ CAR+ cells/kg
Level 3	$52.5x10^6$ CAR+ cells/kg

*Dose is defined as ±45% of intended number of live, CAR+ T-cells per the patient's screening weight in kg.

The safe and appropriate starting dose for this MG study was established clinically in an ongoing Phase I/II trial of Descartes-08 in patients with relapsed/refractory multiple myeloma [redacted]

It is important to note that dose considerations for mRNA-modified CAR-T cells are not identical to those for DNA-modified CAR T-cells. In mRNA-modified cells, CAR expression persists for a limited time, measured in days. Also, because the CAR is encoded by mRNA that cannot replicate, overall CAR production does not increase due to CAR T-cell proliferation. Such uncontrolled proliferation, which is a feature of DNA-modified CAR T-cells, underlies CRS and neurotoxicity. Thus, CAR T-cell activity-related toxicities are expected to be self-limited with Descartes-08.

Three- to five-fold dose escalation between dose levels is customary for ascending dose studies, including studies of CAR-T cells. The maximum dose for any subject has been capped at the calculated dose for a 100 kg patient. Therefore, for Dose Level 3, the maximum dose will be $52.5x10^6$ CAR+ cells/kg x 100 kg = $5.25x10^9$ CAR+ cells per dose. [redacted] o further explore other dosing frequencies, seropositive patients may be treated according to two other treatment schedules: twice weekly (Arm 1) and once monthly (Arm 3). The once weekly schedule used in Part 1 will be investigated as Arm 2 of Part 2 in two separate cohorts of seropositive and seronegative patients.

4.3 DOSE ESCALATION RULES

While Descartes-08 doses of up to $180x10^6$ CAR+ cells/kg have been administered to myeloma patients without any Descartes-08-related AEs to date, out of an abundance of caution, this study employs an intra-patient dose escalation design in Part 1. Under this design, pending observation and satisfactory safety review, each patient will receive increasing doses infused 1 week apart. The first three patients will also be staggered at least 21 days apart. See Table 3 for Dose levels. The first Dose of $3.5x10^6$ CAR+ cells/kg will be administered on Day 1. The second Dose of $17.5x10^6$ CAR+ cells/kg will be administered on Day 8. The third Dose of $52.5x10^6$ CAR+ cells/kg and will be administered on Day 15.

4.4 DOSE ESCALATION STOPPING RULES

In Part 1, the medical monitor will apply the following rules to determine if it is safe to administer the next Dose, or if dose escalation should stop. Pre-specified rules for pausing or stopping the whole study are described in Section 9.4, and rules for individual patient withdrawal are described in Section 8.2.

If no DLT is observed in the first 3 patients, enrollment in Part 1 will be complete, and the MTD will be Dose Level 3. However, if 1 DLT is observed (see Section 9.1.5 for definition) within 7 days after receiving the cells and is probably or definitely related to Descartes-08 in the first 3 patients, Part 1 will enroll 3 more patients. At any point that 2 DLTs have been observed, dose escalation will be capped at the Dose Level below which either of the 2 DLTs occurred. For example, if 2 DLTs occur at Dose Level 3, dose escalation will be capped at Dose Level 2. But if DLTs occur at Dose Level 2 and Dose Level 3, dose escalation will be capped at Dose Level 1. In cases where a DLT was observed in Part 1, the MTD will be defined as the highest Dose Level at which *all* patients in Part 1 were dosed for which only 1 DLT was observed.

If the patient's CAR T-cells are not sufficient to administer the MTD, the patient may, at the medical monitor's sole discretion, receive as many cells as possible up to the MTD.

If it becomes technically impractical to increase the Dose Level due to cell production constraints and an MTD has not been reached, the maximum Dose Level for which at least 3 patients have been treated will be declared the maximum feasible dose (MFD).

5 STUDY POPULATION

The study will enroll subjects who meet all inclusion and none of the exclusion criteria and those subjects who are expected to comply with the protocol.

5.1 INCLUSION CRITERIA

1. Patient must be at least 18 years of age.
2. Patient must have GMG, defined as MGFA clinical classification grade 3 or 4 (Part 1; dose escalation) or grades 2-4 (Part 2; expansion phase) at the time of screening.
3. Concomitant immunosuppressive drugs must be deemed necessary by the investigator.
4. If a patient is using corticosteroids, the daily dose should not exceed 40 mg/day of prednisone equivalent. The dose must have been stable for a minimum of 4 weeks prior to baseline visit.
5. Seropositive Cohort only: Myasthenia Gravis-specific antibody titer must be above the reference laboratory UNL and documented within 10 years of screening.
6. Seronegative Cohort only: Unequivocal response to cholinesterase inhibitors AND abnormal repetitive nerve stimulation or increased jitter (must not have another neuromuscular disease, which may cause increase jitter).
7. Patient must be willing to return for all study visits.
8. Patient must be able to give written informed consent.
9. Women of reproductive potential must agree to use highly effective birth control from screening through 14 days post last dose of Descartes-08. Women of child-bearing potential is defined as female subjects of reproductive potential (women who have reached menarche and who have not been post-menopausal for at least 24 consecutive months, i.e., who have had menses within the preceding 24 months, or have not undergone a sterilization procedure (hysterectomy, tubal ligation or bilateral oophorectomy)).
10. MG-Activities of Daily Living (MG-ADL) total score ≥ 6

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Major chronic illness that is not well managed at the time of study entry and in the opinion of the investigator may increase the risk to the patient.
2. Treatment with IVIg or plasma exchange within 4 weeks prior to the baseline (Day 1) visit.
3. Treatment with rituximab, ocrelizumab or calcineurin inhibitors, e.g. tacrolimus, cyclosporine or cyclophosphamide or Neonatal Fc receptor antagonists within 3 weeks prior to planned leukapheresis and within 8 weeks prior to baseline (first infusion) visit.

4. Initiation of eculizumab treatment within 8 weeks prior to baseline (first infusion visit). (NOTE: patients who have been receiving eculizumab for more than 8 weeks and meet other criteria for enrollment are eligible for treatment on the trial).
5. Sexually active female patients who are of childbearing age who are pregnant based on serum pregnancy test, lactating, 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); intrauterine device; intrauterine hormone-releasing system; bilateral tubal occlusion; and vasectomized partner.) Male patients must agree to effective contraception (e.g., condoms (male or female) with or without a spermicidal agent, diaphragm or cervical cap with spermicide, or Intrauterine device (IUD) from screening through 14 days post last dose of Descartes-08. True heterosexual sexual abstinence is an acceptable form of contraception. Periodic abstinence and withdrawal are not acceptable methods of contraception.
6. Abnormal PT/INR or PTT increased > 1.5-fold or patient is on anticoagulation therapy (except in cases of elevated PTT with documented lupus anticoagulant, or in patients who have been on stable doses of anticoagulation therapy for more than 6 months of VTE diagnosis, which will not be exclusionary unless, in the investigator's opinion, it makes participation in the study unsafe).
7. ANC < 1000 cells/microliter.
8. Hemoglobin < 8.0 g/dL.
9. Platelets < 50,000/mm^3.
10. ALT and/or AST > 3x above normal.
11. Creatine Clearance less than 30mL/min.
12. History of primary immunodeficiency, organ, or allogeneic bone marrow transplant.
13. Patients must be seronegative for hepatitis B surface antigen.
14. Patients must be seronegative for hepatitis C antibody. If hepatitis C antibody test is positive, then patients must be tested for the presence of viremia by RT-PCR and must be HCV RNA negative.
15. History of positive HIV or positive HIV at screening.
16. Active tuberculosis or positive quantiferon test at screening.
17. Any other laboratory abnormality that, in the opinion of the investigator, may jeopardize the subject's ability to participate in the study.
18. Any active significant cardiac or pulmonary disease. Note: Patients with asthma and COPD controlled with inhaled medications are allowed.
19. 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 is surgically removed and did not require adjuvant chemotherapy or radiotherapy.

20. Treatment with any investigational agent within 2 weeks of screening or 5 half-lives of the investigational drug (whichever is longer).
21. Receipt of a live vaccination within 4 weeks prior to baseline (Day 1) or intent to receive live vaccination during the study (Note: mRNA-based vaccines such as those against SARS-CoV-2 are not considered live; likewise, the Janssen Covid-19 vaccine is not live).
22. History of significant recurrent infections or any active infection that may interfere with the patient's participation in the opinion of the investigator.
23. Any known psychiatric illness that may interfere with the patient's participation in the study in the opinion of the investigator.

5.3 SCREEN FAILURES

Trial participation begins with written informed consent. Screen failures are defined as subjects who consent to participate in the clinical trial but are not subsequently administered the open-label study treatment. Patients who fail screening for this study will continue to receive the standard of care for their MG. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demographics, reasons for screen failure, eligibility criteria, and any serious adverse event (SAE). Subjects may be rescreened if the reason for screen failure is acute illness or its consequences.

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Adult patients with anti-nAChR or anti-MuSK positive GMG who have not required more than 40 mg/day prednisone-equivalent for at least the 4 immediately preceding weeks and have not been treated with steroid-sparing immunosuppressive agents other than mycophenolate mofetil, azathioprine, and methotrexate, or who have been treated with a C5a inhibitor (e.g. eculizumab) for more than 8 weeks and remain symptomatic, will be approached for potential participation in this study. The study will be conducted in multiple centers where a significant number of GMG patients are cared for. The study will be registered with clinicaltrials.gov. If recruitment goals are not achieved, the addition of other sites with expertise in MG will be considered. Flyers will be prepared to be sent to community neurologists. Study information will be given to patient organizations, including Myasthenia Gravis Foundation of America, Conquer MG and the Muscular Dystrophy Association. We will obtain a partial HIPAA waiver from the IRB so that the site coordinator or investigator(s) may contact potential participants.

Patients who have completed the protocol and have remaining cells are allowed to reconsent into the current protocol version provided that they continue to meet eligibility criteria. Rescreening for such patients is not necessary if less than 45 days have elapsed since screening assessments were performed.

5.5 IMMUNOSUPPRESSION FOR MYASTHENIA GRAVIS TREATMENT

Because corticosteroids may significantly inhibit T-cell function, patients will be allowed to be on a maximum stable dose of 40 mg prednisone equivalent daily. Prednisone dose and justification

for dose–modification will be recorded at every study visit. Azathioprine, Mycophenolate Mofetil, and Methotrexate are permitted during the study, as are C5a inhibitors (e.g. eculizumab) started more than 8 weeks prior to baseline visit; but other immunosuppressive drugs are not permitted during the study.

Eculizumab, a complement inhibitor that targets complement C5, has recently been approved by the US FDA for treatment of gMG. In the registration trial, all responding patients achieved their maximum response per QMG score by week 8 of treatment, after more than 3 years of median follow-up.[45] Patients who have been treated with eculizumab for at least 8 weeks and still meet criteria for enrollment are therefore eligible for treatment with Descartes-08, and may continue receiving eculizumab while on trial.

Rituximab, ocrelizumab or other biologics (including Neonatal Fc receptor antagonists) that may result in immunomodulation are not permitted during the study. Washout period for all biological agents is 3 weeks prior to apheresis and 8 weeks prior to infusion.

Patients will be asked to keep a log of their steroid, other immunosuppressive and pyridostigmine use starting on Day 1 until they are off-study.

IVIg and Plasma exchange are not permitted from 4 weeks prior to the baseline (Day 1) visit until completion of the study. Patients who receive these rescue therapies will not be given further doses of the investigational product and will be taken off study, provided that other criteria for study withdrawal are met (see Section 8.2). The proportion of patients who need rescue therapy and the number and type of therapies will be reported at the end of the study.

6 STUDY PROCEDURES

This section explains the clinical and laboratory tests that will be performed in each study visit. See Section 1.2 for study visit schedule. Please contact Sponsor for clarification in the event of conflict between Section 6 and Section 1.2.

6.1 SCREENING

Screening is split into at least two days since patients need to hold their long-acting acetylcholine esterase inhibitor for 24 hours and short-acting acetylcholine esterase inhibitor for 12 hours prior to collection of the clinical scales. On the first day of screening, the following assessments and laboratory tests will be performed:

- Informed consent
- Demographics, medical history
- Documentation of Myasthenia Gravis-specific autoantibody titers (record within 10 years of screening is accepted)
- Vaccination history from past 3 years (documentation of vaccination date if possible or else patient's own history is sufficient)
- Concomitant medications
- Vital signs (including pulse oximetry)
- Full physical examination
- PT/INR, PTT
- CRP, Ferritin
- CBC with differential (should include lymphocyte and neutrophil count, platelet count)
- Serum chemistry: Glucose, Ca, Mg, Phos, ALP, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, uric acid, Cr, ALT, AST, LDH, amylase
- Urinalysis
- Serum β-hCG in women of child-bearing age
- Anti-HIV antibody, anti-Hepatitis B antibody, Hepatitis B antigen, Hepatitis C Antibody, Hepatitis C RNA, QuantiFERON
- Echocardiogram if not performed within the past 3 months (not required in Part 2)
- Lymphocyte subset (should include absolute number and percentages of CD19+, CD4+, CD8+, CD3+, CD16/CD56+ cells in peripheral blood)
- Immunoglobulins (IgG, IgM, IgA and IgE and HAMA). For HAMA see Section 7.4 for details.
- Blood samples for exploratory analyses (See Section 7.4 for details)
- Electrocardiogram (not required in Part 2)
- MG QoL 15R

- MG ADL

Patient will come for visit 2 to complete the following scales after holding long-acting acetylcholine esterase inhibitor for at least 24 hours and short-acting acetylcholine esterase inhibitor for at least 12 hours:

- Concomitant medications
- Adverse event review and evaluation
- Vital signs (including pulse oximetry)
- QMG
- MG Composite
- MGFA Class
- Assessment of peripheral veins for suitability for leukapheresis

NOTE: Screening visits 1 and 2 may be performed on the same day, provided that the patient has held their long-acting acetylcholine esterase inhibitor for at least 24 hours or a short-acting acetylcholine esterase inhibitor for at least 12 hours prior.

6.2 LEUKAPHERESIS

Before leukapheresis, the following assessments should be completed:

- Vital signs (including pulse oximetry)
- Concomitant medications
- CBC with differential (should include lymphocyte and neutrophil count, platelet count)

After leukapheresis, the following assessments should be completed:

- Adverse event review and evaluation
- CBC with differential (Pre and Post leukapheresis)

For patients enrolled to Part 2 of the study, assessments before and after leukapheresis should be done according to institutional policies and are not required to follow the above schedule.

6.3 DAY 1 DESCARTES-08 INFUSION

For Both Part 1 and Part 2: On Day 1, the first Descartes-08 infusion will be administered. The following assessments should be completed before the infusion of the investigational product:

- Vital signs (including pulse oximetry)
- Adverse event evaluation
- Concomitant medications
- ICE score (serves as baseline for subsequent monitoring) – Only Part 1
- CBC with differential (should include lymphocyte and neutrophil count, platelet count)
- Serum chemistry: Glucose, Ca, Mg, Phos, ALP, Albumin, Total protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, uric acid, Cr, ALT, AST, LDH, amylase

- Urinalysis
- Urine pregnancy test in women of child-bearing age
- Electrocardiogram (Only for Part 1)
- QMG QoL 15R
- QMG
- MG ADL
- MG Composite
- MGFA Class
- Medication Diary

After Descartes-08 infusion, the following assessments should be completed:

- Vital signs (See Section 7.1.2.4 for details)

6.4 BLOOD SAMPLES FOR PK (SEE SECTION 7.4 FOR DETAILS) DAY 4 (ONLY IN PART 2)

In Part 2 ***Arm 1*****,** Day 4 is the second Descartes-08 infusion day, and the following assessments should be completed before the infusion of Descartes-08:

- Vital signs (including pulse oximetry)
- Concomitant medications
- Adverse event evaluation
- Review Medication Diaries
- Urine pregnancy test in women of child-bearing age

After Descartes-08 infusion following assessments should be completed:

- Vital signs (See Section 7.1.2.4 for details)

6.5 DAY 8

In Part 1, Day 8 is the primary safety visit and second Dose infusion day, and the following assessments should be completed before the infusion of Descartes-08:

- Vital signs (including pulse oximetry)
- Full physical examination
- ICE Score
- Concomitant medications
- Adverse event evaluation
- Review Temperature log and Medication Diaries
- CBC with differential (should include lymphocyte and neutrophil count, platelet count)

- CRP, Ferritin
- Serum chemistry: Glucose, Ca, Mg, Phos, ALP, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, uric acid, Cr, ALT, AST, LDH, amylase
- Urinalysis
- Urine pregnancy test in women of child-bearing age
- Immunoglobulins (IgG, IgM, IgA, IgE, and HAMA (see Section 7.4 for HAMA detail)
- Research Blood (See Section 7.4 for details)
- Electrocardiogram
- MG QoL 15R
- QMG
- MG Composite
- MG ADL
- MGFA Class
- MGFA Post-intervention Status

In Part 2 *Arm 1* and *Arm 2*, Day 8 is the third and second Descartes-08 infusion days, respectively, and the following assessments should be completed before the infusion of Descartes-08:

- Vital signs (including pulse oximetry)
- Concomitant medications
- Adverse event evaluation
- Review Medication Diaries
- CBC with differential (should include lymphocyte and neutrophil count, platelet count)
- Serum chemistry: Glucose, Ca, Mg, Phos, ALP, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, uric acid, Cr, ALT, AST, LDH, amylase
- Urinalysis
- Urine pregnancy test in women of child-bearing age
- Research Blood (See Section 7.4 for details)

For both Parts, after Descartes-08 infusion, the following assessments should be completed:

- Vital signs (See Section 7.1.2.4 for details)

6.6 DAY 11 (ONLY IN PART 2)

In Part 2 *Arm 1*, Day 11 is the fourth Descartes-08 infusion day, and the following assessments should be completed before infusion of Descartes-08:

- Vital signs (including pulse oximetry)
- Concomitant medications
- Adverse event evaluation

- Review Medication Diaries
- Urine pregnancy test in women of child-bearing age

After Descartes-08 infusion following assessments should be completed:

- Vital signs (See Section 7.1.2.4 for details)

6.7 DAY 15

In Part 1, Day 15 is a safety monitoring visit and third Descartes-08 infusion day, and the following assessments should be completed before infusion of Descartes-08:

- Vital signs (including pulse oximetry)
- Concomitant medications
- Adverse event evaluation
- Review Temperature Log and Medication Diaries
- Full physical examination
- Immune Effector-Cell Associated Encephalopathy ICE score
- CBC with differential (should include lymphocyte and neutrophil count, platelet count)
- Serum chemistry: Glucose, Ca, Mg, Phos, ALP, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, uric acid, Cr, ALT, AST, LDH, amylase
- CRP, Ferritin
- Urinalysis
- Urine pregnancy test in women of child-bearing age
- Research Blood (See Section 7.4 for details)
- Electrocardiogram
- MG QoL 15RQMG
- MG Composite
- MG ADL
- MGFA Class
- MGFA Post-intervention Status

In Part 2 ***Arm 1*** **and** ***Arm 2,*** Day 15 is the fifth and third Descartes-08 infusion days, respectively, and the following assessments should be completed before the infusion of Descartes-08:

- Vital signs
- Concomitant medications
- Adverse event evaluation
- Medication Diaries
- CBC with differential (should include lymphocyte and neutrophil count, platelet count)

- Serum chemistry: Glucose, Ca, Mg, Phos, ALP, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, uric acid, Cr, ALT, AST, LDH, amylase
- Urinalysis
- Urine pregnancy test in women of child-bearing age
- MG QoL 15R
- MG ADL
- QMG
- MG Composite
- MGFA Class
- MGFA Post-intervention Status

For both Parts, after Descartes-08 infusion following assessments should be completed:

- Vital signs (See Section 7.1.2.4 for details)

6.8 DAY 18 (ONLY IN PART 2)

In Part 2 ***Arm 1*** on Day 18, the sixth Descartes-08 infusion will be administered, and the following assessments should be completed before the infusion of Descartes-08:

- Vital signs (including pulse oximetry)
- Concomitant medications
- Adverse event evaluation
- Review Temperature log and Medication Diaries
- Urine pregnancy test in women of child-bearing age

After Descartes-08 infusion following assessments should be completed:

6.9 VITAL SIGNS (SEE SECTION 7.1.2.4 FOR DETAILS) DAY 22

In Part 1, Day 22 is a safety monitoring visit, and following assessments should be completed:

- Vital signs (including pulse oximetry)
- Concomitant medications
- Adverse event evaluation
- Review Temperature Log and Medication Diaries
- Full physical examination
- CBC with differential (should include lymphocyte and neutrophil count, platelet count)
- Serum chemistry: Glucose, Ca, Mg, Phos, ALP, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, uric acid, Cr, ALT, AST, LDH, amylase
- Urinalysis
- Urine pregnancy test in women of child-bearing age

- Research Blood (See Section 7.4 for details)
- Immune Effector-Cell Associated Encephalopathy ICE Scale
- Electrocardiogram

In Part 2 ***Arm 2*** Day 22 is the fourth Descartes-08 infusion days, respectively, and the following assessments should be completed before the infusion of Descartes-08:

- Vital signs
- Concomitant medications
- Adverse event evaluation
- Medication Diaries
- CBC with differential (should include lymphocyte and neutrophil count, platelet count)
- Serum chemistry: Glucose, Ca, Mg, Phos, ALP, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, uric acid, Cr, ALT, AST, LDH, amylase
- Urinalysis
- Urine pregnancy test in women of child-bearing age

For both Parts, after Descartes-08 infusion following assessments should be completed:

- Vital signs (See Section 7.1.2.4 for details)

6.10 DAY(S) 29, 57, 85

In Part 1 and Part 2 ***Arm 1*****,** Day(s) 29, 57, 85 are monitoring visits, and the following assessments should be completed:

- Vital signs (including pulse oximetry)
- Full physical examination
- Concomitant medications
- Adverse event evaluation
- Medication Diaries
- Immunoglobulins (IgG, IgM, IgA, IgE, and HAMA) (For HAMA see Section 7.4 for details)
- Research Blood (See Section 7.4 for details)
- MG QoL 15R
- QMG
- MG ADL
- MG Composite
- MGFA Class
- MGFA Post-intervention Status

In Part 2 *Arm 2* on Day 29 and *Arm 3* on **Days 29, 57, 85**, there is Descartes-08 infusion, and the following assessments should be completed:

- CBC with differential (should include lymphocyte and neutrophil count, platelet count)
- Serum chemistry: Glucose, Ca, Mg, Phos, ALP, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, uric acid, Cr, ALT, AST, LDH, amylase
- Urinalysis
- Immunoglobulins (IgG, IgM, IgA, IgE, and HAMA) (For HAMA see Section 7.4 for details)
- Research Blood (See Section 7.4 for details)
- MG QoL 15R
- QMG
- MG ADL
- MG Composite
- MGFA Class
- MGFA Post-intervention Status

6.11 DAY 36 (ONLY IN PART 2)

In Part 2 *Arm 2* on Day 36, sixth Descartes-08 infusion will be administered, and the following assessments should be completed before the infusion of Descartes-08:

- Vital signs (including pulse oximetry)
- Concomitant medications
- Adverse event evaluation
- Medication Diaries
- Urine pregnancy test in women of child-bearing age
- CBC with differential (should include lymphocyte and neutrophil count, platelet count)
- Serum chemistry: Glucose, Ca, Mg, Phos, ALP, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, uric acid, Cr, ALT, AST, LDH, amylase
- Urinalysis
- Immunoglobulins (IgG, IgM, IgA, IgE, and HAMA) (For HAMA see Section 7.4 for details)
- Research Blood (See Section 7.4 for details)

After Descartes-08 infusion following assessments should be completed:

- Vital signs (See Section 7.1.2.4 for details)

6.12 DAY 113 AND 141 (ONLY IN PART 2 ARM 3)

In Part 2 ***Arm(s) 1 and 2*** Day(s) 113 and 141 are monitoring visits, and the following assessments should be completed:

- Vital signs (including pulse oximetry)
- Full physical examination
- Concomitant medications
- Adverse event evaluation
- Medication Diaries
- Immunoglobulins (IgG, IgM, IgA, IgE, and HAMA) (For HAMA see Section 7.4 for details)
- Research Blood (See Section 7.4 for details)
- MG QoL 15R
- QMG
- MG ADL
- MG Composite
- MGFA Class
- MGFA Post-intervention Status

In Part 2 ***Arm 3*****,** Days 113 and 141 are Descartes-08 infusion visits, and the following assessments should be completed:

- Vital signs (including pulse oximetry)
- Full physical examination
- Concomitant medications
- Adverse event evaluation
- Medication Diaries
- CBC with differential (should include lymphocyte and neutrophil count, platelet count)
- Serum chemistry: Glucose, Ca, Mg, Phos, ALP, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, uric acid, Cr, ALT, AST, LDH, amylase
- Urinalysis
- Immunoglobulins (IgG, IgM, IgA, IgE, and HAMA) (For HAMA see Section 7.4 for details)
- Research Blood (See Section 7.4 for details)
- MG QoL 15R
- QMG
- MG ADL
- MG Composite

- MGFA Class
- MGFA Post-intervention Status

6.13 MONTH(S) 6, 9, 12

In Part 1: Month 6 is end of study visit, and the following assessments should be completed:

- Vital signs (including pulse oximetry)
- Full physical examination
- Concomitant medications
- Adverse event evaluation
- Medication Diaries
- CBC with differential (should include lymphocyte and neutrophil count, platelet count)
- Serum chemistry: Glucose, Ca, Mg, Phos, ALP, Albumin, Total Protein, Total Bilirubin, K, Na, Cl, HCO3, BUN, uric acid, Cr, ALT, AST, LDH, amylase
- PT/INR, PTT
- Urinalysis
- Immunoglobulins (IgG, IgM, IgA, IgE, and HAMA) (See Section 7.4 for details)
- Research Blood (See Section 7.4 for details)
- Electrocardiogram
- MG QoL 15R
- QMG
- MG ADL
- MG Composite
- MGFA Class
- MGFA Post-intervention Status

In Part 2, Month(s) 6, 9 and 12 are long-term monitoring visits, and the following assessments should be completed:

- Vital signs (including pulse oximetry)
- Full physical examination
- Concomitant medications
- Adverse event evaluation
- Medication Diaries
- Immunoglobulins (IgG, IgM, IgA, IgE, and HAMA) (For HAMA see Section 7.4 for details)
- Research Blood (See Section 7.4 for details)
- MG QoL 15R

- QMG
- MG ADL
- MG Composite
- MGFA Class
- MGFA Post-intervention Status

7 STUDY INTERVENTION

7.1 STUDY INTERVENTION(S) ADMINISTRATION

7.1.1 STUDY INTERVENTION DESCRIPTION

Descartes-08 is an autologous T-cell product modified to transiently express a CAR for BCMA. The study drug will be manufactured by Cartesian Therapeutics, Inc. Please see the Investigator's Brochure for more details about the product components and the preclinical data.

7.1.2 DOSING AND ADMINISTRATION

7.1.2.1 LEUKAPHARESIS

At least 10 days prior to infusion of Descartes-08, subjects will undergo leukapheresis at the study site according to institutional standard operation procedures. A peripheral or central line will be placed prior to leukapheresis. To minimize patient discomfort, a peripheral line is preferable. A pre-procedure complete blood count analysis will be performed. Up to 15L of blood volume will be processed to collect PBMCs that will be used for Descartes-08 manufacturing. Apheresis blood volume will be determined by the Sponsor based on the peripheral blood cell counts during the Screening visit. [redacted]atients will be observed for 1 hour and will be discharged if the investigator at the site determines that it is safe. A post-procedure complete blood analysis will be performed. The apheresis product will be packaged and shipped to a central manufacturing site [redacted] Since this is an autologous product, strict rules for cross-verification of the product identity need to be followed. Refer to "Product Tracking and Segregation at Clinical Sites" manual for instructions for labeling the apheresis product with non-personal patient identifiers.

7.1.2.2 ADMINISTRATION

Descartes-08 cells will be prepared at a central manufacturing facility and shipped overnight to the clinical site. Cells will be shipped to arrive no later than Day 1. Upon receipt at the clinical site, the cells should be logged-in and stored in a secured freezer at -70 to -90 ^{0}C until Day 1. **On the day of infusion before thawing the Descartes-08 vials, staff should verify that the patient identifiers shown on the vial-labels positively match the intended patient.** Detailed instructions for thawing the cells and preparing for administration are written in the manual titled "Descartes-08 Myasthenia Gravis Clinic Storage, Handling and Administration"**.**

Prior to each infusion, patients must meet the following criteria:

1. Temperature is less than 37.9ºC;
2. There are no signs of an active infection;
3. No investigational treatment-related ongoing AEs above Grade 2;
4. No evidence of ongoing or impending MG crisis or severe exacerbation;
5. There has been a minimum of 12 hours since the last dose of any immunosuppressive medication including corticosteroids; and

6. No IVIG or plasma exchange in the past 4 weeks.

Pre-medication for the cell infusion will be given approximately 30 minutes prior to infusion. The pre-medications are acetaminophen 500-1000 mg orally and diphenhydramine 25-50 mg intravenously or by mouth. Prior to infusion, the cell product identity label is double-checked by two authorized staff (MD or RN), and identification of the product and documentation of administration are entered in the research record as is done for blood banking protocols**.** Please see detailed infusion instructions in the manual "Descartes-08 Myasthenia Gravis Clinic Storage, Handling and Administration".

7.1.2.3 DELAY OF CELL INFUSION

Patients who do not meet the pre-infusion criteria outlined in Section 7.1.2.2 will have their infusion schedule delayed up to 4 weeks unless in the documented opinion of the medical monitor it is reasonable to proceed. During this period, patients will be assessed as frequently as needed based on the medical condition, and the investigator will decide whether the patient meets the criteria for cell infusion. Cell infusion can also be delayed up to 4 weeks based on PI discretion. After 4 weeks of delay, the patient will be taken off-therapy. See Section 8.2 for off-study criteria.

In Part 2, infusions can be given +/- 3 days due to scheduling or holidays.

7.1.2.4 POST-INFUSION OBSERVATION

Emergency medical equipment (i.e., emergency trolley) will be available during the infusion in case the subject has an allergic response, severe hypotensive crisis, or any other reaction to the infusion. Vital signs (temperature, respiration rate, pulse, blood pressure and oxygen saturation by pulse oximetry) will be measured pre-infusion, within 10 minutes after completing the infusion, then every 30 minutes (±15 minutes) for 1 hour for a total of 4 recordings. Following the 1-hour mandatory observation, the investigator will decide whether it is safe to discharge the patient. If the vital signs are not satisfactory and not stable 1-hour post-infusion, vital signs will continue to be monitored at a minimum of every hour (+/- 15 minutes) or as clinically indicated until stable. If necessary, acetaminophen and diphenhydramine may be repeated every six hours as needed. A short course of non-steroidal anti-inflammatory medication may be prescribed if the patient has fever not relieved by acetaminophen.

7.1.2.5 SAFETY MONITORING PERIOD

In Part 1, safety monitoring period starts with Day 1 and ends at Day 22 with safety review visit. During this period patients will need to remain within 60-minute driving distance to the clinic. In Part 2, safety reviews will be conducted on the day of infusions. **Unscheduled** follow-up assessments due to suspected direct drug-related toxicities should include vital signs and a focused physical exam. At a minimum, cardiovascular status, pulmonary examination, and an assessment of the subjects' targeted neurological examination (including mental status, cranial nerve and motor examination abnormalities related to MG) should be performed. See Section Lab Manual for blood collection if treatment-related CRS or neurotoxicity is suspected.

7.1.2.6 MANAGEMENT OF EXPECTED TOXICITIES

For CAR T-cells, significant toxicities, if any, typically occur within one week of administration and include infusion reactions, CRS, and neurotoxicity. Since Descartes-08 cells express CAR transiently, any potential toxicities are expected to rapidly resolve as the CAR T-cell population naturally diminishes.

The guidelines below to manage these toxicities are recommendations only and can be tailored to individual patient's needs based on the judgment of the investigator. Not following these recommendations precisely will not be considered a protocol deviation.

7.1.2.6.1 FEBRILE REACTION

Within 7 days after each Descartes-08 infusion, fevers greater than 37.9°C will be assessed by the clinician and should be admitted for observation. If a patient is admitted for fever it is recommended to perform the procedures listed below and these recommendations can be modified based on PI's discretion and/or medical necessity:

a. Infectious disease work-up with blood cultures should be initiated each time CRS is suspected. Empiric broad-spectrum intravenous antibiotics are recommended.

b. Vital signs should be checked at least every 4 hours with strict urine input and output monitoring.

c. Patients with poor oral intake should be started on intravenous fluids. Patients with 80% of their baseline systolic blood pressure (or if systolic BP<90mmHg) should be given a 0.5-1L fluid bolus. Fluid boluses can be repeated as needed; however, they should be kept to a minimum with a low threshold for fluid overload.

d. Patients should be transferred to the Intensive Care Unit (ICU) if:
   I. the patient's systolic pressure does not respond to the first fluid bolus;
   II. the patient requires 2 or more fluid boluses within 24 hours;
   III. the patient's heart rate remains above 125/min for at least 4 hours;
   IV. the patient's supplemental oxygen requirement is more than 40% FiO2; or
   V. the patient has >Grade 2 neurotoxicity.

If patient is suspected to have CRS, please see Section 7.1.2.6.4 for treatment recommendations.

To treat ordinary fever, a dose of > 500 mg acetaminophen is recommended, and cooling blankets may be given if fever is greater than 40°C. NSAIDs should only be prescribed if acetaminophen fails to treat the fever as they may cause gastritis, hemorrhage, and renal failure. If a contaminated CAR T-cell product is suspected, the product will be retested for sterility using archived samples that are stored in the central manufacturing facility.

7.1.2.6.2 INFUSION REACTION

Infusion-related reactions that occur during or within 24 hours following infusion are reported in **less than 10% of the patients who receive traditional CAR T-cell products,** and most of the episodes were recorded as Grade 1 with a few reported as Grade 2 reactions[37]. The most frequently reported adverse events are nausea and taste disturbance (most likely due to the cryoprotectant[37], DMSO and usually do not require any medical intervention. Oral ondansetron or prochlorperazine can be given for mild to moderate nausea. Additional doses of diphenhydramine and acetaminophen (if the patient does not have > Grade 2 transaminitis) can be administered for mild to moderate infusion-related chills, itching, rash.

7.1.2.6.3 ALLERGIC REACTIONS

Infusion-related allergic reactions should not occur frequently since Descartes-08 is an autologous cell product. Although highly unlikely, anaphylaxis has been reported in one patient and therefore, an emergency cart should be present in the area where the patient receives the infusion. The local clinical research center standard protocol for the management of anaphylaxis should be utilized. In addition, the serum should be collected in the first 2 hours of the reaction to measure tryptase levels to confirm diagnosis while a minimum of two 3 ml-aliquots of this serum should be frozen for future analysis.

7.1.2.6.4 CYTOKINE RELEASE SYNDROME

The grading system for CRS and neurotoxicity developed by ASBMT (See Table 1**,** Section 2.2 for the grading) will be used to grade these two treatment-related toxicities. The first sign of CRS is usually fever. Any fever that is above 37.9^0C should be assessed by the investigator or designee, and all patients with a suspicion of CRS should be hospitalized. All patients with Grade 3 and 4 CRS should receive tocilizumab at a dose of 8 mg/kg (max 800 mg) infused over 1 hour and can be repeated if symptoms do not resolve within 24 hours. For patients having Grade 2 CRS, tocilizumab should be given only when the patient is not responding to supportive treatment based on the judgement of the principal investigator.

In patients refractory to tocilizumab, methyl-prednisolone 1-2mg/kg/day is recommended until symptom resolution. For an explanation of blood collection for measurement of cytokines during CRS is explained in detail in Laboratory Manual.

7.1.2.6.5 NEUROTOXICITY

Like CRS, neurotoxicity is reported to be mediated by IL-6 elevation in the CNS fluid[38]. However, tocilizumab is not expected to cross the blood-brain barrier and therefore has no role in the management of this complication. For Grade 3 and 4 neurotoxicity, typically dexamethasone 0.5 mg/kg, is given every 6-8 hours until toxicities are improved to Grade 1 or less.

7.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

7.2.1 ACQUISITION AND ACCOUNTABILITY

Autologous Descartes-08 cells will be manufactured at a central facility, a sample of the final product will be analyzed, and the product will only be released only if it meets the pre-specified

criteria for its quality. Upon release, cell product will be shipped overnight to the clinical site on dry ice using a designated courier to arrive no later than Day 1. Upon receipt at the clinical site, the non-personal patient identifiers will be used to verify the identity of the product. Please see "Product Tracking and Segregation at Clinical Sites" manual for detailed instructions on label cross-verification. The product than is logged and stored in a secured freezer at -70 to -90 degrees C until Day 1.

7.2.2 PREPARATION

On the day of infusion before thawing the Descartes-08, it should be verified that the patient identifiers shown on the product labels positively match the intended patient. Product is thawed and prepared for infusion following the "Descartes-08 Myasthenia Gravis Clinic Storage, Handling and Administration". Thawed cells should be infused as quickly as possible; infusion should be completed before the expiration time.

7.2.3 RETURN OR DESTRUCTION OF STUDY DRUG

Descartes-08 cells may require a return to the central manufacturing facility for a variety of reasons, including but not limited to 1) condition of patient prohibits infusion/injection or 2) subject refuses infusion/injection. Sponsor will perform ongoing reconciliation of drug shipped, drug consumed, and drug remaining. Once the patient completes all intended infusions, remaining unused drug product will be shipped to the Sponsor.

7.3 CONCOMITANT THERAPY

7.3.1 IMMUNOSUPPRESSION FOR MYASTHENIA GRAVIS

Patients will be asked to hold their steroid medication for a minimum of 12 hours prior to Descartes-08 infusion and for a minimum of 12 hours following the infusion. If a patient is on mycophenolate mofetil, azathioprine or methotrexate, their dose should be held from a minimum of 12 hours pre-infusion to a minimum of 12 hours post-infusion. If a patient is on eculizumab, the dose should not be administered for at least 24 hours before and 48 hours after the infusion. In both parts of the study, the dose of corticosteroids or steroid-sparing agents should not be changed for the first 28 days unless medically necessary. The dose of corticosteroids and steroid-sparing immunomodulatory agents will be recorded by the patient using a daily log.

7.3.2 ACETYLCHOLINE ESTERASE INHIBITORS

Patients who are on symptomatic therapy with pyridostigmine will be asked to hold their long-acting acetylcholine esterase inhibitor for at least 24 hours and short-acting acetylcholine esterase inhibitor for at least 12 hours before follow-up visits when MG clinical severity scales will be performed. The dose of pyridostigmine use will be monitored by the patient using a daily log.

7.4 BLOOD COLLECTION FOR EXPLORATORY ANALYSIS

Blood collected for research will be used for the measurement of cytokines for markers of activity and toxicity, serum BCMA levels and vaccination titers as long-lived plasma cells and levels of peripheral blood B-cells with detailed analysis of their immunophenotype. Additional research

blood will be collected in the event of CRS or anaphylaxis. Where indicated in Section 6, collected research samples will be used to measure Myasthenia Gravis-specific antibodies, and HAMA antibodies. Please refer to the Laboratory Manual for specific collection volumes and procedures.

8 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

8.1 DISCONTINUATION OF STUDY INTERVENTION

Patients will be taken off treatment for the following but will remain in study unless they meet criteria for coming off-study described in Section 8.2:

- Greater than grade 2 toxicity probably or definitely related to Descartes-08 cells;
- If the patient does not meet infusion criteria after 4 weeks of delay
- General or specific changes in the patient's condition renders the patient ineligible for further treatment on this study in the judgment of the investigator; or
- Use of immunosuppressants or biologics other than azathioprine, mycophenolate mofetil, methotrexate or C5a inhibitors (e.g. eculizumab).
- Use of prednisone more than 40mg daily
- Pregnancy

8.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Patients will be taken off study for the following:

- patient voluntarily withdraws;
- significant patient noncompliance;
- death;
- start of a new MG-specific medication or initiation of MG rescue therapies (i.e., IVIG, plasma exchange).

Patients must be followed until all adverse events have resolved to grade 2 or less except for lymphopenia. If an adverse event is not expected to resolve to grade 2 or less, this will be noted in the patient medical record, and the patient will be taken off study.

9 SAFETY ASSESSMENT AND PROCEDURES

9.1 DEFINITIONS

9.1.1 ADVERSE EVENTS (AE)

An adverse event (AE) is defined as any reaction, side effect, or untoward event that occurs during the clinical trial associated with the use of an experimental agent in humans, whether the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or worsening of a pre-existing condition or abnormality is considered an AE. An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- is associated with clinical signs or symptoms
- requires treatment or any other therapeutic intervention
- is associated with death or another serious adverse event, including hospitalization; or
- is judged by the Investigator to be of significant clinical impact.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution.

9.1.2 SUSPECTED ADVERSE REACTION

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the experimental agent caused the adverse event. For the purposes of IND safety reporting, “reasonable possibility” means there is evidence to suggest a probable or definite causal relationship between the investigational product and the adverse event.

9.1.3 SERIOUS UNEXPECTED ADVERSE REACTION (SUSAR)

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator Brochure or is not listed at the specificity or severity that has been observed, or is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected" also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of the test article or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the test article under investigation.

9.1.4 SERIOUS ADVERSE EVENT (SAE)

An adverse event or suspected adverse reaction is considered serious if, in the view of the investigator or the sponsor, it results in any of the following:

- Death within 30 days of the last dose of test article;
- Grade 4 or 5 CRS, infusion reaction, or neurotoxicity;
- Inpatient hospitalization or prolongation of existing hospitalization (except for protocol-mandated ~24-hour admission for observation due to new-onset fever);
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- A congenital anomaly/birth defect; or
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE experience when based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.1.5 DOSE LIMITING TOXICITY (DLT)

DLT criteria are as follows:

- any treatment-emergent Grade 3 or Grade 4 CRS or neurotoxicity (ASBMT grading);
- any treatment-emergent Grade 2 CRS (ASBMT grading) that does not resolve to ≤ Grade 1 within 14 days;
- any treatment-emergent autoimmune toxicity ≥ Grade 3 (CTCAE v5.0);
- CTCAE v 5.0 Grade 3-5 allergic reactions related to the study cell infusion;
- CTCAE v 5.0 Grades 3 and greater organ toxicity (cardiac, dermatologic, gastrointestinal, hepatic, pulmonary, renal/genitourinary) not pre-existing or due to the underlying malignancy and occurring within the 30-day period following study product infusion; or
- CTCAE v 5.0 hematologic Grade 4 toxicity that does not resolve within 21 days.

9.2 RECORDING OF ADVERSE EVENTS

9.2.1 ADVERSE EVENT RECORDING PERIOD

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the protocol therapy completion. For this study, collection of adverse events will begin with date of consent until the subject is off-study or until the last study visit. For patients who withdraw early, adverse events should be collected until 30 days after the last dose of the test article. Serious Adverse Event reporting period starts with leukapheresis and ends at 7 days after last Descartes-08 infusion.

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any suspected adverse event(s) that might reasonably be related to participation in this study. The investigator should notify the Sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation if the event may reasonably be related to this study. The Sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

9.2.2 HOSPITALIZATION AND SURGERY

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in Section 9.1.4 and as below. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event. Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful;
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless there is clinical worsening or an increase in the frequency of hospital admissions as judged by the clinical investigator.

9.2.3 PREGNANCY

To ensure patient safety, each pregnancy in a patient on study treatment must be reported to the Sponsor within 24 hours of learning of its occurrence. The pregnancy must be followed up to determine the outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to the Sponsor. Pregnancy follow-up should be recorded on the same form and must include an assessment of the possible relationship to the study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form. Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

9.2.4 RECORDING OF ADVERSE EVENTS

At each contact with the subject during the adverse event recording period (defined in Section 9.2.1), the investigator or his/her designee must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should

be recorded immediately in the source document, and in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though it should be grouped under one diagnosis.

Conditions that were already present at the time of informed consent should be recorded in the Medical History CRF. Any condition listed in a subject's medical history for which the severity increases at the time of, or post-Descartes-08 infusion, should be captured as an adverse event.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. As detailed as possible, each adverse event should be evaluated to determine:

- the severity grade (for CRS and neurotoxicity use the ASBMT grading Grade 1-5 and for rest of the toxicities use CTCAE Version 5.0 Grade 1-5);
- its duration (start and end dates);
- its relationship to the study treatment (i.e., is there a reasonable possibility that the AE is related to the study treatment, and if yes, is the event definitely, probably, possibly or unlikely related to the investigational treatment);
- action is taken with respect to study or investigational treatment (i.e., none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable);
- whether medication or therapy taken (i.e., no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy); and
- whether it is serious, as defined in Section 9.1.4.

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF. Adverse events should be entered into the eCRF system within 5 working days from the knowledge of the event took place. Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

9.3 SAE AND SUSAR REPORTING

To ensure patient safety, every SAE and SUSAR, regardless of suspected causality, occurring during the adverse event reporting period defined in Section 9.2.1, must be reported to the Sponsor within 24 hours of learning of its occurrence. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up information is received. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

9.3.1 STUDY SPONSOR NOTIFICATION

Any SUSAR and SAE as defined in Section 9.1.3 and Section 9.1.4 must be reported to the Sponsor by **fax within 24 hours** of knowledge of the event. SUSARs and SAEs should also be discussed via email or telephone contact with the Sponsor Medical Monitor. To the extent possible, adverse events should be recorded as a diagnosis. Do not list symptoms if a diagnosis can be assigned. At the time of the initial notification, a serious adverse event (SAE) report form should be filled. The following information will be collected in the form:

- subject identifying information;
- a description of the event (if there is a diagnosis, it should be included);
- date of onset;
- current status;
- whether study treatment was discontinued;
- reason why the event is classified as serious;
- investigator assessment of the association between the event and study treatment;
- concomitant medications when the event happened; and
- narrative summary of the event.

Follow-up information on this event should be reported when received. The follow-up information should describe 1) whether the event has resolved (with or without sequelae) or continues; 2) if and how it was treated; and 3) whether the patient continued or withdrew from study participation.

9.3.2 IRB NOTIFICATION

Information that indicates a change to the patient risks or potential benefits of the research, in terms of severity or frequency, should be communicated to the IRB in the following scenarios:

- safety monitoring indicates that a particular side effect is more severe, or more frequent than initially expected;
- change in FDA safety labeling or withdrawal from the marketing of a drug, device, or biologic used in a research protocol;
- breach of confidentiality;
- change to the protocol taken without prior IRB review to eliminate an apparent immediate hazard to a research participant;
- complaint by a participant when the complaint indicates unexpected risks, or the complaint cannot be resolved by the research team; or
- protocol violation (meaning an accidental or unintentional deviation from the IRB approved protocol) that in the opinion of the investigator placed one or more participants at increased risk or affects the rights or welfare of subjects.

Deaths that occur during the study should be reported within the IRB-specified time frame. For reportable deaths, the initial submission to the IRB may be made by contacting the IRB Director or Associate Director. The AE/Unanticipated Problem Form is required as a follow up to the initial submission.

9.3.3 FDA NOTIFICATION

The Sponsor is required to report certain study events in an expedited fashion to the FDA. These written notifications of adverse events are referred to as IND safety reports. The sponsor must report an IND safety reports as described in:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf

The following describes the safety reporting requirements by timeline for reporting and associated type of event:

- **within 7 Calendar Days** any study event that is unexpected, fatal or life-threatening suspected adverse reaction; or
- **within 15 Calendar Days** any study event that is unexpected, suspected adverse reaction that is serious, but not fatal or life-threatening -or- a previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting, any finding from tests in laboratory animals that suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity or reports of significant organ toxicity at or near the expected human exposure.

9.4 STUDY PAUSING AND STOPPING RULES

Premature termination of the clinical trial may occur because of a regulatory authority decision, change in opinion of the IRB or medical monitor. Additionally, recruitment may be stopped for reasons of particularly low recruitment, protocol violations, or inadequate data recording. Specifically, study will be stopped if:

- Study Sponsor or a Regulatory Body decides for any reason that subject safety may be compromised by continuing the study.
- The Sponsor decides to discontinue the development of the intervention to be used in this study.

The study will be **paused if:**

- There is death that is reasonably attributed to study drug within the first 30 days after first infusion
- Two subjects with Grade 4 adverse events to vital organs that are assessed as possibly, probably or definitely related to study drug within the first 30 days after first infusion

If the study is paused for the reasons above, the PI and members of the study team will meet in person or by teleconference within 24 hours of the event to have a thorough discussion of the event. Meeting minutes capturing the review of any ongoing investigations, including next steps in the management of the subject and any proposed changes to the protocol will be forwarded to the medical monitor. If all parties agree as to the event resolution, then the pause will be lifted. If the study is paused for manufacturing reasons, the Sponsor will make recommendations for process improvements to be implemented. Pending successful completion of a process validation run, the manufacturing pause will be lifted.

10 STATISTICAL CONSIDERATIONS

10.1 SAMPLE SIZE

As this is an early-phase open-label study with a dose-escalation regimen, no formal sample size calculations have been performed. The sample size has been selected for practical considerations and is based upon experience from similar past clinical study designs. The selected number of subjects is considered sufficient to achieve the clinical study objectives, which are not of an inferential statistical nature.

10.2 SAFETY

The following safety parameters will be tabulated and analyzed descriptively: adverse events, clinical laboratory tests, ECGs, physical examinations, and vital signs. Dose escalation rule determination of MTD or MFD is described in Section 4.4.

10.3 EFFICACY

[redacted]

Percent change at each post-dose time point for myasthenia-specific antibodies in addition to total immunoglobulin subtypes (IgG, IgM, IgA, IgE), maximum percentage reduction value (E_{max}) and area under the percentage of reduction curve (AUEC) will be described as pharmacodynamic parameters for each dose level. In Part 2, three different dosing schedules will be tested and a patient demonstrating a ≥50% reduction in autoantibody titer will be considered to be an immunological responder. In both Part 1 and Part 2, QMG, MG Composite, MG ADL, MG PIS and MG QoL-15-R scores will be graphed to describe the changes in clinical severity over time. These are clinically validated scores for the following rules:[39-44] A 3-point change in MG-composite (overall score 0 to 50), a 2-point change in QMG (overall score 0 to 39) and a 2-point change in MG ADL will be considered as clinically meaningful. In patients using a corticosteroid, area under the dose-time curve (AUDTC) will be measured starting at Day +28 until the patient is off-study.

The following efficacy endpoints will be assessed:

1. The proportion of patients achieving a ≥2-point change from Baseline up to Day 169 in the MG Activities of Daily Living (MG-ADL) score and Quantitative Myasthenia Gravis (QMG) score.
2. The proportion of patients achieving a ≥3-point change from Baseline up to Day 169 in the MG Composite (MGC) score.
3. The mean change from Baseline up to Day 169 in the MG-ADL, QMG, MG-QoL 15R, and MGC scores.
4. The proportion of patients achieving ≥50% reduction from Baseline up to Year 1 in autoantibody titers.

5. The optimal Descartes-08 administration schedule that can achieve either ≥50% reduction in autoantibody titers or the greatest mean change in MG-ADL, QMG, MG-QoL 15R and MGC scores.

10.4 PHARMACOKINETICS

Proportionality between the dose administered and the PK parameters will be assessed by means of a mixed-effects analysis of variance (ANOVA) model with arm and dose (nested within arm) as fixed effects, and subject (nested within arm) as random effect in the model on the following parameters: Cmax/dose, AUC (0-1h)/, AUC inf/dose, total Ae%, CLR and t1/2, λz (if possible). In the case of significant dose-effect observed on these parameters, the comparison between doses will be performed using Tukey's test.

11 SUPPORTING DOCUMENTATION AND PROCEDURES

11.1 INFORMED CONSENT PROCESS

In obtaining and documenting informed consent, the investigator must comply with applicable regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and should adhere to ICH GCP. Prior to the beginning of the trial, the investigator should have the IRB's written approval for the protocol and the written informed consent form(s) and any other written information to be provided to the participants.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be IRB-approved, and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

11.2 MEDICAL MONITOR

The medical monitor will be a Sponsor physician or Sponsor-appointed physician with appropriate experience to oversee study conduct on the Sponsor's behalf, consult with site investigators, review and synthesize safety information from the various clinical sites, and to apply study-stopping criteria. All decisions by the medical monitor affecting study conduct, including the application of study-stopping or dose-escalation rules, will be documented in the study record.

11.3 RECORDING OF PROTOCOL DEVIATION

If the impact of the protocol deviation disrupts the study design, may affect the outcome (objectives), or compromises the safety and welfare of the subjects, the deviation must be reported to the medical monitor within three business days. Include the following information on the Sponsor-supplied exception/deviation form: protocol number, subject study number, description of the exception/deviation from protocol and rationale. Ensure all completed exception/deviation forms are signed by the Site Investigator and submitted to the Study Sponsor and medical monitor for review. Once approval of the exception request or acknowledgment of the deviation has been granted by the Sponsor and medical monitor, the exception or deviation will be submitted to IRB and all other applicable committees.

11.4 DATA HANDLING AND RECORD KEEPING

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

11.4.1 SOURCE DATA

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents and data records include hospital records, clinical and office charts, laboratory notes, memoranda, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

11.4.2 CASE REPORT FORMS

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All entries will be entered into an electronic data capture system (eCRF). The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

11.4.3 CONFIDENTIALITY

The investigator must ensure the anonymity of the patients; patients must not be identified by names in any documents submitted to the sponsor. Signed informed consent forms and patient enrollment log must be kept strictly confidential to enable patient identification at the site. Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- what protected health information (PHI) will be collected from subjects in this study;
- who will have access to that information and why;
- who will use or disclose that information; and
- the rights of a research subject to revoke their authorization for the use of their PHI.

If a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission

to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

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13 APPENDIX 1

Cartesian THERAPEUTICS

Immune Effector-Cell Associated Encephalopathy (ICE) Score

Date: _____

Patient ID#: _____

Date of last Descartes-08 infusion: _____

Question	Points
What year is it? *If correct, scores 1 point*	
What month is it? *If correct, scores 1 point*	
What city are we in? *If correct, scores 1 point*	
What hospital are you getting your treatment? *If correct, scores 1 point*	
Name these three objects. *Point to a pen, clock, button. Each correct object scores 1 point*	
Close your eyes and stick your tongue. *If follows correctly, scores 1 point*	
Write a sentence in the box below. *If writes legible, scores 1 point*	
Count backward from 100 by 10. *If counts correctly, scores 1 point*	
TOTAL SCORE	

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