Preliminary Safety and Efficacy Of ATA188, a Pre-manufactured, Unrelated Donor (Off-the-shelf, Allogeneic) Epstein-Barr Virus-targeted T-cell Immunotherapy for Patients With Progressive Forms of Multiple Sclerosis

Abstract #A-1026-0000-02651

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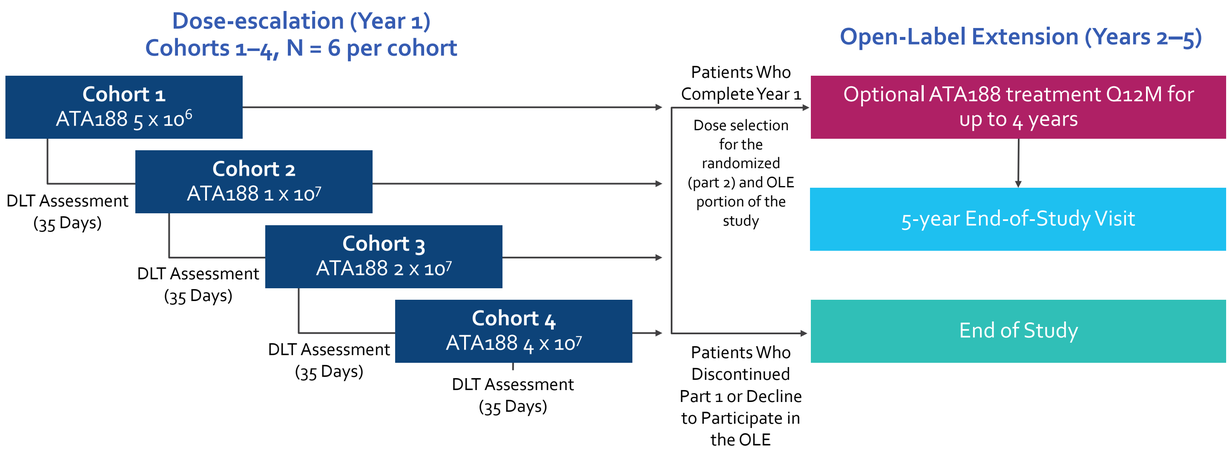
BACKGROUND

- Epstein-Barr Virus (EBV) infection is associated with the pathogenesis of multiple sclerosis (MS)[1,2]
- In a small phase 1 study of patients with progressive forms of MS, treatment with autologous EBV-specific T cells was associated with limited MS progression and improved clinical symptoms. Additionally, treatment response seemed to correlate with the EBV reactivity of T cells[3]
- ATA188 is a pre-manufactured, unrelated donor (off-the-shelf, allogeneic) EBV-targeted T cell immunotherapy comprised of partially HLA-matched, in vitro-expanded, cytotoxic T lymphocytes, specific for EBV protein antigens
- A first-in-human, phase 1, multicenter, two-part study (open-label dose-escalation and double-blind, placebo-controlled dose-expansion study) is underway to evaluate the safety and efficacy of ATA188 in adults with progressive forms of MS (ClinicalTrials.gov: NCT03283826)
- Here we report preliminary safety and efficacy of ATA188 as of July 29, 2019

STUDY DESIGN

Part 1 Study Schema



Treatment is staggered by 8 days for the first 3 patients in each cohort. ATA188 is administered as 3 infusions on days 1, 8, and 15 (1 cycle); patients receive 2 cycles of treatment. After the third infusion of each cycle, patients are observed for 20 days. End-of-study visit is ≥ 24 months after day 1 of cycle 1 unless the patient enters the OLE. DLT = dose-limiting toxicity; OLE = open-label extension

Key Eligibility Criteria

- Age 18 to < 66 years (Part 2 maximum age is < 56 years)
- History of progressive form of MS
- EBV-seropositive
- EDSS score of 3.0–7.0 (Part 2 maximum EDSS score is 6.5)
- Previous MS therapies washed out prior to dosing
- Written informed consent

Primary Endpoint (Part 1)

- Incidence of adverse events (AEs) and clinically significant changes in laboratory tests, ECGs, and vital signs; identification of the dose for the randomized (part 2) and OLE portion of the study.

Secondary Endpoint (Part 1)

- Change from baseline in Expanded Disability Status Scale (EDSS) score

Key Exploratory Endpoints (Part 1)

- Change from baseline in exploratory biomarkers
- Change from baseline in outcome measurements: Multiple Sclerosis Impact Scale-29 (MSIS) score, Fatigue Severity Scale (FSS) score, Visual Acuity (VA), Color Vision (CV), Multiple Sclerosis Functional Composite (MSFC) score, with supporting 12-Item Multiple Sclerosis Walking Scale (MSWS-12).

Statistical Analysis

- Efficacy and safety endpoints will be analyzed using descriptive statistics

Definition of Outcome Criteria (Clinical Response)

- Because of small sample size as well as short follow up, we developed a novel way of evaluating outcomes, for this analysis. Clinical outcomes were assessed at baseline and approximately 3, 6, and 12 months follow up from initial dose
- Using multiple clinically recognized scales for MS symptoms, function, and disability, an *a priori* classification of outcomes was developed to categorize patients.
- The natural history of progressive forms of MS without treatment is to decline; therefore, we defined categories based on patients who: 'decline', remain 'stable', exhibit 'partial clinical improvement' or 'clinical improvement'

Clinical Efficacy Criteria

Assessment	Minimal Clinically Significant Improvement*
Fatigue Severity Score	-0.7
MS Impact Scale-29 (physical)	-8
T25FW	-20%
9-hole peg test	-20%
MSWS-12	-8
EDSS	-1 (EDSS 3-5) -0.5 (EDSS 5.5-7.0)
VA (logmar)	≥ -0.1 decrease in either eye

*Clinically significant decline is defined as the same magnitude as improvement but in the opposite direction.
** 12-month response must include 12-month timepoint

Outcome Criteria

Outcome	Definition
Clinical Decline	• Clinically significant decline in ≥ 2 scales at ≥ 1 timepoint • Clinical decline takes precedence over improvement
Stable	• Does not fulfill criteria for decline or improvement
Partial Clinical Improvement	• Minimal clinically significant improvement or greater on ≥ 2 evaluations compared to baseline at ≥ 1 post-baseline timepoint
Clinical Improvement	• Minimal clinically significant improvement or greater on 2 evaluations compared to baseline sustained over ≥ 2 consecutive timepoints compared to baseline**

RESULTS

Patient Baseline Characteristics[a]

	Cohort 1 N = 6	Cohort 2 N = 6	Cohort 3 N = 6	Cohort 4 N = 6[b]	All Patients N = 24
Sex					
Male, n (%)	3 (50)	1 (17)	5 (83)	4 (67)	13 (54)
Female, n (%)	3 (50)	5 (83)	1 (17)	2 (33)	11 (46)
Age, median (range), years	58 (56–63)	56 (51–63)	49 (29–59)	54 (38–64)	56 (29–64)
Time from initial diagnosis, median (range), months	90 (7–357)	152 (21–237)	132 (62–345)	136 (37–249)	132 (7–357)
Prior medication for MS, n (%)					
Cladribine	0 (0)	0 (0)	2 (33)	0	2 (8)
Corticosteroids	3 (50)	1 (16.7)	3 (50)	4 (67)	11 (46)
Dimethyl Fumarate	0 (0)	1 (16.7)	3 (50)	3 (50)	7 (29)
Fingolimod	0 (0)	0 (0)	4 (67)	2 (33)	6 (25)
Glatiramer Acetate	1 (17)	0 (0)	2 (33)	2 (33)	5 (21)
Interferon	2 (33)	2 (33.3)	3 (50)	4 (67)	11 (46)
Natalizumab	1 (17)	0	2 (33)	0	3 (13)
Rituximab	0 (0)	0 (0)	1 (17)	3 (50)	4 (17)
Ocrelizumab	0 (0)	0 (0)	3 (50)	3 (50)	6 (25)
Gadolinium enhancing T1 lesion count, n (%)					
0	5 (83)	6 (100)	5 (83)	4 (67)	20 (83)
1	1 (17)	0	0	1 (17)	2 (8)
2	0	0	0	1 (17)	1 (4)
Missing	0	0	1 (17)	0	1 (4)
Type of progressive MS					
Secondary progressive MS	4	3	2	4	13
Primary progressive MS	2	3	4	3	12

Analyzed baseline characteristics included sex, ethnicity, race, age, weight, height, BMI, BSA, time from initial diagnosis, prior MS medication, gadolinium enhancing lesion count, and normalized brain volume.
[a]Baseline characteristics that differed among cohorts are presented. [b]Seven patients were enrolled in cohort 4. The analysis included all subjects who received at least one dose of ATA188 at the time of data snapshot. One patient who had MS relapse at the time of dosing was replaced. MS = multiple sclerosis.

ATA188 Dosing	Cohort 1 N = 6	Cohort 2 N = 6	Cohort 3 N = 6	Cohort 4 N = 6	All Patients N = 24
Average cells admin/dose (10^6 cells/kg)					
Mean (SD)	5.0 (0.0)	10.0 (0.0)	21.5 (2.4)	40.0 (0.0)	19.1 (13.8)
Total cells administered (10^6 cells/kg)					
Mean (SD)	30.0 (0.0)	60.0 (0.0)	129.2 (14.3)	153.3 (77.6)	93.1 (63.0)

- The total dose for subjects in the autologous Phase 1 study was 50 x 10^6 cells with the highest single dose of 20 x 10^6 cells[3]. In this off-the-shelf, allogeneic ATA188 Phase 1a study, Cohorts 2 and 3 are most similar to the autologous Phase 1 study where the subjects in Cohort 2 received a total dose of 60 x 10^6 cells at 10 x 10^6 cells/dose and subjects in Cohort 3 received ~120 x 10^6 cells at ~20 x 10^6 cells/dose.

RESULTS (continued)

Safety: Summary of Subject Incidence of Treatment-Emergent Adverse Events (TEAEs)

	Cohort 1 N = 6	Cohort 2 N = 6	Cohort 3 N = 6	Cohort 4 N = 6[a]	All Patients N = 24
TEAEs, n (%)	4 (67)	3 (50)	4 (67)	3 (50)	14 (58)
Worst grade ≥ 3	0 (0)	0 (0)	0 (0)	1 (17)	1 (4)
Serious	0 (0)	0 (0)	1 (17)	1 (17)	2 (8)
Leading to study treatment discontinuation	0 (0)	0 (0)	0 (0)	1 (17)	1 (4)
Treatment-related TEAEs, n (%)	3 (50)	1[b] (17)	2 (33)	3 (50)	9 (38)
Worst grade ≥ 3	0 (0)	0 (0)	0 (0)	1 (17)	1 (4)
Serious	0 (0)	0 (0)	0 (0)	1 (17)	1 (4)
Leading to study treatment discontinuation	0 (0)	0 (0)	0 (0)	1 (17)	1 (4)

Safety: Most Common Treatment-Emergent Adverse Events[c]

	Cohort 1 N = 6	Cohort 2 N = 6	Cohort 3 N = 6	Cohort 4 N = 6[a]	All Patients N = 24
TEAEs, n (%)	4 (67)	3 (50)	4 (67)	3 (50)	14 (58)
Fall	2 (33)	2 (33)	0 (0)	1 (17)	5 (21)
Contusion	2 (33)	0 (0)	0 (0)	0 (0)	2 (8)
Diarrhea	1 (17)	1 (17)	0 (0)	0 (0)	2 (8)
Fatigue	1 (17)	1 (17)	0 (0)	0 (0)	2 (8)
Headache	0 (0)	2 (33)	0 (0)	0 (0)	2 (8)
Infusion related reaction[d]	0 (0)	0 (0)	1 (17)	1 (17)	2 (8)
Rhinorrhea	2 (33)	0 (0)	0 (0)	0 (0)	2 (8)

[a]Seven patients were enrolled in cohort 4. The analysis included all subjects who received at least one dose of ATA188 at the time of data snapshot. One patient who had MS relapse at the time of dosing was replaced. [b]Serious, grade 3 pelvic neoplasm (suspected benign uterine fibroid) not related to treatment was reported in 1 patient in cohort 2. [c]In at least 2 patients, overall. [d]Post-infusion weakness; altered taste and smell.
TEAEs = treatment-emergent adverse events.

- No DLTs and no fatal AEs have been reported
- 6 patients (25%), 7 patients (29%), and 1 patient (4%), experienced maximum grade 1, 2, and 3 TEAEs, respectively
- One patient in cohort 4 had a grade 3 serious AE of MS relapse 7 days after dosing in the setting of ongoing URI symptoms and possible dental infection
- As of the data cutoff date, no clinically significant laboratory abnormalities have been reported in any cohort

Cytokines

	Cohort 1 (*n*=6) Median (Range)[b]			Cohort 2 (*n*=6) Median (Range)[b]			Cohort 3 (*n*=6) Median (Range)[b]		
	Baseline (pg/mL)[a]	Peak Post-Dose (pg/mL)[a]	Peak Fold Change from Baseline (log_2)[c]	Baseline (pg/mL)[a]	Peak Post-Dose (pg/mL)[a]	Peak Fold Change from Baseline (log_2)[c]	Baseline (pg/mL)[a]	Peak Post-Dose (pg/mL)[a]	Peak Fold Change from Baseline (log_2)[c]
IL-1β	≤7.8 (≤7.8, 8.7)	≤7.8 (≤7.8)	0 (-0.16, 0)	≤7.8 (≤7.8, 9.3)	≤7.8 (≤7.8, 323.5)	0 (-0.07, 5.4)	≤7.8 (≤7.8, 30.0)	≤7.8 (≤7.8)	0 (-1.9, 0)
IL-2	≤31.1 (≤31.1)	≤31.1 (≤31.1)	0 (0)	≤31.1 (≤31.1)	≤31.1 (≤31.1)	0 (0)	≤31.1 (≤31.1)	≤31.1 (≤31.1)	0 (0)
IL-6	≤3.1 (≤3.1, 8.1)	3.32 (≤3.1, 9.4)	0 (-0.75, 0.20)	3.55 (≤3.1, 6.5)	≤3.1 (≤3.1, 271.3)	0 (-1.04, 6.1)	4.05 (≤3.1, 14.6)	≤3.1 (≤3.1, 14.0)	-0.08 (-2.2, 0.9)
TNF-α	≤15.6 (≤15.6)	≤15.6 (≤15.6)	0 (0)	≤15.6 (≤15.6, 22.9)	≤15.6 (≤15.6, 34.7)	0 (0, 1.5)	≤15.6 (≤15.6)	≤15.6 (≤15.6)	0 (0)

[a]Median values ≤ LLOQ are shown as ≤ LLOQ concentration. [b]Ranges with Min and Max values of ≤ LLOQ are shown as ≤ LLOQ concentration. [c]When calculating fold change, values ≤ LLOQ were set at the respective LLOQ concentration. Data for Cohort 4 are pending cytokine testing. LLOQ = Lower Limit of Quantitation.

Efficacy: Clinical Outcomes for Cohorts 1 and 2

Response Type	6 Months		12 Months
	Cohort 1 N = 6	Cohort 2 N = 6	Cohort 1 N = 6
Clinical Decline	4	0	4
Stable	0	0	1
Partial clinical improvement	1	4	0
Clinical improvement	1	2	1

Efficacy: Clinically Significant Improvement or Decline at 6 Months

Scale	Cohort 1 N = 6		Cohort 2 N = 6	
	Improved/Stable	Decline	Improved/Stable	Decline
FSS score	4	2	6	0
MS Impact Scale-29	5	1	6	0
MSWS-12 score	4	2	6	0
25-foot walk[a]	3	3	5	1
9-Hole Peg Test[a]	5	1	6	0
EDSS[a]	6	0	6	0
Any disability scale[a]	6	4	6	1

[a]Disability related assessments; data are not mutually exclusive. EDSS = Expanded Disability Status Scale; FSS = Fatigue Severity Scale; MS = multiple sclerosis; MSWS = Multiple Sclerosis Walking Scale.

CONCLUSIONS

- **Initial safety data indicate ATA188 is well tolerated by adults with progressive forms of MS with no evidence of cytokine release syndrome or graft versus host disease**
- **There is a lower proportion of patients in cohort 2 showing deterioration than cohort 1. This occurs with increasing dose.**
- **Off-the-shelf, allogeneic, EBV-specific T-cell immunotherapy (ATA188) appears to have a similar clinical profile to autologous EBV-specific T-cell immunotherapy in this patient population[3]**
- **These data support continuing part 1 to identify the dose for both the OLE and the randomized, double-blind, placebo-controlled portion (part 2) of the study.**

DISCLOSURES

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