Phase 1 Study of the Safety and Efficacy of ATA188, an Off-the-shelf, Allogeneic Epstein-Barr Virus-targeted T-cell Immunotherapy to Treat Progressive Forms of Multiple Sclerosis

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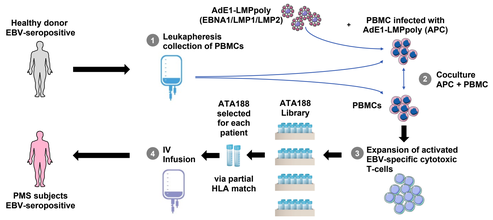
BACKGROUND

- Although many risk factors have been implicated in the development of MS, EBV is the only necessary risk factor to be identified. Evidence demonstrates that 100 percent of patients with MS have been exposed to EBV and people who do not display EBV seropositivity will not develop MS.[1-6]
- 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[7]
- 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 April 2020

Figure 1. Manufacturing of Allogeneic ATA188 EBV-specific T cells

- Major steps in ATA188 T-cell immunotherapy manufacturing

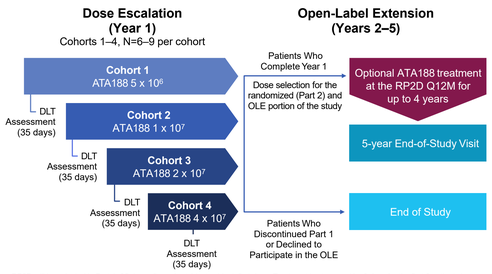


Step 1. Leukapheresis collection of PBMCs: To generate EBV-specific T-cells, peripheral blood mononuclear cells (PBMCs) are first harvested from venous blood

Step 2. Coculture APC + PBMC: PBMCs are then cocultured with autologous PBMCs infected with recombinant adenoviral vector AdE1-LMPpoly encoding CD8+ T-cell epitopes from EBV nuclear antigen 1 (EBNA1), latent membrane protein 1 (LMP1), and LMP2A allowing stimulation and expansion of EBV-specific CD8+ T cells

Step 3. Expansion of activated EBV-specific cytotoxic T-cells: Expanded T-cells are tested for antigen specificity and microbial contamination prior to selection and infusion (**step 4**).

Figure 2. Phase 1 Part 1 Study Schema (NCT03283826)



RP2D will be selected in Part 1, 35 days after cohort 4 last subject, first dose. 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; RP2D = recommended part 2 dose.

Primary Endpoints

- Incidence of adverse events (AEs) and clinically significant changes in laboratory tests, ECGs, and vital signs; identification of the recommended part 2 dose of ATA188

Secondary Endpoint

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

Key Exploratory Endpoints

- 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)

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

METHODS

- Two composite clinical outcome scales were assessed. The first composite scale focuses on measuring sustained disability improvement (SDI) via an adapted outcome measure used in a recent phase 3 study (NCT02936037), the first phase 3 study to have this endpoint accepted for use, which utilizes improvement in EDSS and T25FW from baseline

Sustained Disability Improvement

Outcome	Definition
Sustained Disability Improvement (SDI)	• Disability improvement (DI) – Improvement in EDSS (≥1-point decrease compared with baseline ≤ 5, or ≥ 0.5-point decrease compared with baseline >5); or – Improvement in 25-foot walk time (≥20% decrease compared with baseline) • SDI at 6 months = DI at 3 months and confirmed at 6 months • SDI at 12 months = DI at 6 months and confirmed at 12 months

EDSS = expanded disability status scale; T25FW = timed 25-foot walk.

- The second composite scale is an *a priori* classification of patient outcomes incorporating seven clinically recognized scales for MS symptoms, function, and disability. This scale was designed to enable earlier decision-making for advancing into the Part 2 RCT study, due to the small sample size and shorter follow up time in Part 1. Clinical outcomes were assessed at baseline and approximately 3, 6, and 12 months follow up from initial dose.
- 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
T25FWT	-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

Clinical Outcome Classification

Outcome	Definition
Clinical Decline	• Clinically significant decline in ≥2 scales at ≥1 time point • 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 time point
Clinical Improvement	• Minimal clinically significant improvement or greater on 2 evaluations compared to baseline sustained over ≥2 consecutive time points compared to baseline**

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

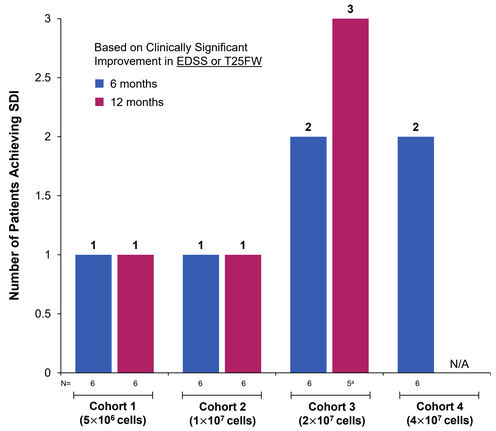
Table 1. Patient Baseline Characteristics[a] – All Subjects Receiving at Least One Dose

	Cohort 1 (N=6) 5x10^6	Cohort 2 (N=6) 1x10^7	Cohort 3 (N=6) 2x10^7	Cohort 4[b] (N=7) 4×10^7	All Patients N=25
Sex					
Male, n (%)	3 (50.0)	1 (16.7)	5 (83.3)	5 (71.4)	14 (56.0)
Female, n (%)	3 (50.0)	5 (83.3)	1 (16.7)	2 (28.6)	11 (44.0)
Age					
Median (range), years	57.5 (56, 63)	56.0 (51, 63)	49.0 (29, 59)	56.0 (38, 64)	56.0 (29, 64)
Time from initial diagnosis					
Median (range), months	90.0 (6.8, 356.5)	151.6 (20.5, 236.7)	132.3 (62.1, 344.7)	178.9 (37.0, 249.3)	145.6 (6.8, 356.5)
Gadolinium enhancing T1 lesion count, n (%)					
0	5 (83.3)	6 (100)	6 (100)	4 (57.1)	21 (84.0)
1	1 (16.7)	0	0	2 (28.6)	3 (12.0)
2	0	0	0	1 (14.3)	1 (4.0)
Type of progressive MS, n (%)					
Primary progressive MS	2 (33.3)	3 (50.0)	4 (66.7)	3 (42.9)	12 (48.0)
Secondary progressive MS	4 (66.7)	3 (50.0)	2 (33.3)	4 (57.1)	13 (52.0)
Prior medication for MS, n (%)					
Cladribine	0	0	2 (33.3)	0	2 (8.0)
Corticosteroids	3 (50.0)	1 (16.7)	3 (50.0)	5 (71.4)	12 (48.0)
Dimethyl Fumarate	0	1 (16.7)	3 (50.0)	4 (57.1)	8 (32.0)
Fingolimod	0	0	4 (66.7)	2 (28.6)	6 (24.0)
Glatiramer Acetate	1 (16.7)	0	2 (33.3)	2 (28.6)	5 (20.0)
Interferon	2 (33.3)	2 (33.3)	3 (50.0)	5 (71.4)	12 (48.0)
Natalizumab	1 (16.7)	0	2 (33.3)	1 (14.3)	4 (16.0)
Rituximab	0	0	1 (16.7)	3 (42.9)	4 (16.0)
Ocrelizumab	0	0	3 (50.0)	3 (42.9)	6 (24.0)
EDSS step score					
Median (range) EDSS step score	6.0 (4.5, 6.5)	6.0 (4.0, 6.5)	6.0 (4.5, 6.5)	6.0 (5.5, 6.5)	6.0 (4.0, 6.5)

[a]Baseline characteristics that differed among cohorts are presented. 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. [b]Seven patients were enrolled in cohort 4. One grade 3 event of MS relapse in Cohort 4 was assessed as possibly treatment-related. The event occurred 7 days after dosing in the setting of ongoing upper respiratory tract infection symptoms and possible dental infection. The event led to treatment discontinuation. EDSS = expanded disability status scale, MS = multiple sclerosis.

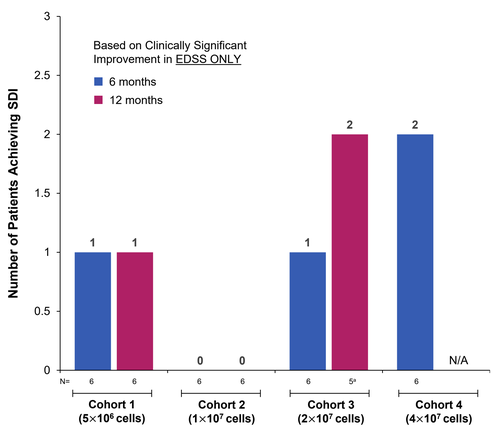
RESULTS

Figure 3. Dose-Related Increase in Number of Patients/Cohort Exhibiting Sustained Disability Improvement in EDSS or T25FW



These analyses include subjects receiving all 6 doses
*1 patient in Cohort 3 was withdrawn, moved out of the country, and is lost to 12-month follow-up.
N/A = not available.

Figure 4. Dose-Related Increase in Number of Patients/Cohort Exhibiting Sustained Disability Improvement in EDSS



These analyses include subjects receiving all 6 doses
*1 patient in Cohort 3 was withdrawn, moved out of the country, and is lost to 12-month follow-up.
N/A = not available.

Figure 5: *A Priori* Clinical Outcome Classification at 6 and 12 Months

Response Type as Determined by Prespecified Criteria	Cohort 1 (5×10^6 cells)		Cohort 2 (1×10^7 cells)		Cohort 3 (2×10^7 cells)		Cohort 4 (4×10^7 cells)	
Timepoint	6 months (N=6)	12 months (N=6)	6 months (N=6)	12 months (N=6)	6 months (N=6)	12 months (N=5)[a]	6 months (N=6)	12 months
Clinical Decline	4	5	1	1	2	2	2	N/A
Stable	0	0	0	0	1	0	0	N/A
Partial clinical improvement	1	0	3	2	0	0	4	N/A
Clinical improvement	1	1	2	3	3	3	0	N/A

Durable clinical improvement from 6 to 12 months in the same patients

These analyses include subjects receiving all 6 doses
*1 patient in Cohort 3 was withdrawn, moved out of the country, and is lost to 12-month follow-up.
N/A = not available.

SAFETY

Table 2. Treatment-emergent Adverse Events (TEAEs)[a]

	Cohort 1 N = 6	Cohort 2 N = 6	Cohort 3 N = 6	Cohort 4 N = 7[b]	All Patients N = 25
TEAEs, n (%)	5 (83.3)	3 (50.0)	4 (66.7)	4 (57.1)	16 (64.0)
Worst grade ≥3	0 (0)	0 (0)	0 (0)	1[d] (14.3)	1 (4.0)
Serious	0 (0)	0 (0)	1[c] (16.7)	1[d] (14.3)	2 (8.0)
Fatal	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Leading to study treatment discontinuation	0 (0)	0 (0)	0 (0)	1[d] (14.3)	1 (4.0)
Treatment-related TEAEs, n (%)	3 (50.0)	1 (16.7)	2 (33.3)	2 (28.6)	8 (32.0)
Worst grade ≥3	0 (0)	0 (0)	0 (0)	1[d] (14.3)	1 (4.0)
Serious	0 (0)	0 (0)	0 (0)	1[d] (14.3)	1 (4.0)
Fatal	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Leading to study treatment discontinuation	0 (0)	0 (0)	0 (0)	1[d] (14.3)	1 (4.0)

[a]This analysis included all subjects who received at least one dose of ATA188 at the time of data snapshot. [b]Cohort 4 includes withdrawn patient referred to in footnote d. [c]One grade 2 event of muscle spasticity in Cohort 3, assessed as unrelated to treatment. [d]One grade 3 event of MS relapse in Cohort 4 was assessed as possibly treatment-related. The event occurred 7 days after dosing in the setting of ongoing upper respiratory tract infection symptoms and possible dental infection. The event led to treatment discontinuation.

Table 3. Most Common Treatment-related TEAEs[a]

	Cohort 1 N = 6	Cohort 2 N = 6	Cohort 3 N = 6	Cohort 4 N = 7[b]	All Patients N = 25
Subjects reporting any related TEAEs, n (%)	3 (50.0)	1 (16.7)	2 (33.3)	2 (28.6)	8 (32.0)
Rhinorrhea	2 (33.3)	0	0	0	2 (8.0)

[a]This analysis included all subjects who received at least one dose of ATA188 at the time of data snapshot. [b]Seven patients were enrolled in cohort 4. One grade 3 event of MS relapse in Cohort 4 was assessed as possibly treatment-related. The event occurred 7 days after dosing in the setting of ongoing upper respiratory tract infection symptoms and possible dental infection. The event led to treatment discontinuation.
TEAEs = treatment-emergent adverse events.

- Rhinorrhea is the only treatment-related event that occurred in more than one subject. All other treatment-related events were single events. No particular safety trend was identified across cohorts.

Safety Summary

- As of the data cutoff date, no DLTs and no fatal AEs have been reported.
- All events were grade 1 and 2 in severity, except 1 grade 3 event of MS relapse in Cohort 4.
- Two treatment-emergent SAEs were reported:
  - One patient in Cohort 3 had a grade 2 SAE of muscle spasticity assessed as unrelated to study treatment
  - One patient in Cohort 4 had a grade 3 SAE of MS relapse 7 days after dosing in the setting of ongoing upper respiratory tract infection symptoms and possible dental infection. The event was assessed as possibly treatment-related and led to treatment discontinuation
- Rhinorrhea is the only treatment-related event that occurred in more than one subject. All other treatment-related events were single events. No particular safety trend was identified across cohorts.

Cytokine Analysis Summary

- ATA188 infusion shows no clinically meaningful effect on cytokine production post-infusion (data not shown). The cytokine profiling data (IL-1β, IL-2, IL-6 and TNF-α) corroborate with clinical observations (no cytokine release syndrome).

CONCLUSIONS

- **These data from Part 1 of this Phase 1 trial successfully demonstrated safety of ATA188 at the doses studied and provided clinical signals to support the selection of the Cohort 3 dose for the Part 2 RCT, with the potential to add the Cohort 4 dose, pending 12-month data for Cohort 4.**
- **There was a possible signal on clinical outcome measures including those measuring disability, with a higher proportion of patients showing sustained disability improvement with increasing dose. Although encouraging, this needs to be confirmed in a larger, blinded, randomized trial.**

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DISCLOSURES

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