Preliminary Phase 1 Safety 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 #1303

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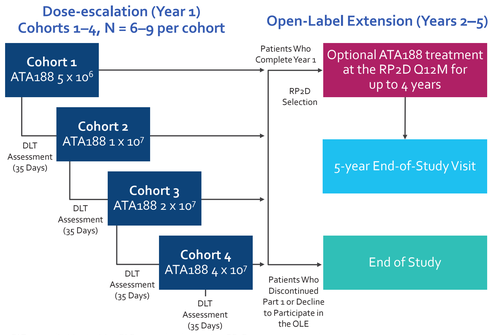
BACKGROUND

- Evidence suggests that Epstein-Barr Virus (EBV) infection is associated with the pathogenesis of multiple sclerosis (MS)[1,2]
- A phase 1 study of 10 patients with progressive forms of MS demonstrated that treatment with autologous EBV-specific T cells may prevent MS progression and improve clinical symptoms[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
- We are conducting a first-in-human, phase 1, multicenter, two-part study (open-label dose-escalation and double-blind, placebo-controlled dose-expansion study) to evaluate the safety and efficacy of ATA188 in adults with progressive forms of MS (ClinicalTrials.gov: NCT03283826)
- Here we report initial safety data for the first 3 cohorts of the dose-escalation part of the study

METHODS

Part 1 Study Schema



DLT = dose-limiting toxicity; OLE = open-label extension; RP2D = recommended phase 2 dose.
RP2D will be selected in Part 1, 35 days after cohort 4 last subject, first dose

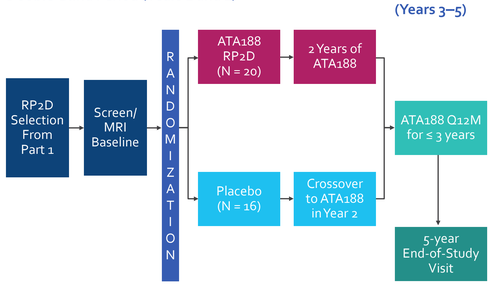
Primary Endpoints

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

Secondary Endpoint

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

Part 2 Study Schema



MRI = magnetic resonance imaging; Q12M = once every 12 months; RP2D = recommended phase 2 dose.
RP2D will be selected in Part 1, 35 days after cohort 4 last subject, first dose

Primary Endpoints

- Change from baseline in IgG index, including quantification of IgG production; incidence of AEs

Secondary Endpoints

- Change from baseline in cervical spinal cord volume and whole brain volume; change from baseline in the number of Gd-enhancing and new or enlarging T2 lesions; change from baseline in clinical disability, as assessed by the EDSS score and/or Timed 25-foot Walk and/or 9-Hole Peg Test

STUDY DESIGN

Part 1: Open-label, Dose-escalation Period

- 6–9 patients per cohort are enrolled sequentially into cohorts 1–4
- Target Dose of ATA188:
  - Cohort 1: 5 x 10^6 cells
  - Cohort 2: 1 x 10^7 cells
  - Cohort 3: 2 x 10^7 cells
  - Cohort 4: 4 x 10^7 cells
- If 1 of 6 patients has a dose-limiting toxicity (DLT; within the 35-day DLT assessment window), 3 additional patients will be enrolled into that dose cohort.
- If no DLTs are observed among the additional 3 patients, dose escalation to the next dose cohort will proceed
- If ≥ 2 of patients within a cohort have DLTs, the previous dose level will be considered the maximum tolerated dose (MTD)
- 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; patients are then followed for ≥ 2 years after the first dose of ATA188

Part 2: Double-blind Period

- The protocol has been amended to allow a randomized, double-blind, placebo-controlled period pending safety from the open-label period.

Key Eligibility Criteria

Part 1: 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)
- Prior MS therapies washed out prior to dosing
- Written informed consent

Statistical Analysis

- Efficacy and safety endpoints will be analyzed using descriptive statistics

Patient Baseline Characteristics

	Cohort 1 N = 6	Cohort 2 N = 6	Cohort 3 N = 6	All Patients N = 18
Sex				
Male, n (%)	3 (50)	1 (17)	5 (83)	9 (50)
Female, n (%)	3 (50)	5 (83)	1 (17)	9 (50)
Race				
White	6 (100)	6 (100)	6 (100)	18 (100)
Age, median (range), years	58 (56–63)	56 (51–63)	49 (29–59)	56 (29–63)
Prior medication for MS, n (%)				
Cladribine	0 (0)	0 (0)	2 (33)	2 (11)
Corticosteroids	3 (50)	1 (16.7)	3 (50)	7 (39)
Dimethyl Fumarate	0 (0)	1 (16.7)	3 (50)	4 (22)
Fingolimod	0 (0)	0 (0)	4 (67)	4 (22)
Glatiramer Acetate	1 (17)	0 (0)	2 (33)	3 (17)
Interferon	2 (33)	2 (33.3)	3 (50)	7 (39)
Natalizumab	1 (17)	0	2 (33)	3 (17)
Rituximab	0 (0)	0 (0)	1 (17)	1 (6)

MS = multiple sclerosis; SD = standard deviation.

MS-Specific Characteristics at Baseline

	Cohort 1 N = 6	Cohort 2 N = 6	Cohort 3 N = 6	All Patients N = 18
EDSS score, mean (SD)	5.8 (0.8)	5.5 (1.2)	5.8 (0.7)	5.7 (0.9)
FSS score, mean (SD)	5.6 (1.9)	5.5 (1.0)	5.8 (0.7)	5.6 (1.2)
MS Impact Scale-29, mean (SD)	52.3 (7.4)	60.0 (12.9)	63.0 (7.7)	58.4 (10.2)
Visual acuity, mean (SD)				
Left eye logMAR	0.55 (0.38)	0.60 (0.43)	0.30 (0.37)	0.48 (0.39)
Right eye logMAR	0.52 (0.37)	0.50 (0.37)	0.26 (0.39)	0.43 (0.37)
MSWS-12 score, mean (SD)	79.4 (9.9)	85.3 (17.7)	87.8 (5.7)	84.2 (12.0)
MSFC				
25-foot walk, mean (SD), seconds	12.12 (8.56)	10.96 (3.98)	10.68 (6.29)	11.25 (6.19)
9-Hole Peg Test, mean (SD), seconds	29.69 (12.57)	34.32 (16.15)	28.29 (5.85)	30.56 (11.48)
PASAT-3 total correct , mean (SD)	38.50 (12.21)	32.75 (13.89)	39.50 (18.13)	37.44 (14.35)
Z Score , mean (SD)	-0.04 (0.76)	-0.05 (0.80)	0.02 (0.62)	-0.02 (0.67)

EDSS = Expanded Disability Status Scale; FSS = Fatigue Severity Scale; logMAR = logarithm of the minimum angle of resolution; MS = multiple sclerosis; MSFC = Multiple Sclerosis Functional Composite; MSWS = Multiple Sclerosis Walking Scale; PASAT-3 = Paced Auditory Serial Addition Test-3; SD = standard deviation.

RESULTS

As of April 8th, 2019, 6 participants in cohorts 1, 6 in cohort 2, and 6 in cohort 3 have received ≥ 1 dose of ATA188

ATA188 Dosing

	Cohort 1 N = 6	Cohort 2 N = 6	Cohort 3 N = 6*
Average number of cells administered/dose (10^6 cells/kg)			
Mean (SD)	5.0 (0.0)	12.5 (6.1)	22.8 (2.6)
Total cells administered (10^6 cells/kg)			
Mean (SD)	30.0 (0.0)	75.0 (36.7)	96.0 (32.3)
Duration of treatment			
Median (range), month	1.6 (1.6–1.6)	1.6 (1.6–1.7)	0.8 (0.5–1.6)
Number of doses, n	6.0	6.0	3.0 or 6.0
Number of cycles, n (%)			
1	0	0	3 (50.0)
2	6 (100)	6 (100)	3 (50.0)

* Data cutoff was prior to all subjects in cohort 3 completing 2 cycles

Safety: Incidence of Adverse Events

- No DLTs or AEs leading to dose interruption, withholding, or discontinuation have been reported
- No fatal AEs have been reported

	Cohort 1 N = 6	Cohort 2 N = 6	Cohort 3 N = 6	All Patients N = 18
TEAEs, n (%)	4 (67)	3 (50)	2 (33)	9 (50)
Worst grade ≥ 3	0 (0)	1 (17)	0 (0)	1 (6)
Serious	0 (0)	1 (17)	0 (0)	1 (6)
Treatment-related TEAEs, n (%)	3 (50)	1 (17)	1 (17)	5 (28)
Worst grade ≥ 3	0 (0)	0 (0)	0 (0)	0 (0)
Serious	0 (0)	0 (0)	0 (0)	0 (0)

TEAEs = treatment-emergent adverse events.

Safety: Most Common Adverse Events[a]

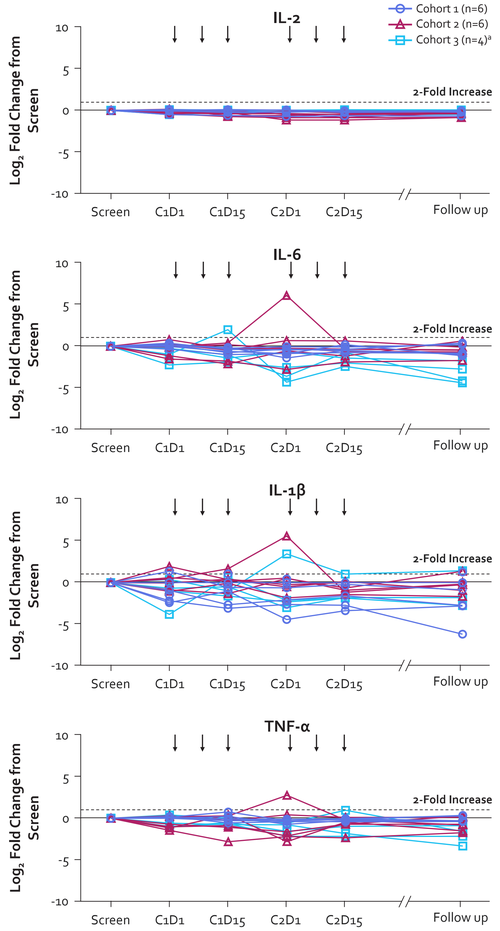
	Cohort 1 N = 6	Cohort 2 N = 6	Cohort 3 N = 6	All Patients N = 18
TEAEs, n (%)	4 (67)	3 (50)	2 (33)	9 (50)
Fall	2 (33)	2 (33)	0 (0)	4 (22)
Contusion	2 (33)	0 (0)	0 (0)	2 (11)
Diarrhea	1 (17)	1 (17)	0 (0)	2 (11)
Fatigue	1 (17)	1 (17)	0 (0)	2 (11)
Headache	0 (0)	2 (33)	0 (0)	2 (11)
Rhinorrhea	2 (33)	0 (0)	0 (0)	2 (11)

[a]In > 10 patients overall. TEAEs = treatment-emergent adverse events.

SAFETY

- 2 patients (11%), 6 patients (33%), and 1 patient (6%), experienced maximum grade 1, 2, and 3 TEAEs, respectively
- Serious, grade 3 pelvic neoplasm (not related to treatment) was reported by 1 patient in cohort 2
- As of the data cutoff date, no clinically significant laboratory abnormalities have been reported in any cohort

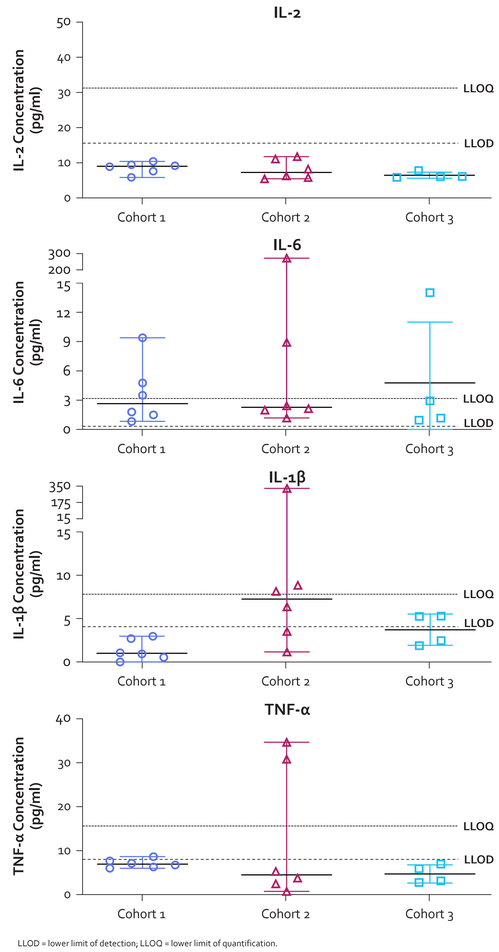
Cytokine Levels: Fold Change from Baseline at Screening



Individual patient data. Arrows represent administration of ATA188. [a]Data for the last 2 patients enrolled in cohort 3 not available at time of presentation. C = cycle; D = day.

- The patient in cohort 2 who had elevated levels of IL6 and TNF-α on day 1 of cycle 1 did not show evidence of cytokine release syndrome or neurological adverse events
- Analyses of circulating cytokine biomarkers are consistent with lack of clinically observed incidence of CRS

Cytokine Peak Levels Post-Dose



LLOD = lower limit of detection; LLOQ = lower limit of quantification.

CONCLUSIONS

- **Initial safety data indicate ATA188 is well tolerated by adults with progressive forms of MS and support proceeding with the study and identification of recommended phase 2 dose**
- **The randomized, double-blind, placebo-controlled Part 2 of the study is planned pending review of Part 1 safety data**

REFERENCES

1. Ascherio, et al. *Nat Rev Neurol.* 2012;8:602–612.
2. Pender, et al. *Clin Transl Immunology.* 2014;3(10):e27.
3. Pender, et al. *JCI Insight.* 2018;3:e124714. https://doi.org/10.1172/jci.insight.124714.

ACKNOWLEDGMENTS

Writing support for this poster was funded by Atara Biotherapeutics and provided by Kathryn Boorer, PhD.

DISCLOSURES

This study is sponsored and funded by Atara Biotherapeutics (NCT03283826).
Michael P. Pender: reports grants from MS Queensland, a research grant from Atara Biotherapeutics, personal consulting fees from Atara Biotherapeutics, travel support from Atara Biotherapeutics, and membership of the Neurology Clinical Advisory Panel of Atara Biotherapeutics.
Suzanne Hodgkinson: reports clinical trial support from Atara Biotherapeutics and honoraria for advisory boards from Biogen, Novartis, Merck, Roche and Sanofi.
Simon Broadley: reports clinical trial support through Griffith University from Atara Biotherapeutics.
John W. Lindsey: reports clinical trial support from Atara Biotherapeutics.
Zara A. Loannides: nothing to disclose.
Blake T. Aftab, Daniel Munson, Kevin Rasor, Farahnaz Forozan, Philippe Foubert, Laurence Gamelin, Amy Feng, and Jonathan Willmer: employees and stockholders of Atara.