Phase I study of ATA188, an off-the-shelf, allogeneic Epstein-Barr virus-targeted T-cell immunotherapy for progressive forms of multiple sclerosis

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BACKGROUND

ATA188 in Progressive MS

- Many studies show that EBV infection, particularly in B cells, is strongly involved with the pathogenesis of MS[1-12]
- In an open-label phase 1 study of patients with progressive forms of MS (n=10), treatment with autologous EBV-targeting T cells was well tolerated and may have been associated with clinical benefit[13]
- **ATA188 is an investigational, off-the-shelf, allogeneic, T-cell immunotherapy that targets EBV-infected cells and is selected for each patient from an existing inventory based on an appropriate HLA restriction and allele profile (Figure 1)**
- ATA188 inventory is sourced and produced from unrelated, EBV-seropositive, immunologically diverse donors

Figure 1: ATA188 manufacturing and selection based on HLA restriction

ATA188 manufacturing

I. PBMCs are harvested using leukapheresis to generate EBV-targeting T-cells

II. PBMCs are then cocultured with irradiated 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-targeting CD8+T cells

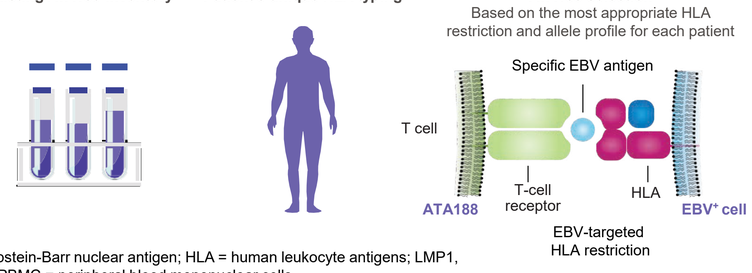
III. EBV-targeted T cells are cryopreserved and characterized for EBV-targeted reactivity and HLA restriction

ATA188 selection based on HLA restriction

1 Existing ATA188 inventory

2 Patient's unique HLA typing

3 ATA188 selection
Based on the most appropriate HLA restriction and allele profile for each patient



APC = antigen-presenting cell; EBV = Epstein-Barr virus; EBNA = Epstein-Barr nuclear antigen; HLA = human leukocyte antigens; LMP1, LMP2 = latent membrane proteins 1 and 2; MS = multiple sclerosis; PBMC = peripheral blood mononuclear cells.

METHODS

Objective: Part 1 of this Phase 1 study evaluated the safety and potential efficacy of off-the-shelf, allogeneic EBV-targeted T-cell immunotherapy (ATA188) in adults with progressive forms of MS (NCT03283826)

Study Design: Details of the study design were previously reported[13]

- Part 1 of this study involved 4 dose escalation cohorts where each subject was treated with 2 cycles of ATA188 and followed for 12 months
- Subjects completing 12 months were eligible for a 4-year open-label extension (OLE) where they are treated annually with one cycle of ATA188 at the RP2D (cohort 3 dose)

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 (primary); change from baseline in Expanded Disability Status Scale (EDSS) score

- The following were also assessed: 25-foot walk time (T25FW), 9 hole PEG test time (9HPT), Fatigue severity scale (FSS), MS impact scale (MSIS; physical), MS walking scale (MSWS), and whole brain volume (assessed via magnetic resonance imaging)
- Sustained disability improvement (SDI) was evaluated (**Table 1**)

Here, we report data on 24 subjects from the 12-month dose escalation portion of the trial, 16 of whom entered the OLE and have ≥15-month data available as of October 2020

Table 1: Sustained Disability Improvement (SDI)

Definition	Details
Disability Improvement (DI)	Improvement from baseline in EDSS[a] or in 25-foot walk time[a]
SDI at 6 months	DI at 3 months and confirmed at 6 months using the same scale
SDI at 12 months	DI at 6 months and confirmed at 12 months using the same scale
SDI in the OLE	DI at any two consecutive visits (eg, at 12 months and confirmed at 15 months)

[a]Minimal clinically significant improvement: EDSS (–1 for baseline EDSS 3–5; –0.5 for baseline EDSS 5.5–7.0); T25FW (–20%).

ECG = electrocardiogram; EDSS = Expanded Disability Status Scale; MS = multiple sclerosis; T25FW, timed 25-foot walk.

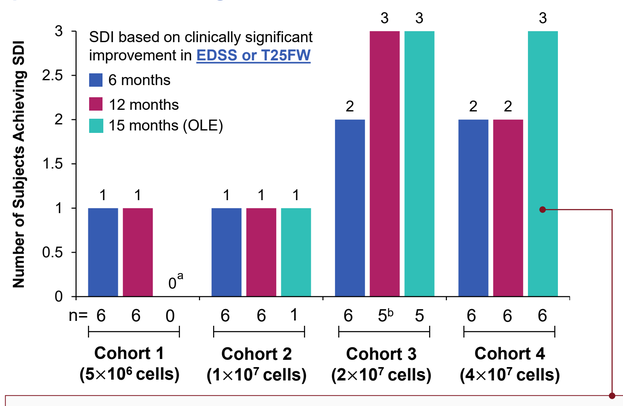
RESULTS

Baseline characteristics: Baseline characteristics were previously reported[13]

Safety: Safety was previously reported.[1] No grade >3 events, dose-limiting toxicities, cytokine release syndrome, graft vs host disease, or infusion reactions were observed. Two treatment-emergent serious adverse events were reported: muscle spasticity (grade 2; not treatment related) and MS relapse (grade 3; possibly treatment related)

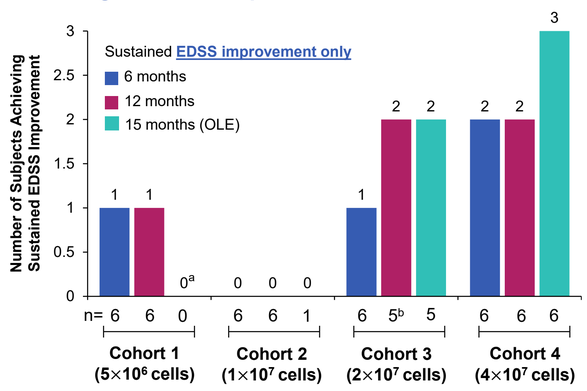
SDI: A higher proportion of subjects showed SDI with higher doses (**Figure 2**), which was largely driven by sustained EDSS improvement (**Figure 3**)

Figure 2: Dose-related increase in subjects per cohort exhibiting SDI over 15 months



- Two subjects in cohort 4 met SDI criteria at 6 and 12 months and maintained it at 15 months; an additional subject in cohort 4 met SDI criteria at 15 months
- SDI was driven by EDSS (vs T25FW) in 5 of the 7 subjects who met SDI criteria at 12 months

Figure 3: Dose-related increase in subjects per cohort exhibiting sustained improvement in EDSS over 15 months

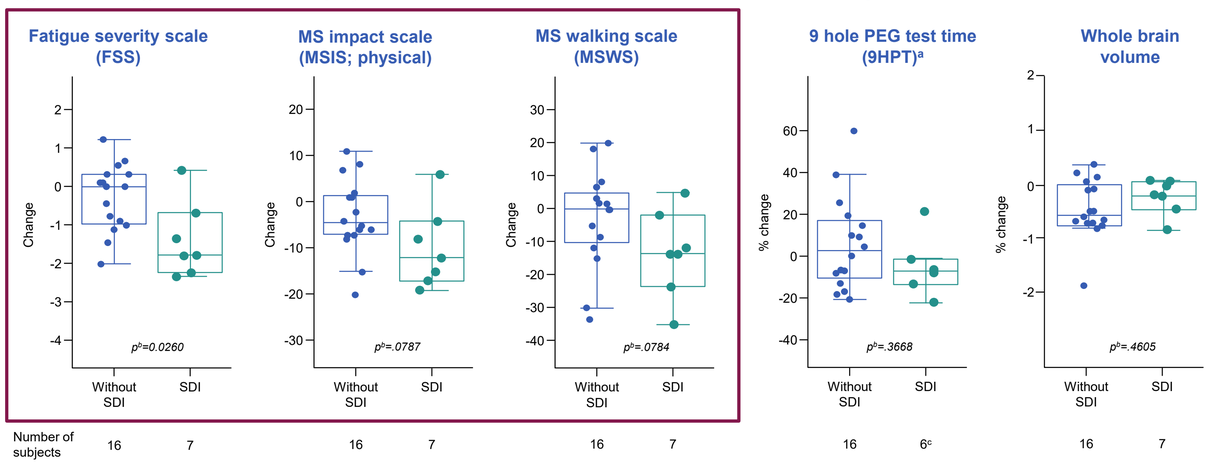


Analyses include subjects receiving all 6 doses. SDI defined as improvement in EDSS or T25FW at ≥2 consecutive time points. [a]The subject in Cohort 1 who met SDI criteria at 6 and 12 months did not enroll in the OLE. [b]1 subject in Cohort 3 was withdrawn, moved out of the country, and is lost to 12-month follow up.

EDSS = Expanded Disability Status Scale; OLE = open-label extension; MS = multiple sclerosis; SDI = sustained disability improvement; T25FW, timed 25-foot walk.

SDI Responders: Subjects from Cohorts 1–4 with SDI at 12 months (vs those without) tended to have greater improvements in FSS, MSWS-12, and MSIS (physical) scores (**Figure 4**).

Figure 4: Fatigue, measures of physical function, and whole brain volume in SDI responders



[a]Average of results in both hands. [b]Comparing SDI and no SDI at 12 months. [c]One of the seven subjects with SDI at 12 months did not receive an 9HPT evaluation at 12 months. 15-month data are not presented here as only 12 of the 23 subjects included in the 12-month analysis had 15-month data.

MRI = magnetic resonance imaging; MS = multiple sclerosis; SDI = sustained disability improvement.

RESULTS CONT.

Long-term SDI: As of October 2020, OLE data were available for 16 subjects (**Tables 2A and 2B**):

- 6 of these subjects had SDI at 12 months, which was maintained at all timepoints evaluated during the OLE (**Table 2A**)
- An additional 2 subjects who did not meet SDI criteria during the initial 12 months met it during the OLE
- 1 subject with SDI in the first 12 months did not enroll in the OLE, but is included in **Table 2A** for completeness
- Subjects who did not meet SDI criteria are shown in **Table 2B**

Table 2A: EDSS, T25FW and 9HPT[a] results among subjects in Cohorts 1–4 who met SDI criteria within the first 12 months and/or during the OLE

Cohort	Subject	SDI (Yes/No)	Scale	Baseline	3 Months	6 Months	12 Months	15 Months	18 Months	21 Months	24 Months	27 Months	30 Months
1 (5 x 10⁶ cells)	A (101-003)	Yes – 6 and 12 months	EDSS Score	4.5	3.0	3.0	3.0	Subject A did not enroll in OLE					
			ΔT25FW	–	–3%	+15%	–3%						
			Δ9HPT	–	–14%	–10%	–4%						
	H (103-001)[b]	Yes – 24 and 27 months	EDSS Score	5.5	5.5	5.5	5.5	–	–	5.0	5.0	3.5	–
			ΔT25FW	–	–11%	–22%	–19%	–	–	–31%	–41%	–38%	–
			Δ9HPT	–	+14%	–16%	0	–	–	–4%	–6%	–12%	–
2 (1 x 10⁷ cells)	B (103-010)[b]	Yes – 6, 12, 15, 18, and 21 months	EDSS Score	6.0	6.0	6.0	6.0	6.0	6.0	6.0	–	–	–
			ΔT25FW	–	–21%	–37%	–38%	–32%	–30%	–29%	–	–	–
			Δ9HPT	–	+7%	+9%	+6%	–2%	+6%	–2%	–	–	–
3 (2 x 10⁷ cells)	C (101-004)	Yes – 12, 15, and 18 months	EDSS Score	6.0	6.0	5.0	5.0	5.0	5.0	–	–	–	–
			ΔT25FW	–	–8%	–10%	–	–18%	–7%	–	–	–	–
			Δ9HPT	–	–6%	+12%	–	+14%	–14%	–	–	–	–
	D (103-007)	Yes – 6, 12, 15, and 18 months	EDSS Score	6.0	6.0	6.0	6.0	6.0	6.0	–	–	–	–
			ΔT25FW	–	–35%	–41%	–58%	–49%	–58%	–	–	–	–
			Δ9HPT	–	–12%	–19.6%	–19%	–23%	–10%	–	–	–	–
	E (103-008)	Yes – 6, 12, 15, and 18 months	EDSS Score	5.5	3.5	3.5	3.5	3.0	4.0	–	–	–	–
			ΔT25FW	–	–11%	–13%	–1%	–19%	–3%	–	–	–	–
			Δ9HPT	–	–2%	–21%	–12%	–19%	–5%	–	–	–	–
4 (4 x 10⁷ cells)	F (210-001)	Yes – 6, 12, and 15 months	EDSS Score	6.5	6.0	6.0	6.0	6.0	–	–	–	–	–
			ΔT25FW	–	–1%	–11%	–3%	+53%	–	–	–	–	–
			Δ9HPT	–	–15%	–7%	–2%	–9%	–	–	–	–	–
	G (210-003)	Yes – 6, 12, and 15 months	EDSS Score	6.0	5.5	5.0	4.5	5.0	–	–	–	–	–
			ΔT25FW	–	+15%	–8%	–16%	–8%	–	–	–	–	–
			Δ9HPT	–	–13%	+17%	–7%	–3%	–	–	–	–	–
	K (210-006)	Yes – 15 months	EDSS Score	5.5	5.5	5.5	4.5	4.5	–	–	–	–	–
			ΔT25FW	–	+15%	–13%	+17%	+9%	–	–	–	–	–
			Δ9HPT	–	+11%	0	+1%	–13%	–	–	–	–	–

Table 2B: EDSS, T25FW and 9HPT[a] results among subjects in Cohorts 1–4 with OLE data – subjects without SDI

Cohort	Subject	SDI (Yes/No)	Scale	Baseline	3 Months	6 Months	12 Months	15 Months	18 Months	21 Months	24 Months	27 Months	30 Months
1 (5 x 10⁶ cells)	P (101-005)	No	EDSS Score	6.0	6.0	6.0	6.0	–	–	–	–	6.0	6.0
			ΔT25FW	–	+17%	+17%	+46%	–	–	–	–	+30%	+22%
			Δ9HPT	–	+8%	+29%	+24%	–	–	–	–	+2%	+2%
2 (1 x 10⁷ cells)	L (201-003)	No	EDSS Score	4.0	4.0	4.0	4.0	–	4.0	4.0	–	–	–
			ΔT25FW	–	–21%	–19.9%	–17%	–	–13%	–15%	–	–	–
			Δ9HPT	–	–4%	+8%	–6%	–	–8%	–9%	–	–	–
	R (102-002)	No	EDSS Score	6.5	6.5	6.5	6.5	–	–	6.5	–	–	–
			ΔT25FW	–	+31%	+59%	+65%	–	–	+178%	–	–	–
			Δ9HPT	–	+11%	0%	–3%	–	–	+1%	–	–	–
3 (2 x 10⁷ cells)	I (101-002)	No	EDSS Score	6.5	6.5	6.5	6.5	6.0	6.5	–	–	–	–
			ΔT25FW	–	+19%	+44%	+25%	+48%	+48%	–	–	–	–
			Δ9HPT	–	–4%	–11%	–16%	–21%	–21%	–	–	–	–
	J (103-006)	No	EDSS Score	4.5	4.5	6.0	6.0	6.0	6.0	–	–	–	–
			ΔT25FW	–	–5%	–13%	+23%	+9%	–15%	–	–	–	–
			Δ9HPT	–	–8%	–17%	–7%	–15%	–10%	–	–	–	–
4 (4 x 10⁷ cells)	M (101-011)	No	EDSS Score	6.0	6.0	6.0	6.0	6.0	–	–	–	–	–
			ΔT25FW	–	+24%	+11%	–8%	+10%	–	–	–	–	–
			Δ9HPT	–	–1%	–3%	+7%	–4%	–	–	–	–	–
	N (102-004)	No	EDSS Score	6.0	6.0	6.0	6.5	7.0	–	–	–	–	–
			ΔT25FW	–	+3%	+31%	+65%	–[c]	–	–	–	–	–
			Δ9HPT	–	+9%	+17%	+26%	+26%	–	–	–	–	–
	O (210-002)	No	EDSS Score	6.0	5.5	6.0	6.0	6.0	–	–	–	–	–
			ΔT25FW	–	+3%	–3%	–22%	+31%	–	–	–	–	–
			Δ9HPT	–	–15%	–1%	–13%	–24%	–	–	–	–	–

Clinically significant improvement; Trend for improvement/stable; Clinically significant decline; Trend for decline; Re-dosed for OLE - Cohort 3 dose

[a]Results in best hand. Time is anchored to baseline (ie, first dose received). [b]Following the 12-month assessment, the subject had a treatment gap before re-dosing for the OLE and did not undergo any scheduled assessments during the interim period. [c]Subject was unable to complete the test at this timepoint due to weakness in the legs; therefore, the result was recorded as 'decline' with no associated numerical value.

Minimal clinically significant improvement: EDSS (–1 for baseline EDSS 3–5; –0.5 for baseline EDSS 5.5–7.0); T25FWT (–20%); 9-hole PEG test (–20%). Clinically significant decline is defined as the same magnitude as improvement but in the opposite direction.

ΔT25FW, change in T25FW from baseline; Δ9HPT, change in 9HPT from baseline; 9HPT = 9-hole PEG test time; EDSS = Expanded Disability Status Scale; OLE = open-label extension; SDI = sustained disability improvement; T25FW = timed 25-foot walk.

Long-term Safety: No new safety concerns were identified during the OLE

RESULTS/SUMMARY

Data from Part 1 of this Phase 1 trial demonstrated safety of ATA188 at the doses studied and provided clinical signals to support proceeding to the Part 1 OLE and to the Part 2 randomized, placebo-controlled trial at the Cohort 3 dose

- Beneficial effects were observed on clinical parameters, including disability, with higher doses associated with higher rates of sustained disability improvement (SDI)
- Nine subjects in total have met SDI criteria either in the Part 1 dose finding portion of the study (n=7) or within the OLE (n=2) to date
  - There was a dose-related increase in the number of subjects meeting SDI criteria; in the two highest dose cohorts 5/12 (42%) and 6/12 (50%) met SDI criteria at 12 and 15 months, respectively
  - At the 12-month timepoint, subjects who met SDI criteria also tended to show improvements in fatigue, physical function, and MS walking scale at 12 months, compared to those without SDI
- Specifically for the OLE, 16 subjects have data available beyond 12 months
  - Six of the seven subjects who met SDI criteria at 12 months entered the OLE – all have maintained SDI at all future timepoints
  - 2 additional subjects met SDI criteria during the OLE
- Although encouraging, a randomized placebo-controlled trial (RCT) is currently in progress to confirm the results from the open label part of the trial

The part 2 RCT was initially started at the Cohort 3 dose; however, the 15 month OLE data suggests that the Cohort 4 dose is as efficacious (subjects with SDI: 3 each in Cohort 3 and 4) or better (subjects with sustained EDSS improvement: 2 in Cohort 3 and 3 in Cohort 4) compared to the Cohort 3 dose. Therefore, the RCT will continue to enroll subjects and switch to the Cohort 4 dose with the next protocol amendment

DISCLOSURES

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REFERENCES

1. Bar-Or A et al. *Trends Mol Med*, 2020; 26:296-310. 2. Pender MP et al. *Clin Transl Immunology,* 2014;3:e27. 3. Pakpoor J et al. *Mult Scler*, 2013;19:162-166. 4. Dobson R et al. *Neurol Neuroimmunol Neuroinflamm*, 2017;4:e318. 5. Ruprecht K et al. *ECTRIMS*, 2018. 6. Munger KL et al. *Mult Scler*, 2011;17:1185-1193. 7. Levin LI et al. *Ann Neurology*, 2010;67:824-830. 8. Ascherio A et al. *Nat Rev Neurol*, 2012;8:602-612. 9. Serafini B et al. *J Exp Med,* 2007;204:2899-2912. 10. Moreno MA et al. *Neurol Neuroimmunol Neuroinflamm*, 2018;5:e466. 11. Pender MP et al. *Clin Transl Immunology*, 2017;6:e126. 12. Pender MP. *Trends Immunol*, 2003;24:584-588. 13. Pender MP et al. *JCI Insight*, 2018; 3:e124714. 13. Pender MP, *et al. Eur J Neurol* 2020; 27 (Suppl. 1),1268–1307; LB130.