Debamestrocel Long-Term Benefits on Survival and Neurodegeneration in ALS Expanded Access Program

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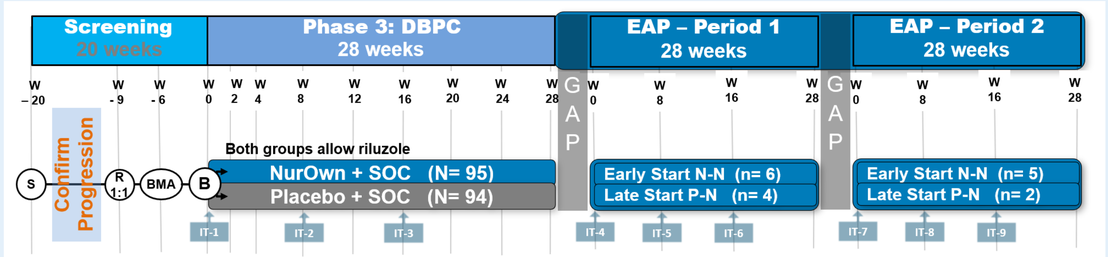
Background

After completing a Phase 3 trial of Debamestrocel in ALS (BCT-002-US), ten participants (6 Debamestrocel, 4 placebo) enrolled in an open label Expanded Access Program (EAP, BCT-003-US). The EAP spanned two 28-week periods, with participants receiving an intrathecal dose of Debamestrocel every 8 weeks, for a maximum of 6 doses.

Debamestrocel Phase 3 Clinical Trial & Follow-on EAP



Hypothesis

- Extended Debamestrocel treatment shows long-term survival benefit
- Neurofilament Light (NfL), a biomarker of neurodegeneration, shows continual decline in the EAP study

Methods

Long-Term Survival Benefit

Analysis Datasets
Treated Datasets: BCT-003 (N=10)
- **Duration**: 56-week expanded access program, divided into two 28-week periods.
- **Dosing Schedule**: Participants dosed at weeks 0, 8, and 16, with a follow-up of 12 additional weeks in each periods
- **Participants**: Selected after completing their participation in the BCT-002-US phase 3 clinical trial
- **Death Information**:
  - Only 1 death in BCT-003 (voluntary euthanasia)
  - Censoring date for participants who did not die is based on the last ALSFRS-R visit.

PRO-ACT Historical Database
Selection Criteria:
- **Initial cohort**: 9,994 control subjects from historical trials.
- **Baseline ALSFRS-R data**: Reduced to 2,960 subjects who has baseline information
- **Matching covariates**: 1,729 subjects with known baseline covariates (time since onset, pre-baseline slope, age, and SVC/FVC).
- **Mortality information**: Further reduced to 1,279 subjects with known death dates or alive at end of follow-up.
- **Left censoring**: Cohort reduced to 669 subjects who were alive at the start of the EAP

Propensity Score Matching Algorithm
Propensity score matching (PSM) is a statistical technique used to reduce selection bias in observational studies by matching participants with similar characteristics from different treatment groups. The propensity score is the probability of a participant receiving a particular treatment given their baseline covariates. In PSM, participants from the treatment and control groups with similar propensity scores are paired to create matched groups, ensuring that the distribution of covariates is balanced between them. This helps approximate the conditions of a randomized controlled trial, allowing for a more accurate comparison of treatment effects.

Matching to PRO-ACT
- Matched based on baseline data at entry into the phase 3 study.
- PRO-ACT participants must be alive when the treated participant started EAP
  - Timing: Start dates of EAP range from 13 to 32 months after the phase 3 baseline visit.
- Calculate propensity score using the following covariates
  - Time since onset
  - ALSFRS-R pre-baseline slope
  - Age at baseline
  - SVC / FVC at baseline
  - Site of onset (bulbar vs. other)
- 10:1 matching ratio

Long-Term Effect on NfL

For each participant, the percentage change from the phase 3 baseline is calculated to assess the long-term effect of Debamestrocel on NfL. Summary statistics are obtained by treatment group (Early Start: participants who received Debamestrocel in both the phase 3 and the EAP; Delayed Start: participants who received placebo in the phase 3 and switched to Debamestrocel in the EAP).
Longitudinal plots of NfL across the phase 3 and EAP periods are generated.

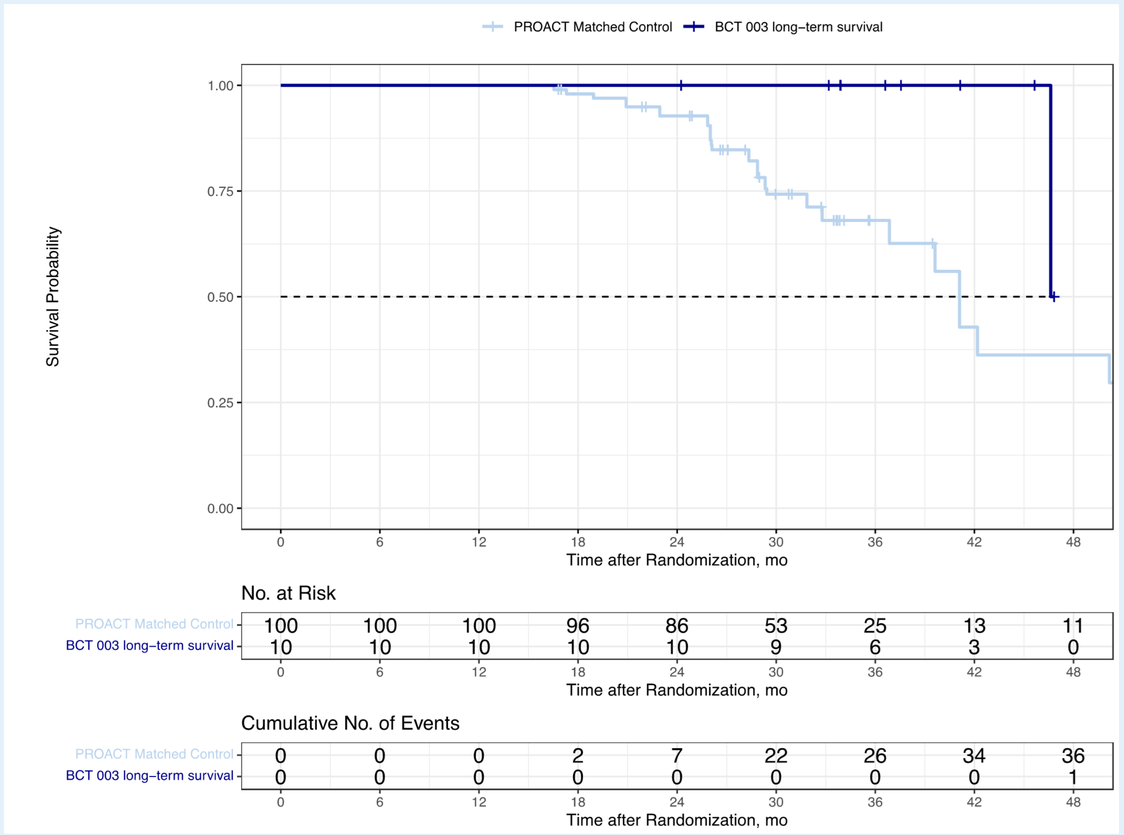
Results

Long-Term Survival Results

Using a 10:1 matching ratio with PSM based on Phase 3 baseline data, the matched participants exhibit comparable baseline disease characteristics to those in the EAP for Time since onset, ALSFRS-R pre-baseline slope, Age at baseline, SVC / FVC at baseline, Site of disease onset (bulbar vs. other).
The mean follow up time for the PROACT participants is 33.48 month while that for the EAP is 37.95 month.

Summary Follow-up and Baseline Covariates Overall		
	PROACT Matched Set	EAP Long-term survival
N	100	10
Follow-up (Months); Mean; SD; Range	33.48; 11.61; (16.54,68.38)	37.95; 7.22; (24.23,46.82)
Time Since Onset at baseline (Months); Mean; SD; Range	20.35; 9.24; (4.44,35.15)	19.33; 6.28; (10.45,27.81)
ALSFRS-R pre-baseline slope (per month); Mean; SD; Range	0.63; 0.46; (0.15,2.34)	0.68; 0.24; (0.39,1.12)
SVC/FVC at baseline; Mean; SD; Range	0.91; 0.16; (0.65,1.37)	0.92; 0.14; (0.74,1.18)
Age at baseline; Mean; SD; Range	44.91; 7.62; (24.56,63.58)	41.4; 9.34; (29,51)
Site of onset (% Bulbar)	0	0

Kaplan-Meier (KM) Curve of EAP participants as compared to PRO-ACT matched control



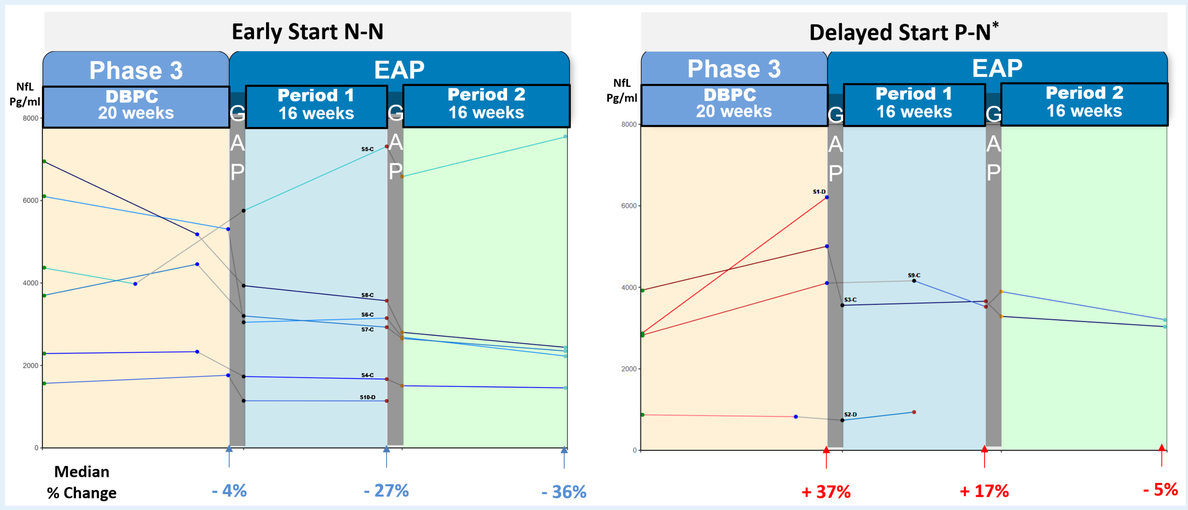
The Median Survival time (in month)
- **Control group:** 41.1 months
- **EAP participants:** 46.6 months
- **Difference:** 5.5 months
- **P-value from LRT test = 0.0379**

Note in the KM curve, the two group overlaps in the first ~17 months as there is no death prior to the initiation of the EAP, as we require that the PRO-ACT participants to be alive when the EAP starts, in order to reduce bias.

Long-Term Effect on NfL Results

The 10 participants in the EAP study exhibit milder ALS compared to the phase 3 population. The mean ALSFRS-R score at the phase 3 baseline for EAP participants is 35.8, compared to 30.9 for the entire phase 3 population. Additionally, the mean NfL level at the phase 3 baseline for EAP participants is 3,545 pg/ml, compared to 6,042 pg/ml for the phase 3 population, indicating less severe neurodegeneration.

The median percentage changes by group for each period were displayed at the bottom of each graph. Among participants who received Debamestrocel in both the phase 3 and the EAP, a continual group-level reduction in NfL was observed. In contrast, for those who received Placebo in the phase 3, the group median NfL change was 37% by the end of phase 3, indicating worsening neurodegeneration. However, after these participants received Debamestrocel in the EAP, the majority showed a stabilization in NfL levels.



*One outlier (S1-D) with 630% increase in NfL at Week 8 (EAP Period 1) in the Delayed Start group. Included in treatment level median % change, not included on graph
C=Completed, D=Discontinued

Conclusions

- Promising long-term survival benefits were observed in Debamestrocel-treated participants compared to the PRO-ACT-matched controls.
- Early treatment with Debamestrocel resulted in greater reductions in NfL levels.
- However, due to the small sample size of ten participants and the potential influence of outliers, these findings are considered hypothesis-generating.
- These hypotheses will be further explored in a planned Phase 3b clinical trial of Debamestrocel in mild to moderate ALS, under a Special Protocol Assessment (SPA) agreement with the FDA.