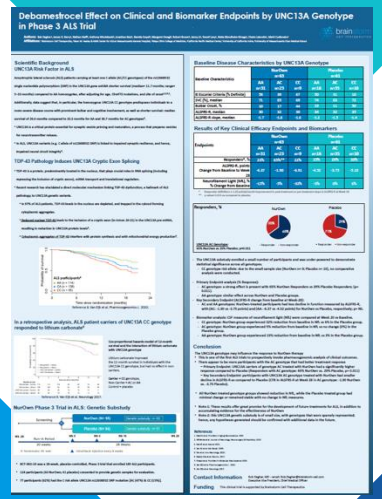
NurOwn® Phase 3 Clinical Program in ALS

Debamestrocel Effect on Clinical and Biomarker Endpoints by UNC13A Genotype in Phase 3 ALS Trial

Authors: Bob Dagher[1], James D. Berry[2], Nathan Staff[3], Anthony Windebank[3], Jonathan Katz[4], Namita Goyal[5], Margaret Owegi[6], Robert Brown[6], Jenny Li[1], Yossef Levy[1], Netta Blondheim-Shraga[1], Chaim Lebovits[1], Merit Cudkowicz[2]
Affiliations: [1]Brainstorm Cell Therapeutics, [2]Sean M. Healey & AMG Center for ALS at Massachusetts General Hospital, [3]Mayo Clinic College of Medicine, [4]California Pacific Medical Center, [5]University of California Irvine, [6]University of Massachusetts Chan Medical School



- Poster ID: 2
- Category: Mesenchymal Stem/Stromal Cells

Bob Dagher, MD

Executive Vice President & Chief Medical Officer

May 08, 2025

Background on UNC13A & TDP-43 Pathology in ALS

- **ALS and UNC13A**
  - UNC13A protein critical for synaptic vesicle priming and neurotransmitter release
  - UNC13A gene variant (rs12608932 **C** allele) linked to shorter survival and more severe ALS
    - Dysfunctional UNC13A protein: impaired synaptic transmission
    - Higher age at onset with higher incidence of bulbar-onset: respiratory dysfunction with cognitive and behavioral disturbances
- **TDP-43 pathology**
  - TDP-43 (nuclear protein) plays crucial role in RNA splicing (e.g. repressing the inclusion of cryptic exons), mRNA transport and translational regulation
  - Depletion of nuclear TDP-43 (97% ALS): inclusion of cryptic exon in the UNC13A pre-mRNA (in intron 20-21) → dysfunctional UNC13A protein
  - Cytoplasmic TDP-43 aggregates: disrupt protein synthesis and mitochondria

NurOwn® Development Program in ALS

Phase 1/2	Phase 2a	Phase 2	Phase 3	EAP	Phase 3b *planned*
N=12	N=14	N=48	N=189	N=10	N=200

R: Randomization

▲ Intrathecal Injection every 8 weeks

brainstorm cell therapeutics

NurOwn Phase 3 Trial: UNC13A Genetic Substudy

- **Baseline Disease Characteristics by UNC13A Genotype**
  - N= 124 participants (63 NurOwn; 61 placebo)
  - **C risk allele (CC & CA):** 77 participants (62%)
    - Homozygous CC (15%): NurOwn n= 9; Placebo n= 10; no comparative analysis were conducted
    - Heterozygous AC (47%): NurOwn n= 23; Placebo n= 35

Baseline Characteristics	NurOwn n=63			Placebo n=61		
	AA n=31	AC n=23	CC n=9	AA n=16	AC n=35	CC n=10
El Escorial Criteria (% Definite)	58	39	67	50	31	10
SVC (%), median	71	85	69	74	83	72
Bulbar Onset, %	10	17	44	19	11	50
ALSFRS-R, median	30	32	30	34	32	35
ALSFRS-R slope, median	-1.7	-1.6	-1.6	-1.2	-1.5	-1.4

UNC13A Genetic Substudy: Primary & Key Secondary Endpoints

Endpoints	NurOwn n=63			Placebo n=61		
	AA n=31	AC n=23	CC n=9	AA n=16	AC n=35	CC n=10
Responders*, %	23%	65%	22%	25%	29%	20%
ALSFRS-R, points Change from Baseline to Week 28	-6.37	-1.90	-6.91	-4.52	-3.75	-5.18
Neurofilament Light (NfL), % % Change from Baseline	-15%	-5%	-32%	-3%	0%	6%

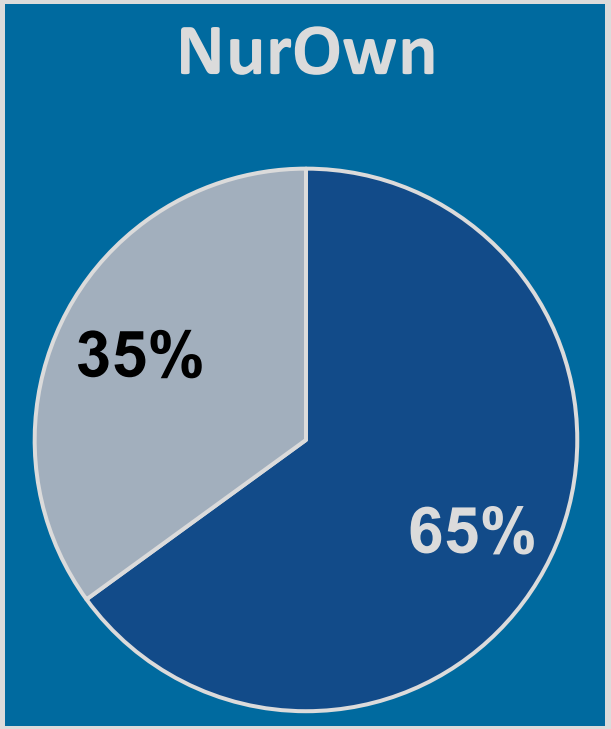
- **Primary Endpoint Analysis (% Response)**
  - CC genotype Responders: NurOwn 22% vs Placebo 20%
  - AC genotype Responders: NurOwn 65% vs Placebo 29%; p= 0.011
- **Key Secondary Endpoint (ALSFRS-R change from baseline at Week-28)**
  - CC genotype: NurOwn -6.91 vs Placebo -5.18 points
  - AC genotype: NurOwn -1.90 vs Placebo -3.75 points; p= 0.167

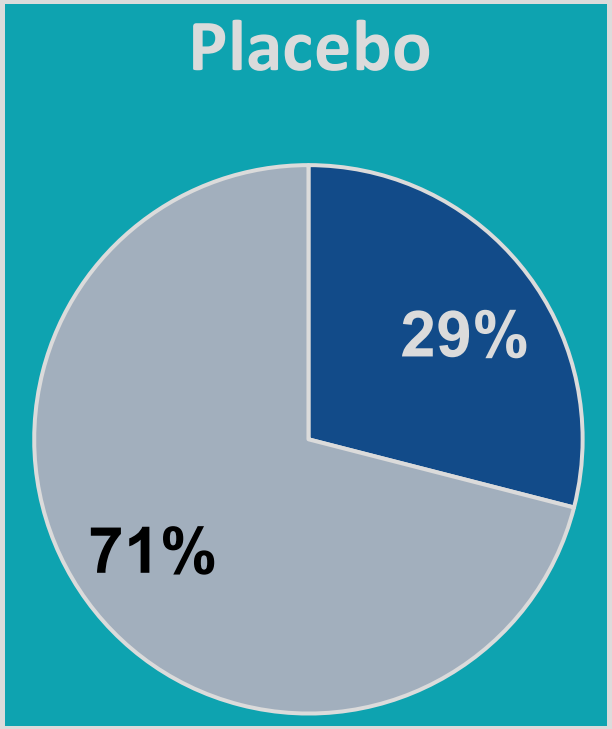
* Responder definition: ≥ 1.25 points/month improvement in post-treatment vs pre-treatment slope in ALSFRS-R at Week 28

Primary Endpoint: Broad Population & UNC13A AC Genotype

- **% Responders, Overall Population**
  - NurOwn 33% vs Placebo 28%; p= 0.453

- **% Responders, AC Genotype**
  - NurOwn 65% vs Placebo 29%
    p=0.011





Responders Non-Responders

* Responder definition: ≥ 1.25 points/month improvement in post-treatment vs pre-treatment slope in ALSFRS-R at Week 28

brainstorm cell therapeutics

UNC13A Genetic Substudy: Interpretation & Conclusions

- UNC13A genotype influences response to NurOwn therapy
- AC genotype carriers showed significant clinical benefit and biomarker improvement
- CC genotype associated with severe disease; small sample size limits conclusions
- Informative pharmacogenomic analysis for future Trials in ALS
- Findings support further investigation of UNC13A genotype-guided therapy in ALS

brainstorm
cell therapeutics

Thank You