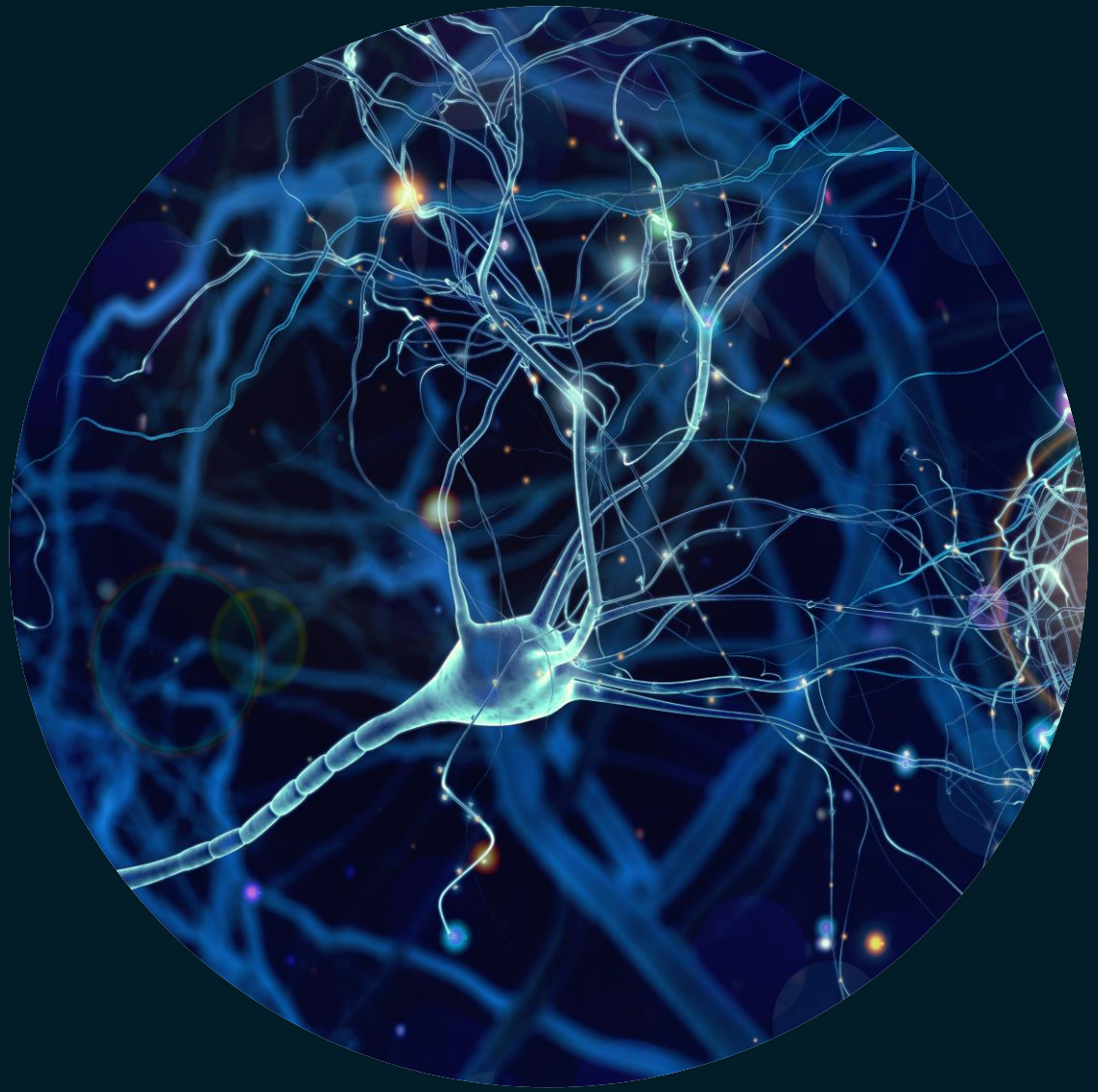

Relationship UNC13A Single-Nucleotide Polymorphisms to Clinical Outcomes in NurOwn Phase 3 ALS Clinical Trial

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March 16, 2022
MDA Clinical and Scientific Conference
Nashville, TN

Relationship UNC13A Single-Nucleotide Polymorphisms to Clinical Outcomes in NurOwn Phase 3 ALS Clinical Trial

- **124 of 189 participants (63 NurOwn; 61 placebo) were evaluated for 31 pre-specified ALS related genes and 4 SNPs**
- **8 of 124 (6.5%) participants in NurOwn ALS trial harbor seven different ALS gene mutations**
- **UNC13A rs12608932 SNP risk allele, which potentiates the deleterious effects of TDP-43, appear in 62% of the patients.**
- **BCT-002, NurOwn Phase 3 trial data suggest that NurOwn treatment may influence disease progression in ALS patients who possess this risk allele and provides a basis for further genetic characterization in clinical trials.**

Pre-defined Focus of BCT-002 Genetic Substudy

31 ALS related genes/known mutations, 4 SNPs

124 participants (63 NurOwn, 61 Placebo) underwent mutational testing.

Gene/SNP (#, % with positive risk allele)				
ANG	CX3CR1	MAPT	SOD1 (1, 0.8%)	UNC13A gene
ANXA11	FUS (1, 0.8%)	OPTN (1, 0.8%)	SQSTM1	VAPB
ARHGEF28	GRN	PFN1	TARDBP (1, 0.8%)	VCP
C9orf72 (3, 2.4%)	HNRNPA1	PSEN1	TBK1 (1, 0.8%)	UNC13A (77, 62%)
CDH13	HNRNPA2B1	PSEN2 (1, 0.8%)	TMEM106B	CAMTA1 (59, 48%)
CHGB	KIF5A	SETX	TREM2	MOBP (112, 90%)
CHMP2B	KIFAP3	SLC11A2	UBQLN2	ZNF12B (53, 43%)

SNPs

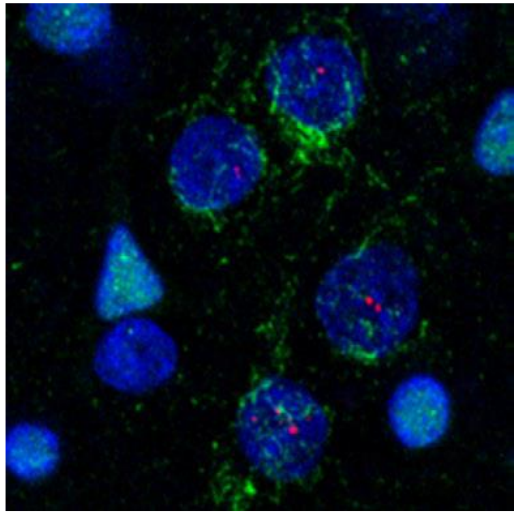
Focus of presentation will be UNC13A

Samples analyzed by Prevention Genetics

A direct function link found between UNC13A SNP and loss of TDP-43 protein expression[1]

- **UNC13A is a member of family of pre-synaptic proteins which primes synaptic vesicles[2,3]**
- **The C allele of the rs12608932 SNP has been identified as a risk variant for both ALS and frontotemporal dementia (FTD)[2].**
- **In 97% of ALS patients, TDP-43 gets trapped in the cytosol, where it forms deposits. As TDP-43 protein levels fall in the nucleus, splicing errors that it would normally prevent begin to magnify.**
- **TDP-43 depletion induces robust inclusion of a cryptic exon within UNC13A; neurons lacking nuclear TDP-43 make less of the protein**
- **In neurons from people who had ALS/FTD with TDP-43 deposits, mis-splicing was highest in cells carrying the UNC13A risk variants.**

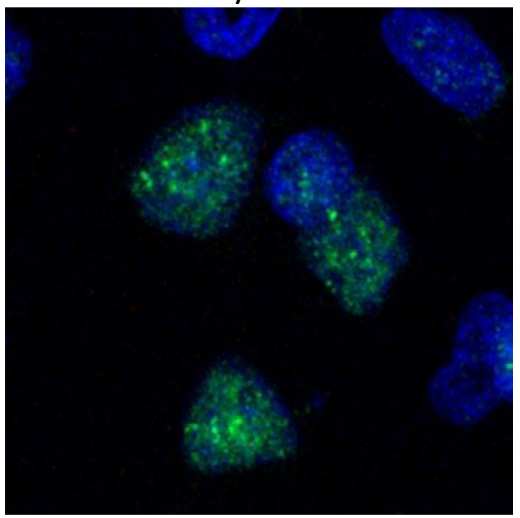
FTD-MND



UNC13A cryptic exon

TDP-43

Healthy control

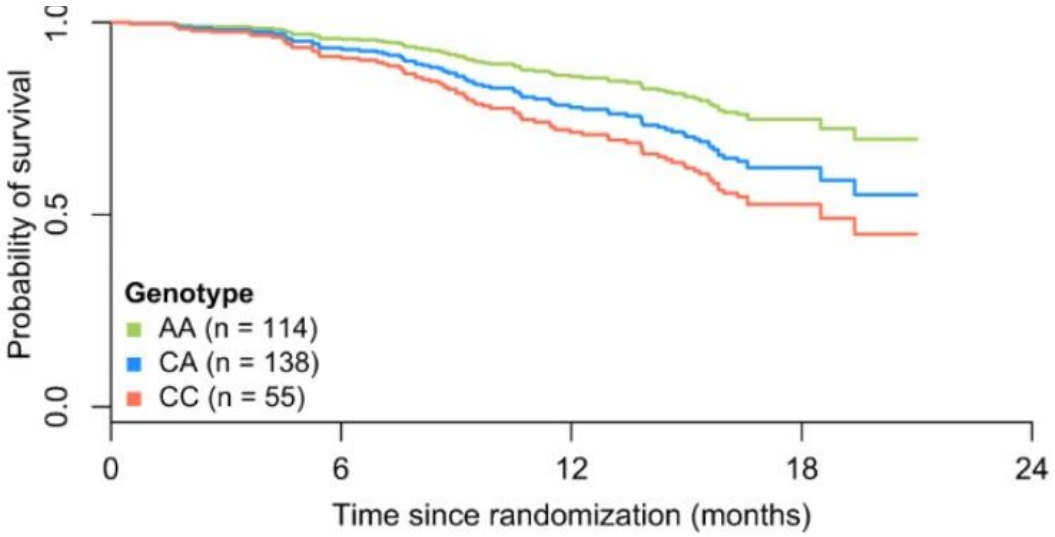


[1]Ma XR et al. Nature. 2022 Mar;603(7899):124-130, [2]Van Es, et al, Nat Genet. 2009 41(10):1083-7.
[3]Reddy-Alla, S, et al. Neuron, 2017

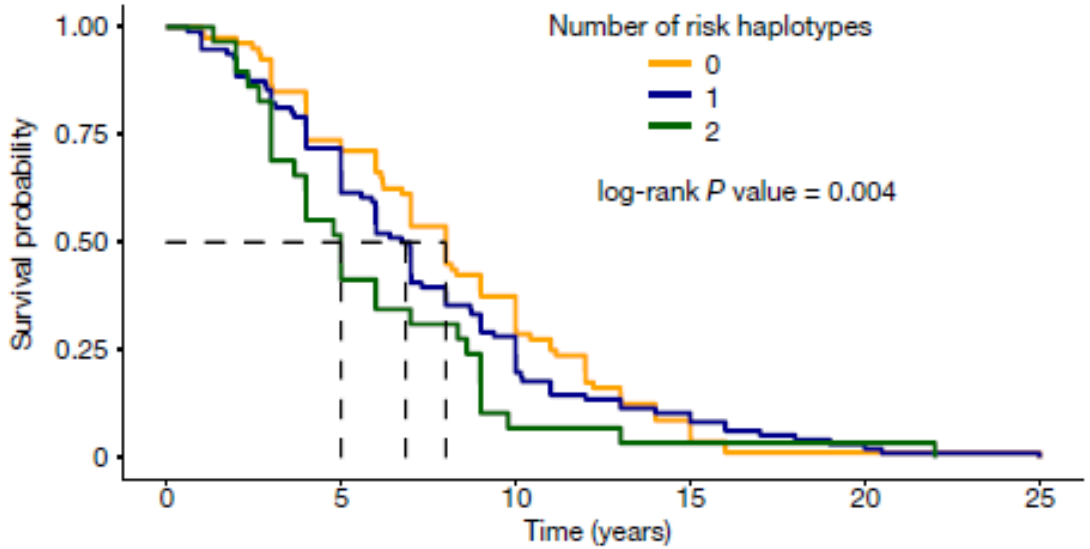
ALS patients with C risk allele of UNC13A have shorter survival

Data provides a direct functional link between UNC13A genetic variants and loss of TDP-43 Function and survival[1]

ALS participants[2]



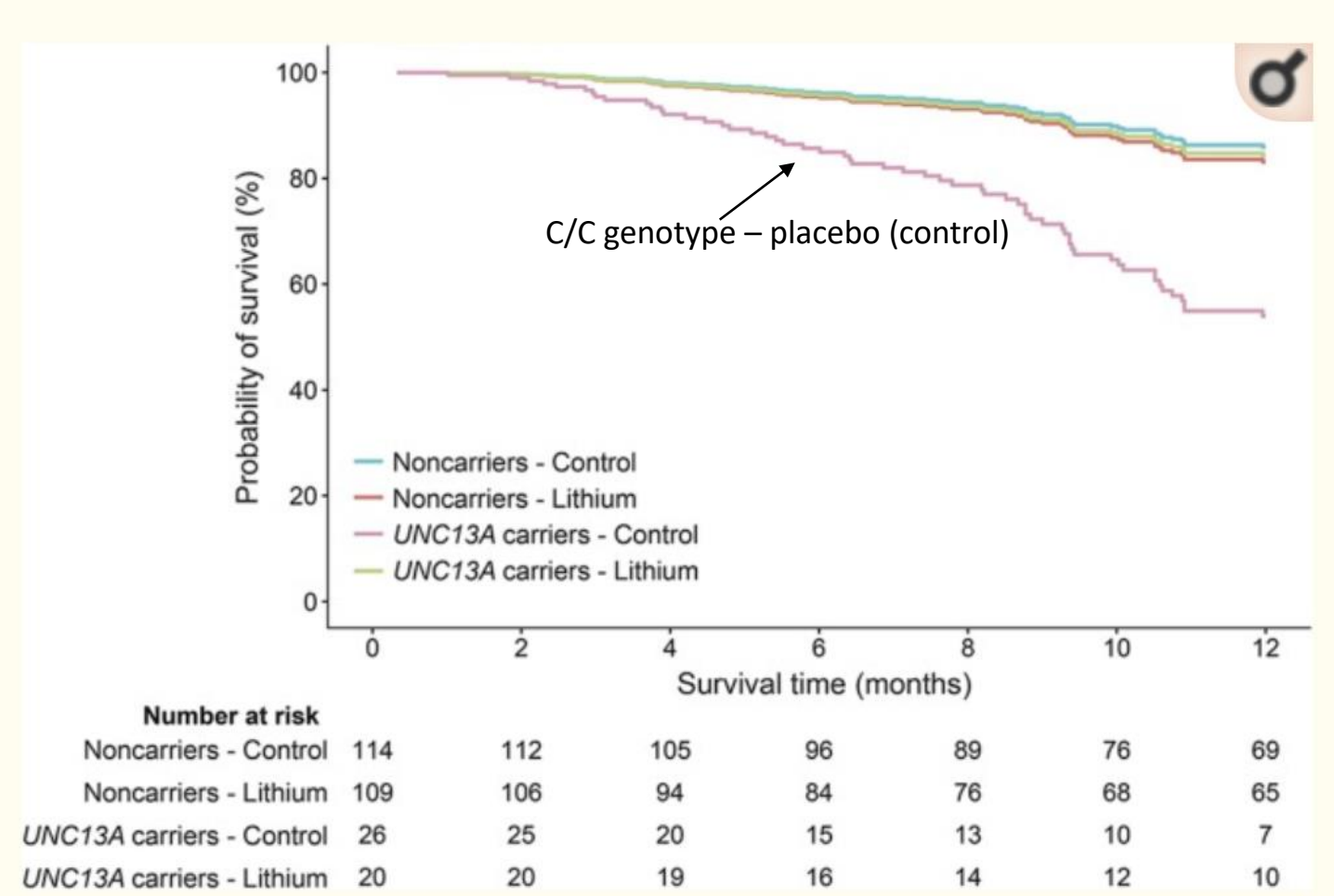
Frontotemporal Dementia participants[1]



The C allele of the rs12608932 SNP has been identified as a risk locus for both ALS and frontotemporal dementia (FTD)[2]

[1]Ma et. al., Nature Research (2022), [2]van Eijk et al., Pharmocogenomics J (2020)

In a retrospective analysis, C/C genotype patients responded to lithium carbonate



Number at risk							
Noncarriers - Control	114	112	105	96	89	76	69
Noncarriers - Lithium	109	106	94	84	76	68	65
UNC13A carriers - Control	26	25	20	15	13	10	7
UNC13A carriers - Lithium	20	20	19	16	14	12	10

Cox proportional hazards model of 12-month survival and the interaction of lithium carbonate with UNC13A genotype

UNC13A carrier status: there was a significant effect of lithium carbonate (p = 0.027) and no effect in noncarriers.

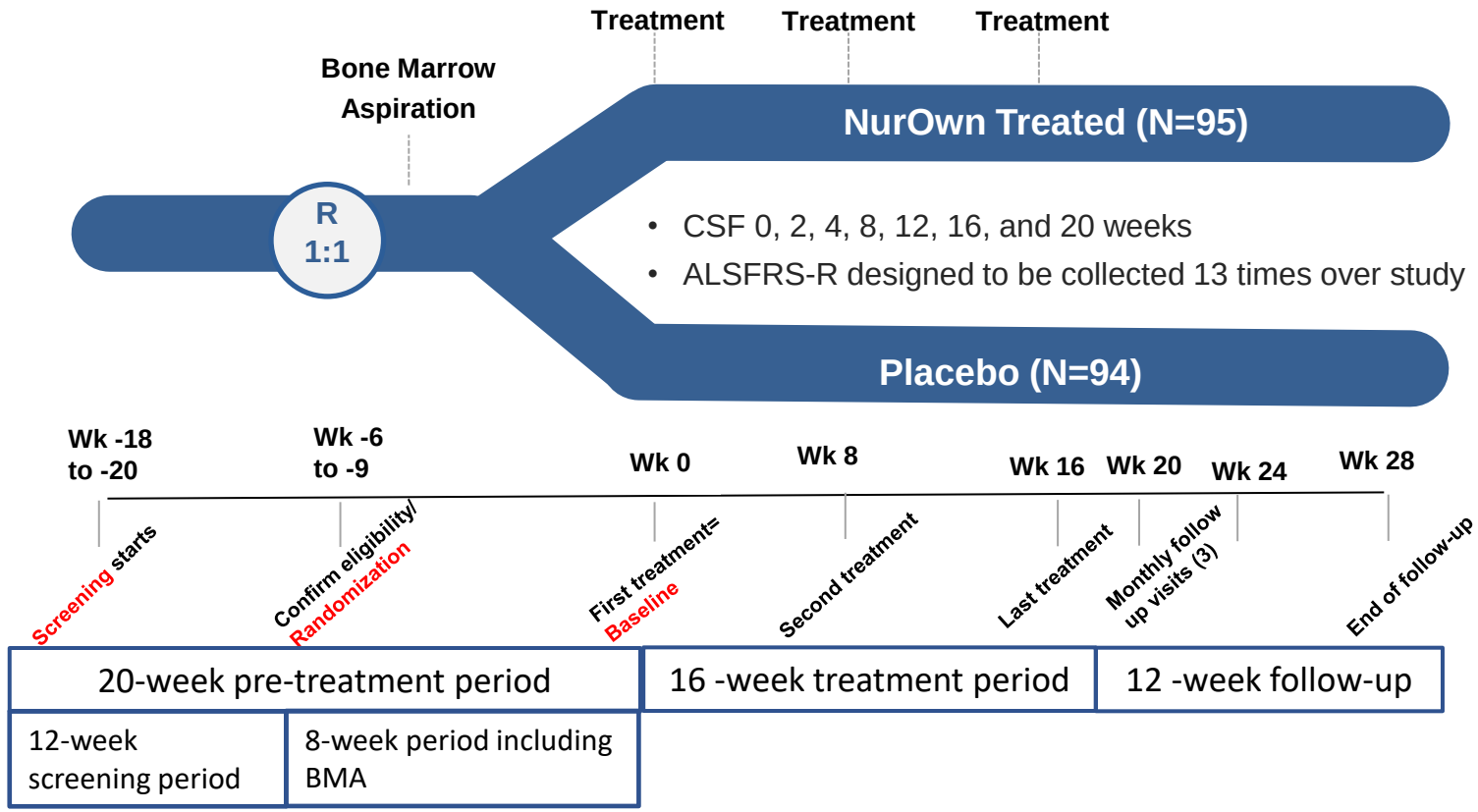
Carrier = C/C genotype,
Non-Carrier = A/C or A/A
Control = placebo

van Eijk et al., Neurology. 2017 Oct 31; 89(18): 1915–1922

The Phase 3 NurOwn study was a double-blind, placebo-controlled trial.

Designed to exclude slow progressors. Inclusion criteria specified:

- ALSFRS-R ≥ 25 at Screening Visit (Not at Baseline).
- Decline in ALSFRS-R total score of 3 or more points in the 12 weeks before randomization.



Primary Endpoint

Proportion of participants with ≥1.25 point/month improvement in post-treatment vs pre-treatment slope in ALSFRS-R score at 28 weeks

Secondary Endpoints

Safety

ALSFRS-R change from baseline

Percentage of participants with post-treatment slope improved ≥ 100%

Combined Analysis of Function and Survival

Slow Vital Capacity

CSF/Blood biomarkers

Cudkowitz, M, et al Musc Nerve, 2022

Distribution of UNC13A alleles match that of larger series

UNC13A Genotype	BCT-002 n (% of Genetic substudy)	ALS Population based Study Netherlands[1]
A/A	47 (37%)	854 (38.5%)
A/C	58 (47%)	988 (44.6%)
C/C	19 (15%)	374 (16.9%)
Total UNC13A Genetic Substudy	**124**	**2,816**
UNC13A Genotype Missing	65	0
Total Study	189	2,816

Hardy Weinberg, test of equilibrium: χ^2=0.04, p=0.84

[1]Tan et al., Annals of Neurology, 2020

Baseline Clinical Characteristics are generally balanced between Treatment groups

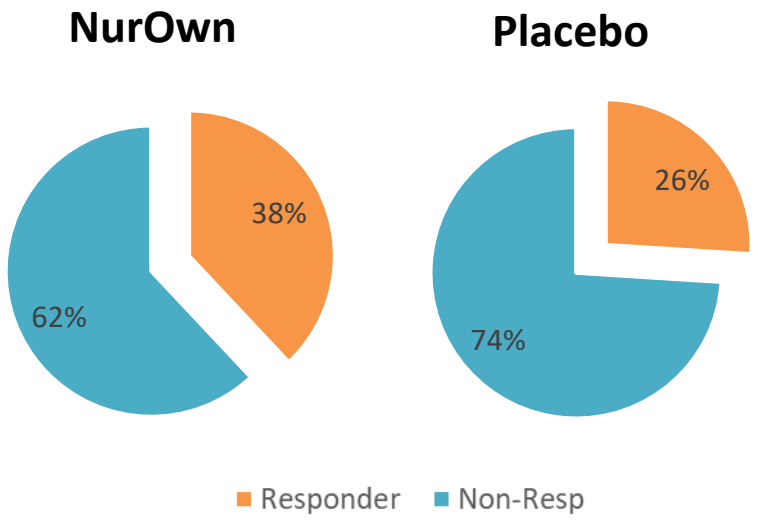
C/C group is a sparsely sample with more advanced ALS with NurOwn Participants

Clinical Characteristics at Baseline	BCT-002 NurOwn n=63			BCT-002 Placebo n=61		
	A/A n=31	A/C n=23	C/C n=9	A/A n=16	A/C n=35	C/C n=10
El Escorial Criteria for ALS, % Definite	58	39	67	50	31	10
SVC (% predicted), 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

Cudkowicz et al, Muscle and Nerve, 2021

The Rate of Response is larger in this Genetic SubStudy

Total participants: 189 (95 NurOwn, 94, Placebo), %Response: 33% NurOwn, 28% Placebo
Genetic Substudy: 124 participants (63 NurOwn, 61 Placebo, all participants who consented)



Overall Response Rate from Genetic Substudy participants:

38% NurOwn vs. 26% Placebo, p=0.215

- **Generally, Genetic Substudy baseline characteristics by treatment resembled the full trial characteristics[1]**

[1]Cudkowicz et al, Muscle and Nerve, 2021

NurOwn subgroup with the A/C genotype responded better to NurOwn treatment

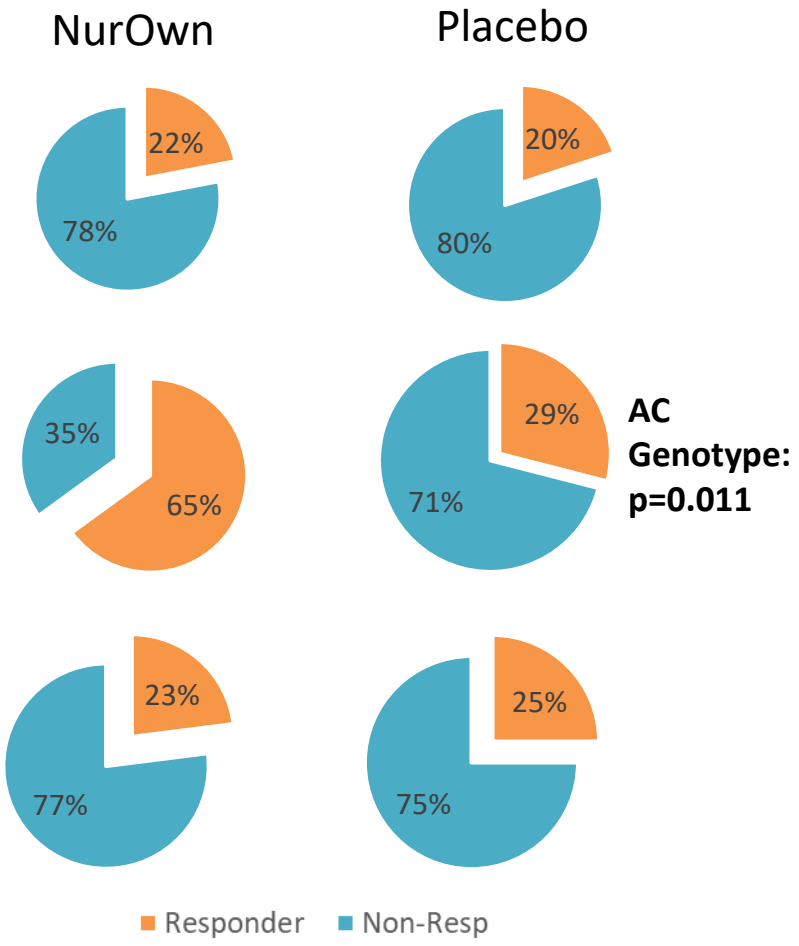
Significantly more NurOwn response in A/C Genotype, Effect was not seen in the C/C genotype

Total Genetic Substudy Population

Genotype C/C n= all
NurOwn: n=9 (14%)
Placebo: n= 10 (17%)
15% of genetic sub-study

Genotype A/C n= all
NurOwn: n=23 (37%)
Placebo: n=35 (57%)
~50% of the genetic sub-study

Genotype A/A n= all
NurOwn: n=31 (49%)
Placebo: n=16 (26%)
~35% of the genetic sub-study

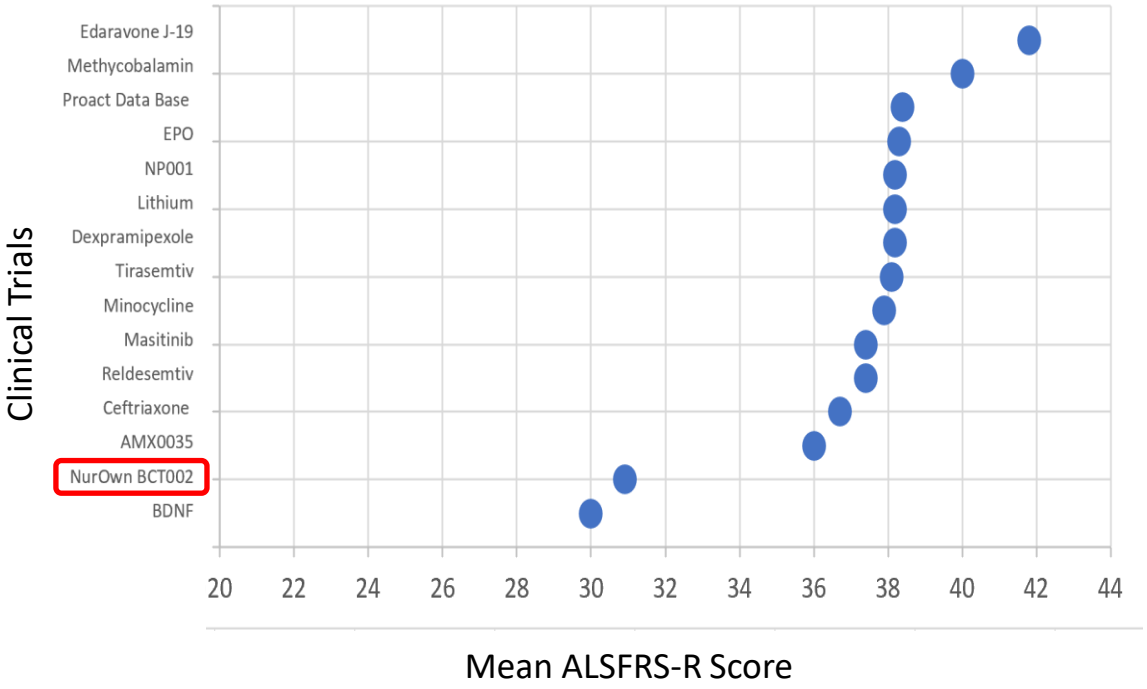


Note:
C/C Genotype has sparce sample

A/C, A/A Genotypes have a treatment imbalance

Data Source: SP079_Brainstorm_Results_SNPs_17Dec21 (002).xlsx

BCT-002 included participants with advanced ALS, ALSFRS-R floor effect observed in this trial Baseline ALSFRS-R ≤ 25



% participants with ALSFRS-R item=0 at baseline

Baseline ALSFRS-R ≤ 25				
	Item 1	Item 2	Item 3	Average
Bulbar	10%	3%	3%	5%
Fine Motor	42%	42%	35%	40%
Gross Motor	19%	10%	74%	34%
Respiratory	0%	0%	0%	0%

- **Inability to measure progression in participants may result in misclassification of response**
- **Analysis focused on baseline ALSFRS-R > 25 minimizes the impact of the floor effect and leverages high percentage of data from trial.**

NurOwn subgroup with the A/C genotype responded better to NurOwn treatment

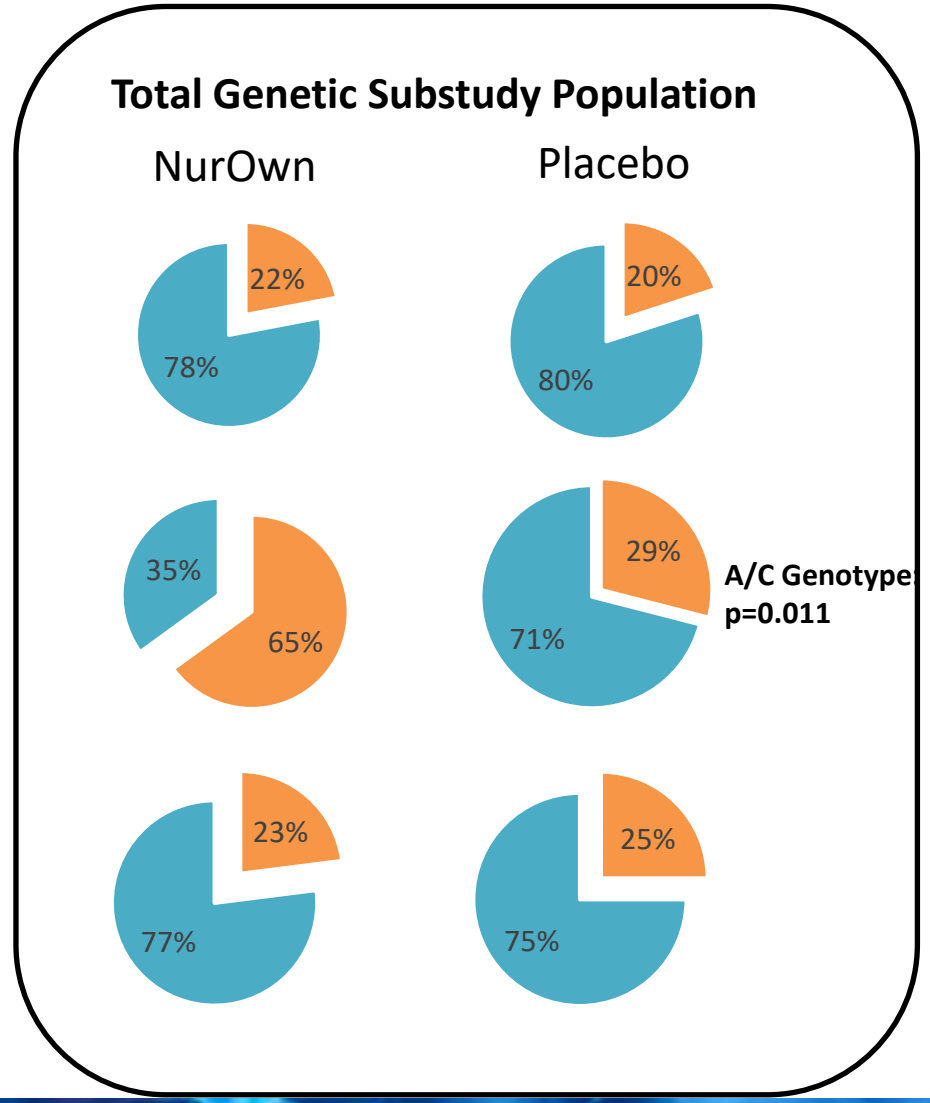
124 participants (63 NurOwn, 61 Placebo) consented for Genetic Substudy:

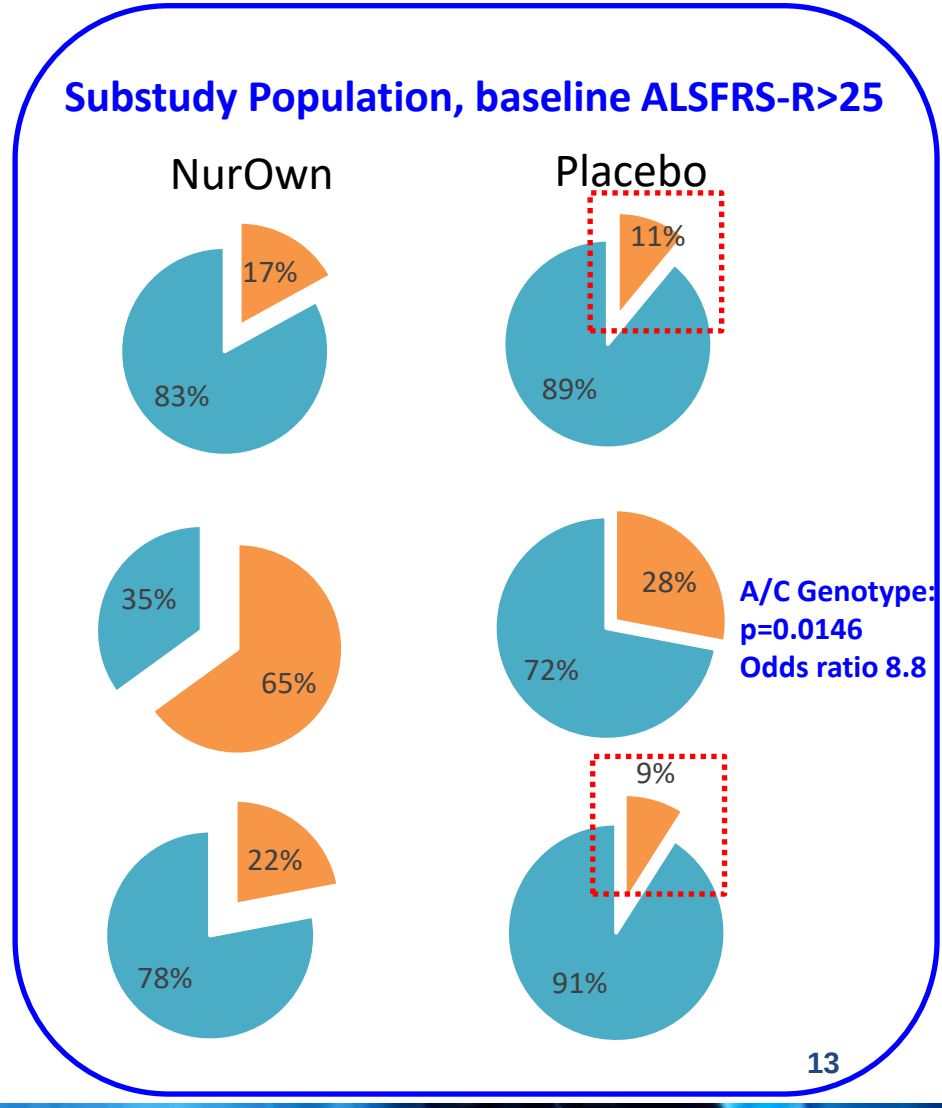
98 Participants (49 NurOwn, 49 Placebo) with Baseline ALSFRS-R >25

Genotype C/C n= all → n=ALSFRS-R >25
NurOwn: n=9 → n=6
Placebo: n= 10 → n=9
15% of genetic sub-study

Genotype A/C n= all → n=ALSFRS-R >25
NurOwn: n=23 → n=20
Placebo: n=35 → n=29
~50% of the genetic sub-study

Genotype A/A n= all → n=ALSFRS-R >25
NurOwn: n=31 → n=23
Placebo: n=16 → n=11
~35% of the genetic sub-study





Data Source: SP079_Brainstorm_Results_SNPs_17Dec21 (002).xlsx

UNC13A Genotype may influence the response to NurOwn therapy

This is one of the first ALS trials to prospectively invoke pharmacogenomic analysis of clinical outcome

There appear to be more participants with treatment response with the A/C Genotype

- Primary Endpoint: UNC13A Carriers, particularly Genotype AC, treated with NurOwn had a significantly higher response compared to Placebo (A/C Genotype, 65% NurOwn vs. 29% Placebo, p=.011)

Ongoing in-vitro research will evaluate the MOA of NurOwn in the different UNC13A genotypes

These results offer great promise for the development of future treatments for ALS, in addition to accumulating evidence for the effectiveness of NurOwn

Some Genotypes are sparsely represented, and hypotheses generated should be confirmed

Manufacturing Sites

City of Hope Center for Biomedicine & Genetics

Dana-Farber Harvard Cancer Center
Cell Manipulation Core

Treatment Centers

University of Massachusetts Medical School

Massachusetts General Hospital

Mayo Clinic

UC Irvine

Cedars-Sinai

Sutter Health
Sutter Pacific Medical Foundation

Funding

CIRM
California's Stem Cell Agency

ALS Association

I AM ALS