NurOwn

SPONSOR BRIEFING DOCUMENT

CELLULAR, TISSUE AND GENE THERAPIES ADVISORY COMMITTEE

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List of Abbreviations

Abbreviation	Definition
AE	adverse event
AIC	Akaike information criterion
ALS	amyotrophic lateral sclerosis
ALSFRS-R	Revised Amyotrophic Lateral Sclerosis Functional Rating Scale
BDNF	brain-derived neurotrophic factor
BiPAP	bilevel positive airway pressure
BLA	Biologics License Application
CAFS	combined assessment of function and survival
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CHIT-1	chitotriosidase
CMAP	compound muscle action potential
CNS	central nervous system
CNTF	ciliary neurotrophic factor
CSF	cerebrospinal fluid
DVT	deep vein thrombosis
EAE	experimental autoimmune encephalomyelitis
EAP	expanded access program
FAS	full analysis set
FDA	Food and Drug Administration
FVC	forced vital capacity
Gal-1	galectin-1
GDNF	glial-derived neurotrophic factor
G-tube	gastrostomy tube
HGF	hepatocyte growth factor
ICV	intracerebroventricular
IM	intramuscular
IT	intrathecal
ITT	intent-to-treat
LAP	latency-associated peptide
LAP of TGF-β1	TGF-β1 sequestered by LAP, simplified to TGF-β1
LIF	leukemia inhibitory factor
LS	least squares
MAR	Missing at random
MCP-1	monocyte chemoattractant protein-1
MI-MAR	multiple imputation-missing at random
MI-MNAR	multiple imputation-missing not at random

Abbreviation	Definition
mITT	modified intent-to-treat
MMRM	mixed effect model repeated measures
MNAR	Missing not at random
MoA	mechanism of action
MRI	magnetic resonance imaging
MS	multiple sclerosis
MSC	mesenchymal stem cells
MSC-NTF	mesenchymal stem cells secreting neurotrophic factors
NfL	neurofilament light chains
NTF	neurotrophic factors
OR	odds ratio
PDUFA	Prescription Drug User Fee Act
pNfH	phosphorylated neurofilament heavy chain
PW	piecewise
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SDF-1-a	stromal cell derived factor-1-a
SNP	single nucleotide polymorphisms
SOD1	superoxide dismutase 1
SVC	slow vital capacity
AE	treatment-emergent adverse event
TGF-β1	transforming growth factor beta-1
US	United States
VEGF	vascular endothelial growth factor

1 EXECUTIVE SUMMARY

1.1 Introduction

This briefing document presents the positive benefit-risk assessment for approval of NurOwn, a mesenchymal stem cell (MSC) secreting neurotrophic factors (MSC-NTF cells) therapy from BrainStorm Cell Therapeutics Ltd. (Sponsor), for treatment of people living with amyotrophic lateral sclerosis (ALS). Overall, the totality of evidence shows that NurOwn has a consistent and clinically meaningful treatment effect across a broad range of patients with ALS, which is further supported by significant results across multiple biomarkers. Additionally, the data support the safety of repeat intrathecal (IT) administration of NurOwn in patients with ALS, a devastating disease with significant unmet medical need and too few treatment options.

1.2 Background and Unmet Need

ALS is a relentlessly progressive neurodegenerative disease that results in the dysfunction and death of motoneurons in the brain and spinal cord. When motoneurons become damaged and eventually die, the denervated muscles are atrophied with resulting weakness in function that progresses to muscle paralysis. With the progressive loss of function in their bulbar, limb and respiratory muscles, people living with ALS lose their ability to speak, eat, move, and eventually breathe.

The biological mechanisms underlying ALS are complex, although recent scientific progress indicates that neurodegeneration may be linked to deficient neuroprotection and neuroinflammation (Zhang, Xiao, Mao, & Xia, 2023). In this universally fatal, heterogeneous disease, the median survival is only 2-to-5 years from clinical onset. Currently approved treatments offer modest benefit, highlighting the significant unmet in ALS.

This underscores the importance of exercising regulatory flexibility in applying the statutory standards to therapies for serious diseases and assessing the sufficiency of evidence of a treatment effect. The Food and Drug Administration's (FDA's) guidance on ALS explains that “FDA has long stressed the appropriateness of exercising regulatory flexibility in applying the statutory standards to drugs for serious diseases with unmet medical needs, while preserving appropriate assurance of safety and effectiveness” (FDA, 2019). This includes FDA’s recognition that evidence of a treatment effect can be assessed by “less decline, stabilization, [or] improvement” in function and that objective findings “even if of relatively small magnitude” can demonstrate efficacy.

Guiding principles of medical ethics also are critical to the determination here. These include the principles of beneficence and patient autonomy when there is sufficient evidence of safety and efficacy. As Dr. Janet Woodcock, Principal Deputy Commissioner of FDA, has observed, FDA must consider the risks of not approving a therapy that could be efficacious: ““A type II error, and failing to get a good drug on the market, could hurt

patients as much as a type I error of allowing a bad drug to slip through the regulatory gateway" (Minokadeh, 2023).

The potential harm here is not hypothetical. In the words of a person living with ALS who also is a physician, "While some might believe that waiting for multiple phase 3 trials to confirm efficacy is required, I can tell you that as a person living with ALS, we do not have the time to wait for this. If we have to wait five years for another phase 3 trial, 30,000 people with ALS will die waiting" (Sampat, 2023). Indeed, time is the one thing that people living with ALS do not have on their side. The word time was mentioned 152 times in the public comments by 125 people who had posted in advance of this briefing document being finalized. In the words of one such comment by a physician living with ALS: "We do not have the luxury to await the results of another trial. We will not survive the time period this will take. I implore you to demonstrate the regulatory flexibility that has been promised to us" (Lewin, 2023).

1.3 Product Description

NurOwn has a unique, multimodal mechanism of action (MoA) that simultaneously targets multiple biological deficiencies associated with ALS, specifically modulating neuroprotective and neuroinflammatory pathways resulting in a reduction of neurodegeneration and cell death. The relationship between pro- and anti-inflammatory effects and neurodegeneration in ALS is intricate and currently subject to great investigation. Inflammation can initially play a protective role in clearing cellular debris resulting from motoneuron degeneration, but chronic inflammation can exacerbate the disease by damaging neurons (Liu & Wang, 2017; Zhang et al., 2023). Different from existing therapies, NurOwn is a stem cell therapy, consisting of autologous bone marrow-derived MSCs that have been induced ex-vivo by a culture based process to secrete neurotrophic factors (NTFs) such as glial-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), Galectin-1 (Gal-1), and leukemia inhibitory factor (LIF) (Section 3.2). NurOwn, through its MSC-NTFs, balances the immune response through modulation of inflammation and by preserving the dynamics of the interplay with neurodegenerative processes.

NurOwn has the dual capacity to offer the benefits both of MSCs (promoting neurogenesis, modulating neuroinflammation, and contributing to neuroprotection) and of NTFs (enhancing neuronal survival and function), in close proximity to damaged motoneurons in the central nervous system (CNS) (Figure 7; Section 3.3). This approach overcomes several limitations of previous clinical studies of NTFs, which have relatively short plasma half-lives and cannot cross the blood-brain barrier (BDNF Study Group, 1999b; Pardridge, 2002a, 2002b; Pradat et al., 2001).

NurOwn is delivered intrathecally as a treatment course composed of three individual doses of 100-125 × 10^6 MSC-NTF cells administered every eight weeks. After completing a single treatment course of NurOwn, participants will have received a total of

300-375 × 10^6 MSC-NTF cells into the subarachnoid space, which allows NurOwn to reach the targeted areas of neuronal damage in the CNS.

1.4 Development Program

NurOwn has received Orphan Drug and Fast-Track designations from the FDA.

The clinical development program for NurOwn includes four completed clinical trials: one Phase 1/2 and one Phase 2a study (both open-label), one Phase 2 study (double-blind and placebo-controlled trial, where the primary endpoint of safety was met), and one Phase 3 study (double-blind and placebo-controlled). There also has been an expanded access program (EAP) and an additional Phase 3b/4 study is in development with enrollment targeted in the first half of 2024.

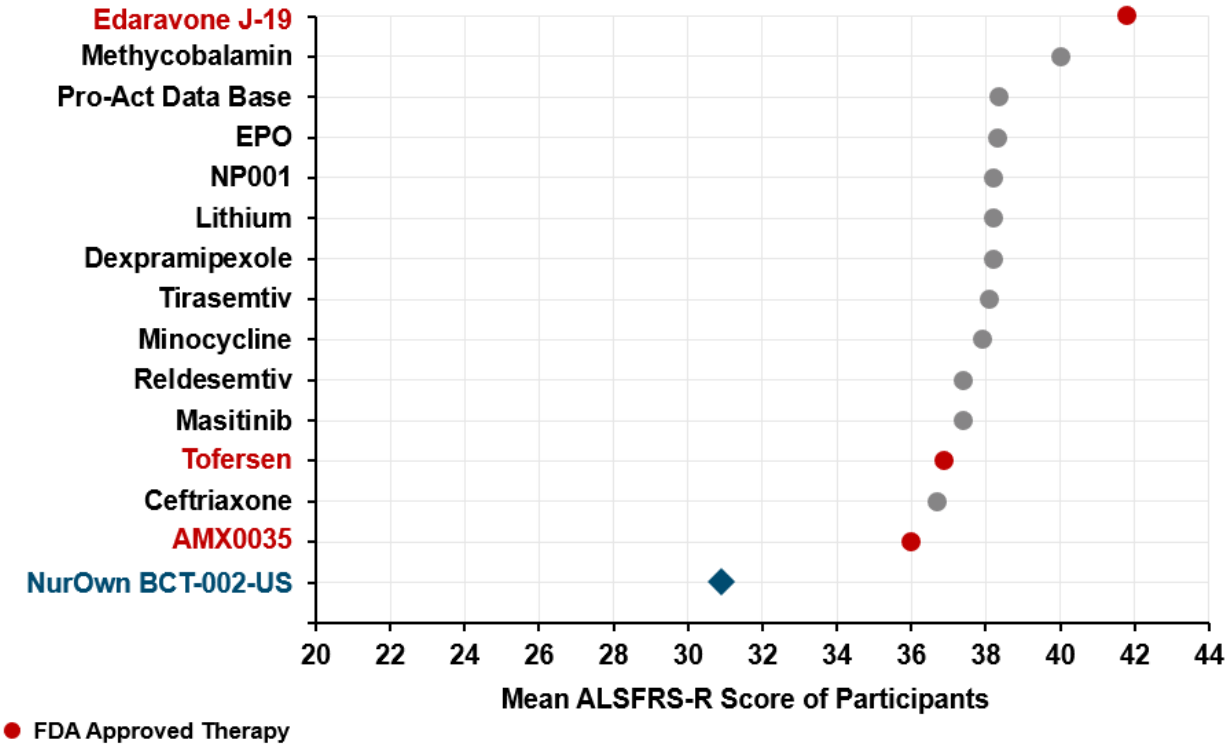
1.5 Efficacy Overview

Clinical trial results show that NurOwn is effective across a broad range of participants, who reflect the heterogenous, real-world population of patients with ALS. The pivotal Phase 3 trial did not meet its primary endpoint given the factors described below, but NurOwn overall produced a consistent, clinically meaningful treatment effect on important endpoints across pre-specified and post-hoc subgroups, including the primary endpoint and key secondary endpoint average change from baseline in the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R).

It is important to note that the Phase 3 trial enrolled a larger number of participants (23%) with advanced ALS at the start of the study, as indicated by a lower baseline ALSFRS-R total score average, as compared to other late-phase trials in ALS (Figure 1). For example, the baseline average score of the NurOwn population was five points below that of AMX0035 or RELYVRIO (sodium phenylbutyrate and taurursodiol) and six points below tofersen or QALSODY, two ALS therapies recently approved by CDER. Notably, these therapies were granted approval even though CDER had “considerable concerns that [AMX0035] data may not be sufficiently robust” to be approved and tofersen did not meet its primary endpoint in its Phase 3 trial (FDA, 2022).

While the ALSFRS-R is the most widely used assessment tool in ALS, analysis of the NurOwn Phase 3 trial (BCT-002-US) data uncovered an inherent floor effect in the ALSFRS-R scale, not previously appreciated by the ALS community, which impacted the results (see Sections 6.1.1 for additional details regarding the instrument and the floor effect, respectively). Even though the floor effect was not appreciated in historical trials at the time they were run, there is evidence of a floor effect occurring in past studies albeit to a lesser degree (PRO-ACT: 5%, Phase 3: 22%, Section 6.3.7.3). The impact in this Phase 3 trial results in participants automatically achieving clinical response criteria on the primary endpoint as a result of the floor effect, a misclassification of clinical response.

Figure 1: Phase 3 Study BCT-002-US: Participants with Advanced ALS Disease Compared to Published Phase 2 and Phase 3 Clinical Trials



Note: Treatments in red represent FDA-approved products for treatment of ALS. Number of BCT-002-US participants with baseline ALSFRS-R ≤ 25 = 44 of 189 (23.3%).
Sources: (Atassi et al., 2014; Cudkowicz et al., 2014; Cudkowicz et al., 2013; Gordon et al., 2007; Group et al., 2013; Kaji et al., 2019; Lauria et al., 2015; Miller et al., 2015; Mora et al., 2019; Paganoni et al., 2020; Jeremy M. Shefner et al., 2021; J.M. Shefner et al., 2019; Writing & Edaravone, 2017).

A floor effect is observed due to the inability of a scale to capture progression in participants with the lowest scores on individual items. As FDA has explained, a floor effect occurs “when the lower extreme of the concept(s) assessed by item response categories or by the scale core of the instrument does not sufficient match the level of the lower extreme of the target population” (FDA, 2018). This effect was observed to the greatest extent on the ALSFRS-R in the subset of participants with the lowest baseline scores (23% of Phase 3 participants) and impacted the overall results. Importantly, in the majority of participants where ongoing decline could be measured, a consistent and meaningful effect was observed across endpoints, including a nominally significant treatment effect in a pre-specified subgroup ($p = 0.05$) and across several post-hoc sensitivity analyses ($p < 0.05$) (Section 6.3.4.2 and Section 6.3.7). (Note that all p-values for the Phase 3 study in this document are reported as nominal p-values.)

Furthermore, biomarker assessments showed significant improvements with NurOwn treatment compared to placebo in an analysis incorporating all trial participants (Section 6.3.8). These findings were consistent across biomarkers that belong to three main categories or disease pathways: neuroinflammation, neurodegeneration and

neuroprotection. Importantly, this benefit was observed in those participants with advanced ALS disease, i.e., those for whom the ALSFRS-R demonstrated measurement challenges.

Additionally, neurofilament light chains (NfL), transforming growth factor beta-1 (TGF-β1), and Gal-1 demonstrated a strong relationship with and were predictive of clinical outcomes, as measured by ALSFRS-R scores. Specifically, lower NfL and higher TGF-β1 levels at baseline reflective of less neurodegeneration and neuroinflammation, and improved neuroprotection, as measured by an increase in Gal-1 from baseline, were associated with slower functional decline in the trial. Furthermore, reductions in NfL corresponded with preservation of function, as measured by the ALSFRS-R. Overall, the biomarker data demonstrated a consistent biological effect with NurOwn in an analysis of all trial participants across multiple biomarkers.

Patient-reported changes in daily activity showed meaningful improvements observed as a result of the NurOwn Expanded Access Program (Stevens Nation, 2022), including:

- “walk without a walker, walk longer distances, walk in sand or farm field,”
- “swallow dense foods like fried chicken, rice, sushi,”
- “speak more clearly without needing a caregiver to translate,”
- “use a cell phone to text and type,” and
- “breathe stronger as evidenced by improved FVC [forced vital capacity].”

(Additional details on patient reports are provided in Appendix 10.1.)

Overall, the pivotal Phase 3 trial demonstrated both clinically and biologically meaningful effects, as shown across clinical endpoints and CSF biomarkers. When the confounding effects in the data are addressed through a subgroup of participants with no floor effect at baseline, NurOwn demonstrated a consistent treatment benefit across all endpoints, with a significant ($p < 0.05$) treatment effect across the primary and key secondary endpoints. These results are supported by comprehensive prespecified and post-hoc subgroup analyses, which account for limitations of the ALSFRS-R. Importantly, the clinical benefit is observed across all four functional subscales of the ALSFRS-R (i.e., bulbar, gross motor, fine motor, and respiratory). In addition, analyses of totality of evidence were conducted by combining evidence of treatment benefit observed across different timepoints for clinical endpoints, different functional subscales, and different biomarkers in order to examine the likelihood of these results occurring by chance. The resulting significant p-values in these analyses show strong statistical evidence of a true treatment effect, through the consistent pattern observed in the trial in favor of NurOwn, differentiating NurOwn results over placebo.

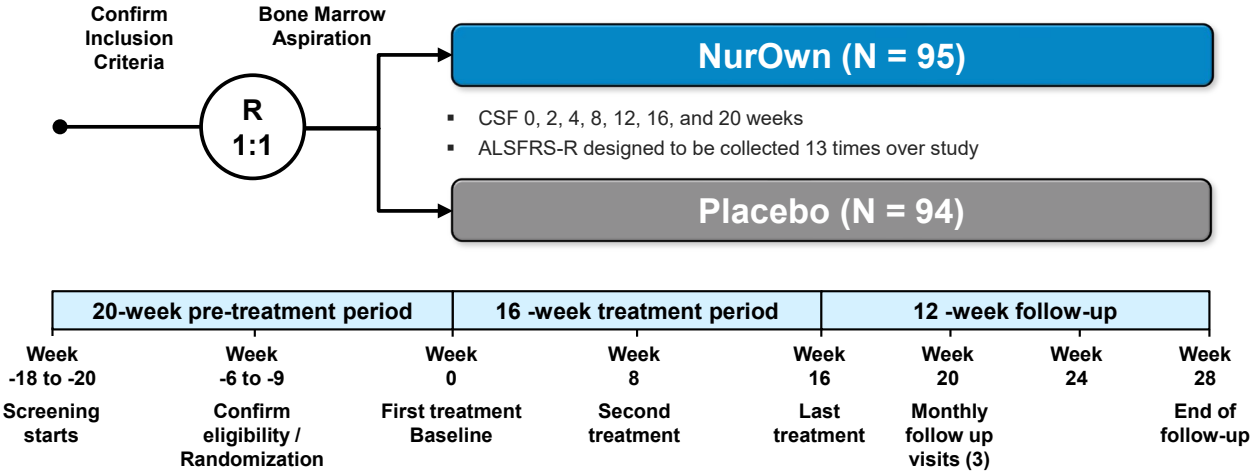
1.6 Efficacy Findings

1.6.1 Pivotal Phase 3 Study (BCT-002-US) Design

Study BCT-002-US was the pivotal, multicenter, randomized, double-blind, placebo-controlled Phase 3 study of NurOwn for the treatment of people living with ALS.

- Participants with ALSFRS-R scores ≥ 25 at the time of screening, in addition to a decline of ≥ 3 points during the 12 weeks before randomization, were eligible for randomization and continuation of the study (Figure 2).
- Participants eligible for continuation at Week -6 to -9 were randomized 1:1 and allowed to progress to the Baseline visit (Week 0) to receive the first of three doses of either a total of 100-125 × 10^6 cells of NurOwn or placebo.
- To complete the treatment course, two additional doses were provided at 8-week intervals, i.e., at the Week 8 and Week 16 visits.
- Three additional monthly follow-up visits were conducted, resulting in a total duration of the double-blind, placebo-controlled period of 28 weeks.
- A total of 196 participants were randomized (1:1) to receive NurOwn (N=98) or placebo (N=98). Of these, 189 participants received at least one dose of treatment (NurOwn: N=95; placebo: N=94) with 153 (81%) participants receiving the entire treatment course (NurOwn: 73 [77%]; placebo: 80 [85%]).

Figure 2: Phase 3: Randomized, Placebo-Controlled, Double-Blind Trial



CSF=cerebrospinal fluid; R=randomization.

1.6.2 Background on ALSFRS-R in Clinical Trials

ALSFRS-R was the primary measure of motor function used to determine participant's response to treatment in the Phase 2 and Phase 3 studies. The instrument is a questionnaire comprising 12 items, with each item scored on a scale of 0 (no function) to 4 (full function) across four subscales: bulbar, fine motor, gross motor, and respiratory,

thus generating an ALSFRS-R total score, which ranges from 0 (maximum disability) to 48 (no disability) (Cedarbaum et al., 1999). The ALSFRS-R is the most widely used assessment tool available as a primary measure of functional status and disease progression in ALS. This measurement tool has its strengths, including ease of use and correlation with survival. One of the main challenges with the ALSFRS-R is its poor discrimination capability to measure degrees of change among participants with higher and lower functional status, described as ceiling and floor effects (Hartmaier et al., 2022), which have the potential to interfere with evaluation of treatment effect, particularly in studies of relatively small size and short duration.

A floor effect occurs when there is a defined lower limit, and a participant's functional status can continue to deteriorate beyond the measure of the scale. For example, if a participant's score on one of the items of the ALSFRS-R is a 0, that participant's ongoing decline can no longer be measured despite further and progressive loss of function.

The floor effect is further described through public comments:

> "*An acknowledged floor effect on the ALSFRS-R scale impacted the Debamestrocel data. The tool is not sensitive enough to detect ongoing changes once people have a zero in any of their functional domains. An example of the Floor Effect can be found in the three Fine Motor Skill questions that relate to: (1) handwriting; (2) ability to groom oneself and take care of daily hygiene; and (3) ability to cut food and feed oneself with utensils. If you are unable to do these three tasks, you get 0/12 possible points.*
>
> *However, as I can attest from my brother's own ALS, there are still many things you can do with your hands and upper limbs. You can type, text, operate a mouse, gaming device, remote control, hold a urinal bottle, push a call button for a caregiver and most importantly, operate a wheelchair joystick. You can still hold a child in your arms. All of these are very clinically meaningful. But once you have a "0" in the above three questions, the ALSFRS doesn't measure when you continue to decline and can no longer do these clinically meaningful tasks"* (Minokadeh, 2023).

In the Phase 3 study, 83 (44%) participants had an item-level floor effect — i.e., at least one item with a value of 0 — at baseline. This finding becomes more prominent in participants with lower total baseline ALSFRS-R scores (Figure 31). In trial participants with a baseline score below 25, 100% of participants had an item-level floor effect. Moreover, participants with a baseline score of ≤ 25 had a high rate of zero scores in the items within the fine and gross motor subscales that averaged approximately 40% of those items (Table 6). This circumstance can result in participants automatically achieving clinical response criteria on the primary endpoint (described below) as a result of the floor effect, a misclassification of clinical response.

In order to account for the floor effect of the ALSFRS-R scale and mitigate the confounding effects at the lower end of the scale, a series of prespecified and post-hoc subgroup analyses were conducted (floor effect details are provided in Section 6.3.7).

1.6.3 Phase 3 Primary and Secondary Endpoints and Results

All efficacy analyses were performed using the modified intent-to-treat (mITT) population, which included all participants who were randomized, treated, and had at least three ALSFRS-R assessments: one pre-treatment assessment of ALSFRS-R prior to the baseline assessment, a baseline assessment, and at least one post-treatment assessment.

The efficacy endpoints in the Phase 3 study included the following:

- **Primary Endpoint**: Responder analysis of change in rate of decline as assessed by the ALSFRS-R.
    - Responder definition: ≥ 1.25 points/month improvement in post-treatment vs pre-treatment slope in ALSFRS-R score at Week 28.
- **Key Secondary Endpoint**: ALSFRS-R total score change from Baseline to Week 28.
- **Other Secondary Endpoints**:
    - Responder analysis: post-treatment slope improving by ≥ 100%.
    - Combined assessment of function and survival (CAFS).
    - Slow vital capacity (SVC) change from Baseline to Week 28.
    - Time to death due to disease progression and death due to any reason as a sensitivity analysis.
    - Time to death or tracheotomy. (Note: analysis not completed as there were no tracheotomies in the study.)
    - Cerebrospinal fluid (CSF) biomarkers analysis in relationship to clinical efficacy.

Pre-specified subgroup analyses of all endpoints were conducted on participants divided into groups based on a baseline ALSFRS-R score threshold of ≥ 35. As summarized in Section 6.3.7, while the subgroup ≥ 35 effectively minimized the impact of the floor effect on pre-specified endpoints, this threshold was chosen as it was the anticipated baseline average for the trial and would have identified two subgroups of similar size. The baseline average was lower, however, due to the inclusion of participants with advanced ALS and therefore the subgroup of participants ≥ 35 included 31% of the trial and had very low power.

In discussions between the Sponsor and the FDA, the parties both recognized the importance of the key secondary endpoint (average change in ALSFRS-R total score from baseline to Week 28) and discussed whether it should be the primary endpoint. The FDA emphasized that its evaluation of the evidence would be based on the totality of data (additional details are provided in Section 4.1).

Results from these prespecified efficacy analyses were as follows:

- Primary endpoint results showed that 32.6% of participants treated with NurOwn responded to study treatment versus 27.7% for placebo (Figure 21). These numerically favorable results were not statistically significant (odds ratio [OR]=1.33; p=0.45).
    - Primary endpoint results in the prespecified subgroup ≥ 35 showed 34.6% of participants with NurOwn responded to study treatment versus 15.6% for placebo (Figure 22). The 19% difference in response rate observed between treatments, aligned with the power calculations assumptions of a 35% response rate with NurOwn versus 15% with placebo, but was not statistically significant (p=0.305).
    - In the pre-specified subgroup < 35, the rate of response between NurOwn and placebo treated participants was similar (31.9% NurOwn, 33.9% placebo, p=0.744).
- For the key secondary endpoint of change from baseline to Week 28 in ALSFRS-R total score in all trial participants, participants in the NurOwn group showed numerically favorable but not significant change compared to placebo: -5.52 points vs -5.88 points, respectively, for a treatment difference of 0.36 points (p=0.693; Figure 25).
    - The prespecified subgroup analysis in participants with ALSFRS-R scores ≥ 35 points at baseline showed a clinically meaningful and statistically significant difference in the mean change from baseline to Week 28 in ALSFRS-R score: -1.56 points for participants receiving NurOwn versus -3.65 for placebo, for a treatment difference of 2.09 points (p=0.050; Figure 26).[1]
    - In the subgroup of participants with a baseline ALSFRS-R total score < 35, the change in ALSFRS-R total score were similar between the NurOwn and placebo groups (-6.95 and -7.00, respectively; p=0.968), which is the same pattern observed for the primary efficacy endpoint.

Results for other secondary endpoints are summarized in Table 1, and additional details on secondary endpoints are provided in Section 6.3.6. Biomarkers were assessed using a separate statistical analysis plan (Section 6.3.1.5.5), and results are discussed in Sections 1.6.5 and 6.3.8.

[1] The original analyses published in Muscle and Nerve in March 2022 contained an error in the subgroup analysis for the key endpoint of average change from baseline to endpoint in ALSFRS-R. The analyses included an incorrect model, incorporating interaction terms between the subgroup and treatment. The analyses were corrected, and an erratum was published on 12 August 2022 to ensure that data from the trial is shown correctly and in accordance with the prespecified analysis plan. The revised results are reported in this document. Erratum available at: (2022), Erratum. Muscle & Nerve, 66: E26-E27.

Table 1: Phase 3 Study BCT-002-US — Other Secondary Endpoints

Secondary Endpoints (through Week 28)	All Trial Participants NurOwn (N=95)	All Trial Participants Placebo (N=94)	ALSFRS-R ≥ 35 NurOwn (N=26)	ALSFRS-R ≥ 35 Placebo (N=32)
≥ 100% improvement in ALSFRS-R slope, n (%), through Week 28	13 (13.7%)	13 (13.8%)	7 (26.9%)	5 (15.6%)
Combined Assessment of Function and Survival (CAFS), average rank at Week 28	73.7	72.2	93.7	78.3
Slow vital capacity (SVC), average change to Week 28*	-12.9	-11.6	-5.8	-4.8
Event-free probability for deaths due to disease progression, through Week 32	90.4	92.2	> 99†	> 99†
Event-free probability for deaths due to any cause, through Week 32	88.3	89.2	> 99†	90‡

* 60% SVC data were missing due to COVID-19 pandemic hospital restrictions at Week 28.
Note: Results from secondary endpoints through Week 32 do not include two deaths that occurred in participants randomized to placebo that occurred before treatment.
†: No deaths occurred through Week 32.
‡: One death occurred through Week 32.

As detailed below, an appreciation of the role of the floor effect is necessary to understanding this data.

1.6.4 Prespecified and Post-Hoc Subgroup Analyses to Minimize Confounding of Floor Effect

Importantly, while the baseline demographics and disease characteristics were relatively balanced in the trial at a treatment level, the unexpectedly large number of participants enrolled in the trial with advanced ALS resulted in the inability to measure decline on impacted items, which confounded the ability to measure treatment effect in the trial. The rate of zero (0) values, specifically on fine motor and gross motor, for participants with baseline ALSFRS-R $\leq$ 25 (~40% across all six items) is especially problematic to the measurement of functional decline because the fine and gross motor subscales account for 70% of the decline in trials. In participants with high susceptibility to the floor effect, resulting from fine and gross motor items starting at 0, this led to the ALSFRS-R inaccurately reflecting changes in the rate of decline, as used to define clinical response in the primary endpoint. This scenario can misrepresent treatment response and result in a participant being automatically classified as a “responder” on the primary endpoint due to the floor effect. Additionally, in the placebo treatment group, there were more participants with lower ALSFRS-R scores who also had more rapidly progressing disease, increasing the likelihood of scores being impacted by the floor effect (Figure 30) and promotes misinterpreting the higher rate of placebo participants meeting the response criteria as an elevated placebo response. The floor effect must be addressed to draw valid treatment conclusions from the trial.

In order to accurately evaluate the treatment response and minimize the confounding floor effect, prespecified and post-hoc subgroup analyses were performed on the primary

endpoint and key secondary endpoint. These analyses can be grouped into two categories: methods that are more comprehensive in removing the influence of confounding due to the floor effect, and those that are more conservative and allow a greater influence of the confounding into analyses. The former methods are more selective for the number of participants, while the latter includes more trial participants.

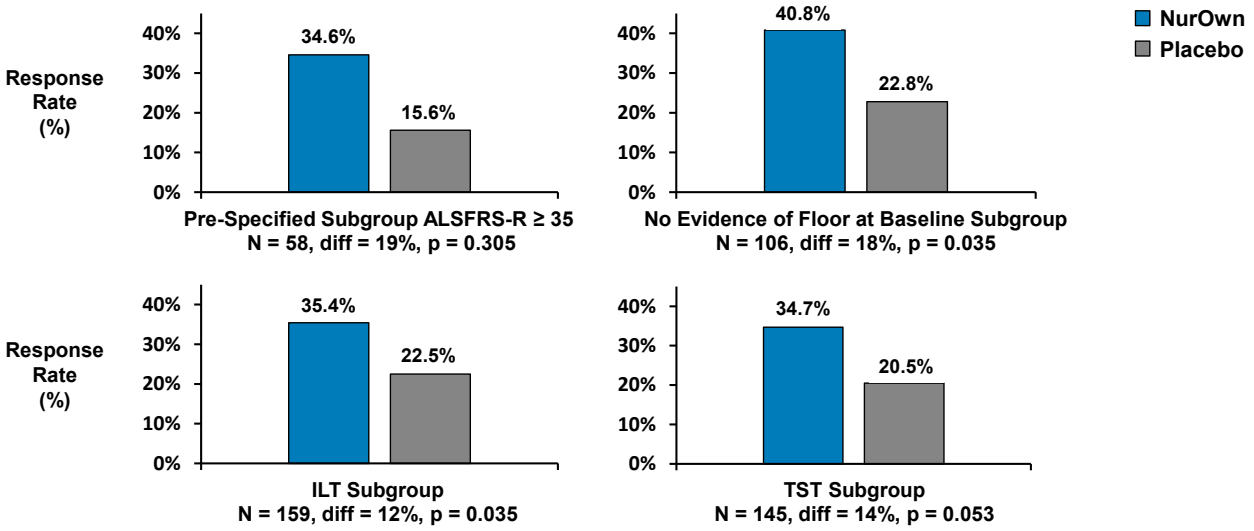
- More Comprehensive Approaches:
    - **Prespecified total score threshold: Subgroup by ALSFRS-R ≥ 35**, which includes only participants who had a baseline ALSFRS-R total score of ≥ 35. This group included 31% of the mITT population, or 58 participants.
    - **Post-hoc item-level threshold: Subgroup with No Evidence of Floor Effect**, which includes only participants with no evidence of floor effect at baseline (i.e., all ALSFRS-R items had score ≥ 1 at baseline). This group included 56% of the mITT population, or 106 participants.
- More Conservative Approaches:
    - **Post-hoc total score threshold: Subgroup by ALSFRS-R > 25**, which includes only participants with baseline ALSFRS-R scores > 25. This group included 77% of the mITT population, or 145 participants.
    - **Post-hoc item-level threshold**: **Subgroup of Individuals with a Minimum of Two Items with Baseline Scores of ≥ 2**, which includes only participants who had a minimum of two (out of six possible) fine and gross motor subscale items with baseline scores of ≥ 2. This group included 84% of the mITT population, or 159 participants.

As illustrated below, in the more comprehensive post-hoc approach, the item-level threshold (N=106 [56.1%]) who had all ALSFRS-R items ≥ 1 (i.e., no item-level floor effect at baseline):

- A higher response rate at Week 28 with NurOwn (40.8%) vs placebo (22.8%) was significant (p=0.035 Figure 3 [upper-right panel]) and
- Participants treated with NurOwn retained an average 2.3 more points on the ALSFRS-R total score at Week 28 compared to placebo (-2.7 vs -5.0 points, respectively; p=0.040; Figure 4 [upper-right panel]).

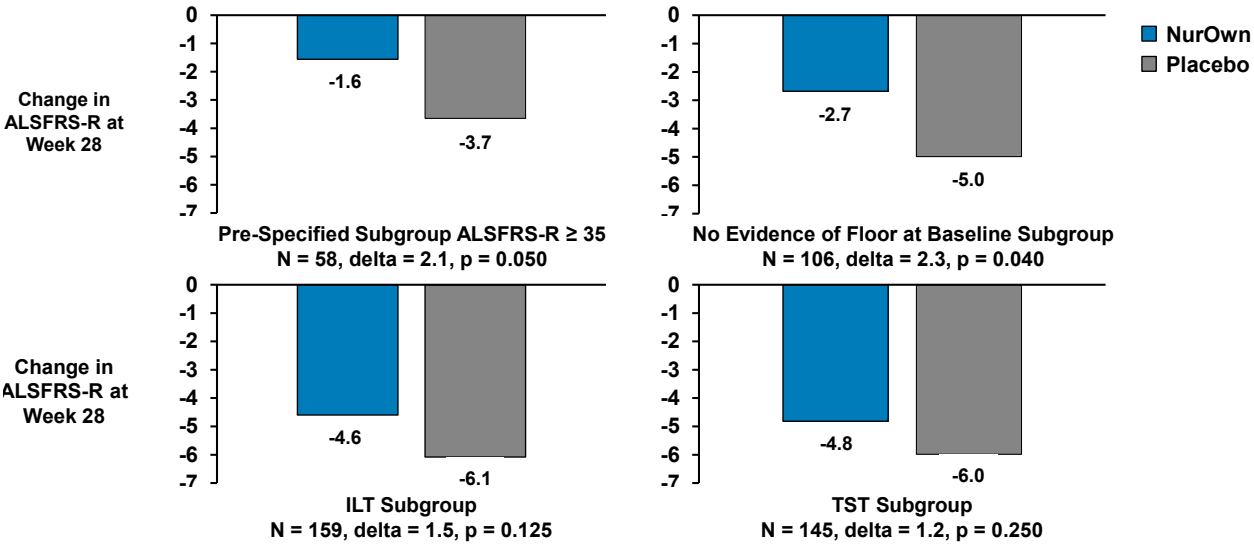
Results from the other analysis approaches to examine the floor effect similarly supported clinically meaningful benefit on clinical endpoints; additional details on the results of the post-hoc subgroup analyses minimizing the floor effect are provided in Section 6.3.7.

Figure 3: Phase 3 Study BCT-002-US — Pre-Specified and Post-Hoc Subgroup Analyses on Primary Endpoint to Mitigate the Floor Effect



Abbreviations: ILT=item-level threshold; TST=total score threshold.
Note: No Evidence of Floor at Baseline Subgroup=participants with all 12 items score > 0 at baseline. TST subgroup=participants with baseline ALSFRS-R total score > 25. ILT Subgroup=participants with at least two of the six fine and gross motor subscale items scores ≥ 2 at baseline.

Figure 4: Phase 3 Study BCT-002-US — Pre-Specified and Post-Hoc Subgroup Analyses on Key Secondary Endpoint to Mitigate the Floor Effect



Abbreviations: ILT=item-level threshold; TST=total score threshold.
Note: No Evidence of Floor at Baseline Subgroup=participants with all 12 items score > 0 at baseline. TST subgroup=participants with baseline ALSFRS-R total score > 25. ILT Subgroup=participants with at least two of the six fine and gross motor subscale items scores ≥ 2 at baseline.

1.6.5 Biomarker Results

The field of biomarkers in ALS is emerging with notable interest and published data supporting the relationship between certain biomarkers and ALS decline. In the advisory committee meeting for the recently FDA-approved therapy tofersen, the committee was unanimously in agreement (Yes: 9, No: 0, Abstain: 0) to Question 1 that the available evidence was sufficient to conclude that a reduction in plasma NfL concentration in tofersen treated participant was reasonably likely to predict clinical benefit in the treatment of patients with SOD-1 ALS. The Committee members further cited reasons discussed with respect this question as the rationale for their vote, with several members emphasizing the totality of the evidence was supportive of a reduction in plasma NfL concentrations as a biomarker or surrogate for clinical benefit. Please see the transcript for details of the committee's discussion (FDA, 2023c).

Here, the Phase 3 study included a comprehensive assessment of 45 ALS-related biomarkers expected to be present in the CSF of participants (Section 6.3.1.5.5). CSF was collected at baseline, Week 2, and Week 4 and then every four weeks through Week 20. Additional CSF collections at Weeks 10 and 18, which would have required an additional spinal tap, were not added to minimize participant burden. Therefore, we do not know whether the same maximal change observed two weeks after the first treatment for some of the biomarkers would have been observed two weeks after treatments two and three.

Biomarker results from the Phase 3 study (Section 6.3.8) show robust and favorable changes over time among participants treated with NurOwn. Significant improvements with NurOwn compared to placebo were observed on ALS biomarkers across key disease pathways of neurodegeneration, neuroinflammation (both pro-inflammatory and anti-inflammatory), and neuroprotection in all participants in the trial (Table 2).

Table 2: Phase 3 Study BCT-002-US — Biomarkers for Neuroinflammation, Neurodegeneration, and Neuroprotection with Treatment Effect from NurOwn

Primary Pathway	Biomarkers with Significant Treatment Effect*
Neurodegeneration	DR6, NfL, pNfH, TWEAK
Neuroinflammation: Pro-inflammatory	MCP-1, OPG, S100B, SDF-1a
Neuroinflammation: Anti-inflammatory	Fetuin-A, has-miR-146a-5p, has-miR-146b-5p, IL-37, MSR1, TGF-β1
Neuroprotection	BDNF, Clusterin/ApoJ, Galectin-1, G-CSF, GDF-15, HGF, NMNAT1, VEGF

* $p < 0.05$, overall treatment effect or treatment by time effect that favored NurOwn

The impact of NurOwn treatment across many biomarkers was rapid, as measured by the large magnitude of change from baseline recorded two weeks after the first treatment (Figure 5; Section 6.3.8), while other biomarkers had gradual change with the largest

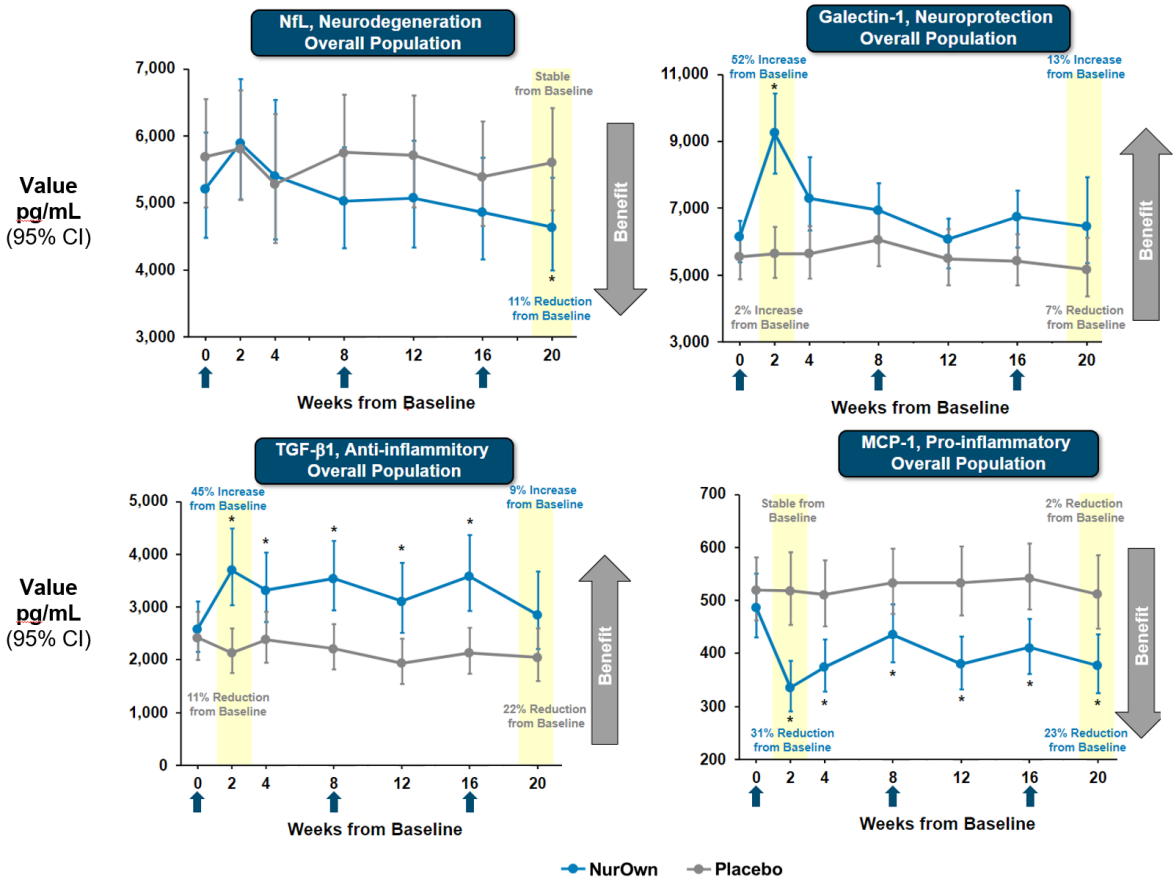
change observed from baseline at the final assessment at Week 20. When reviewing the CSF biomarker levels over time for biomarkers that changed rapidly after the first treatment (e.g., Gal-1, TGF-β1, and monocyte chemoattractant protein-1 [MCP-1]), a pharmacodynamic relationship is observed (Figure 5).

Similar patterns were observed for the subset of participants with baseline ALSFRS-R total scores ≤ 25, i.e., participants with advanced disease where the ALSFRS-R often fails to accurately measure clinical progression (Figure 37; Section 6.3.8.1. The similarity in patterns of this subgroup and the overall trial population in biomarkers suggests that NurOwn is biologically active in all trial participants.

Importantly, converging lines of evidence suggest a connection between early favorable changes in many of the neuroinflammation and neuroprotection CSF biomarkers assessed in the Phase 3 study and long-term patient outcomes, including markers of neurodegeneration, such as NfL (Beers & Appel, 2019; Beers et al., 2017).

As discussed in Section 1.3, the pathophysiology of ALS is characterized by a complex interplay between inflammation and neurodegeneration. Inflammatory processes, involving microglia and glial cells, can contribute to the progressive damage of motoneurons; while protein misfolding, excitotoxicity, and mitochondrial dysfunction collectively contribute to the degenerative process (Liu & Wang, 2017; Zhang et al., 2023). Hence, NurOwn's early effect on neuroinflammation and neuroprotection, with the change detectable as early as two weeks post-dosing in some biomarkers and lasting over several weeks/months, are important to halting the self-perpetuating cycle of neurodegeneration (Zhang et al., 2023).

Figure 5: CSF Biomarker Levels Across Key Disease Pathways at Week 20 (mITT Population)



CI=confidence interval; CSF=cerebrospinal fluid.
Note: Blue arrows indicate treatment days. Levels are adjusted for baseline disease covariates, as discussed in the Statistical Analysis Plan for biomarker analyses (Section 6.3.1.5.5).

Importantly, NfL, TGF-β1, and Gal-1 demonstrated a strong relationship with clinical outcomes, as measured by ALSFRS-R scores. A model designed to identify biomarkers predictive of clinical outcomes observed in the trial, which was unconstrained in the final choice of biomarkers or inclusion of pathways, selected these three biomarkers spanning neurodegeneration, neuroinflammation and neuroprotection. Specifically, lower NfL and higher TGF-β1 levels at baseline reflective of less neurodegeneration and neuroinflammation, and improved neuroprotection, as measured by an increase in Gal-1 from baseline, were associated with slower functional decline in the trial.

Additionally, a causal inference that assesses the relationship between change in NfL from baseline to Week 20 and change in ALSFRS-R from baseline to Week 28 shows that when accounting for baseline ALS disease characteristics, the reductions in NfL are

associated with less decline in the ALSFRS-R (r = -2.52, p=0.08) and confirms the same relationship observed in another recent ALS trial.

The robust and sustained changes with NurOwn compared to placebo observed in important biomarkers in ALS provide additional evidence of the treatment effect on ALS disease progression and NurOwn's MoA.

1.6.6 Totality of Evidence Analyses

When the confounding floor effect is addressed, using data from the subgroup of participants with no floor effect (post-hoc item-level threshold), strong evidence of NurOwn's superiority over placebo is observed in totality of evidence analyses, using a simple non-parametric method (Li et al., 2020; Wei & Lachin, 1984). These analyses assess the treatment benefit across multiple timepoints, subscales of the ALSFRS-R, and biomarkers, using the data collected. Regarding the primary endpoint (clinical response rates over time), the treatment benefit began early and was sustained over time, with a difference in response rates of approximately 20% between the NurOwn and placebo treatments groups in favor of NurOwn (Figure 45). The question is, if there were no true temporal treatment benefit from NurOwn, what would be the chance of observing such a large and consistent separation over time? With 3000 permutation samples, the one-sided p-value is 0.005 (the probability that these 3000 mean z-scores > 2.10). A similar question regarding the likelihood of observing a consistent benefit of NurOwn over time on the secondary endpoint (average change from baseline on the ALSFRS-R), results in a one-sided p-value of 0.007. Both results suggest that the chance of observing this profile is quite small if there were no true treatment benefit from NurOwn.

Next, instead of using the total ALSFRS-R score, we explored how NurOwn impacts the four subscales (bulbar, respiratory, fine motor and gross motor) over time. The question of interest is, if there were no true treatment effects from NurOwn for each subscale, what would be the chance of observing the consistent, positive trend in favor of NurOwn (Figure 46). Using the same method (Li et al., 2020), the z-scores from four subscales are combined, and the one-sided p-value is 0.007 (Figure 47), again suggesting strong statistical evidence of the treatment benefit.

Lastly, the totality of evidence can be examined by combining the treatment benefit observed across different biomarkers over the study period. Specifically, we focus on four biomarkers from four different pathways: NfL (neurodegeneration), TGF-β1 (anti-inflammatory), MCP-1 (inflammatory) and Gal-1 (neuroprotection). The question we wish to explore is, what is the likelihood of observing a consistent, positive trend in favor of NurOwn across these four biomarkers if there were no true treatment effect of NurOwn (Figure 48). Using the method of Li (Li et al., 2020), the z-scores from the four biomarkers are combined, and the one-sided p-value <0.0001 (Figure 49), again suggesting the likelihood is very small if there were no true benefit of NurOwn.

In summary, by examining the totality of data and looking across different timepoints, subscales, and biomarkers, we conclude that the consistent treatment effect observed

with NurOwn, in the subgroup of participants with no floor effect, is likely driven by a true treatment effect and not a spurious finding.

1.7 Safety Findings

NurOwn treatment was well-tolerated and had a manageable safety profile.

In the Phase 3 study, most adverse events (AEs) were mild to moderate in intensity and transient in duration. (Table 10; Section 7.3.1). Procedural complications were the most commonly reported AEs and were similar in both groups (Table 11; Section 7.3.2). The incidences of specific terms of procedural pain and post-procedural complication were higher in the NurOwn group; procedural headache was similar in both groups; and fall and post lumbar puncture syndrome were higher in the placebo group. Musculoskeletal pain, back pain, and headache were more common in the NurOwn group.

Serious adverse events (SAEs) were consistent with progression of ALS and with respiratory failure/distress, the most commonly reported SAE in the treated group. More participants in the NurOwn-treated group experienced SAEs, although only three participants with SAEs were considered related to study drug by the Principal Investigator or sponsor: two in the placebo and one in the NurOwn group (Section 7.3.3).

Few participants in either group had AEs leading to treatment withdrawal or discontinuation: one in the NurOwn group and three in placebo (Section 7.3.4).

There were 16 deaths in the trial (10 in the NurOwn group, 6 in the placebo group), none of which were considered by the Investigator or Sponsor as related to study drug in either treatment group (Section 7.3.5). Fourteen of these participants (10 in the NurOwn group and four placebo) died after receiving treatment. Two participants in the placebo group died before receiving any treatment. Seventy five percent (12/16) of deaths were due to progression of ALS or respiratory failure in both the NurOwn (8) and placebo (4) groups (Table 13). The deaths occurred in participants with lower ALSFRS-R scores, lower SVC % predicted scores, and higher rate of decline in pre-treatment ALSFRS-R slope, compared to the total study population.

1.8 Benefit-Risk Summary

NurOwn treatment was well-tolerated and had a manageable safety profile. While the primary endpoint was not achieved, analysis of the key secondary endpoint (change from baseline to Week 28 in ALSFRS-R total score) in a prespecified subgroup revealed a significant effect (p=0.050). Post-hoc analyses accounting for the ALSFRS-R floor effect further reveal a statistically significant treatment effect of NurOwn compared to placebo in both the primary and key secondary endpoints. Additionally, biomarker data from all trial participants demonstrate NurOwn's biological activity across multiple pathways, including neuroinflammation, neurodegeneration, and neuroprotection, and show that treatment-driven reductions in NfL are reasonably likely to be associated with clinical benefit in ALS. The clinical benefit of NurOwn using statistical methodology to estimate the totality of evidence is consistent across different timepoints for clinical endpoints,

ALSFRS-R subscales, and different biomarkers demonstrating strong statistical evidence for a treatment effect. In summary, for participants with the unrelenting and fatal disease of ALS, the totality of data supports the overall benefit-risk profile of NurOwn as a valued treatment in ALS that benefits patients in a clinically meaningful way.

2 BACKGROUND ON AMYOTROPHIC LATERAL SCLEROSIS

Summary

- ALS is a progressive, incurable, and universally fatal disease resulting in degeneration of motoneurons in the brain and spinal cord.
- Survival typically ranges from 2 to 5 years from clinical onset, with most fatalities caused by respiratory failure from damage to the nerves that control breathing.
- Hallmarks of ALS include muscle weakness, stiffness, lack of coordination, muscular atrophy, loss of ambulation, and eventually loss of breathing.
- There are too few options available to treat ALS, highlighting the significant unmet need for safe and effective treatments that will slow the progression of ALS.
- When administered intrathecally, MSCs secreting NTFs have the potential to overcome many limitations of other investigational therapies, delivering critical growth factors directly to the CNS.

2.1 Overview of ALS

Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive, presently incurable, degenerative motor neuron disease of the brain and spinal cord that causes muscle weakness, disability, and eventually death, with a median survival of 2 to 5 years from clinical onset. The disease has an annual incidence of 1-2 cases per 100,000 people and a prevalence of approximately 3-5 cases per 100,000 people (Brown & Al-Chalabi, 2017; J. J. Chen, 2020).

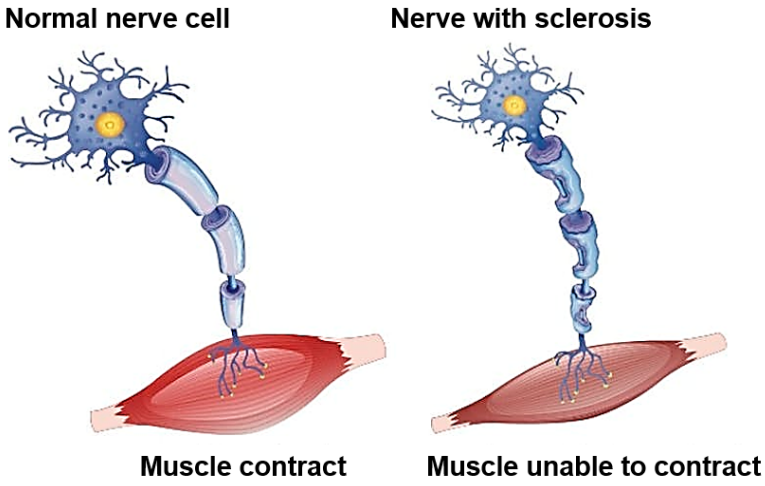
ALS is characterized by cortical cell death with retrograde axonal loss and gliosis in the corticospinal tract (upper motor neurons). The spinal cord becomes atrophic along with thinning of ventral roots and loss of large, myelinated fibers in motor nerves (lower motor neurons). As motor pathways degenerate and eventually die, the denervated muscles are atrophied with resulting weakness in function that progresses to muscle paralysis.

The clinical hallmarks of ALS include involvement of limb muscles (fine and gross motor movement), bulbar muscles, and respiratory muscles. Symptoms include muscle atrophy, progressive muscle weakness to paralysis, hypotonia, fasciculations, stiffness and lack of coordination. Persistent and irreversible deficits lead to limited mobility, inability to perform activities of daily living (e.g., eating and eliminating), facial paralysis, loss of vocal function, and dysphagia. Over time, the disease continues to progress to affect major muscle groups, including the diaphragm, the primary muscle of respiration, leading to respiratory failure and death (Brown & Al-Chalabi, 2017) (Figure 6).

The exact etiology of ALS remains largely unknown. A number of potential mechanisms have been proposed, including abnormal RNA processing with aggregation of abnormal proteins, excitotoxicity, cytoskeletal derangement, mitochondrial dysfunction, apoptosis, inflammatory responses, growth factor abnormalities and others. Hence, the pathophysiology of ALS is complex with joint contributions from deficient

neuroinflammatory, neuroprotective and neurodegenerative mechanisms (J. J. Chen, 2020).

Figure 6: Amyotrophic Lateral Sclerosis — Progressive Neurodegenerative Disease



- Degeneration and death of motor neurons in brain and spinal cord
- Brain no longer controls muscle actions

2.2 Current Treatment Options

There are no available treatments that offer a substantial clinical benefit or a cure for patients with ALS. Hence, current management of the disease relies largely on palliative care aimed at relieving symptoms and ameliorating quality of life. The mainstay of care for patients with ALS is timely intervention to manage symptoms, including use of nasogastric feeding, prevention of aspiration (control of salivary secretions and use of cough-assist devices), and provision of ventilatory support (usually with bilevel positive airway pressure (BiPAP) (Brown & Al-Chalabi, 2017).

2.2.1 FDA-Approved Treatments

There are three FDA-approved drugs for slowing progression of ALS (in addition to other supportive treatments that address ALS symptoms):

- Riluzole was first approved in 1995.
- Edaravone was first approved in 2017.
- Sodium phenylbutyrate and taurursodiol was approved in 2022.
- Tofersen received accelerated approval in April 2023 for a subset of patients with ALS caused by a variation in the *SOD1* gene.

Of the current investigational therapies, a novel, multipotent stem cell treatment has the potential to synergistically tackle the interrelated mechanisms of disease pathology, building on consistent demonstration of neuroprotective effects of NTFs in a variety of motoneuron models. However, outside of NurOwn, clinical trials with NTFs in participants with ALS have yielded disappointing results, possibly because of the inherent limitations

with either using single trophic factors in non-living delivery systems (interference from the blood-brain barrier, protein stability over time, short half-life, lack of synergism from using multiple NTFs) or by facing the challenges of systemic cell/vector delivery routes, failure to adequately reach the target brain tissue, unfavorable safety profile, etc. The need for synergic association of numerous NTFs is highlighted (Abati, Bresolin, Comi, & Corti, 2019; Gouel, Rolland, Devedjian, Burnouf, & Devos, 2019). In contrast, NurOwn is different as autologous bone marrow-derived MSCs that have been induced ex-vivo by a culture based process to secrete NTFs, balancing the immune response through modulation of inflammation and by preserving the dynamics of the interplay with neurodegenerative processes.

2.3 Unmet Medical Need

ALS is a universally fatal, heterogeneous disease with a median survival of 2 to 5 years from clinical onset. There are very few treatment options available, all of which offer only marginal delays in clinical progression. There is no cure, and no available therapies can stop progression or restore lost function. There is a significant and urgent unmet need for additional efficacious and safe treatments that slow the progression of ALS.

3 PRODUCT DESCRIPTION

Summary

- NurOwn is a novel autologous cell therapy developed by harvesting adult MSCs from bone marrow aspirate in a culture-rich milieu, and inducing them to secrete several NTFs, such as glial- and brain-derived NTFs (GDNF and BDNF), VEGF, HGF, Galectin-1, and LIF.
- MSCs have an intrinsic capacity to enhance neurogenesis, modulate neuroinflammation (e.g., by secreting anti-inflammatory cytokines), and contribute to neuroprotection (e.g., by secreting factors that promote cell survival and inhibit cell death). The NTFs delivered by NurOwn are composed of a large variety of NTFs leveraging their additive and synergistic activity targeting multiple pathways involved in the pathobiology of ALS.
- NurOwn or MSC-NTF cells has a multi-modal MoA that simultaneously delivers neuroprotective and immunomodulatory agents directly to the site of neuronal damage resulting in the reduction of neurodegeneration and cell death.
- In this respect, NurOwn is distinct from other therapies that have received recent study Although pre-clinical data appeared promising, clinical trials for other therapies using NTFs have failed to demonstrate clinical benefit, possibly because of their inherent limitations with either using single trophic factors in non-living delivery systems (protein stability over time, relatively short half-life, route of administration, inability to cross the blood-brain barrier, failure to adequately reach the targeted degenerating tissues and lack of synergism from using multiple NTFs)) or by facing the challenges of systemic cell/vector delivery routes and having unfavorable safety profile etc.
- By contrast, NurOwn as MSC-NTFs have been induced ex-vivo by a culture-based process to secrete NTFs, balancing the immune response through modulation of inflammation and by preserving the dynamics of the interplay with neurodegenerative processes.
- Autologous, bone-marrow-derived MSC have a favorable and well-characterized safety profile

3.1 Proposed Indication

BrainStorm Cell Therapeutics Ltd. Seeks marketing approval of NurOwn for the treatment of ALS.

3.2 Product Overview

NurOwn, a proprietary cell therapy platform, is a novel and innovative cell-therapeutic approach to treating ALS. NurOwn is based on an innovative manufacturing process that leverages cell culture-medium methods to induce the differentiation of purified and expanded bone marrow-derived MSC that are enriched from an individual's own bone marrow, and consistently generates cells that release high levels of multiple neurotrophic factors (MSC-NTF cells) such as glial-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF), hepatocyte

growth factor (HGF), Galectin-1, and leukemia inhibitory factor (LIF), to modulate neuroinflammatory and neurodegenerative disease processes, promote neuronal survival, and improve neurological function.

Delivery of multiple NTFs to the immediate cellular environment of affected motoneurons further leverages the demonstrated synergic effect of the combining trophic factors (e.g., GDNF and VEGF; CNTF and BDNF) with an increased survival, protection of neuromuscular junction and motoneuron degeneration, greater than either growth factor delivered individually (Krakora et al., 2013).

The autologous NurOwn cell therapy is administered by IT injection into the CSF by lumbar puncture (intrathecally) with administration of 100 – 125 × 10^6 MSC-NTF cells in each dose. One treatment course is composed of three individual doses of 100-125 × 10^6 MSC-NTF cells administered every eight weeks. The MSC-NTF cells manufacturing process is free of antibiotics and xeno-derived proteins, and does not involve genetic modifications, or use viral vectors. Because the cells are the recipient's own cells there is no risk of immune rejection and therefore no need for immunosuppressive agents, which can be associated with unwanted side-effects, increasing the survival of the MCS-NTF cells and their activities into the recipient body.

3.3 Mechanism of Action

Stem cells of various origin have the potential to synergistically secrete/deliver growth factors directly into the central nervous system (CNS) when administered intrathecally. A beneficial effect of MSC is related to their intrinsic capacity for immunomodulation. This is especially relevant when considering the growing evidence for the role of neuroinflammation in ALS pathogenesis and progression (Abati et al., 2019). The key therapeutic strategy of delivering neuroprotective and immunomodulatory agents directly to the CNS, behind the blood-brain barrier by an innovative autologous cellular therapy, holds great promise in ALS.

MSCs have the intrinsic capacity to enhance neurogenesis, modulate neuroinflammation, and contribute to neuroprotection (Fan, Zhang, Li, & Fu, 2020). NTFs are potent survival and regeneration factors for embryonic, neonatal, and adult neurons and are therefore considered potential therapeutic candidates for ALS. For example, Galectin-1 is an essential regulatory factor, secreted by native astrocytes and by administered MSCs, that has direct neuroprotective effects and indirectly reduces inflammation-related neurodegeneration through modulation of microglial activation via NF-kB-dependent signaling pathways (Starossom et al., 2012). NTFs are also known to be deficient in several neurodegenerative diseases, including ALS; VEGF genetic variants associated with reductions of VEGF protein expression are associated with a significant increase in the risk of developing ALS (da Costa, de Lima, da Cruz Pereira Bento, da Silva Santos, & da Silva Reis, 2022).

Delivery of multiple NTFs to the immediate cellular environment of affected motoneurons in individuals with ALS therefore is expected to improve neuron survival and function, thus

delaying disease progression and alleviating symptoms. Intrathecal administration of MSC-NTF cells is a novel cell-therapeutic approach aimed at effectively and simultaneously delivering multiple NTFs and immunomodulatory molecules in close proximity to the site of damage in individuals with ALS (Figure 7).

Consistent with this view, MSC treatment has been shown to delay motor neuron degeneration, improve motor performance and prolong survival in the superoxide dismutase 1 (*SOD1*) mouse model of ALS (Forostyak, Jendelova, Kapcalova, Arboleda, & Sykova, 2011; Marconi et al., 2013; Uccelli et al., 2012). The benefits of MSC treatment are attributed in part to significant upregulation of various NTFs (Marconi et al., 2013). In the mouse SOD1 model, intramuscular (IM) administration of human MSC engineered to secrete GDNF significantly delayed disease progression by abolishing neuromuscular junction denervation, providing motor neuron protection, improving motor function, and significantly increasing survival compared to naïve MSC (Suzuki et al., 2008). Intrathecal administration of VEGF-secreting MSCs have shown consistent benefits, including motor neuron protection and reduced glial activation in the mouse SOD1 model (Ciervo et al., 2021). Immunomodulation has also been demonstrated as an important mechanism contributing to the favorable effects of MSC therapy in ALS and other neurodegenerative diseases (Boido et al., 2014; Sadan, Shemesh, Cohen, Melamed, & Offen, 2009).

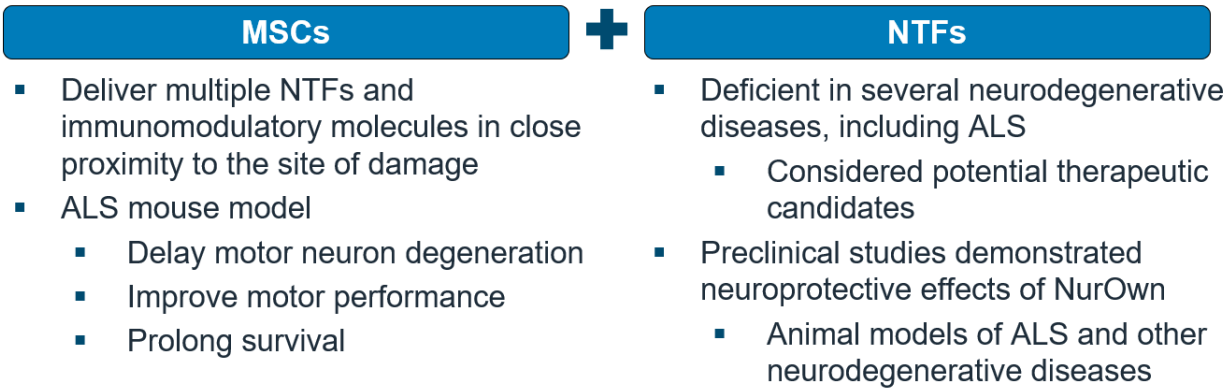
The outcomes of pilot clinical studies of MSC therapy suggest neurological stabilization in people with ALS (Feldman et al., 2014; Karussis et al., 2010; L. Mazzini et al., 2010; Letizia Mazzini et al., 2012), evidence of structural, functional, and physiological improvement of optic nerves in progressive multiple sclerosis (Connick et al., 2012) and positive clinical effects in multiple system atrophy (Lee et al., 2012). There is a growing body of knowledge about the use of MSC therapy in various neurological diseases with a goal of promoting neurorepair and neuroprotection (Connick et al., 2012; Feldman et al., 2014; Karussis et al., 2010; Lee et al., 2012; Llufriu et al., 2014; L. Mazzini et al., 2010; Letizia Mazzini et al., 2012). Autologous bone marrow-derived MSC have become the most common type of adult stem cells used in clinical trials owing to their consistent safety profile and synergistic neuroprotective and immunomodulatory effects (Karussis, 2012; Thomsen, Gowing, Svendsen, & Svendsen, 2014).

Although NTFs have been shown to extend the survival of motoneurons in ALS preclinical models, peripheral/systemic administration of single NTFs, such as recombinant human ciliary neurotrophic factor (CNTF) or recombinant human BDNF, has not demonstrated clinical benefit (BDNF Study Group, 1999a; Miller et al., 1996), possibly due to short plasma half-lives and their inability to cross the blood-brain barrier that prevented therapeutic levels from reaching the target tissues.

Direct delivery of multiple cell-secreted NTFs to the CNS through intrathecal administration may effectively leverage the CSF lymphatic delivery route (Benveniste et al., 2021; Hladky & Barrand, 2014), as well as the synergy associated with simultaneous and direct administration of multiple neuroprotective NTFs within the CNS compartment (Krakora et al., 2013).

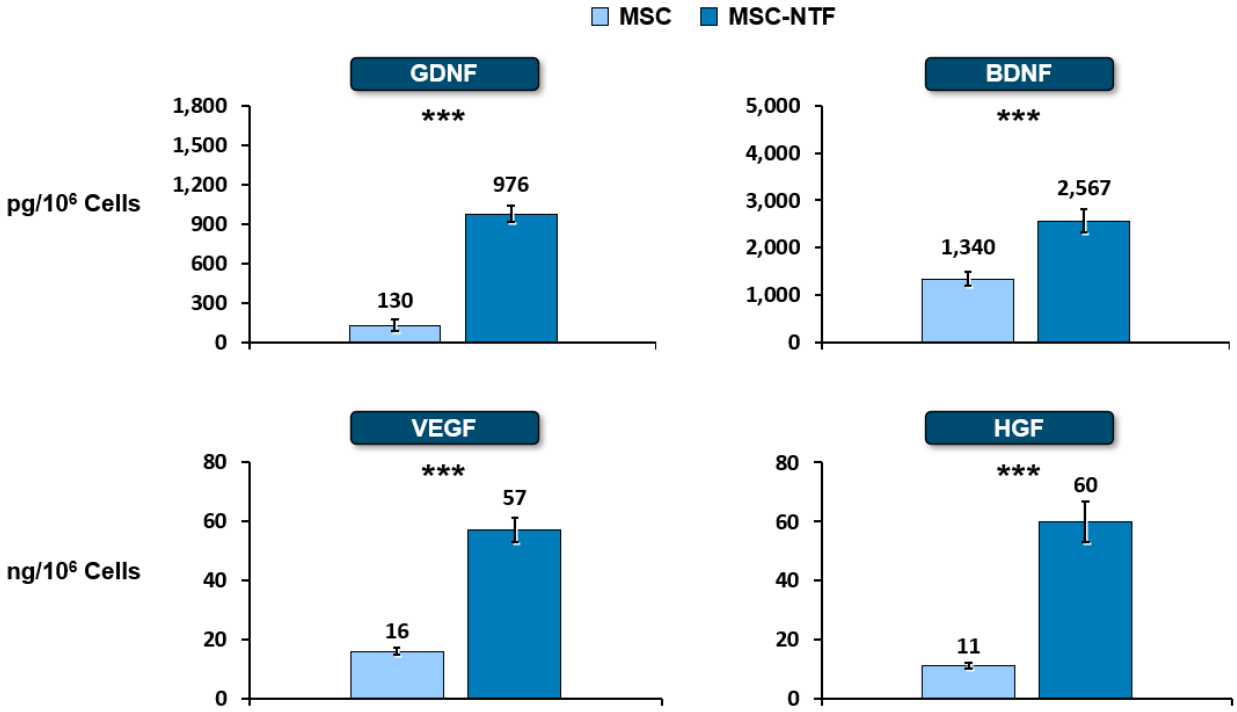
Phase 2 data indicate that NurOwn significantly reduces pro-inflammatory monocyte chemoattractant protein-1 (MCP-1) in the CSF of ALS patients two weeks following treatment while it remained unchanged in participants receiving placebo (Figure 18). The *in-vitro* data demonstrate that MSC-NTF cells secrete higher levels of neuroprotective factors compared to naïve MSC cells of the same patients prior to differentiation (Figure 8, Figure 11).

Figure 7: NurOwn Delivers Synergistic Benefits of MSC and NTFs to Site of Damage in ALS



(Dadon-Nachum, Sadan, Srugo, Melamed, & Offen, 2011; Forostyak et al., 2011; Marconi et al., 2013; Perets et al., 2017; Sadan et al., 2012; Uccelli et al., 2012; Uccelli, Moretta, & Pistoia, 2008)

Figure 8: Levels of Neurotrophic Factors Secreted from MSC-NTF Cells Compared to Naïve MSC From the Same Patients



*** p < 0.001
BDNF=Brain-derived neurotrophic factor; GDNF=glial cell line derived neurotrophic factor; VEGF=vascular endothelial growth factor; HGF=hepatocyte growth factor; MSC=mesenchymal stem cells; NTF=neurotrophic factors. Data from ALS Phase 1/2 and Phase 2a studies.

3.4 Background Regarding Autologous Process of NurOwn

The NurOwn (MSC-NTF cells) therapy is based on IT administration of autologous bone marrow derived MSCs, which are enriched from the patient's own bone marrow, propagated *ex vivo* and induced to secrete neurotrophic factors (NTFs).

The autologous production process is on a per-patient basis and begins upon fresh bone marrow aspirate arrival to the manufacturing facility and is completed once the MSC-NTF cells are ready for injection (Figure 9). The main steps of MSC-NTF cells productions are:

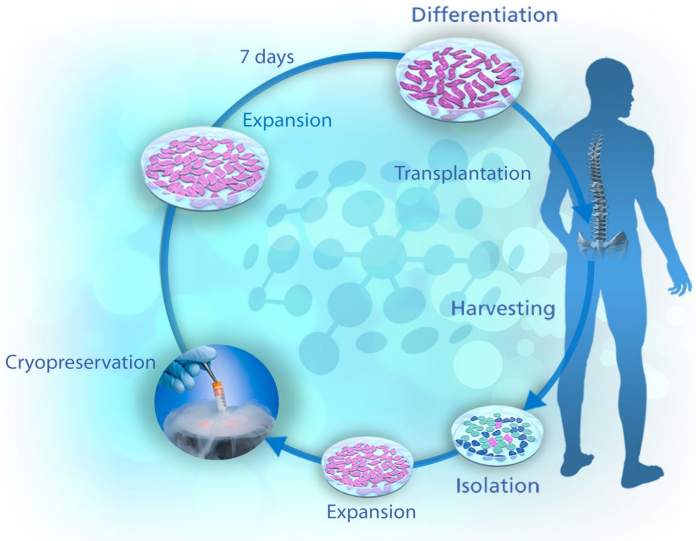
1. Bone marrow is aspirated from the iliac crest of the pelvic bone.
2. Mononuclear cells (from the bone marrow) are separated by density gradient centrifugation.
3. MSCs are isolated from the bone marrow mononuclear cell fraction by their characteristic plastic adherence and cultured in culture medium.
4. MSCs are propagated for about 2-3 weeks and cryopreserved.
5. Before cryopreservation MSC are characterized based on a set of minimal criteria defined by the International Society for Cellular Therapy including

expression of a characteristic set of surface markers, such as cluster of expression of (CD)73, CD90, and CD105, while lacking expression of CD14, CD34, CD45, and human leukocyte antigen-DR (HLA-DR).

6. In advance of each treatment, MSCs are thawed, further expanded, and induced to differentiate into MSC-NTF cells (NurOwn product) by a culture medium based induction process (with no genetic manipulation).
7. A total of approximately 130-160 x 10^6 MSC-NTF cells are harvested for providing the 100-125 x 10^6 clinical dose and cells for quality control release tests, including viability, apoptosis, cell count, potency, identity, visual inspection and safety testing (Sterility, Mycoplasma, Gram satin and endotoxin tests).
8. Freshly prefilled ready to use syringe with MSC-NTFs Cells is delivered to the clinical sites and administered by intrathecal injection.

The total time from bone marrow aspiration up to the first IT treatment is between 4-6 weeks. Production of NurOwn for subsequent treatments takes about 8 days from the time of thawing autologous MSCs through NTFs differentiation and harvesting. The autologous MSC-NTF cells are freshly administered once the product meets specifications and release criteria are confirmed. Multiple vials of MSCs are cryopreserved to allow for thawing the cells for additional expansion and generation of MSC-NTF cell doses, such that one bone marrow aspirate yields enough autologous cells to produce two to three years of treatment with NurOwn at the recommended dosing schedule. To date, for each study, all study participants have received their NurOwn doses from a single bone marrow aspiration procedure.

Figure 9: Overview of NurOwn Production



MSC are well known and have been the subject of research for over 30 years. A meta-analysis summarizing the safety of MSC administration over the past 15 years concludes

that MSC are safe across different patient populations. No serious safety events other than transient fever, administration site AEs, sleeplessness and constipation were found to be potentially related to the application of MSCs (Wang, Yi, & Song, 2021).

4 REGULATORY AND DEVELOPMENT HISTORY

Summary

- NurOwn has received orphan drug and fast-track designation from the FDA for investigation of treatment of ALS.
- The NurOwn clinical development program in ALS consists of four completed clinical trials and a recently completed expanded access program.
- NurOwn is also being studied as a treatment for multiple sclerosis, with a Phase 2 clinical trial that enrolled 18 participants; the study is complete.

4.1 Regulatory and Clinical Milestones

NurOwn was granted Orphan Drug designation and Fast-Track designation by the FDA for the treatment of ALS.

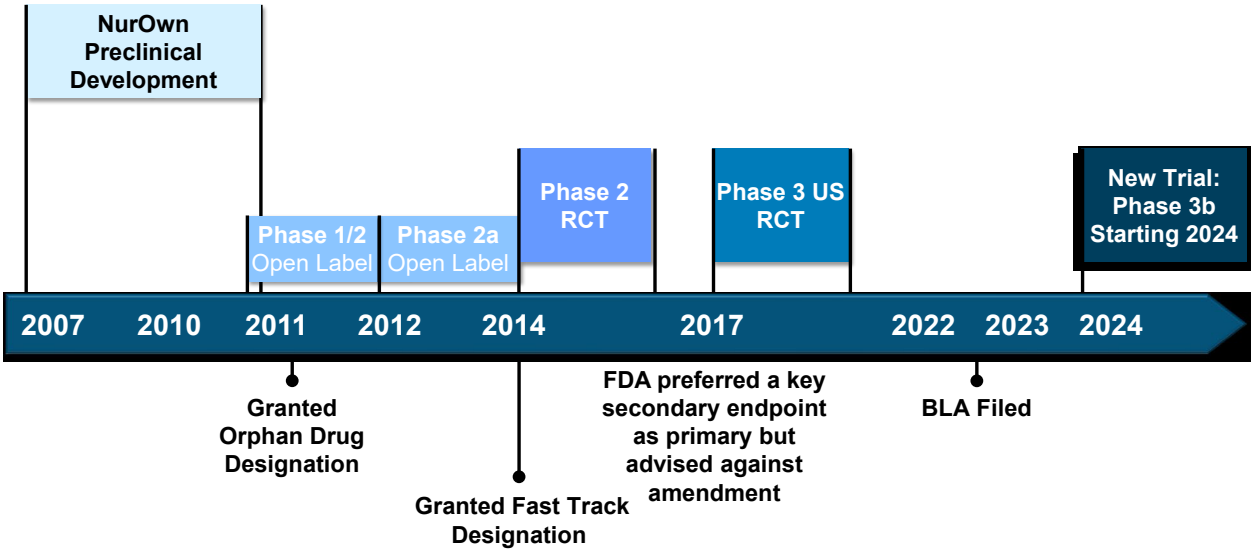
Key regulatory and clinical milestones for NurOwn are summarized in Figure 10 and additional details are provided below.

- 2007-2010: NurOwn preclinical development
- 2011: NurOwn granted Orphan Drug designation
- 2011-2012: Phase 1/2 Open Label Study
- 2012-2014: Phase 2a Open Label Study
- 2014: NurOwn granted Fast Track designation
- 2014-2016: Phase 2 US randomized controlled trial
- 2017-2020: Phase 3 US randomized controlled trial
    - The primary endpoint was a responder analysis of change in rate of decline as assessed by the ALSFRS-R.
    - In discussions between the Sponsor and the Agency, the FDA preferred the key secondary endpoint (average change in ALSFRS-R total score from baseline to Week 28) as the primary endpoint, citing ease of interpretation of the clinical meaningfulness, but advised against amending the protocol. This endpoint also has regulatory precedence of being used as a primary endpoint in multiple regulatory reviews and approvals. However, in discussions with the FDA during development of the Phase 3 clinical protocol, the FDA strongly recommended against changing the primary endpoint in order to minimize and avoid unnecessary burden from the implementation of a protocol amendment. This advice was captured in the minutes from a meeting on February 6, 2020, where “FDA emphasized that we are committed to looking at the totality of the evidence that comes in from the Phase 3 trial, which has been reasonably designed to collect the

important data elements relevant to an evaluation of efficacy, independent of the stated primary statistical endpoint."

- September 9, 2022: NurOwn Biologics License Application (BLA) submitted.
- November 8, 2022: FDA issues refusal to file letter for the NurOwn BLA.
- January 11, 2023: Type A meeting held with OTAT.
- January 25, 2023: Dispute resolution meeting held with Center for Biologics Evaluation and Research (CBER).
- February 7, 2023: BLA application filed over protest.
- July 27, 2023: Federal Register notice regarding advisory committee meeting.
- December 8, 2023: Revised Prescription Drug User Fee Act (PDUFA) date.

Figure 10: Key Clinical and Regulatory Milestones for NurOwn



4.2 Clinical Development Program

The clinical development program for NurOwn in ALS includes four clinical trials and a recently completed expanded access program (EAP):

- Pivotal Phase 3 trial: BCT-002-US, a Phase 3, randomized, double-blind, placebo-controlled multicenter study to evaluate efficacy and safety of NurOwn in participants with ALS with an ALSFRS-R score ≥ 25 at screening and a decline of ≥ 3 points in the 12 weeks preceding randomization (completed). (For details on the ALSFRS-R assessment, see Section 6.1.)
- Supportive Phase 2 trial: BCT-001-US, a Phase 2, randomized, double-blind, placebo-controlled multicenter study to evaluate safety and efficacy of NurOwn in participants with ALS with an ALSFRS-R ≥ 30 at screening (completed).

- Supportive early-phase clinical trials:
  - MSC-NTF-002-IL, a Phase 2a, open-label, dose-escalating clinical study to evaluate the safety, tolerability, and therapeutic effects of NurOwn in participants with ALS (completed).
  - MSC-NTF-001-IL, a Phase 1/2, open-label clinical study to evaluate the safety, tolerability, and therapeutic effects of NurOwn in participants with ALS (completed).
- Supportive EAP: BCT-003-US, an EAP (Open Label extension) to evaluate safety and efficacy of additional treatments in participants with ALS who completed the BCT-002-US. The trial was recently completed. The Clinical Study Report will be submitted to FDA once completed in the normal course, and before the PDUFA date.

Additional details on the clinical trials are provided in Table 3.

NurOwn has also been investigated in a completed Phase 2 clinical trial in participants with multiple sclerosis (MS) (BCT-101-US) (Cohen et al., 2023).

Table 3: Summary of Clinical Studies of NurOwn in ALS

Study Identifier/ Type/Status	Objective	Study Design and Type of Control	Test Product(s): Dosage Regimen; Route of Administration	Total Pts, N	Duration of Study
MSC-NTF-001-IL Phase 1/2 First-in-Human (completed)	Safety, preliminary efficacy	Open-label, uncontrolled	MSC-NTF cells, administered once; 24×10^6 intramuscular (IM) in early ALS stage and ~60×10^6 intrathecal (IT) in progressive ALS stage	12	3 months pre-treatment, 6 months post-treatment
MSC-NTF-002-IL Phase 2a Dose-Escalation (completed)	Safety, preliminary efficacy	Open-label, dose escalating uncontrolled	MSC-NTF cells, administered once; Total dose: 94×10^6, 141×10^6, 188×10^6 IT and IM	14	3 months pre-treatment, 6 months post-treatment
BCT-001-US (Study 001) Phase 2 Safety (completed)	Safety, preliminary efficacy	Randomized, double-blind Placebo controlled	MSC-NTF cells, administered once, 100-125 $\times 10^6$ IT and 48×10^6 IM	48	12-16 weeks pre-treatment, 24 weeks post-treatment
BCT-002-US (BCT-002) Pivotal Phase 3 Efficacy and Safety (completed)	Efficacy	Randomized, double-blind Placebo controlled	MSC-NTF cells, administered 3 times, 8 weeks apart; 100-125 $\times 10^6$ IT	196	18-20 weeks pre-treatment, 28 weeks post-treatment

Study Identifier/ Type/Status	Objective	Study Design and Type of Control	Test Product(s): Dosage Regimen; Route of Administration	Total Pts, N	Duration of Study
BCT-003-US Efficacy and Safety (completed)	Efficacy and Safety	Expanded access program	MSC-NTF cells, administered 6 times; first treatment course: 3 doses given 8 weeks apart followed by 12 weeks observation; second treatment course: 3 doses given 8 weeks apart followed by 12 weeks observation; 100-125 × 10^6 IT	10	34 weeks (first treatment course); 34 weeks (second treatment course). Each treatment course consists of up to 6-week pre-treatment period; 16-week treatment period; 12-week post treatment follow-up period

Abbreviations: IM=intramuscular; IT=intrathecal; MSC NTF=autologous mesenchymal stem cells secreting neurotrophic factors (NurOwn); Pts=participants.
Note: In addition to the above clinical trials, a total of 19 participants (two of whom were initially treated in Study MSC-NTF-002-IL) with ALS have been treated with NurOwn under compassionate use; however, no formal assessments were performed.

5 PHARMACOLOGY

Summary

- In animal models, NurOwn consistently produced neuroprotective effects, including preservation of neurons and axon terminals, increased neuroprotective factors, and electrophysiological changes consistent with restoration of physiological function that are accompanied by significant behavioral and survival effects.
- Administration of NurOwn in animal studies was associated with significant behavioral and survival effects across a variety of neurodegenerative disease models.
- NurOwn is not expected to have any drug-drug interactions, or require any anti-rejection therapies, because the cells originate from autologous bone marrow.

5.1 Clinical Pharmacology

No clinical pharmacology studies have been conducted. The pharmacological profile of NurOwn is based on nonclinical studies in animal models and *ex-vivo* culture media.

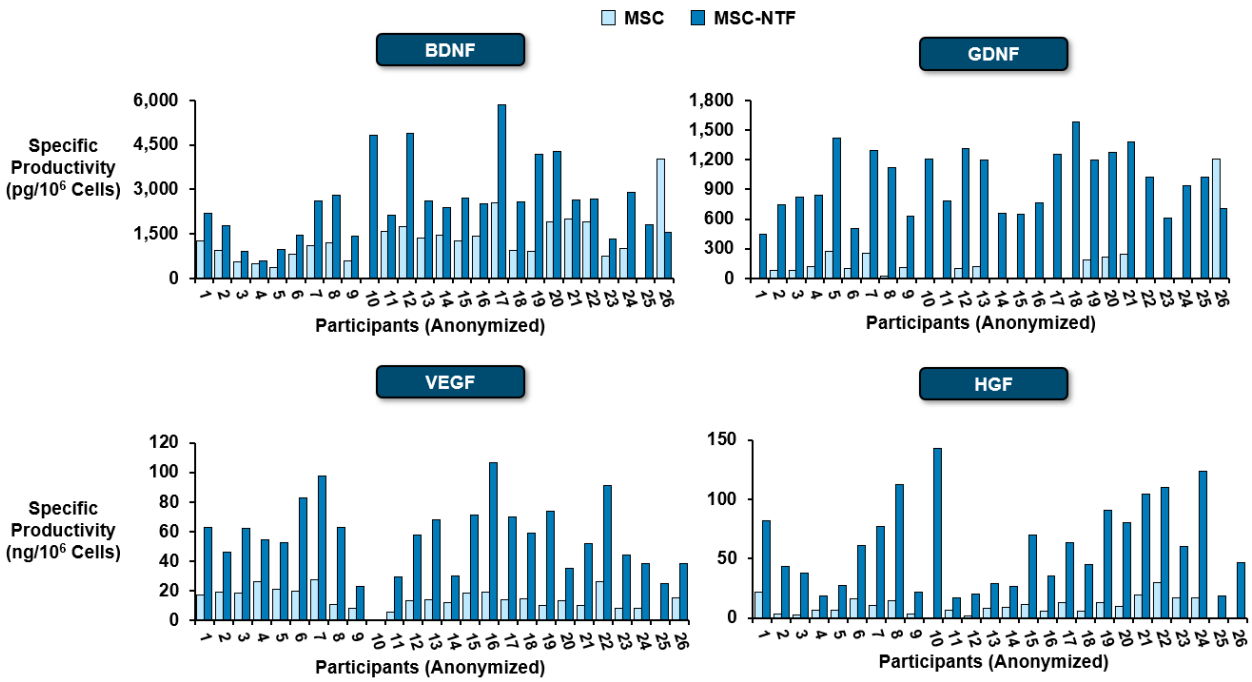
5.2 Nonclinical Pharmacology

The primary pharmacodynamics of MSC-NTF cells (NurOwn), as well as distribution and safety pharmacology, were evaluated in several relevant animal models. Safety pharmacology studies in C57BL/6J mice were performed to investigate the toxicity and tolerability of repeated intramuscular injections (IM) of cryopreserved human NurOwn.

5.2.1 Primary Pharmacodynamics

The nonclinical studies conducted to support NurOwn demonstrated, using a culture medium-based induction protocol, that MSCs can be induced to become NTF-secreting cells with markedly enhanced secretion of NTFs, such as GDNF, BDNF, VEGF, Gal-1, and HGF (Dadon-Nachum et al., 2011; Gothelf, Kaspi, Abramov, & Aricha, 2017; Ofer Sadan et al., 2009; Sadan et al., 2008; Sadan et al., 2012), among others. Additionally, participant level data from Phase 1/2 and 2a demonstrate that MSC-NTF cells secrete higher levels of neuroprotective factors compared to naïve MSC cells of the same patients prior to differentiation (Figure 11).

Figure 11: Summary of Neurotrophic Factors (NTF) Secretion by MSC and MSC-NTF Cells



Abbreviations: BDNF=brain-derived neurotrophic factor; GDNF=glial-derived neurotrophic factor; HGF=hepatocyte growth factor; MSC=mesenchymal stem cell; NTF=neurotrophic factors; VEGF=vascular endothelial growth factor.
Note: GDNF, BDNF (pg/10^6 cells) VEGF and HGF specific productivity (ng/10^6 cells) of MSC-NTF cells (red) at the end of differentiation (Day 3), as compared to the secretion of MSC (blue) of the same ALS patient prior to differentiation, analyzed by commercially available ELISA assays.

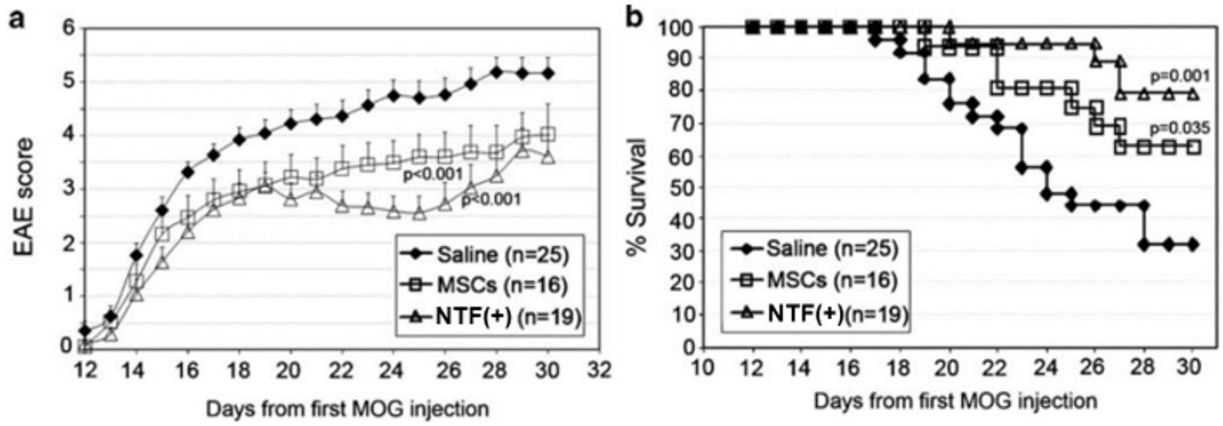
Additionally, *in-vivo* studies in several animal models of neurodegenerative diseases showed that NTF-secreting cells consistently induce neuroprotective effects, including preservation of neurons and axon terminals, increased tissue levels of neuroprotective factors, and electrophysiological changes consistent with restoration of physiological function that are accompanied by significant behavioral and survival effects (Barhum et al., 2010; Dadon-Nachum et al., 2011; Levkovitch-Verbin et al., 2010; Offen, 2013; Perets et al., 2017; Ofer Sadan et al., 2009; Sadan et al., 2012).

In these studies, cell persistence and continued secretory activity for up to three months and homing to site of damage in the disease microenvironment were observed. Furthermore, the therapeutic potential of NTF-secreting cells (also referred to as NurOwn or MSC-NTF cells) was observed to be superior to the MSCs of origin in the studied SOD1 ALS animal model and in several other neurodegenerative diseases. In a rat sciatic nerve injury model, where the right hind limb sciatic nerve of male Sprague-Dawley rats was crushed, NTF-secreting cells markedly preserved motor function, improved electrophysiological function, significantly inhibited the degeneration of neuromuscular junctions, preserved myelinated motor axons, and were superior to MSC (Dadon-Nachum et al., 2011). Three weeks after sciatic nerve crush and cell transplantation, high levels of

BDNF were observed in NTF-secreting cells and their surrounding muscle tissue, but BDNF was not detected in or surrounding the MSC. This study found that NTF-secreting cells survived and maintained function in transplanted tissue three weeks after transplantation.

Similarly, in a mouse-model of experimental autoimmune encephalomyelitis (EAE, the most widely accepted animal model for multiple sclerosis, a human inflammatory demyelinating disease), mice treated with NTF+ (MSC-NTF) cells via the intracerebroventricular (ICV) route showed marked delay in disease symptoms and prolonged overall survival vs mice treated with MSCs only or control (Figure 12).

Figure 12: MSC-NTF Cells Protection in the Mouse EAE Model of Multiple Sclerosis



Abbreviations: EAE=experimental autoimmune encephalomyelitis; ICV=intracerebroventricular route; MOG=myelin oligodendrocyte glycoprotein; MSC=mesenchymal stem cells; NTF=neurotrophic factors; NTF+=MSCs secreting NTFs; PBS=phosphate-buffered saline.
Note: EAE clinical score and survival of EAE mice following bilateral ICV treatment with human mesenchymal stem cells or differentiated human neurotrophic factors secreting cells. MOG-EAE-induced mice were injected with human MSCs, human MSC-NTF cells, or with PBS as control six days after MOG injection. Mice were scored for clinical signs using a score scale: 0, no paralysis; 1, loss of tail tonicity; 2, mild hind limb weakness; 3, complete hind limb paralysis; 4, paralysis of four limbs; 5, total paralysis; and 6, death. Clinical score and survival rate were monitored for one month from the first MOG injection. (A) Clinical score and (B) survival rate were monitored through one month from first MOG injection (p values are presented in relation to saline-injected group).

5.2.2 Toxicology

The non-clinical toxicology program conducted with NurOwn includes single-dose and repeated-dose toxicity studies (four-week studies) conducted in mice. The toxicity and tolerability of three consecutive IM injections of cryopreserved human MSC-NTF cells in C57BL/B6 mice was investigated in study BRS002 (Gothelf, Abramov, Harel, & Offen, 2014). Monitoring clinical signs and immune parameters revealed that repeated MSC-NTF cell injections were not associated with any SAEs. Blood biochemistry parameters were found to be within the normal range. Histopathological evaluation specifically did not reveal tumor formation or pathological findings in any major organ. Although treatment-related local effects were noted, repeated IM injections were not associated with lesions

or any systemic adverse effects. Based on the results of this study, it was concluded that cryopreserved MSC-NTF cells, when administered to mice by either one, two or three IM injections interspaced by four weeks does not generate any significant systemic toxicity, and only a minimal local effect was noted at the injection sites (Gothelf et al., 2014). These findings provide additional preclinical support for the safety of repeat administration of MSC-NTF cells.

5.3 Drug Interactions

NurOwn is not expected to have any drug-drug interactions; formal drug-drug interaction studies have not been conducted, but NurOwn cells are the recipient's own cells. This sourcing also removes the risk of rejection and the need for immunosuppressive agents.

6 CLINICAL EFFICACY

Summary

- The pivotal Phase 3 Study BCT-002-US enrolled a broad ALS population, including a larger than usual number of participants with advanced ALS disease compared to recent large ALS trials.
- For the primary endpoint, NurOwn demonstrated a numerically higher but not statistically significant response rate with NurOwn compared to placebo in the full study population (32.6% vs 27.7%; p=0.453).
- For the key secondary endpoint, NurOwn showed a numerically favorable but not statistically significant change from baseline compared to placebo (-5.52 points vs -5.88 points; p=0.693). An appreciation of the floor effect is necessary for understanding these results.
- An enhanced treatment effect was observed in a prespecified subgroup analysis of participants with less advanced ALS, baseline ALSFRS-R ≥ 35, in the primary and key secondary endpoint:
    - The percentage response on the primary endpoint was: NurOwn 34.6% vs placebo 15.6%, p=0.305), aligning with the power assumptions for the trial of 35% NurOwn response vs 15% placebo but failing to be significant due to the reduced sample (58 of 189 participants or 31%), resulting in low power.
    - A significant treatment difference of 2.09 points (p=0.050) was observed on the key secondary endpoint of average change from baseline to Week 28.
    - Replacing the ALSFRS-R ≥ 35 threshold with the actual baseline mean (ALSFRS-R ≥ 31) revealed a large, significant and clinically meaningful treatment effect of 35.4% for NurOwn vs 15.4% for placebo (p=0.043).
- Post-hoc analyses accounting for the ALSFRS-R floor effect further show a statistically significant treatment effect of NurOwn compared to placebo in both the primary and key secondary endpoints.
    - In a subgroup of participants (N=106 [56%]) who had all ALSFRS-R items > 0 (i.e., participants with no item-level floor effect at baseline), the response rate with NurOwn (40.8%) vs placebo (22.8%) was statistically significant (p=0.035). Additionally in this subgroup, on the key secondary endpoint, participants treated with NurOwn retained more function, on average 2.3 points in the ALSFRS-R score by Week 28 compared to placebo (p=0.040).
- NurOwn produced significant improvements compared to placebo across CSF biomarkers in multiple pathways and in all participants, including those with advanced ALS disease where the ALSFRS-R is less sensitive to change, providing additional evidence of NurOwn's treatment effect and MoA.
    - CSF biomarkers NfL, TGF-β1, and Gal-1 were identified as predictive of clinical outcomes, and reductions in NfL were associated with less decline in ALSFRS-R.
    - NurOwn significantly reduced NfL compared to placebo ($p < 0.05$).

- The combined evidence of treatment effect observed across multiple timepoints in clinical endpoints, across four subscales of the ALSFRS-R, as well as across multiple biomarkers support the totality of evidence that there is a significant treatment benefit with NurOwn ($p < 0.01$).

6.1 Assessment of ALS Disease Progression

6.1.1 ALSFRS-R: Measuring ALS Disease Progression

The ALSFRS-R is the primary tool used for capturing ALS functional status and disease progression in clinical trials (Cedarbaum et al., 1999) and was used to establish participant eligibility and assess treatment efficacy in all NurOwn ALS studies.

The ALSFRS-R is a validated, ordinal rating scale used to evaluate the level of impairment of people living with ALS in 12 functional activities. Each activity is rated from 0 to 4, with lower numbers associated with lower functioning: a score of 4 is normal function and 0 is the worst function (Figure 13). The 12 functional areas are further grouped into four subscales that encompass gross motor tasks, fine motor tasks, bulbar functions, and respiratory function. It has been estimated that around 70% of decline in clinical trials occurs in the fine and gross motor scale items, with bulbar and respiratory items often having limited decline due to inclusion criteria designed to ensure participants remain alive and able to receive potential benefits for the duration of the trial (Rooney, Burke, Vajda, Heverin, & Hardiman, 2016).

On the ALSFRS-R, a one-point increase can mean preserved physical function and sustained quality of life. Each point reduction on the ALSFRS-R scale is accompanied by a 7% decline in quality of life (EQ-5D) (Ilse et al., 2015). Examples of one-point difference on ALSFRS-R include:

- Ability to turn in bed without assistance.
- Requiring a wheelchair versus walking with assistance.
- Ability to still feed themself.
- Independence to dress oneself.

Figure 13: ALSFRS-R Tool for Assessing ALS Disease Progression

Bulbar	Fine Motor	Gross Motor	Respiratory
Speech	Handwriting	Turning in bed	Dyspnea (difficulty breathing)
Salivation	Cutting food/using utensils	Walking	Orthopenea (shortness of breath while lying down)
Swallowing	Dressing and hygiene	Climbing stairs	Breathing insufficiency

The heterogeneity in ALS progression further confounds this issue as clinical progression varies widely among participants, as can scoring across subscales of the ALSFRS-R within the same individual. For example, respiratory function can decline to the point of death in an individual participant while the disease progressed slowly in other subscales. Furthermore, the clinical presentation of ALS can affect subscales and scores over the course of the disease. For instance, bulbar (face and neck) onset generally leads to more rapid decline in functional activities like speech and swallowing, while limb onset (estimated to occur in about 75% of patients) generally leads to more rapid deterioration of fine and gross motor skills (Rooney et al., 2016). This can affect results of clinical trials because approximately 70% of the decline reported in trials is observed in the fine and gross motor subscales (Rooney et al., 2016).

6.1.1.1 Floor Effect: Limitations on Measurement of ALS Progression with the ALSFRS-R

While the ALSFRS-R is the most widely used assessment of disease progression, its utility in clinical trials is hampered by its limited ability to measure physical function among patients at either end of the clinical spectrum (i.e., those with either high or low functional status). This effect can be magnified in ALS trials because of their relatively short duration, which must be limited for ethical reasons. The floor effect associated with the ALSFRS-R is important because treatment effect and magnitude can be difficult to measure accurately among participants with lower baseline ratings. Specifically, the ALSFRS-R is less sensitive to disease progression among patients with more advanced disease (Franchignoni, Mora, Giordano, Volanti, & Chiò, 2013; Mandrioli et al., 2015; Voustianiouk et al., 2008; Wicks, Massagli, Wolf, & Heywood, 2009). This means individual scale items may inaccurately reflect disease progression, and responses may misrepresent disease severity (Bacci et al., 2016; Hartmaier et al., 2022). The floor effect and its impact has been recognized by the FDA (FDA, 2018).

6.1.1.2 Inclusion Criteria in BCT-001-US and BCT-002-US and Resulting Impact

Differences in ALSFRS-R inclusion criteria between the Phase 2 (≥ 30 points at screening) and Phase 3 (≥ 25 points at screening and decline of ≥ 3 points in the 12 weeks before randomization) studies resulted in an increased risk of floor effect in Phase 3, relative to Phase 2. In short, the Phase 3 study allowed participants with more advanced disease to enroll in the trial.

Inclusion of participants with advanced ALS disease in the trial resulted in many participants starting the trial with baseline scores of zero on more than half of the ALSFRS-R individual items. Because the scale cannot measure progression below zero, measurement of disease progression in these participants cannot be accurately assessed.

6.1.1.3 Participants with Advanced ALS in Phase 3 Study BCT-002-US

Overall, almost a quarter of participants enrolled in the Phase 3 study had advanced ALS, i.e., a baseline ALSFRS-R score ≤ 25. Figure 1 shows the mean baseline ALSFRS-R scores of participants in recent large ALS clinical trials, with recently approved ALS drugs shown in red. The NurOwn population (shown at the bottom of the graph) is an outlier, with a mean overall ALSFRS-R score at baseline of 31 (ranging from 16 to 46), resulting in a unique and atypical trial population that included 23.3% of participants with advanced ALS, who had a baseline ALSFRS-R score ranging between 16 and 25.

It should be noted that, at the time that the study was being designed, the floor effect of the ALSFRS-R was not well understood. However, after observing the large number of participants with advanced ALS, it became critical to understand how this floor effect could impact the results.

When we look at the different ALSFRS-R domains in the NurOwn Phase 3 trial, the participants with advanced ALS had a high rate of zeros in items within the fine motor and gross motor subscales, which averaged 40% of those items. Thus, the high percentage of zeros in those domains that tend to most decline during clinical trials (Rooney et al., 2016) needed to be addressed in order to draw valid study conclusions. Evidence of floor effect both in our trial and external trials is further described in Section 6.3.7.3.

A floor effect could be misinterpreted as halting or slowing functional decline and thereby be misclassified as a clinical response. While the floor effect can confound results, post-hoc analyses are able to estimate the treatment effect in the Phase 3 trial.

6.1.2 ALS Disease Biomarkers

Biomarker data collected during Study BCT-002-US represents the most robust CSF biomarker study conducted in people with ALS. Forty-five ALS-related biomarkers were studied, with 33 markers grouped into three key disease pathways of neurodegeneration, neuroinflammation (both pro-inflammatory and anti-inflammatory), and neuroprotection in all participants in the trial. The remaining 12 biomarkers were exploratory and broad in their potential relevance to ALS.

Emerging scientific insights have linked several CSF biomarkers to key cellular changes associated with the ALS disease process (von Neuhoff et al., 2012). Examples include neurofilament light chains (NfL) (Xu, Henderson, David, & McCombe, 2016), galectin-1 (Gal-1) (Ramirez Hernandez et al., 2020), MCP-1, and latency-associated peptide (LAP) of TGF-β1 (Galbiati et al., 2020; Iłzecka, Stelmasiak, & Dobosz, 2002).

Recent progress in the development and application of CSF biomarkers enables the use of a panel of biomarkers to interrogate disease activity across several known ALS disease pathways (Vijayakumar et al., 2019), and to provide reliable biomarker outcomes in ALS clinical trials (Huang et al., 2020; Vu & Bowser, 2017).

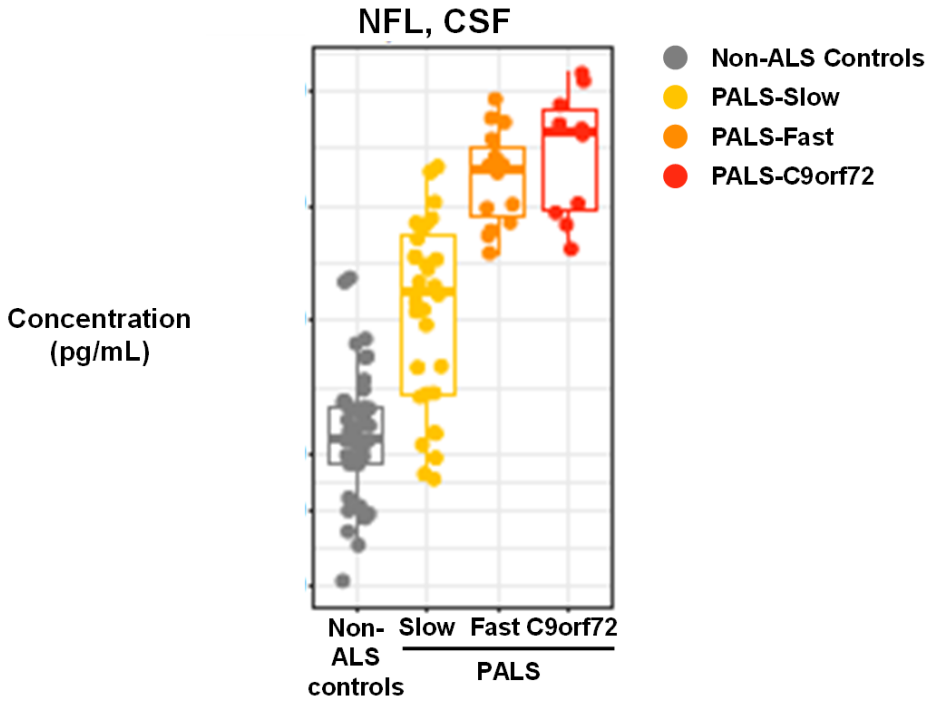
The pathophysiology of ALS is complex and involves multiple interconnected mechanisms, with inflammation and neurodegeneration being key players in its progression (Glass, Saijo, Winner, Marchetto, & Gage, 2010). The dysregulation of the immune system in ALS might involve both exaggerated pro-inflammatory responses and impaired anti-inflammatory responses (Beers & Appel, 2019; Zhang et al., 2023) that play a crucial role in mediating neuronal injury and disease progression (Khalid, Ampie, Kelly, Ladha, & Dardis, 2017). Motoneurons degeneration is primarily driven by the brain's local immune resident cells: microglia and astrocytes, in concert with the infiltrating peripheral immune cells (once the blood-brain barrier is disrupted by inflammation) such as monocytes, macrophages and T lymphocytes, with resulting release of toxic substances (Liu & Wang, 2017). Both microglia (M) and T-cells have central roles in the propagation of the disease. As in other organs, once activated in response to injury or antigen, microglia and helper T-cells (Th) differentiate into a pro-inflammatory (M1 and Th1) phenotype. In acute injury: once the inciting event has been dealt with, these cells transition to an anti-inflammatory phenotype (M2 and Th2).

In ALS where the pathogenic stimulus is not adequately cleared and persists over time, chronic inflammation develops with persistent M1, Th1 activity that leads to unintended injury to local tissues. This imbalance can lead to an environment where inflammation is no longer beneficial (e.g., for debris removal) but instead contributes to the neurodegenerative process.

This chronic inflammation contributes to the progression of ALS by creating a feedback loop where inflammation begets more inflammation, leading to a self-perpetuating cycle of neurodegeneration.

An example of an established ALS biomarker in recent literature includes NfL, a marker of motor neuron integrity and an integral structural component of neurons. Converging lines of evidence identify NfL concentrations as elevated in people living with ALS (Figure 14) compared to healthy controls, and as a strong prognostic marker of the rate of disease progression (Gaiani et al., 2017; Meyer et al., 2023; Thompson et al., 2022). Confidence in the strength of NfL as a predictor of progression has reached the point where multiple FDA marketing approvals have cited NfL as a surrogate endpoint biomarker for which reductions can be reasonable likely to be associated with less functional decline (FDA, 2023b).

Figure 14: CSF Neurofilament Light Chains (NfL) as Biomarker of ALS Disease Progression



Abbreviations: *C9orf72*=people with variations in the *C9orf72* gene, which is generally causative for ALS and associated with rapid disease progression; CSF=cerebrospinal fluid; NFL=neurofilament light; PALS=person living with ALS.
Note: X-axis indicates four groups identified in Huang et al. (2020) as part of a retrospective biomarker study performed on preserved CSF samples from 108 people with ALS and 35 healthy controls.
Source: (Huang et al., 2020).

6.2 Phase 2 Study BCT-001-US

6.2.1 Investigational Plan

BCT-001-US (Study 001) was a Phase 2 multicenter, randomized, double-blind, placebo-controlled study conducted in people with early-stage ALS. A total of 59 participants were screened, and 51 potential participants were enrolled. Of these, 48 completed the 12-week pre-treatment period and were randomly assigned 3:1 to receive NurOwn (n=36) or placebo (n=12). NurOwn was administered by a single IT injection (100-125 × 10^6 cells), and 24 separate IM injections (each 2 × 10^6 cells for a total of 48 × 10^6 cells IM). Participants were then followed for six months. CSF was obtained immediately prior to the treatment and two weeks following treatment for biomarker analysis.

Efficacy was evaluated in the Full Analysis Set (FAS; all randomized participants) and in a prespecified subpopulation of rapid progressors. Participants included in the subpopulation (i.e., rapid progressors) were defined as having a decrease of two points or more (change ≥ -2 points) between Screening and Baseline in ALSFRS-R total score (n=15 in the NurOwn group and n=6 in the placebo group).

Efficacy endpoints included ALSFRS-R and SVC from Screening through 24 weeks post treatment, and through 16-week follow-up periods for ALSFRS-R and SVC. The significance level for this trial was < 0.1.

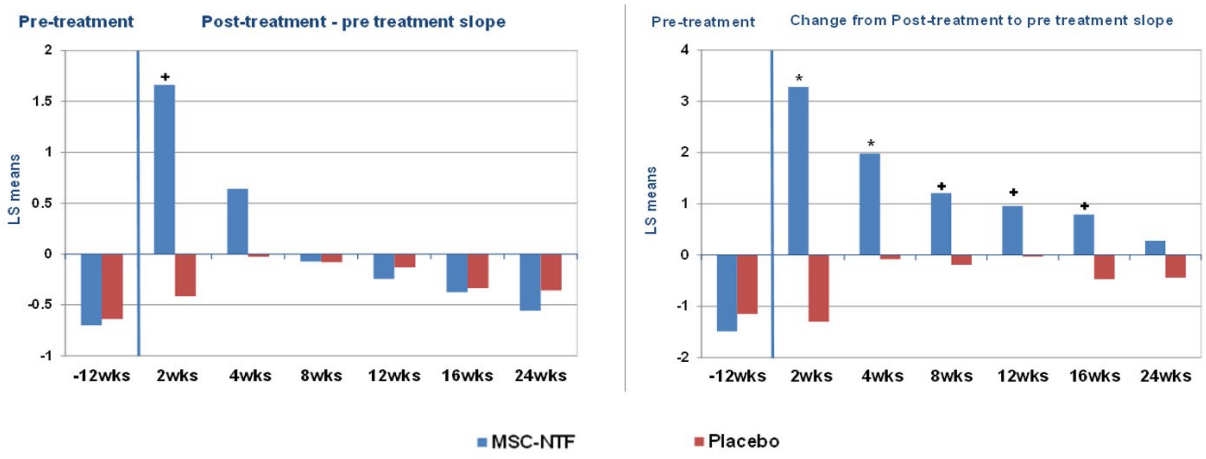
6.2.2 Study BCT-001 Efficacy Results

6.2.2.1 ALSFRS-R Results

In the FAS population, the median age was 53 (range: 26 to 71) years. Participants were white (100%) and predominantly male (72.9%). Demographic and baseline characteristics were generally balanced between NurOwn and placebo treatment groups.

In the FAS population, a clinically meaningful and statistically significant improvement was observed in the change in least-squares (LS) mean slope of ALSFRS-R for the NurOwn group at two weeks post-treatment compared to pre-treatment. Improvement between the NurOwn and placebo groups continued at four and eight weeks post-treatment, although the results did not achieve statistical significance at these later timepoints (Figure 15).

Figure 15: Changes in ALSFRS-R Total Slope over Time (Study BCT-001-US, FAS [left] and Rapid Progressors [right])



Abbreviations: MSC-NTF=mesenchymal stem cells secreting neurotrophic factors; FAS=Full Analysis Set; wks=weeks.
Note: The difference between the treated and placebo groups was statistically significant at the 2-week time point (p=0.110 indicated by + for p < 0.2 two-sided).

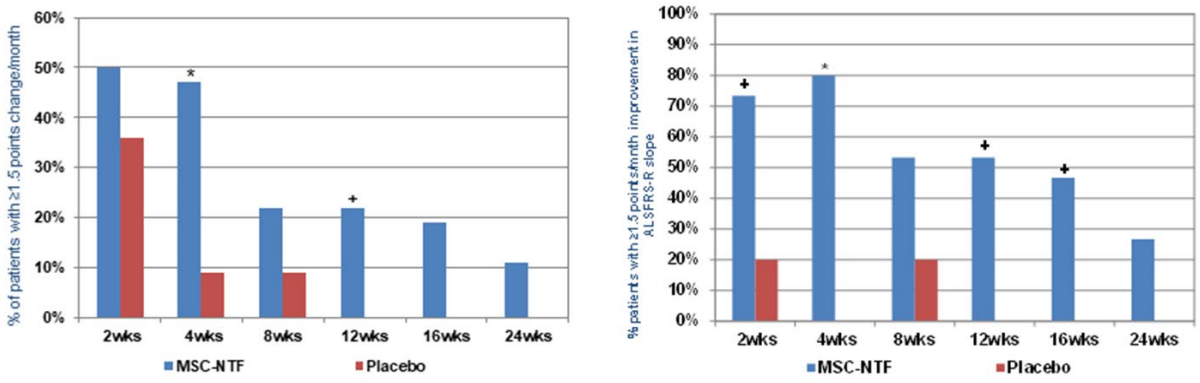
The improvements in ALSFRS-R total slope were attributable to improvements in Respiratory and Gross Motor subscale slopes. In the subgroup of rapid progressors, the comparison between NurOwn and placebo for the change in the post-treatment ALSFRS-R slope (LS mean) compared to pre-treatment indicated an improvement in the NurOwn group at all time points, achieving statistical significance at all time points except at 24-weeks (Figure 15).

In the FAS, responder analyses based on percent improvement from baseline indicated that the percentage of responders with at least 100% improvement on ALSFRS-R slope

was higher in the NurOwn group compared to placebo at all follow-up time points except after eight weeks, and statistical significance was observed at two weeks (one-sided, p=0.081). In the rapid progressors, the percentage of participants with ≥ 100% improvement on ALSFRS-R slope was higher in the NurOwn group compared to placebo at all follow-up time points, achieving statistical significance compared to placebo at the 2-week (p=0.005), 4-week (p=0.031), and 16-week (p=0.092) follow-up time points.

In the FAS, a higher percentage of participants achieved a ≥ 1.5 point/month improvement in the NurOwn group compared to placebo at all time points, achieving statistical significance at the 4-week (one-sided, p=0.023) and 12-week (one-sided p=0.080) follow-up time points (Figure 16). In the rapid progressors, the percentage of participants with ≥ 1.5 points/month improvement was also higher in the NurOwn group compared to placebo at all follow-up time points, achieving statistical significance at the 2-week (p=0.058), 4-week (p=0.004), 12-week (p=0.032), and 16-week (p=0.055) follow-up time points.

Figure 16: Participants with ≥ 1.5 Points/Month Improvement in ALSFRS-R Score in FAS (left) and Rapid Progressors (right) (Study BCT-001-US)



Abbreviations: FAS=Full Analysis Set; MSC-NTF=mesenchymal stem cells secreting neurotrophic factors; wks=weeks.
Note: In the FAS, the difference between the treated and placebo groups was statistically significant at the 4 and 12-week time points (p=0.023 and 0.080, indicated by *p < 0.025 or + for p < 0.1 one-sided). Among rapid progressors, the difference between the treated and placebo groups was statistically significant at the 2-, 4-, 12-, and 16-week time points (p=0.058, 0.004, 0.032, and 0.055 respectively, indicated by * for p < 0.025 or + for p < 0.1 one-sided)

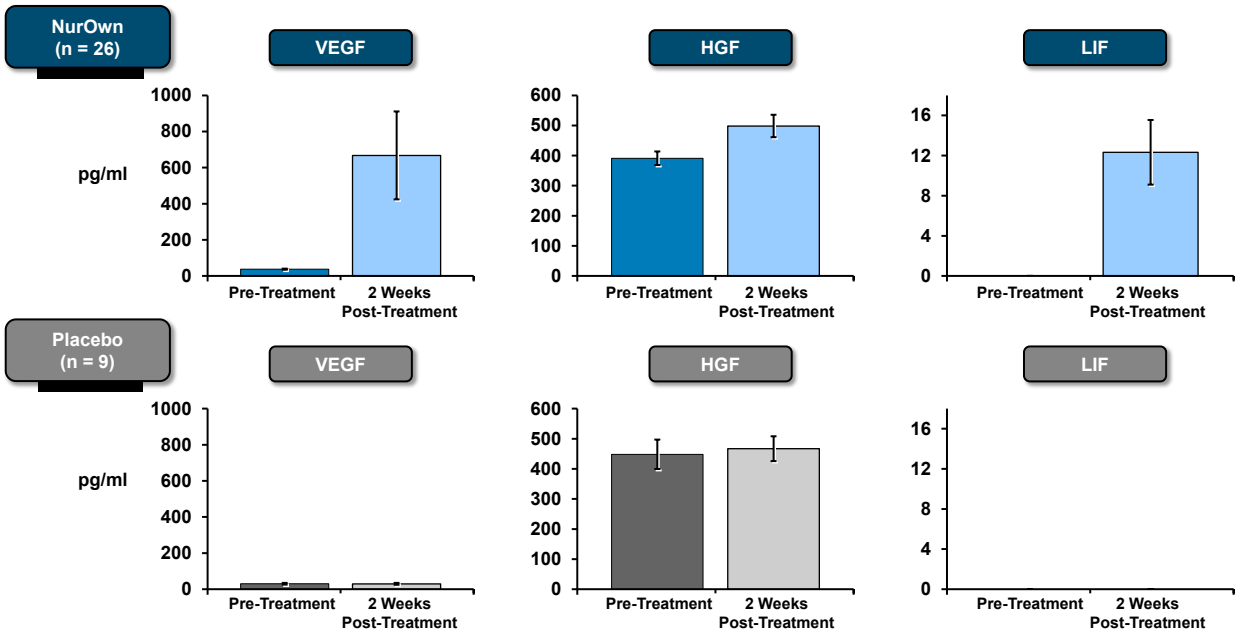
6.2.2.2 Biomarkers in the Cerebrospinal Fluid (CSF)

CSF samples for analysis of biomarkers were collected prior to treatment and two weeks after treatment. All reported findings were statistically significant with p-values < 0.05.

6.2.2.2.1 Neurotrophic Factors (NTFs)

The levels of VEGF (p < 0.05), HGF (p < 0.01), and LIF (p < 0.001) in the CSF were increased at two weeks post-treatment in the NurOwn group (n=26) but not placebo (n=9) (Figure 17). In addition, changes from pre- to post-treatment for LIF was statistically significant between the treatment groups (p=0.033).

Figure 17: Neurotrophic Factor Levels (Study BCT-001-US)



Abbreviations: HGF=hepatocyte growth factor; LIF=leukemia inhibitory factor; VEGF=vascular endothelial growth factor.

6.2.2.2.2 Inflammatory Biomarkers

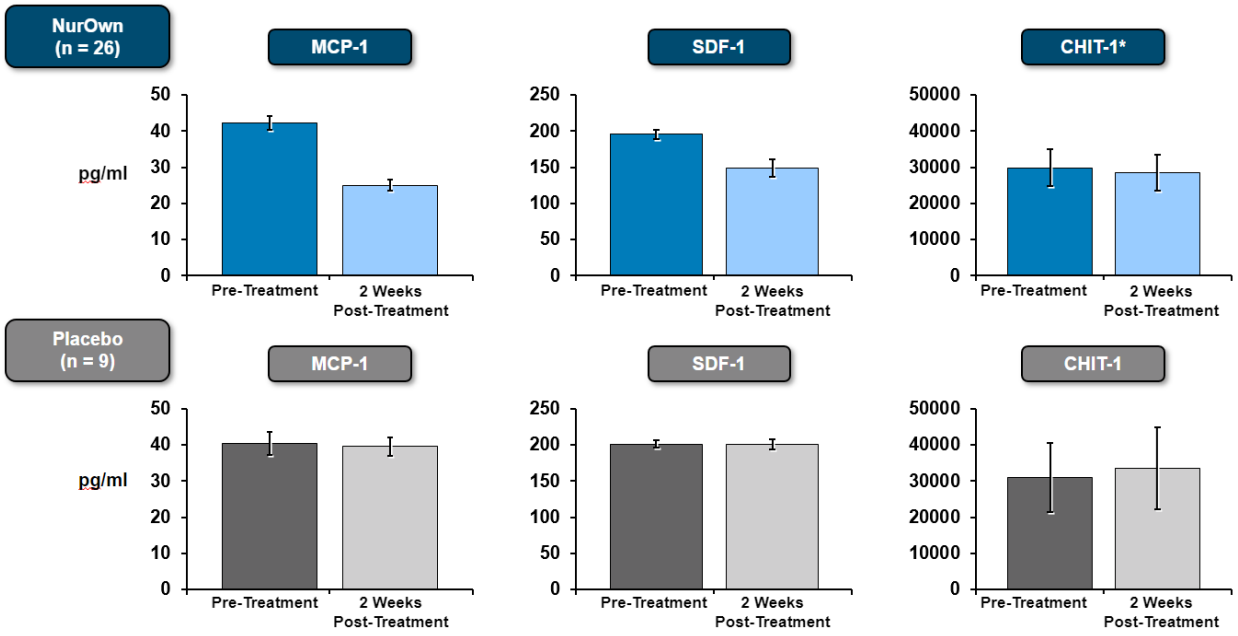
At two weeks post-treatment, statistically significant decreases ($p < 0.01$) in CSF inflammatory biomarkers, MCP-1 and stromal cell-derived factor 1-alpha (SDF-1), were observed in the NurOwn group, while there were no observed changes in the placebo group (Figure 18). Specifically, a 41% reduction in CSF MCP-1 was observed two weeks following NurOwn treatment ($p < 0.0001$), while the placebo group showed no change ($p=0.708$). Furthermore, post-treatment CSF MCP-1 was inversely correlated with ALSFRS-R slope improvement at different weeks, while placebo showed no correlation. The correlation of post-treatment CSF MCP-1 levels to ALSFRS-R slope improvement was also significant at Week 4 ($p=0.002$), Weeks 12 ($p=0.008$), Week 16 ($p=0.035$) and 24 ($p=0.017$).

CSF MCP-1 showed an inverse correlation with CSF VEGF at two weeks ($p=0.003$) while placebo showed no correlation ($p=0.580$). In ALS, the ratio of CSF MCP-1/VEGF is uniquely high compared to other neurodegenerative diseases (Nagata et al., 2007) and the CSF MCP-1/VEGF ratio was corrected following treatment ($p=0.003$). A similar and consistent inverse correlation was observed for CSF LIF and HGF and other inflammatory biomarkers (MCP-1 and SDF-1) suggesting that NurOwn treatment consistently shifted the balance in neuroprotective and neuroinflammatory biomarkers (VEGF/SDF-1; $p < 0.0001$). These important CSF biomarker changes were not observed in placebo.

There was no significant post-treatment change in the levels of macrophage inflammatory protein-1β or C-reactive protein in either group.

Chitinase-1 (CHIT-1) demonstrated a small and significant decrease in the NurOwn group (p=0.027) and a small nonsignificant increase in the placebo group.

Figure 18: Modulation of Inflammatory Markers in the CSF of Treated and Placebo Patients (Study BCT-001-US)



Abbreviations: CSF=cerebral spinal fluid; CHIT=Chitotriosidase; MCP-1=monocyte chemoattractant protein-1; NTF=neurotrophic factors; SDF-1=stromal cell-derived factor 1.

Note: CSF was sampled pre-treatment and two weeks post-treatment. A significant decrease of MCP-1, SDF-1, and CHIT-1 is shown in the CSF of the MSC-NTF treated patients (upper panels) with no significant change in the placebo group (lower panels).

6.2.2.2.3 Other CSF Biomarkers

Caspase-3, a key mediator of neuronal apoptosis, was significantly reduced post-treatment in the NurOwn group ($p < 0.0001$) but not in the placebo group. Increases in CSF neuroprotective microRNA species (miR-132, miR-34a-5p) and CSF anti-inflammatory microRNA species (miR-146a) were higher in treatment responders compared to non-responders. It has been previously demonstrated that these miRNA species are increased in MSC-NTF cells compared to their MSC of origin (Gothelf et al., 2017). NfL was not measured in the Phase 2 study.

6.3 BCT-002-US - Pivotal Phase 3 Study

6.3.1 Investigational Plan

6.3.1.1 Overall Design

BCT-002-US was a multicenter, Phase 3, randomized, double-blind, placebo-controlled study conducted in people with ALS having ALSFRS-R scores ≥ 25 at screening

(Figure 2). The study comprised three periods, an approximately 20-week pre-treatment period, a 16-week treatment period, and a 12-week post-treatment follow-up period. Participants were randomized 1:1 to receive NurOwn (100-125 × 10^6 cells) or placebo by IT administration.

6.3.1.2 Randomization and Treatments

Participants were treated IT with either NurOwn (100-125 × 10^6 cells, corresponding to the highest dose that was safely administered in the previous clinical trials in people with ALS) or matching placebo (one 5 mL syringe containing 4 mL of excipient) by standard lumbar puncture. A treatment course consisted of three individual doses of 100-125 × 10^6 cells, with each dose administered 8 weeks apart (Weeks 0, 8, and 16).

6.3.1.3 Primary and Secondary Endpoints

The primary efficacy endpoint was a responder analysis to evaluate the efficacy of NurOwn compared to placebo as measured by the proportion of participants with a ≥ 1.25 points/month improvement in post-treatment slope versus pre-treatment slope of the ALSFRS-R score at 28 weeks following the first treatment. (Details on the ALSFRS-R assessment are provided in Section 6.1.) Participants who died due to disease progression were considered non-responders, irrespective of their ALSFRS-R data.

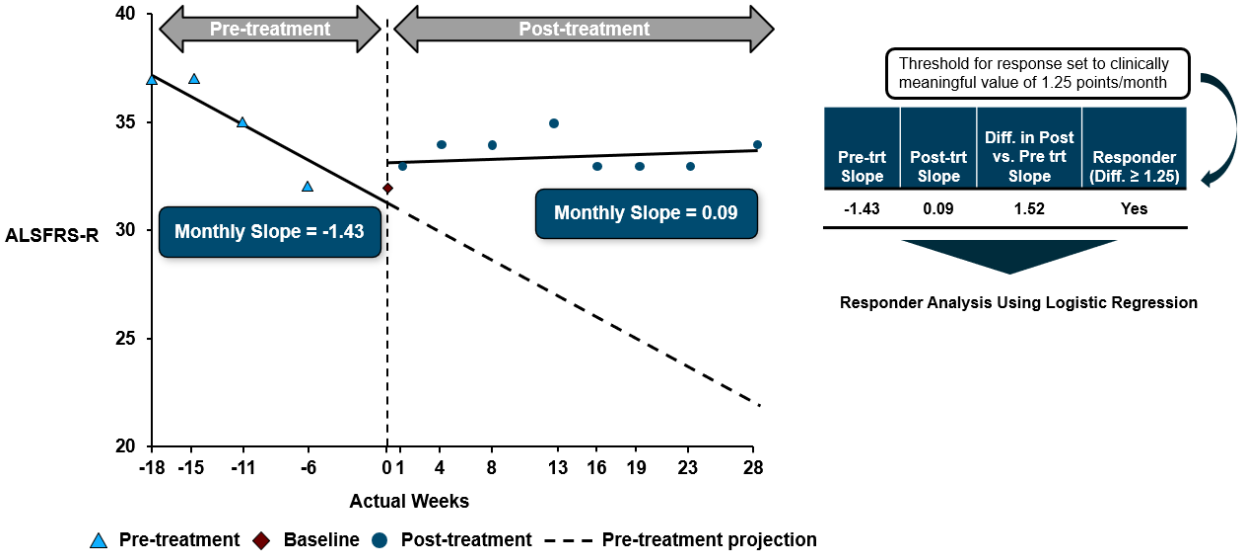
The average change from baseline in ALSFRS-R at Week 28 was included as a key secondary endpoint.

Additional secondary endpoints included:

- Response analysis: post-treatment slope improving by ≥ 100%.
- CAFS.
- SVC change from Baseline to Week 28.
- Time to death due to disease progression and death due to any reason as a sensitivity analysis.
- Time to death or tracheotomy (note that analysis not completed as there were no tracheotomies in the study).
- CSF/Blood biomarkers analysis in relationship to clinical efficacy.

An illustration of the primary endpoint using an individual profile of a participant treated with NurOwn from Study BCT-002-US is provided in Figure 19. This participant met the criteria for clinical response for the primary endpoint. Prior to treatment, this participant had a rate of decline of -1.43 points per month, which slowed during the treatment period by 1.52 points per month (more than the response definition threshold of 1.25 points/month) to a stable trajectory with a slope that is positive (slight increase) and near zero. This 1.25 criterion is a substantial bar for clinical response.

Figure 19: Phase 3 Study BCT-002-US — Illustration of Primary Endpoint Using Individual Patient Profile



6.3.1.4 Inclusion/Exclusion Criteria: Selection of Study Population

This study was conducted in participants with a clinical diagnosis of ALS who met the El Escorial criteria (Brooks, Miller, Swash, & Munsat, 2000) for possible, laboratory-supported probable, probable, or definite ALS. Additional key inclusion criteria were:

- Participants were male or female between the ages of 18 to 60 years old, who presented an onset of ALS disease symptoms, including limb weakness, within 24 months of the screening visit.
- Participants had an ALSFRS-R ≥ 25 at the screening visit, with a decline in ALSFRS-R total score of ≥ 3 points in the 12 weeks preceding randomization.
- Participants had an upright SVC measure ≥ 65% of predicted for gender, height, and age at the screening visit.
- Participants on a stable dose of riluzole were permitted.

Prior stem cell therapy and active participation in an ALS interventional study were exclusionary criteria.

6.3.1.5 Statistical Analysis

Two statistical analysis plans (SAPs) were finalized and submitted to the FDA before database lock: a primary SAP for clinical data and a secondary SAP focused on biomarker data, which included analyses of biomarkers in relation to clinical outcomes.

6.3.1.5.1 Data Sets Analyzed

All efficacy analyses were performed using the mITT population, which included all participants who were randomized, treated, and had at least three ALSFRS-R

assessments: one pre-treatment assessment prior to the baseline assessment, a baseline assessment, and at least one post-treatment assessment. Baseline was the ALSFRS-R assessment at the first treatment visit (Week 0, Visit 6) prior to treatment.

6.3.1.5.2 Analyses of the Primary and Secondary Efficacy Endpoints

Unless otherwise stated, any statistical tests performed used 2-sided tests at the 5% significance level.

6.3.1.5.3 Pre-Specified and Post Hoc Analyses to Address Floor Effect

The extent of the floor effect that was observed in the trial was not anticipated in Study BCT-002-US (see Section 6.1.1.3 for additional details). However, a prespecified subgroup analysis based on the baseline ALSFRS-R threshold of 35 provided an estimate of the treatment effect in participants in less advanced disease, who are less likely to be impacted by the floor effect of the ALSFRS-R. This threshold was set because it was the anticipated baseline average for the study, yet it resulted in approximately 30% of the overall population instead of 50%. Because the final study population had lower baseline scores than anticipated, additional post-hoc analyses to account for the unforeseen baseline scores were performed (see Section 6.3.7.4).

6.3.1.5.4 ALS Baseline Disease Covariates Prognostic of Outcomes

It is widely accepted in the ALS community and by the FDA that ALS disease characteristics of individual people living with ALS influence their prognosis, over and above any measure of treatment effect, and need to be incorporated as baseline covariates in analysis of data. In the prespecified statistical analysis plan, the efficacy model included the following disease characteristics: baseline ALSFRS-R, baseline slope, time since symptom onset to first treatment, use of riluzole, and site of onset. These baseline covariates were not prespecified in the biomarker analysis plan. But after showing the importance of including them in analysis, they were added as part of the final biomarker analysis model (FDA, 2023a).

6.3.1.5.5 Biomarker Analyses

A mixed-effect model with treatment, week, and treatment-by-week interactions as well as the above baseline disease covariates as fixed effects was applied to the log-scale biomarker data.

Forty-five biomarkers were analyzed, of which 33 were classified as having the primary pathways of: neuroinflammation (16), neurodegeneration (8), and neuroprotection (9), in addition to 12 other biomarkers of interest.

A classical stepwise regression model was used to identify biomarkers with the highest predictive value associated with clinical outcomes in the trial for each treatment group, separately, with rate of decline assessed by the ALSFRS-R total score, as estimated by a prespecified mixed-effect piecewise (PW) linear model (V. M. Muggeo & Adelfio, 2011) that models the pre- and post-treatment data simultaneously with a change point. The stepwise regression model uses a mixed selection approach, with probability to enter the

model of 0.25, and probability to remain in the model of 0.05, was used to identify biomarkers that are more likely to be related with the clinical outcomes.

Baseline ALS disease characteristics were added to the final biomarker model to establish the relevance of disease characteristics, in the context of the relationship between PW slope and these predictive biomarkers (both pre- and post-treatment values). UNC13A C risk status, represented as a categorical variable reflecting the number of risk haplotypes, was also added to the final biomarker model to establish the relationship between the PW slope and UNC13A C risk status (Section 6.3.8).

Causal inference models (Richardson et al., 2020; Torbicki et al., 2019), also referred to as natural disease models, were used in two analyses focused on data in participants who had no evidence of a floor effect at baseline. Due to the COVID-19 pandemic, approximately 50% of participants had missing CSF samples at the last biomarker timepoint, Week 20, while many of these participants had data at earlier timepoints. In order to include data from participants with observed data at other visits, multiple imputation was used assuming data were missing at random. An analysis of those with observed Week 20 data was run as a sensitivity analysis.

There are several benefits of this approach including:

- The ability to adjust for baseline imbalances between treatments with the heterogeneity that exists at a participant level, essentially using each person as their own control and
- Isolating the treatment effect of NurOwn by removing the anticipated decline for each person based on the natural disease progression using observed placebo data in the trial.

The first natural disease model used baseline NfL levels and prespecified disease covariates of participants who received placebo to simulate natural disease progression as scores on the ALSFRS-R over time. The resulting model was then applied to NurOwn-treated participants to predict their declines in ALSFRS-R scores had they instead received placebo.

The second natural disease model used NfL and ALSFRS-R data in order to understand the relationship between change in NfL and change in ALSFRS-R. This analysis built natural disease progression models for change from baseline in both NfL and in the ALSFRS-R. Models used to estimate the anticipated decline from baseline in both measures (ALSFRS-R and NfL) employed baseline NfL and prespecified disease covariates in participants randomized to placebo in the trial, with the model to estimate predicted decline in ALSFRS-R also incorporating change from baseline in NfL at Week 20. Predicted values of NfL and ALSFRS-R for NurOwn-treated participants were obtained from the natural disease progression models. These predicted values were compared to the observed changes from baseline to last measurements in the trial to obtain the NurOwn-driven changes.

6.3.1.5.6 Determination of Sample Size

The sample size of 100 participants per arm (200 participants total) to be randomized was based upon estimation of the percentage of NurOwn participants who were rapid progressors, who were responders at 12 weeks in the Phase 2 study. In the Phase 2 study, at 12 weeks post-treatment, 53% of NurOwn-treated rapid progressors were observed to have an improvement in post-treatment slope using either the thresholds of ≥ 1.0 points/month or ≥ 1.5 points/month. The best estimate of the percentage of placebo participants who would have been responders was based upon the percentage of responders among those receiving placebo at 24 weeks, leveraging BCT-001-US and the PRO-ACT database. At 24 weeks post-treatment, 17% of placebo participants were responders using the threshold of ≥ 1.0 points/month and 0% using the threshold of ≥ 1.5 points/month.

Accounting for the longer duration of the study, missing data due to discontinuations, and potentially fewer responders in the NurOwn-treated group, the true percentage of responders who would improve ≥ 1.25 point/month on NurOwn was estimated to be 35%, and on placebo to be 15%. Utilizing a Chi-square test with Type I error rate of 0.05 two-sided and 90% power, 97 participants per treatment arm were required.

6.3.1.5.7 Handling of Death, Missing and Linearity Assumption

Handling of deaths and missing data were pre-specified in the SAP. Missing data can be non-monotone (missed visits) or monotone (deaths or discontinuations from the study). Multiple imputation using both missing at random (MAR) and missing not at random (MNAR) were pre-specified as sensitivity analyses. Deaths are a special type of missing data handled separately. For the primary and secondary endpoints involving responder analyses, deaths due to disease progression were defined as non-responders, with a planned sensitivity analysis considering all deaths as non-responders (12 of the 16 deaths were due to disease progression with 10 randomized to NurOwn and 6 to placebo; two in the placebo group were prior to treatment). In the prespecified mixed effect model repeated measures (MMRM) analyses, missing data due to deaths were not treated differently from missing data due to discontinuations. However, a joint longitudinal-survival mixed effect model (Guo & Carlin, 2004) was used to adjust for survival at a treatment level by modeling the correlation between ALSFRS-R score and survival, as a sensitivity analysis to the MMRM, thereby accounting for death in the MMRM analyses. The CAFS analysis accounts for deaths as the worst outcome with earlier deaths ranked lower than later deaths in computing the CAFS score and subsequent ranks at any timepoint. For CAFS analyses, if participants had missing data due to discontinuations, the CAFS rank was carried forward.

As prespecified in SAP, for participants who discontinued the trial before Visit 14 (Week 28), the slope was calculated using all scheduled and unscheduled visits through Visit 14 (Week 28). For these participants, the estimate of slope at Visit 14 (Week 28) was assumed to be the same slope as calculated through the last observed ALSFRS-R. This assumes continuation at the same rate of disease progression.

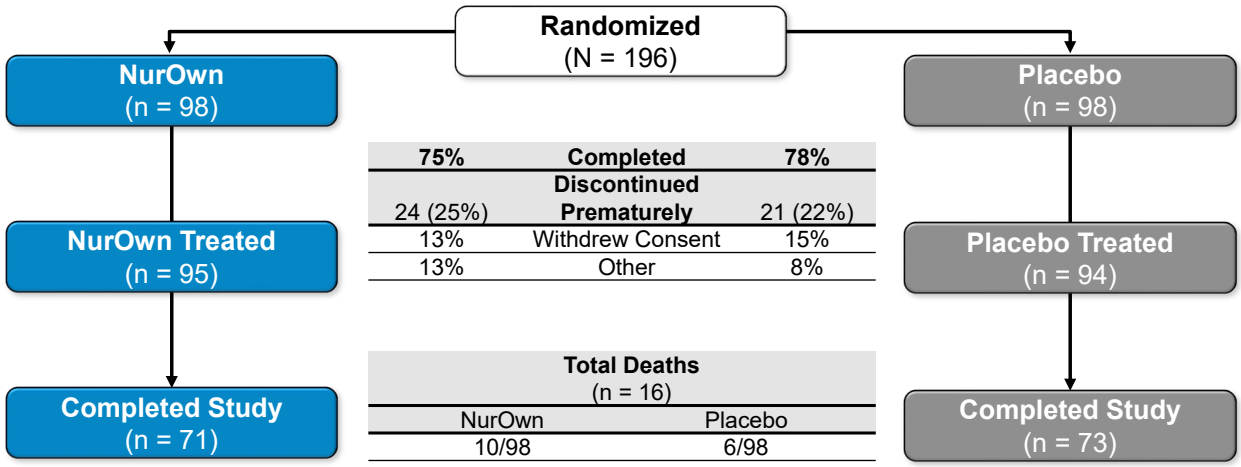
Efficacy endpoints built based on ALSFRS-R slope (primary endpoint and ≥ 100% improvement in ALSFRS-R slope) assumes ALSFRS-R progress in a linear fashion during the trial conduct time frame, a formal statistical evaluation was undertaken to establish the appropriateness of this assumption. The evaluation is done by comparing the model fit (AIC) of a mixed effect model assuming linearity of ALSFRS-R in time versus that of a mixed effect model with quadratic terms of time. Note for the key secondary efficacy endpoint change in ALSFRS-R using MMRM, the model does not require linearity of ALSFRS-R progressing over time as it allows each visit to have its own mean structure, which is a more flexible assumption.

6.3.2 Study Participants

6.3.2.1 Disposition

A total of 263 participants were screened and 196 participants were randomized (1:1) to treatment with either NurOwn (N=98) or placebo (N=98) (Figure 20). Of these, 189 participants received at least one treatment (NurOwn: N=95, placebo: N=94). More than 75% of participants in both groups received all three treatments.

Figure 20: Phase 3 Study BCT-002-US — Participant Disposition



Note: Two of six deaths in the placebo group occurred prior to treatment.

6.3.2.2 Baseline Demographics and Characteristics

Demographic characteristics were balanced between NurOwn and placebo treatment groups (Table 4).

The baseline characteristics for all participants are summarized in Table 5. Baseline characteristics are generally balanced between treatment groups.

The inclusion of participants with advanced ALS is represented by the high number of participants with a baseline ASLFRS-R ≤ 25 who had a baseline score of zero on the subscales of the ALSFRS-R. Specifically, 37% and 42% on gross and fine motor subscale items have item value equal to 0, respectively in this subgroup (Table 6). Almost every

participant with baseline ALSFRS-R ≤ 25 had at least one item starting at zero (Figure 31).

Table 4: Phase 3 Study BCT-002-US — Participant Demographics

Parameter, n (%):	NurOwn (N=95)	Placebo (N=94)
Age (year) Mean (SD)	48.1 (9.71%)	49.1 (8.38%)
Age Group (year): < 55	65 (68.4%)	63 (67.0%)
Age Group (year): ≥ 55	30 (31.6%)	31 (33.0%)
Gender: Female	27 (28.4%)	35 (37.2%)
Gender: Male	68 (71.6%)	59 (62.8%)
Race: Asian	5 (5.3%)	7 (7.4%)
Race: Black or African American	3 (3.2%)	3 (3.2%)
Race: Native Hawaiian or Other Pacific Islander	0	1 (1.1%)
Race: White	87 (91.6%)	81 (86.2%)
Race: Other	0	2 (2.1%)
Ethnicity: Hispanic or Latino	5 (5.3%)	3 (3.2%)
Ethnicity: Not Hispanic or Latino	90 (94.7%)	91 (96.8%)

SD=Standard Deviation.

Table 5: Phase 3 Study BCT-002-US — Participant Baseline Characteristics

Parameter, n (%):	NurOwn (N=95)	Placebo (N=94)
Baseline ALSFRS-R Score, mean (SD)	30.3 (6.5)	31.4 (6.1)
Baseline SVC (% Predicted) Score, mean (SD)	76.2 (20.9)	75.0 (19.8)
Baseline ALSFRS-R Score: < 35	69 (72.6%)	62 (66.0%)
Baseline ALSFRS-R Score: ≥ 35	26 (27.4%)	32 (34.0%)
El Escorial Criteria for ALS: Possible	6 (6.3%)	6 (6.4%)
El Escorial Criteria for ALS: Laboratory-supported Probable	15 (15.8%)	23 (24.5%)
El Escorial Criteria for ALS: Probable	24 (25.3%)	31 (33.0%)
El Escorial Criteria for ALS: Definite	50 (52.6%)	34 (36.2%)
Months since diagnosis, mean (SD)	6.8 (4.35)	6.1 (4.80)
Months since first symptom to first treatment, mean (SD)	19.6 (5.17)	19.1 (4.90)
Duration since first symptom to first treatment, n (%): < 1.5 years	39 (41.1%)	43 (45.7%)
Duration since first symptom to first treatment, n (%): ≥ 1.5 years	56 (58.9%)	51 (54.3%)
Site of disease onset, n (%): Limb	80 (84.2%)	73 (77.7%)
Site of disease onset, n (%): Bulbar	15 (15.8%)	21 (22.3%)
Use of riluzole at baseline, n (%): Yes	65 (68.4%)	56 (59.6%)

Parameter, n (%):	NurOwn (N=95)	Placebo (N=94)
Use of riluzole at baseline, n (%): No	30 (31.6%)	38 (40.4%)

Table 6: Phase 3 Study BCT-002-US — Percentage of Participants with a Baseline of Zero in Participants with Baseline ALSFRS-R ≤ 25

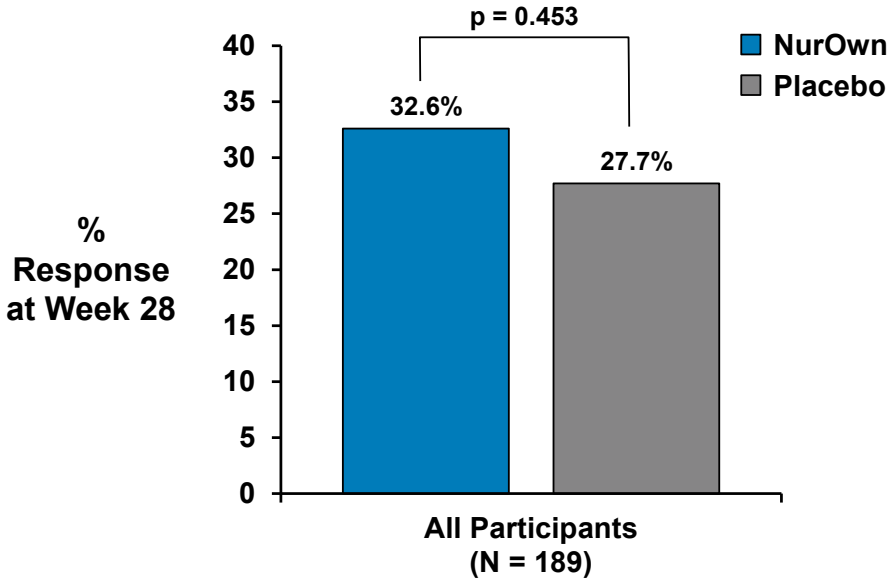
	Item 1	Item 2	Item 3	Average
Bulbar items	11%	7%	2%	7%
Fine Motor items	43%	43%	39%	42%
Gross Motor items	23%	14%	75%	37%
Respiratory items	0	2%	0	1%

6.3.3 Efficacy Results: Primary Efficacy Endpoint

6.3.3.1 Primary Efficacy Results

Analysis of ALSFRS-R scores of all mITT participants in BCT-002-US showed that 32.6% of participants in the NurOwn group responded to study treatment (≥ 1.25 points improvement per month, or slope), compared with 27.7% of participants in the placebo group (left side of Figure 21). The difference between treatment groups was numerically higher but not statistically significant (OR=1.33, p=0.453). As a result of the planned hierarchical testing approach to control type I error, all remaining p-values are reported as nominal.

Figure 21: Phase 3 Study BCT-002-US — Primary Endpoint of Response Rate at Week 28



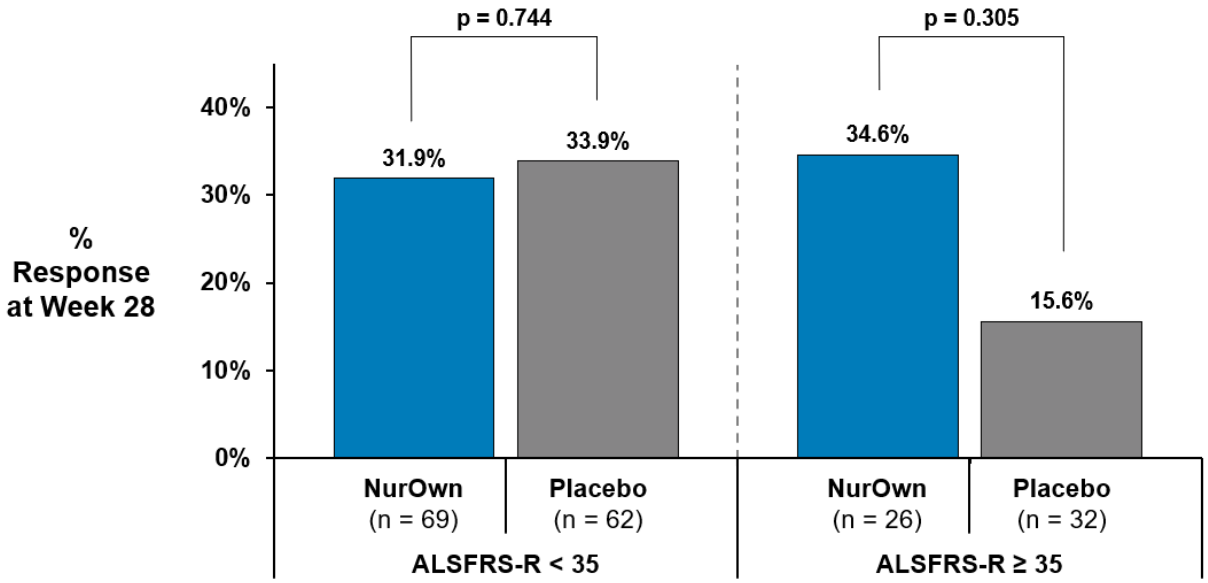
6.3.3.2 *Primary Efficacy Results: Pre-Specified Subgroup with Baseline ALSFRS-R ≥ 35*

The rate of clinical response with NurOwn versus placebo for the primary endpoint in the prespecified subgroup of participants with a baseline ALSFRS-R score ≥ 35 at Week 28 is presented in Figure 22.

The difference in the response rate between the treatment groups is larger in the prespecified subgroup of participants with less advanced ALS disease (i.e., ALSFRS-R score ≥ 35, shown on the right in Figure 22) than in the primary analysis of the mITT population. In this group of participants with less advanced disease, a difference of approximately 19% between the treatment groups is observed, which matches with the power assumption. However, given the relatively large number of participants with advanced ALS included in the study, the observed baseline mean ALSFRS-R score was 31 instead of the anticipated value of 35, resulting in only approximately a third of participant falling into this subgroup (ALSFRS-R score ≥ 35), instead of the expected 50%, which impacts the statistical power.

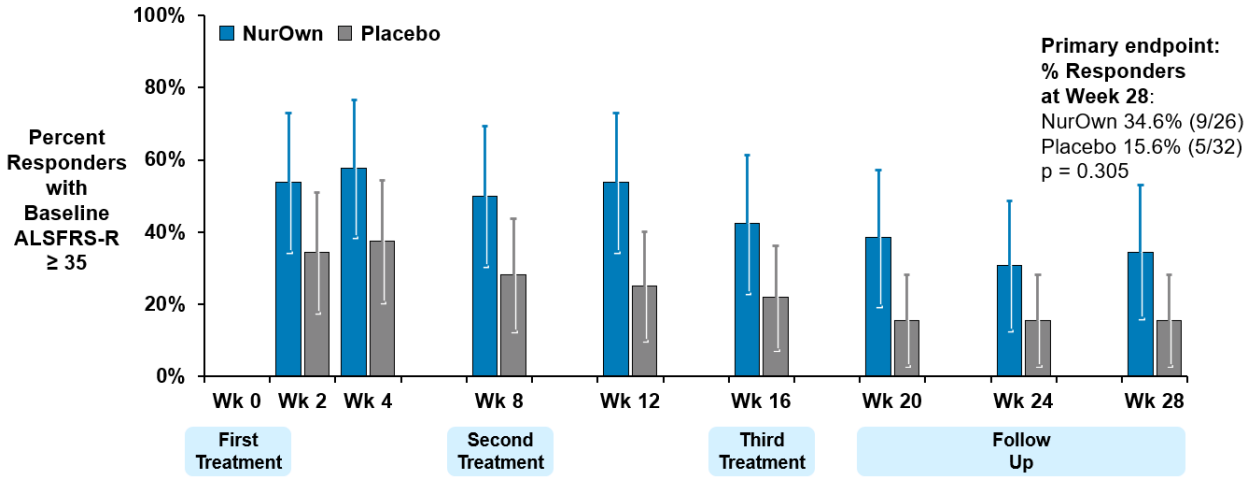
In the subgroup of participants with a baseline ALSFRS-R < 35 (i.e., those participants with more advanced disease, shown on the left in Figure 22), the rate of response was comparable between NurOwn and placebo, with a difference between the treatment groups of approximately 2%. Usually when superior results are observed in one subgroup, it is expected to see the exact opposite happening in the other subgroup. The fact that this was not the case prompted a closer look at what was happening at the lower end of the scale, leading to additional subgroup analyses that uncovered the floor effect.

Figure 22: Phase 3 Study BCT-002-US — Response Rate at Week 28 with NurOwn vs Placebo for Prespecified Subgroups with ALSFRS-R Scores ≥ 35 or < 35



When looking at the temporal trend of the primary endpoint in this pre-specified subgroup, a consistently higher response rate was observed in the NurOwn treatment group starting from Week 2, the first post-treatment time point where the ALSFRS-R was measured, and at each subsequent time point at which the ALSFRS-R was measured across the trial (Figure 23).

Figure 23: Phase 3 Study BCT-002-US — Rate of Response Over Time with NurOwn vs Placebo for Prespecified Subgroup with Baseline ALSFRS-R Score ≥ 35

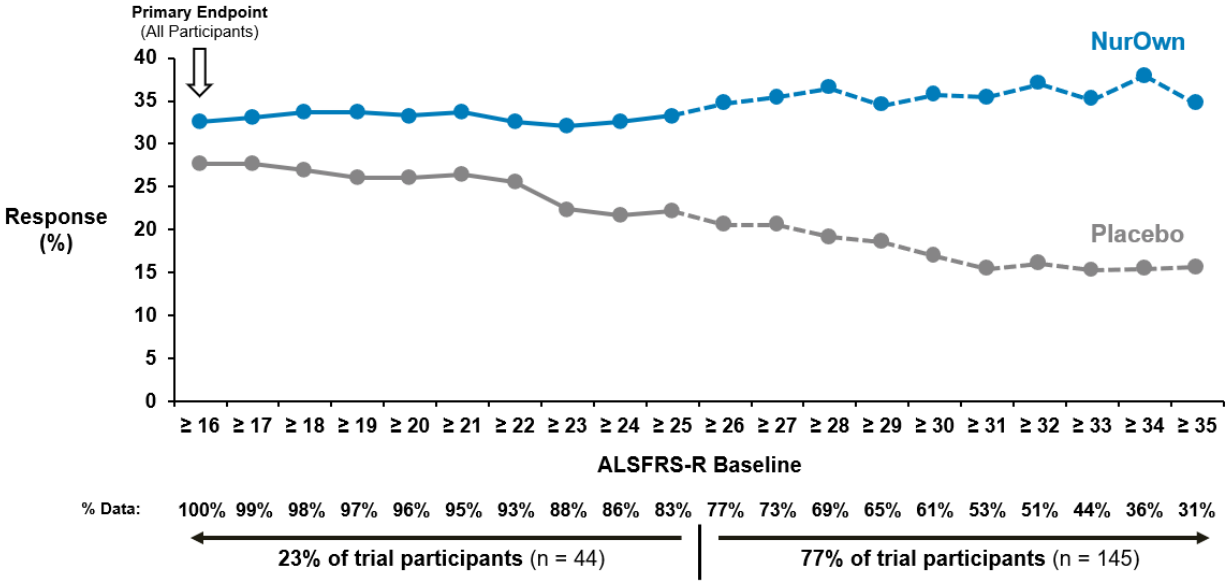


Note: Responder ≥ 1.25 points/month improvement in post-treatment vs. pre-treatment slope in ALSFRS-R score at Week 28.

6.3.3.3 Primary Efficacy Results: Sensitivity Analyses by Threshold

The results from the primary endpoint responder analyses, using all ALSFRS-R thresholds from ≥ 16 to ≥ 35 points, show a higher proportion of responders treated with NurOwn compared to placebo (Figure 24). Participants with baseline scores ≥ 26 represent approximately 77% of the data from the study. In this subgroup, the rate of clinical response for NurOwn is consistent and approximately 15-20% points higher compared to placebo.

Figure 24: Phase 3 Study BCT-002-US — Response Rate with NurOwn Over Placebo Across ALSFRS-R Baseline Thresholds

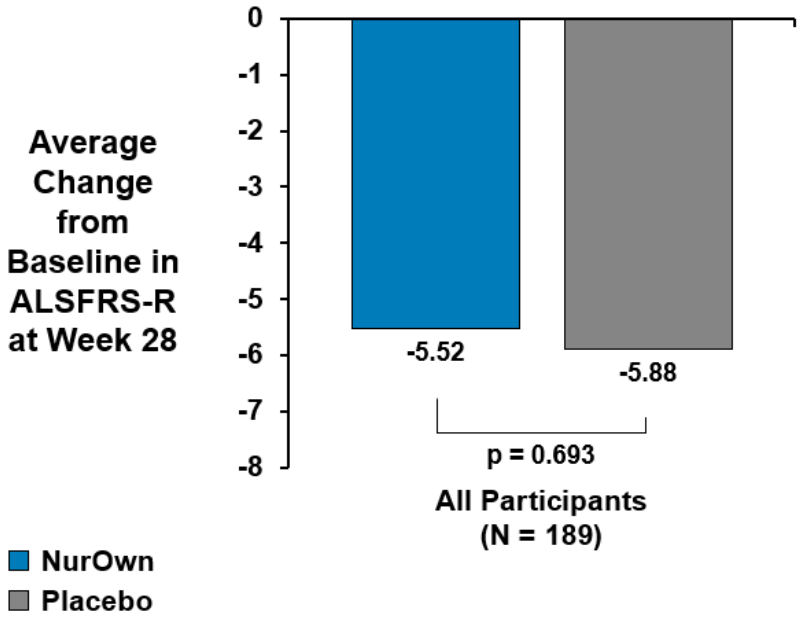


6.3.4 Efficacy Results: Key Secondary Endpoints

6.3.4.1 Key Secondary Efficacy Results

For the key secondary endpoint of average change from baseline in ALSFRS-R to Week 28 in the mITT population, there was again a numerical improvement observed with NurOwn (-5.52 points) over placebo -5.88 points); with a LS mean treatment difference of 0.37 (p=0.693) (Figure 25).

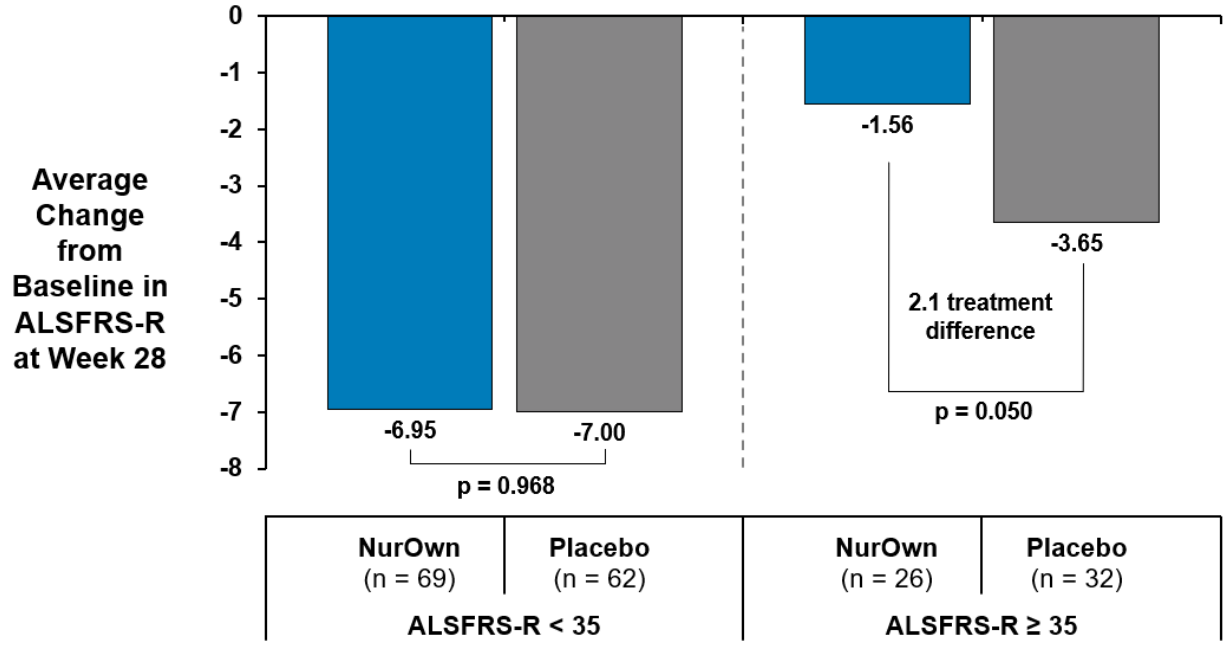
Figure 25: Phase 3 Study BCT-002-US — Key Secondary Endpoint Result



6.3.4.2 *Key Secondary Efficacy Results: Pre-specified Subgroup with Baseline ALSFRS-R ≥ 35*

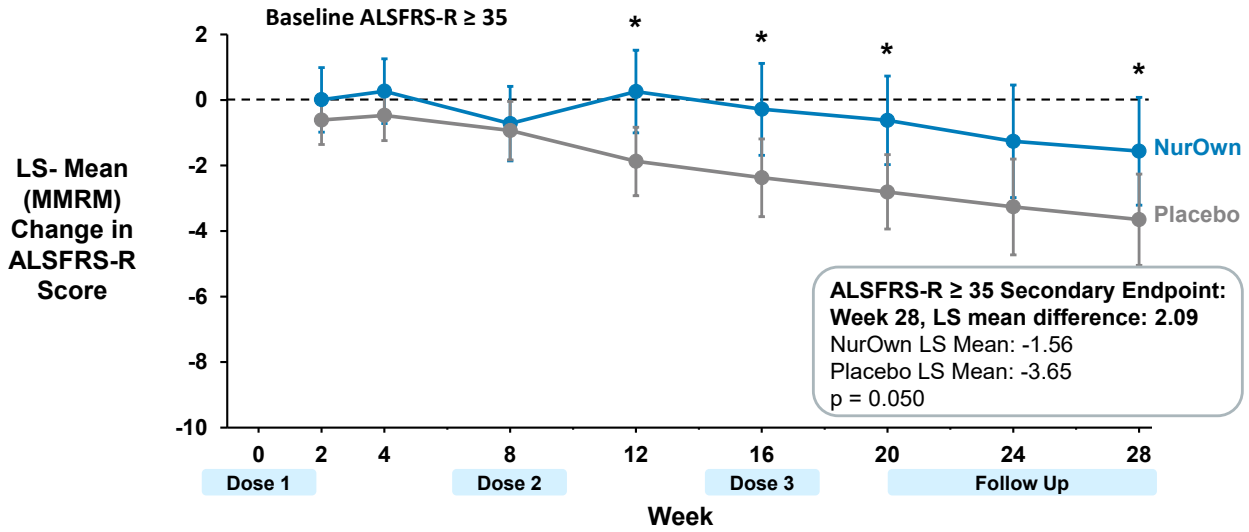
The prespecified subgroup analysis in participants with less-severe disease (ALSFRS-R ≥ 35: shown on the right in Figure 26), there is an observed LS mean change from baseline with NurOwn (-1.56 points) compared to placebo (-3.65 points). This treatment difference in the ALSFRS-R total score of 2.09-point improvement with NurOwn compared to placebo had a significant p-value of 0.050. In the subgroup of participants with a baseline ALSFRS-R < 35, the change in ALSFRS-R total score was almost the same between NurOwn and placebo, which is the same trend observed for the primary efficacy endpoint.

Figure 26: Phase 3 Study BCT-002-US — Key Secondary Endpoint Result by Disease Severity in Pre-Specified Subgroup with Baseline ALSFRS-R Score threshold of 35



Average change from baseline across each time point of ALSFRS-R assessment illustrates the amount of function lost over time by treatment group (Figure 27). The results show a separation between treatment groups after the second treatment, with NurOwn participants retaining more function, and a 2-point difference in function maintained through the end of the trial. There were significant differences over time, with $p < 0.050$ at multiple time points, including at the end of the trial (p=0.050).

Figure 27: Phase 3 Study BCT-002-US — Mean Change in ALSFRS-R Total Score from Baseline Over 28 Weeks in Pre-Specified Subgroup of Participants with Baseline ALSFRS-R Score ≥ 35

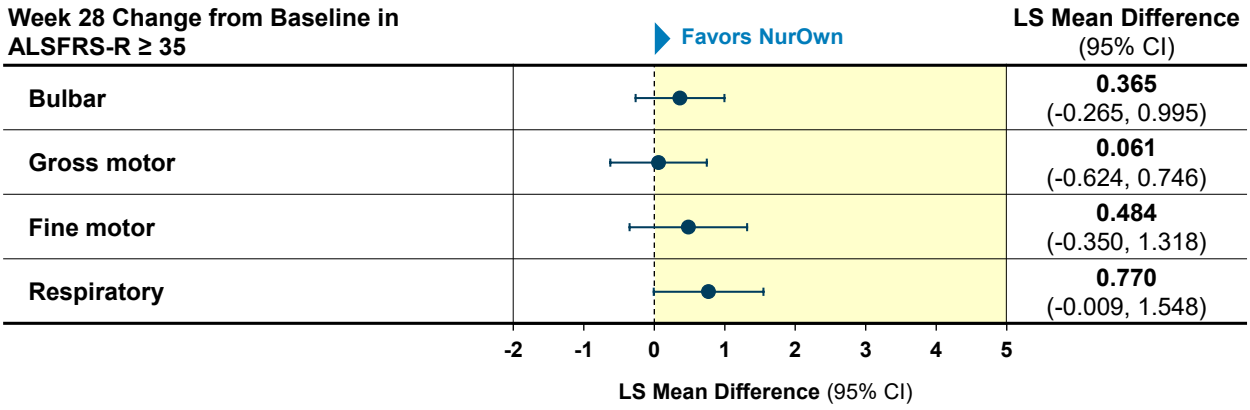


* p ≤ 0.05

LS=least-squares; MMRM=mixed models for repeated measures.

The consistency of treatment effect is also observed in the subscales of the ALSFRS-R. The forest plot in Figure 28 shows that the treatment effect with NurOwn is not driven by more than one subscale, i.e., there is less decline in function in the NurOwn arm compared to placebo in the individual subscales, as well as in the total score.

Figure 28: Phase 3 Study BCT-002-US — Treatment Effect by ALSFRS-R Subscale



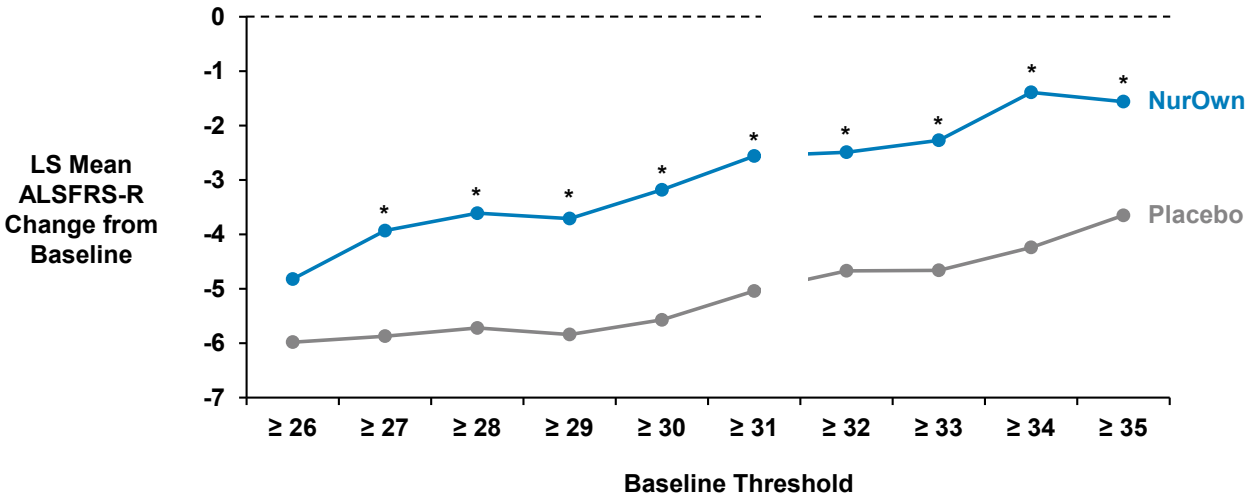
LS=least-squares.

6.3.4.3 Key Secondary Efficacy Results: Sensitivity Analyses by Threshold

The sensitivity analysis of average change from baseline to Week 28 by threshold was also performed for the key secondary endpoint. Figure 29 shows the range of ALSFRS-R baseline scores from ≥ 26 to ≥ 35. Using the actual baseline study mean, ALSFRS-R

scores ≥ 31, which is approximately 50% of trial participants, shows a 2.48-point treatment difference in the average change from baseline to Week 28 on the ALSFRS-R, with a significant p-value of 0.020. For each of these thresholds above 26, the average change from baseline to Week 28 on the ALSFRS-R, also has a significant p ≤ 0.05.

Figure 29: Phase 3 Study BCT-002-US — Key Secondary Endpoint for NurOwn Over Placebo Across ALSFRS-R Baseline Thresholds



*p ≤ 0.05

LS=least-squares.

6.3.5 Results: Assess the Impact of Missing Data and Linearity Assumption

The results of multiple imputation under MAR and MNAR assumption are consistent with the primary analysis for the primary and the key secondary endpoint. The joint longitudinal-survival mixed effect model also shows consistent results as MMRM for threshold analysis across 26 to 35. The consistency of conclusions drawn across these analyses to account for missing data and death offers confidence that treatment effects are robustly discernable across these endpoints, and are not unduly influenced by missing data or death.

The assessment of the linearity assumption shows the model which assumes linearity over time using week has a better model fit (lower AIC value) than a model with quadratic terms of week, with the p-values for the quadratic terms being non-significant (p=0.367 for week^2 and p=0.102 for week^2 by treatment interaction). These results support the linearity assumption in the trial.

6.3.6 Results: Other Secondary Endpoints

Additional secondary endpoint results are displayed in Table 7. With the exception of SVC, the results for all secondary endpoints in those with less advanced disease (ALSFRS-R ≥ 35) showed a more pronounced treatment difference compared to placebo, although none were statistically significant, likely due to the reduced power from the small number of participants in this subgroup.

The change from baseline in predicted SVC was smaller for placebo compared to NurOwn, although there was a major impact on the collection of SVC assessments due to the COVID-19 pandemic. Pandemic hospital restrictions resulted in rates of SVC missing data of approximately 60% in both treatment groups at Week 28 (57.9% NurOwn and 61.7% placebo participants).

In the participants with more severe baseline disease (ALSFRS-R < 35), the treatment groups were generally more similar across endpoints, with participants in the placebo group having a higher CAFS rank.

The Kaplan-Meier estimates for event-free survival, with death due to ALS disease progression or any cause, were similar between treatment groups, with slightly higher probabilities in the placebo group compared to NurOwn. The differences were not statistically significant.

Table 7: Phase 3 Study BCT-002-US — Other Secondary Endpoints

Secondary Endpoints,	All Trial Participants NurOwn (N=95)	All Trial Participants Placebo (N=94)	ALSFRS-R < 35 NurOwn (N=69)	ALSFRS-R < 35 Placebo (N=62)	ALSFRS-R ≥ 35 NurOwn (N=26)	ALSFRS-R ≥ 35 Placebo (N=32)
≥ 100% improvement in ALSFRS-R slope, n (%), through Week 28	13 (13.7%)	13 (13.8%)	6 (8.7%)	8 (12.9%)	7 (26.9%)	5 (15.6%)
Combined Assessment of Function and Survival (CAFS), average rank at Week 28	73.7	72.2	66.4	72.1	93.7	78.3
Slow vital capacity (SVC), average change to Week 28*	-12.9	-11.6	-18.1	-14.8	-5.8	-4.8
Event-free probability for deaths due to disease progression, through Week 32	90.4	92.2	86.8	89.6	> 99†	> 99†
Event-free probability for deaths due to any cause, through Week 32	88.3	89.2	83.9	89.6	> 99†	90‡

* 60% SVC data was missing due to COVID-19 pandemic hospital restrictions at Week 28.
Note: Results from secondary endpoints through Week 32 do not include two deaths that occurred in participants randomized to placebo which occurred prior to treatment.
†: No deaths occurred through Week 32; ‡ one death occurred through Week 32.

6.3.7 Results: Post-Hoc Efficacy Analyses Adjusting for Floor Effect

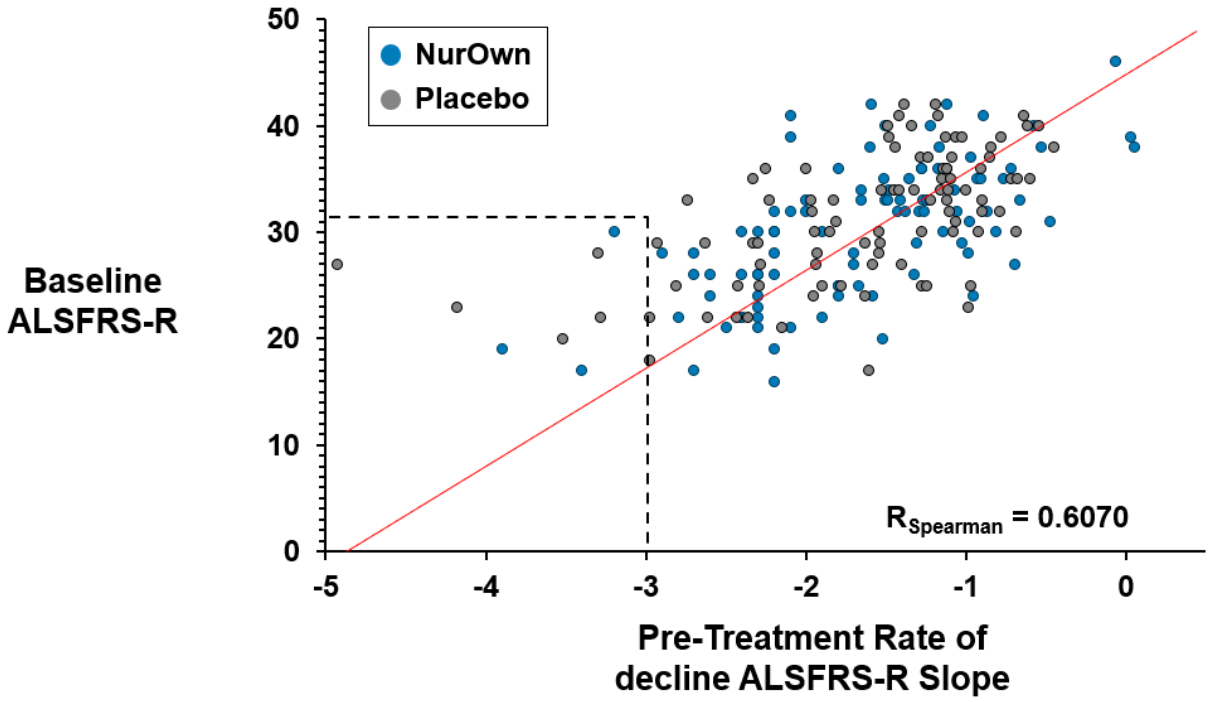
In consideration of the identified floor effect in the ALSFRS-R among participants with advanced disease (as described in Section 6.1.1.1), post-hoc analyses were performed to examine its impact on the study results.

6.3.7.1 *Imbalance in NurOwn vs Placebo Participants with Baseline Scores Indicative of Confounding from Floor Effect*

Participants with baseline ALSFRS-R scores ≤ 25 (i.e., those with the most advanced disease) had high rates of baseline scores equal to zero across all fine motor and gross motor items. Specifically, an average of approximately 40% of the six fine motor and gross motor items were zero in this subgroup at baseline (Table 6).

While the baseline demographics and disease characteristics were relatively balanced, the placebo group had an imbalanced number of participants with lower baseline ALSFRS-R scores and more rapidly progressing disease (Figure 30). In the set of participants who had baseline scores ≤ 31 points and who also declined ≥ 3 points/month in the pre-treatment screening period, there were seven placebo participants versus only three NurOwn participants. A lower baseline score leads to less runway left before the total score hits the floor. Similarly, a larger decline rate leads to a shorter time before the total score reaches the plateau. Hence, participants whose disease met both of these characteristics (i.e., baseline ALSFRS-R ≤ 31 and decline ≥ 3 points/month during screening) were more susceptible to the floor effect, and, thus, more likely that interpretation of their study results could be misinterpreted. Because there are more placebo participants in this box, this could be why the rate of placebo participants meeting the responder criteria, albeit due to floor effect, increases in participants with the lowest ALSFRS-R scores, leading to a smaller observed treatment difference between the two groups.

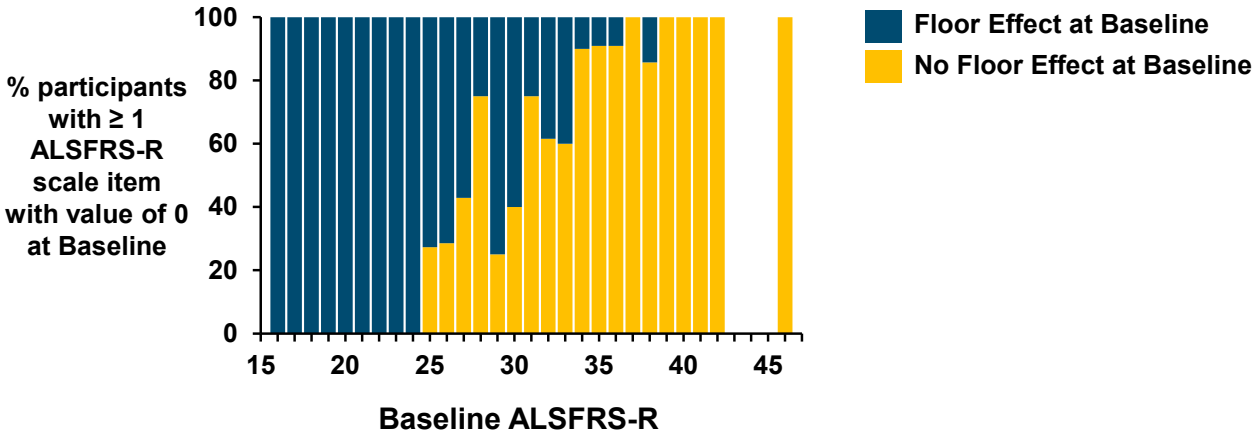
Figure 30: Phase 3 Study BCT-002-US — Relationship Between Baseline ALSFRS-R and Baseline ALS Progression in Participants Treated with NurOwn vs Placebo



6.3.7.2 Magnitude of Floor Effect Based on Lower ALSFRS-R Scores

Participants with lower baseline ALSFRS-R scores were more susceptible to the floor effect as a result of having higher number of items with a score of zero. This effect tends to diminish as baseline ALSFRS-R scores increased. In the graph below (Figure 31), the blue bars show the percentage of all participants in the BCT-002-US trial that had at least one item with a score of zero at baseline and are therefore susceptible to the floor effect. These percentages are then binned by each baseline ALSFRS-R score. Importantly, 44% of participants had a baseline of at least one zero on an item level score. Note that 100% of participants with an ALSFRS-R score of ≤ 24 had at least one score of zero at baseline. In fact, participants in this group had an average of three items starting with a value of zero at baseline, with that number of zero items going as high as six at baseline. These criteria were used to define a post-hoc subgroup of participants that had no evidence of floor effect at baseline, which is 56% of participants, as shown in the figure with yellow bars.

Figure 31: Phase 3 Study BCT-002-US — % Participants with Possible Floor Effect by Baseline ALSFRS-R Score

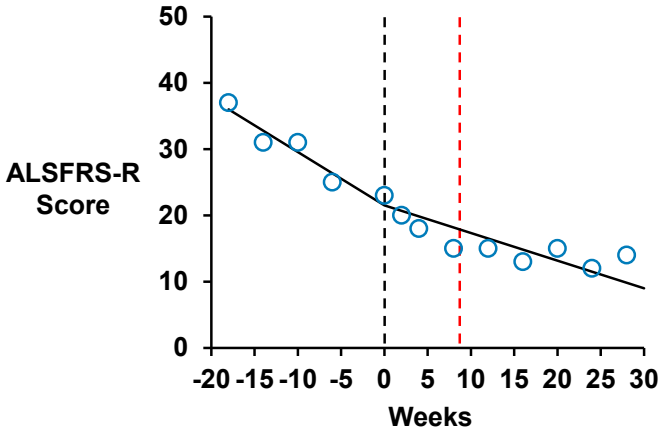


6.3.7.3 Example of Impact of Floor Effect in Study BCT-002-US

The impact of the floor effect at an individual participant level is illustrated by ALSFRS-R scores over time for a participant in the BCT-002-US study (Figure 32). The example illustrates a participant's scores decreasing during the pre-treatment period and shortly after receiving the first dose of treatment, until they reach a point where the rate of decline plateaus. The data for this participant is potentially misinterpreted for meeting criteria for clinical response on the primary endpoint analysis. This participant was included in the placebo group and had five of six fine and gross motor items that reached zero in addition to two of three respiratory items that also reached zero during the trial. The interpretation of the primary endpoint results (≥ 1.25 points/month improvement in ALSFRS-R slope over baseline) is thus greatly impacted by the ALSFRS-R floor effect; this is further amplified in participants who reach a plateauing of the total ALSFRS-R score during the trial, likely resulting in misclassification of clinical response.

In order to identify how frequently this occurred in the Phase 3 study and in addition to historical trials through the PRO-ACT database, we used a segmented regression model or piecewise linear regression model (V. M. Muggeo, 2003; V. M. R. Muggeo, 2008). PRO-ACT is the largest publicly available repository of ALS clinical trials. As shown in Figure 1, the trials in PRO-ACT included fewer participants with advanced ALS, yet the rate of plateau due to the floor effect was 5% compared to 22% in the Phase 3 trial. This shows there is evidence of a floor effect in other studies.

Figure 32: Example of Susceptibility to the Floor Effect in ALSFRS-R from Participants in Study BCT-002-US



- 5 of 6 Fine and Gross Motor items reached 0
- 2 of 3 Respiratory items reached 0

6.3.7.4 Post-Hoc Analyses on Primary Endpoint to Mitigate the Floor Effect

Given the high proportion of participants with advanced ALS, and the high number of advanced participants with ALSFRS--R item scores of zero at baseline, post-hoc analyses were performed to provide a comprehensive interpretation of the primary endpoint (defined as proportion of participants with ≥ 1.25 points/month improvement in post-treatment slope versus pre-treatment slope of the ALSFRS-R score at 28 weeks following the first treatment). These analyses can be grouped into two categories: methods that are more comprehensive in removing the influence of confounding due to the floor effect, and those that are more conservative and allow a greater influence of the confounding into analyses. The former methods are more selective for the number of participants, while the latter includes more trial participants.

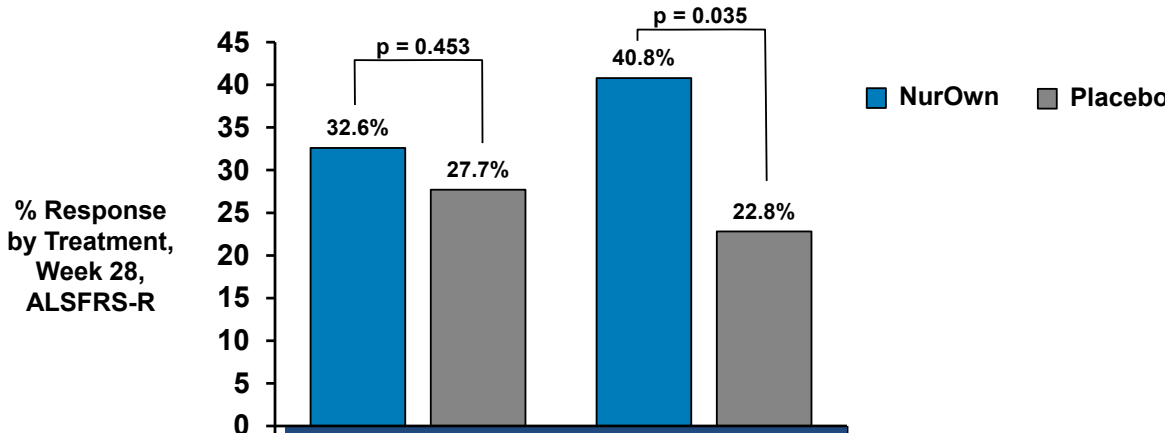
- More Comprehensive Approaches:
  - **Prespecified total score threshold: Subgroup by ALSFRS-R ≥ 35**, which includes only participants who had a baseline ALSFRS-R total score of ≥ 35. This group included 31% of the mITT population, or 58 participants.
  - **Post-hoc item-level threshold: Subgroup with No Evidence of Floor Effect**, which includes only participants with no evidence of floor effect at baseline (i.e., all ALSFRS-R items had score ≥ 1 at baseline). This group included 56% of the mITT population, or 106 participants.
- More Conservative Approaches:
  - **Post-hoc total score threshold: Subgroup by ALSFRS-R > 25**, which includes only participants with baseline ALSFRS-R scores > 25. This group included 77% of the mITT population, or 145 participants.
  - **Post-hoc item-level threshold**: **Subgroup of Individuals with a Minimum of Two Items with Baseline Scores of ≥ 2**, which includes only

participants who had a minimum of two (out of six possible) fine and gross motor subscale items with baseline scores of ≥ 2. This group included 84% of the mITT population, or 159 participants.

As shown in Figure 3 , when the floor effect is appropriately addressed in analyses, the primary endpoint of Study BCT-002-US shows consistent and clinically meaningful improvements for participants treated with NurOwn vs placebo.

When compared side-by-side, the adjusted floor effect versus unadjusted analyses shows substantial differences. Specifically, focusing on participants who did not have any evidence of a floor effect at baseline showed a response rate of 41% in participants treated with NurOwn vs 23% in placebo that is significant; p=0.035 (Figure 33).

Figure 33: Phase 3 Study BCT-002-US — Comparison of Primary Endpoint Results with and Without Subgroup Analysis to Mitigate the Floor Effect

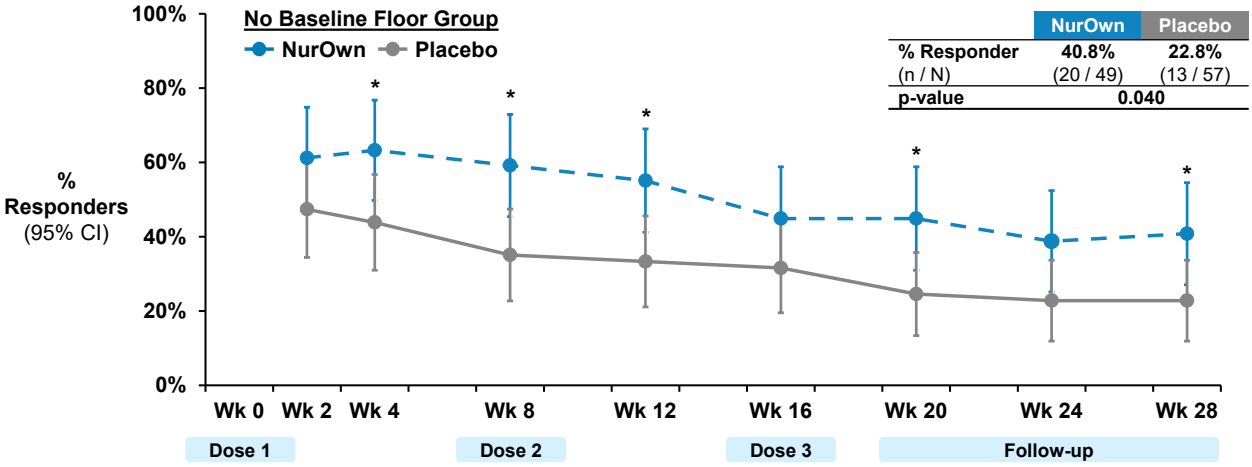


	All Participants (N = 189)	No Floor at Baseline (n = 106)
NurOwn	32.6%	40.8%
Placebo	27.7%	22.8%
Difference	4.9%	18.0%

Note: Nominal p-values reported.

Given the targeted definition of the subgroup (no evidence of floor effect at baseline) relative to the measurement issue observed in this trial, results of the primary and key secondary endpoints over time were evaluated. The response rate observed over time in participants with no evidence of a floor effect at baseline is shown in Figure 34. The response rate favors NurOwn across all timepoints, with significant differences across many timepoints.

Figure 34: Phase 3 Study BCT-002-US — Response Rate Over Time with NurOwn vs Placebo in Participants with No Evidence of Floor Effect at Baseline



* p ≤ 0.05

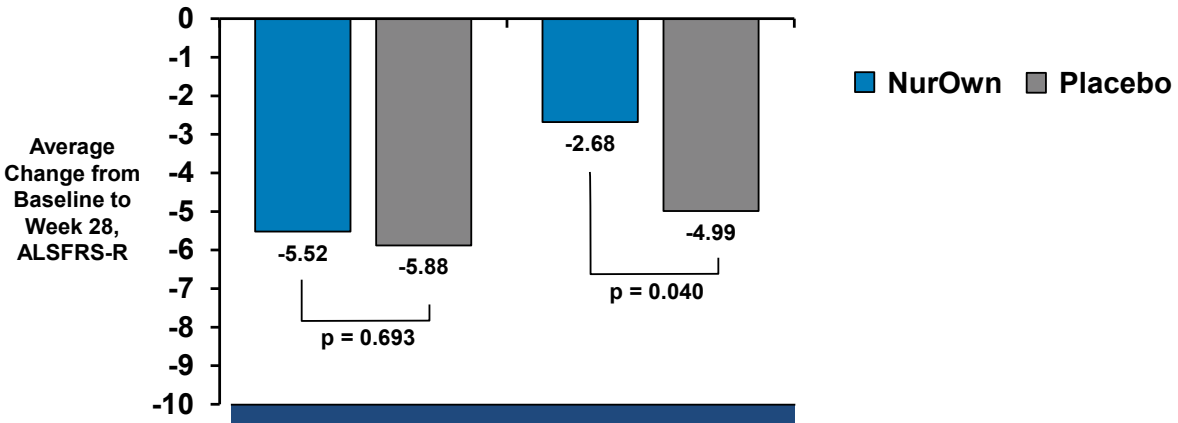
CI=confidence interval.

6.3.7.5 Post-Hoc Analyses on Key Secondary Endpoint to Mitigate the Floor Effect

The same four analyses described above for the primary endpoint (Section 6.3.7.4) were also performed on the key secondary endpoint of Study BCT-002-US (defined as average change from baseline in ALSFRS-R at Week 28) (Figure 4), where the same trend was observed.

The adjusted analysis, which focused on participants with no evidence of floor effect at baseline, showed an improvement with NurOwn versus placebo in the average change from baseline to Week 28 of 2.31 points (p=0.040) (Figure 35).

Figure 35: Phase 3 Study BCT-002-US — Key Secondary Endpoint Results in All Participants and Those with No Floor Effect at Baseline

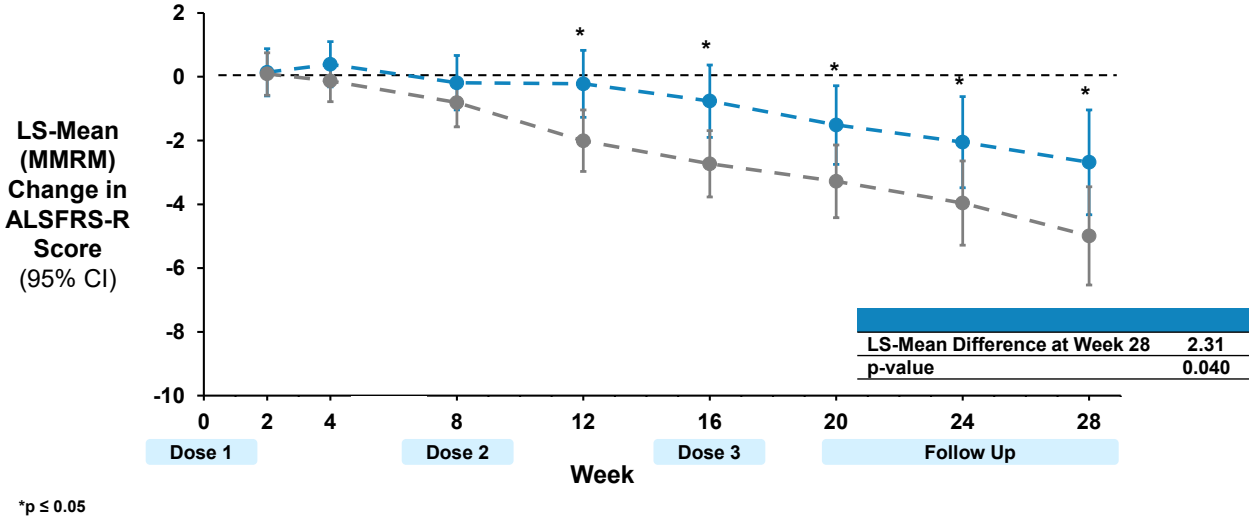


	All Participants (N = 189)	No Floor at Baseline (n = 106)
NurOwn	-5.52	-2.68
Placebo	-5.88	-4.99
Difference	0.36	2.31

Note: Nominal p-values reported.

The mean change from baseline across each time point of the ALSFRS-R assessment illustrates the separation between treatment groups in participants with no evidence of floor effect at baseline, as shown in Figure 36. After the second dose, participants treated with NurOwn lost less function compared to those receiving placebo, with an approximately 2-point difference in function that was maintained through the end of the study. There were significant differences between the treatment groups over time, with significant p-values at multiple different timepoints, including at the end of the study.

Figure 36: Phase 3 Study BCT-002-US — Mean Change in ALSFRS-R Total Score from Baseline to Week 28 in Participants with No Evidence of Floor Effect at Baseline



LS=least squares; MMRM=mixed models for repeated measures.

6.3.8 Results: CSF Biomarker Data

Background information on ALS biomarkers, including literature support for the relevance of biomarker analysis in clinical trials, is provided in Section 6.1.2.

6.3.8.1 Overview of Biomarker Analyses in Study BCT-002-US

Biomarker data collected during Study BCT-002-US represents the most robust collection of CSF clinical trial biomarker data to date in people with ALS. The COVID-19 pandemic triggered an unplanned reduction in the number of clinic visits, which were limited to only treatment days as a safety consideration for study participants. Therefore, missingness of CSF biomarker data is higher at Week 20 than earlier visits. For example, 50% of biomarker data were missing for NfL at Week 20, compared to 25% across all timepoints. Similarly, 44% of NfL data were missing for the no-floor effect subgroup at Week 20, compared to 20% at all timepoints. Longitudinal data using MMRM include all data available while the causal inference presented in this section utilized multiple imputed datasets under MAR and MNAR assumptions. (See Section 6.3.1.5.5 for additional details on analytical methods.)

Biomarkers are grouped into the three categories of neuroinflammation, neurodegeneration, and neuroprotection, based on their role in the MoA of NurOwn. Published literature confirms their relevance in ALS.

Analysis of these biomarker data led to four conclusions:

- There were significant improvements with NurOwn compared to placebo on ALS biomarkers across key pathways of neuroinflammation, neurodegeneration and neuroprotection in all participants in the trial.
- In a subset of participants with a floor effect, baseline ALSFRS-R ≤ 25 (see Section 6.3.8.1), key biomarkers exhibit directional changes reflective of NurOwn treatment (Figure 37) showing NurOwn is biologically active in all participants.
- A pre-specified statistical model identified CSF biomarkers NfL and TGF-β1 levels, in addition to ALS disease characteristics, as predictive of clinical outcomes.
- NurOwn significantly reduced NfL levels from baseline compared to placebo in the trial ($p < 0.05$; Section 6.3.8.2). A relationship between change in NfL from baseline to Week 20 and change in ALSFRS-R from baseline to Week 28 was observed in BCT-002, showing that reductions in NfL are reasonably likely associated with less decline in the ALSFRS-R and confirming the same relationship observed in another recent ALS trial.

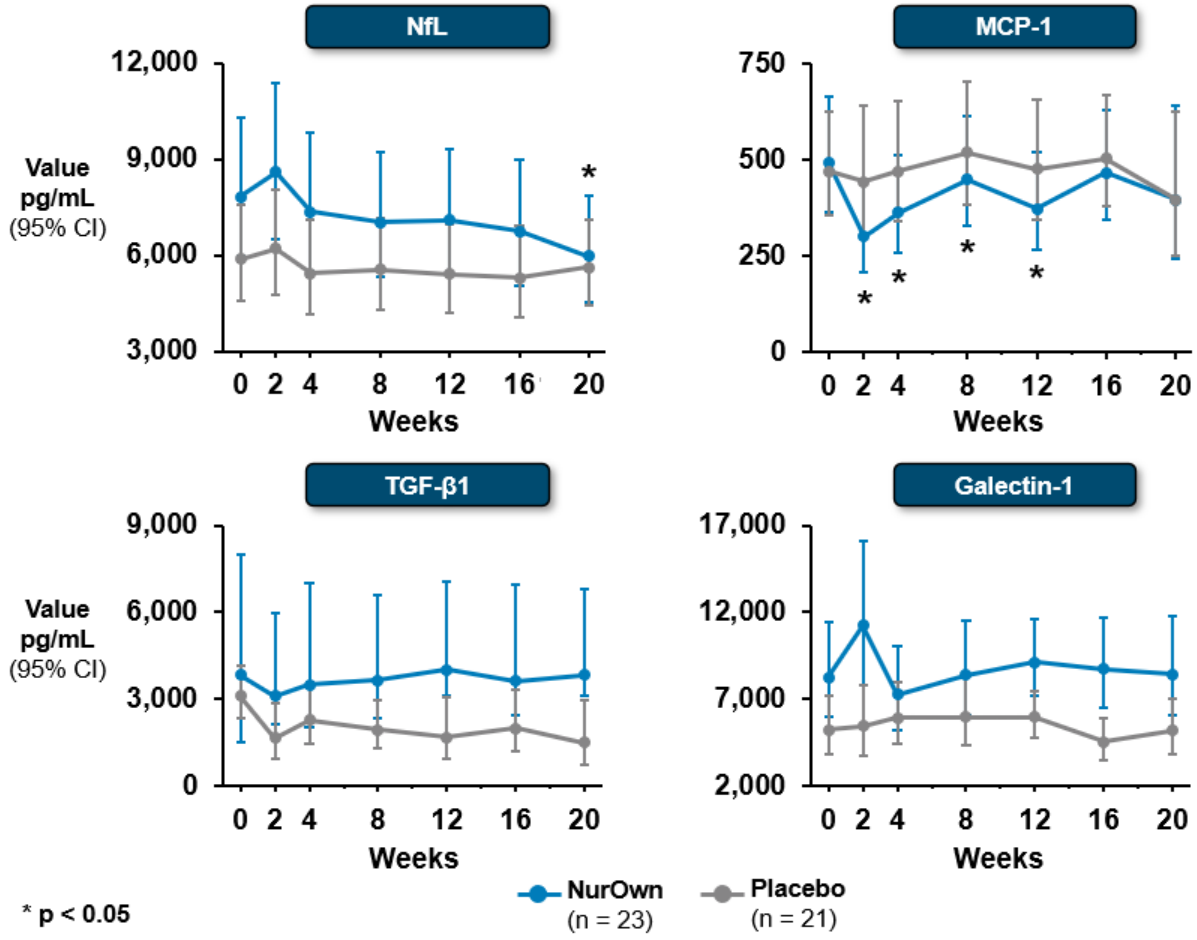
The impact of NurOwn treatment across many biomarkers was rapid, as measured by the large magnitude of change from baseline recorded two weeks after the first treatment (Figure 5; Section 6.3.8), while other biomarkers had gradual change with the largest change observed from baseline at the final assessment at Week 20. When reviewing the CSF biomarker levels over time for biomarkers that changed rapidly after the first treatment (e.g., Gal-1, TGF-β1, and MCP-1), a pharmacodynamic relationship is observed. Focusing on one biomarker from each pathway, including those identified as being predictive of clinical outcomes (Table 8) effects observed across the trial were:

- Neurodegeneration biomarker NfL: after an initial increase at Week 2, values drop across the study with NurOwn compared to placebo: -11.0% for NurOwn vs -1.6% for placebo ($p=0.037$).
- Neuroprotection biomarker Gal-1: increased significantly at Week 2 with NurOwn treatment relative to placebo at Week 2 ($p < 0.001$) and remained elevated from baseline at Week 20 with NurOwn: +13.2% for NurOwn vs -7.2% for placebo ($p=0.064$).
- Anti-inflammatory biomarker TGF-β1 increased significantly at Week 2 with NurOwn compared to placebo ($p=0.001$) and remained elevated from baseline at Week 20: +8.8% for NurOwn vs -21.5% for placebo ($p=0.067$).
- Pro-inflammatory biomarker MCP-1: decreased significantly at Week 2 with NurOwn treatment relative to placebo ($p < 0.001$) which remained decreased from baseline at Week 20 by -22.6% for NurOwn vs -1.5% for placebo ($p < 0.001$).

The number of biomarkers by each pathway where there was a significant ($p < 0.05$) overall treatment effect or treatment by time effect that favored NurOwn are shown in Table 2. Furthermore, data from participants with baseline ALSFRS-R ≤ 25, show a general trend in the longitudinal pattern which is similar to the treatment patterns in all

participants (Figure 37), This suggests that NurOwn is biologically active in the overall population, which includes participants with advanced ALS disease where the ALSFRS-R demonstrated measurement challenges.

Figure 37: CSF Biomarker Levels Across Key Disease Pathways at Week 20 in Participants with Baseline ALSRFS-R Total Score ≤ 25



CI=confidence interval; CSF=cerebrospinal fluid.
Note: Levels are adjusted for baseline disease covariates, as discussed in the Statistical Analysis Plan for biomarker analyses (Section 6.3.1.5.5).

While there were large changes observed across many CSF biomarkers, three were identified by a classical stepwise regression model, which was prespecified in the biomarker analysis plan (Section 6.3.1.5.5), as predictive of clinical outcomes following NurOwn treatment (Table 8). This model was not constrained to select biomarkers from any pathway, nor to select any specific biomarker for the final model. The selection of NfL, TGF-β1 and Gal-1 by this model spanning core ALS disease pathways highlights the relevance of NurOwn's MoA and the relevance of modulating neuroprotective and neuroinflammatory pathways resulting in a reduction in cell death and ultimately slowing the rate of clinical decline.

Table 8: Phase 3 Study BCT-002-US — Biomarkers Identified as Statistically Predictive of Clinical Outcomes After Treatment with NurOwn

Biomarker Predictive of Treatment Effect:	p-value*
Baseline NfL (neurodegeneration)	< 0.0001
Baseline TGF-β1 (neuroinflammation)	0.009
Change in Galectin-1 (neuroprotection)	0.004
UNC13A	0.026

* p-value is from Type-3 test for overall significance of each factor in the model.
Note: Model used is a linear regression model with the post-treatment piecewise slope as the response variable. All terms are included as the covariates.

After accounting for baseline ALS disease characteristics, using covariates as described in the Biomarkers SAP (Section 6.3.1.5.5), two biomarkers, Baseline NfL and TGF-β1 remained predictive of clinical outcomes (Table 9). Specifically, lower NfL and higher TGF-β1 levels at baseline and an increase in Gal-1 from baseline, were associated with slower functional decline in the trial.

Table 9: Phase 3 Study BCT-002-US — Biomarkers Identified as Statistically Predictive of Clinical Outcomes After Treatment with NurOwn, Accounting for Baseline ALS Disease Characteristics

Biomarker Predictive of Treatment Effect:	p-value*
Baseline ALSFRS-R	< 0.0001
Baseline Slope	< 0.0001
Time since symptom onset to first treatment	< 0.0001
Use of Riluzole	< 0.0001
Site of onset	0.002
Baseline NfL (neurodegeneration)	< 0.0001
Baseline TGF-β1 (neuroinflammation)	0.029
Change Galectin-1 (neuroprotection)	0.538
UNC13A	0.594

* p-value is from Type-3 test for overall significance of each factor in the model.
Note: Model used is a linear regression model with the post-treatment piecewise slope as the response variable. All terms are included as the covariates.

6.3.8.2 Biomarker Analysis of Neurofilament Light Chain (NfL) (Protein Marker of Neuronal Injury)

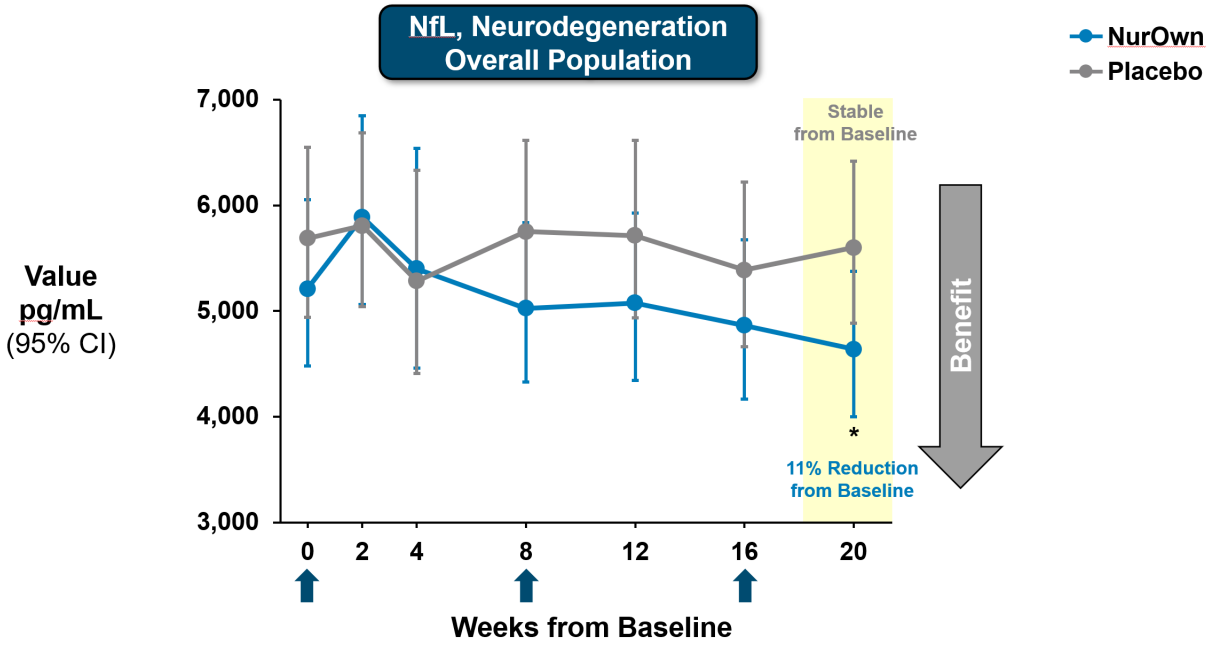
Neurofilament light chain (NfL) is an important biomarker of neurodegeneration in ALS that corresponds inversely with motor neuron integrity. Therefore, the desired outcome is decreased levels in CSF after treatment, which would indicate preservation of neuronal integrity and motor function. NfL levels have been found to be prognostic for disease progression and survival in ALS (Benatar et al., 2020; Dreger et al., 2021; Feneberg et

al., 2018; Meyer et al., 2023; Steinacker et al., 2016; Thouvenot et al., 2020) and have been used as a surrogate endpoint for efficacy in previous approvals.

6.3.8.2.1 Prespecified Analyses of Neurofilament Light Chain (NfL)

In Study BCT-002-US, NfL values increased initially in NurOwn-treated participants, followed by a steady decline over the course of the study, ultimately reaching a 11% reduction from baseline at the end of the study (Figure 38). Placebo values remained largely unchanged relative to baseline across the study. This initial increase has been observed with other IT administered products and is assumed to be procedure related.

Figure 38: Phase 3 Study BCT-002-US — Neurodegenerative Biomarker Neurofilament Light Chain (NfL) Over Time



* p < 0.05
Note: Blue arrows indicate treatment days. Baseline covariates: time since symptom onset to first treatment, use of riluzole, site of onset, baseline slope, baseline ALSFRS-R total score, baseline.

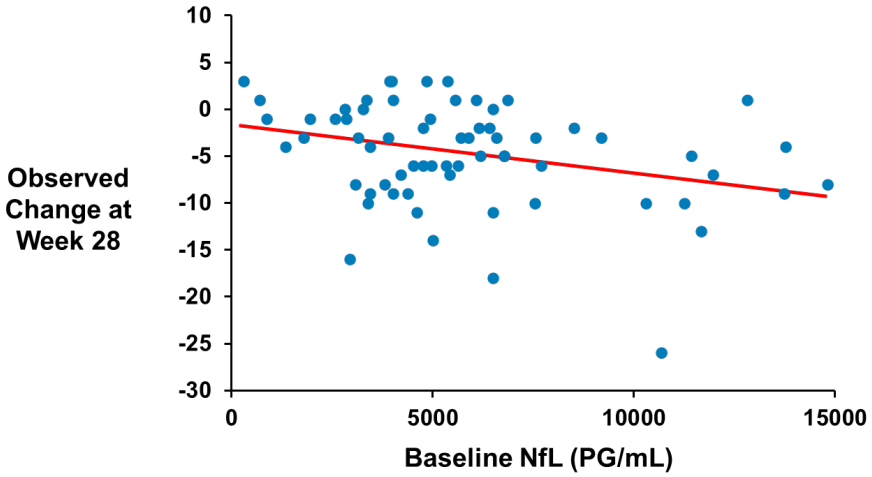
Declines in other neurodegenerative biomarkers were observed, with some decreasing rapidly after treatment. DR6, for example, dropped to half of its baseline level by Week 2. Other neurodegenerative biomarkers, such as phosphorylated neurofilament heavy chain (pNfH), demonstrated decreasing trends more consistent with the rates exhibited by NfL. Specifically, pNfH was reduced by 13% from baseline at the end of the study.

6.3.8.2.2 Post-hoc Analyses of Neurofilament Light Chain (NfL)

Post-hoc analyses of NfL data from the placebo-treated participants in the Phase 3 study reaffirmed the negative correlation between baseline NfL levels and ALS disease progression (Figure 39). Specifically, placebo-treated participants with higher baseline NfL values had greater decline from baseline at Week 28 as measured by ALSFRS-R

total score: r = -0.31; p=0.011. This analysis confirms similar findings from other ALS trials (Gaiani et al., 2017; Miller et al., 2021) that baseline NfL is prognostic of ALS clinical decline.

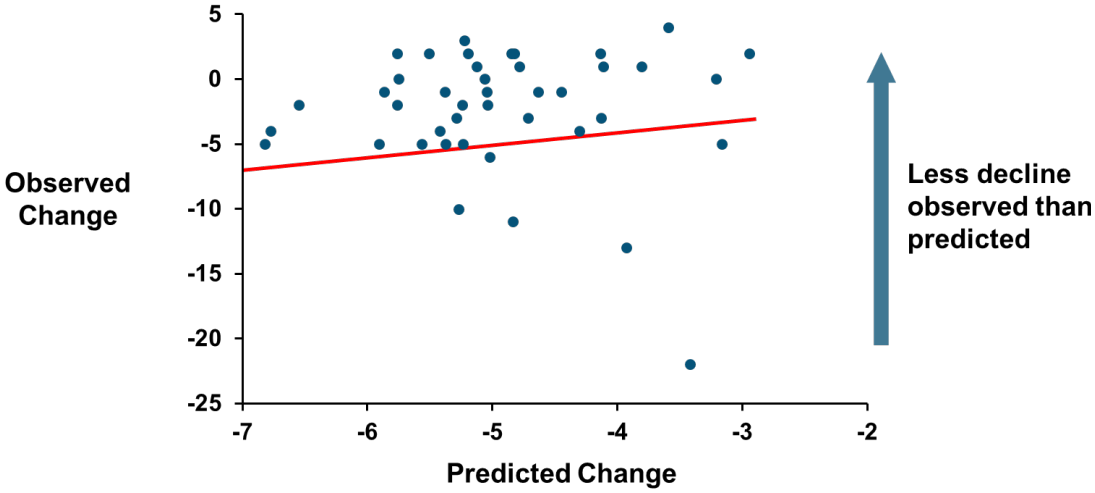
Figure 39: Relationship between Baseline NfL and Average Change from Baseline to Week 28 in ALSFRS-R in Placebo-Treated Participants



Notes: Red line represents the linear regression line. Analysis performed on mITT population.

Comparison of the change in ALSFRS-R scores from baseline to Week 28 for each NurOwn-treated participant to their predicted progression without treatment (i.e., had they received placebo, see Section 6.3.1.5.5 for more information about the causal inference model) shows 86% of participants treated with NurOwn had smaller changes in ALSFRS-R scores than their placebo-predicted scores. This means that the magnitude of NurOwn's clinical effect from baseline through the end of the study was consistently higher with less functional decline observed than the anticipated for the majority of participants (points above the line; Figure 40).

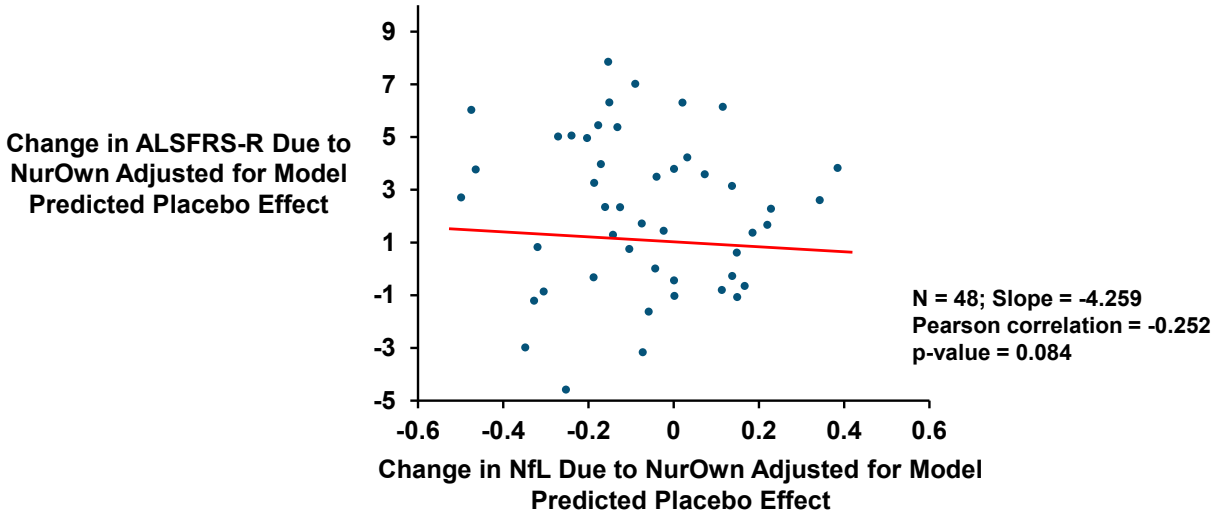
Figure 40: Phase 3 Study BCS-002-US — Predicted vs Actual Change in ALSFRS-R Scores for NurOwn-Treated Participants at Week 28



Notes: Population included in analysis includes participants with all ALSFRS-R items >=1 at baseline (n=49 debamestrocel-treated participants). The red line is the y=x or 45 degree line.

A causal inference model was employed to calculate the correlation between NurOwn-driven changes at the final measurement of NfL (Week 20) and ALSFRS-R (Week 28), (Figure 41, Section 6.3.1.5.5 for more information about the model). The correlation was r = -0.252, p=0.084, confirming that NurOwn-driven reductions of NfL were associated with less decline in ALSFRS-R from baseline across the 28-week trial. In other words, reductions in NfL corresponded with more favorable clinical outcomes. The results were similar in analyses with participants with observed data at Week 20 and multiple imputed datasets assuming data were missing not at random.

Figure 41: Phase 3 Study BCS-002-US — Clinical Impact of NfL Changes from Baseline to Week 20 on ALSFRS-R Changes from Baseline to Week 28 Due to NurOwn Treatment, Adjusting for Natural Disease Progression

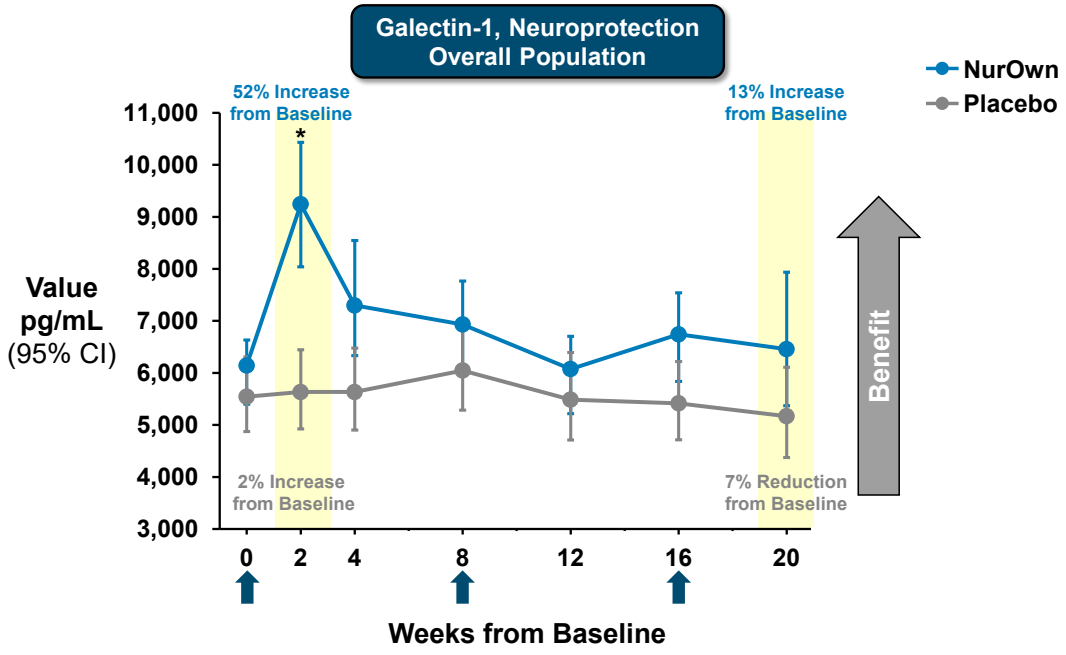


Notes: Analyses are based on a missing at random multiple imputed dataset for NfL and ALSFRS-R. There is one participant who did not have any NfL data collected in the study and thus cannot be imputed. Only N=48 participants are included in the plot. NfL is analyzed and presented in log-scale. Analysis based on a regression model estimated from placebo data, employing baseline NfL, ALS disease covariates from the primary efficacy model, and predicted NfL change from baseline at Week 20 are included as covariates. Analysis performed on subset of participants with no evidence of floor effect at baseline.

6.3.8.3 Biomarker Analysis of Galectin-1 (Neuroprotective Protein)

Galectin-1 (Gal-1) is a biomarker of neuroprotection (Cai et al., 2022; Marques et al., 2019). Therefore, the desired outcome is increased levels in CSF after treatment. In Study BCT-002-US, participants who received NurOwn showed a 52% increase in Gal-1 values in the first two weeks, which was sustained at 13% above baseline through the end of the trial. Values for Gal-1 in the placebo group decreased, or worsened, by 7% from baseline to Week 20, the last CSF sample in the trial (Figure 42). Changes in Gal-1 in the trial were associated with slower functional decline in the trial (p=0.004; Table 8).

Figure 42: Phase 3 Study BCT-002-US — Neuroprotective Biomarker Galectin-1 Over Time

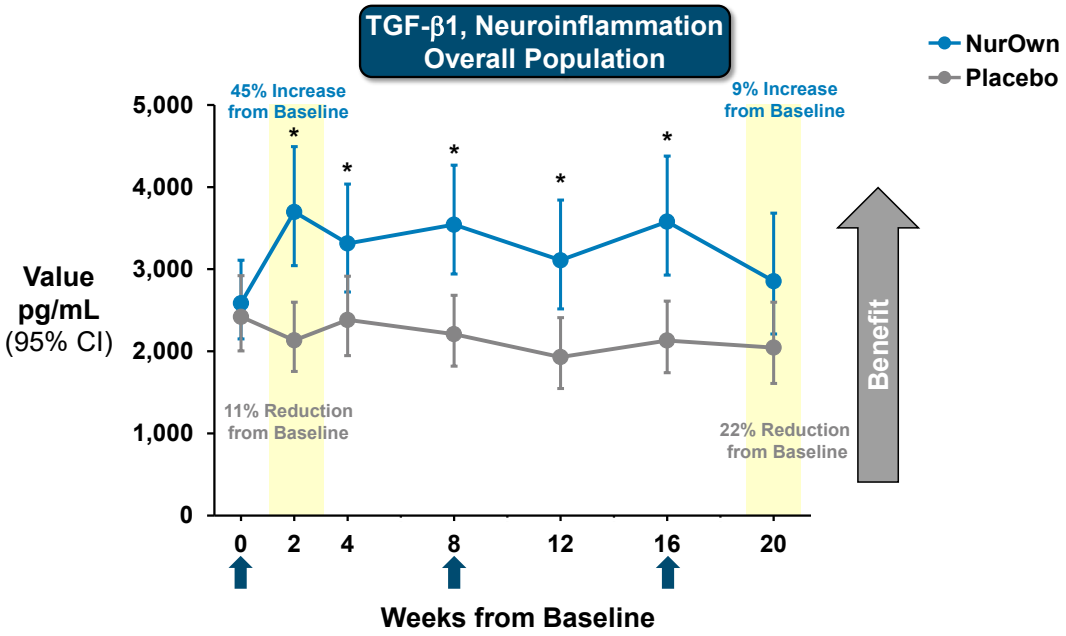


* p < 0.05
CI=confidence interval.
Note: Blue arrows indicate treatment days.

6.3.8.4 Biomarker Analysis of TGF-β1 (Anti-inflammatory Cytokine)

TGF-β1 is an anti-inflammatory cytokine, that executes anti-inflammatory activity and protects from neurodegeneration (J. H. Chen, Ke, Lu, Qiu, & Peng, 2015; Prehn et al., 1996; Tesseur et al., 2006). Therefore, the desired outcome is increased levels in the CSF after treatment. In BCT-002, participants who received NurOwn showed a 45% increase in TGF-β1 values in the first two weeks, which was sustained at 9% above baseline through the end of the trial. Values for TGF-β1 in the placebo group decreased, or worsened, by 22% from baseline to Week 20, the last CSF sample in the trial (Figure 43). The treatment differences at multiple time points during the trial are significantly different.

Figure 43: Phase 3 Study BCT-002-US — Neuroinflammatory Biomarker TGF-β1 Over Time

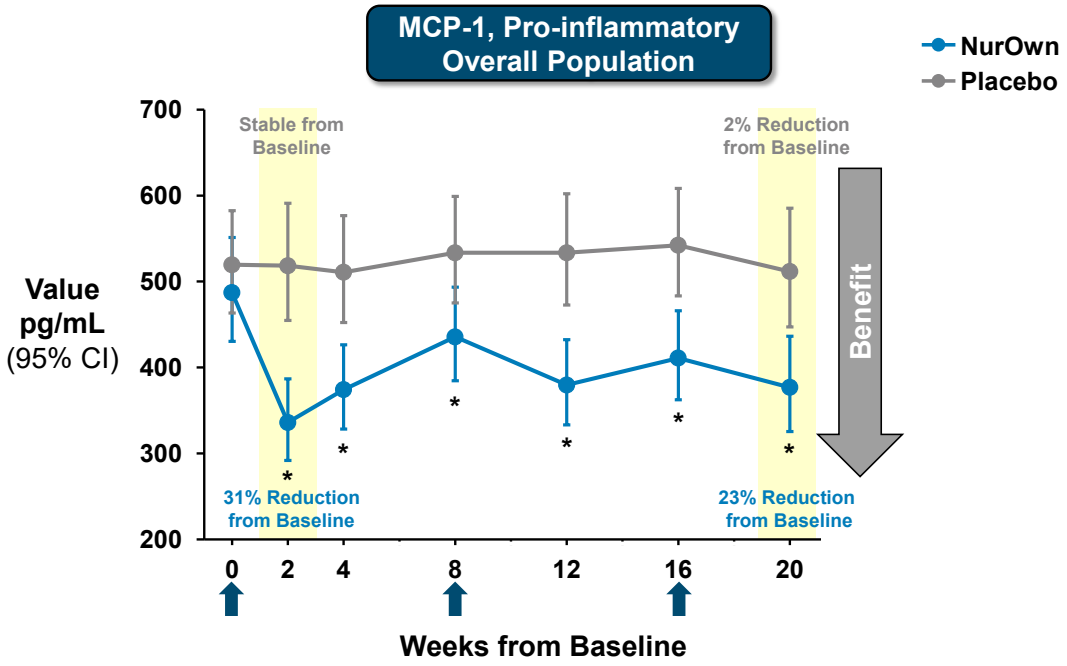


* p < 0.05
Note: Blue arrows indicate treatment days.

6.3.8.5 Biomarker Analysis of MCP-1 (Pro-inflammatory Chemokine)

MCP-1 is a pro-inflammatory cytokine. Therefore, the desired outcome is decreased levels after treatment with NurOwn. MCP-1 exhibited early and sustained reduction in CSF levels in the NurOwn treatment group compared to placebo (Figure 44). The treatment differences at all time points during the trial are significantly different.

Figure 44: Phase 3 Study BCT-002-US — Pro-inflammatory Biomarker MCP-1 Over Time



* p < 0.05
Note: Blue arrows indicate treatment days.

6.3.8.6 Biomarker Conclusions

These biomarker results offer further support to the underlying benefit of NurOwn on the complex disease pathophysiology which involves multiple interconnected mechanisms including exaggerated pro-inflammatory reactions, impaired anti-inflammatory responses that mediate neuronal injury and neurodegeneration.

NurOwn's robust and innovative mechanism was able to address many aspects of the disease pathophysiology and provided a synergistic response. NurOwn produced significant benefits on inflammation over placebo, with an increase in anti-inflammatory activity (demonstrated with an early rise of TGF-β1 values 2 weeks after first treatment and sustained through the end of the trial), along with a decrease of pro-inflammatory activity (demonstrated by the reduction of the pro-inflammatory chemokine MCP-1 that started 2 weeks after first treatment and was sustained through the end of the trial).

Combined with its beneficial effect over placebo on markers of neurodegeneration such as NfL, these data suggest that NurOwn's pharmacodynamic effects are the basis of the observed clinical benefits of slowing disease progression and halting neuronal death.

6.3.9 Totality of Evidence Analysis

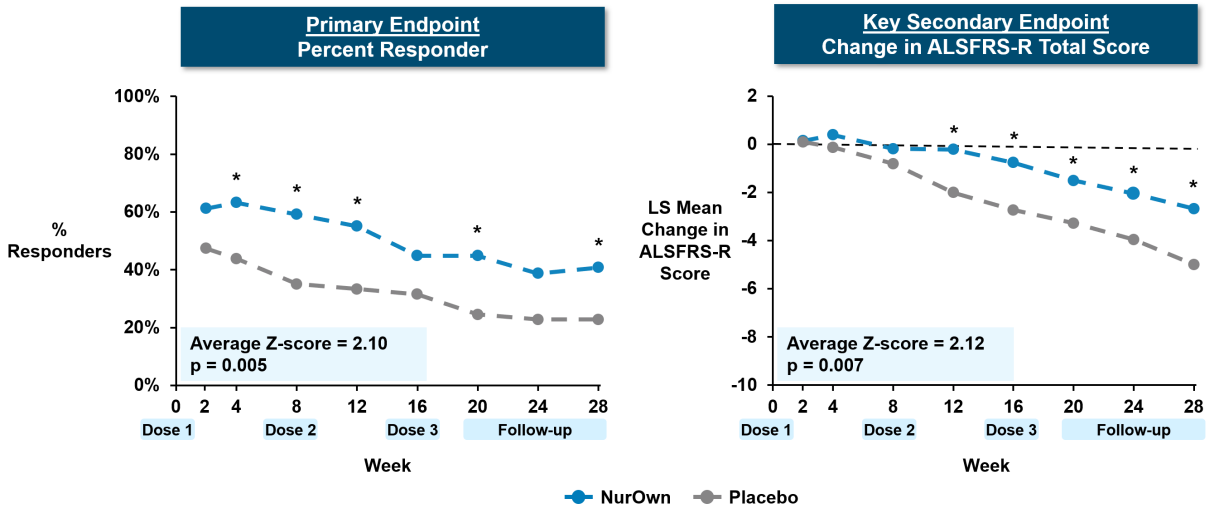
When adjusting for the floor effect, both the primary and key secondary endpoint results are statistically significant at Week 28. In the Phase 3 Study, extensive data in multiple clinical outcomes were collected from each participant. Like in other rare disease clinical

studies with a heterogeneous patient population, it is informative to utilize outcome data observed from various angles to assess the overall treatment benefit beyond the primary endpoint analysis. This common practice for dealing with rare disease drug development programs can shed more light on NurOwn's true treatment effect.

As an illustration, in Figure 45, the left panel provides the response rates over time. The blue curve (NurOwn) is entirely above the gray curve (placebo) from Week 2 to Week 28. The treatment benefit began early and was sustained over time, with an approximately 20% difference in the response rate between the two curves. An interesting question is, if there was no true temporal treatment benefit from NurOwn, what would be the chance of observing such a large and consistent separation between the two curves over time? To this end, one may use a simple non-parametric method (Li et al., 2020; Wei & Lachin, 1984) to handle this question. Specifically, for each time point, we have calculated the z-score, which is simply the response rate difference between two groups divided by its standard error. A large z-score suggests a positive treatment effect. The average of the z-scores is then taken across all time points where the data were collected. For the present case, the observed mean z-score is 2.10. The standard permutation test procedure is then used to generate the distribution of the mean z-score under the null hypothesis. With 3000 permutation samples, the one-sided p-value is 0.005 (the probability that these 3000 mean z-scores > 2.10). This result suggests that the chance of observing the profile of the two curves or more extreme for the left panel in Figure 45 is quite small if there were not a true treatment benefit from NurOwn.

In the right panel of Figure 45, the results for the change from baseline in terms of the total ALSFRS-R score are shown. Again, the separation of the two curves started at an early time point and was persistent at the end of the study. The one-sided p=0.007 by combining the z-score over time, suggesting a strong temporal treatment effect.

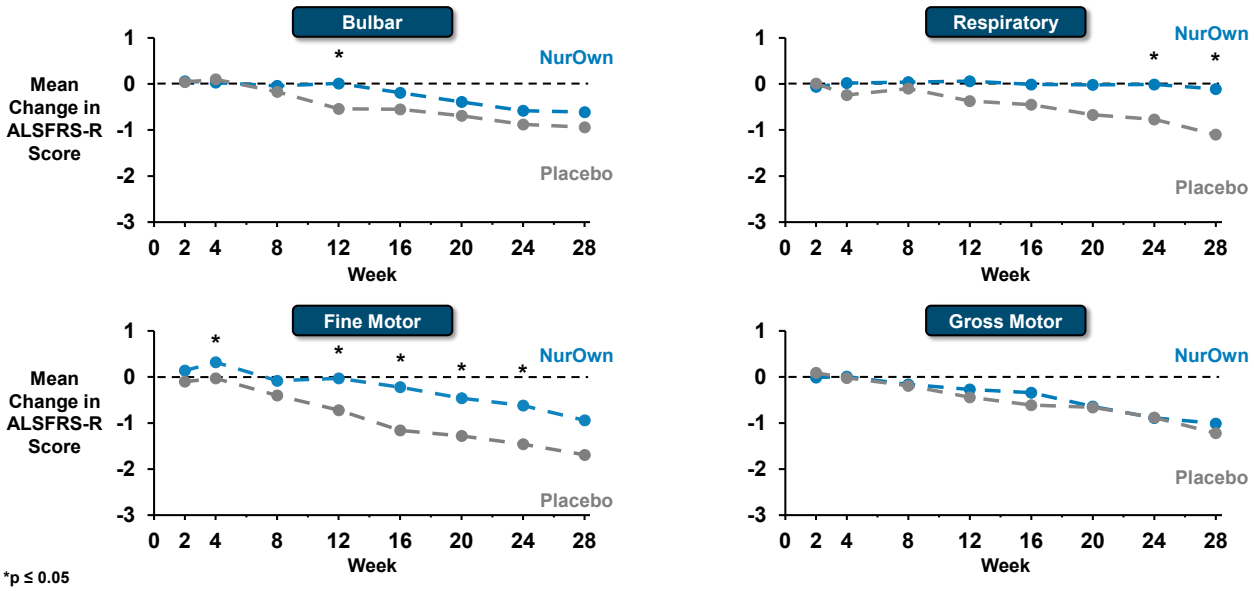
Figure 45: Phase 3 Study BCT-002-US — NurOwn Treatment Effects from Week 8 to Week 28



* p ≤ 0.05

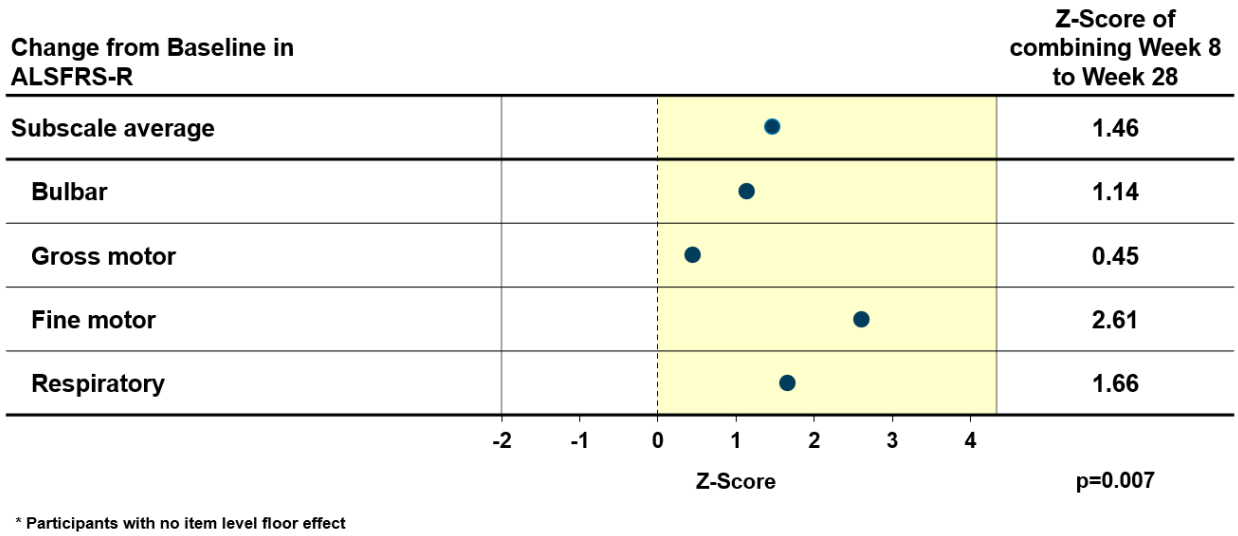
Next, instead of using the total ALSFRS-R score, we explored NurOwn's impact on each of the four subscales (bulbar, respiratory, fine motor and gross motor). In Figure 46, for each subscale, the NurOwn and placebo curves over time are presented with the change from baseline subscale scores. The question is, if there were no true treatment effects from NurOwn for each subscale, what would be the chance of observing this consistent, positive trend in favor of NurOwn?

Figure 46: Phase 3 Study BCT-002-US — ALSFRS-R Subscales Over the Entire Study Period



Using the same method (Li et al., 2020), the z-scores from four subscales are combined in Figure 47, and the one-sided p=0.007.

Figure 47: Phase 3 Study BCT-002-US — Treatment Effect from Week 8 to Week 28 in Four Subscales of ALSFRS-R



Lastly, the totality of evidence can also be examined by combining the treatment benefit observed across different biomarkers over the study period. The longitudinal profile the four biomarkers (NfL, MCP-1, Gal-1 and TGF β1) is shown in Figure 48. Specifically, we focus on four biomarkers from four different pathways: NfL (neurodegeneration), TGF β1 (anti-inflammatory), MCP-1 (pro-inflammatory) and Gal-1(neuroprotection) and look at the treatment effect across week 8 to week 20. The resulting one-sided p-value is <0.0001 by combining these z-scores, which is shown in Figure 49.

In summary, these results looking across time, subscales, and endpoints provide strong statistical evidence of a true treatment benefit.

Figure 48: Phase 3 Study BCT-002-US — Analysis of Longitudinal Treatment Effect in Biomarkers

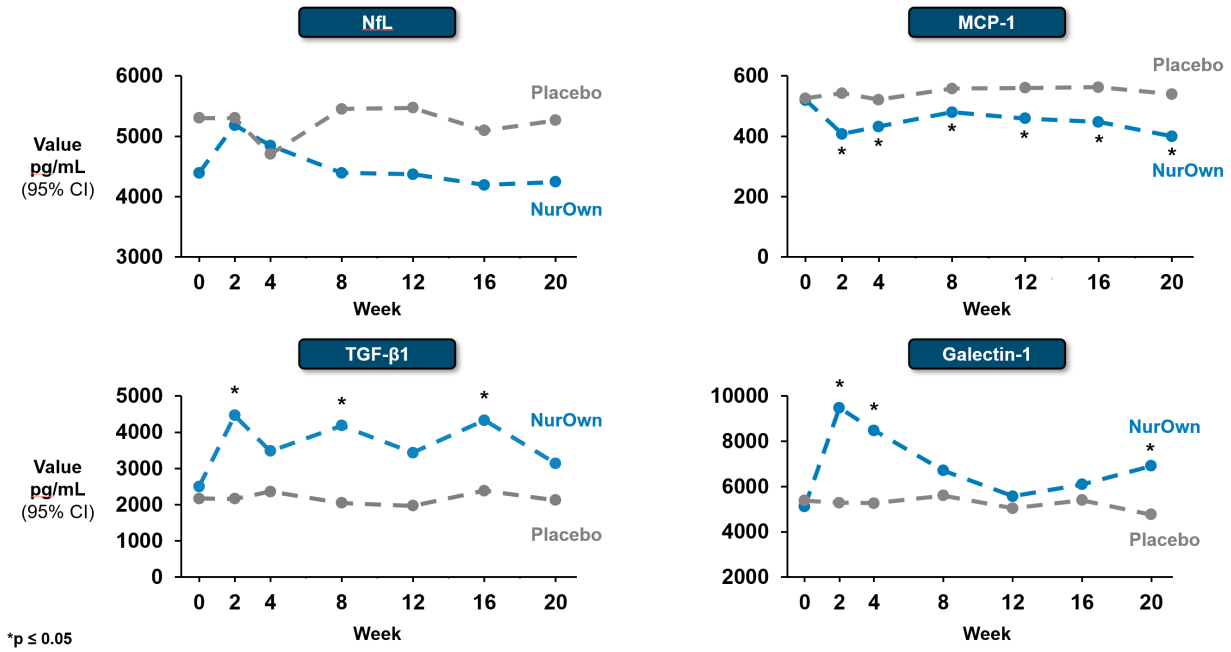
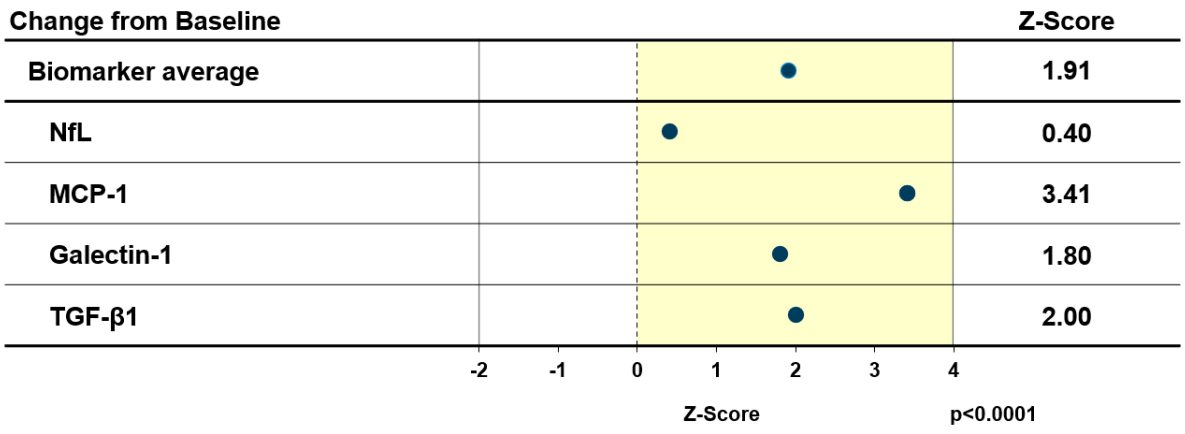


Figure 49: Phase 3 Study BCT-002-US — Treatment Effect in Biomarkers from Week 8 to Week 20

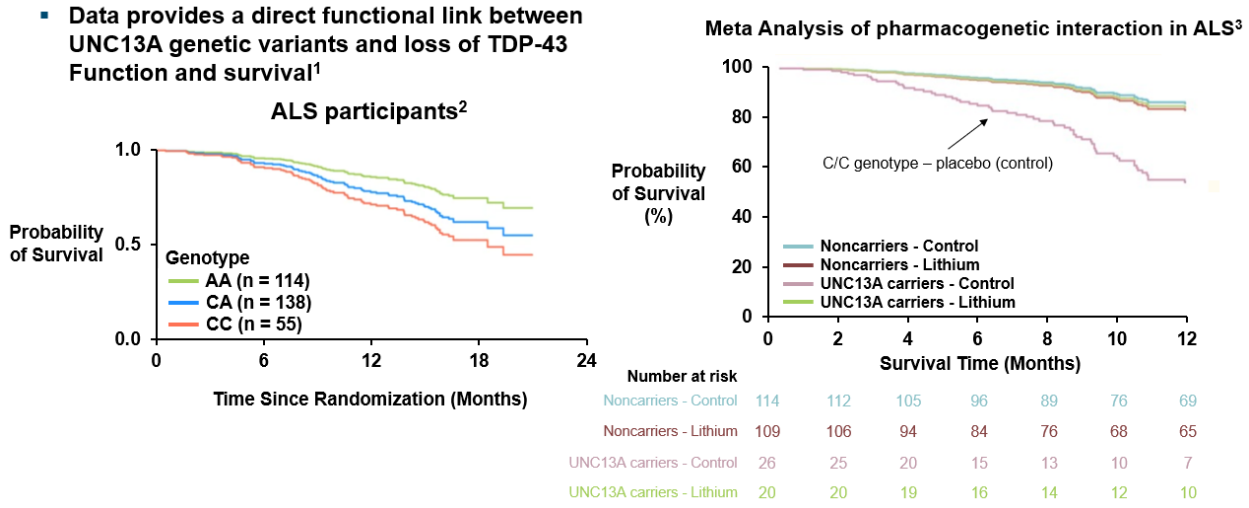


6.3.10 BCT-002 Pharmacogenomic Analyses

A genetic study, based on a prospective evaluation of genetic variants, was performed in 124 of 189 participants who provided informed consent for genetic testing. A total of 31 known ALS-related genes, C9orf72 repeat expansion, and four single nucleotide polymorphisms (SNPs) known to be related to ALS were evaluated. Eight of 124 participants harbor seven different ALS gene mutations. The distribution of UNC13A genotypes observed in this study matched rates in the overall ALS population (Tan et al., 2020). While ALS patients with a C risk allele (genotype A/C or C/C) have a shorter survival (van Eijk et al., 2020), a retrospective analysis of lithium carbonate data suggests that carriers of the C risk allele differentially responded to treatment (van Eijk et al., 2017).

Participants with heterozygous (A/C) UNC13A respond better to NurOwn treatment than participants with homozygous AA and CC UNC13A (Figure 50). In the overall population, higher response rates were observed in participants with heterozygous UNC13A (A/C genotype): 65% response rate for NurOwn vs 29% for placebo (p=0.011; OR=7.5). These results were consistent when adjusting for the floor effect in the ALSFRS-R scale: 65% response rate for NurOwn vs 28% for placebo (p=0.015; OR=8.8). Results of the genetic analysis suggest that NurOwn treatment may influence disease progression in ALS participants who possess UNC13A risk allele.

Figure 50: Phase 3 Study BCT-002-US — Probability of Survival and Response to Lithium Carbonate in ALS Patients with C Risk Allele of UNC13A



Note: AA is homozygous for no risk-alleles in *UNC13A*; CA is heterozygous for one risk-allele; CC is homozygous fortwo risk-alleles.
1 (Ma et al., 2022)
2 (van Eijk et al., 2020)
3 (van Eijk et al., 2017)

6.4 Supportive Early Phase Clinical Trials

6.4.1 Phase 1/2 Study MSC-NTF-001-IL

An open-label, first-in-human study of NurOwn was conducted in 12 participants with ALS (MSC-NTF-001-IL). Six participants with early-stage ALS (ALSFRS-R scores ≥ 30) received IM injections of NurOwn, and 6 participants with more progressive disease (ALSFRS-R > 15 and < 30) received NurOwn by IT treatment. The six participants with early-stage ALS received an IM dose of ~24 × 10^6 cells. Those with more advanced disease received an IT dose of ~60 × 10^6 cells. Participants were followed for three months before and six months after treatment. The study explored secondary preliminary efficacy endpoints.

Although not statistically significant, the changes from baseline demonstrated and support the improvement in clinical symptoms following NurOwn treatment on the rate of ALS progression as reflected in several ALS clinical outcomes (ALSFRS-R score, total neurological examination score, forced vital capacity [FVC], and compound muscle action potential [CMAP] of the biceps) measurements in both IM and IT treated groups. The improvements were more pronounced for participants who received NurOwn intrathecally.

6.4.2 Phase 2a Study MSC-NTF-002-IL

A Phase 2a dose-escalating study in 14 participants was designed to evaluate the safety and preliminary efficacy of escalating doses of NurOwn administered by combination treatment of IM and IT treatment in three cohorts of participants with early-stage ALS. Participants were followed for three months before and six months after treatment.

The results of the study demonstrated a clear tendency of improvement with slowing the ALS disease progression rate as reflected in several of the efficacy endpoints related to ALS etiology.

7 CLINICAL SAFETY

Summary

- The safety profile of NurOwn was largely consistent across the clinical development program, in which 174 participants received ≥ 1 treatment with NurOwn.
- Primary safety data come from the placebo-controlled pivotal Phase 3 Study BCT-002-US, in which 95 participants received NurOwn and 94 received placebo.
- Almost all participants in both NurOwn and placebo treatment groups experienced ≥ 1 AE (98.9% vs 97.9%, respectively).
    - The most common AEs affecting participants treated with NurOwn were procedural pain (52.6%), headache (47.4%), and back pain (44.2%).
    - Several AEs were more frequent in the placebo group, including fall, post-lumbar puncture syndrome, nausea, dysphagia, and muscular weakness.
    - Most AEs were mild-to-moderate in severity and resolved within a few days.
- All SAEs were consistent with progression of ALS.
- Only one participant discontinued NurOwn due to an AE (muscle spasms).
- No deaths were reported as related to study treatment by either the Investigator or Sponsor.

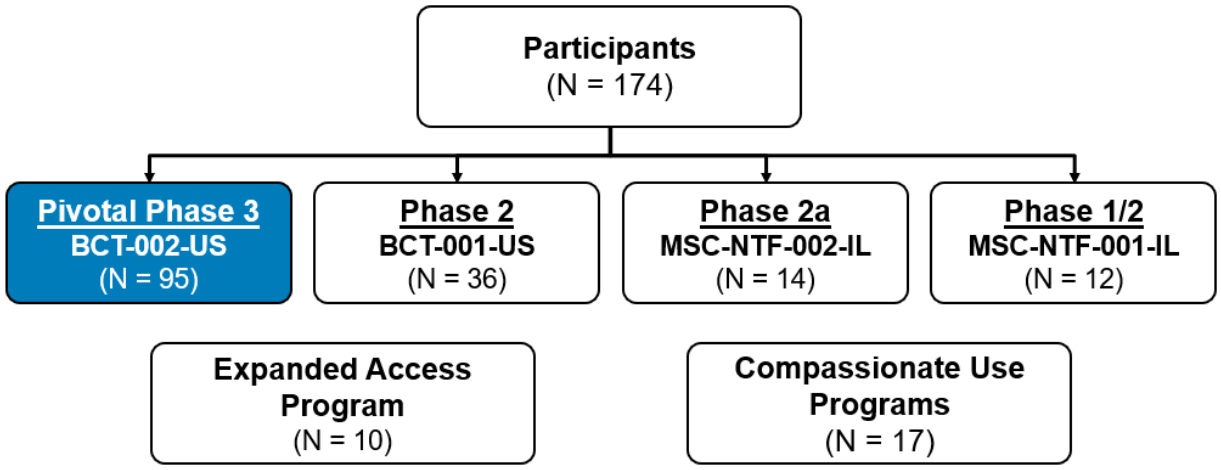
7.1 Overview of the Safety Program

Given the differences in the treatments administered and routes of administration in the early phase, open-label clinical trials (MSC-NTF-001-IL and MSC-NTF-002-IL), in addition to key differences (e.g., different treatment regimens) between the Phase 2 (BCT-001-US) and the Phase 3 (BCT-002-US) studies, pooling of safety results is not considered appropriate. Therefore, the safety profile of NurOwn is characterized primarily by results from the Safety Population in the pivotal Phase 3 study.

7.2 Treatment Exposure

A total of 174 adult participants living with ALS have been treated with NurOwn in the clinical program. 17 participants received NurOwn through the compassionate use programs, including 10 BCT-002-US participants who continued into the EAP (Figure 51).

Figure 51: NurOwn Exposures Across Clinical Program



7.3 Safety in Pivotal Phase 3 Study BCT-002-US

The Safety Population of the Phase 3 study was defined as all participants who received ≥ 1 study treatment and includes 95 participants treated with NurOwn and 94 participants treated with placebo. Participants were followed for up to 28 weeks after their final treatment.

7.3.1 Overview of Adverse Events

Adverse events (AEs) were balanced between groups and occurred in nearly all participants in both treatment groups (98.9% vs 97.9% for NurOwn and placebo, respectively; Table 10). Most AEs were mild-to-moderate in severity, with few participants experiencing Grade ≥ 3 events in either the NurOwn (30.5%) or placebo (20.2%) treatment groups. Most AEs were transient (NurOwn 87.4%, 86.3% placebo), lasting less than 30 days, and most resolved on average within 6 days from start and were manageable with supportive care. More participants in the NurOwn group (24.2%) experienced SAEs compared to placebo (18.1%). More participants in the placebo group (3.2%) discontinued the study due to an AE than participants treated with NurOwn (1.1%). There were a total of 16 deaths in the study, 10 in the NurOwn group and 6 in the placebo group. Two participants in the placebo group died before receiving treatment. Importantly, no participant in either treatment group had a treatment-related AE, characterized by either the Investigator or Sponsor as leading to death, and the majority of deaths were characterized as due to disease progression.

Table 10: Phase 3 Study BCT-002-US — Overview of Adverse Events

Participants with AE, n (%):	NurOwn (N=95)	Placebo (N=94)
Any AE	94 (98.9)	92 (97.9)
Grade 1	15 (15.8)	23 (24.5)
Grade 2	50 (52.6)	50 (53.2)

Participants with AE, n (%):	NurOwn (N=95)	Placebo (N=94)
Grade ≥ 3 AE	29 (30.5)	19 (20.2)
Grade ≥ 3 AE related to treatment*	7 (7.4)	3 (3.2)
Serious AE	23 (24.2)	17 (18.1)
Serious AE related to treatment*	1 (1.1)	1 (1.1)
AE leading to treatment withdrawal	1 (1.1)	1 (1.1)
AE leading to study discontinuation	1 (1.1)	3 (3.2)
Duration of AEs related* to treatment: Mean (SD), days	5.8 (13.9)	6.5 (11.2)
Duration of AEs related* to treatment: Median, days	2.0	3.0
AEs lasting ≥ 30 days†, n/total (%)	51/404 (12.6)	35/255 (13.7)
Deaths (ITT Population)	10 / 98 (10.2)	6 / 98 (6.1)
Treatment related AE leading to death	0	0

Note: Two of the deaths that occurred in the placebo group died prior to receiving any dose.
* Relatedness was as reported by Investigator as “definitely,” “probably,” or “possibly” related to study treatment.
† Includes AEs lasting ≥ 30 days (n=26) and AEs that were ongoing at the end of follow-up (n=60), regardless of duration.

7.3.2 Common Adverse Events

The most commonly reported AEs in the NurOwn treatment group, compared to placebo, by preferred term were procedural pain (52.6% vs 36.2%, respectively), headache (47.4% vs 34.0%), and back pain (44.2% vs 25.5%) (Table 11).

Table 11: Phase 3 Study BCT-002-US — Common Adverse Events (Experienced by ≥ 10% of Participants in Either Treatment Group)

Preferred Term, n (%):	NurOwn (N=95)	Placebo (N=94)
Participants with ≥ 1 AE	94 (98.9)	92 (97.9)
Procedural pain	50 (52.6)	34 (36.2)
Headache	45 (47.4)	32 (34.0)
Back pain	42 (44.2)	24 (25.5)
Procedural headache	31 (32.6)	30 (31.9)
Fall	29 (30.5)	34 (36.2)
Post-lumbar puncture syndrome	22 (23.2)	29 (30.9)
Nausea	16 (16.8)	18 (19.1)
Pain in extremity	16 (16.8)	11 (11.7)
Post-procedural complication	16 (16.8)	7 (7.4)
Musculoskeletal pain	15 (15.8)	8 (8.5)
Muscular weakness	11 (11.6)	12 (12.8)
Dysphagia	11 (11.6)	7 (7.4)

Preferred Term, n (%):	NurOwn (N=95)	Placebo (N=94)
Coccydynia	11 (11.6)	1 (1.1)
Arthralgia	10 (10.5)	7 (7.4)
Laceration	7 (7.4)	11 (11.7)
Upper respiratory tract infection	6 (6.3)	12 (12.8)

7.3.3 Serious Adverse Events

In the Phase 3 study, SAEs occurred in 23 (24.2%) participants treated with NurOwn and 17 (18.1%) of participants treated with placebo (Table 12). The most common SAE in both treatment groups was respiratory failure (5.3% vs 3.2% for NurOwn and placebo, respectively). All SAEs were consistent with progression of ALS. One participant in the NurOwn treatment group and one participant in the placebo treatment group had a venous thromboembolism. A separate participant in the NurOwn arm had a fatal, saddle pulmonary embolism. These SAEs are addressed below in Section 7.3.6, AEs of Special Interest.

Table 12: Phase 3 Study BCT-002-US — Serious Adverse Events in ≥ 2 Participants in Either Group

Preferred Term, n (%):	NurOwn (N=95)	Placebo (N=94)
Participants with ≥ 1 SAE	23 (24.2)	17 (18.1)
Respiratory failure	5 (5.3)	3 (3.2)
Dysphagia	3 (3.2)	2 (2.1)
Venous thromboembolism (deep vein thrombosis [DVT], pulmonary embolism)*	1 (1.1)	3 (3.2)†
Pneumonia	2 (2.1)	2 (2.1)
Respiratory distress	2 (2.1)	0
Disease progression	1 (1.1)	2 (2.1)

* See Section 7.3.6.1 for additional information.

† Participant experienced an SAE of cerebral hemorrhage after falling from a scooter, and subsequently bilateral pulmonary embolism. The SAE resolved after 14 days, and the participant discontinued from the study because of increased risk from anticoagulant therapy.

7.3.4 Adverse Events Leading to Discontinuation

Four participants discontinued treatment in the Phase 3 study due to an AE (one participant in the NurOwn treatment group vs three in the placebo group). This does not include the 11 participants who died during the study.

The participant in the NurOwn group who discontinued had severe muscle spasms two weeks after receiving the first treatment but continued in the study to receive a second treatment before discontinuing. This AE was not considered related to either the procedure or study medication. In the placebo group, three participants discontinued (due

to events of “myalgia,” “pneumonia,” and “procedural headache and dizziness,” respectively).

7.3.5 Deaths

Sixteen participants died during the Phase 3 study (10 participants in the NurOwn treatment group and 6 in the placebo group; Table 13). Importantly, there were no deaths reported as related to study treatment by either Investigator or Sponsor, and there was no statistical difference in survival between groups.

Of the 16 participants who died during the study, 12 were reported as due to disease progression (8 participants in the NurOwn treatment group and 4 in the placebo group). Most participants who died had ALSFRS-R scores ≤ 25 at baseline, which indicates more advanced disease at the start of the study (see Table 14).

Table 13: Phase 3 Study BCT-002-US — Listing of Deaths in Study

Cause of Death Verbatim Term:	Baseline ALSFRS-R Score	Disease Progression
NurOwn: Voluntary euthanasia	32	No
NurOwn: Massive saddle embolism	30	No
NurOwn: Respiratory failure due to ALS	29	Yes
NurOwn: Respiratory distress secondary to ALS	26	Yes
NurOwn: Progression of ALS	25	Yes
NurOwn: Respiratory failure due to ALS	24	Yes
NurOwn: Respiratory failure due to ALS	21	Yes
NurOwn: Respiratory arrest due to ALS	19	Yes
NurOwn: Respiratory failure due to ALS	17	Yes
NurOwn: Respiratory failure due to disease progression	16	Yes
Placebo: Cardiac arrest; respiratory failure from drowning	36	No
Placebo: Respiratory failure secondary to ALS	32	Yes
Placebo: Death due to progression of ALS	25	Yes
Placebo: Cardiac arrest*	22	No
Placebo: Progression of ALS	20	Yes
Placebo: Progression of ALS*	14	Yes

* Participant died before receiving treatment.

Importantly, participants who died during the study, and particularly those who died due to disease progression, on average had lower baseline functioning than the overall study population, as evidenced by baseline assessments (Table 14).

Table 14: Phase 3 Study BCT-002-US — Baseline Characteristics of Participants Who Died During Study

Parameter:	Deaths Due to Progression of ALS NurOwn (N=8)	Deaths Due to Progression of ALS Placebo (N=4)	All Deaths NurOwn (N=10)	All Deaths Placebo (N=6)	Total Study Population (N=196)
Mean baseline ALSFRS-R score[a]	22.1	22.8	23.9	24.8	30.7
Mean baseline SVC% predicted[b]	60.0	52.3	67.8	60.9	75.4
Mean pre-treatment slope[c]	-2.23	-2.60	-2.15	-2.85	-1.70

SVC=slow vital capacity.

a. For seven participants randomized but not treated, baseline ALSFRS-R value is the last before discontinuation.

b. Baseline SVC is defined as SVC measured at Visit 6 (baseline) only and not from a prior visit, since SVC was only measured at screening and baseline. Due to the long duration between screening and baseline, if baseline SVC was missing it was not imputed using screening SVC. Out of the seven participants who were randomized and not treated only one had a baseline value at Visit 6.

c. Rate of decline in ALSFRS-R score per month from screening to baseline.

Per the FDA's request as part of the study conduct, the Sponsor continued recording any deaths made known to them after participants completed the study up to four months past study conclusion. Total deaths in the trial and follow-up period in NurOwn-treated participants was 22 and 21 in placebo-treated participants. These reports of deaths were collected passively, through a variety of sources, and do not represent complete data regarding deaths following the study.

7.3.6 Adverse Events of Special Interest

7.3.6.1 Venous Thromboembolism

Venous thromboembolism (deep vein thrombosis [DVT], pulmonary embolism) is a known complication in participants with ALS due to increased immobility, lower extremity weakness, and age. In the Phase 3 study, the following events occurred:

- One (1.1%) participant in the NurOwn group had one fatal SAE of pulmonary embolism after treatment; this participant died during the study secondary to hemodynamic collapse from a saddle embolism of the pulmonary artery bifurcation.
- One (1.1%) participant in the NurOwn group had one SAE of DVT during screening before treatment, therefore this event was not treatment emergent. This participant completed the study.
- One (1.1%) participant in placebo group had one SAE of bilateral DVTs after treatment (ultimately confirmed heterozygote for Factor V Leiden, a known risk factor for DVT); this participant completed the study.

- Two (2.1%) participants in the placebo group had pulmonary embolism. One participant recovered and completed the study, this instance of pulmonary embolism was captured as an SAE unrelated to treatment. The second participant experienced an additional SAE of cerebral hemorrhage and was discontinued from the trial.

7.3.6.2 Arachnoiditis

Arachnoiditis is a pain disorder associated with inflammation of the arachnoid membrane that surrounds and protects the nerves of the spinal cord. It has been reported following routine lumbar puncture, epidural steroid injection, intrathecal treatment, and frequently in the context of lumbar degenerative disc disease (Jackson & Isherwood, 1994).

Typical clinical features include back pain (increased by activity), leg pain (often bilateral), hyporeflexia, decreased range of movement of the trunk, sensory abnormalities, decreased straight leg raising, and urinary sphincter dysfunction. Arachnoiditis may be confirmed by MRI imaging as clumping of lumbar nerve roots, although the MRI features lack specificity and may not always be accompanied by symptoms (Parenti et al., 2020). Two SAEs of arachnoiditis were confirmed in the Phase 2 MS study (BCT-101-US), with magnetic resonance imaging findings in both cases showing characteristic clumping of lumbar roots. Due to these findings, the AEs in the Phase 3 ALS study (BCT-002-US) were assessed for possible cases of arachnoiditis. While some participants had low-back pain with radicular features, no cases of arachnoiditis were reported in the study.

7.3.7 Other Safety Information

7.3.7.1 Non-Invasive Ventilation

Non-invasive ventilation is a cornerstone of symptomatic treatment in ALS and may improve survival and quality of life (Barć & Kuźma-Kozakiewicz, 2020; Dorst & Ludolph, 2019). In the Phase 3 study, the presence of non-invasive ventilation was based on scores of 1, 2, or 3 from ALSFRS-R Question 12.

The number of participants with BiPAP was generally similar in both groups, with 25 (26.3%) participants in the NurOwn group and 27 (28.7%) participants in the placebo group requiring BiPAP at some point during the study.

7.3.7.2 Gastrostomy Tubes

Gastrostomy is a common intervention for participants with ALS who have developed significant weight loss, dysphagia, and/or aspiration. Use of gastrostomy tubes (G-tubes) may improve quality of life but does not appear to influence disease progression (Barć & Kuźma-Kozakiewicz, 2020). In the Phase 3 study, the requirement for G-tubes was assessed using data derived from the ALSFRS-R questionnaire.

The numbers of participants who required a G-tube at a specific visit and at any visit were generally similar in both groups (18 [18.9%] participants in the NurOwn group vs 16 [17.0%] in placebo). However, 15 (16.0%) participants in the placebo group required

G-tubes for more than 50% of their food at any visit following treatment, as compared to 9 (9.5%) participants in the NurOwn group.

7.4 Safety Across All Studies

The safety profile of NurOwn was consistent across the clinical development program for ALS, with findings in the pivotal Phase 3 Study BCT-002-US largely reflective of initial findings from the Phase 1 and 2 portion of the clinical program (Table 15).

Table 15: Overall Summary of Adverse Events in All ALS Studies

Parameter, n (%):	Phase 3 BCT-002-US NurOwn (N=95)	Phase 3 BCT-002-US Placebo (N=94)	Phase 2 BCT-001-US NurOwn (N=36)	Phase 2 BCT-001-US Placebo (N=12)	Phase 1/2 MSC-NTF-001-IL NurOwn (N=12)	Phase 2a MSC-NTF-002-IL NurOwn (N=14)
Total treatment doses (route of administration)	3 2 months apart (IT)	3 2 months apart (IT)	1 (IT & IM)	1 (IT & IM)	1 (IT & IM)	1 (IT & IM)
Participants with AE, n (%): Any AE	94 (98.9)	92 (97.9)	36 (100)	12 (100)	6 (50)	14 (100)
Participants with AE, n (%): Severe AE[a]	29 (30.5)	19 (20.2)	3 (8.3)	1 (8.3)	0	3 (21.4)
Participants with AE, n (%): Serious AE (SAE)	23 (24.2)	17 (18.1)	8 (22.2)	1 (8.3)	1 (8.3)	3 (21.4)
Participants with AE, n (%): Serious-related AE	1 (1.1)	1 (1.1)	0	0	0	0
Participants with AE, n (%): AE leading to treatment withdrawal	1 (1.1)	1 (1.1)[b]	0	0	0	0
Participants with AE, n (%): AE leading to discontinuation from study	1 (1.1)	3 (3.2)	0	0	0	1 (7.1)
Participants with AE, n (%): AE leading to death	10 (10.5)	4 (4.3)	0	0	0	2 (14.3)
Participants with AE, n (%): Treatment-related AE leading to death	0	0	0	0	0	0

IM=intramuscular; IT=intrathecal

a. Severe AEs includes severe and potentially life-threatening.

b. There are two more participants in placebo group of BCT-002-US whose treatments were discontinued due to AE. One participant received only two treatments; however, completed through Visit 14 (Week 28) and is considered having completed the study. Two participants discontinued treatment; however, had an error in the AE Action taken not reflecting this. The participants' status for discontinuing treatment due to an AE is correctly reflected in BCT-002-US.

8 BENEFIT-RISK CONCLUSIONS

8.1 Analysis of Condition

ALS is a devastating neurodegenerative disease with a high unmet medical need.

ALS is caused by the degeneration and death of motoneurons in the brain and spinal cord. The disease is relentlessly progressive and fatal, with a median survival of 2 to 5 years from clinical onset. Death is usually related to respiratory failure, caused by damage to the motor nerves that control breathing and consequent weakening of respiratory muscles (Brown & Al-Chalabi, 2017).

8.2 Current Treatment Options

As of April 25, 2023, the FDA has approved three treatments for ALS: riluzole, edaravone, and sodium phenylbutyrate/taurusodiol. Tofersen received accelerated approval in a subset (approximately 2%) of patients with ALS.

There is currently no cure for ALS, and no treatment has been shown to substantially halt or reverse disease progression. The biological mechanisms underlying ALS are complex, although recent scientific progress indicates that neurodegeneration may be linked to deficient neuroprotection and neuroinflammation (J. J. Chen, 2020). Of the current investigational therapies, stem cell treatment has the potential to tackle these interrelated pathological mechanisms building on consistent demonstration of neuroprotective effects of NTFs in a variety of motor neuron models. However, clinical trials with other potential therapies involving NTFs in participants with ALS has yielded disappointing results to date, possibly because of the interference of the blood-brain barrier (Abati et al., 2019) and their short half-life clinical trials with NTFs in participants with ALS have yielded disappointing results to date, possibly because of the inherent limitations with either using single trophic factors in non-living delivery systems (interference from the blood-brain barrier, protein stability over time, short half-life, lack of synergism from using multiple NTFs) or by facing the challenges of systemic cell/vector delivery routes, failure to adequately reach the target brain tissue, unfavorable safety profile, etc. The need for synergic association of numerous NTFs is highlighted (Abati et al., 2019; Gouel et al., 2019). Conversely, stem cells of various origin have the potential to secrete/deliver growth factors directly in the CNS when administered IT. A further beneficial synergistic effect of MSC is related to their intrinsic capacity for immunomodulation, which is especially relevant considering the growing evidence of the role of neuroinflammation in ALS pathogenesis (Abati et al., 2019). Therefore, these key therapeutic strategies of neuroprotection and immunomodulation, delivered directly to the CNS behind the blood-brain barrier by a cellular therapy, hold great promise in ALS.

8.3 Benefit

NurOwn has shown consistent treatment benefit across multiple clinical and biomarker endpoints.

In the Phase 3 study, the primary and secondary endpoints failed to reach statistical significance in the overall study population, due to the floor effect associated with the lower scores of ALSFRS-R. This resulted in the inability for the ALSFRS-R to sensitively detect changes in the extremes of the population studied in the Phase 3 trial. In a prespecified subgroup analysis of participants above the anticipated baseline mean ALSFRS-R (baseline ALSFRS-R ≥ 35), an enhanced treatment effect was observed with a 19% higher response rate with NurOwn over that observed for the placebo group on the primary endpoint (34.6% vs 15.6%, p=0.305), closely aligning with the power assumptions for the trial of 35% NurOwn response vs 15% placebo. On the key secondary endpoint (average change from baseline to Week 28) in this prespecified subgroup, a treatment difference of 2.09 points was observed which reached a nominally significant p-value (p=0.050) despite the reduced sample size. Sensitivity analyses utilizing different thresholds of baseline ALSFRS-R, spanning 26 to 35, further supports NurOwn has a clinical meaningful effect when the disease progression can be measured by ALSFRS-R, for example in participants with no item level floor effect at baseline.

Floor effect associated with the ALSFRS-R was evident in BCT-002-US, which is represented by the fact that an unexpected high number of participants in both treatment groups with advanced ALS at baseline (ALSFRS-R ≤25) had values of zero at baseline on the fine motor and gross motor subscales of the ALSFRS-R. Once physical function is lost and the value of an item reaching 0, further loss cannot be measured even as a participant's condition further deteriorates. Thus, the floor effect must be addressed before valid conclusions can be drawn. The post-hoc analyses based on individuals with no evidence of the floor effect at baseline (participants with all ALSFRS-R items above 0 at baseline) assessed the treatment effect in participants for whom the scale could measure decline across all attributes of ALS disease. This analysis showed a response rate of 41% in NurOwn-treated participants versus a 23% response rate in placebo-treated participants, for an 18% difference in primary endpoint (p-value of 0.035). Analysis for the key secondary endpoint in this population shows a 2.3 points slower decline in the ALSFRS-R at Week 28 for NurOwn compared to placebo (with a p-value of 0.040). The consistency of results offers confidence that the treatment effect is robust when the methodological challenges of the ALSFRS-R at the lower end of the scale are minimized.

Furthermore, NurOwn has been shown to result in statistically significant improvements across multiple neuroprotective, neuroinflammatory, and neurodegenerative biomarkers, including NfL in all participants. The biomarker results from two independent clinical trials (Phase 2 and 3) provide strong mechanistic support linking these biomarkers of ALS pathogenesis and the proposed MoA of NurOwn. In addition, there is an important relationship between biomarker modifications and clinical benefit, specifically, the Phase 3 trial shows treatment-driven reductions in neurofilament are reasonably likely to be associated with clinical benefit in ALS.

It is worth noting that the treatment benefit of NurOwn is not a snapshot observation in a single efficacy endpoint. Instead, a consistent treatment benefit is observed across different timepoints and endpoints, as well as across four subscales of the ALSFRS-R,

meaning the result is not purely dominated by a single subscale. In the effort to combine the multidimensional evidence of clinical benefit, totality of evidence analyses that combine the treatment effect observed across different timepoints of clinical endpoints, subscales, and biomarkers was conducted. Importantly, all show significant p-values via permutation tests. This means if there were no treatment effects, one would not expect to see such a sustained clinical benefit of NurOwn across all subscales of ALSFRS-R and across multiple clinical and biomarker endpoints that starts early in the trial and are maintained across the trial. In short, these analyses suggest strong statistical evidence of the treatment benefit with NurOwn.

For participants with the unrelenting and fatal disease of ALS, the totality of data supports that NurOwn benefits a broad range of people, who reflect the heterogeneous, real-world population of people living with ALS, in a clinically meaningful way.

8.4 Risk and Risk Management

Overall, NurOwn was well-tolerated with a manageable safety profile relative to the standard of care. Most AEs were mild to moderate and transient. Procedural complications were the most commonly reported AEs, with the incidences of procedural pain, post procedural pain, musculoskeletal pain, back pain, and headache higher in the NurOwn group compared to placebo. Adverse events were generally minor and limited in duration.

Adequate and well controlled trials support the safety of NurOwn for the treatment of ALS. The usual post-marketing collection and reporting of AEs is expected to be sufficient. No additional risk management actions are proposed.

8.5 Conclusion

The totality of the evidence demonstrates a positive benefit-risk profile for NurOwn that supports its approval for patients living with ALS.

While the primary endpoint was not achieved in the Phase 3 trial, analysis of the key secondary endpoint (average change from baseline to Week 28) in a prespecified subgroup revealed a significant effect (p=0.050). Post-hoc analyses also reveal a statistically significant treatment effect of NurOwn compared to placebo in both the primary (p=0.035) and the key secondary efficacy endpoint (p=0.040), after accounting for the ALSFRS-R floor effect. Additionally, biomarker data demonstrate that NurOwn's synergistic effects on neuroinflammation, neurodegeneration and neuroprotection pathways, with the NurOwn-driven reductions on NfL, are linked to NurOwn's impact on the observed clinical response. When looking at the totality of evidence, an approach that is particularly informative for rare disease trials with limited sample size, NurOwn showed a significant temporal trend in both the primary (p=0.005) and key secondary endpoint (p=0.007), with significant evidence of a treatment effect across subscales (p=0.007) as well as across biomarkers that span all key pathways (p<0.0001). In addition, NurOwn

has a favorable safety profile especially when viewed against the background risks posed to patients by this devastating illness.

Overall, the body of evidence for NurOwn supports approval of NurOwn for people living with ALS, a universally fatal disease with too few treatment options.

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10 APPENDICES

10.1 Patient Reports of Changes in Daily Activity in the Expanded Access Program

Patient reported changes in daily activity were documented during the Expanded Access Program for NurOwn (Stevens Nation, 2022). The meaningful improvements reported as a result of NurOwn treatment include:

- “walk without a walker, walk longer distances, walk in sand or farm field”,
- “rise out of a chair unassisted and get up off the floor unassisted”
- “climb up and down stairs”, “climb up into a four-wheel drive vehicle”
- “decreased or halted fasciculations”
- “improved balance and less falls when walking”
- “put our arms over our heads and wash our bodies and hair unassisted”
- “use the bathroom or hold a urinal”
- “open water bottles, pill bottles and food jars”
- “hold a pen to write”
- “use a cell phone to text and type”
- “speak more clearly without needing a caregiver to translate”
- “pull the throttle on a lawnmower and push the lawnmower to mow the grass”
- “grip a glass and lift it to drink”
- “operate a wheelchair with one finger”
- “throw a ball to the dogs or throw rocks with the kids”
- “swallow dense foods like fried chicken, rice, sushi”
- “speak for longer periods of time between use of bipap”
- “breathe stronger as evidenced by improved FVC”