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U.S. FOOD & DRUG ADMINISTRATION

Cellular, Tissue, and Gene Therapies Advisory Committee

BLA 125782

Application for debamestrocel (MSC-NTF) for Treatment of Amyotrophic Lateral Sclerosis (ALS)

Applicant: Brainstorm Cell Therapeutics

Advisory Committee Planning Working Group
Office of Therapeutic Products (OTP)
Center for Biologics Evaluation and Research, FDA

September 27, 2023

Outline

- Product Evaluation [Chemistry, Manufacturing, and Controls (CMC)]
- Clinical Overview
- Biostatistical Considerations
- Biomarker Analyses
- Totality of Evidence

Key Points

- Critical manufacturing controls not in place and/or incomplete, rendering substantive review not possible
- Adequate product quality not established
- Two randomized, double-blind, placebo-controlled studies failed to show efficacy
- Survival data are limited and unfavorable
- Subgroup analyses are exploratory
- Biomarker data do not indicate a clear association between any assessed biomarker and clinical benefit

For either the original or new clinical indication, data on MSC-NTF do not support approval

PRODUCT EVALUATION

[Chemistry, Manufacturing, and Controls (CMC)]

Tom Finn, PhD
Office of Cellular Therapy & Human Tissue CMC
OTP, CBER

Product Overview (debamestrocel/MSC-NTF/NurOwn)

- Autologous product derived from a single bone marrow collection
- Composed of mesenchymal stromal/stem cells (MSC) cultured under conditions to increase neurotrophic factor secretion to produce MSC-NTF cells
- Three patient-specific lots of 100-125 million cells are generated from a frozen intermediate timed to provide treatment at 8-week intervals
- Product lots are provided as a 4 ml suspension of MSC-NTF cells in a prefilled 5 ml syringe
- Neurotrophic factor (NTF) secretion in the cerebrospinal fluid (CSF) is proposed as a key mechanism of action (MOA)

Neurotrophic Factors for ALS Treatment

BDNF

- Neurotrophic factors are proteins that play a critical role in the survival, differentiation, maturation, and neurite outgrowth of peripheral and central nervous system (CNS) neurons
- Proteins with neurotrophic activity discovered by the field include NGF, BDNF, NT-3, NT-4, CNTF, GDNF, and VEGF

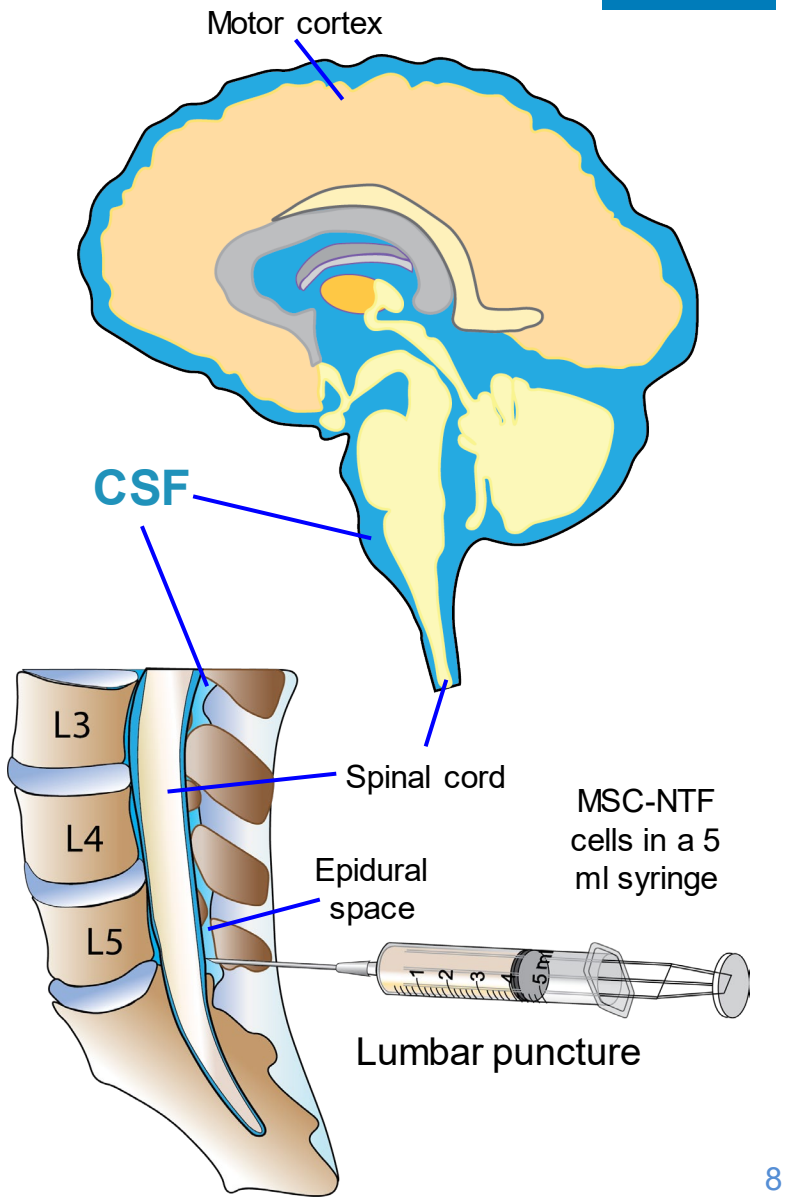
- Though considered a promising potential therapy for treatment of neurodegenerative diseases, limitations in delivery of purified neurotrophic factors in vivo, rapid turnover, and in some cases serious side effects have hampered their usefulness
- Cell and gene therapies have been proposed as an alternative way of providing elevated levels of neurotrophic factors in the CNS

Product Specifications for NTF Secretion Not Adequately Justified

- Secretion of different NTFs varies widely per MSC-NTF lot
- NTF secretion varies from the same frozen intermediate
- NTF secretion measured for product release under optimized conditions may not be reflective of secretion levels and duration under conditions expected in vivo
- Only a single NTF measured for potency in the Phase 3 study

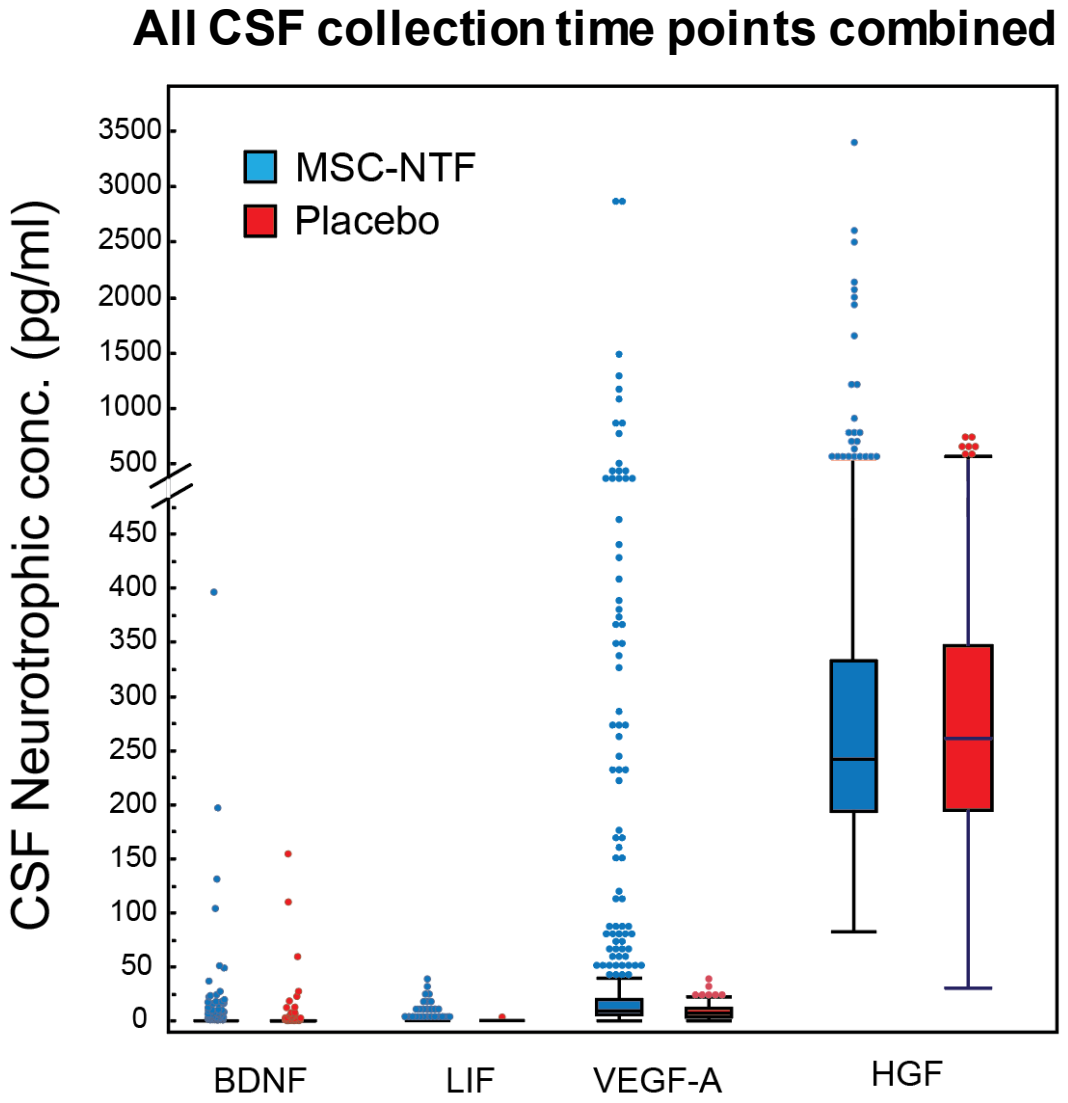
Limited Information on MSC-NTF Function In Vivo

- Unclear how far cells or secreted molecules travel within the CSF
- Unclear how long MSC-NTF cells persist in vivo
- We found no correlation between product release properties and:
  - Level of CSF neurotrophic factors measured as biomarkers
  - ALSFRS-R clinical scores



Minimal Difference in CSF NTF Levels Between Treatment Arms

- CSF levels of BDNF, LIF, VEGF, and HGF varied widely, but differed little between MSC-NTF and placebo
- Difference observed with VEGF mostly due to a fraction of samples that were elevated well above median levels, and varied by collection time point

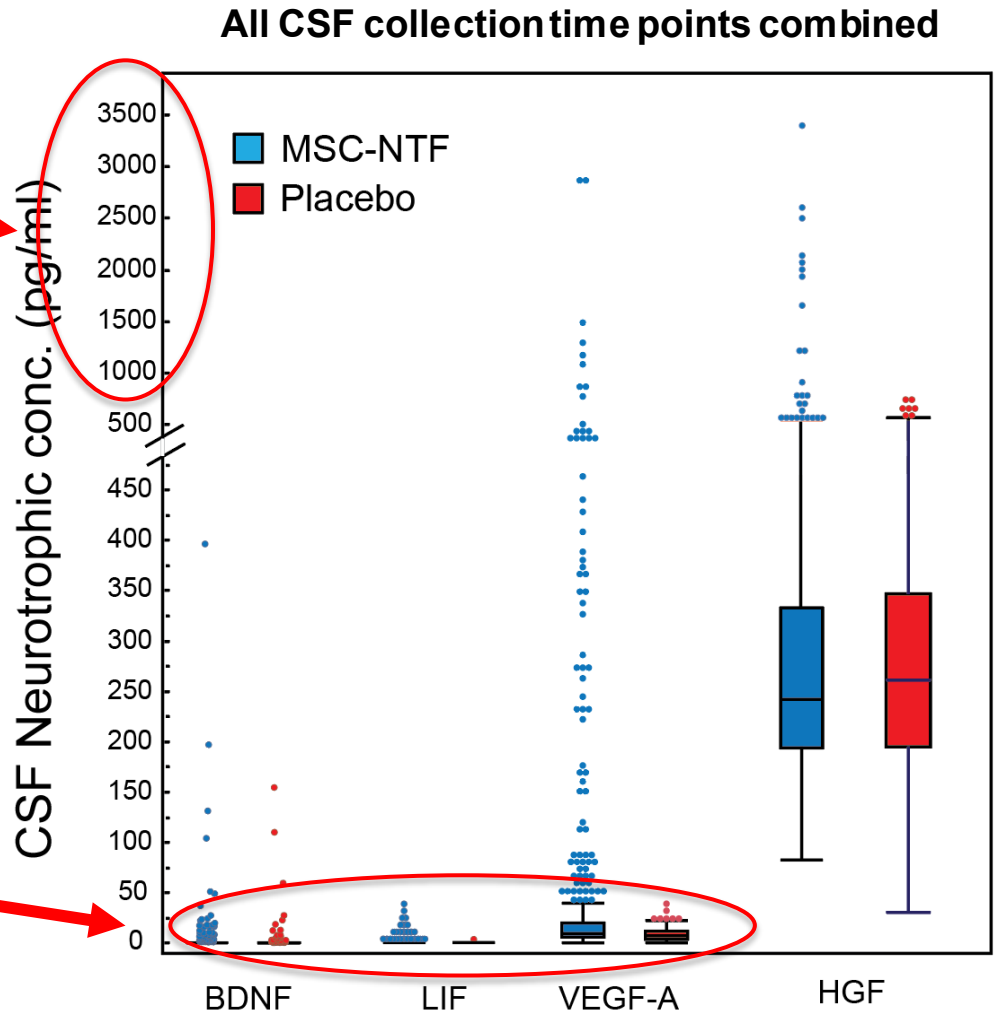


Low CSF NTF Levels Observed for Most Patients

- Median BDNF, LIF, and VEGF CSF NTF concentrations (**pg/ml**) are well below the concentrations typically used for neuronal cell culture (**ng/ml** range [1 ng =1000 pg])
  - Research studies typically conducted using 10-250 ng/ml in vitro on neuronal cultures

Median post-administration time point samples (pg/ml)

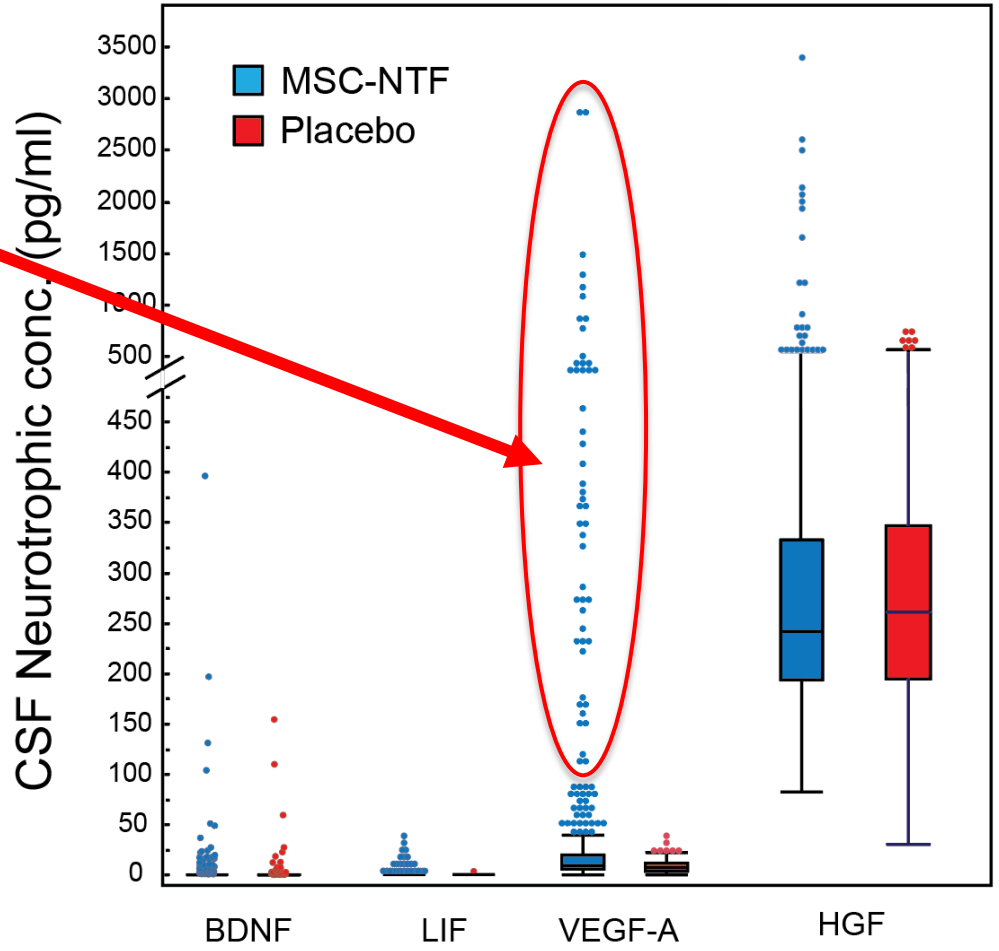
	MSC-NTF	Placebo
BDNF	0.12 (n=393)	0.08 (n=406)
VEGF	12.2 (n=407)	7.1 (n=416)



- Any secreted molecule could be diluted by the 150 ml CSF total volume, and CSF is continuously produced and turns over 4 times per day

Higher CSF VEGF Levels Do Not Correlate with Better Clinical Outcome

- Elevated VEGF levels observed in a fraction of MSC-NTF patients
- **No clear trend in clinical improvement** found in ALSFRS-R scores in patients who had high VEGF levels versus low VEGF levels or placebo. This held true even in:
  - ≥35 ASLFRS-R baseline subpopulation
  - Excluding the maximum floor effect



Manufacturing Issues – Potential Impact on Clinical Studies and Commercial Product

Product used in Clinical Studies	Concerns
Consistency of product across different clinical studies (e.g., Phase 2 & 3, Expanded Access)	• Comparability analysis not performed • Changes to process, specifications, facilities
Control of product variability for Phase 3 study	• It is unclear how consistent the upstream process was for Phase 3 • Variability in how the frozen intermediate is generated • Variable dose

Additional concerns for future clinical studies and proposed commercial product
Control of critical materials
Change in facilities
Process validation not performed
Product stability

Product Control Strategy Inadequate to Support Proposed Immunomodulatory MOA

- No immunomodulatory properties measured as in-process or final product release testing to ensure product quality of MSC-NTF
- No manufacturing control strategy for all relevant biological activities other than NTF secretion
- Measurement of NTF levels for release does not appear predictive of immunomodulatory properties:
  - No correlation between CSF levels of VEGF and MCP-1 in the same patient (at any time point)
  - NTF levels measured for release do not correlate with CSF MCP-1 levels

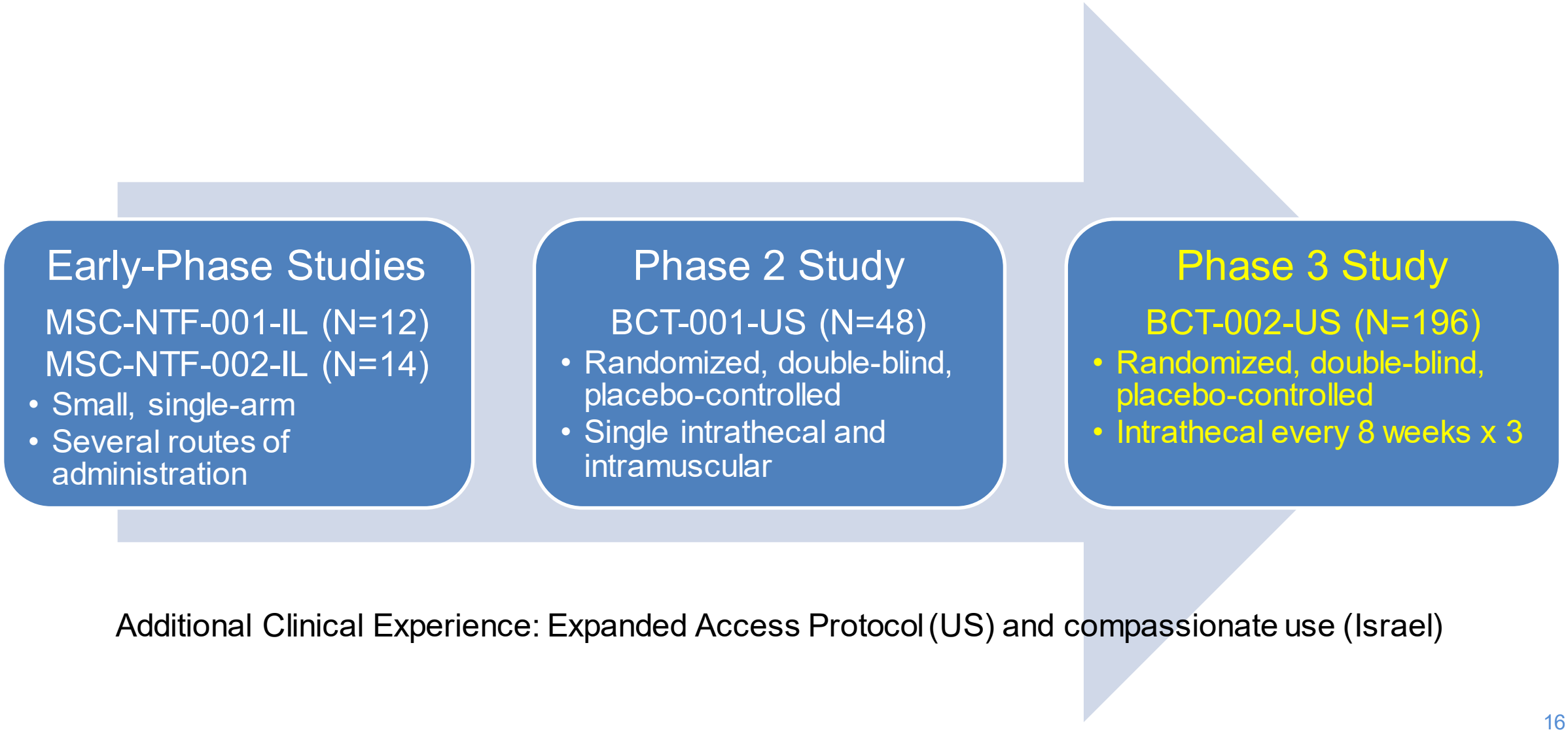
Summary From CMC Evaluation

- **Critical manufacturing controls not in place and/or incomplete, rendering substantive review not possible:**
  - Manufacturing consistency has not been demonstrated because sufficient manufacturing data have not been provided, product variability has not been explained, and process validation has not been performed
  - Comparability not demonstrated between trials or after manufacturing changes
- **Adequate product quality has not been established for NTF or immunomodulatory MOAs:**
  - NTF quality based on measurement of a single protein for product release, even though product development data show high NTF variability, and it is unclear whether the cells have the capacity to produce enough NTFs to overcome challenges with this route of administration and disease
  - Immunomodulatory quality is not measured

CLINICAL OVERVIEW

Gumei Liu, MD, PhD
Office of Clinical Evaluation
OTP, CBER

Clinical Development of MSC-NTF

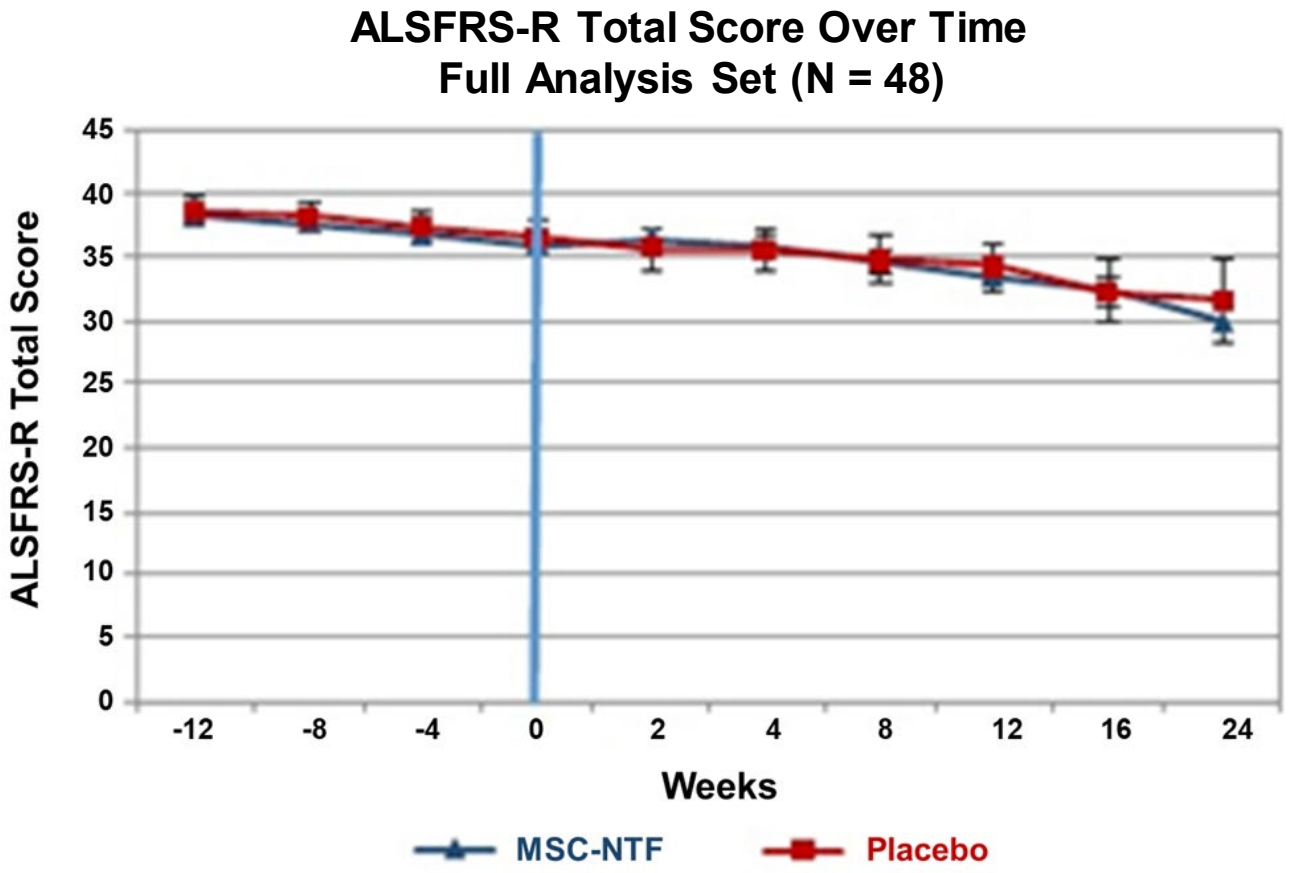


Additional Clinical Experience: Expanded Access Protocol (US) and compassionate use (Israel)

BCT-001-US (Phase 2): Study Overview

Phase 2 study did not show efficacy

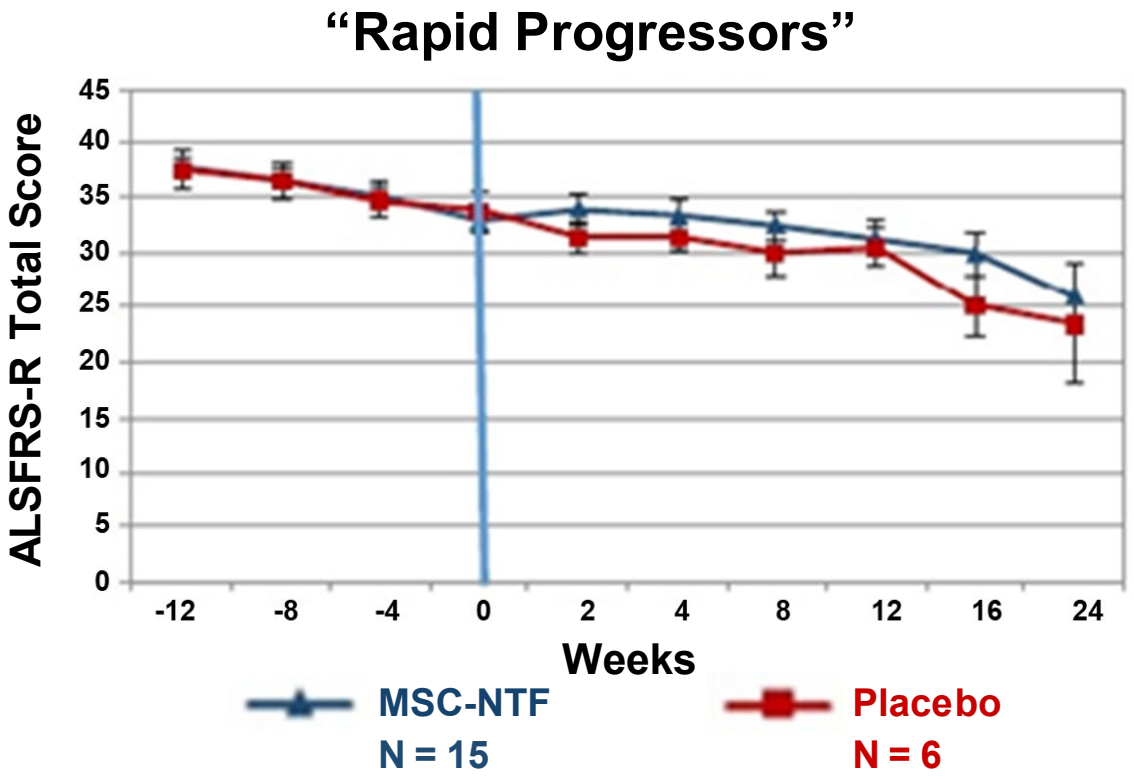
- Randomized, double-blind, placebo-controlled, multicenter
- Safety and preliminary efficacy
- One-time administration of MSC-NTF or placebo: intrathecal and intramuscular
- 48 patients, randomized 3:1 (MSC-NTF to placebo)
- Duration: ~12 weeks pre-treatment, 24 weeks post-treatment
- Eligibility criteria: ALS Functional Rating Scale-Revised (ALSFRS-R) ≥ 30, disease onset 12-24 months, slow vital capacity (SVC) ≥ 65%

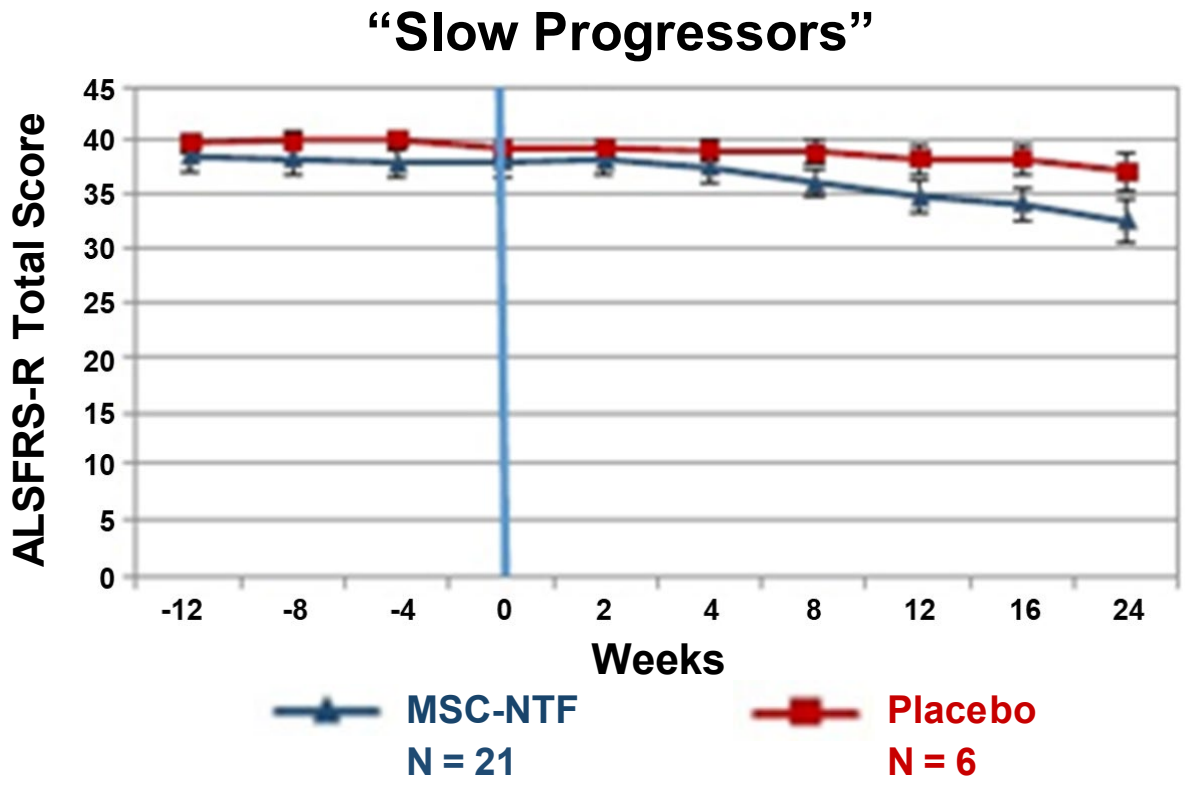


Source: Modified from Applicant

BCT-001-US: Subgroup Analyses

Patients with more rapid pre-treatment decline in ALSFRS-R total score were hypothesized to be more responsive to MSC-NTF treatment





Source: Modified from Applicant

BCT-002-US (Phase 3): Study Design

- Multicenter, randomized, double-blind, placebo-controlled
- Pre-treatment period
  - Initial screening
  - 12-week run-in period to identify "rapid progressors"
  - Randomization 1:1 (MSC-NTF or placebo)
  - Bone marrow aspiration
- Three intrathecal administrations of 100-125 x 10^6 MSC-NTF cells or placebo, 8 weeks apart
- Study follow-up: 28 weeks (± 5 days) after the first treatment

BCT-002-US: Study Population

- Key eligibility criteria
  - Revised El Escorial criteria: definite, probable, laboratory-supported probable, or possible
  - Symptom onset <2 years
  - Upright slow vital capacity (SVC) ≥65% of predicted at screening
  - Stable dose of riluzole or riluzole-naïve
  - ALSFRS-R ≥25 at screening
  - Decline in ALSFRS-R total score of ≥3 points during the 12 weeks prior to randomization

- Analysis population
  - 263 screened, 196 randomized, 189 treated, 144 completed study
  - Intend-to-treat (ITT) population: all randomized patients (n=196)
  - Modified intend-to-treat (mITT) population: randomized patients who received at least one treatment (n=189, MSC-NTF=95, placebo=94) and had at least three ALSFRS-R assessments (one pre-treatment, one baseline and one post-treatment)
    - Balanced in demographics and baseline disease characteristics

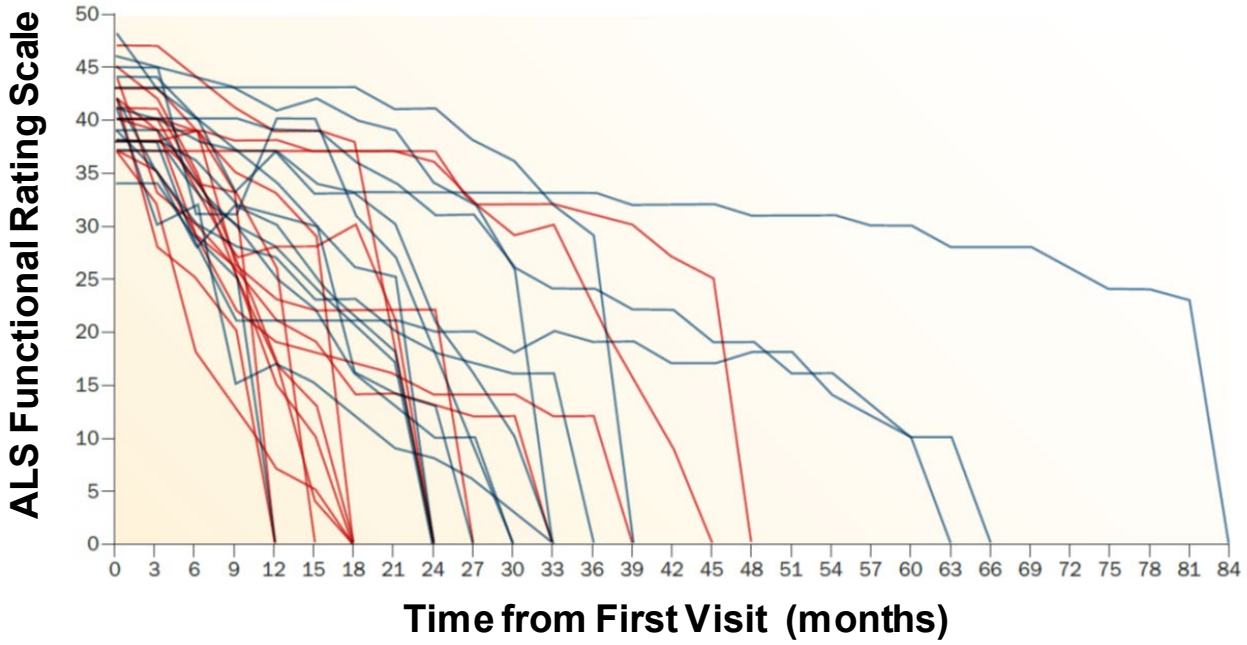
BCT-002-US: Efficacy Endpoints

- Primary Efficacy Endpoint
  - Proportion of “responders” in the MSC-NTF group versus placebo group
    - Responder definition: a patient with a ≥1.25 points/month improvement in post-treatment slope vs pre-treatment slope of the ALSFRS-R total score at week 28 following the first treatment
- Key Secondary Efficacy Endpoints
  - Proportion of patients with a 100% or greater improvement in post-treatment slope vs pre-treatment slope in the ALSFRS-R at week 28
  - Change in ALSFRS-R total score (Δ ALSFRS-R) from baseline to week 28
  - Combined Analysis of Function and Survival (CAFS) at week 28
  - Change in SVC from baseline to week 28
  - Tracheostomy-free survival
  - Survival

Efficacy Endpoints Considerations

- ALSFRS-R
  - Ordinal scale assessing four functional domains: bulbar, fine motor, gross motor, respiratory
  - 12 items, each rated from 0 (unable to perform) to 4 (normal ability); maximum score = 48
- Applicant chose to use primary efficacy endpoint based on change in ALSFRS-R linear regression slope

- ALS progression is not linear
- Patients may experience period(s) of plateau and/or reversal before further deterioration



Swinnen, B and W Robberecht, 2014, The phenotypic variability of amyotrophic lateral sclerosis, Nat Rev Neurol, 10(11):661-670.

Efficacy Review

- FDA did not agree with Applicant's choice of primary efficacy endpoint for Phase 3 study

- FDA evaluated results for the primary efficacy endpoint and all key secondary efficacy endpoints to determine whether the study demonstrated substantial evidence of effectiveness
  - Survival
  - Tracheostomy-free survival
  - ALSFRS-R total score change from baseline
  - Slow vital capacity
  - CAFS
  - ALSFRS-R slope change

BCT-002-US: Efficacy Results (mITT)

Failed all primary and key secondary efficacy endpoints

Efficacy Endpoints	MSC-NTF (N=95)	Placebo (N=94)	Statistic
Primary endpoint			
Proportion of responders: ≥1.25 points improvement in slope, n (%)	**31 (32.6)**	**26 (27.7)**	**Odds ratio (95% CI): 1.33 (0.63, 2.80), p=0.45**
Key Secondary Endpoints			
Proportion of responders: ≥100% improvement in slope, n (%)	13 (13.7)	13 (13.8)	Odds ratio (95% CI): 1.00 (0.42, 2.40)
ALSFRS-R Change from Baseline, LS mean (SE)	**-5.52 (0.67)**	**-5.88 (0.67)**	**LS mean difference (95% CI): 0.37 (-1.47, 2.20), p=0.69[1]**
CAFS score, LS mean (SE)	96.5 (5.1)	93.5 (5.1)	LS mean difference (95% CI): 3.0 (-11.4, 17.4), p=0.68[1]
Slow vital capacity change (SVC) from baseline, LS mean (SE)	**-12.94 (1.80)**	**-11.55 (1.81)**	**LS mean difference (95% CI): -1.39 (-6.15, 3.38), p=0.56[1]**
All-cause mortality[2], number (%)	10 (10.5%)	3 (3%)	Hazard ratio (95% CI): 3.3 (0.87, 12.66)

Source: FDA Statistician

[1] Nominal p-values are calculated without multiplicity protection, and consequently lack interpretability

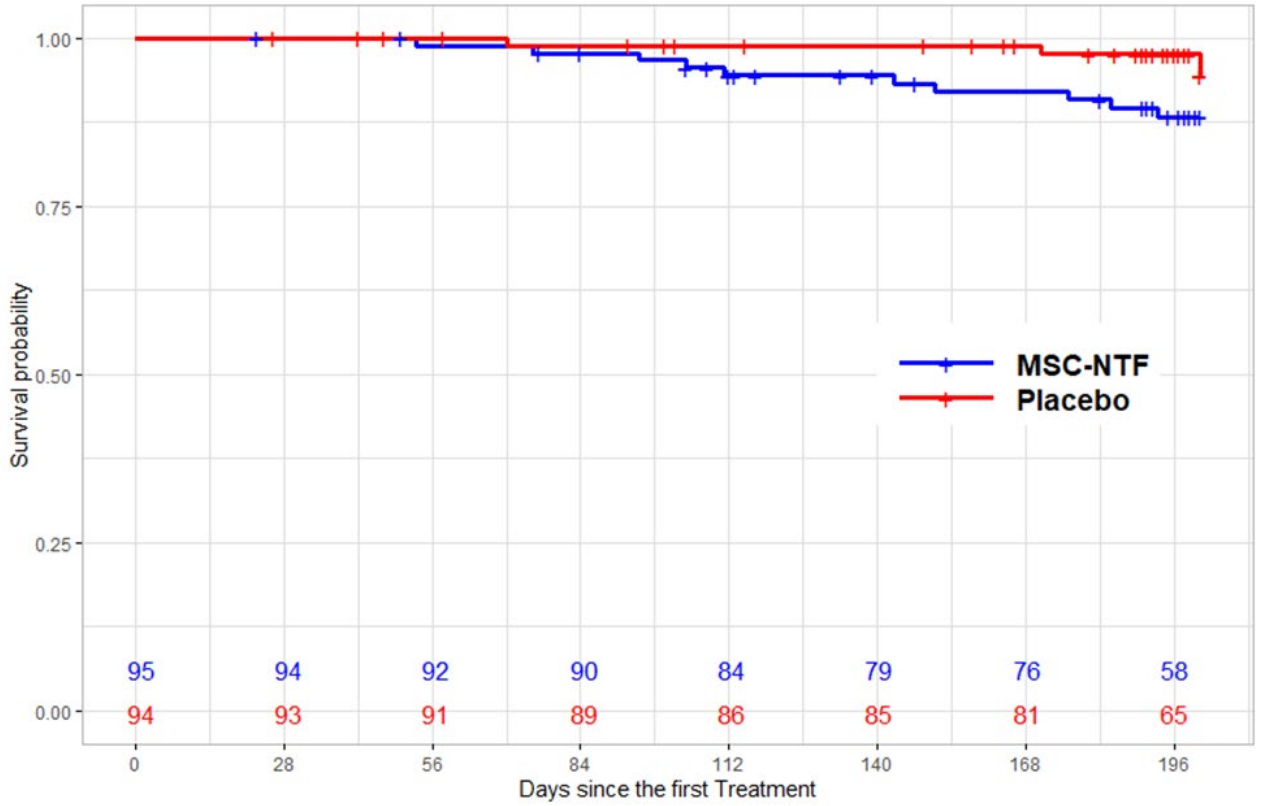
[2] Protocol defined study follow-up: 28 weeks±5 days

Abbreviations: ALSFRS-R, ALS Functional Rating Scale–Revised; CAFS, Combined Assessment of Function and Survival; mITT, modified intention-to-treat population; SE, standard error.

BCT-002-US: Overall Survival (mITT)

Survival was worse in MSC-NTF group

- Divergence in Kaplan-Meier estimate of survival favoring placebo.
  - 88.3% (95% CI: 79.3, 93.6) for the MSC-NTF group and 94.4% (95% CI: 81.2, 98.4) for the placebo group, nominal p-value of 0.04 (log-rank test)
- Protocol defined study follow-up: 28 weeks ± 5 days
- No planned long-term follow-up beyond 28 weeks



Source: FDA statistician

BCT-002-US: Safety Summary (I)

- Higher number of deaths in MSC-NTF group compared to placebo group in ITT population (all randomized patients)
  - A total of 16 deaths reported: 10 in MSC-NTF group, 6 in placebo group
  - Before 1st treatment:
    - Two deaths after randomized to placebo group
  - After treatment:
    - 10 deaths in MSC-NTF group and 3 deaths in placebo group during study follow-up (28 weeks ± 5 days)
    - One additional death in placebo group reported shortly after 28 weeks (± 5 days)

BCT-002-US: Safety Summary (II)

- Respiratory failure[1] was the most common treatment-emergent serious adverse event (SAE)
  - 7 (7.4%) in MSC-NTF group vs 3 (3.2%) in placebo group, relative risk: 2.3, 95% CI: 0.6, 8.7
- Higher frequency of pain in MSC-NTF group, e.g.,
  - back pain: 44.2% vs 25.5%
  - musculoskeletal pain[2]: 18.9% vs 9.6%
  - coccydynia: 11.6% vs 1.1%
- Higher frequency of muscle spasms[3] (12.6% vs 6.4%) and dysphagia (11.6% vs 7.4%) in MSC-NTF group

[1]Respiratory failure includes respiratory failure, respiratory arrest, respiratory distress
[2]Musculoskeletal pain includes musculoskeletal pain and myalgia.
[3]Muscle spasms includes muscle spasms and muscle spasticity

BCT-002-US: Exploratory Analyses

- Pre-defined subgroup analyses per Statistical Analysis Plan (SAP):
  - Patients with onset of symptoms <1.5 years vs ≥1.5 years
  - Patients with baseline ALSFRS-R total score <35 vs ≥35
  - Riluzole use
  - Sex
  - Race
- Post-hoc “floor effect” subgroup analyses
- Biomarker and genetic analyses

BIOSTATISTICAL CONSIDERATIONS

Xue (Mary) Lin, PhD
Office of Biostatistics and Pharmacovigilance, CBER

Key Points (Study BCT-002-US)

- MSC-NTF showed no efficacy compared to placebo on primary and all key secondary endpoints in the overall population
- Exploratory and post-hoc subgroup analyses cannot provide substantial evidence of effectiveness

Statistical Analysis Methods

- **Combined Analysis of Function and Survival (CAFS) score**
  - ANCOVA adjusting for baseline ALSFRS-R score, duration from onset of symptoms to first treatment, site of onset (limb vs bulbar & limb), riluzole use, ALSFRS-R slope pre-treatment
- **Change from baseline in ALSFRS-R at Week 28**
  - Mixed effects repeated measures (MMRM) adjusting for the same covariates
- **Binary endpoints**
  - Logistic regression adjusting for the same covariates
- **Change from baseline in SVC at Week 28**
  - Same as change from baseline in ALSFRS-R
- **Tracheostomy-free survival, overall survival**
  - Cox model adjusting for the same covariates, log rank test

Other Statistical Considerations

Analysis Population

- Primary analysis population was the mITT population
  - Randomized, treated, and had at least three ALSFRS-R assessments (prior to baseline, baseline, and post-treatment)

Type I Error Control

- Sequential testing strategy: if primary endpoint result is statistically significant, then test key secondary endpoints in pre-determined order

Lack of Efficacy on the Primary and All Key Secondary Efficacy Endpoints

(mITT population)

Endpoint	Statistic	MSC-NTF (N=95)	Placebo (N=94)
ALSFRS-R ≥1.25 points improvement in slope	Yes, n (%)	31 (32.6)	26 (27.7)
	Odds ratio (95% CI)	1.33 (0.63, 2.80)	
	p-value	0.45	
ALSFRS-R ≥100% improvement in slope	Yes, n (%)	13 (13.7)	13 (13.8)
	Odds ratio (95% CI)	0.998 (0.42, 2.40)	
ALSFRS-R change from baseline at Week 28	LS Mean (SE)	-5.52 (0.67)	-5.88 (0.67)
	LS mean difference (95% CI)	0.37 (-1.47, 2.20)	
CAFS score	LS Mean (SE)	96.5 (5.1)	93.5 (5.1)
	LS mean difference (95% CI)	3.0 (-11.4, 17.4)	
SVC change from baseline at Week 28	LS Mean (SE)	-12.94 (1.80)	-11.55 (1.81)
	LS mean difference (95% CI)	-1.39 (-6.15, 3.38)	
Survival[1]	Number of patients died (%)	10 (10.5%)	3 (3%)
	Hazard ratio (95% CI)	3.3 (0.87, 12.66)	

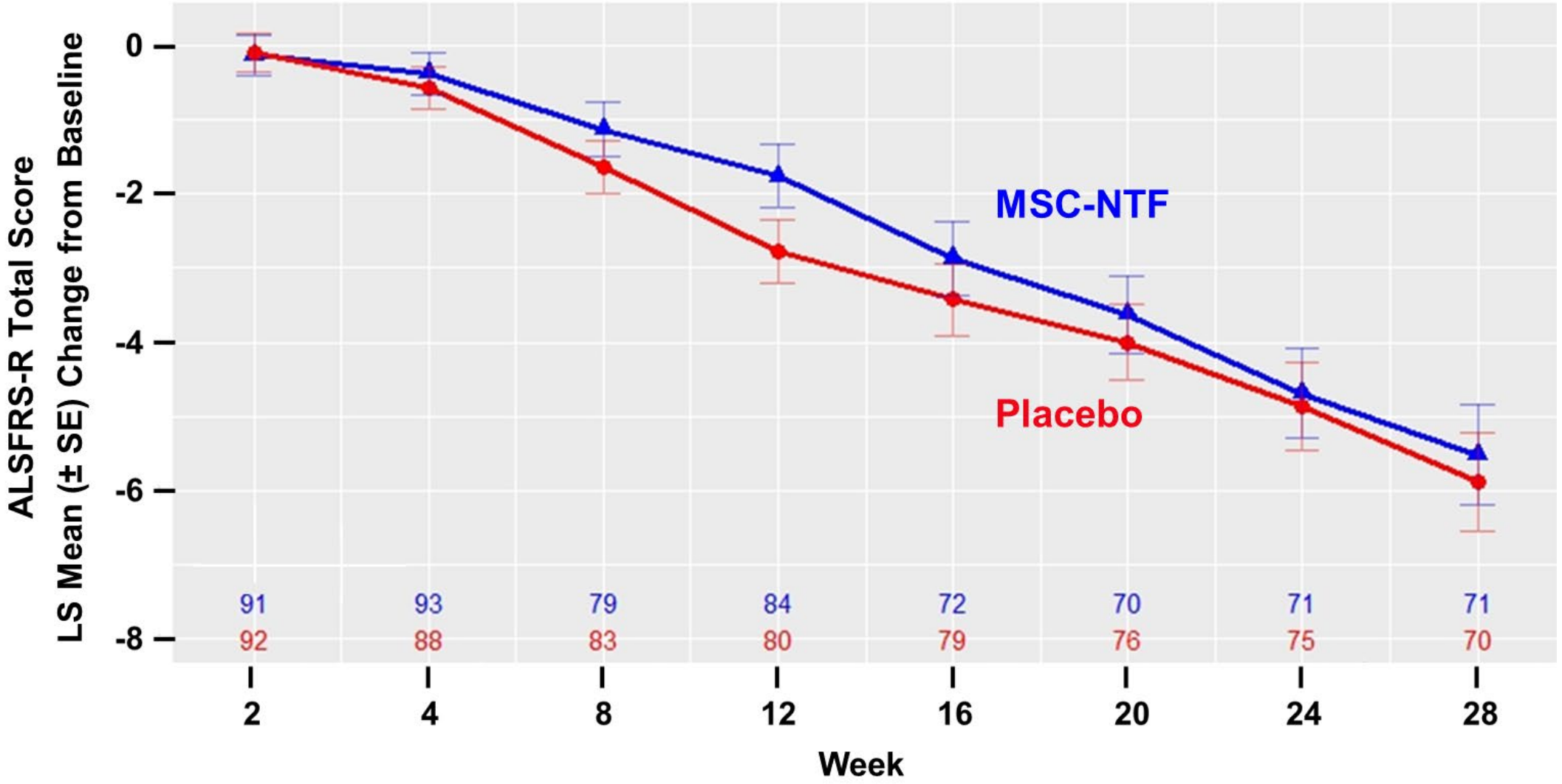
Source: FDA Statistician

[1] cutoff = Week 28 + 5 days

Abbreviations: ALSFRS-R, ALS Functional Rating Scale–Revised; CAFS, Combined Assessment of Function and Survival; CI, confidence interval; mITT, modified intent-to-treat; SE, standard error; SVC, slow vital capacity.

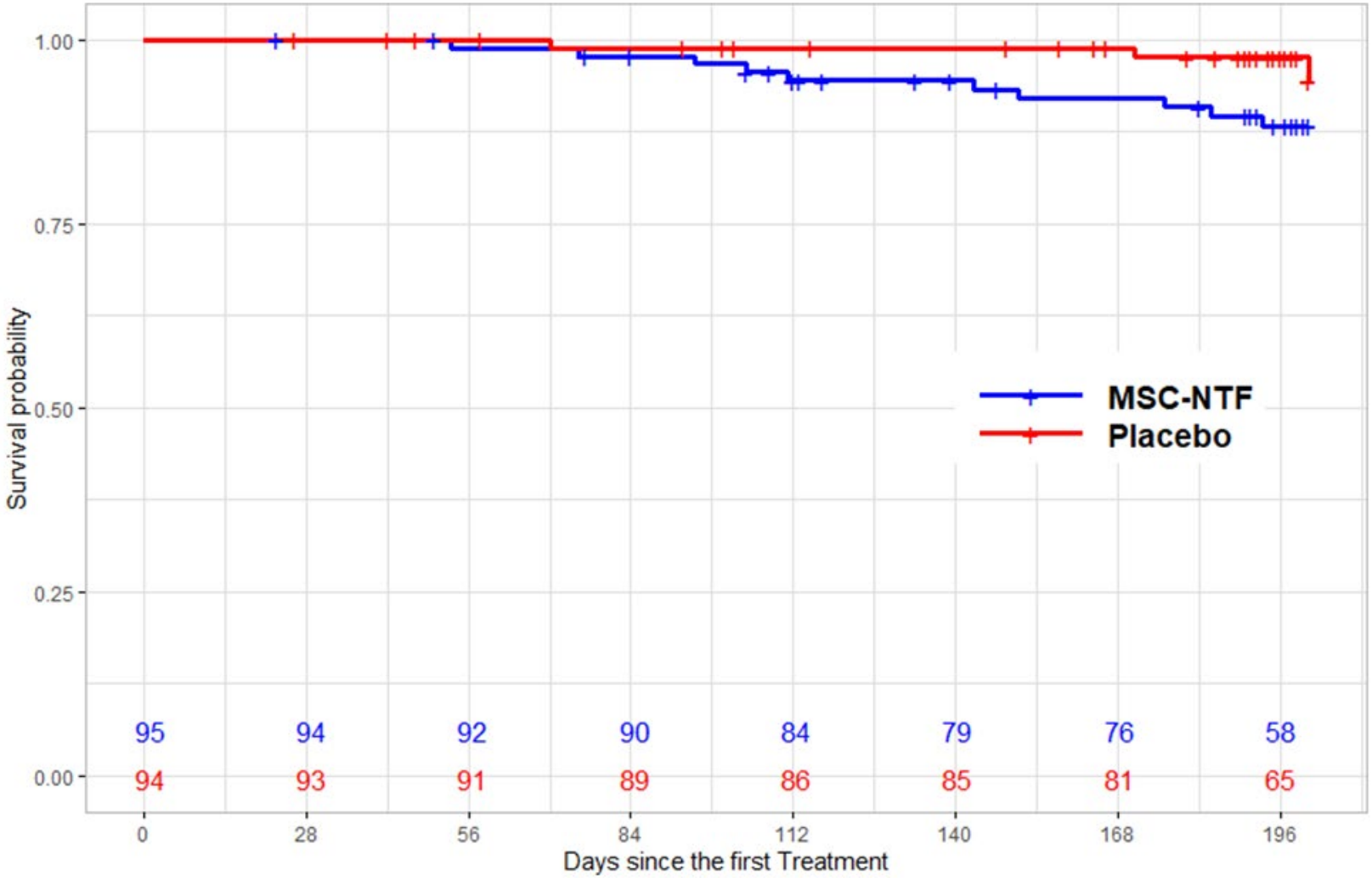
BCT-002-US:

Similar ALSFRS-R LS Mean Change from Baseline on all study visits



Worse Overall Survival in MSC-NTF Group

Kaplan-Meier Plot (mITT Population)
Cutoff: Week 28 + 5 Days



The Applicant Tried to Rescue the Failed Study

- MSC-NTF showed no efficacy compared to placebo on primary and all key secondary endpoints in the overall population
- The Applicant then tried to rescue the failed study by exploring various subgroups
- Exploratory and post-hoc subgroup analyses cannot provide substantial evidence of effectiveness to support regulatory approval
  - High risk of obtaining false positive results
  - Lack of control for multiple hypothesis testing
  - Breaking randomization → imbalance in measured and unmeasured baseline prognostic factors → confounding
  - Pre-specification is the cornerstone of reliable regulatory evidence

Applicant's Exploratory Subgroup Analyses: Floor Effect (I)

- Applicant's argument:
  - *Once physical function is lost, and the value of an item reaches 0, further loss cannot be measured even as a patient's condition further deteriorates*
  - *ALSFRS-R cannot measure further decline once items reach 0, making a treatment effect difficult to measure in participants with lower ratings*
  - *A floor effect could appear as an improvement or slowing of decline and thereby be misclassified as a clinical response*

Applicant conjectured that lack of efficacy in overall population was due to inability to detect efficacy in subgroup impacted by floor effect

Applicant's Exploratory Subgroup Analyses: Floor Effect (II)

To support conjecture, Applicant conducted post-hoc subgroup analyses to identify patients **not** impacted by "floor effect" of ALSFRS-R

- Definition 1: Total Score threshold
  - *Baseline ALSFRS-R total score >25 (n = 145)*
- Definition 2: Item Level threshold
  - *At least 2 of the six items in Fine Motor and Gross Motor scales of ALSFRS-R with baseline values ≥2 (n = 159)*
- Definition 3:
  - *No ALSFRS-R item with value of 0 at baseline (n = 106)*

FDA will refer to each subgroup as "no floor effect subgroup" and its respective complement as "with floor effect subgroup"

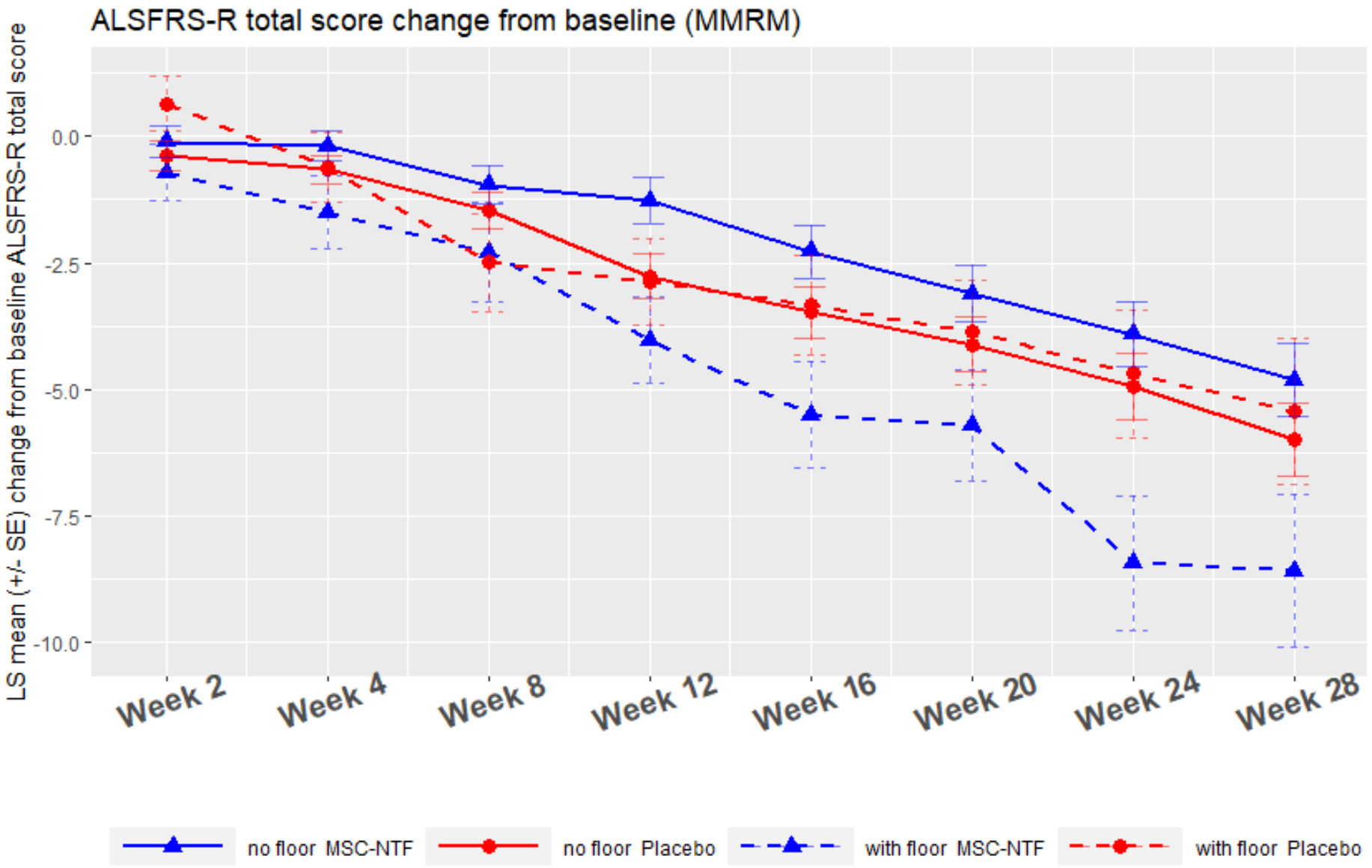
FDA's Analyses of Floor Effect: Post-Hoc Spurious Findings

- Spurious findings
  - Extensive subgroup exploration is always likely to find both positive and negative results that are not real signals or patterns, but spurious findings due to random chance or selection bias

- FDA did not observe an actual floor effect in the "with floor effect subgroups" identified by Applicant
  - If floor effect were present, "with floor effect subgroups" would have shown lower bound for ALSFRS-R total score post baseline, preventing much further decline
  - But Applicant's "with floor effect subgroups" had drastically **steeper** decline in ALSFRS-R total score from baseline than the "no floor effect subgroups"

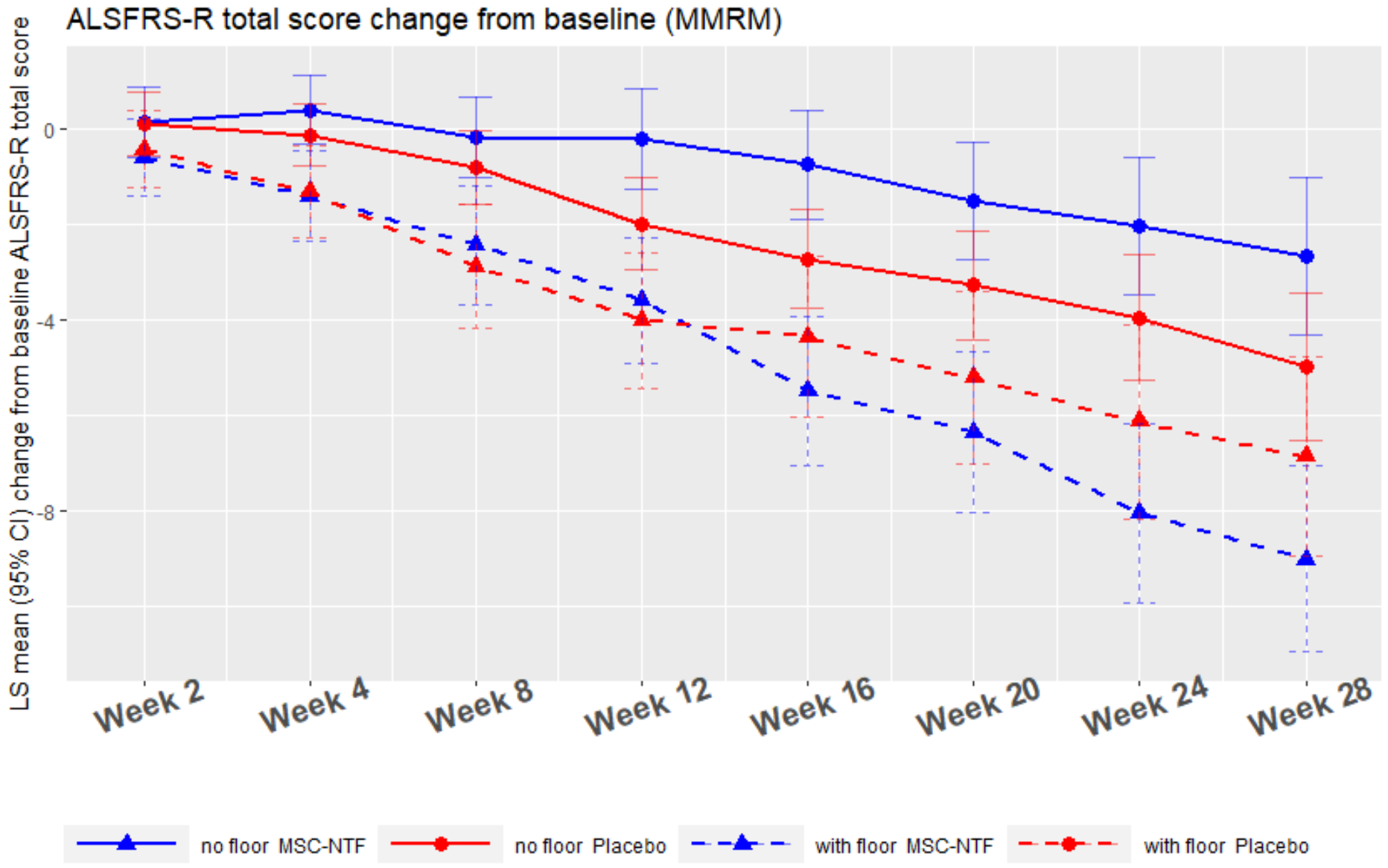
Definition 1

"No Floor Effect Subgroup" — Baseline ALSFRS-R total score > 25



Definition 3

"No Floor Effect Subgroup" — All Baseline ALSFRS-R Item Scores > 0



Comment on Applicant's "Totality of Evidence" Analysis

- The "totality of evidence" analysis were performed in the exploratory subgroup of patients with baseline ALSFRS-R ≥ 35 and post hoc subgroup of claimed "no floor effect" patients
  - True totality of evidence would include failure on primary and all key secondary endpoints in the overall study population, plus suggestion of survival disadvantage
- This analysis is subject to the same inflated chance of false positive findings as Applicant's other post hoc and exploratory subgroup analyses
  - With additional multiple testing issues due to further exploratory analysis
- The p-values are uninterpretable
  - The permutation test does not protect from uncontrolled Type I error inflation associated with post hoc or exploratory testing in any way
  - Methodological papers cited by applicant do not propose this method be applied to post hoc or exploratory subgroups

Study BCT-002-US: Summary of Statistical Findings

- MSC-NTF showed **no efficacy** compared to placebo on primary and all key secondary endpoints in the overall population

- Exploratory and post-hoc subgroup analyses **cannot** provide substantial evidence of effectiveness

BIOMARKER CONSIDERATIONS

Xiaofei Wang, PhD
Office of Clinical Evaluation
OTP, CBER

Study BCT-002-US: Overview of Biomarker Analysis

- MSC-NTF or placebo administered intrathecally at Week 0, 8, and 16
- CSF samples for biomarker analysis collected at baseline and at Weeks 2, 4, 8, 12, 16, & 20
- 45 biomarkers analyzed, in four categories
- Large amount of missing data (~50%) at Week 20

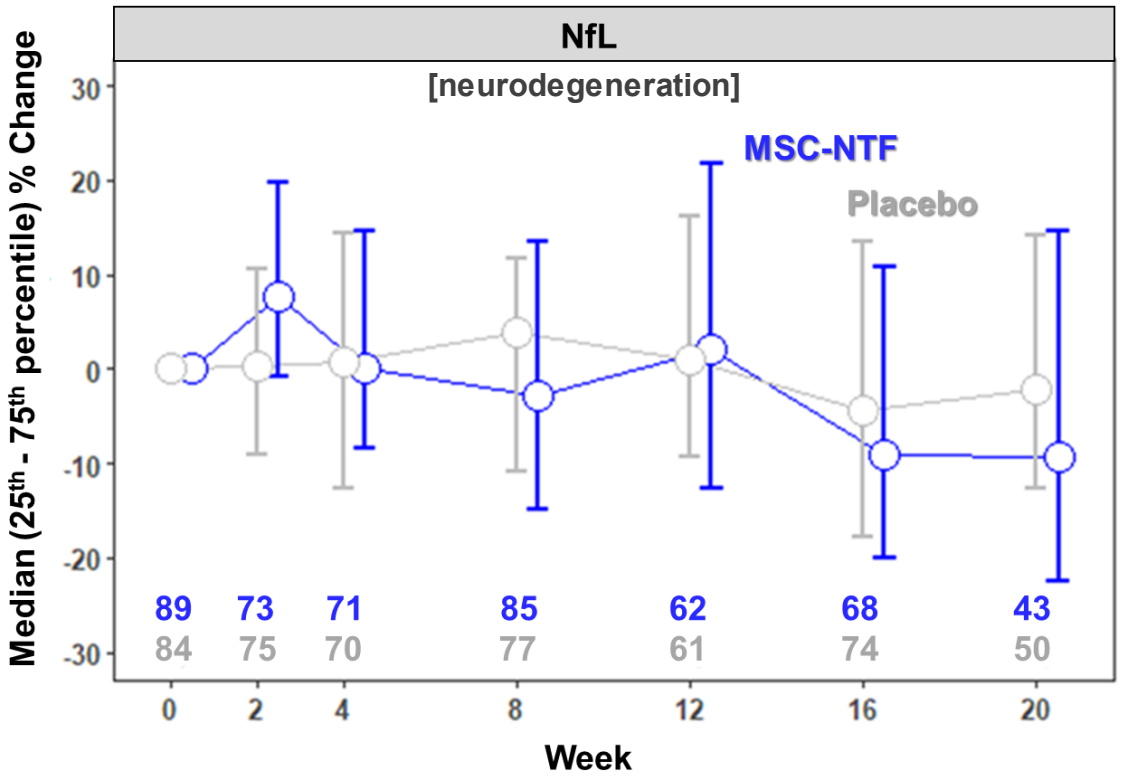
16
NEUROINFLAMMATION BIOMARKERS
(anti-inflammatory & pro-inflammatory)

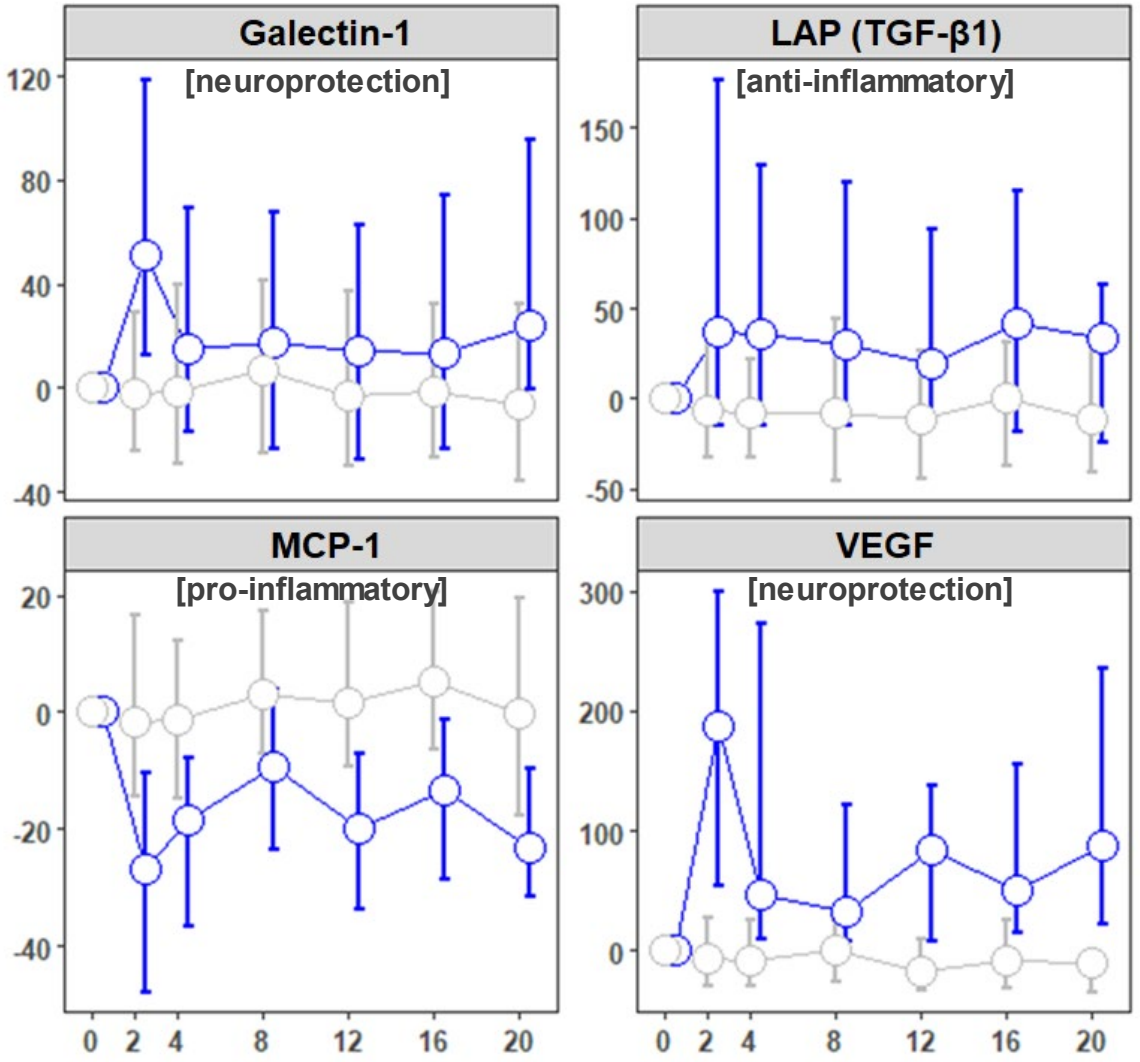
8
NEURODEGENERATION BIOMARKERS

9
NEUROPROTECTION BIOMARKERS

12
OTHER BIOMARKERS

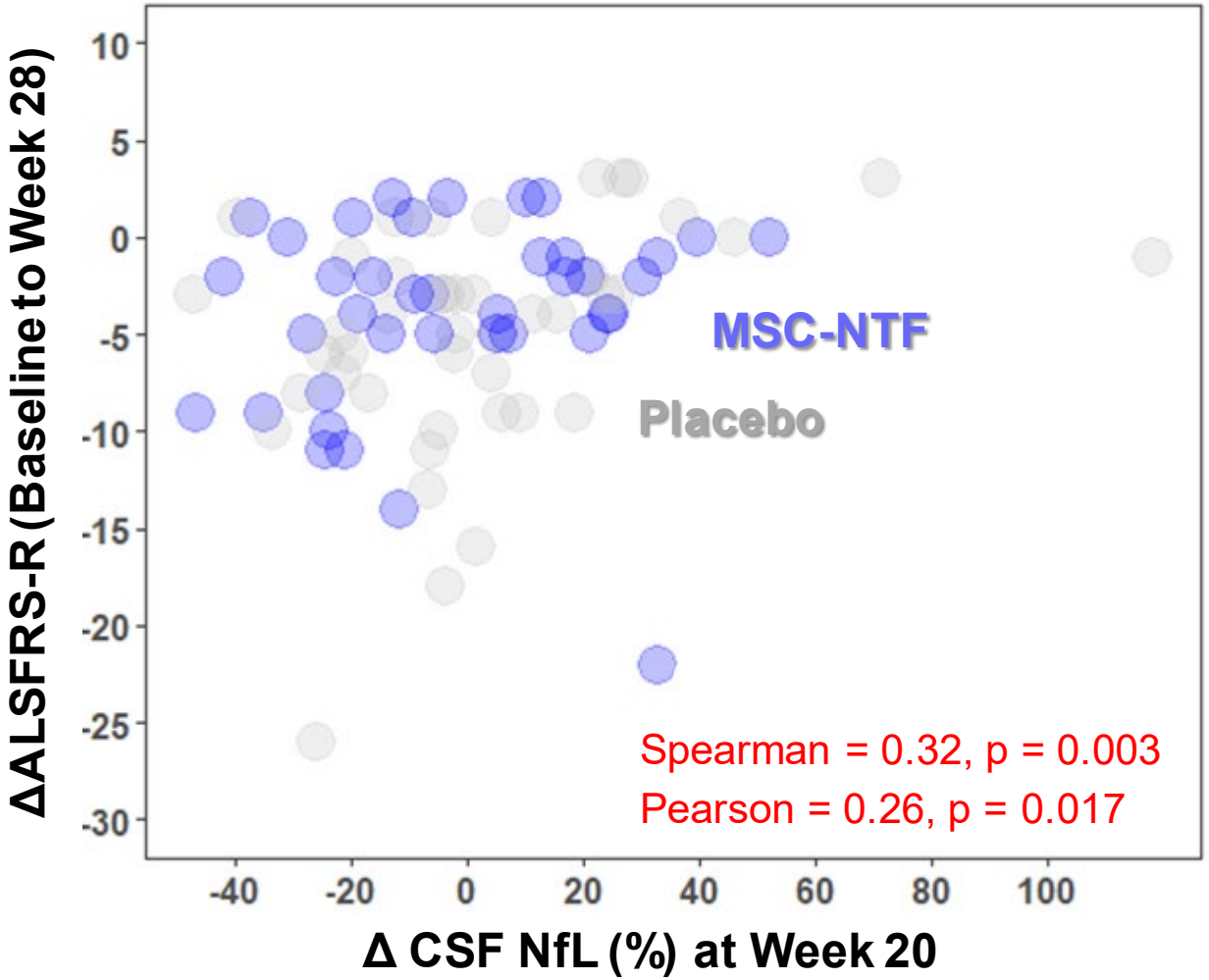
BCT-002-US: Biomarkers Potentially Associated with ALS Progression





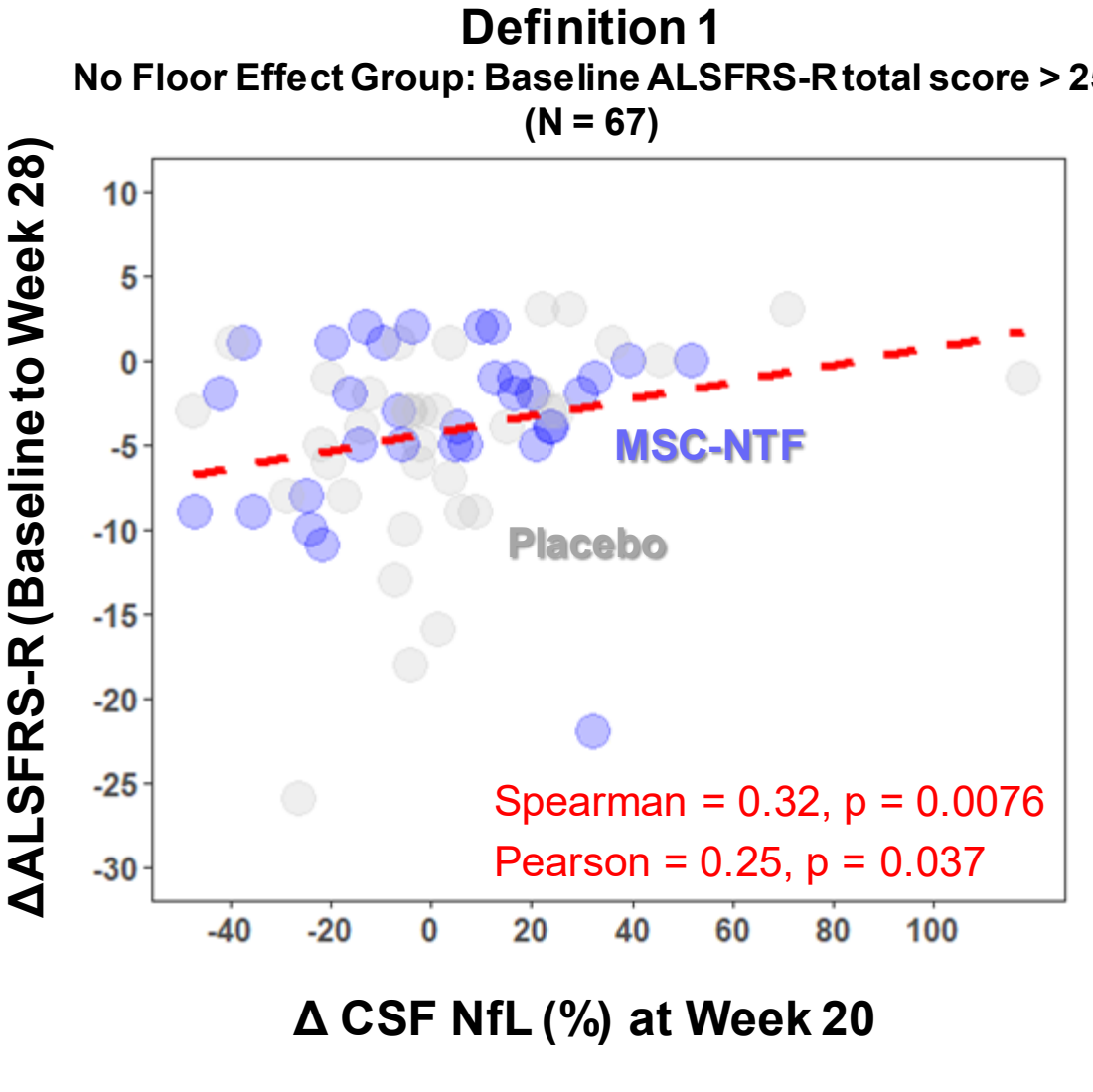
- High variability in biomarker data, especially in MSC-NTF group
- 9% reduction of CSF Neurofilament light chain (NfL) in MSC-NTF group compared to placebo group

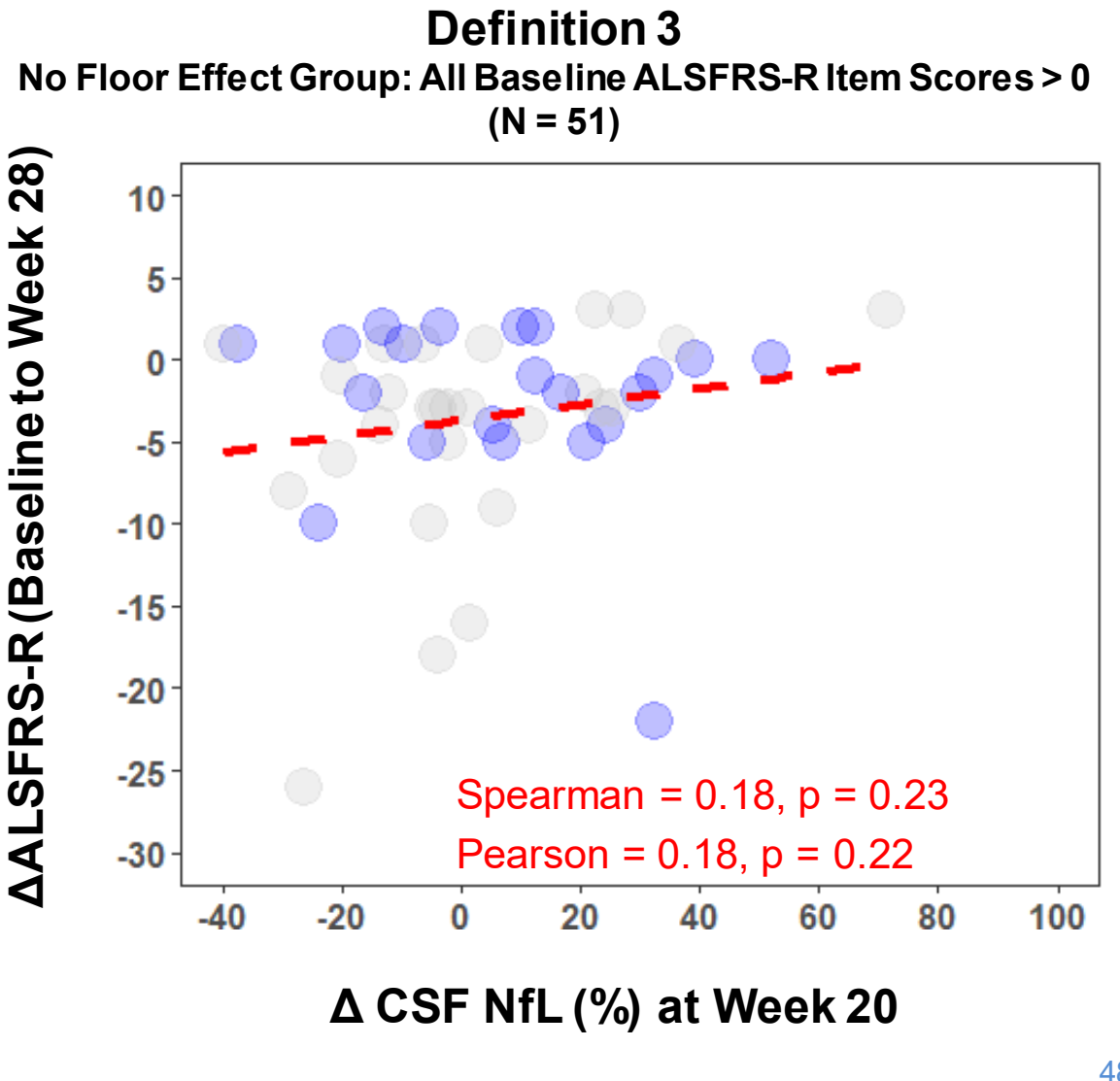
Greater Reduction of CSF NfL Levels Associated with Greater Functional Decline – Opposite of Expected



- **Greater reduction of CSF NfL** levels at Week 20 was observed in patients with **greater decline of ALSFRS-R** → **opposite** of expected
- This observation could be due to ~50% missing NfL data at Week 20, and overall relatively small changes in CSF NfL

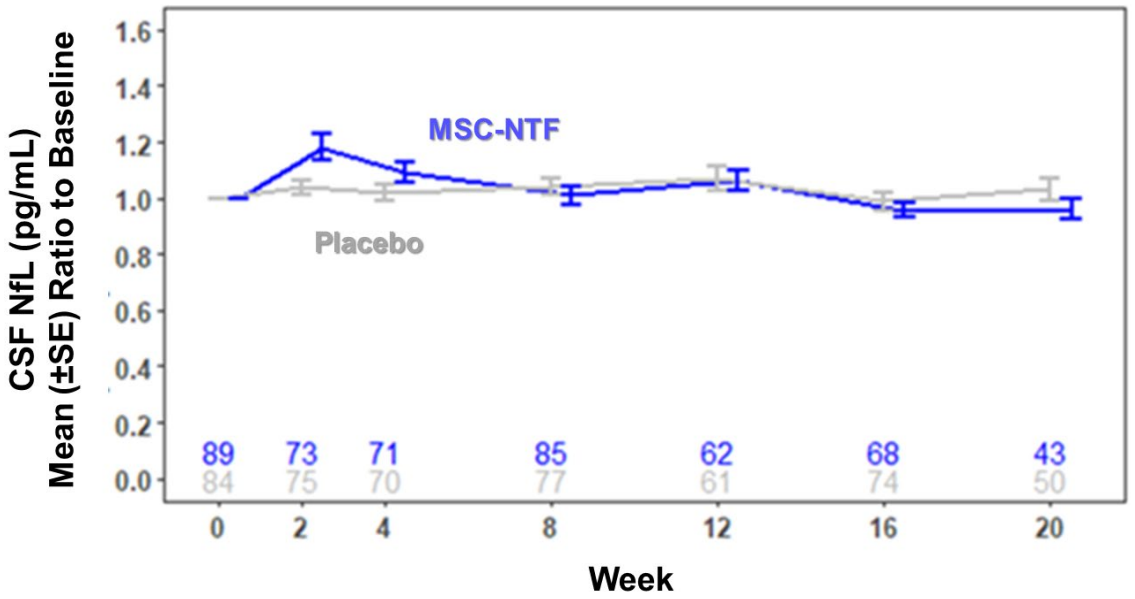
Exploratory Subgroup Analysis Based on 'Floor Effect Definition' Showed Similar Trends Between NfL and ALSFRS-R Change





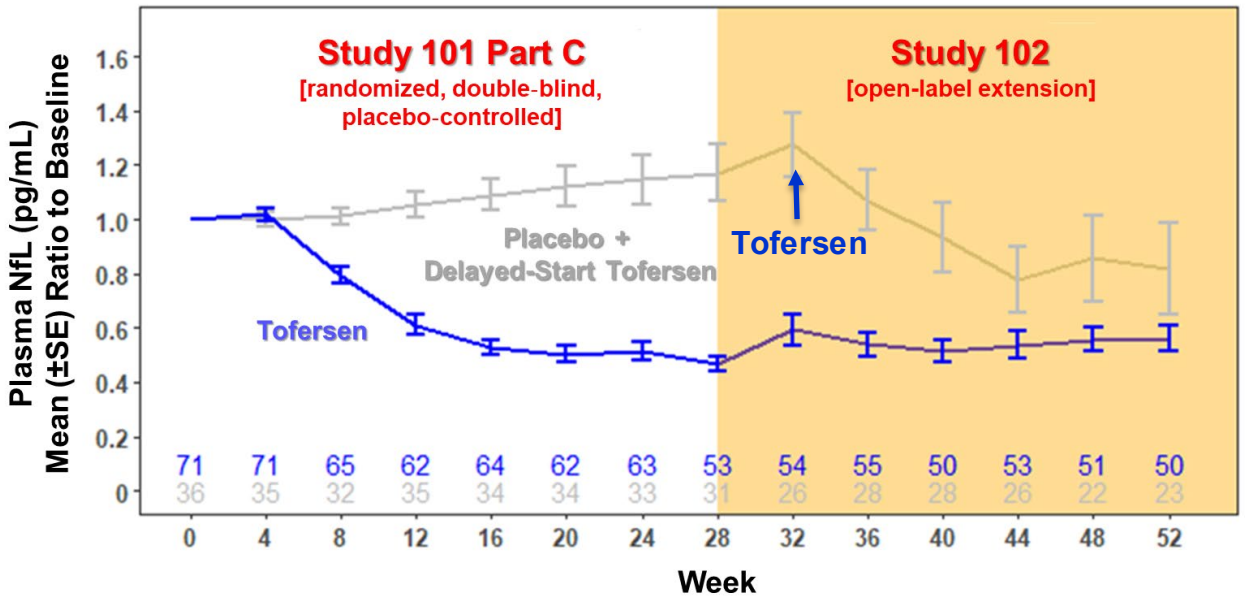
Change in NfL Over Time: BCT-002-US and Tofersen Studies

BCT-002-US (mITT population)



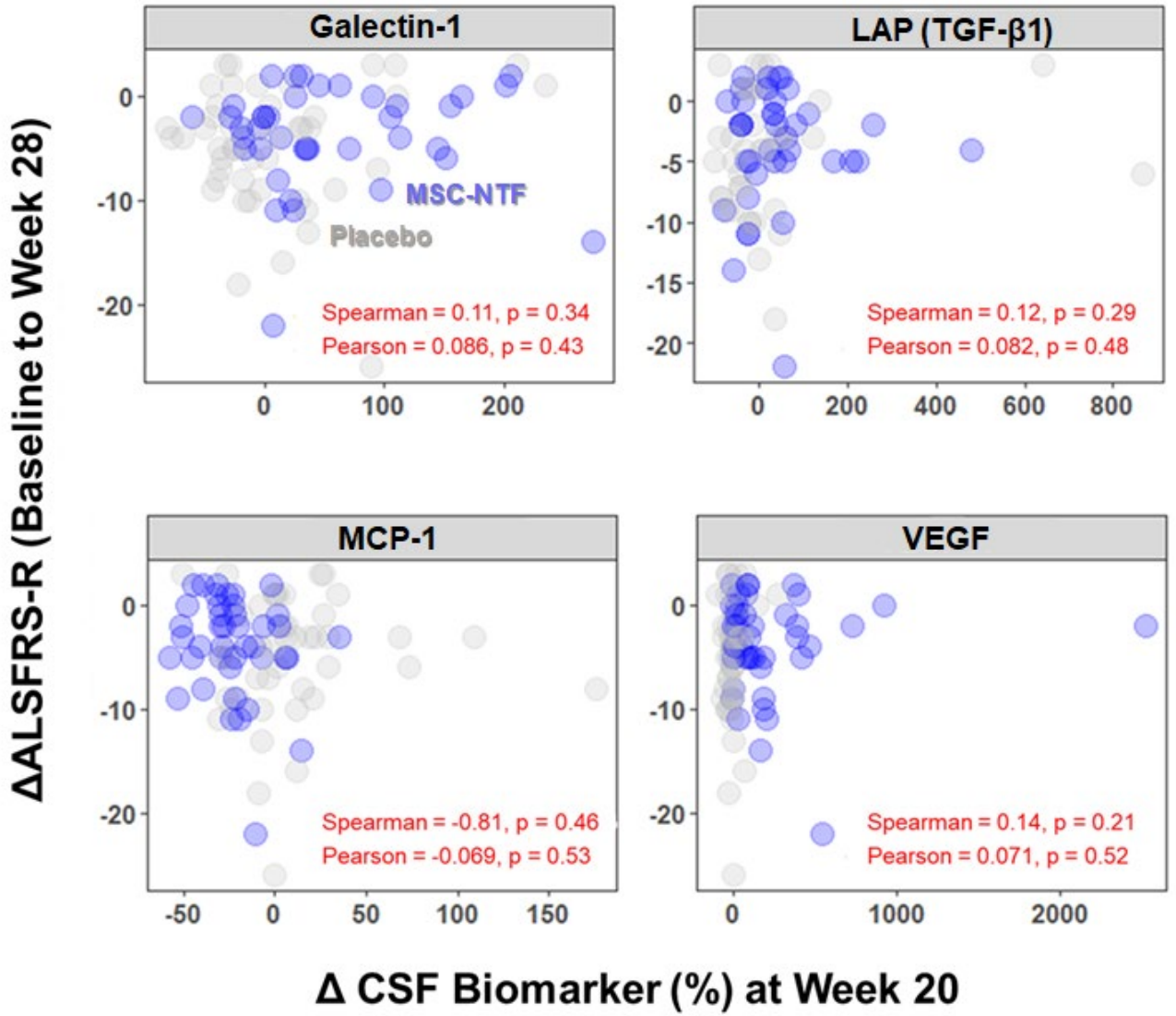
- 9% CSF NfL reduction at Week 20
- Similar for MSC-NTF and placebo

Tofersen (mITT population)



- 67% plasma NfL reduction with tofersen vs placebo, with effect sustained to Week 28 (end of the placebo-controlled study)

Biomarker Changes Do Not Predict Change in ALSFRS-R



Summary of Biomarker Analysis (I)

- Large amount of missing data for biomarker measurements at Week 20
  - Missing data could compromise the validity of the analyses, and could lead to over-estimation of the correlations between the biomarkers and efficacy endpoints
- No clear association between the change of selected biomarkers and clinical benefit
  - NfL: patients experiencing greater loss of function (measured by change in ALSFRS-R total score from baseline to Week 28) appeared to have more reduction of CSF NfL
  - Other possible ALS progression-related biomarkers: galectin-1, LAP (TGF-β1), MCP-1, and VEGF: no evident association was observed between their percent change from baseline to Week 20 and change in ALSFRS-R total score from baseline to study completion at Week 28

Summary of Biomarker Analysis (II)

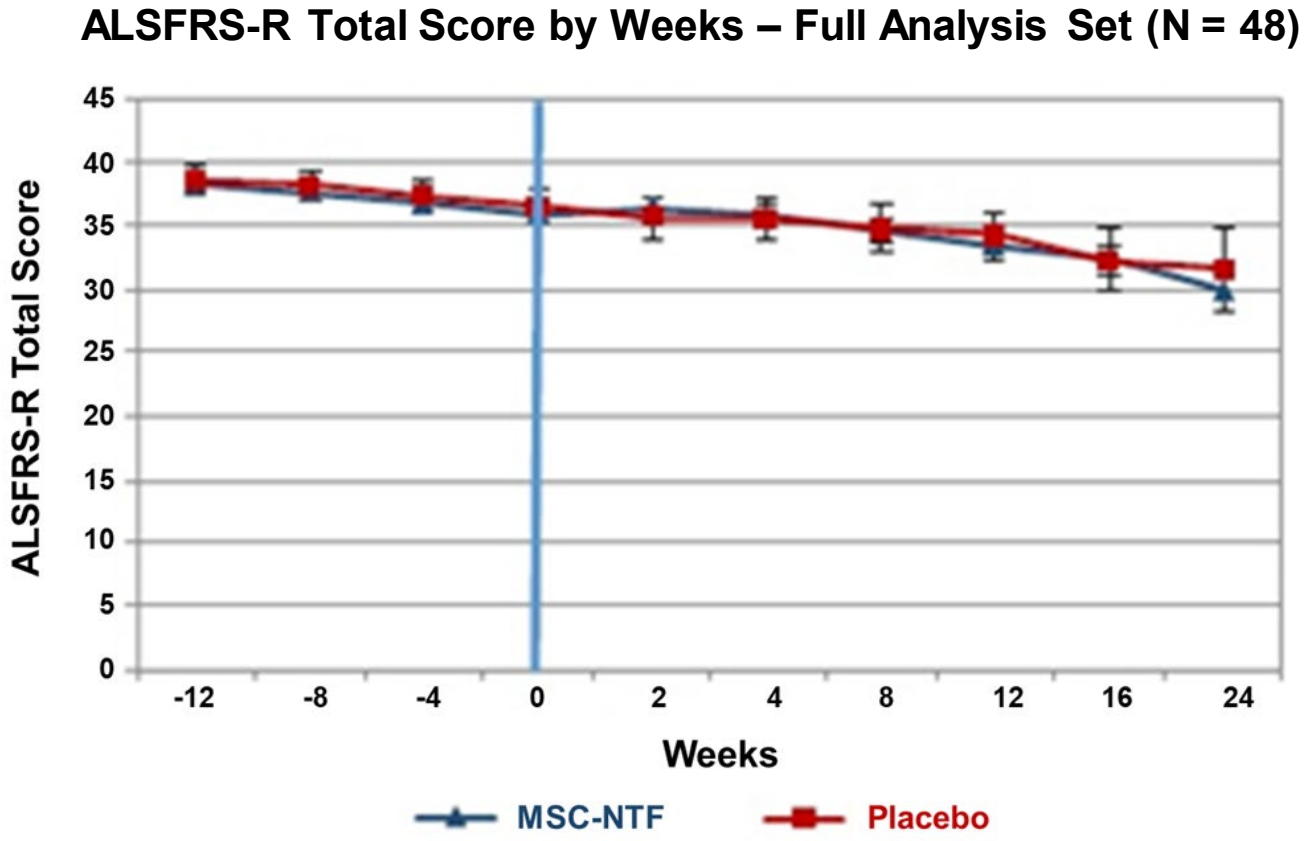
- Statistical concerns
  - Applicant's analyses did not include multiplicity adjustment → results not interpretable, because no overall Type I error rate control (any nominal "statistical significance" could be due to chance alone)
  - Post-hoc analyses are highly susceptible to bias: data are unblinded, and analyses may be selected to yield results favorable to MSC-NTF
- Available biomarker data
  - Do **not** indicate persuasive association between any assessed biomarker change and clinical benefit
  - Do **not** provide supportive evidence of effectiveness of MSC-NTF

TOTALITY OF EVIDENCE

Gumei Liu, MD, PhD
Office of Clinical Evaluation
OTP, CBER

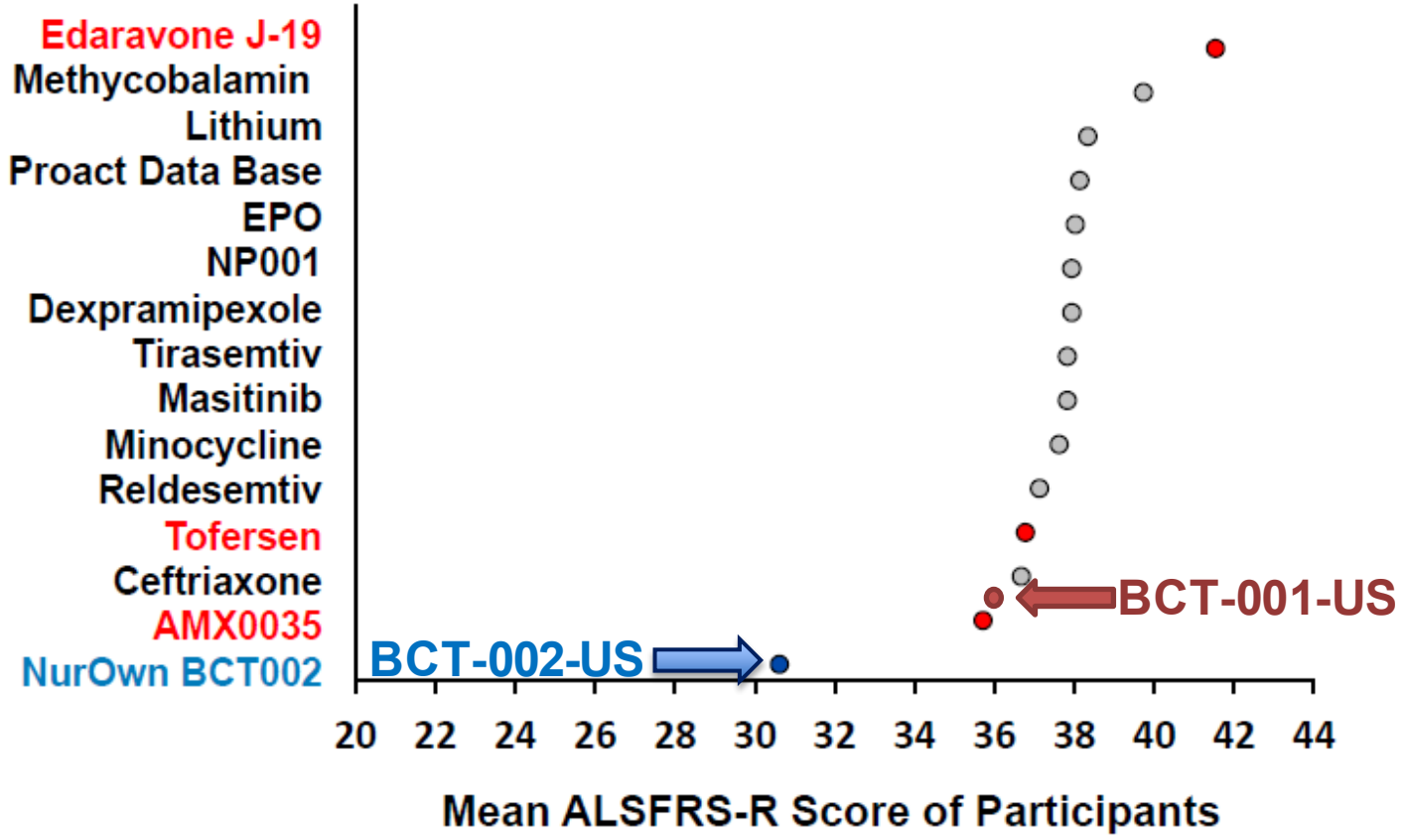
Phase 2 Study Did Not Show Efficacy

- Randomized, double-blind, placebo-controlled study
- Different treatment regimen
- Enrolled patients with less-advanced disease



Source: Applicant

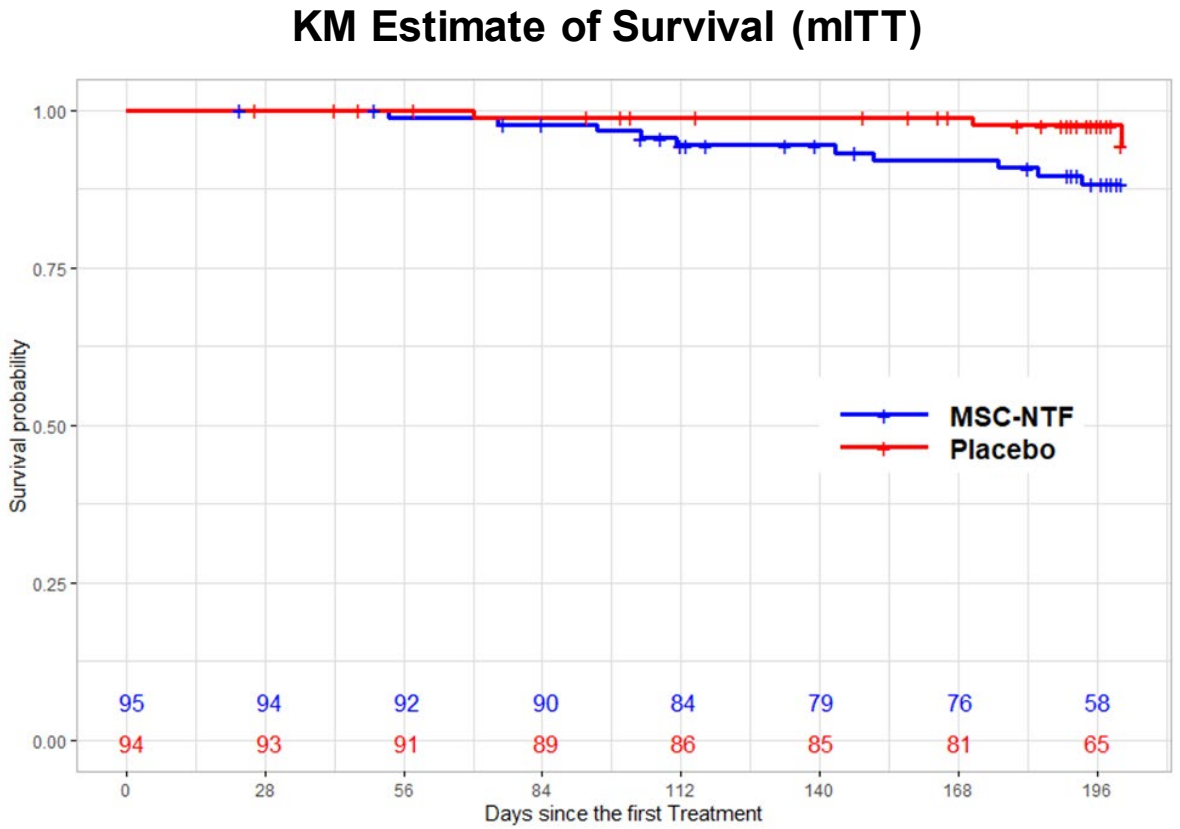
Phase 2 and Phase 3 Study Populations



Modified from Applicant's Type A meeting Presentation

Phase 3 Study Was Negative

- Failed the primary and all key secondary efficacy endpoints
- Survival was worse in MSC-NTF group at study completion



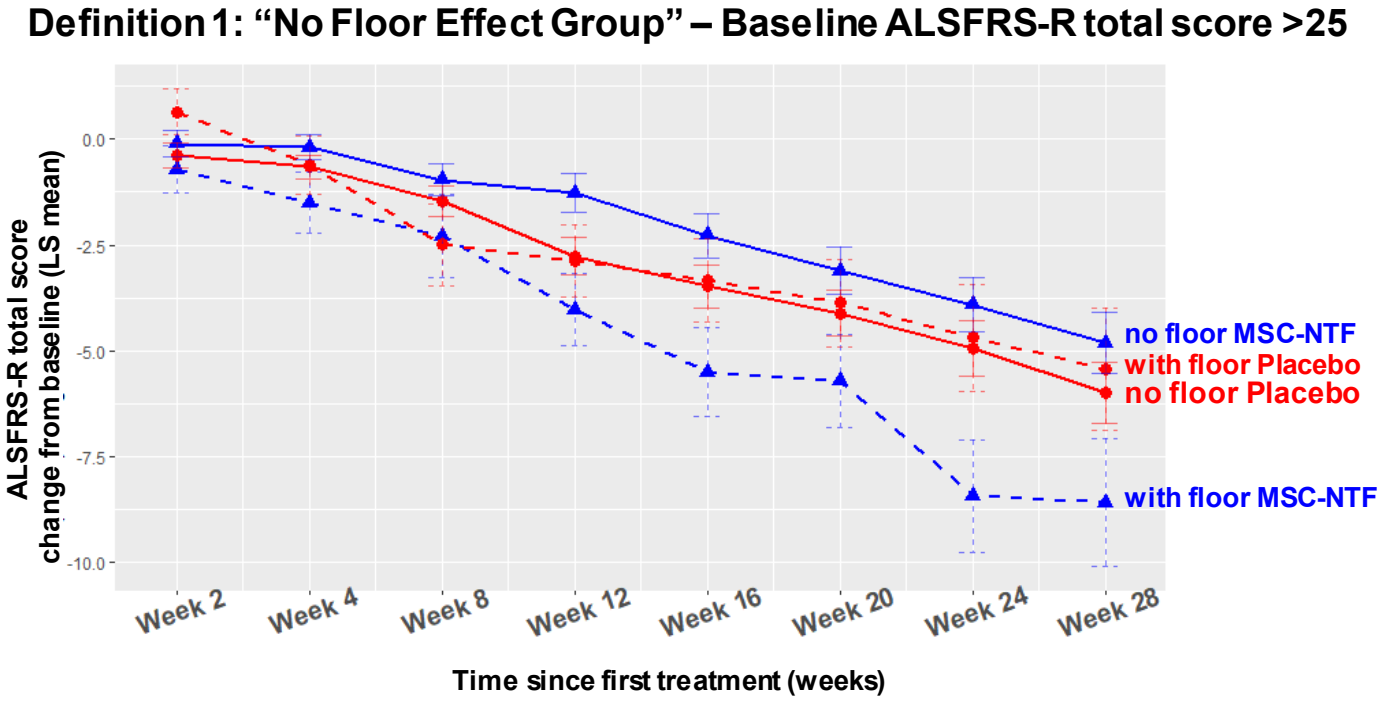
Source: FDA Statistician

Subgroup Analyses Are Exploratory

- The Applicant's claim of effectiveness primarily relied on exploratory subgroup analyses
- Subgroup analyses are subject to incidental findings
  - Higher responder rate in males treated with MSC-NTF (35.3%) compared to placebo (22%), nominal p vale of 0.04
  - Deemed spurious by Applicant (FDA concurs)
- Same principle and caution is applicable to all subgroup analyses, e.g., demographics, disease severity or other baseline characteristics
  - e.g., baseline ALSFRS-R score ≥35 (accounting for 31% of mITT)
- Can be used to generate hypotheses and potentially identify subpopulations for targeted follow-up studies

Lack of Efficacy
Not Due to "Floor Effect"

- Placebo patients showed similar decline between "with floor effect" and "no floor effect" subgroups
  - No evident "floor effect" observed in the "with floor effect" subgroup
- MSC-NTF patients in the "with floor effect" subgroup experienced larger decline than corresponding placebo subgroup
  - Worsening of function cannot be explained by "floor effect"



Source: FDA Statistician

Biomarker Analyses Do Not Support Efficacy

- In mITT population, greater reduction of NfL was associated with worse outcome (measured by decline in ALSFRS-R total score)
- No clear association between changes of the selected biomarkers and clinical benefits, e.g., galectin-1, LAP (TGF-β1), MCP-1, and VEGF

Summary & Conclusions (I)

- Two randomized, double blind, placebo-controlled studies failed to show efficacy
- Survival data were limited and unfavorable
- Subgroup analyses are exploratory
  - Lack of efficacy cannot be explained by floor effect
- Biomarker analyses are exploratory
  - Correlation analyses do not support clinical benefit
- Product characterization and manufacturing controls are inadequate

Summary & Conclusions (II)

- Totality of data submitted in this BLA do not demonstrate substantial evidence of effectiveness of MSC-NTF for treatment of patients with ALS

- New adequate and well-controlled clinical study(ies) would be needed to demonstrate substantial evidence of effectiveness of MSC-NTF for treatment of patients with ALS

Thank You!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