The Northeast ALS Consortium

ALS Clinical Therapeutic Pipeline

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Remarkable Successes in ALS

- Three FDA approved treatments
  - Riluzole, Nuedexta and Edaravone
- Understanding causes/# scientists and models
- Pioneers in
  - antisense trials for neurological disorder (SOD1)
  - spinal cord delivery of stem cells studies
  - clinical trial methodologies
- Shared clinical datasets, biosamples
- Multiple Consortium working together

…more successes

- Leaders in improving start up efficiencies
  - Central IRB for ALS studies (Treat ALS supported initiative)
- 100+ research advocates for clinical research (NEALS course)
- 100+ Experienced trial centers –US/Europe/Canada
- 60+Experienced global principal investigators for trials
- Several positive trial results (masitinib, tirasemtiv, NP001, Nurown, nuedexta, high calorie diet)

The ALS pipeline has many treatments in development for ALS that are repurposed drugs

- **Edaravone/Radicava**
- **Nuedexta**
- Masitinib
- Tirasemtiv
- Methylcobalamin
- Inosine*
- Retigabine*
- Mexiletine*
- Tocilizumab*
- Ibudilast*
- RNS60*
- NP001*
- T regs and IL2*
- AMX0035
- GDC 0134*
- Biotin
- CuAtsm*
- Pimozide*
- NurOwn™
- MSCs (South Korea)
- Neuralstem
- CIRM (Svendsen)*
- FALS SOD1/C9Orf72
  - ASOs*,aav silencing

www.neals.org www.clinicaltrials.gov
Clinical Trial Liaison: Toll-free phone: 1 (855) 437-4823
Email: alstrials@neals.org

* = recruiting currently

RADICAVA™ Clinical Pharmacology

What is RADICAVA?

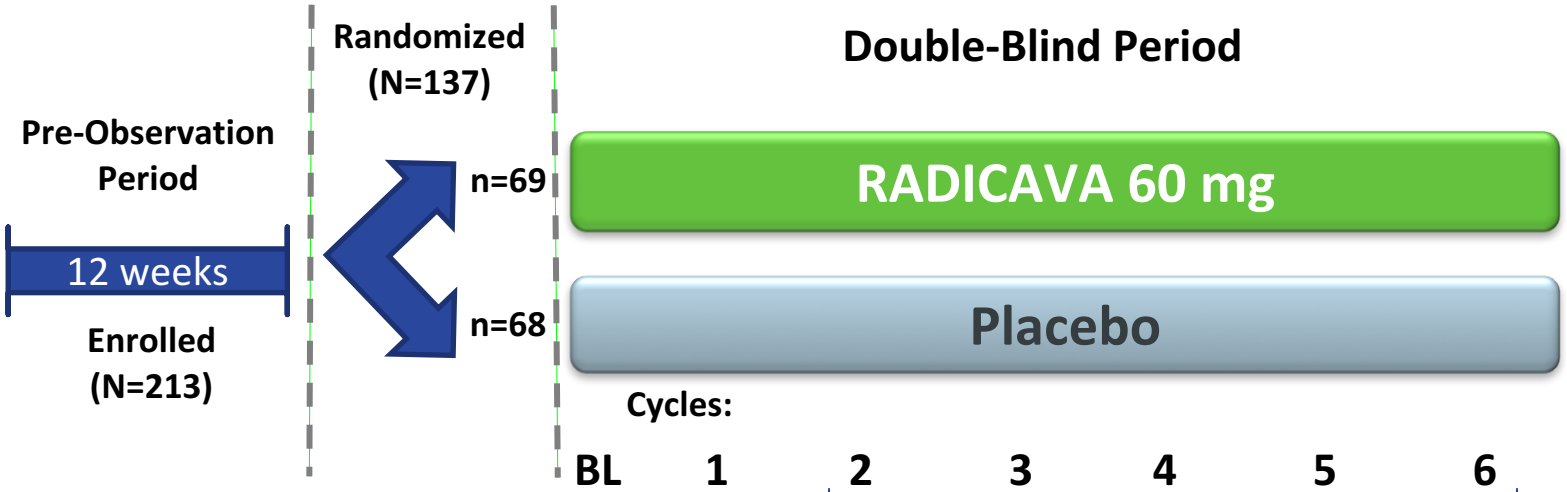
- RADICAVA is edaravone, which is a member of the substituted 2-pyrazolin-5-one class[1]

How is RADICAVA believed to work?

- The exact mechanism in ALS is unknown[1]; however, preclinical studies suggest RADICAVA may be a free radical scavenger[2]

1. RADICAVA™ (edaravone) Prescribing Information. Jersey City, NJ: MT Pharma America, Inc.; 2017.
2. Kikuchi K et al. *Int J Mol Med*. 2011;28:899-906.

RADICAVA™ Demonstrated Statistical Significance on the Primary Endpoint (24 weeks)[1,2]



Pivotal Study: Phase III randomized, double-blind, placebo-controlled study

BL=baseline; QD=once-daily.

1. RADICAVA ™ (edaravone) Prescribing Information. Jersey City, NJ: MT Pharma America, Inc.; 2017.
2. Data on File. Jersey City, NJ: MT Pharma America, Inc.

Key Inclusion and Exclusion Criteria[1,2]

• Inclusion Criteria*

- Definite or probable ALS with:
  - Patients at Grade 1 or 2 in the Japan ALS severity classification
  - Baseline score of 2 points or better on each individual item of ALSFRS-R
  - Normal respiratory function (percent-predicted forced vital capacity [% FVC] ≥80%)
  - Disease duration ≤2 years
  - Patients in whom change in ALSFRS-R score during the 12-week pre-observation is -1 to -4 points

• Exclusion Criteria*

- Patients with renal impairment indicated by creatinine clearance ≤50 mL/min within 28 days before treatment
- Decreased respiratory function and dyspnea (a score of ≤3 points on ALSFRS-R items for dyspnea, orthopnea, or respiratory insufficiency)
- History of spinal surgery after the onset of ALS or a plan for it during the study period
- Other possible causes for current symptoms not ruled out (eg, cervical spondylosis or multifocal motor neuropathy)
- Previous use of edaravone or other investigational agent use within 12 weeks prior to enrollment

*Not all inclusion and exclusion criteria used for patient enrollment in this study are listed here.

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2. Data on file. Jersey City, NJ: MT Pharma America, Inc.

Patients Were Well Matched at Baseline Between Active Drug and Placebo[1*†]

Characteristics		RADICAVA™ (N=69)	Placebo (N=68)
Gender	Male/Female, (%)	55.1%/44.9%	60.3%/39.7%
Age	Mean ± SD, (y)	60.5 ± 10.1	60.1 ± 9.6
	<65 y, (%)	66.7%	67.6%
Body weight	Mean ± SD, kg	57.9 ± 12.9	57.8 ± 9.3
Duration of disease	Mean ± SD, (y)	1.13 ± 0.46	1.06 ± 0.47
Initial symptoms	Bulbar, (%)	23.2%	20.6%
	Limb, (%)	76.8%	79.4%
ALS diagnosis	Sporadic, (%)	98.6%	97.1%
Diagnostic criteria[‡]	Definite ALS, (%)	40.6%	39.7%
	Probable ALS, (%)	59.4%	60.3%
Change in ALSFRS-R score during pre-observation period	-4,-3, (%)	17.4%	16.2%
	-2,-1, (%)	82.6%	83.8%

Most patients were taking concomitant riluzole
RADICAVA: 91.3% (n=63); placebo: 91.2% (n=62)

*Full analysis set.
†1:1 dynamic allocation of subjects to the RADICAVA and placebo groups used following 3 factors: Change (difference, -1, -2/-3, -4) in the ALSFRS-R score between baseline in the pre-observation period and completion of the pre-observation period (12 weeks); El Escorial revised Airlie House diagnostic criteria (definite/probable); and age (≥65/<65 years).
[‡]El Escorial-revised Airlie House diagnostic criteria.[2] SD=standard deviation.

1. Data on file. Jersey City, NJ: MT Pharma America, Inc.
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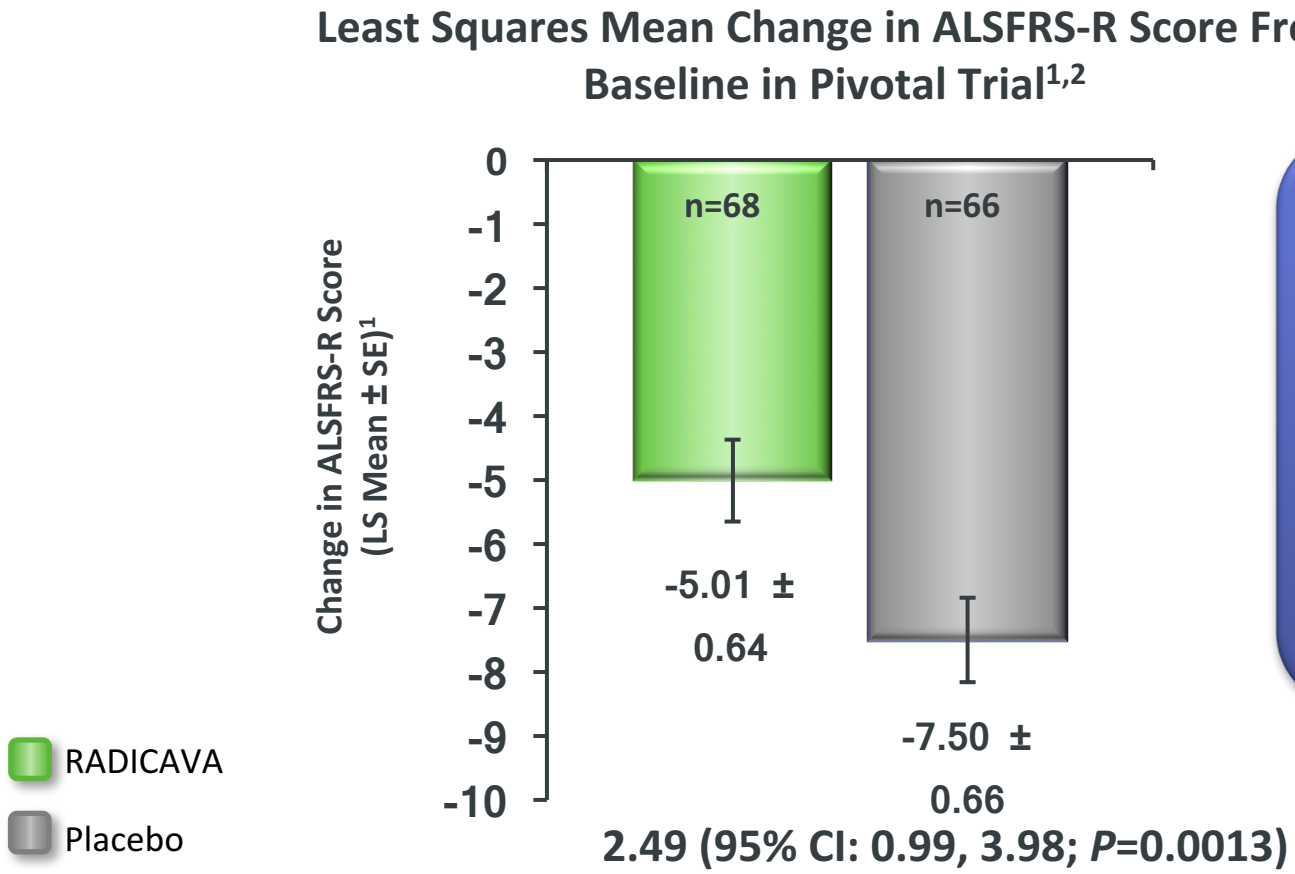
RADICAVA™ Demonstrated Statistical Significance on the Primary Endpoint (24 weeks)[1,2]



33%
less change from baseline
2.49 (95% CI: 0.99, 3.98; *P*=0.0013)

CI=confidence interval.

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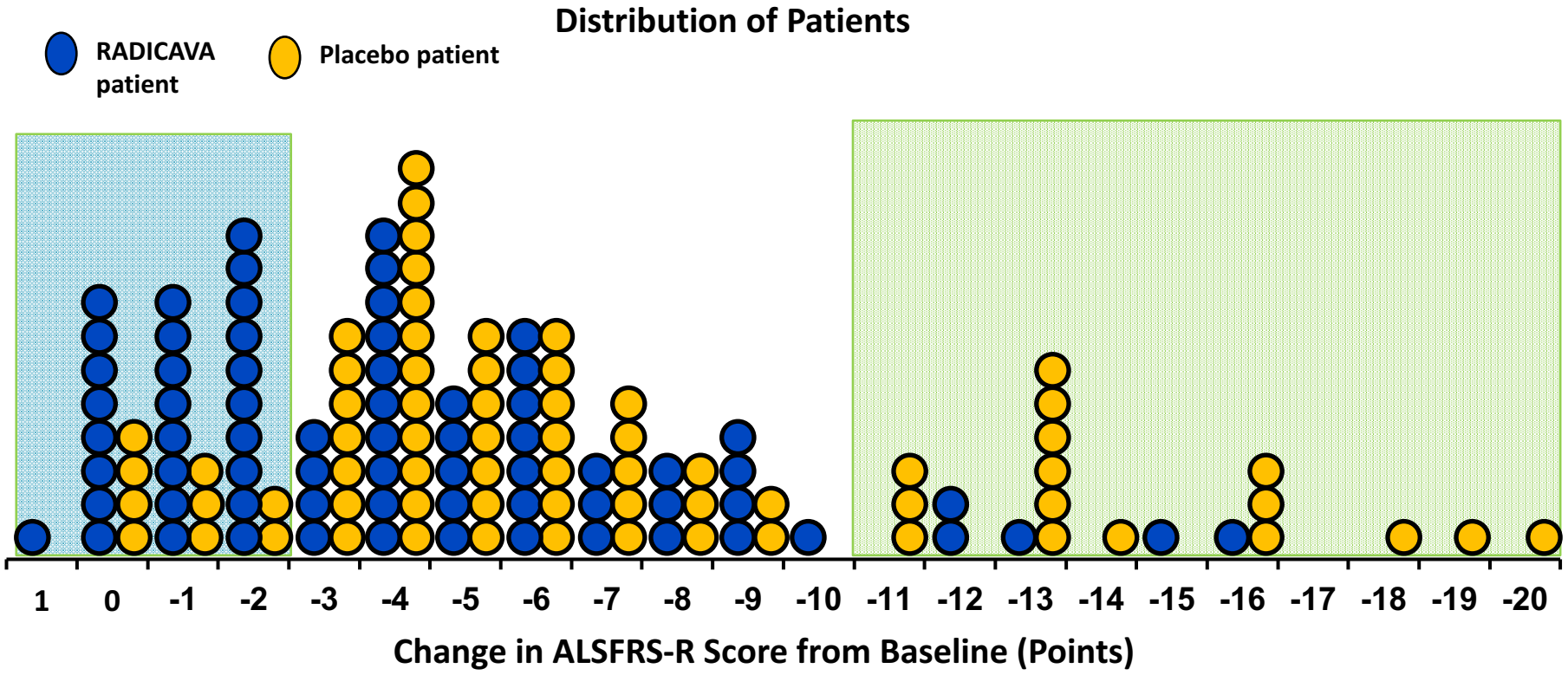
Distribution of Changes in ALSFRS-R After 24 Weeks

- Functionality over 6 cycles based on ALSFRS-R score:
  - No decline in scores in 13.0% on RADICAVA vs 5.9% on placebo
  - Minimal functional decline (≤2 points) in 39.1% on RADICAVA vs 13.2% on placebo
  - Severe functional decline (≥10 points) in 7% on RADICAVA vs 24% on placebo
- Median shift was confirmed with the Hodges-Lehmann estimator (2, 95% CI:1.00, 3.00) and the Wilcoxon rank sum test (P=0.0034) (post-hoc analysis)



Adverse Reactions From Pooled Placebo-Controlled Trials*†

Adverse Reaction	RADICAVA ™ (n=184)	Placebo (n=184)
Contusion	15%	9%
Gait disturbance	13%	9%
Headache	10%	6%
Dermatitis	8%	5%
Eczema	7%	4%
Respiratory failure, respiratory disorder, hypoxia	6%	4%
Glycosuria	4%	2%
Tinea infection	4%	2%

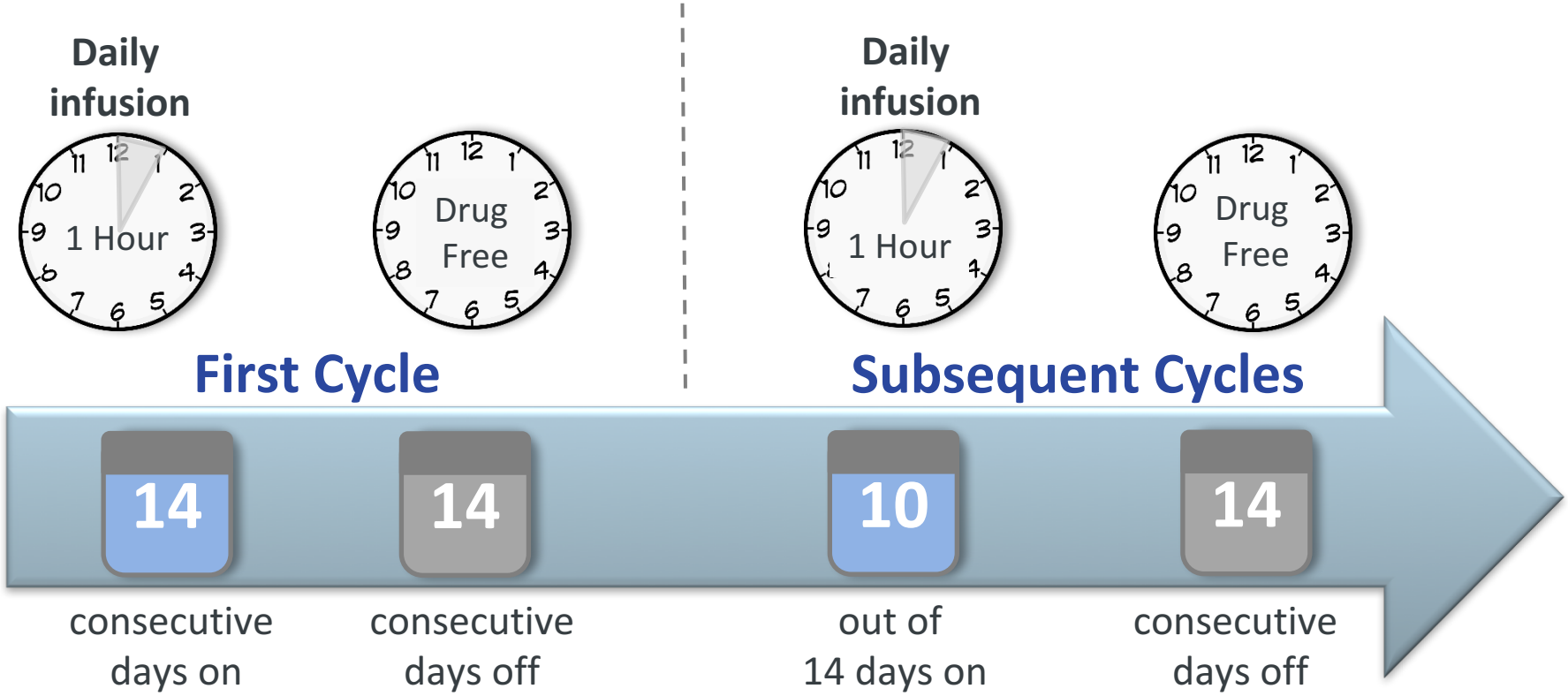
*Adverse reactions occurring in ≥2% of RADICAVA-treated patients and ≥2% more frequently than in placebo patients.

†Pooled placebo-controlled trials include two additional trials with 231 additional patients, all using the same treatment regimen.

RADICAVA ™ (edaravone) Prescribing Information. Jersey City, NJ: MT Pharma America, Inc.; 2017.

RADICAVA™ Dosing, Administration, and Infusion Schedule

- 60 mg total dose administered as two 30 mg/100 mL intravenous bags, at a rate of approximately 1 mg/minute (60 minutes per dose)
- May be prescribed concomitantly with riluzole



RADICAVA™ (edaravone) Prescribing Information. Jersey City, NJ: MT Pharma America, Inc.; 2017.

Trials were in Early/Rapid ALS. Can We Generalize the Results to Everyone?

Possibility 1: Radicava biologically works better in people with early/rapid ALS

- There may be more inflammation/oxidative toxicity in this subgroup
- We don't have any proof of this

Possibility 2: Studying people with early/rapid ALS just reduced variability and the results apply to all people with ALS?

- Variability between participants makes it challenging to *demonstrate* a drug effect in a trial
- The researchers reduced variability by focusing on a subgroup of patients

FDA Approval is broad – **All People with ALS**

- Ultimately the decision will be between a person with ALS and his/her physician.

- Must discuss with your physician before starting Radicava if you:
  - Have asthma
  - Are allergic to other medications
  - Are pregnant, breastfeeding, or planning to become pregnant

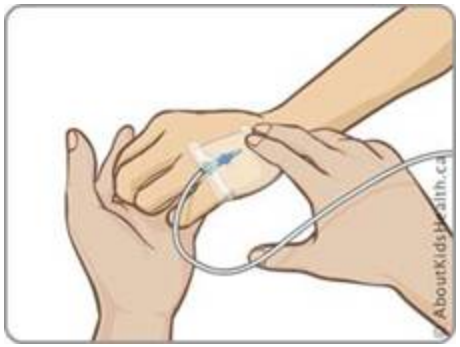
- For those in trials now: We anticipate that most trials will allow people to start Radicava and remain in the study, but this will be trial dependent.

- Edaravone infusions do not have to be given in the presence of a physician.
  - Medically speaking, can be performed at:

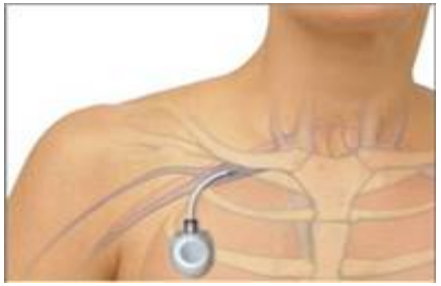
Infusion Center or Home

- Can we give the infusions at home?
  - We anticipate the infusions to be delivered at home. This needs to be discussed and decided with your provider. There may be situations that require infusion centers to administer this.
- The difference is convenience.

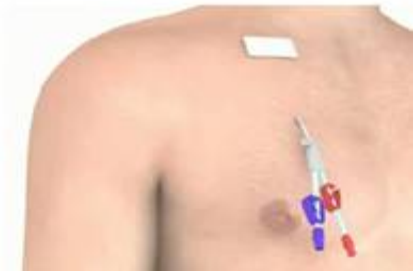
Various options for long term drug administration



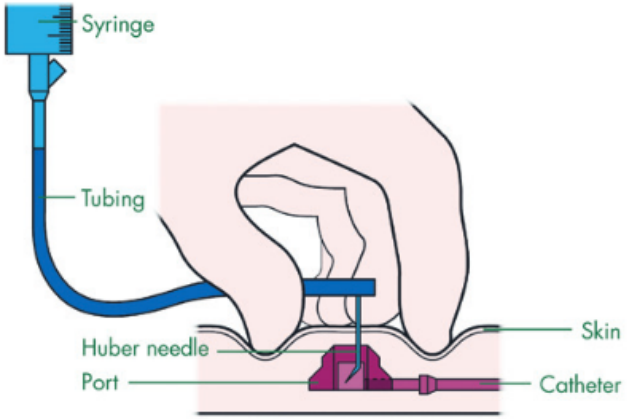
Peripheral IV

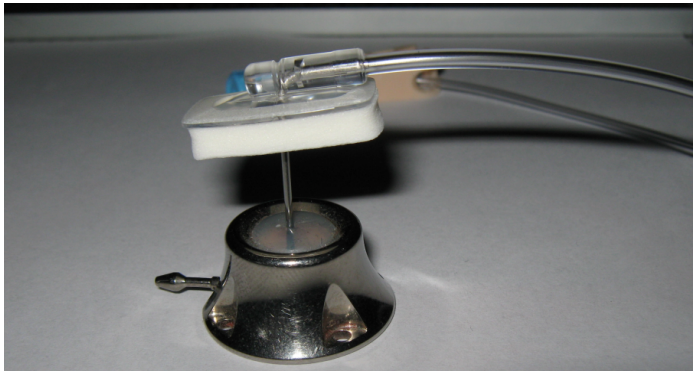


Port-a-cath



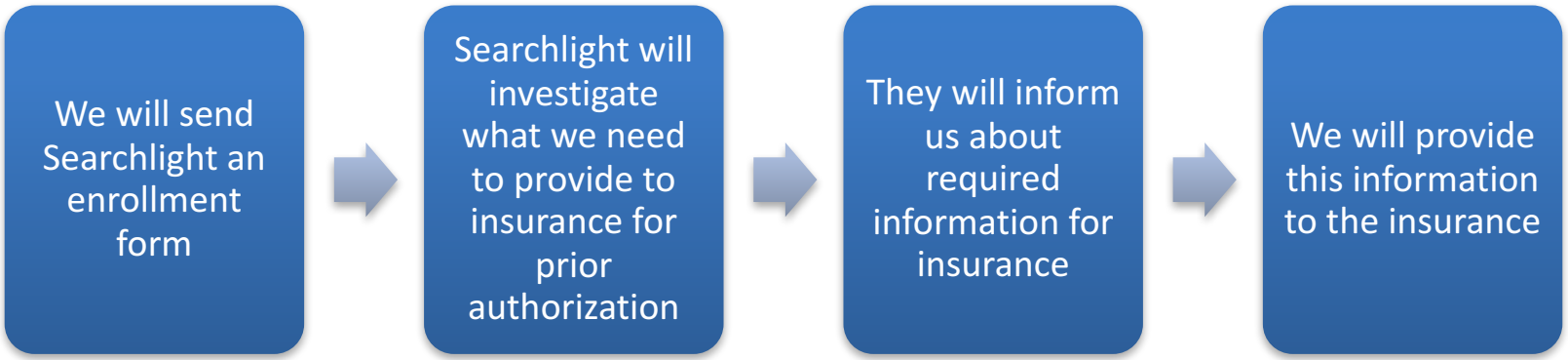
Central line





Insurance Coverage: We don't know yet

- Cost is about $150,000 per year for drug; this does not include cost of infusions
- All infusions require prior authorization from insurance.
- Because this is a new drug we anticipate insurances will require more information for prior approvals
- MT Pharma has contracted with a company to set up a hub (Searchlight) to help with insurance prior authorization
  - May provide access to co-pay assistance and nursing Q&A



- Different insurances have different requirements.
- The process can take 3-4 weeks.
- Searchlight will probably start helping with prior authorizations in July.

Additional Resources

- MT pharma's Medical information call center:
  1-888-292-0058

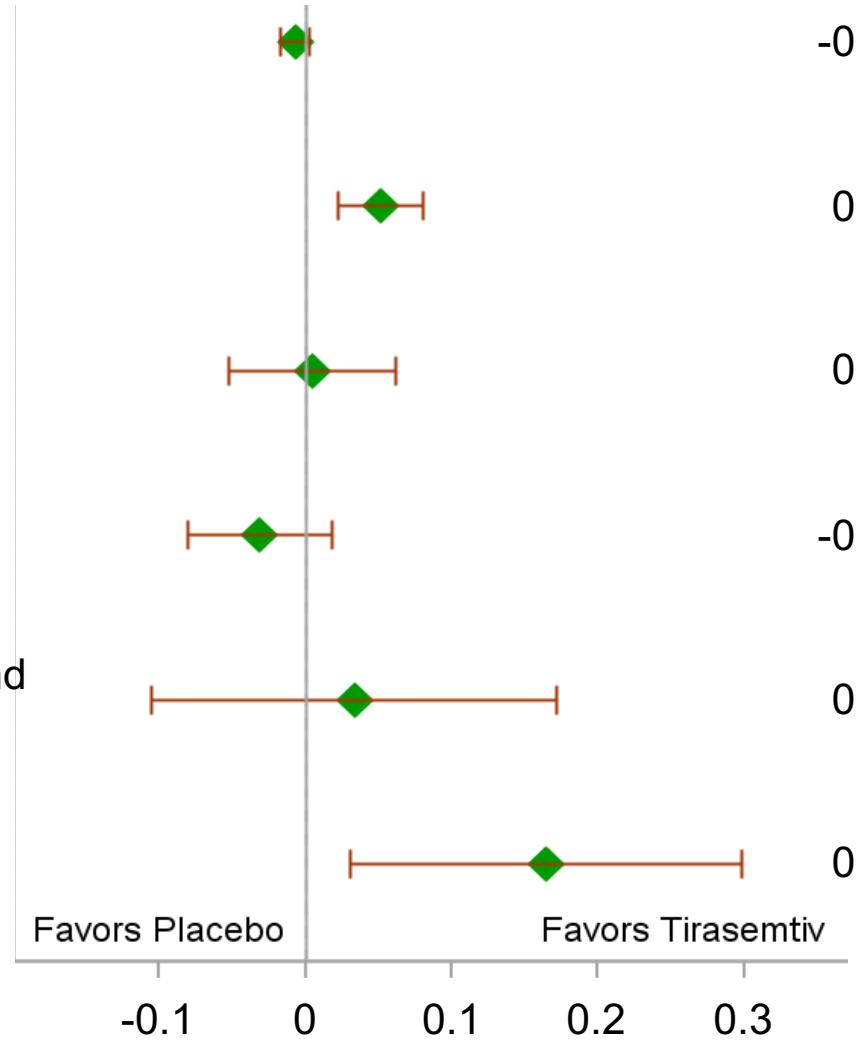
- Call Searchlight for information and support:
  - 844-SRCHLGT (844-772-4548)

- Sign up with MT Pharma's Patient ListServe
  - www.radicava.com/patient/

- ALS Association Website: www.alsa.org
- MDA Website: www.mda.org
- NEALS Website: www.NEALS.org

Slope of Change from Baseline: Difference between *Tirasemtiv* and Placebo

Endpoint	Difference	p-value
ALSFRS-R (points/day)	-0.007	0.1572
% Predicted SVC (percentage points/day)	0.051	0.0006
MVV (L/min/day)	0.004	0.8799
SNIP (cm H_2O/day)	-0.031	0.2108
Grip Fatigue – Weaker Hand (seconds/day)	0.033	0.6372
Mega-Score (% change/day)	0.165	0.0158



BENEFIT-ALS

Vitality ALS

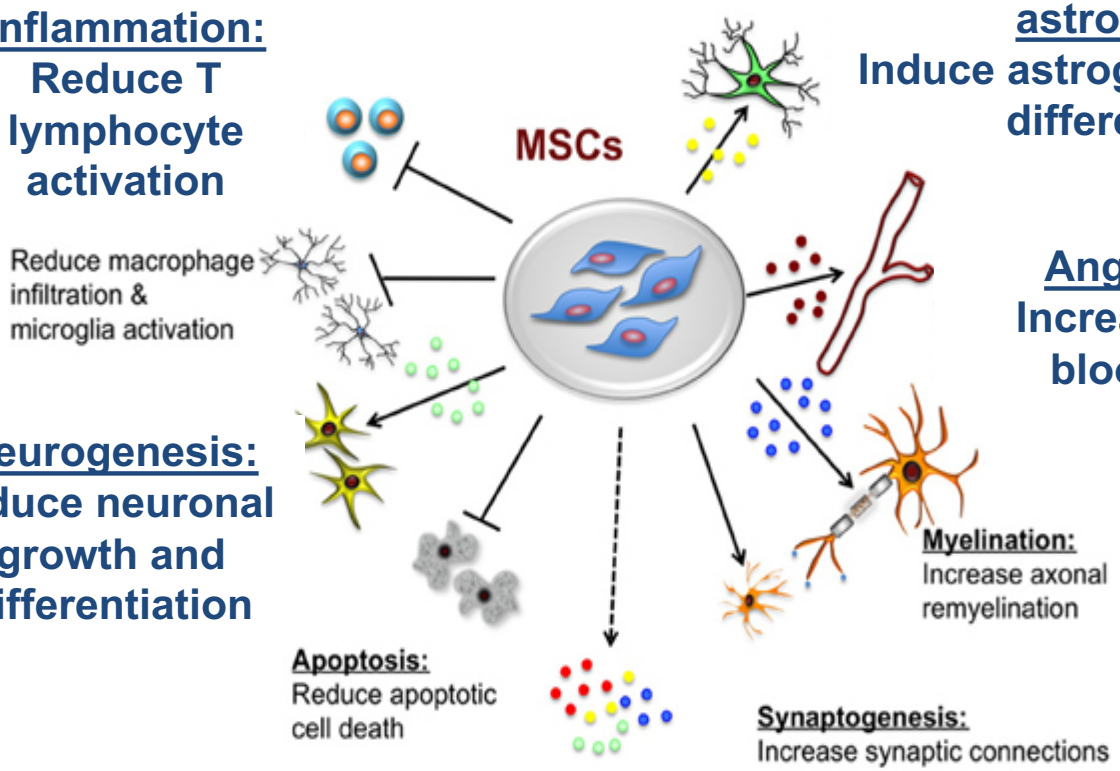
- A phase 3, trial testing 3 doses of tirasemtiv
- 48 weeks of active treatment; however, primary outcome is change in vital capacity at 24 weeks
- Secondary outcomes include time to important respiratory outcomes, muscle strength after 48 weeks
- Tolerability of tirasemtiv addressed with a 2 week open label period prior to randomization
- Enrollment complete as of August, 2016

MSC therapeutic effects

The beneficial effects of MSCs are primarily mediated by paracrine mechanisms

Inflammation:
Reduce T lymphocyte activation

Increase reactive astrocytosis:
Induce astroglial growth and differentiation



Trophic factors:
Secretion of neurotrophic and angiogenic factors

From: Castillo-Melendez, M et al Frontiers in Neuroendocrine Science 24 Oct 2013

BCT-001-US Clinical Trial overview

Phase II Study:

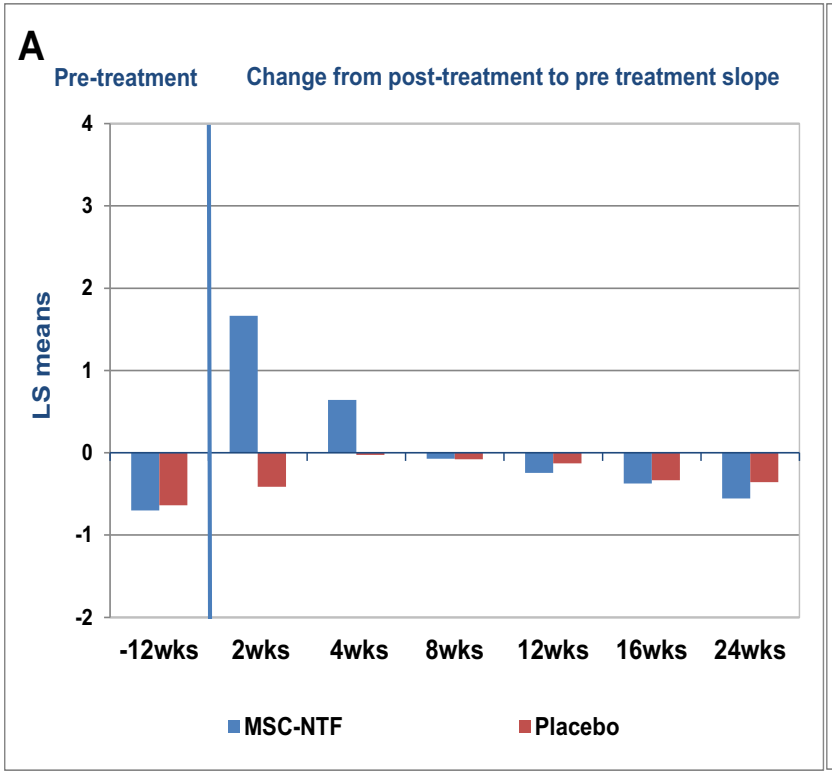
- 2 FDA approved manufacturing sites
- 48 ALS Patients, 16 patients/site
- 36 treatment, 12 randomized to placebo
- Combined Intrathecal + Intramuscular administration
- Treatment protocol 9 months (3 months pre- and 6 months post-transplant)

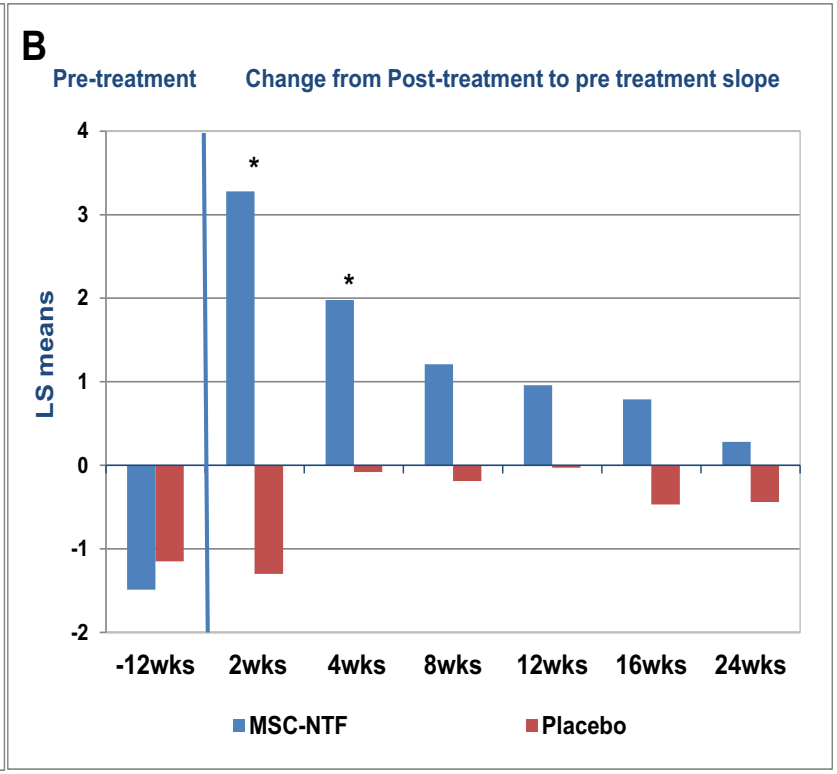
Baseline Characteristics were balanced & treatment found safe

Disposition/Demographics	MSC-NTF (N=36)	Placebo (N=12)	All Subjects (N=48)
Male Gender (%)	25 (69.4)	10 (83.3)	35 (72.9)
Mean Age (SD)	50.3 (11.9)	53.5 (9.11)	51.1 (11.27)
EEC Possible	3 (8.3)	1 (8.3)	4 (8.3)
Laboratory-Supported Probable	5 (13.9)	1 (8.3)	6 (12.5)
Probable	16 (44.4)	7 (58.3)	23 (47.9)
Definite	12 (33.3)	3 (25.0)	15 (31.3)
Months Since ALS Diagnosis – Mean (SD)	9 (5.6)	9 (4.6)	9 (5.3)
Months Since First Weakness – Mean (SD)	18 (3.8)	17 (3.1)	17 (3.6)
Completed*	33 (91.7)	10 (83.3)	43 (89.6)
Discontinued Follow-up	3 (8.3)	2 (16.7)	5 (10.4)

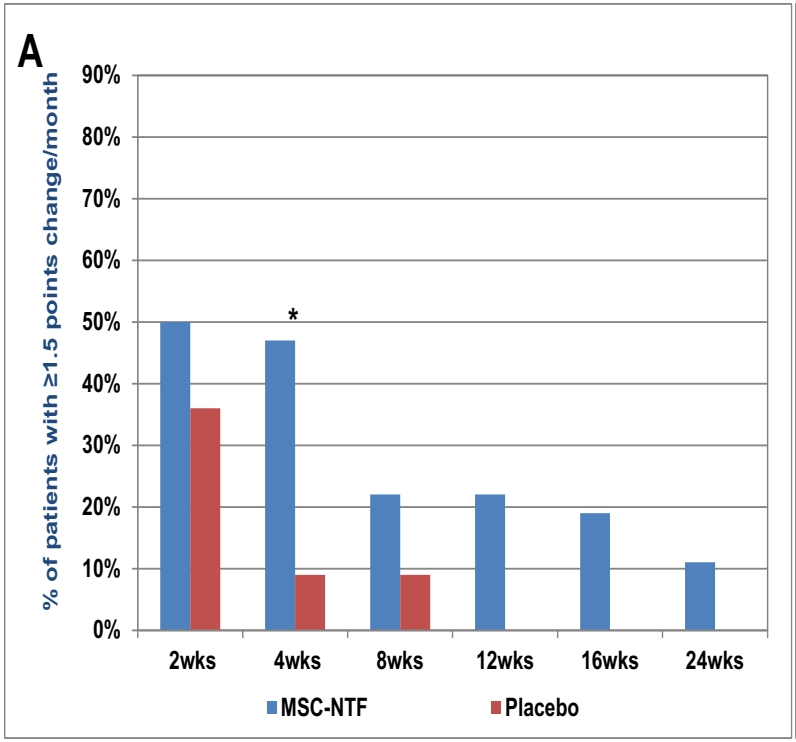
* ITT analyses included all participants

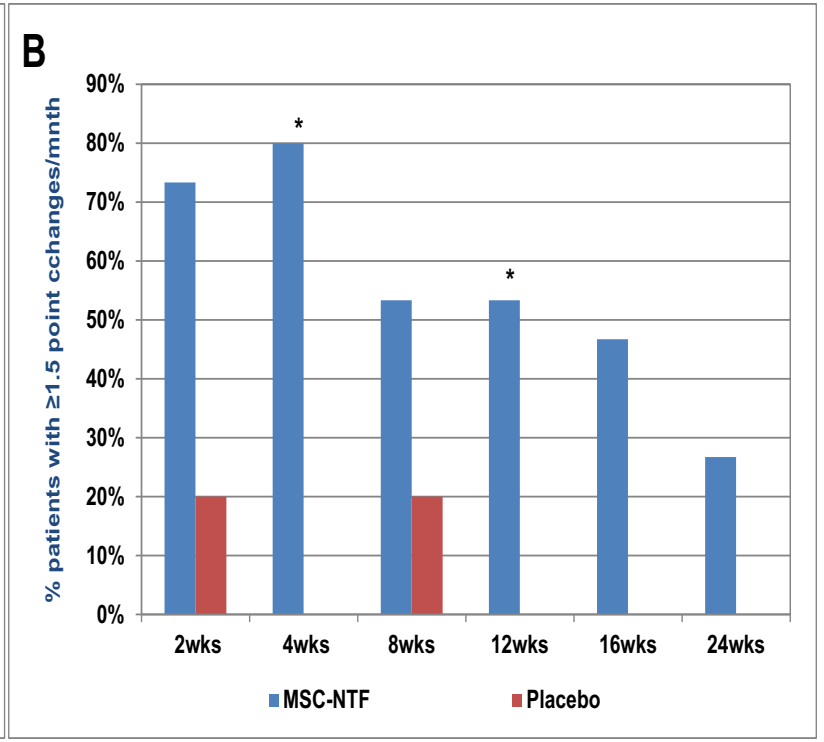
ALSFRS-R: Mean slope over time shows initial slowing in the treatment group





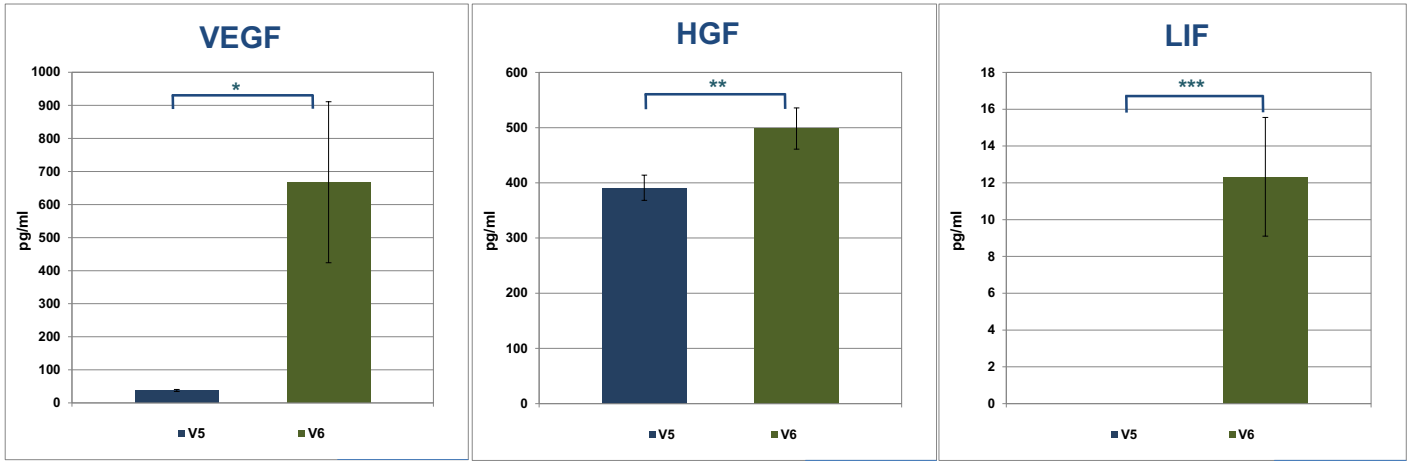
Responder analyses: ≥1.5 point ALSFRS-R slope improvement over the post treatment follow up period



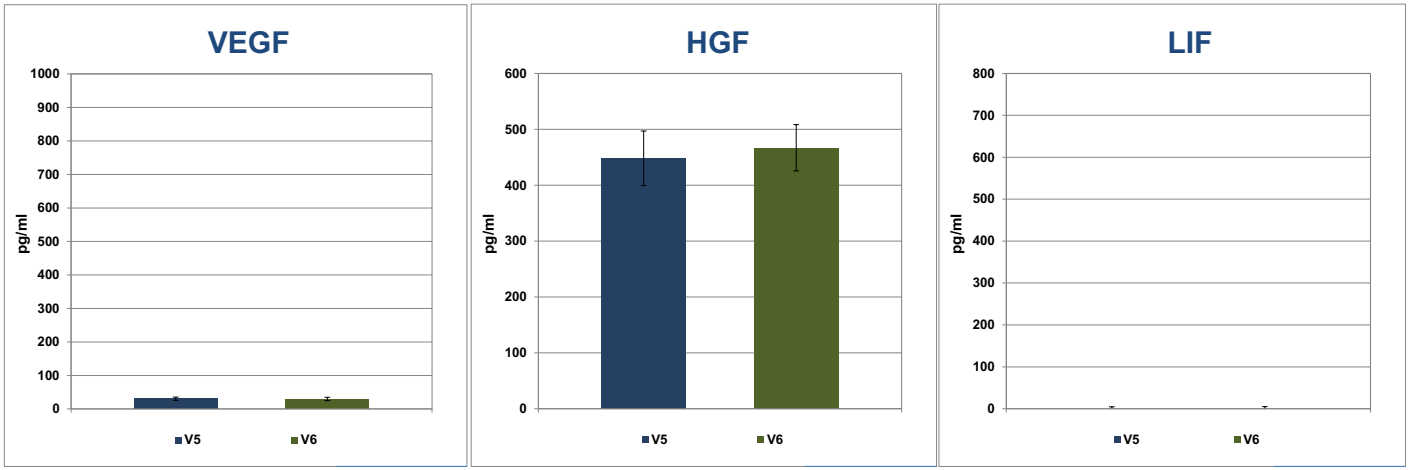


Neurotrophic factors
increased in MSC-NTF group at Week 2

MSC-NTF cells



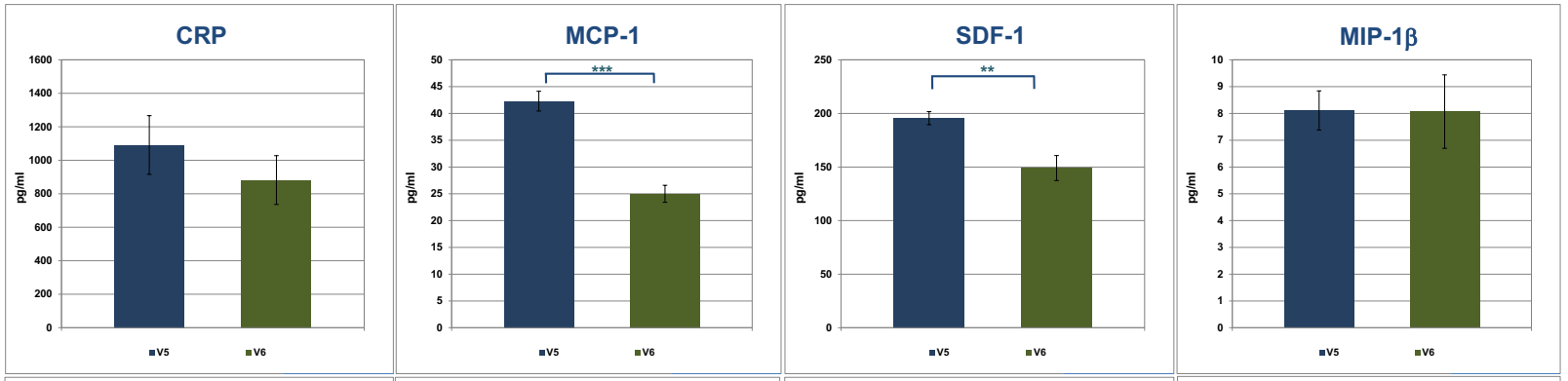
Placebo



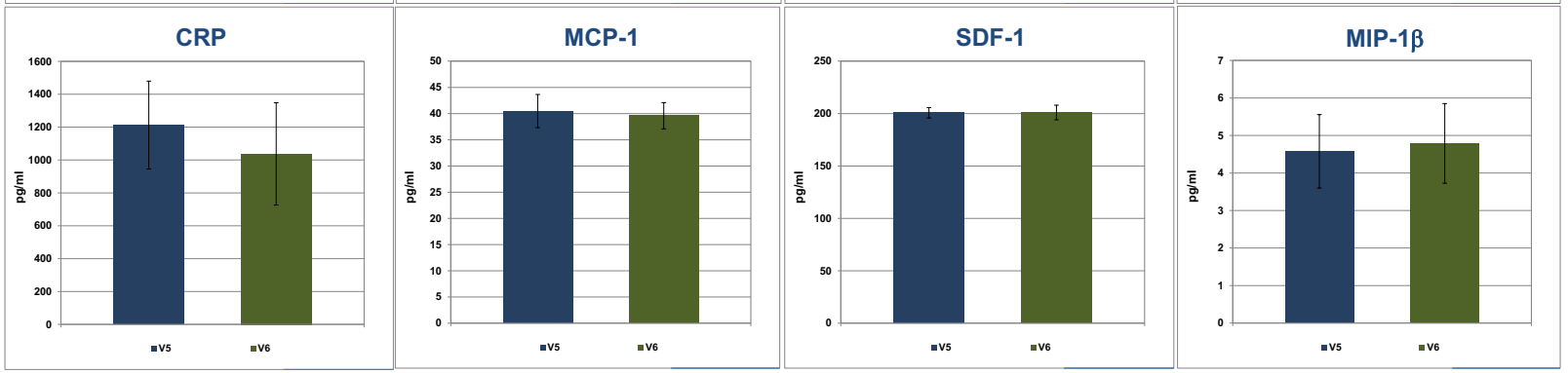
Average ± SEM
* p< 0.05 ** p<0.01 *** p< 0.001
Ref.: Table 14_02_9

Some inflammatory markers decreased in CSF in MSC-NTF group

MSC-NTF cells



Placebo



C-reactive protein (CRP) is a liver produced protein widely used as an inflammation marker due to its high magnitude of increase in the serum and its correlation with inflammation

Monocyte chemoattractant protein-1 (MCP-1), induces chemotaxis of macrophages and microglia, leading to pathological microgliosis and inflammatory activation. MCP-1 levels is significantly higher in the CSF of ALS patients . A positive correlation was found between MCP-1 levels in CSF of ALS patients and the total Norris scale

Stromal cell-derived factors 1-(SDF-1) is a small cytokine which activates leukocytes and is often induced by proinflammatory stimuli.
Activates microglia

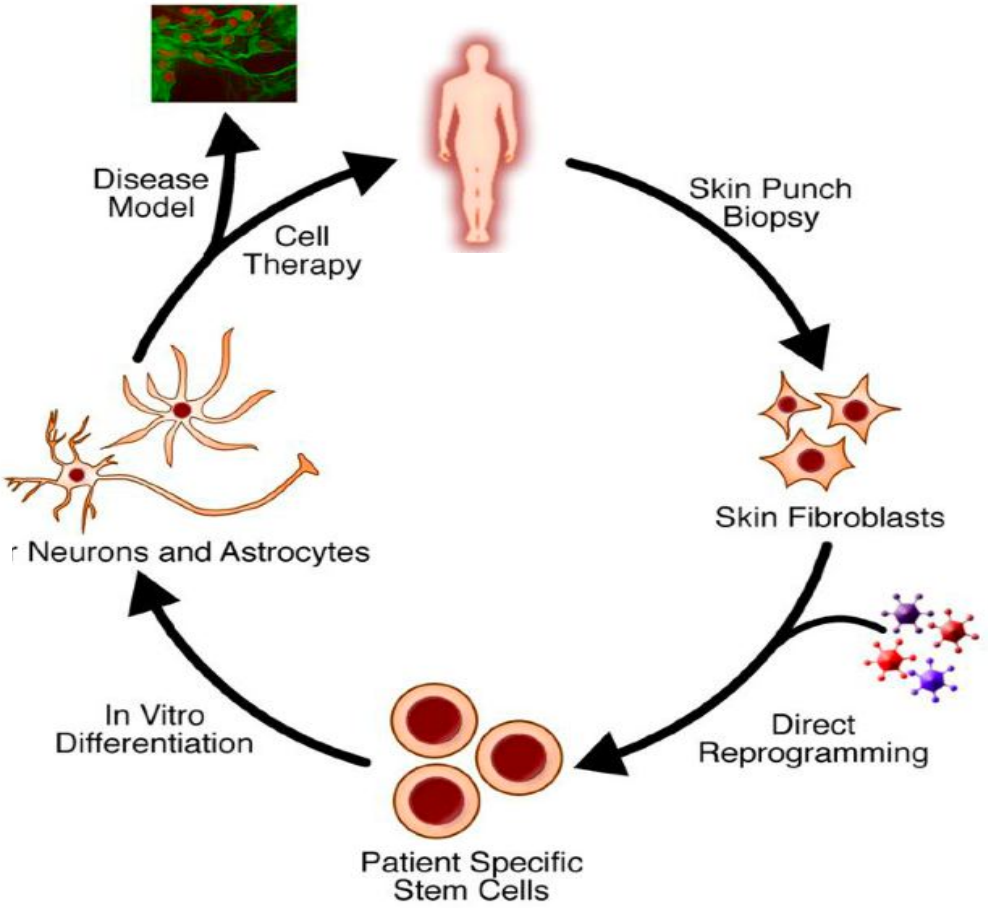
Macrophage Inflammatory Proteins (MIP) belong to the family of chemotactic cytokines. It is crucial for immune responses towards infection and inflammation

Average ± SEM ** p<0.01 *** p< 0.001
Ref.: Table 14_02_9

MSC-NTF was safe and well tolerated.

- Related AEs occurred immediately after treatment were self-limited
  - pyrexia/chills, arthralgias, headache
- A single administration of MSC-NTF demonstrated preliminary signs of benefit in ALSFRS-R and an encouraging CSF biomarker profile
- Next Step: Larger confirmatory trial with repeat dosing at 8 to 12 weeks.

Stem Cell-Based Disease Modeling to Investigate Excitability in Human Motor Neurons - Retigabine



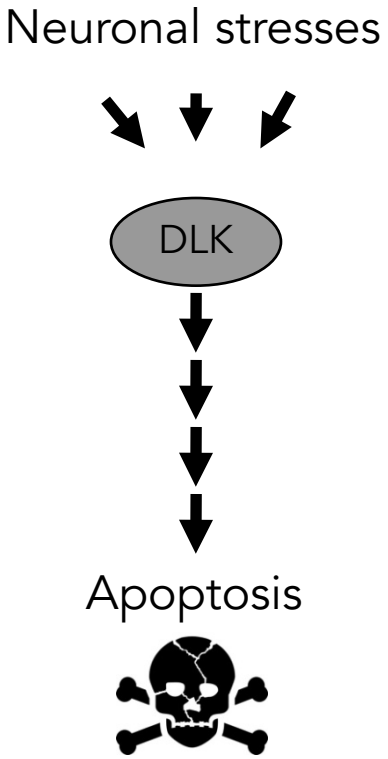
Sites involved in Retigabine Study

- Barrow Neurological Institute (Arizona)
- Beth Israel Deaconess Medical Center (Massachusetts)
- Cedars Sinai Medical Center (California)
- California Pacific Medical Center (California)
- Duke University (North Carolina)
- Georgia Regents University (Georgia)
- Johns Hopkins (Maryland)
- Hospital for Special Surgery (New York)
- Mayo Clinic (Florida)
- Massachusetts General Hospital (Massachusetts)
- University of California Irvine (California)
- University of Michigan (Michigan)

For more information, contact Sylvia Baedorf Kassis at sbaedorfkassis@partners.org or (617) 643-5582.

Genentech is developing GDC-0134 as a brand new way to fight ALS

- GDC-0134 is an oral drug designed to block DLK (dual leucine zipper kinase)
  - DLK is an enzyme found in nerve cells of the brain and spinal cord
  - DLK leads to activation of cell death pathways, causing nerve cells to die when they come under stress
  - Basic science experiments show that blocking or removing DLK is beneficial in a variety of models, including the SOD1 mouse model of ALS



- Therefore, the hope is that GDC-0134, by blocking DLK, may prevent motor nerve cells from dying in ALS

GDC-0134 is being tested in Phase I Currently enrolling*!*

- Participants with ALS are needed for a Phase I Multiple Ascending Dose Study
  - Small groups of particiapnts will take a given dose of GDC-0134 or placebo once daily for 28 days
  - The first group will try a low dose; if GDC-0134 is safe at this low dose, then the next group will try a higher dose; and so on…
  - The objective is to discover what doses of GDC-0134 are safe, and what the possible side effects may be

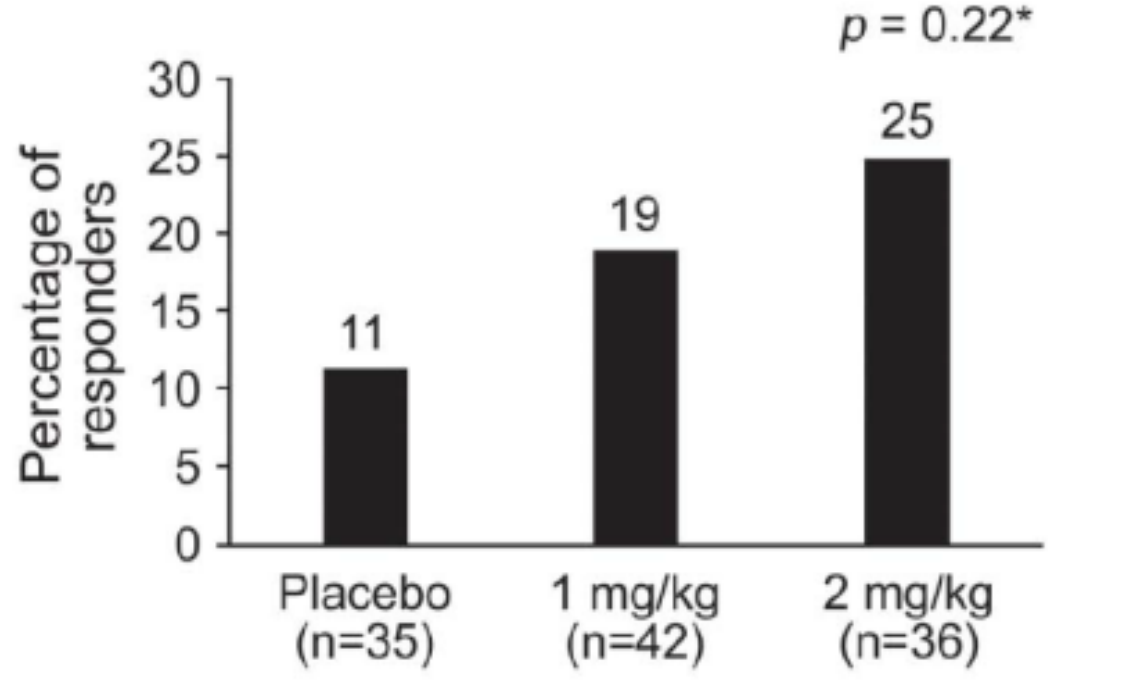
- While a Phase I study will not prove whether or not GDC-0134 successfully treats ALS, it is a necessary step towards that goal

- Please see clinicaltrials.gov for more details on this Phase I study, and for a list of centers conducting the study

Evidence of immune system's role

- Inflammatory macrophages phagocytize apoptotic and non-apoptotic neurons in ALS spinal cords (*Graves et al, 2004*)
- wtSOD1 induces IL-1 and IL-6 production in PBMCs from ALS patients (*Fiala, 2010*)
- PET imaging shows microglial activation in ALS brains (*Turner et al, 2004*)
- Regulatory T cells are reduced in ALS animal models and in humans with aggressive disease (Appel, 2015)

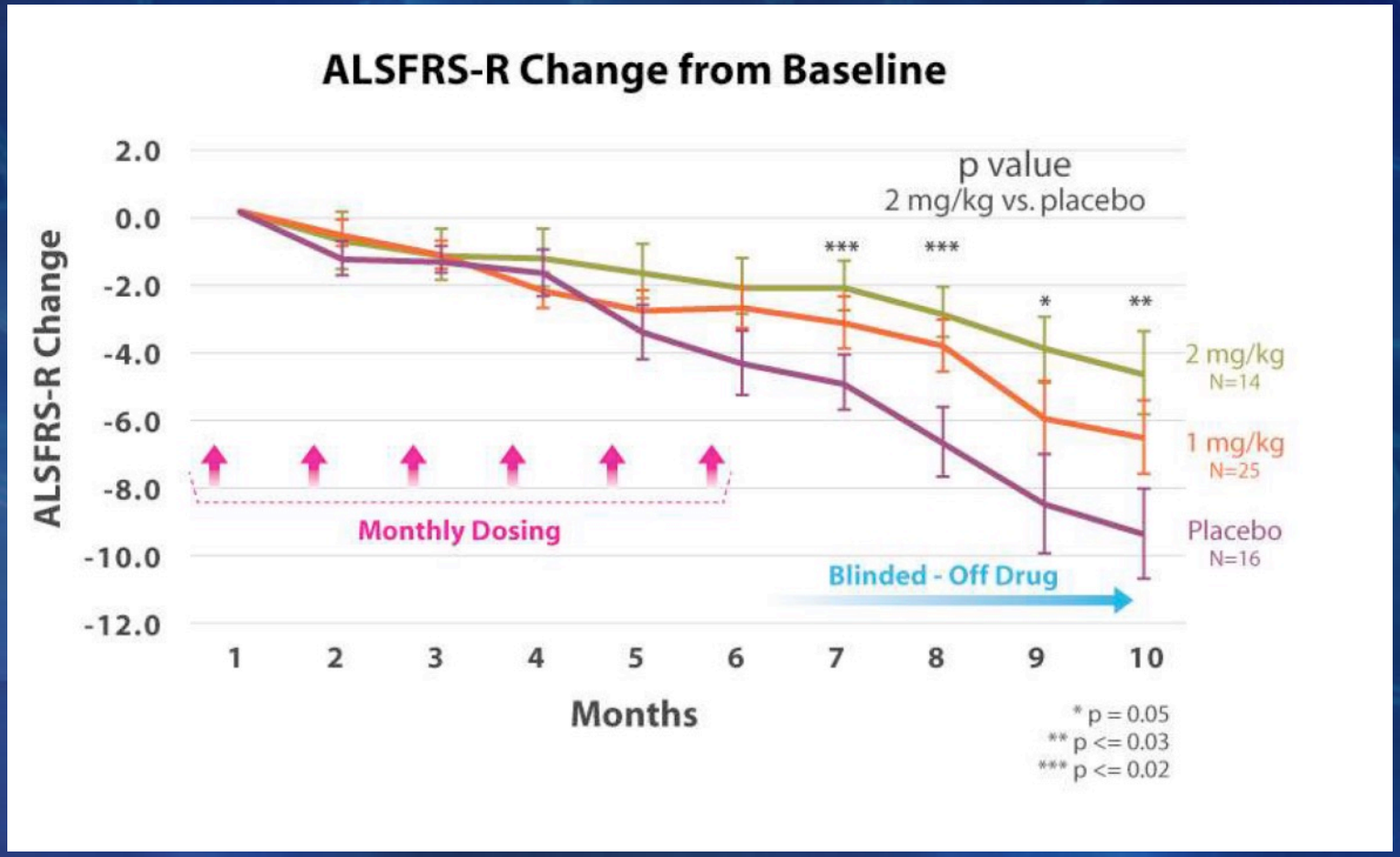
Neuraltus Phase 2a Study



Responder analysis: how many participants did not change in ALSFRS-R

From Miller et al., 2015

Change in ALSFRS-R in Patients with high c-reactive protein



Patients with CRP greater than median level

Courtesy Robert Miller

New study of NP001 now enrolling

- Will preselect participants for the presence of inflammation as measured by c-reactive protein.
- Double blind, placebo controlled trial
- Primary outcome measure will be change in ALSFRS-r
- 120 participants, 6 month treatment
- www.clinicaltrials.gov for sites

Masitinib in ALS

- Developed by AB Science
- Masitinib is a tyrosine kinase inhibitor
  - Inhibits degranulation of mast cells
  - Alters microglia balance toward neuroprotective state
- Studied in multiple neurological and non neurological conditions

Masitinib in ALS Patients

- April 4, 2016: AB Science reported that a predefined interim analysis for its phase 3 randomized controlled trial evaluating masitinib in the treatment of amyotrophic lateral sclerosis has met its primary objective.
- Masitinib at 2 doses was compared against riluzole control group; interim analysis performed once 191 patients (50% of the study population) reached 48 weeks
- Recently full results presented- 27% slowing of illness

ALS ACT
ALS Accelerated Therapeutics

- Phase II biomarker driven call for grants (up to 1.5 M; use NEALS infrastructure for speed
- Partnership ALSA, ALS Finding A Cure Foundation and MGH Phase II Fund

  – Already funded following trials :
    - Nuedexta, mexiletine, retigabine, actermra, AMX0035, RNS60
  – Other disease organizations – initiating similar programs (model approach!)

Questions: Lucie Bruijn (ALSA), Merit Cudkowicz (MGH) or Tara Lincoln (NEALS)

NEALS

ALS Association TREAT ALS Translational Research Advancing Therapy for ALS

Many Other Clinical Research Studies in ALS

- Genetic Studies
- ANSWER ALS
- Biofluids and Imaging
- Epidemiology

Community working together to wipe out ALS

How Can I Find out More about Trials?

www.neals.org 1-855-437-4823 alstrials@neals.org

www.clinicaltrials.gov

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