NCT02238626

Ibudilast

Bi-modal Therapy with Riluzole in Early and Advanced ALS Patients

Adaptive Design Single Center Phosphodiesterase Type 4 (PDE4) Inhibitor – Ibudilast (MN-166) Phase 1b / 2a Clinical Trial [NCT02238626] for Amyotrophic Lateral Sclerosis (ALS) Patients [1] Not Requiring Non-Invasive Ventilation (no-NIV) up to 5 years and [2] Requiring Non-Invasive Ventilation (NIV) up to 10 years from Disease Onset

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Joanna Dojillo MS is an employee of Medicinova
Yuichi Iwaki MD PhD is an employee of Medicinova.
Kazuko Matsuda MD PhD is an employee of Medicinova

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Ibudilast - Glial Pathology MS, ALS, Glioblastoma Treatment Development

Ibudilast Pharmacology - Target Engagement

Adaptive Protocol - Early Cohort (EC)
- Advanced Non-Invasive Ventilation Cohort (ANC)
- Vital Status post Ibudilast Washout

Un-Blinded Tolerability and Safety Analysis - 0-6 and 6-12 months

Un-Blinded Clinical Endpoint Exploratory Analysis - 0-6 and 6-12 months

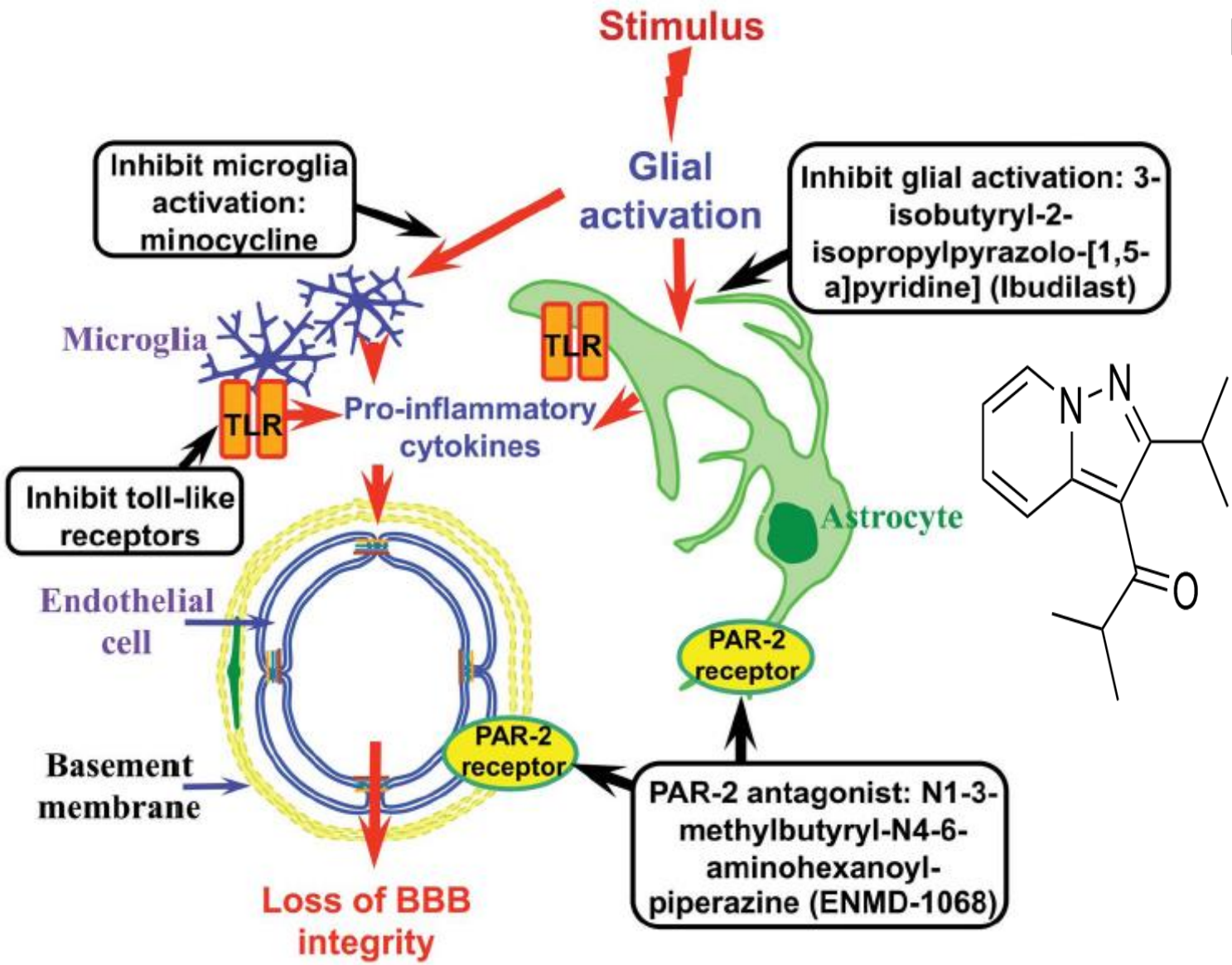
Manual Muscle Testing No Progression
- MMT Responders

ALS Quality of Life No Progression
- ALSAQ-5 Responders

ALS Functional Rating Scale - Revised No Progression
- ALSFRS-R Responders

Survival Per Protocol Completion - due to ALSFRS-R responders

Conclusions



MS

NN102 SPRINT-MS

ALS

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Carolinas HealthCare System

Ibudilast (MN-166) in Subjects With Amyotrophic Lateral Sclerosis (ALS) (IBU-ALS-1201)

This study is ongoing, but not recruiting participants.

Sponsor:
MediciNova

ClinicalTrials.gov Identifier:
NCT02238626

First Posted: September 12, 2014
Last Update Posted: October 20, 2017

U.S. National Library of Medicine
ClinicalTrials.gov

MGH 1811

A Biomarker Study to Evaluate MN-166 (Ibudilast) in Subjects With Amyotrophic Literal Sclerosis (ALS)

This study is currently recruiting participants.

See Contacts and Locations

Verified August 2017 by MediciNova

Sponsor:
MediciNova

ClinicalTrials.gov Identifier:
NCT02714036

First Posted: March 21, 2016
Last Update Posted: August 14, 2017

28th International symposium on ALS/MND Boston USA

The Carolinas Neuromuscular ALS - MDA Center
MEDICINOVA
ALS MDA ALS DIVISION
Carolinas Medical Center

NCT02238626

ECTRIMS
EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

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MSPARIS2017
7TH JOINT ECTRIMS – ACTRIMS MEETING
25–28 OCTOBER 2017, PARIS, FRANCE

SPRINT-MS/NN 102 Phase II Trial of Ibudilast in Progressive MS: Top-Line Results

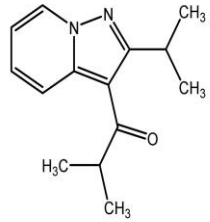
SPRINT-MS
Neuro NEXT

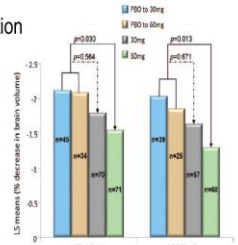
R.J. Fox, C.S. Coffey, M.E. Cudkowicz, T. Gleason, A. Goodman, E.C. Klawiter, K. Matsuda, M. McGovern, R. Conwit, R. Naismith, A. Ashokkumar, D. Eckund, E. Klinger, M. Koepp, S. Natarajan, B. Thornell, J. Yankey, R.A. Bermel, X. Huang, M.J. Lowe, K. Nakamura, S. Narayanan, K.E. Sakaie, J.P. Debbins, X. Zhou, E. Alvarez, M. Apperson, K. Bashir, B. Cohen, P. Coyle, S. Delgado, D. Dewitt, A. Flores, B. Giesser, M. Goldman, B. Jubelt, N. Lava, S. Lynch, H. Moses, D. Ontaneda, J. Perumal, M. Racke, P. Repovic, C. Riley, C. Severson, S. Shinnar, V. Suski, B. Weinstock Guttman, V. Yadav, A. Zabeti

National Institute of Neurological Disorders and Stroke
Cleveland Clinic Neurological Institute
The University of Iowa
Massachusetts General Hospital

Ibudilast (MN-166, AV411)

- Orally-available small molecule
  - Macrophage migration inhibitor factor (MIF) inhibitor
  - Phosphodiesterase (PDE)-4 and PDE-10 inhibitor
  - Toll-like receptor 4 inhibitor
- Approved in Japan in 1989
  - Bronchial asthma
  - Post-stroke dizziness
- Reduces atrophy progression and black hole formation in RRMS
- Animal models suggest neuroprotection:
  - Krabbe's disease
  - Spinal cord injury
  - Traumatic brain injury
  - Chronic neuropathic pain
  - Cerebral aneurysm

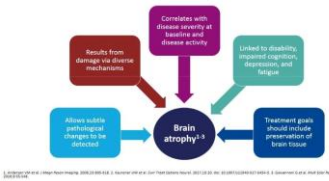




Barkhof et al, Neurol 2010

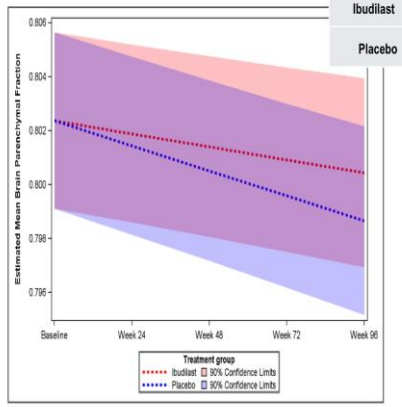
SPRINT-MS

Brain Atrophy Is Clinically Relevant During Disease Progression



Primary Objective 1: BPF

Estimated Rate of Annual BPF Change		
Treatment Group	Estimate (90% CI)	P-Value
Ibudilast	-0.00105 (-0.00160, -0.00049)	0.040
Placebo	-0.00202 (-0.00256, -0.00147)	



Primary results show significant difference in slope of BPF over time.

Treatment with ibudilast was associated with a 48% slowing in rate of decline.

SPRINT-MS

ALS
MDA Muscular Dystrophy Association ALS DIVISION
Carolinas HealthCare System
ALS

J Neurooncol (2016) 127:427–434
DOI 10.1007/s11060-016-2080-6

TOPIC REVIEW

The challenges associated with molecular targeted therapies for glioblastoma

Toni Rose Jue[1] · Kerrie L. McDonald[1]

Received: 30 September 2015 / Accepted: 15 February 2016 / Published online: 22 February 2016

Abstract Glioblastoma (GBM) is the most aggressive malignant brain tumor in adults. Improvements in the treatment of GBM have remained static since the advent of the standard therapy which includes radiation with concurrent and adjuvant temozolomide treatment. Developing treatment and diagnostic or companion biomarker combinations is transforming the way we treat numerous cancers. However, can this emerging paradigm be also effective for GBM? Can GBM be treated the same way as other cancers? Here we review the challenges for a personalized molecular targeted therapeutic approach in GBM. The specific challenges for establishing a personalized molecular targeted medicine program for GBM patients include overcoming the blood brain barrier, unravelling the intra- and inter-heterogeneity that exists and the importance of developing more relevant animal models that recapitulate a patient's GBM tumor.

5 years. GBM are highly refractory to treatment with local tumor recurrence occurring 2–3 cm from the original resection cavity (the area exposed to radiation treatment) frequently observed. Relapsed GBMs are difficult to manage with a median survival of only a few months after recurrence [1]. Increasingly, the development of novel therapies involve defining drug-diagnostic combinations where the presence of a molecular target or marker identifies patients who are most likely to respond to a specific therapy. This model of developing treatment and diagnostic/companion biomarker combinations is the emerging paradigm for novel drug and diagnostic development [2–4] with a recent example being the use of BRAF inhibitors, which target a specific activating mutation of BRAF (V600E) in melanoma [5]. GBM is characterized by inter- and intra-patient genomic and histopathological diversity, arising from the complex dynamics that underpin its development. Given this, a single "bullet" approach is unrealistic.

Neuro-Oncology

P01.20 Treatment of recurrent glioblastoma with the cytokine inhibitor, ibudilast in combination with temozolomide

K. L. McDonald, W. Ha, M. Khasraw

Neuro-Oncology, Volume 19, Issue suppl_3, 1 May 2017, Pages iii27,
https://doi.org/10.1093/neuonc/nox036.096
Published: 19 April 2017

Cite Permissions Share

Abstract

BACKGROUND: Recurrence in patients with glioblastoma (GBM) is inevitable, even in patients with *O-6-Methylguanine-DNA Methyl Transferase* (*MGMT*) methylation. We identified increased expression of the inflammatory cytokine, Macrophage Inhibitory Factor (MIF) and its receptor CD74 in patients with recurrent tumours. High levels of MIF and CD74 were associated with poor overall survival in GBM patients. This study aims to determine efficacy of Ibudliast (AV411; 3-isobutyryl-2-isopropylpyrazolo-[1,5-a]pyridine) to block MIF expression and decrease tumour burden. Ibudilast is an anti-inflammatory drug that was developed for the treatment of bronchial asthma.

METHODS: The patient derived cell lines (PDCLs) RN1 (*MGMT* unmethylated), BAH1 (*MGMT* methylated), and HW1 (*MGMT* methylated) were treated *in vitro* with different concentrations of ibudilast in combination with temozolomide (TMZ). Patient derived xenograft (PDX) models of GBM were developed and treated with the combination of

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Ibudilast Pharmacology

Target Engagement

NCT02238626 Background

Riluzole Pharmacology

Riluzole currently slows the rate of loss of ALSFRS-R by 25-28% when administered at 50mg-twice-daily to achieve levels of 30-1552 ng/mL corresponding to 0.15-6.6 µM (Groeneveld, 2003).

Tissue levels are 10-fold higher (Milane, 2009) providing *in vivo* levels that permit multiple pharmacological activities including

CREB-mediated enhancement of neurotrophic factors (Tsuchioka, 2011)

CREB-mediated glutamate transport activation (Hayashida, 2010)

Riluzole has weak phosphodiesterase (PDE) inhibitor activity (Duprat, 2000).

NCT02238626 Background

Enhance Riluzole Pharmacology

Both riluzole and some PDE inhibitors reduce infarct size following transient cerebral artery occlusion (O'Neill, 1997).

Ibudilast, achieves this reduced infarct size at serum levels achievable in humans (Lee, 2011).

Decreased Cytokine Production by Microglia

Reduction in TNFalpha production by activated microglia (Kiebala,2011, Hama,2012) and astroctyes (Yoshikawa, 2002).

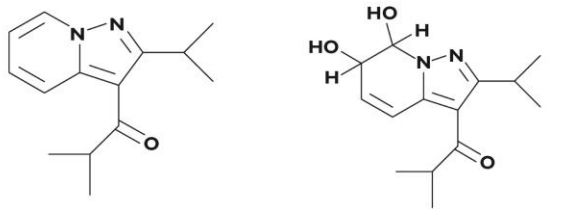
Inhibition Matrix Metalloproteinase-9

Inhibition of matrix metallo-proteinase-9 (Yagi, 2010) which may be a key factor in ALS progression (Kaplan, 2014).

Ibudilast Pharmacology - Target Engagement

Ibudilast Biochemistry IC_{50}

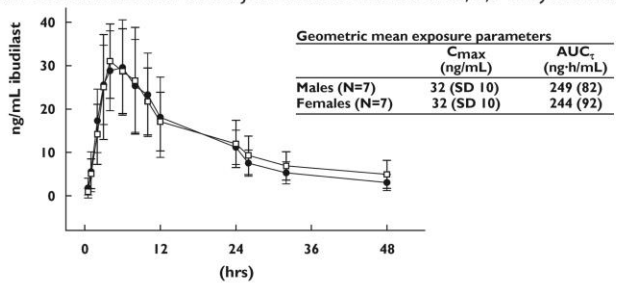
PDE4A - 0.05 μM
PDE4B - 0.06 μM
PDE4C - 0.24 μM
PDE4D - 0.17 μM



Ibudilast
(3-isobutyryl-2-isopropylpyrazolo-[1,5-a]pyridine)

6,7-Dihydrodiol-ibudilast
(6,7-dihydrodiol-3-isobutyryl-2-isopropylpyrazolo-[1,5-a]pyridine)

Figure 1
Chemical structure of ibudilast and its major oxidative metabolite, 6,7-dihydrodiol-ibudilast



Geometric mean exposure parameters

	C_{max} (ng/mL)	AUC_τ (ng·h/mL)
Males (N=7)	32 (SD 10)	249 (82)
Females (N=7)	32 (SD 10)	244 (92)

Chronic daily oral administration of Ibudilast at 30mg twice-daily in humans can achieve peak [0.25 μM] and trough [0.15 μM] serum levels (Yoon, 2009). Brain and spinal cord levels of Ibudilast are higher (Sanftner, 2009).

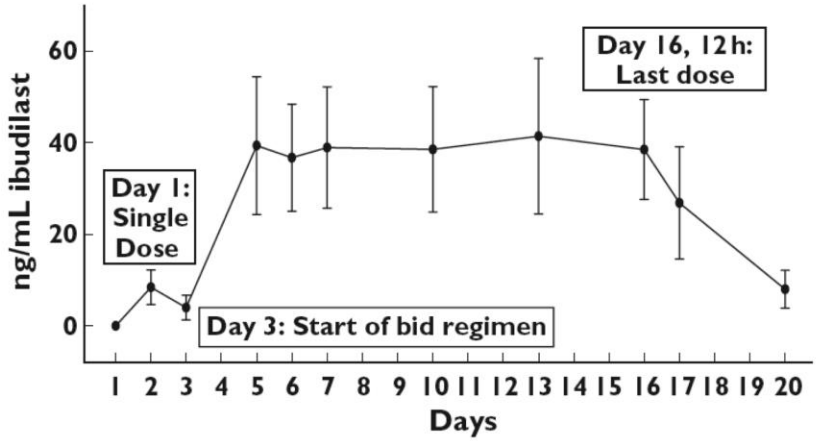


Figure 3 **Ibudilast Pharmacology**
Mean trough plasma concentrations of ibudilast. Trough ibudilast plasma concentrations from $n = 14$ subjects receiving a 30-mg single administration on day 1, followed by $n = 10$ subjects receiving 30 mg b.i.d. from day 3 to day 16. Data represents mean (± SD)

NCT02238626 Protocol Outcome Measures

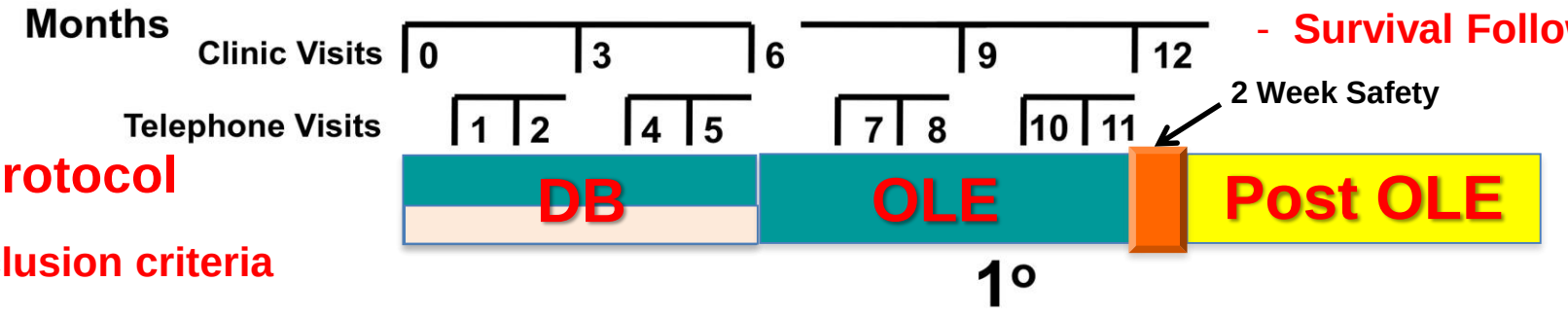
Adaptive Protocol

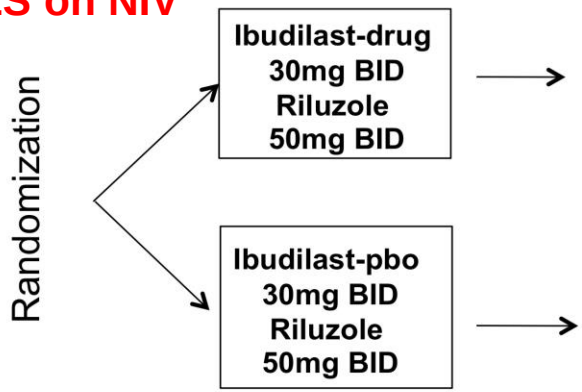
Adaptive Protocol

- Survival Follow-up

Adaptive Protocol

- Riluzole inclusion criteria
- Advanced ALS on NIV





Safety Vital Signs TEAEs TESAEs Labs

Feasibility # 3 mon / Starts
Tolerability # 12 mon / Starts

2º

Rate of VC change

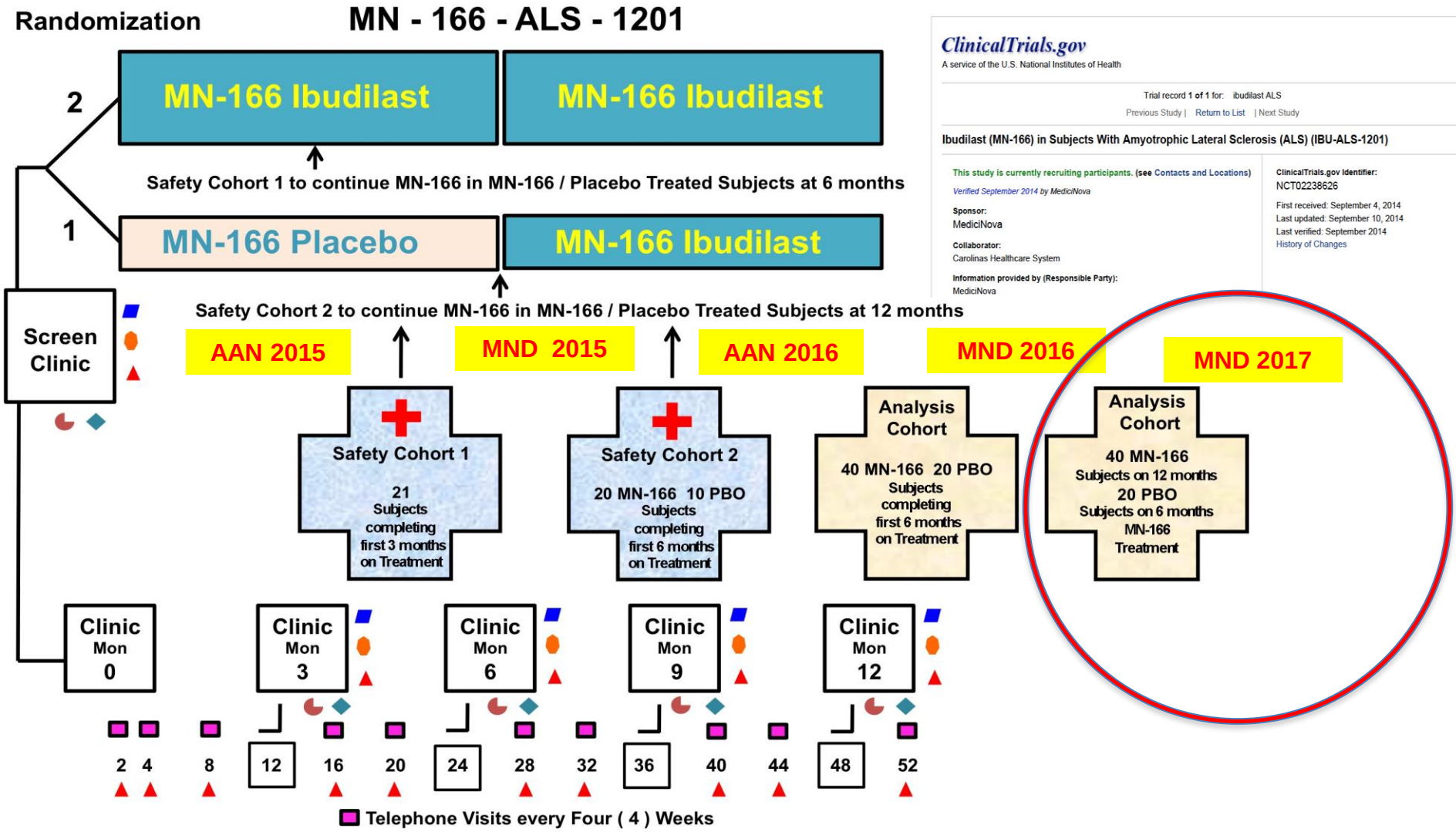
Rate of ALSFRS-R change

NIV Utilization # 3 mon # 6 mon # 9 Mon # 12 mon / Starts

Survival

ALS Biomarker
Rate of Creatinine Change

NCT02238626 Protocol Milestones



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Trial record 1 of 1 for: ibudilast ALS
Previous Study | Return to List | Next Study

Ibudilast (MN-166) in Subjects With Amyotrophic Lateral Sclerosis (ALS) (IBU-ALS-1201)

This study is currently recruiting participants. (see Contacts and Locations)
Verified September 2014 by MediciNova

Sponsor:
MediciNova

Collaborator:
Carolinas Healthcare System

Information provided by (Responsible Party):
MediciNova

ClinicalTrials.gov Identifier:
NCT02238626

First received: September 4, 2014
Last updated: September 10, 2014
Last verified: September 2014
History of Changes

Clinical and Laboratory Outcomes entered into StudyTrax Clinical Trial Database

HPI PMH PEx NEx MMT ALSFRS-R PFTs ALSAQ-5 GCIC IMH ALS Milestones TEAEs TESAEs Con Meds Lab CBC CMP CK UA EKG

Inclusion/Exclusion Criteria

Inclusion:

- Age 18-80 years
- Diagnosis of familial or sporadic ALS
- ALS with onset of $\leq$ 5 yrs for EC
- SVC $\geq$ 60%
- Currently on stable dose of Riluzole

Exclusion:

- Use of Tracheostomy, invasive mechanical ventilation, Non-invasive ventilation NIV
- > 3% predicted loss in post-diagnosis VC per month or a > 1 unit loss in post diagnosis ALSFRS-R total score per month

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EC Baseline characteristics

	Placebo (N=17)	Ibudilast (N=34)
Age	57.5	59.2
Female	5 (29.4%)	11 (32.4%)
Ethnicity •Caucasian •African American •Asian •Unknown	 15 (88.2%) 2 (11.8%) 0% 0%	 31 (91.2%) 1 (2.9%) 1 (2.9%) 1 (2.9%)
Baseline ALSFRS-R	39.0	39.3
Baseline SVC	97.2	92.0
Baseline MIP/NIF	-98.1	-86.0
Baseline MMT (Right)	4.08	4.16
Baseline MMT (Left)	3.97	4.15
Baseline ALSAQ-5	6.4	6.4

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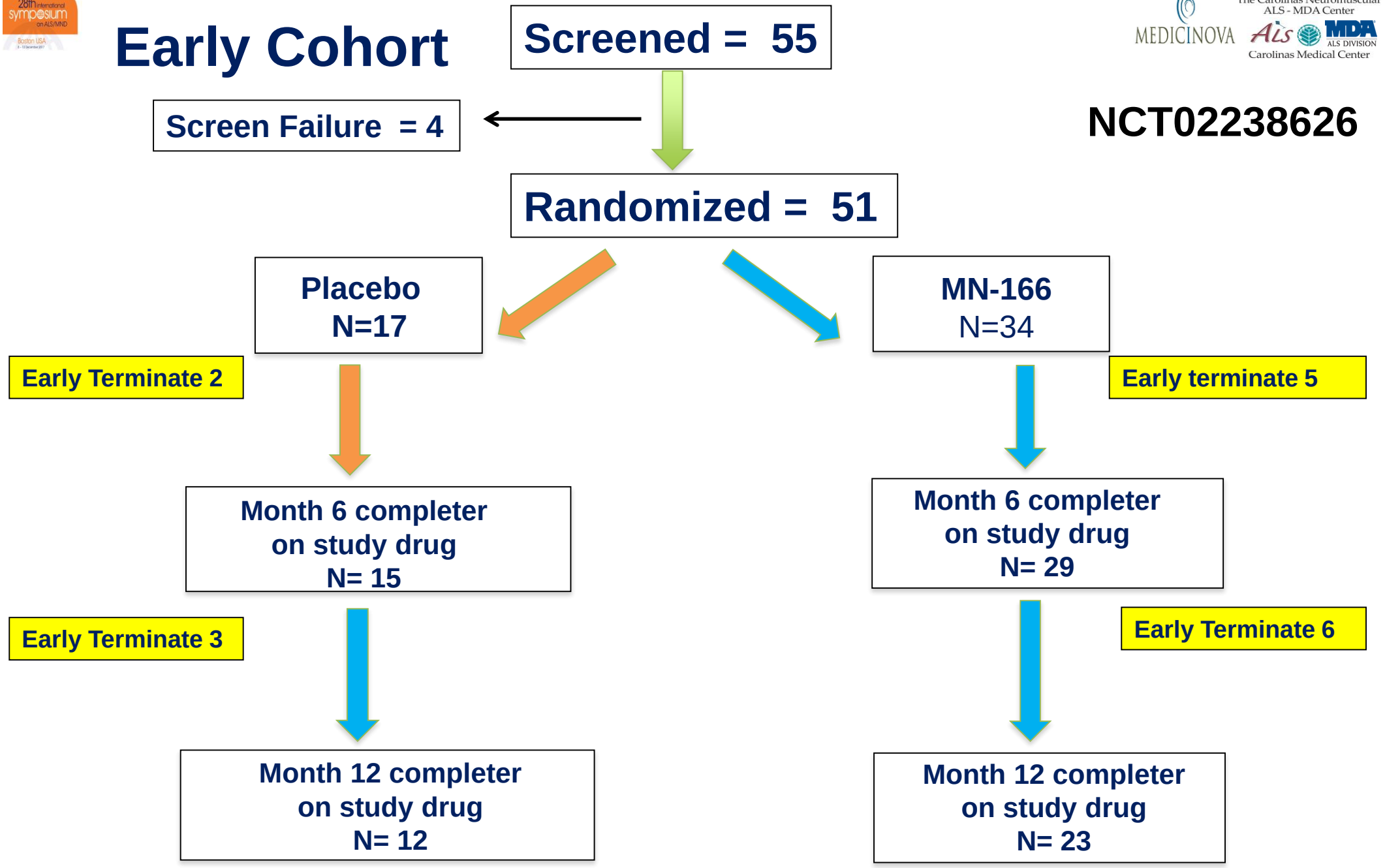
CONSORT Diagram

DB - OLE -12 months

Early Cohort



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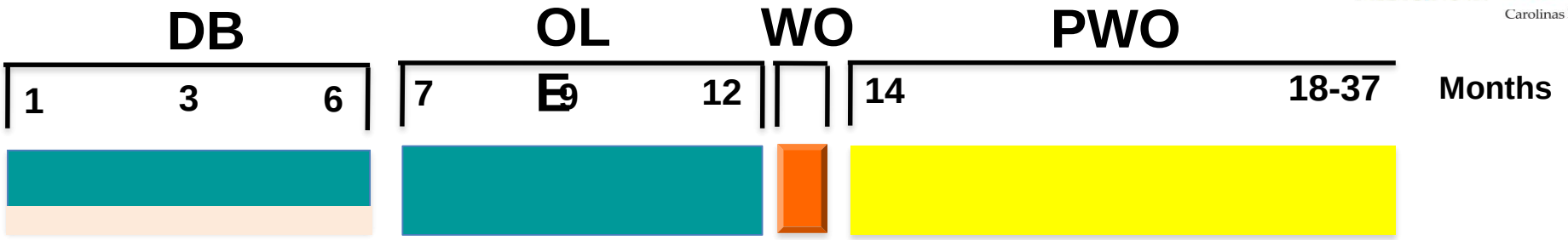

DB

- Feasibility
- Tolerability
- Safety
  - AEs SAEs
- Progression
  - NIV GT Survival
- MMT, ALSAQ-5
- ALS-FRS-R
- SVC
- change from BL
- Modifiers
  - Age Sex
  - Site Onset
  - Onset-Dx Dx-BL
  - ALS-FRS-R
  - delta ALS-FRS-R
    - Onset-Dx Dx-BL
  - Randomization

OLE

- Feasibility
- Tolerability
- Safety
  - AEs SAEs
- Progression
  - NIV GT Survival
- MMT, ALSAQ-5
- ALS-FRS-R
- SVC
  - change from BL
  - change from DB
- Modifiers
  - Age Sex
  - Site Onset
  - Onset-Dx Dx-BL
  - ALS-FRS-R
  - delta ALS-FRS-R
    - Onset-Dx Dx-BL
  - Randomization

WO

- Progression
  - NIV GT Survival
- MMT
- ALS-FRS-R
- SVC
  - change from BL
  - change from DB
  - change from OLE
- Modifiers
  - Age Sex
  - Site Onset
  - Onset-Dx Dx-BL
  - ALS-FRS-R
  - delta ALS-FRS-R
    - Onset-Dx Dx-BL
  - Randomization

Post OLE

- Progression
  - NIV GT Survival
- Modifiers
  - Age Sex
  - Site Onset
  - Onset-Dx Dx-BL
  - ALS-FRS-R
  - delta ALS-FRS-R
    - Onset-Dx Dx-BL
  - Randomization

EC Clinical Trial Endpoints

Primary:

- **Tolerability** – early discontinuation from study or drug
- **Safety** – AEs, SAEs

Secondary Clinical Endpoint Responsiveness

- **MMT(Manual Muscle Test)** DB | OLE epochs
- **ALSAQ-5** DB | OLE epochs
- **ALSFRS-R** DB | OLE epochs
- **Survival** DB | OLE epochs | Post Wash Out Follow-Up
- **Respiratory Function** DB | OLE epochs
- **NIV GT** DB | OLE epochs | Post Wash Out Follow-Up

EC Data Analysis Population

ITT (Intention-To-Treat) population

= all randomized patients

Total = **51** (Placebo = 17; MN-166 = 34)

PP (Per-Protocol) population

= completed study

Double-blind phase

Total = **44** (Placebo = 15; MN-166 = 29)

Open Label Extension

Total = **35** (Placebo = 12; MN-166 = 23)

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Primary Endpoints

Tolerability / Safety

DB - OLE -12 months

NCT02238626

Primary Endpoints : Tolerability

EC Safety Analysis ITT Population

of subjects early study or drug termination

Double-Blind Epoch (0 - 6 month)

	# of Subjects	
	Placebo (N = 17)	**Ibudilast (N = 34)**
Early Study Termination	**2**	**2**
•Due to AEs	1	1
•Any Reason	1	1
Early Drug Termination	**0**	**3**
•Due to AEs	0	2
•Any Reason	0	1

Primary Endpoints : Safety

EC Safety Analysis ITT Population

Treatment Related AEs (TRAEs) # of subjects, # of events

Double-Blind Epoch (0 – 6 month)

	# of Subjects or # of Events	
	Placebo N=17	Ibudilast N=34
# of Subject with at Least one TRAEs	n= 3	n= 4
Total events # of TRAEs	5	8
Severe or Life-threatening TRAEs	0	0
Serious TRAEs	0	0

Primary Endpoints : Safety

EC Safety Analysis ITT Population

Treatment Related AEs (TRAEs) # of events

Double-Blind Epoch (0 – 6 month)

System Organ Code	# of Events	
	Placebo (n=3)	Ibudilast (n=4)
Gastrointestinal system	1	2
Nervous system disorder	3	0
Metabolism and Nutrition	0	4
Investigation	1	1
Injury	0	1

Primary Endpoints : Safety

EC Safety Analysis ITT Population

Treatment Emergent AEs (TEAEs) # of subjects

Entire Study (0-12 months)

	# of Subjects	
	Placebo N = 17	**Ibudilast N = 34**
At Least one TEAEs	n = 17	n = 34
Severe or Life threatening TEAEs	n = 2	n = 4
Serious Adverse Events	n = 1	n = 5
Treatment Related Adverse Events	n = 10	n = 13

Primary Endpoints : Safety

EC Safety Analysis ITT Population Serious Adverse Events Double-Blind and Open Label Extension (0- 12 months)

Subject Reference #	SAEs	Treatment related ?
022	DVT	No
027	Leg fracture	No
028	Dysphagia Bowel obstruction	No
029	Ankle fracture	No
049	Ureteral stone	No
052	Pneumonia	No

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Secondary Endpoints

Clinical Endpoint Responsiveness

DB - OLE -12 months

NCT02238626

Secondary Endpoints

Manual Muscle Testing MMT

Responder =

0 unit loss or gain per 6 months change

Non-Responder =

> 1 unit loss per 6 months change

DB - OLE -12 months

MMT score

NCT02238626

EC ITT population

% of subjects **stable** or **improved** (same or higher score) on 6 months treatment

Double-Blind Phase		Open-Label Phase Ibudilast 6-12 mon treatment	Ibudilast treatment combined
Placebo (N = 17)	Ibudilast (N = 34)	(N = 17)	(N = 51)
4 / 17 (23.5 %)	11 / 34 (32.4 %)	6 / 17 (35.3 %)	17 / 51 (33.3 %)

NCT02238626

Secondary Endpoints

ALSAQ-5

Responder =

0 unit loss or gain per 6 months change

Non-Responder =

> 1 unit loss per 6 months change

DB - OLE -12 months

NCT02238626

ALSAQ-5 score

EC ITT population

% of subjects **stable** or **improved** (same or lower score) on 6 month treatment

Double-Blind Phase		Open-Label Phase Ibudilast 6-12 mon treatment	Ibudilast treatment combined
Placebo (N = 17)	Ibudilast (N = 34)	(N = 17)	(N = 51)
4 / 17 (23.5 %)	17 / 34 (50.0 %)	5 / 17 (29.4%)	22 / 51 (43.1 %)

NCT02238626

Secondary Endpoints

ALSFRS-R total

Responder =

≤ 1 unit loss per 6 months change

Non-Responder =

> 1 unit loss per 6 months change

DB - OLE -12 months

ALSFRS-R Score

NCT02238626

EC ITT population

% of subjects with less than 1 unit change in 6 months **stable** or **improved** on 6 or 12 months treatment

Double-Blind Phase		Open Label Phase		Overall
Placebo (N = 17)	Ibudilast (N = 34)	Ibudilast 0-6 mon treatment (N = 17)	Ibudilast 6-12 mon treatment (N = 34)	Ibudilast 0-12 mon treatment combined (N = 51)
3 / 17 (17.6 %)	10 / 34 (29.4 %)	6 / 17 (35.3 %)	3 * / 34 (8.8 %)	19 * / 51 (37.3 %)

* Removed 2 overwrapped subjects

ALSFRS-R Score

NCT02238626

EC PP population

% of subjects with less than 1 unit change in 6 months **stable** or **improved** on 6 or 12 months treatment

Double-Blind Phase		Open Label Phase		Overall
Placebo (N = 15)	Ibudilast (N = 29)	Ibudilast 0-6 mon treatment (N = 12)	Ibudilast 6-12 mon treatment (N = 23)	Ibudilast 0-12 mon treatment combined (N = 35)
3 / 15 (20.0 %)	10 / 29 (34.5 %)	6 / 12 (50.0 %)	3 * / 23 (13.0 %)	19 * / 35 (54.3 %)

* Removed 2 overwrapped subjects

NCT02238626

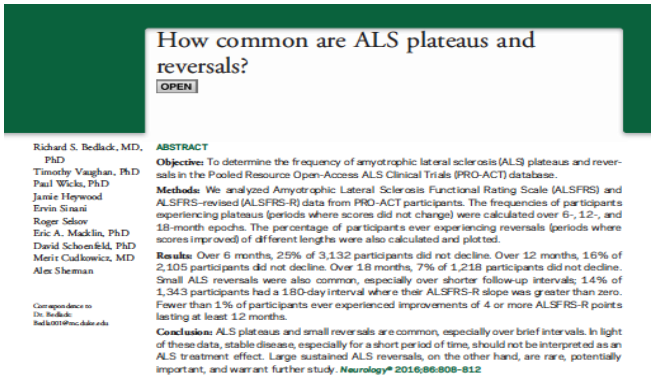
ALSFRS-R Responder Analysis - Comparison

0-6 or 6-12 month Non-Decline ITT

3 / 17 = 17.6 % pbo 0-6 mon
10 / 34 = 29.4 % lbd 0-6 mon
6 / 17 = 35.3 % pbo-lbd 6-12 mon
3 * / 34 = 8.8 % pbo-lbd 6-12 mon
19 * / 51 = 37.3 % lbd 0-12 mon

6 month Non-Decline PP

3 / 15 = 20.0 % pbo 0-6 mon
10 / 29 = 34.5 % lbd 0-6 mon
6 / 12 = 50.0 % pbo-lbd 6-12 mon
3 * / 23 = 21.7 % pbo-lbd 6-12 mon
19 * / 35 = 54.3 % lbd 0-12 mon



How common are ALS plateaus and reversals?

OPEN

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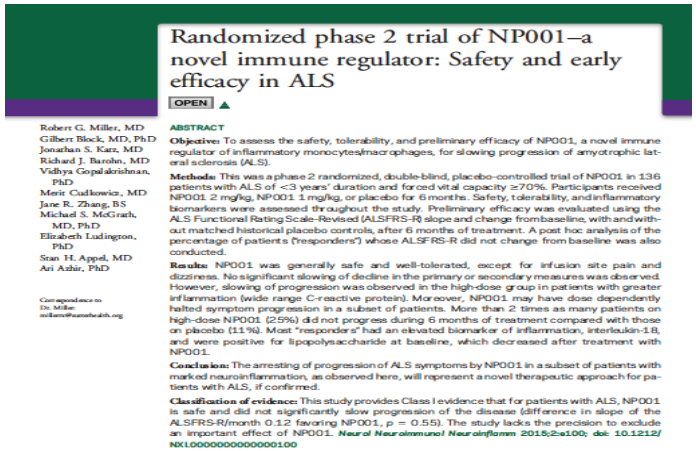
ABSTRACT

Objective: To determine the frequency of amyotrophic lateral sclerosis (ALS) plateaus and reversals in the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database.

Methods: We analyzed Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) and ALSFRS–revised (ALSFRS-R) data from PRO-ACT participants. The frequencies of participants experiencing plateaus (periods where scores did not change) were calculated over 6-, 12-, and 18-month epochs. The percentage of participants ever experiencing reversals (periods where scores improved) of different lengths were also calculated and plotted.

Results: Over 6 months, 25% of 3,132 participants did not decline. Over 12 months, 16% of 2,105 participants did not decline. Over 18 months, 7% of 1,218 participants did not decline. Small ALS reversals were also common, especially over shorter follow-up intervals; 14% of 1,343 participants had a 180-day interval where their ALSFRS-R slope was greater than zero. Fewer than 1% of participants ever experienced improvements of 4 or more ALSFRS-R points lasting at least 12 months.

Conclusion: ALS plateaus and small reversals are common, especially over brief intervals. In light of these data, stable disease, especially for a short period of time, should not be interpreted as an ALS treatment effect. Large sustained ALS reversals, on the other hand, are rare, potentially important, and warrant further study. *Neurology®* 2016;86:808–812



Randomized phase 2 trial of NP001—a novel immune regulator: Safety and early efficacy in ALS

OPEN

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ABSTRACT

Objective: To assess the safety, tolerability, and preliminary efficacy of NP001, a novel immune regulator of inflammatory monocytes/macrophages, for slowing progression of amyotrophic lateral sclerosis (ALS).

Methods: This was a phase 2 randomized, double-blind, placebo-controlled trial of NP001 in 136 patients with ALS of <3 years' duration and forced vital capacity ≥70%. Participants received NP001 2 mg/kg, NP001 1 mg/kg, or placebo for 6 months. Safety, tolerability, and inflammatory biomarkers were assessed throughout the study. Preliminary efficacy was evaluated using the ALS Functional Rating Scale–Revised (ALSFRS-R) slope and change from baseline, with and without matched historical placebo controls, after 6 months of treatment. A post hoc analysis of the percentage of patients ("responders") whose ALSFRS-R did not change from baseline was also conducted.

Results: NP001 was generally safe and well-tolerated, except for infusion site pain and dizziness. No significant slowing of decline in the primary or secondary measures was observed. However, slowing of progression was observed in the high-dose group in patients with greater inflammation (wide range C-reactive protein). Moreover, NP001 may have dose dependently halted symptom progression in a subset of patients. More than 2 times as many patients on high-dose NP001 (25%) did not progress during 6 months of treatment compared with those on placebo (11%). Most "responders" had an elevated biomarker of inflammation, interleukin-18, and were positive for lipopolysaccharide at baseline, which decreased after treatment with NP001.

Conclusion: The arresting of progression of ALS symptoms by NP001 in a subset of patients with marked neuroinflammation, as observed here, will represent a novel therapeutic approach for patients with ALS, if confirmed.

Classification of evidence: This study provides Class I evidence that for patients with ALS, NP001 is safe and did not significantly slow progression of the disease (difference in slope of the ALSFRS-R/month 0.12 favoring NP001, $p = 0.55$). The study lacks the precision to exclude an important effect of NP001. *Neurol Neuroimmunol Neuroinflamm* 2015;2:e100; doi: 10.1212/NXI.0000000000000100

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2017; 18: 11–19

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RESEARCH ARTICLE

A post-hoc subgroup analysis of outcomes in the first phase III clinical study of edaravone (MCI-186) in amyotrophic lateral sclerosis

THE EDARAVONE (MCI-186) ALS 16 STUDY GROUP*

Abstract

Our first phase III study failed to demonstrate efficacy of edaravone for amyotrophic lateral sclerosis (ALS) compared to placebo. Here, we performed post-hoc subgroup analysis to identify a subgroup in which edaravone might be expected to show efficacy. We focussed on two newly defined subgroups, EESP and dpEESP2y. The EESP was defined as the efficacy-expected subpopulation with % forced vital capacity of ≥80%, and ≥2 points for all item scores in the revised ALS functional rating scale (ALSFRS-R) score before treatment. The dpEESP2y was defined as the greater-efficacy-expected subpopulation within EESP having a diagnosis of 'definite' or 'probable' ALS according to the El Escorial revised Airlie House diagnostic criteria and onset of disease within two years. The primary endpoint of the post-hoc analysis was the change in the ALSFRS-R score during the 24-week treatment period. The intergroup differences of the least-squares mean change in the ALSFRS-R score ± standard error during treatment were 0.65 ± 0.78 ($p = 0.4108$) in the full analysis set, 2.20 ± 1.03 ($p = 0.0360$) in the EESP, and 3.01 ± 1.33 ($p = 0.0270$) in the dpEESP2y. Edaravone exhibited efficacy in the dpEESP2y subgroup. A further clinical study in patients meeting dpEESP2y criteria is warranted.

Placebo Non-Decline PP

782 / 3132 = 25 % 6 mon
337 / 2105 = 16 % 12 mon
85 / 1218 = 7 % 18 mon

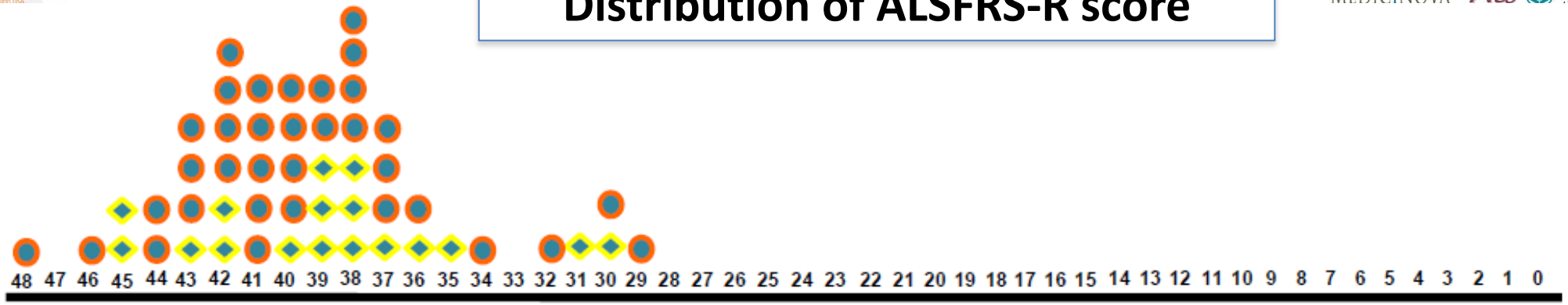
6 month Non-Decline PP

4 / 35 = 11 % pbo
8 / 42 = 19 % NP001 1mg
9 / 36 = 25 % NP001 2mg

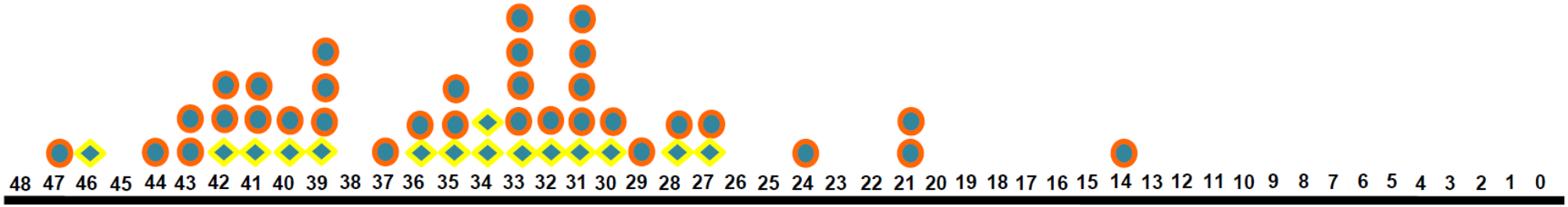
6 month Non-Decline PP

26 / 104 = 25.0 % pbo
25 / 101 = 24.7 % Edaravone

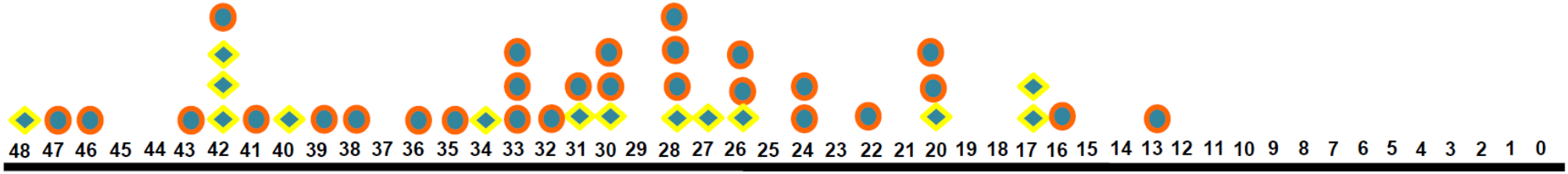
Distribution of ALSFRS-R score



ALSFRS-R total - Baseline

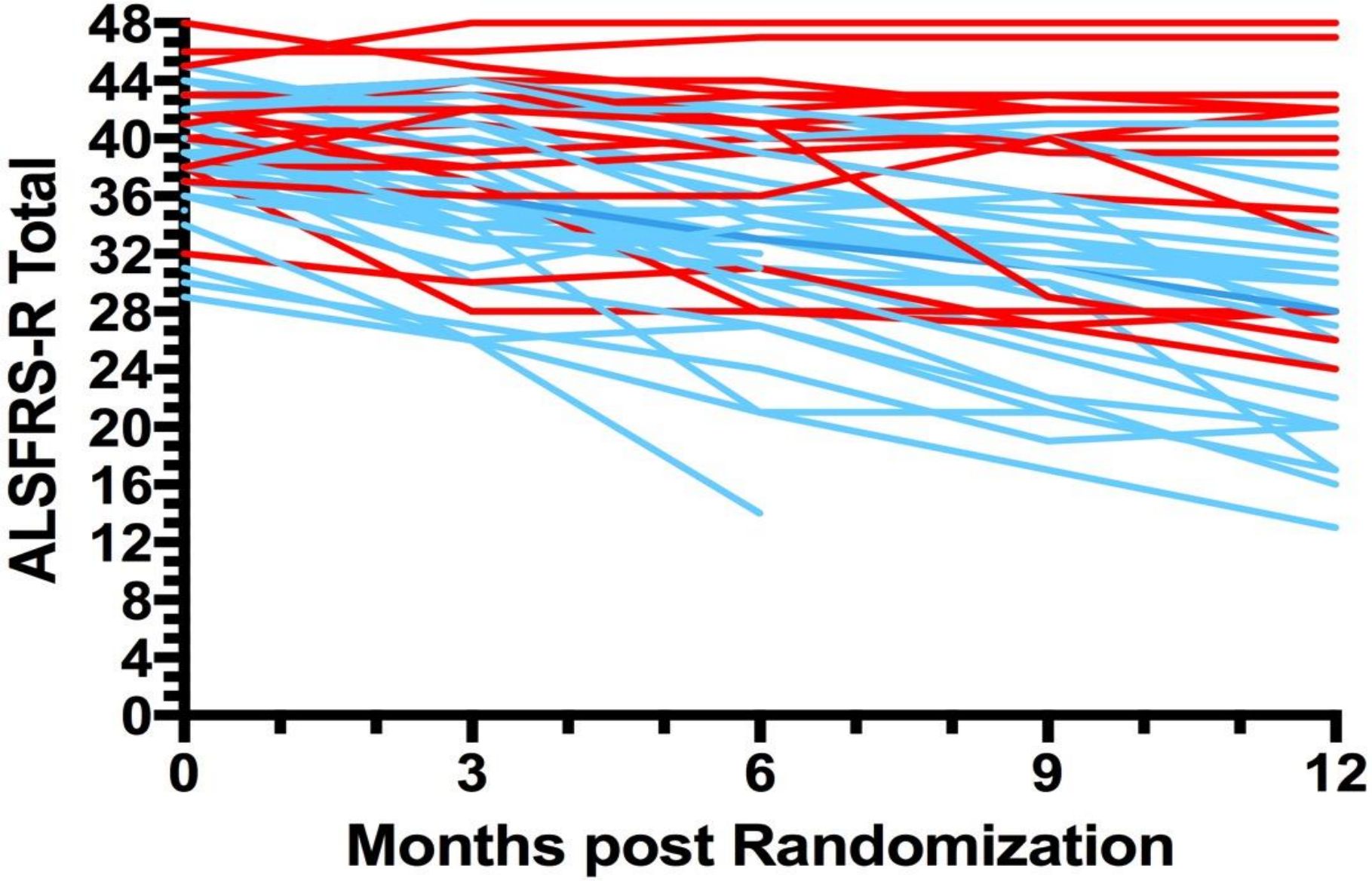


ALSFRS-R total - Month 6



ALSFRS-R total - Month 12

NCT02238626



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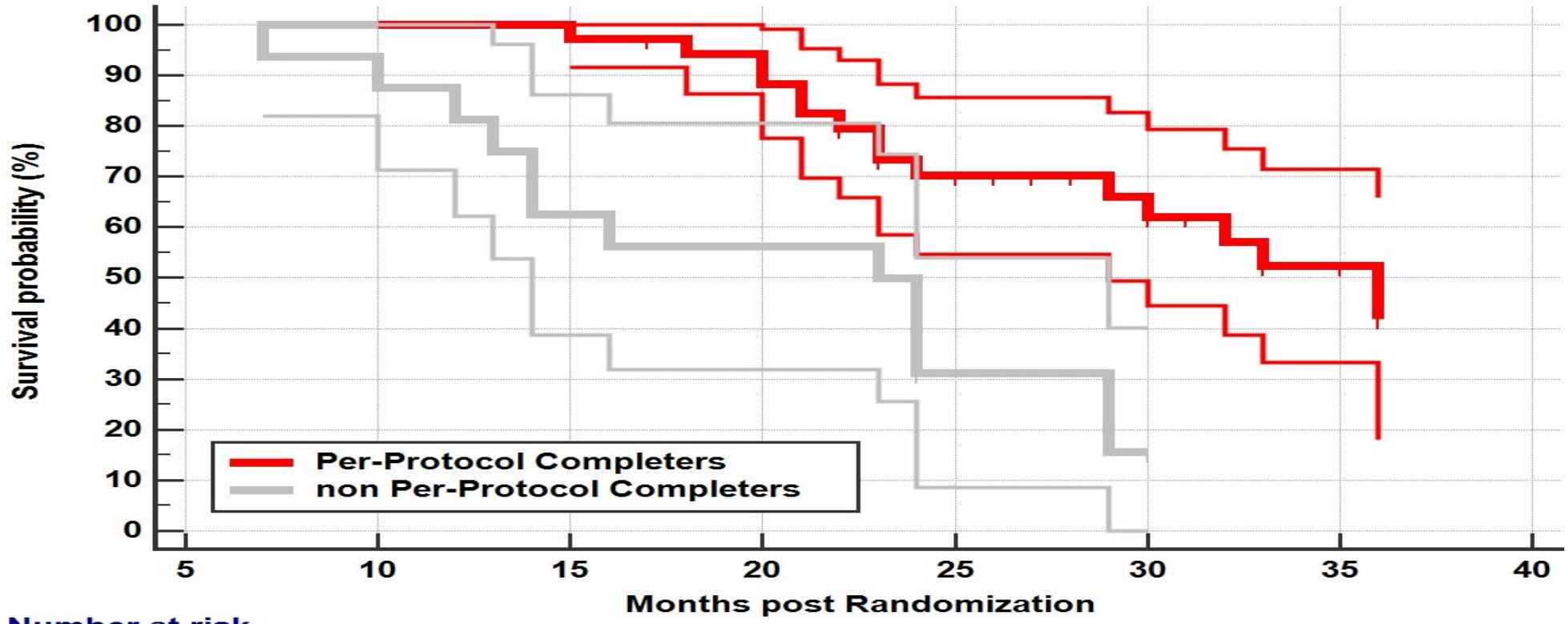
Adaptive Protocol

Per Protocol Analysis Survival

OLE and Post OLE

NCT02238626



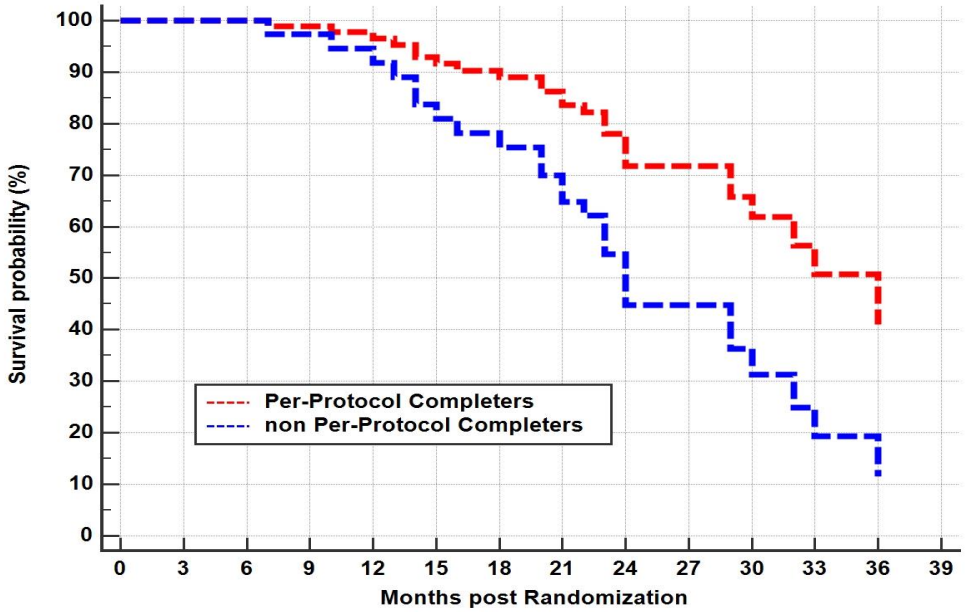
Number at risk

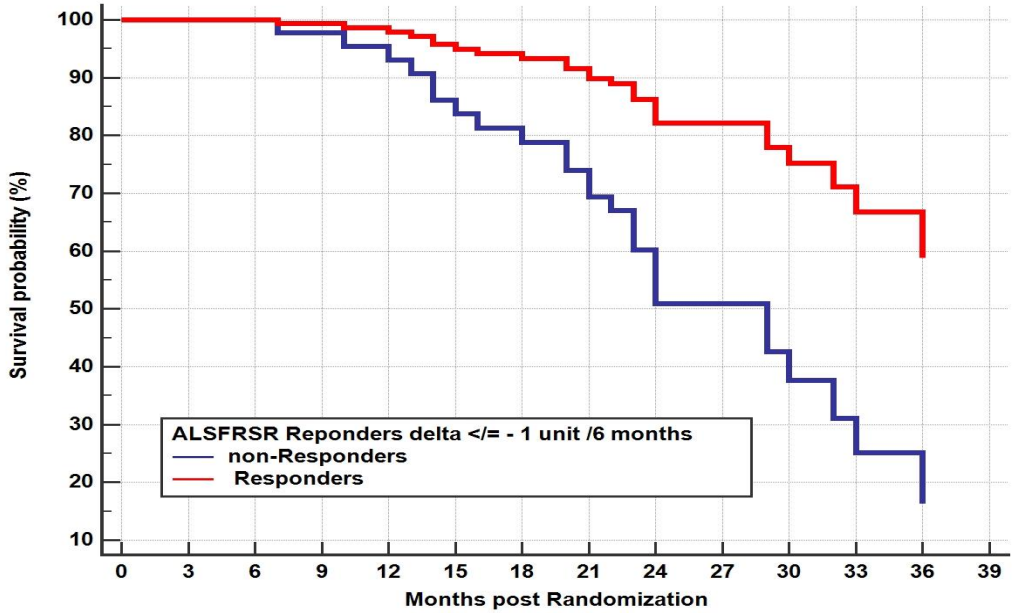
Group: Per-Protocol Completers							
35	35	34	30	21	14	5	0
Group: non Per-Protocol Completers							
16	14	10	9	2	0	0	0

Factor	Mean	SE	95% CI for the mean	Median	95% CI for the median
0	30.585	1.238	28.159 to 33.011	36.000	29.000 to 36.000
1	20.531	1.953	16.703 to 24.360	23.000	14.000 to 29.000
Overall	27.751	1.276	25.250 to 30.253	30.000	24.000 to 36.000

Chi-squared	10.2572
DF	1
Significance	P = 0.0014

NCT02238626





Covariate	b	SE	Wald	P	Exp(b)	95% CI of Exp(b)
nPP1	0.8846	0.4286	4.2591	0.0390	2.4220	1.0455 to 5.6110
ALSFRSR_Early_Reponders	-1.2297	0.5695	4.6615	0.0308	0.2924	0.0958 to 0.8928

Null model -2 Log Likelihood	185.569
Full model -2 Log Likelihood	171.518
Chi-squared	14.051
DF	2
Significance level	P = 0.0009

NCT02238626 Clinical Trial

MN-166 (Ibudilast) bi-modal therapy with riluzole in ALS subjects is

- **feasible, tolerable, and safe,**
- **is associated with the proportion of subjects with no decline in ALSAQ - riluzole-ibudilast responders**
- **is associated with the proportion of subjects with little or no decline in ALSFRS-R total - riluzole-ibudilast responders.**

ALS subjects who successfully complete bi-modal therapy per protocol with riluzole and ibudilast display improved survival compared with non-per-protocol completers.

Improved survival in these patients is associated with having had no progression in ALSFRS-R when on ibudilast and riluzole.

NCT02238626 Clinical Trial

MN-166 (Ibudilast) bi-modal therapy with riluzole in ALS subjects needs further evaluation to assess the potential effect of ibudilast treatment protocols on function and survival in ALS patients and to explicitly exclude biased selection.

The novel statistical analysis employed in this phase 1b/2a clinical trial should be considered as an algorithm to provide a link between functional change with different treatments to later improved survival in ALS patients.

Change in function has been related to survival in cross-sectional and longitudinal clinical studies. This report identifies that ibudilast treatment with stabilization of function during an earlier time epoch may possibly be linked to improved survival during a subsequent off-treatment time epoch. To confirm this observation will need further clinical trials with attention to the correct comparator group.

Carolinas Neuromuscular / ALS-MDA Center

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Clinical Study Drug and Placebo
Clinical Trials Grant

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