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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4 Department of Internal Medicine – Carolinas Medical Center 5 Cabbarus College of Health Sciences – Occupational Therapy, Concord
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Disclosures

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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
ALS

Inhibit microglia activation: minocycline

Inhibit toll-like receptors

Microglia

Pro-inflammatory cytokines

TLR

Inhibit glial activation: 3-isobutylryl-2-isopropylpyrazolo-[1,5-a]pyridine (Ibudilast)

Astrocyte

PAR-2 receptor

PAR-2 antagonist: N1-3-methylbutyryl-N4-6-aminohexanoyl-piperazine (ENMD-1068)

Loss of BBB integrity

Endothelial cell

Basement membrane

Stimulus

MS

ClinicalTrials.gov

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

This study is enrolling, but not recruiting participants.

Sponsor:
Medinova

ClinicalTrials.gov Identifier:
NCT02320809

First Posted: September 12, 2014

Last Updated: October 30, 2017

ClinicalTrials.gov

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

This study is currently recruiting participants.

Sponsor:
Medinova

ClinicalTrials.gov Identifier:
NCT02714490

First Posted: March 21, 2016

Last Updated: August 14, 2017
**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 1999
- 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

**Primary Objective 1: BPF**

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

Treatment with ibudilast was associated with a 48% slowing in rate of decline.
The challenges associated with molecular targeted therapies for glioblastoma

Toni Rose Jue1, Kerrie L. McDonald1

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 involves 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.

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

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


Abstract BACKGROUND: Recurrence in patients with glioblastoma (GBM) is inevitable, even in patients with 0–6-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 ibudilast (AV411; 3-isobutyl-2-isopropyl pyrazolo[1,5-alpyridine) 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 (PDCCL) 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...
Ibudilast Pharmacology

Target Engagement

NCT02238626
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).
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 astrocytes (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).
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).
NCT02238626 Protocol Outcome Measures

**Adaptive Protocol**

- Riluzole inclusion criteria
- Advanced ALS on NIV

**Randomization**

- Ibudilast-drug
  - 30mg BID
  - Riluzole 50mg BID

- Ibudilast-pbo
  - 30mg BID
  - Riluzole 50mg BID

**Clinical Visits**

- 0
- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10
- 11
- 12

**Telephone Visits**

- 1
- 2

**DB**

**OLE**

**Post OLE**

**Survival Follow-up**

- 2 Week Safety

**Safety**

- Vital Signs
- TEAEs
- TESAEs
- Labs

**Feasibility**

- # 3 mon / Starts

**Tolerability**

- # 12 mon / Starts

**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

Randomization

1. MN-166 Placebo
2. MN-166 Ibudilast

Safety Cohort 1 to continue MN-166 in MN-166 / Placebo Treated Subjects at 6 months

Safety Cohort 2 to continue MN-166 in MN-166 / Placebo Treated Subjects at 12 months

Clinic Mon 0
Clinic Mon 3
Clinic Mon 6
Clinic Mon 9
Clinic Mon 12

2 4 8 12 16 20 24 28 32 36 40 44 48 52

Telephone Visits every Four (4) Weeks

AAN 2015
MND 2015
AAN 2016
MND 2016
MND 2017

NCT02238626 Protocol Milestones

MN - 166 - ALS - 1201

MN-166 Ibudilast

Safety Cohort 1
21 Subjects completing first 3 months on Treatment

Safety Cohort 2
20 MN-166 10 PBO Subjects completing first 6 months on Treatment

Analysis Cohort
40 MN-166 20 PBO Subjects on 6 months MN-166 Treatment

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
# EC Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=17)</th>
<th>Ibudilast (N=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>57.5</td>
<td>59.2</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>5 (29.4%)</td>
<td>11 (32.4%)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>15 (88.2%)</td>
<td>31 (91.2%)</td>
</tr>
<tr>
<td>African American</td>
<td>2 (11.8%)</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>Asian</td>
<td>0%</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0%</td>
<td>1 (2.9%)</td>
</tr>
<tr>
<td><strong>Baseline ALSFRS-R</strong></td>
<td>39.0</td>
<td>39.3</td>
</tr>
<tr>
<td><strong>Baseline SVC</strong></td>
<td>97.2</td>
<td>92.0</td>
</tr>
<tr>
<td><strong>Baseline MIP/NIF</strong></td>
<td>-98.1</td>
<td>-86.0</td>
</tr>
<tr>
<td><strong>Baseline MMT (Right)</strong></td>
<td>4.08</td>
<td>4.16</td>
</tr>
<tr>
<td><strong>Baseline MMT (Left)</strong></td>
<td>3.97</td>
<td>4.15</td>
</tr>
<tr>
<td><strong>Baseline ALSAQ-5</strong></td>
<td>6.4</td>
<td>6.4</td>
</tr>
</tbody>
</table>
NCT02238626

CONSORT Diagram

DB - OLE - 12 months
Early Cohort

Screen Failure = 4

Screened = 55

Randomized = 51

Placebo
N=17

Early Terminate 2

Month 6 completer on study drug
N=15

Early Terminate 3

Month 12 completer on study drug
N=12

MN-166
N=34

Early terminate 5

Month 6 completer on study drug
N=29

Early Terminate 6

Month 12 completer on study drug
N=23

Early Terminate 5

Early Terminate 6

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<table>
<thead>
<tr>
<th>DB</th>
<th>OL</th>
<th>WO</th>
<th>PWO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>12</td>
<td>14</td>
</tr>
</tbody>
</table>

### 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

### OL
- 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
- Randomization

Months: 18-37
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

NCT02238626
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)
Primary Endpoints

Tolerability / Safety

DB - OLE -12 months
### Primary Endpoints: Tolerability

**EC Safety Analysis ITT Population**

# of subjects early study or drug termination

Double-Blind Epoch (0 - 6 month)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 17)</th>
<th>Ibudilast (N = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early Study Termination</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Due to AEs</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>• Any Reason</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Early Drug Termination</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Due to AEs</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>• Any Reason</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
## Primary Endpoints: Safety

**EC Safety Analysis ITT Population**

**Treatment Related AEs (TRAEs)**

<table>
<thead>
<tr>
<th># of Subjects or # of Events</th>
<th>Placebo N=17</th>
<th>Ibudilast N=34</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Subject with at Least one TRAEs</td>
<td>n= 3</td>
<td>n= 4</td>
</tr>
<tr>
<td>Total events # of TRAEs</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Severe or Life-threatening TRAEs</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serious TRAEs</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
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Primary Endpoints : Safety

EC Safety Analysis ITT Population

Treatment Related AEs ( TRAEs ) # of events

Double-Blind Epoch ( 0 – 6 month)

<table>
<thead>
<tr>
<th>System Organ Code</th>
<th># of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=3)</td>
</tr>
<tr>
<td>Gastrointestinal system</td>
<td>1</td>
</tr>
<tr>
<td>Nervous system disorder</td>
<td>3</td>
</tr>
<tr>
<td>Metabolism and Nutrition</td>
<td>0</td>
</tr>
<tr>
<td>Investigation</td>
<td>1</td>
</tr>
<tr>
<td>Injury</td>
<td>0</td>
</tr>
</tbody>
</table>
### Primary Endpoints: Safety

#### EC Safety Analysis ITT Population

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Ibudilast</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At Least one TEAEs</strong></td>
<td>( n = 17 )</td>
<td>( n = 34 )</td>
</tr>
<tr>
<td><strong>Severe or Life threatening TEAEs</strong></td>
<td>( n = 2 )</td>
<td>( n = 4 )</td>
</tr>
<tr>
<td><strong>Serious Adverse Events</strong></td>
<td>( n = 1 )</td>
<td>( n = 5 )</td>
</tr>
<tr>
<td><strong>Treatment Related Adverse Events</strong></td>
<td>( n = 10 )</td>
<td>( n = 13 )</td>
</tr>
</tbody>
</table>

**Entire Study (0-12 months)**

- **Placebo**: \( N = 17 \)
- **Ibudilast**: \( N = 34 \)
## PrimaryEndpoints: Safety

**EC Safety Analysis ITT Population Serious Adverse Events**

**Double-Blind and Open Label Extension (0-12 months)**

<table>
<thead>
<tr>
<th>Subject Reference #</th>
<th>SAEs</th>
<th>Treatment related?</th>
</tr>
</thead>
<tbody>
<tr>
<td>022</td>
<td>DVT</td>
<td>No</td>
</tr>
<tr>
<td>027</td>
<td>Leg fracture</td>
<td>No</td>
</tr>
<tr>
<td>028</td>
<td>Dysphagia</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Bowel obstruction</td>
<td></td>
</tr>
<tr>
<td>029</td>
<td>Ankle fracture</td>
<td>No</td>
</tr>
<tr>
<td>049</td>
<td>Ureteral stone</td>
<td>No</td>
</tr>
<tr>
<td>052</td>
<td>Pneumonia</td>
<td>No</td>
</tr>
</tbody>
</table>
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Secondary Endpoints

Clinical Endpoint Responsiveness

DB - OLE -12 months
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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**  

**EC ITT population**  

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

<table>
<thead>
<tr>
<th></th>
<th>Double-Blind Phase</th>
<th>Open-Label Phase</th>
<th>Ibudilast treatment combined</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td>(N = 17)</td>
<td>(N = 17)</td>
<td>(N = 51)</td>
</tr>
<tr>
<td><strong>Ibudilast</strong></td>
<td>(N = 34)</td>
<td>(N = 17)</td>
<td></td>
</tr>
<tr>
<td>4 / 17</td>
<td>11 / 34</td>
<td>6 / 17</td>
<td>17 / 51</td>
</tr>
<tr>
<td>(23.5%)</td>
<td>(32.4%)</td>
<td>(35.3%)</td>
<td>(33.3%)</td>
</tr>
</tbody>
</table>

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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
## ALSAQ-5 score

### EC ITT population

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

<table>
<thead>
<tr>
<th>Double-Blind Phase</th>
<th>Open-Label Phase Ibudilast 6-12 mon treatment</th>
<th>Ibudilast treatment combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Ibudilast</td>
<td></td>
</tr>
<tr>
<td>(N = 17)</td>
<td>(N = 34)</td>
<td>(N = 51)</td>
</tr>
<tr>
<td>4 / 17</td>
<td>17 / 34</td>
<td>22 / 51</td>
</tr>
<tr>
<td>(23.5 %)</td>
<td>(50.0 %)</td>
<td>(43.1 %)</td>
</tr>
</tbody>
</table>

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NCT02238626

Secondary Endpoints

ALSFRS-R total

Responder = \leq 1 \text{ unit loss per 6 months change}

Non-Responder = > 1 \text{ unit loss per 6 months change}

DB - OLE -12 months
## ALSFRS-R Score

**EC ITT population**

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

<table>
<thead>
<tr>
<th></th>
<th>Double-Blind Phase</th>
<th>Open Label Phase</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td>Placebo (N = 17)</td>
<td>Ibudilast (N = 34)</td>
<td>Ibudilast 0-6 mon treatment (N = 17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ibudilast 0-6 mon treatment (N = 17)</td>
<td>Ibudilast 6-12 mon treatment (N = 34)</td>
</tr>
<tr>
<td><strong>3 / 17</strong> (17.6%)</td>
<td>10 / 34 (29.4%)</td>
<td>6 / 17 (35.3%)</td>
<td>3 * / 34 (8.8%)</td>
</tr>
</tbody>
</table>

* Removed 2 overwrapped subjects
### ALSFRS-R Score

**EC PP population**

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

<table>
<thead>
<tr>
<th>Double-Blind Phase</th>
<th>Open Label Phase</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td><strong>Ibudilast</strong></td>
<td><strong>Ibudilast</strong></td>
</tr>
<tr>
<td>( N = 15 )</td>
<td>( N = 29 )</td>
<td>( N = 12 )</td>
</tr>
<tr>
<td>3 / 15 ( 20.0 % )</td>
<td>10 / 29 ( 34.5 % )</td>
<td>6 / 12 ( 50.0 % )</td>
</tr>
<tr>
<td><strong>Ibudilast</strong></td>
<td><strong>Ibudilast</strong></td>
<td><strong>Ibudilast</strong></td>
</tr>
<tr>
<td>0-6 mon treatment</td>
<td>6-12 mon treatment</td>
<td>0-12 mon treatment combined</td>
</tr>
<tr>
<td>( N = 12 )</td>
<td>( N = 23 )</td>
<td>( N = 35 )</td>
</tr>
<tr>
<td>6 / 12 ( 50.0 % )</td>
<td>3 * / 23 ( 13.0 % )</td>
<td>19 * / 35 ( 54.3 % )</td>
</tr>
</tbody>
</table>

* Removed 2 overwrapped subjects

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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

Placebo Non-Decline PP
782 / 3132 = 25 % 6 mon
337 / 2105 = 16 % 12 mon
85 / 1218 = 7 % 18 mon

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

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ALSFRS-R Responder Analysis

How common are ALS plateaus and reversals?

ABSTRACT
Objectives: To determine the frequency of amyotrophic lateral sclerosis (ALS) plateaus and reversals in the Functional Responder Analysis (FRAD-ALS) data set.
Methods: We analyzed 4 consecutive longitudinal Functional Responder Analysis (ALSFRS-R Functional Responder Analysis) data sets (FRAD-ALS) from the functional responder analysis (ALSFRS-R). The percentage of patients experiencing plateaus or reversals was calculated using CUSUM analysis performed over 6,12, and 18 months. Patients were selected at random from a database of 2,116 patients with ALS. The percentage of patients with plateaus or reversals was calculated using CUSUM analysis performed over 6,12, and 18 months. The percentage of patients with plateaus or reversals was calculated using CUSUM analysis performed over 6,12, and 18 months.
Results: The frequency of plateaus and reversals was assessed in a total of 2,116 patients with ALS. The percentage of patients with plateaus and reversals was calculated using CUSUM analysis performed over 6,12, and 18 months. The percentage of patients with plateaus and reversals was calculated using CUSUM analysis performed over 6,12, and 18 months.
Conclusions: ALS plateaus and reversals are more common than previously reported. Further studies are needed to determine the potential mechanisms and clinical implications of these events.

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

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ALSFRS-R Responder Analysis
Distribution of ALSFRS-R score

ALSFRS-R total - Baseline

ALSFRS-R total - Month 6

ALSFRS-R total - Month 12
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Adaptive Protocol

Per Protocol Analysis

Survival

OLE and Post OLE
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.
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.
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Patient Care Services Grant
MDA ALS Outcomes Registry

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