NCT02238626

Novel Composite Endpoint Extended Analysis During Extension of Ibudilast Phase 1b / 2a Clinical Trial Better Predicts Post-Wash-Out Survival

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Ibudilast - Glial Pathology MS, ALS, Glioblastoma Treatment Development

Ibudilast Pharmacology - Target Engagement

Adaptive Protocol - Early Cohort (EC) - DB - OLE -12 months
- Vital Status post Ibudilast Washout

CONSORT Diagram - DB - OLE -12 months

Adaptive Protocol - Loss of Muscle Strength off Ibudilast

Adaptive Protocol - Novel Composite Endpoint

Adaptive Protocol - Relation of Novel Composite Endpoint to Survival

Adaptive Protocol - Relation of Per Protocol Completion to Survival

Conclusions - Multiple Myeloma Stem Cell Therapy ALS Gene Therapy ALS
Ibudilast - Glial Pathology
MS, ALS, Glioblastoma
Treatment Development

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Inhibit microglia activation: minocycline

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

Inhibit toll-like receptors

Pro-inflammatory cytokines

Astrocyte

PAR-2 receptor

Loss of BBB integrity

PAR-2 antagonist: N1-3-methylbutyryl-N4-6-aminohexanoyl-piperazine (ENMD-1068)
SPRINT-MS/NN 102 Phase II Trial of Ibudilast in Progressive MS: Top-Line Results

**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 1986
- 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

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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 as 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 “bullets” approach is unrealistic.

5

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-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...
Ibudilast Pharmacology

Target Engagement

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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 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

**IC$_{50}$**

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

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 1**

Chemical structure of Ibudilast and its major oxidative metabolite, 6,7-dihydroidiol-Ibudilast.

**Figure 3**

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).
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Adaptive Protocol

- Early Cohort (EC)

- DB - OLE -12 months

- Vital Status post Ibudilast Washout
Methods

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
- $>1$ unit loss in post diagnosis ALSFRS-R total score per month
Methods

MN-166-ALS-1201 Adaptive Design Protocol

NCT02238626 Protocol Outcome Measures

Adaptive Protocol

Months

Clinic Visits

Telephone Visits

Randomization

Ibudilast-drug

30mg BID

Riluzole

50mg BID

Ibudilast-pbo

30mg BID

Riluzole

50mg BID

DB

OLE

Post OLE

1°

Safety

Vital Signs

TEAEs

TESAEs

Labs

Feasibility

# 3 mon / Starts

Tolerability

# 12 mon / Starts

2°

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
### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=17)</th>
<th>Ibudilast (N=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>57.5</td>
<td>59.2</td>
</tr>
<tr>
<td>Female</td>
<td>5 (29.4%)</td>
<td>11 (32.4%)</td>
</tr>
<tr>
<td>Ethnicity</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>Baseline ALSFRS-R</td>
<td>39.0</td>
<td>39.3</td>
</tr>
<tr>
<td>Baseline SVC</td>
<td>97.2</td>
<td>92.0</td>
</tr>
<tr>
<td>Baseline MIP/NIF</td>
<td>-98.1</td>
<td>-86.0</td>
</tr>
<tr>
<td>Baseline MMT (Right)</td>
<td>4.08</td>
<td>4.16</td>
</tr>
<tr>
<td>Baseline MMT (Left)</td>
<td>3.97</td>
<td>4.15</td>
</tr>
<tr>
<td>Baseline ALSQ-5</td>
<td>6.4</td>
<td>6.4</td>
</tr>
</tbody>
</table>
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CONSORT Diagram

DB - OLE - 12 months
CONSORT Subject Trajectories

Early Cohort

- Screened = 55
- Randomized = 51

Screen Failure
N = 4

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

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Adaptive Protocol

Loss of Muscle Strength off Ibudilast

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Decreased Strength off Ibudilast

Statistically Significant Decrease in Neck Flexion

2 Weeks post Stopping Ibudilast

MN-166-ALS-1201 Mon 12 + 2 Weeks

Bulbar (N=9) & Limb (N=17)

Neck Flexion

Sample 1
Sample 2

Sample size
10
9

Arbuthnott score
3.92
3.86

BEC (in mm)
4.32 (4.625) - 10.32 (4.11)

Variance
1.41
1.26

Standard deviation
1.82
1.19

Statistical test
P = 0.0038

P = 0.0038

Statistically Significant Decrease in Hip Flexion

2 Weeks post Stopping Ibudilast

MN-166-ALS-1201 Mon 12 + 2 Weeks

Bulbar (N=9) & Limb (N=17)

Hip Flexion

Sample 1
Sample 2

Sample size
32
32

Arbuthnott score
2.84
3.92

BEC (in mm)
3.78 (1.696) - 10.78 (0.535)

Variance
4.24
4.03

Standard deviation
1.90
1.35

Statistical test
P = 0.0010

P = 0.0010

Statistically Significant Decrease in Leg Flexion

2 Weeks post Stopping Ibudilast

MN-166-ALS-1201 Mon 12 + 2 Weeks

Bulbar (N=9) & Limb (N=17)

Hamstrings

Sample 1
Sample 2

Sample size
32
32

Arbuthnott score
2.63
3.12

BEC (in mm)
3.31 (1.647) - 10.31 (0.385)

Variance
3.54
3.22

Standard deviation
1.97
1.89

Statistical test
P = 0.0494

P = 0.0494
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ALSFRS-R Responders

Distribution of ALSFRS-R score

ALSFRS-R total - Baseline

ALSFRS-R total - Month 6

ALSFRS-R total - Month 12
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ALSFRS-R Responders

Months post Randomization

ALSFRS-R Total

0 3 6 9 12

0 4 8 12 16 20 24 28 32 36 40 44 48
Adaptive Protocol

Novel Composite Endpoint

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Novel Composite Endpoint

Composite Endpoint

[a] < 12 unit Drop in ALSFRS-R total score at end of OLE phase
[b] < 1 MMT unit drop in Neck and/or Leg muscles at end of OLE phase

Ibudilast = 11/34
Placebo = 2/17
Chi-Square = 2.5294
P = 0.1117

Ibudilast therapy associated with proportionately more non-progressors compared with placebo therapy
Adaptive Protocol

Relation of Novel Composite Endpoint to Survival

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Subjects who achieved Composite Endpoint during the DB and OLE epochs of the adaptive NCT02238626 clinical trial showed improved survival.
Subjects who achieved Composite Endpoint during the DB and OLE epochs of the adaptive NCT02238626 clinical trial showed improved survival.

### Kaplan-Meier survival analysis

<table>
<thead>
<tr>
<th>Survival time</th>
<th>LABLDeathMon</th>
<th>LABDeath1</th>
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</thead>
<tbody>
<tr>
<td>Endpoint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Factor codes</td>
<td>LAalsfrs_r12NL</td>
<td></td>
</tr>
<tr>
<td>Cases summary</td>
<td>Number of events</td>
<td>Number censored</td>
</tr>
<tr>
<td>Factor</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>0</td>
<td>2</td>
<td>15.38</td>
</tr>
<tr>
<td>1</td>
<td>26</td>
<td>68.42</td>
</tr>
<tr>
<td>Overall</td>
<td>28</td>
<td>54.90</td>
</tr>
</tbody>
</table>

- LADeath1 = 1
- LADeath1 = 0

### Mean and median survival

<table>
<thead>
<tr>
<th>Factor</th>
<th>Mean</th>
<th>SE</th>
<th>95% CI for the mean</th>
<th>Median</th>
<th>95% CI for the median</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>38.944</td>
<td>1.428</td>
<td>36.145 to 41.743</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>26.791</td>
<td>1.724</td>
<td>23.411 to 30.170</td>
<td>24.000</td>
<td>22.000 to 32.000</td>
</tr>
<tr>
<td>Overall</td>
<td>29.977</td>
<td>1.533</td>
<td>26.972 to 32.982</td>
<td>30.000</td>
<td>24.000 to 36.000</td>
</tr>
</tbody>
</table>

### Expected n

<table>
<thead>
<tr>
<th>Endpoint: Observed n</th>
<th>Expected n</th>
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<tbody>
<tr>
<td></td>
<td>2.0</td>
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### Comparison of survival curves (Logrank test)

<table>
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<tr>
<th>Chi-squared</th>
<th>DF</th>
<th>Significance</th>
<th>Hazard ratios* with 95% Confidence Interval</th>
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<tbody>
<tr>
<td>10.8903</td>
<td>1</td>
<td>P = 0.0010</td>
<td></td>
</tr>
<tr>
<td>0.1989</td>
<td>1</td>
<td></td>
<td>0.06342 to 0.2971</td>
</tr>
</tbody>
</table>

* Column/Row
Adaptive Protocol

Relation of Per Protocol Completion to Survival
Subjects who completed the DB and OLE epochs of the adaptive NCT02238626 clinical trial per protocol showed improved survival.
Subjects who completed the DB and OLE epochs of the adaptive NCT02238626 clinical trial per protocol showed improved survival.
Conclusions

Novel composite endpoint defined as less than 12 units (< 1 unit per month) decrease in ALSFRS-R total score and/or not losing 1 MMT unit in neck and leg muscles in the DB and OLE epochs (12 months) was analyzed.
Conclusions

11 / 34 ALS subjects randomized [ (intention-to-treat (ITT)] to ibudilast compared with 2 / 17 subjects randomized to placebo (P=0.1117) showed no progression.

Subjects (ITT) who showed no progression on 6 or 12 months ibudilast showed improved survival (P=0.0010) in the 30 months post ibudilast treatment.
Subjects who completed 6 or 12 months ibudilast treatment [ per-protocol (PP) ] showed improved survival (P=0.0025) in the 30 months post ibudilast treatment.
Conclusions

Multiple Myeloma
treatment epoch biomarker response survival

Stem Cell Therapy
treatment epoch biomarker response survival

Gene Therapy
treatment epoch biomarker response survival
NCT02238626 Supported by

MEDICINova
Logistical and Statistical Support
Clinical Study Drug and Placebo
Clinical Trials Grant

STUDYTRAX
Clinical Trials Database Development / Support

MDA ALS DIVISION
Standard of Care
Patient Care Services Grant
MDA ALS Outcomes Registry

Carolinas HealthCare System
CMC - Neurology
Carolinas Neuromuscular / ALS-MDA Center
CMC - Neurology Research Division
CHS - Office of Clinical and Translational Research
CHS - Dickson Advanced Analytics DA²

Carolinas HealthCare Foundation

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