P6-465

Ibudilast - Phosphodiesterase Type 4 Inhibitor - Bi-Modal Therapy with Riluzole in Early [Not Requiring Non-Invasive Ventilation (NIV)] Cohort (EC) and Advanced [Requiring NIV] (ANC) Amyotrophic Lateral Sclerosis (ALS) Patients - Single-Center Adaptive Design Six-Month Double-Blind (DB) - Placebo-Controlled Phase 1b/2a Epoch Followed by Six-Month Open Label Extension (OLE) Epoch,Washout (WO) and Post-Washout Epoch (PWO) – Final Report and Future Directions

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Objective

Report relationship of randomized DB-delayed-start/placebo-controlled ibudilast treatment combined with OLE treatment on clinical endpoint-responsiveness [ALSFRS-R total/sub/item scores, manual muscle strength measurements in limb / oro-facial muscles, vital capacity, maximal-inspiratory-pressure, maximal-voluntary ventilation, bulbar/limb timed-functional-tests, quality-of-life measures, survival] at end of DB OLE / WO epochs continuing into PWO epoch in Per-Protocol completers (PP) compared with nonPP-completers (nPP) [ECPP= 35;EC-nPP=16; ANC-PP=12; ANC-nPP=7]. Compare apriori statistical plan responder analysis of ≤ 2 units drop in ALSFRS-R in DB epoch with post hoc analysis of novel composite endpoint consisting of [a] < 12 unit drop in ALSFRS-R [b] < 1 MMT unit drop in neck and/or leg strength during DB and OLE epochs on post washout (PWO) survival.

Background

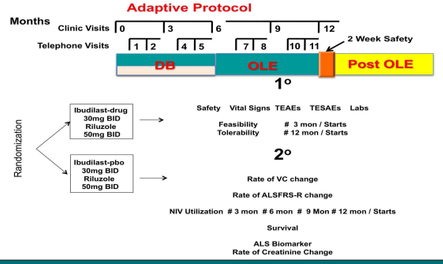
Ibudilast, effective in two ALS-gene-based models, has a known human safety profile that permits assessment of its effectiveness targeting multiple disease pathways at early–distal-axonopathy;late–microglial-activation ALS stages. Ibudilast delays developement of brain atrophy in progressive MS.

Methods

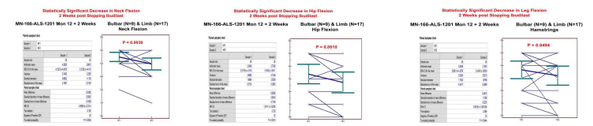
MN-166-ALS-1201 Adaptive Design Protocol

NCT02238626 Protocol Outcome Measures

Adaptive Protocol



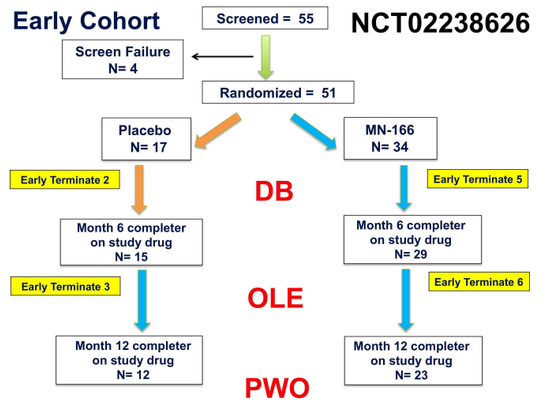
Decreased Strength off Ibudilast



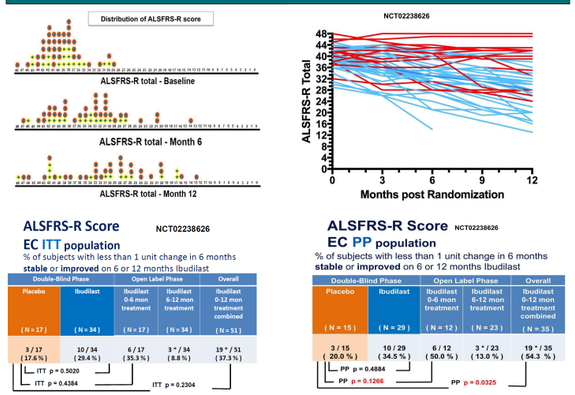
Baseline Characteristics

EC Cohort	Placebo (N=17)	Ibudilast (N=34)
Age	57.5	59.2
Female	5 (29.4%)	11 (32.4%)
Ethnicity		
•Caucasian	15 (88.2%)	31 (91.2%)
•African American	2 (11.8%)	1 (2.9%)
•Asian	0%	1 (2.9%)
•Unknown	0%	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 ALSQ-5	6.4	6.4

CONSORT Subject Trajectories



ALSFRS-R Responders



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 Ibudilast

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 %)

ITT p = 0.5020
ITT p = 0.4384
ITT p = 0.2304

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 Ibudilast

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 %)

PP p = 0.4884
PP p = 0.1266
PP p = 0.0325

Novel 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

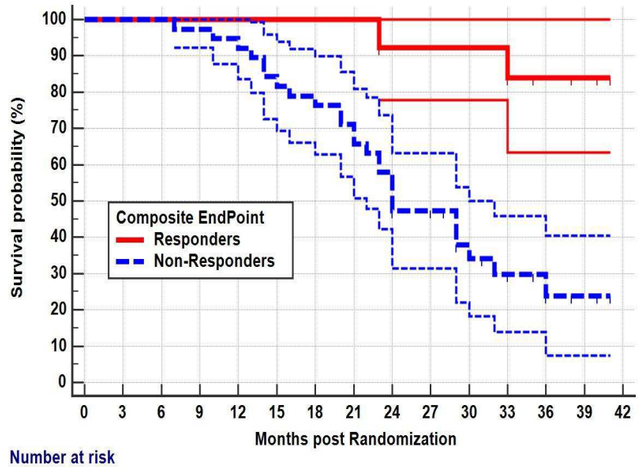
Chi-Square = 2.5294

P = 0.1117

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

Composite Endpoint and Survival

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



Number at risk
Group: Responders
13 13 13 13 13 13 13 13 11 11 11 8 7 4 0
Group: Non-Responders
38 38 38 37 35 31 29 25 17 16 9 6 3 2 0

Kaplan-Meier survival analysis

Survival time	LABLDeathMon
Endpoint	LADeath1
Factor codes	LAalsfrs_r12NL

Cases summary

Factor	Number of events a N	Number of events a %	Number censored b N	Number censored b %	Total sample size
0	2	15.38	11	84.62	13
1	26	68.42	12	31.58	38
Overall	28	54.90	23	45.10	51

a LADeath1 = 1
b LADeath1 = 0

Mean and median survival

Factor	Mean	SE	95% CI for the mean	Median	95% CI for the median
0	38.944	1.428	36.145 to 41.743	24.000	22.000 to 32.000
1	26.791	1.724	23.411 to 30.170	24.000	24.000 to 36.000
Overall	29.977	1.533	26.972 to 32.982	30.000	24.000 to 36.000

Endpoint: Observed n	2.0	26.0
Expected n	10.1	17.9
Observed/Expected	0.1989	1.4489

Comparison of survival curves (Logrank test)

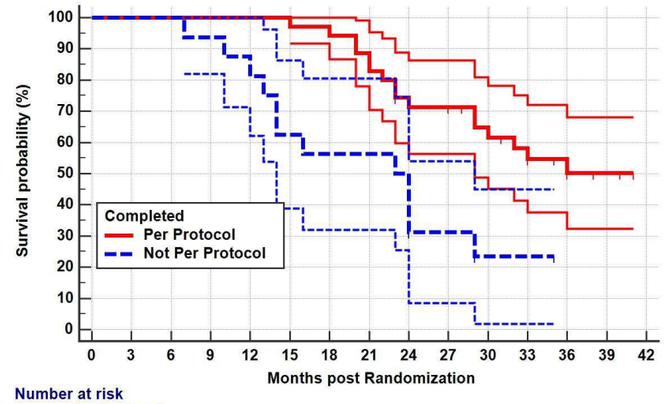
Chi-squared	10.8903
DF	1
Significance	P = 0.0010

Hazard ratios a with 95% Confidence Interval

Factor	0	1
0	-	7.2852
1	0.1373	3.3661 to 15.7671
	0.06342 to 0.2971	-

Per-Protocol and Survival

Subjects who completed the DB and OLE epochs of the adaptive NCT02238626 clinical trial per protocol showed improved survival.



Number at risk
Group: Per Protocol
35 35 35 35 35 34 33 29 24 23 19 13 10 6 0
Group: Not Per Protocol
16 16 16 15 13 10 9 9 4 4 1 1 0 0 0

Kaplan-Meier survival analysis

Survival time	LABLDeathMon
Endpoint	LADeath1
Factor codes	nPP1

Cases summary

Factor	Number of events a N	Number of events a %	Number censored b N	Number censored b %	Total sample size
0	16	45.71	19	54.29	35
1	12	75.00	4	25.00	16
Overall	28	54.90	23	45.10	51

a LADeath1 = 1
b LADeath1 = 0

Mean and median survival

Factor	Mean	SE	95% CI for the mean	Median	95% CI for the median
0	33.236	1.529	30.239 to 36.233		
1	21.781	2.363	17.149 to 26.413	23.000	14.000 to 29.000
Overall	29.977	1.533	26.972 to 32.982	30.000	24.000 to 36.000

Endpoint: Observed n	16.0	12.0
Expected n	22.2	5.8
Observed/Expected	0.7198	2.0790

Comparison of survival curves (Logrank test)

Chi-squared	9.1137
DF	1
Significance	P = 0.0025

Hazard ratios a with 95% Confidence Interval

Factor	0	1
0	-	2.8883
		1.1561 to 7.2161
1	0.3462	-
	0.1386 to 0.8650	

Conclusions

In this phase 1b/2a clinical trial, a 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.

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.

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