



Clinical effect of the neuroprotectant MN-166 in relapsing MS: Year 2 Data

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Abstract

Background: MN-166 (budilast) is an orally administered small molecule with neuroprotectant and anti-inflammatory properties. In Year 1 of this 2-yr study (Drulovic et al,ECTRIMS 2008), MN-166 at 60 mg/d significantly reduced Percent Brain Volume (PBV) loss and prolonged time-to-first relapse by 157 d (p=0.04), but did not significantly reduce cumulative new lesion count, the primary study endpoint, in Relapsing MS (RMS) patients. MN-166 produced a dose-related reduction in the evolution of new inflammatory lesions to PBH (p=0.01; Gammans et al, ENS 2008).

Methods: Relapsing Remitting MS (93%) or Secondary Progressive MS with relapses (7%) patients and ≥ 1 T1 Gd-lesions were randomized to placebo (PBO, n=100) or MN-166 at 30 (n=94) or 60 mg/d (n=98); for year 2 PBO patients were pre-assigned to MN-166 at 30 (n=49) or 60 mg/d (n=51). Clinical and MRI evaluations were every 2 months for 2 years.

Results: 264 (96% of PBO-30 mg/d, 97% of PBO-60 mg/d, 82% of 30 mg/d and 87% of 60 mg/d) patients entered Year 2. Significantly fewer patients treated with MN-166 for 2 yr at 30 or 60 mg/d than patients treated with PBO followed by MN-166 at either dose for 1 year had a sustained disability progression (+1 point on EDSS for ≥ four months) (2 yr MN-166: 10.4%, PBO to MN-166: 21%, p=0.03). MN-166 at 60 mg/d for 2 years significantly (p=0.04) attenuated loss in PBV compared to the remaining groups. MN-166 was well tolerated at either dose. Three of the 85 MN-166 60 mg/d patients discontinued in Year 2 for adverse effects compared to none in the other groups. Only GI events were more frequent in Year 2 on MN-166 at 60 mg/d (11%) and 30 mg/d (4.2%) PBO-to-60 mg/d (2%) PBO to 30 mg/d (0%). Depression was reported in 5% of the 60 mg/d and 3% of the PBO to 60 mg/d patients towards the end of the 2nd year of the study.

Conclusion: The findings suggest that the main effects of treatment with MN-166 in relapsing MS patients is to protect neurons from the persistent damage that results from inflammatory lesions. The findings also suggest that MN-166 is safe and well tolerated.

Study Design

Phase II placebo-controlled, randomized, double-blind study
 n ~ 100 MS patients/group @ 25 sites in Serbia, Ukraine, Belarus, Bulgaria and Romania

Randomization was 1:1:0.5:0.5

Treatment Group	Year 1	Year 2
1	10mg TID / Day	10mg TID / Day
2	20mg TID / Day	20mg TID / Day
3	Placebo	10mg TID / Day
4	Placebo	20mg TID / Day

Major inclusion criteria

- Males or females aged 18 to 55 years, with relapsing remitting (RR) and/or secondary progressive (SP) Multiple Sclerosis with continued relapses;
- A definite diagnosis of relapsing MS using the new International Committee recommendations (MacDonald Criteria);
- One MRI scan taken two weeks prior to treatment start using a standardized MRI protocol with at least one Gd-enhancing lesion;
- An EDSS score of 5.5 or less at the screening and baseline visits.

Major exclusion criteria

- Treatment with systemic immunosuppressants (including investigational treatments), such as infliximab, natalizumab, cyclophosphamide, mitoxantrone, azathioprine, methotrexate, linomide, cyclosporine or deoxyspergualine within 6 months of the Week -2 cranial MRI scan;
- Treatment with total lymphoid irradiation or cladribine at any time;
- Treatment with interferons within 45 days of the Week -2 cranial MRI scan;
- History of recent relapse and treatment with corticosteroids or ACTH within 45 days of the Week -2 cranial MRI scan.

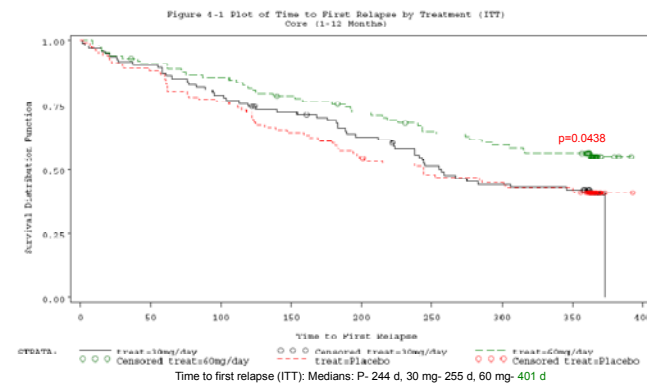
Results

Demographics

Characteristic	TREATMENT			
	PBO to 30 mg	PBO to 60 mg	30 mg	60 mg
# Subjects (ITT)	51	49	94	98
Mean Age	36.5	34.8	35.5	36.2
Mean BMI	24.0	23.5	23.5	22.4
%male / %female	39/61	29/71	39/61	27/73
% relapsing-remitting	94	90	94	93
% secondary progressive	6	10	6	7

Reasons for Study Discontinuation

Reason	TREATMENT				Total
	PBO to 30 mg (N=52)	PBO to 60 mg (N=51)	30 mg (N=95)	60 mg (N=99)	
Pt Withdrew Consent	0 (0.0%)	4 (7.8%)	8 (8.4%)	6 (6.1%)	18 (6.1%)
Pt no longer meets entry criteria	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (0.3%)
Adverse Event	1 (1.9%)	1 (2.0%)	2 (2.1%)	5 (5.1%)	9 (3.0%)
Pt is non-compliant	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.0%)	1 (0.3%)
Pt is lost to follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Investigator's Decision	0 (0.0%)	2 (3.9%)	1 (1.1%)	1 (1.0%)	4 (1.3%)
Pregnancy	0 (0.0%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (0.3%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sponsor stopped the study	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lack of Efficacy	2 (3.8%)	2 (3.9%)	5 (5.3%)	4 (4.0%)	13 (4.4%)
Other	0 (0.0%)	0 (0.0%)	1 (1.1%)	4 (4.0%)	5 (1.7%)
Total	3 (5.8%)	9 (17.6%)	19 (20.0%)	21 (21.2%)	52 (17.5%)



Results

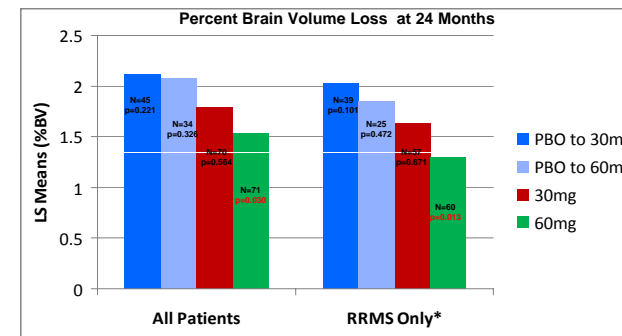
Reduction of Persistent Black Hole (PBH) Formation

Parameter	Treatment Groups		
	Placebo	30 mg/day	60 mg/day
# Patients w. New Lesions at Month 2	72	64	56
Mean Proportion of Lesions Evolving to PBH	0.24	0.20	0.16
Median Proportion of Lesions Evolving to PBH	0.17	0.08	0.04
Relative Risk (for Evolution to PBH) vs. placebo	-	0.74	0.63
p Value	-	0.074	0.011

Parameter	Treatment Groups		
	Placebo	30 mg/day	60 mg/day
# Patients w. New Lesions at Month 2	72	64	56
# of New Lesions	426	338	315
# of Persistent Black Holes	98	58	47
Proportion of Lesions Evolving to PBH	0.23	0.17	0.14
p Value	-	0.036	0.004

Per Cent of Subjects with Disability Progression

Time Period	TREATMENT		
	Placebo to Active (N=100)	30 mg (N=94)	60 mg (N=98)
1 Year	8 (8.0%)	5 (5.3%)	4 (4.1%)
2 Years	(to 30 mg/d) 8/51 (15.7%)	(to 60 mg/d) 13/49 (26.5%)	10 (10.6%) 10 (10.2%)
	21/100 (21%)		20/192 (10.4%) p=0.0264



Results

Cumulative Active Lesions (12 months) Primary Endpoint

Parameter	Treatment Groups		
	Placebo (N=100)	30 mg/day (N=94)	60 mg/day (N=98)
Mean Number of Cumulative Active Lesions	29.9	24.6	22.8
Median Number of Cumulative Active Lesions	15.5	18.0	13.0
Relative Risk of an Active Lesion Per Scan	-	0.961	0.957
p Value	-	0.762	0.735

Safety

MN-166 was very well tolerated; 89% of subjects completed the first 12 months (core) of the study; 82.5% completed 24 months
 Side effects were generally mild and self-limiting
 No patterns of laboratory or ECG findings
 In year 1, Treatment Emergent GI side effects occurred at ~2-fold that of the placebo rate (pbo ~ 7.8%, 30 mg/d ~ 11.6%, 60 mg/d ~ 15.2%) and are likely due to phosphodiesterase IV inhibition
 Tolerance to GI side effects occurred rapidly (2-4 days)
 More depression in 60 mg/d patients late in Year 2
 21 serious adverse events were reported; all were not or unlikely to be attributable to treatment
 No deaths occurred in the study

Conclusions

MN-166 was well safe and well tolerated.

MN-166 demonstrated effect with respect to the following secondary efficacy measures

- Time-to-first relapse
- Disability Progression
- Percent Change in brain volume
- Probability of New Lesions evolving to Persistent Black Holes (PBH)

The analysis of the primary efficacy variable (cumulative number of active lesions) did not produce a statistically significant difference between MN-166 and placebo

These data suggest that MN-166 acts primarily as a neuroprotectant and reduces sustained disability progression in subjects with relapsing MS

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