

Clinical effect of the neuroprotectant MN-166 in relapsing forms of MS

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MN-166-CL-001 investigators

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MN-166 (ibudilast) Mechanism(s) of Action

- **Anti-inflammatory**

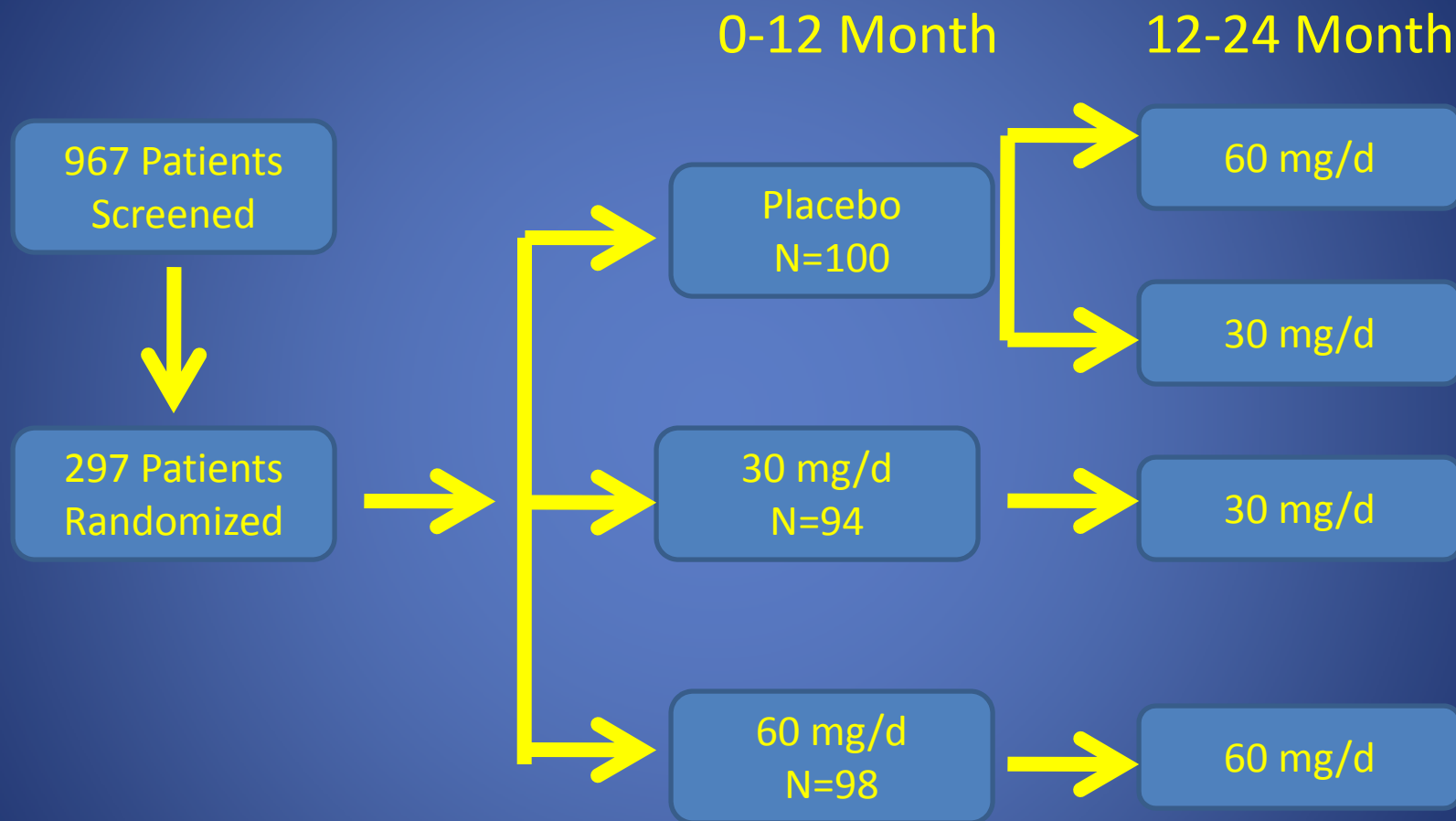
- Phosphodiesterase 3A, 4, 10, 11 inhibitor
- Leukotriene inhibitor
- Inhibits Th1 cytokine production (IFN- γ , TNF- α , IL-1 β , IL-6)
- Stimulates Th2 cytokine production (IL-4, IL-10)

- **Neuroprotective**

- Inhibits nitric oxide and reactive oxygen species production
- Stimulates neurotrophic factor release (NGF, GDNF, NT-4)
- Cerebrovasodilator (via PGI₂ and/or adenosine receptors)

MN-166-CL-001 Scheme

(MRI and Clinical evaluations bi-monthly)



Primary endpoint : cumulative active lesions by MRI

Secondary endpoints: clinical relapses and other MRI measures

MN-166-CL-001 Design

- Key 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.

MN-166-CL-001 Design

- Key Exclusion criteria:
 - Treatment with systemic immunosuppressants (including investigational treatments), such as infliximab, natalizumab, cyclophosphamide, mitoxantrone, azothioprine, methotrexate, linomide, cyclosporine or deoxysperagualine 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.

MN-166-CL-001

Patient characteristics

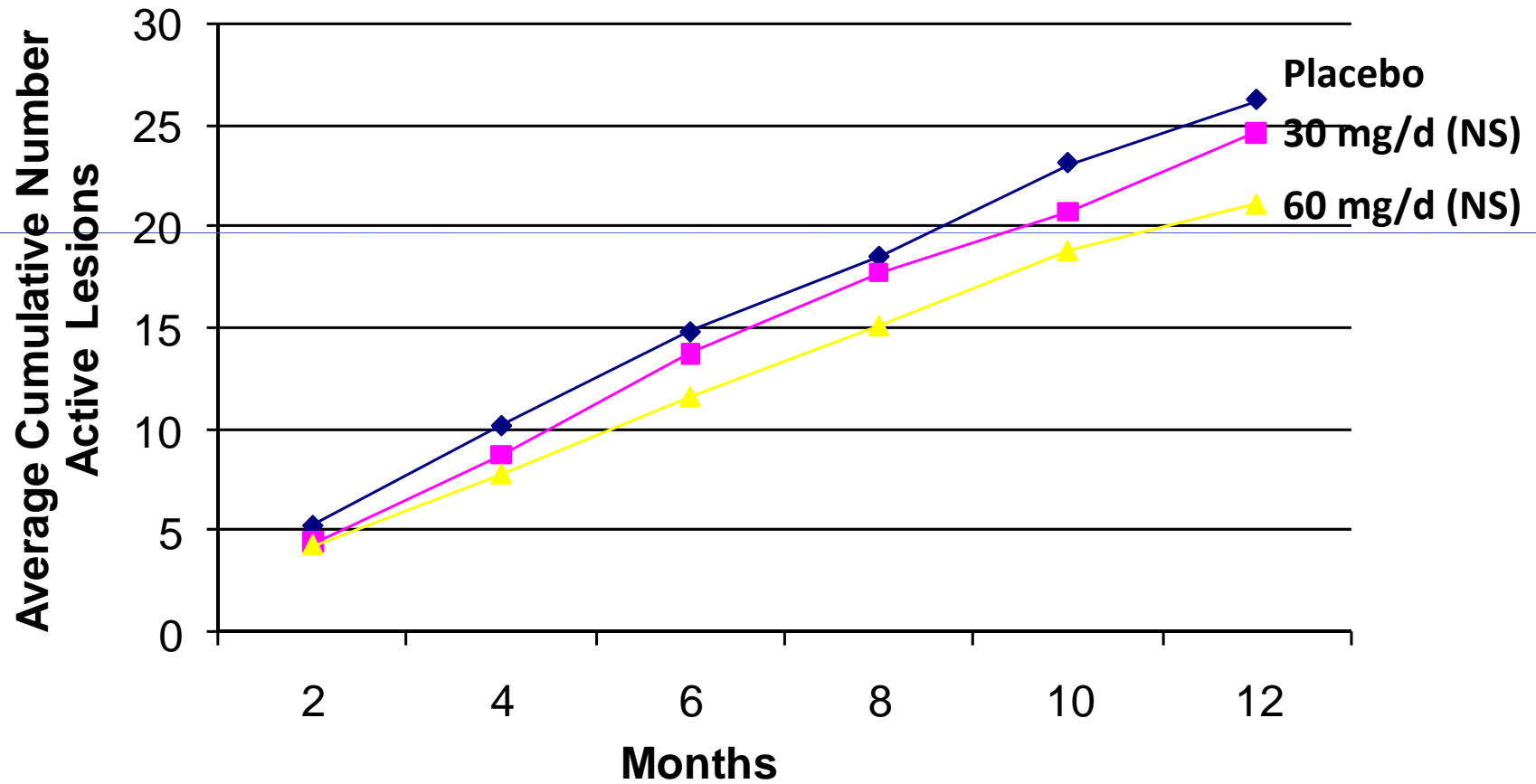
Characteristic	Treatment Group		
	Pbo	30 mg	60 mg
# Subjects (ITT)	100	94	98
Mean Age	35.7	35.5	36.2
Mean BMI	23.8	23.5	22.4
%male / %female	34/66	39/61	27/73
% relapsing-remitting	92	94	93
% secondary progressive	8	6	7
% w. spinal location	49	60	52
% w. cerebrum location	81	76	83
MS diagnosis (mo)	39	50	60
Onset of symptoms (mo)	73	96	98
Resolution of recent exacerbation (mo)	8.9	8.5	10.5
# relapses in last 12 mo	1.0	1.1	1.1
# relapses from 12-24 mo	0.6	0.6	0.5

MN-166-CL-001

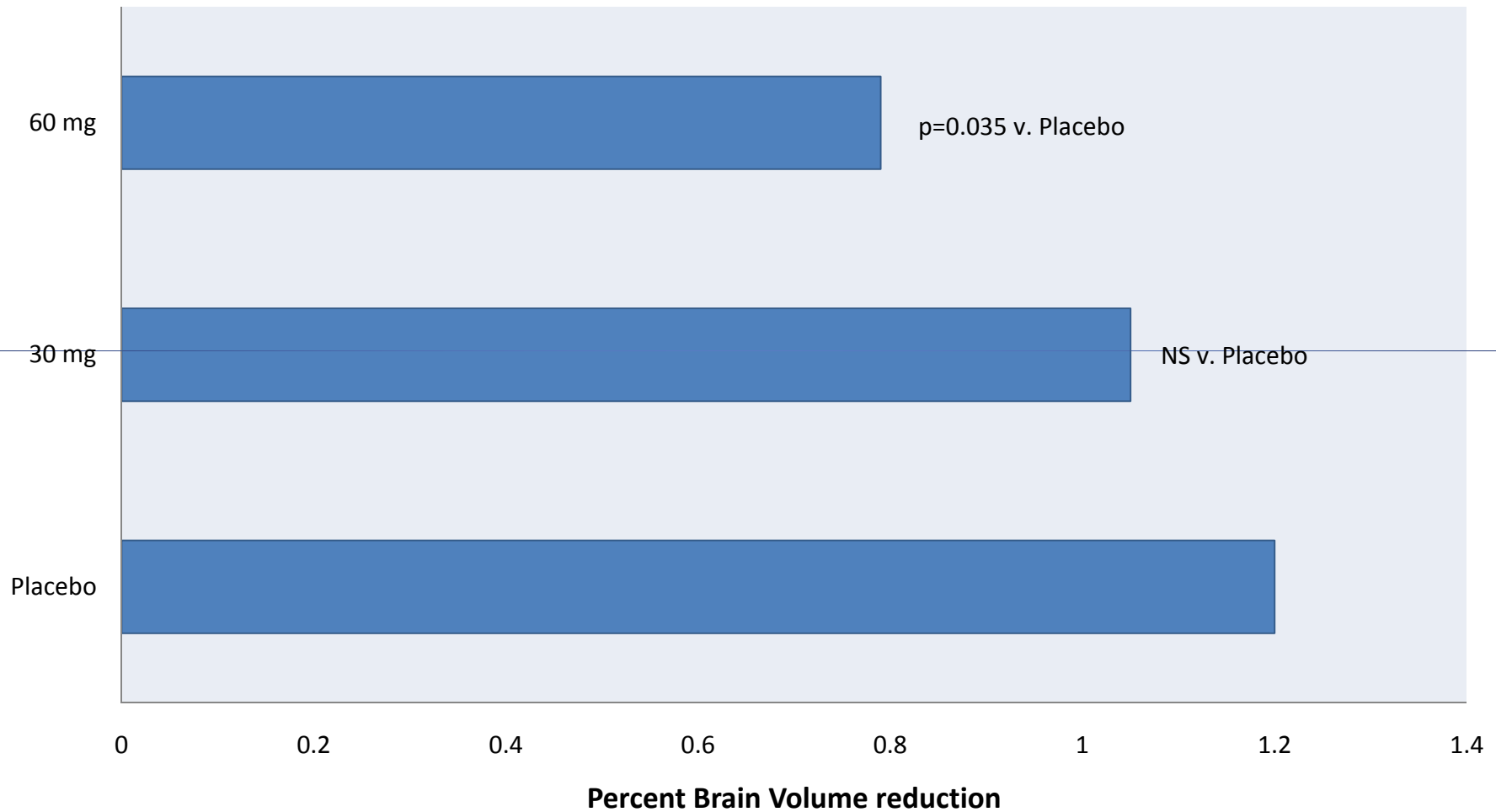
Patient disposition (months 0-12)

Reason for Discontinuation	Treatment Group		
	Pbo N=103	30 mg N=95	60 mg N=99
# Subjects (enrolled)	103	95	99
# Withdrawn consent	2	4	4
# No longer meets entry criteria	0	1	0
# Adverse events	1	2	3
# Non-compliant	0	0	1
# Pregnant	0	1	0
# Lack of efficacy	3	4	4
# Other	0	1	2
Total	6	13	14

Cumulative Number of Active Lesions Over 12 Months Study MN-166-CL-001

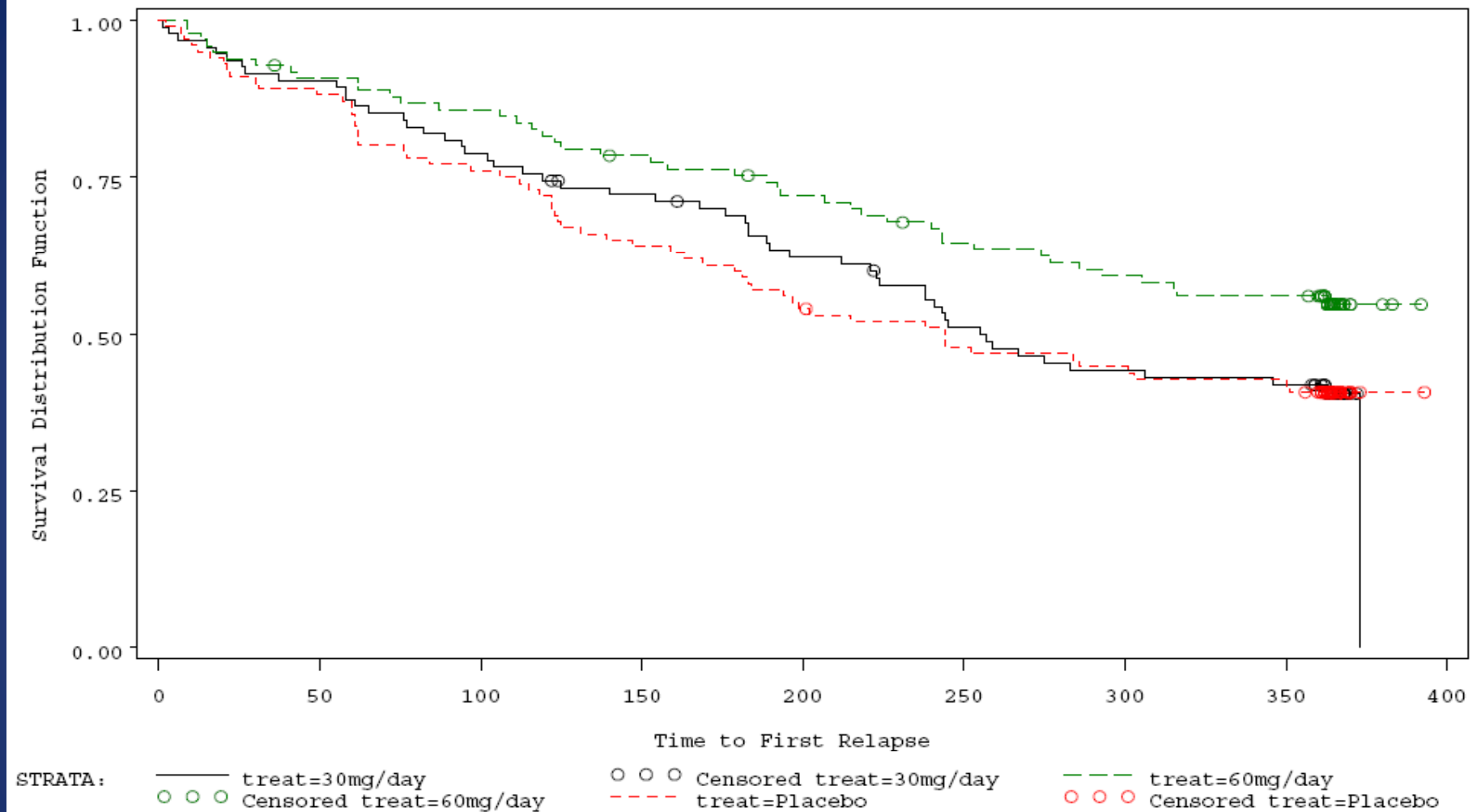


Percent Brain Volume Reduction (0-12 months)



Patients with sustained disability progression on EDSS:
Placebo = 8%, 30mg/d = 5.3%, 60mg/d = 4.1% (NS)

Figure 4-1 Plot of Time to First Relapse by Treatment (ITT)
Core (1-12 Months)



Time to first relapse (days): Median for placebo= 244; 30 mg= 255; 60 mg > 365, p=0.04

Percent of patients relapse-free in Year 1: placebo= 41%; 30mg= 41.5%; 60 mg= 56%, p=0.03

MN-166-CL-001 Safety Findings (0-12 months)

- MN-166 was very well tolerated; 89% of subjects completed the first 12 months of the study
- Discontinuation for AE was infrequent (placebo - 1, 30mg/d - 2, 60 mg/d - 3)
- Side effects were generally mild and self-limiting
- No statistically significant adverse effects were observed
- No adverse laboratory or ECG findings
- GI side effects as a group were the only adverse events to occur at ~2-fold that of the placebo rate (placebo – 7.8%, 30 mg/d – 14.7%, 60 mg/d – 22.2%)
- Tolerance to the GI side effects occurred rapidly (2-4 days)
- 12 serious adverse events were reported (placebo – 4, 30 mg – 2, 60 mg – 6); all were not or unlikely to be attributable to treatment
- No deaths occurred in the study

Summary

- MN-166 was well tolerated at a doses up to 60 mg/d for 1 year
- MN-166 treatment at a dose 60 mg/d did not significantly reduce Cumulative Lesion Count (-18%, NS)
- MN-166 treatment at a dose 60 mg/d significantly prolonged time-to-first relapse (median > 1 yr, $p=0.04$) and % patient relapse free for 1 year (56%, $p=0.03$)
- MN-166 treatment at a dose 60 mg/d significantly attenuated brain volume shrinkage (-38%, $p=0.03$)

Conclusions

- Based on its modest effect on inflammatory lesion count and its pharmacology, we hypothesize that MN-166's clinical benefit at 60 mg/d may result primarily from protecting neurons from damage rather than reducing occurrence of inflammatory lesions.
- With its excellent safety profile at 60mg daily, the safety and efficacy of MN-166 should be evaluated at higher doses in future studies
- The effect of MN-166 in attenuating brain volume loss and the early trend to reduce disability progression suggest that its effect on disease progression and MRI measures of neuroprotection (e.g. T1 black hole evolution) should be evaluated in future studies