



MEDICINOVA

# MN-166 Reduces Conversion of New Lesions to Persistent Black Holes in Multiple Sclerosis Patients

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MN-166-CL-001 investigators



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# MN-166 CL-001 Investigators

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  - Institute for Laboratory Medicine, Clinical University of Leipzig, Germany
  - eRT Inc, Philadelphia PA USA
  - MDSL, Maidenhead UK
- **Sponsor**
  - MediciNova Inc, San Diego CA USA



# MN-166 (ibudilast)

## Mechanism(s) of Action

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- **Anti-inflammatory**

- Phosphodiesterase 3A, 4, 10, 11 inhibitor
- Leukotriene inhibitor
- Inhibits Th1 cytokine production (IFN- $\gamma$ , TNF- $\alpha$ , IL-1 $\beta$ , IL-6)
- Stimulates Th2 cytokine production (IL-4, IL-10)

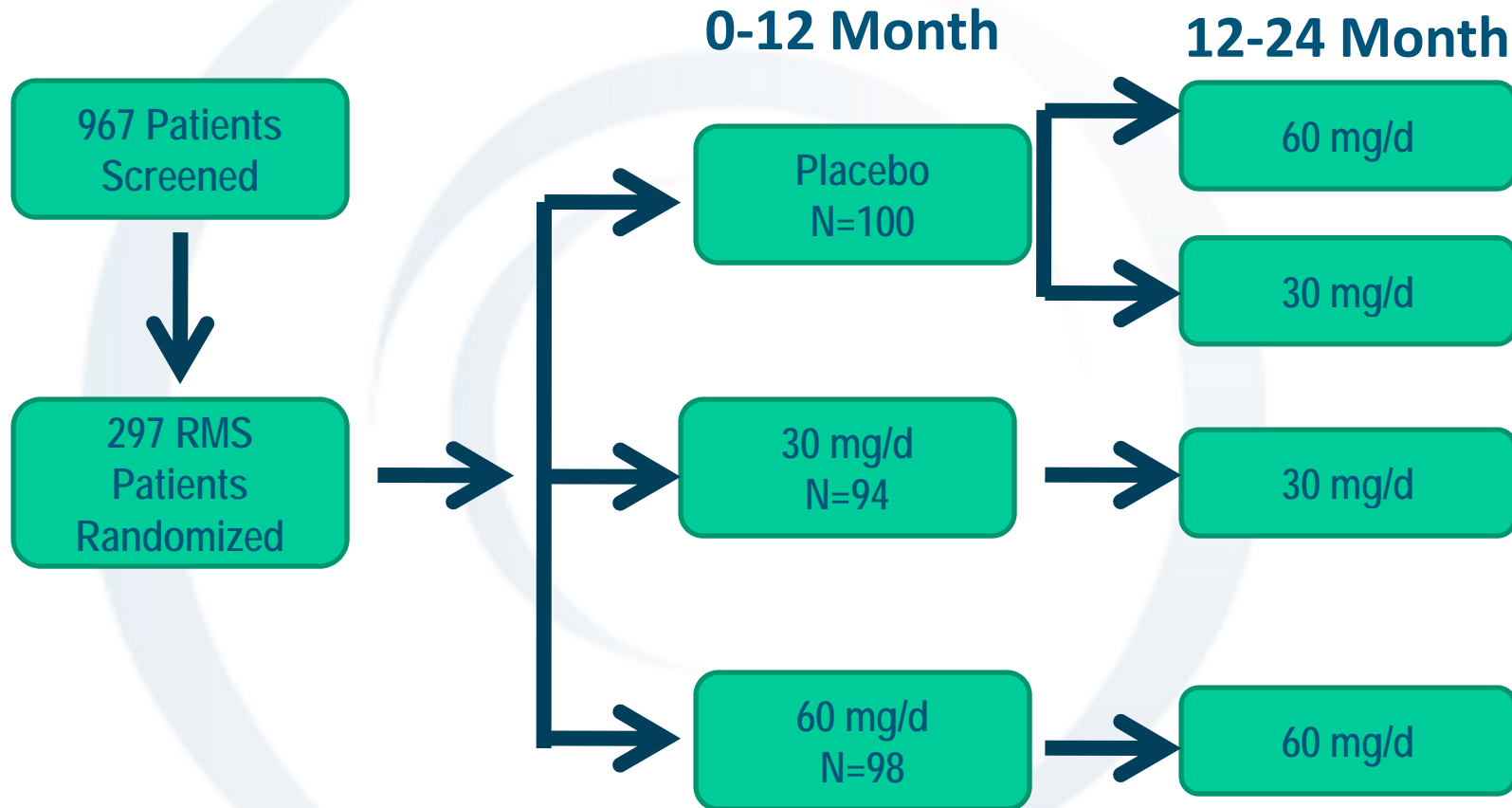
- **Neuroprotective**

- Inhibits nitric oxide and reactive oxygen species production
- Stimulates neurotrophic factor release (NGF, GDNF, NT-4)
- Cerebrovasodilator (via PGI<sub>2</sub> 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



# Main Year 1 Study Findings

(ECTRIMS 2007)

- MN-166 was well tolerated at doses up to 60 mg/d
- MN-166 treatment at a dose of 60 mg/d did not significantly reduce Cumulative Lesion Count (-18%, NS), the Primary Study Endpoint
- MN-166 treatment at a dose 60 mg/d significantly prolonged time-to-first relapse (median =401) by 157 d vs. placebo (median =401, p=0.04)
- MN-166 treatment at a dose 60 mg/d significantly attenuated brain volume shrinkage (-34%, p=0.03)
- Sustained disability progression (EDSS increase  $\geq 1$  for  $\geq 4$  mo) on MN-166 60 mg/d was less (4%) than on Placebo (8%, NS)



# Hypothesis and Objective

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- Hypothesis: Based on its modest effect on inflammatory lesion count, its pharmacology, attenuating brain volume loss, and early trend to reduce sustained disability progression we hypothesized 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
- Objective: To measure the effect of MN-166 on evolution of inflammatory lesions to recovered lesions or persistent black holes, MRI measures of neuroprotection, in formal retrospective study of MRIs collected during year 1 of the MN-166-CL-001 study



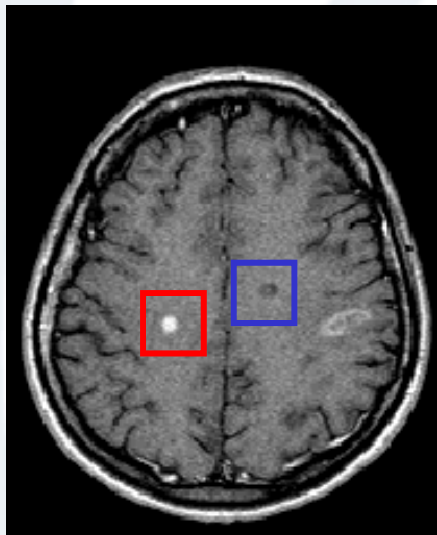
# Methods

## Evolution of new lesions to Persistent Black Holes (PBH) or Recovered Lesions (RL)

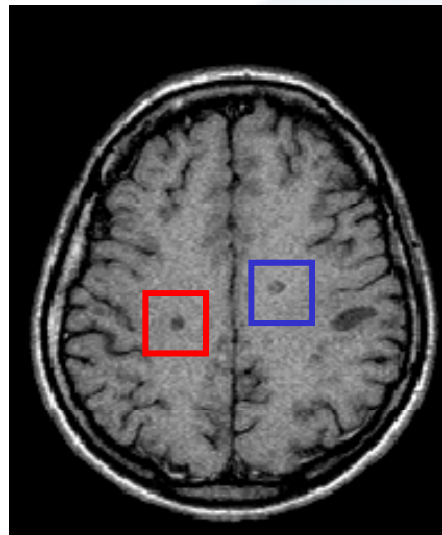
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- Blinded MRI data from year 1 was evaluated by a new rater not previously involved in the study
- New T1 gadolinium-enhancing or new T2 lesions were identified as NL (new lesions) in the first on-study drug MRI at month 2
- These lesions were then followed in the month 4 and 10 MRI, and classified as PBH or RL by pre-defined criteria:
  - PBH = Lesions that were hypointense and inactive at month 10
  - RL = Hypointense lesions at month 2 or 4 that were isointense at month 10
- The relative risk of NL in month 2 evolving to RL or PBH per patient was analyzed (Note: lesions within a patient are assumed not to be independent)

# Example of RL (red box)

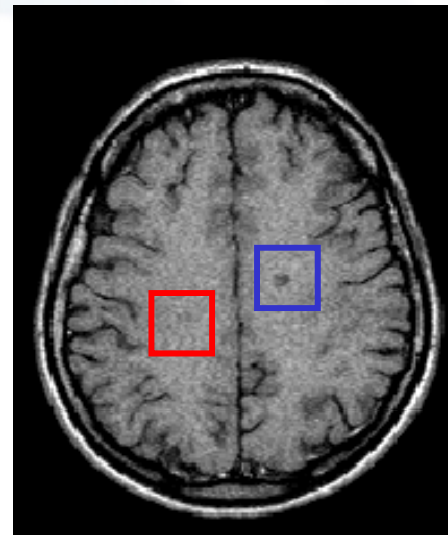


T1 with gadolinium  
Visit 4



T1 without gadolinium  
Visit 4

Month 2



T1 without gadolinium  
Visit 5

Month 4



T1 without gadolinium  
Visit 8

Month 10



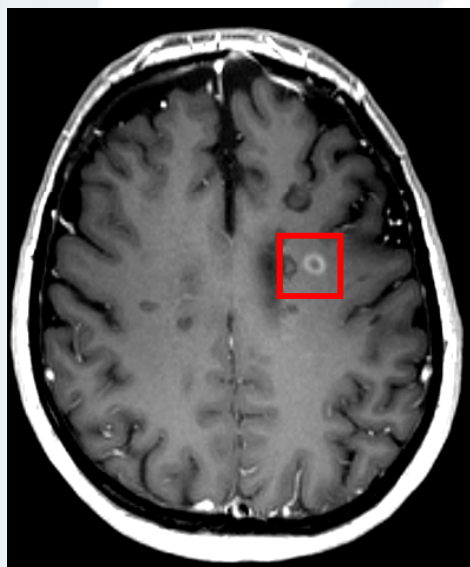
# Assessment of Recovering Lesions

Parameter	Treatment Groups		
	Placebo	30 mg/day	60 mg/day
# Patients w. New Lesions at Month 2	72	64	56
# Patients with $\geq 1$ Recovering Lesion	42 (58.3%)	40 (62.5%)	34 (60.7%)
Mean Proportion of Recovering Lesions	0.24	0.28	0.26
Median Proportion of Recovering Lesions	0.20	0.23	0.22
Relative Risk (for Recovering Lesion Rates) vs. placebo	-	1.135	0.970
p Value	-	0.376	0.836

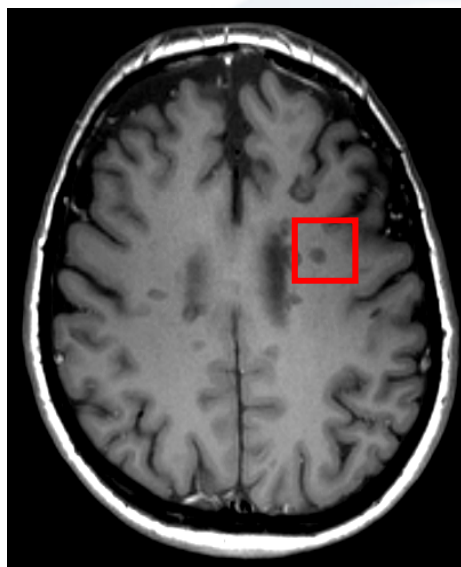
- **New T1 gadolinium-enhancing or new T2 lesions were defined as NL in the first on-study MRI at month 2**
- **Hypointense lesions at month 2 or 4 that were isointense at month 10 were RL**
- **Relative Risk (RR) of NL evolution to PBH and RL per patient was analyzed using a general linear model with the error term from the Poisson distribution**



# Persistent Black Hole – Axonal Loss

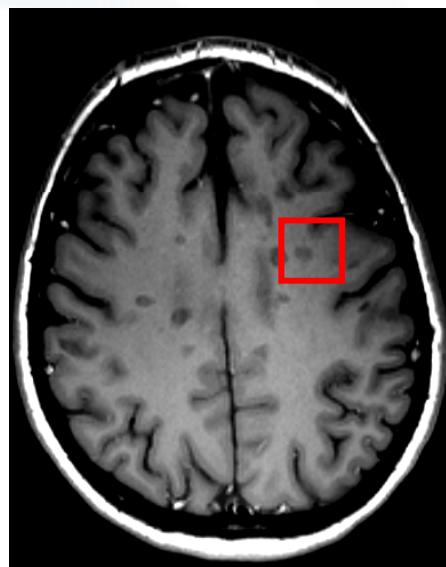


T1 with gadolinium  
Visit 4



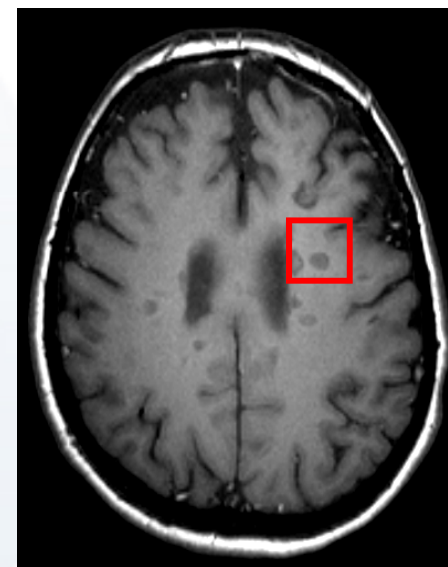
T1 without  
gadolinium  
Visit 4

Month 2



T1 without  
gadolinium  
Visit 5

Month 4



T1 without  
gadolinium  
Visit 8

Month 10



# 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
# Patients w. $\geq 1$ PBH (% of Pts. w. New Lesions)	41 (56.9%)	33 (51.6%)	28 (50%)
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	<b>0.011</b>

- New T1 gadolinium-enhancing or new T2 lesions were defined as NL in the first on-study MRI at month 2
- Lesions that were hypointense and inactive at month 10 were PBH
- Relative Risk (RR) of NL evolution to PBH was analyzed using a general linear model with the error term from the Poisson distribution



# Summary

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- MN-166 had no effect on RL lesion evolution as defined in this study
- MN-166 treatment reduced the Relative Risk that a new inflammatory lesion would evolve to a PBH
  - At 60 mg/d the RR was reduced to 0.63, a 37% reduction,  $p=0.011$
  - At 30 mg/d the RR was reduced to 0.74, a 26% reduction,  $p=0.074$



## Conclusions

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- The findings of this investigation suggest that the main effect of MN-166 treatment in Relapsing MS patients is to protect neurons from the persistent damage that results from inflammatory lesions
- Further study of the effect of MN-166 on sustained disability progression including markers of neuroprotection is warranted