

Ibudilast in relapsing-remitting multiple sclerosis

A neuroprotectant?



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ABSTRACT

Background: Ibudilast is a phosphodiesterase inhibitor influencing inflammation and neurodegeneration in multiple sclerosis (MS). This study evaluated the safety, tolerability, and effects on MRI parameters of 2 different doses of ibudilast in relapsing forms of MS.

Methods: In this multicenter, double-blind, phase 2 trial, patients with relapsing MS and gadolinium-enhancing lesions were randomly assigned 1:1:1 to receive 30 or 60 mg ibudilast or placebo every day for 12 months. The primary endpoint was the cumulative number of newly active lesions on bimonthly brain MRI over 12 months. Secondary endpoints included relapse rate, change in Expanded Disability Status Scale (EDSS) score, T2-hyperintense and T1-hypointense lesion volumes, and percent brain volume change (PBVC).

Results: A total of 297 patients were randomized in 19 centers. During the first 12 months, the mean number of active lesions and relapse rate did not differ between treatment arms. A reduction in PBVC ($p = 0.04$) was found in the 60-mg group (0.8%) compared with placebo (1.2%). Post hoc analysis showed a reduction in the proportion active lesions that evolved into persistent black holes for the 60-mg (0.14; $p = 0.004$) and 30-mg (0.17; $p = 0.036$) groups compared with the placebo group (0.24). Over 2 years, there were fewer patients ($p = 0.026$) with confirmed progression on the EDSS. Treatment with ibudilast was generally safe and well tolerated.

Conclusion: Ibudilast showed no beneficial effect on the rate of newly active lesions and relapses. However, preliminary evidence suggests that ibudilast seems to act in a neuroprotective fashion as measured by 2 independent MRI outcomes, with a possible beneficial clinical effect on disability progression.

Classification of evidence: This interventional study provides Class III evidence on the effect of ibudilast on disease activity. *Neurology*® 2010;74:1-1

GLOSSARY

AE = adverse event; **CI** = confidence interval; **DTPA** = diethylenetriaminepentaacetic acid; **EAE** = experimental autoimmune encephalomyelitis; **EDSS** = Expanded Disability Status Scale; **Gd** = gadolinium; **IAC** = Image Analysis Center; **IFN** = interferon; **IL** = interleukin; **ITT** = intent-to-treat; **mRNA** = messenger RNA; **MS** = multiple sclerosis; **PBH** = persistent black hole; **PBVC** = percent brain volume change; **PDEI** = phosphodiesterase inhibitor; **RR** = relative risk; **TNF** = tumor necrosis factor.

Phosphodiesterase inhibitors (PDEIs) have been considered as possible treatment for multiple sclerosis (MS), given their anti-inflammatory effects. Ibudilast mainly inhibits phosphodiesterase types 3, 4, 10, and 11^{1,2} and inhibits leukotrienes and nitric oxide synthesis mechanisms which are involved in MS.³ Ibudilast is used in Japan and Korea to treat bronchial asthma and cerebrovascular disorders.^{4,5} Ibudilast exerts a number of beneficial effects in the brain,⁶ e.g., the inhibition of tumor necrosis factor (TNF)- α release from the astrocytes and microglial cells,^{2,3} reducing neuronal degeneration.

In chronic cerebral ischemia, treatment with ibudilast reduced white matter lesions and microglia activation.⁷ Ibudilast protects astrocytes against apoptosis⁸ and, in the animal model of Krabbe disease, inhibits oligodendrocyte apoptosis and demyelination.⁹

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Supplemental data at
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In the animal model experimental autoimmune encephalomyelitis (EAE), ibudilast (2 mg/kg and 10 mg/kg orally) in Dark August rats suppressed severity of clinical signs in a dose-dependent manner.¹⁰ The production of TNF- α was inhibited, and production of interferon (IFN)- γ was mildly decreased. Another type 4 PDEI (rolipram) led to reduced TNF- α and interleukin (IL)-2 production in EAE.¹⁰ Interestingly, a reduction of demyelination was shown to be a hallmark of PDE4 inhibition. Besides these histopathologic changes, continuous PDE4 inhibition reduced the clinical signs in a chronic-relapsing model of EAE.¹¹

So far, 2 pilot studies investigating the effects of ibudilast were performed in humans. In 6 patients with active MS, the mean relapse rate was reduced by 48% (from 4.0 ± 0.9 before to 2.1 ± 1.1 after treatment, unpublished data). In another group of 12 patients with MS, 4 weeks of treatment with ibudilast (3×20 mg orally daily) suggested Th1 cytokine messenger RNA (mRNA), such as IFN- γ and TNF- α , to be down-regulated and Th2 cytokine mRNA, such as IL-4 and IL-10, to be up-regulated.¹²

Based on the favorable results from the animal and pilot human studies, we conducted a phase 2, double-blind, placebo-controlled study to evaluate safety and effect of treatment with ibudilast on the development of active brain lesions by MRI and clinical effects in patients with the relapsing forms of MS.

METHODS This was a randomized, double-blind, placebo-controlled study of 3 parallel treatment groups including outpatients (aged 18–55 years) with relapsing-remitting MS¹³ or secondary progressive MS with continued relapses. Key additional inclusion criteria were an Expanded Disability Status Scale (EDSS) score of <5.5 ¹⁴ and active disease, defined as at least 1 gadolinium (Gd)-diethylenetriaminepentaacetic acid (DTPA)-enhancing lesion on the screening MRI (<2 weeks before treatment). Key exclusion criteria were treatment with systemic immunosuppressants (including investigational treatments), such as infliximab, natalizumab, cyclophosphamide, mitoxantrone, azathioprine, methotrexate, linomide, cyclosporine, or deoxyspergualin, within 6 months of the screening MRI scan; treatment with total lymphoid irradiation or cladribine at any time; treatment with interferons within 45 days of the screening MRI scan; history of recent relapse; and treatment with corticosteroids or corticotropin within 45 days of the screening MRI scan.

Eligible patients were randomly assigned to receive 10 mg ibudilast (MN-166; Medicinova Inc., San Diego, CA), 20 mg ibudilast, or placebo orally 3 times daily. The randomization

was performed in blocks stratified by center using a 1:1:1 randomization.

The study consisted of 1 screening visit and 12 regular visits during treatment (follow-up visits at months 2, 4, 6, 8, 10, 12, 13, 14, 16, 18, 20, and 24). Eligible patients received treatment for 12 months, the protocol-specified core period, and were offered extended treatment on active medication for an additional 12 months of treatment (visits 13 through 24 months). To ensure blinding, all capsules were identical in appearance. Patients who were randomly assigned to active treatment in the core period stayed on the same treatment for 24 months. Patients who received placebo in the core period were randomly assigned to either 30 or 60 mg ibudilast per day in the extension period. Safety assessments were performed at every and included adverse events (AEs), serious AEs, physical examinations, vital signs (including weight), EKGs, chest radiographs, clinical laboratory testing, and neurologic examinations.

MRI scans were performed following a standardized MRI protocol using 3-mm-thick slices and roughly 1-mm² pixels. T1-weighted conventional spin-echo images were obtained before and after gadolinium-DTPA (0.1 mmol/kg via a long IV line). Dual echo spin-echo images were obtained after contrast material injection before the postcontrast T1.

Scans were sent to the Image Analysis Center (IAC) in Amsterdam for quality assessment and evaluation. To ensure blinding, investigators did not receive any potentially unmasking information with respect to MRI scans performed. An experienced reader marked the different lesion types (T2 lesions, Gd-enhancing lesions, and T1 hypointense lesions) according to the standardized operating procedures of the IAC and published guidelines.¹⁵ Subsequently, lesion volumes were measured using in-house-developed software. All raters were blinded to treatment allocation during the whole study period (years 1 and 2).

The primary study outcome was the cumulative number of newly active lesions as seen on bimonthly MRI scans over the first 12 months of treatment. Newly active lesions display 1 of the following features:

- new Gd enhancement on T1-weighted images;
- new on T2-weighted images but nonenhancing on T1-weighted images; and
- new enlargement on T2-weighted images but nonenhancing in T1-weighted images.

The secondary outcomes included:

- time to first exacerbation, number of relapses, and annualized relapse rate over 12 months; and
- cumulative volume of Gd-enhancing lesions over 12 months.

Additional outcomes included:

- cumulative number of newly active MRI lesions over 24 months;
- cumulative volume of Gd-enhancing lesions over 24 months;
- change in T1-weighted hypointense lesion volume between screening, 12 months, and 24 months;
- change in T2-weighted lesion volume between screening, 12 months, and 24 months;
- change in EDSS at 12 and 24 months and confirmed EDSS progression (increase ≥ 1 point in EDSS maintained for ≥ 4 consecutive months); and
- percent brain volume change (PBVC) at 12 and 24 months.

Statistical methods. The intent-to-treat (ITT) population was defined as all randomized patients with relapsing MS who had at least 1 Gd-enhancing lesion at screening, had taken at least 1 dose of study medication, and had at least 1 valid post-baseline MRI. The primary outcome (active MRI lesions over 12 months) was analyzed using a generalized analysis of covariance in the ITT dataset. A model that contained terms for treatment, pooled center, and treatment-by-center interaction was used. The number of active (Gd-enhancing) cranial MRI lesions at screening was used as a covariate, the logarithm of the number of valid scans was an offset, the link function was the natural logarithm, and the error term was negative binomially distributed. Estimates of the ratio of lesion rates for each treatment compared with placebo, with associated 95% confidence intervals (CIs), were calculated, and a 2-sided 2.5% significance level for the primary outcome was used to adjust for multiplicity.

Analysis of the secondary efficacy variables 1) cumulative volume of Gd enhancing, 2) T1-weighted hypointense lesion volume, 3) T2-weighted lesion volume and, 4) EDSS were analyzed using analysis of covariance with terms for treatment, pooled center, and treatment-by-pooled center interaction and baseline (as a covariate) included in the model. For T1-weighted hypointense lesion volume and T2-weighted lesion volume, a $\log(x + 1)$ transformation was applied to the dependant variables and to the covariate

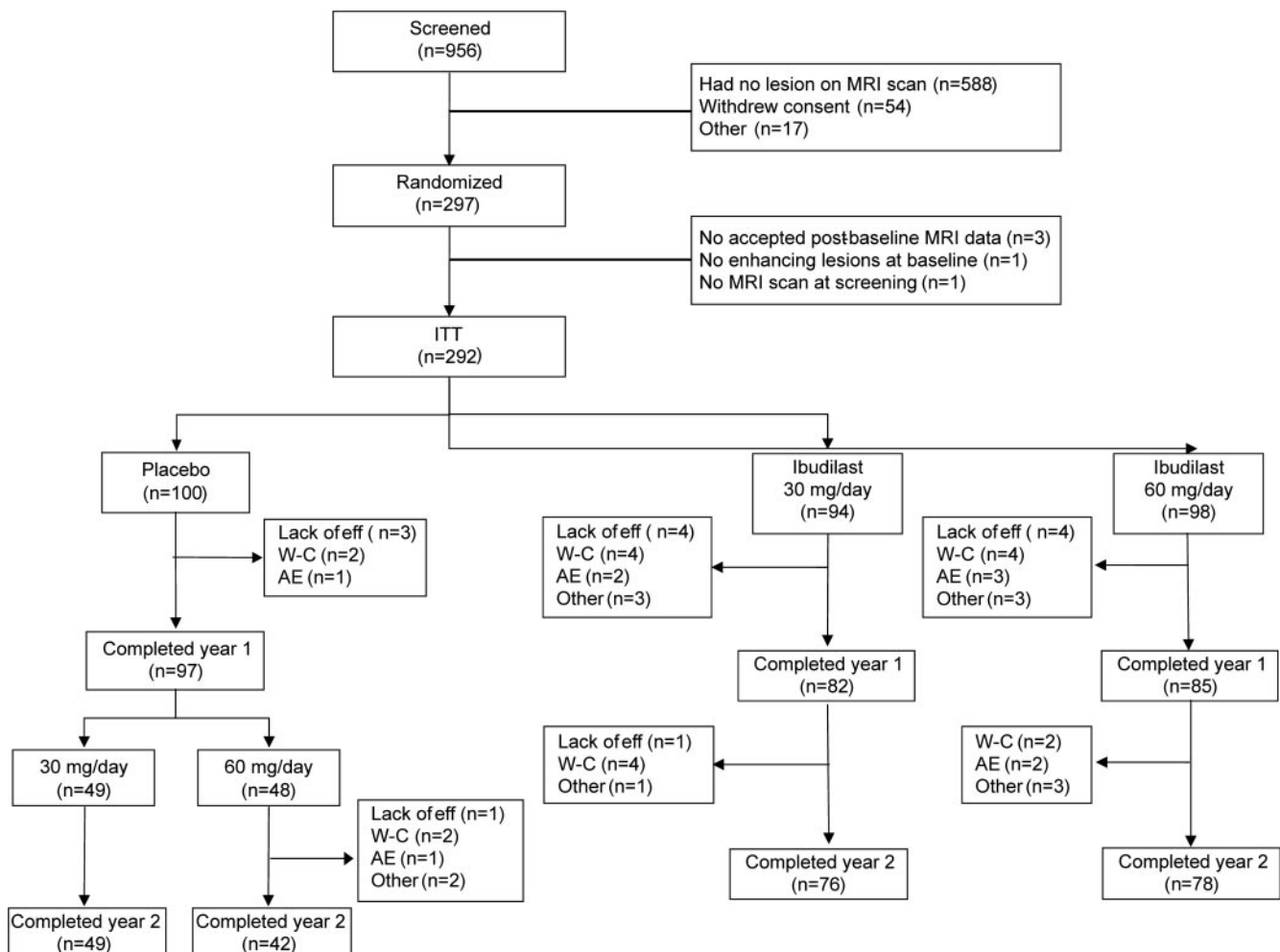
before the analysis. Numbers of 1) relapses over 12 months and 2) cumulative active lesions over 24 months were analyzed via generalized analysis of variance with terms for treatment, pooled center, and treatment-by-pooled center interaction in the model. The link function for these variables was the natural logarithm.

The time to first exacerbation was analyzed with Kaplan-Meier graphs and the stratified log-rank test. PBVC was analyzed using analysis of variance with terms for treatment, pooled center, and treatment-by-pooled center interaction in the model. Confirmed EDSS progression was analyzed using the Cochran-Mantel-Haenszel test stratified by pooled center. Descriptive statistics were provided for the annualized relapse rate.

Standard protocol approvals, registrations, and patient consents. The protocol was approved by the ethic committees of the participating centers before the start of the study. Before any investigation, written informed consent was obtained from all patients.

RESULTS Patients. A total of 956 patients were screened and 297 patients were randomized in 19 European centers (for randomization, see figure 1). Three patients had no accepted postbaseline MRI data, 1 patient had no screening MRI scan, and 1

Figure 1 Patient disposition



AE = adverse event; ITT = intent-to-treat; Lack of eff = lack of effect; W-C = withdrew consent.

Table 1 Baseline demographic and disease characteristics in the intent-to-treat population

Variable	Placebo (n = 100)	Ibudilast 30 mg/d (n = 94)	Ibudilast 60 mg/d (n = 98)
Sex, n (%)			
Male	34 (34.0)	37 (39.0)	26 (27.0)
Female	66 (66.0)	57 (61.0)	72 (73.0)
Age, y, mean (SD)	35.7 (8.8)	35.5 (9.3)	36.2 (9.4)
Disease type, n (%)			
RRMS	92 (92.0)	88 (93.6)	91 (92.9)
SPMS with continued relapses	8 (8)	6 (6.4)	7 (7.1)
Years since diagnosis of MS and visit 1, median (Q1, Q3)	1.9 (0.6, 4.3)	2.7 (0.7, 5.9)	3.4 (1.0, 7.9)
Years since onset of clinical symptoms and visit 1, median (Q1, Q3)	4.7 (2.2, 9.0)	6.4 (3.1, 10.0)	6.8 (3.1, 12.1)
No. of active lesions, ^a median (Q1, Q3)	3.0 (1.0, 6.0)	3.0 (1.0, 6.0)	2.0 (0.0, 5.5)
Normalized brain volume, mean (SD)	1,472.45 (82.03)	1,466.85 (87.20)	1,453.46 (80.44)
No. of relapses in previous 12 mo, median (Q1, Q3)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)
EDSS, mean (SD)	3.3 (1.2)	3.3 (1.3)	3.4 (1.3)
Volume of T1-weighted hypointense lesions, ^b mm ³ , median (Q1, Q3)	1,275.0 (386.0, 2,951.0)	2,043 (692.0, 5,248.0)	1,511 (484.0, 4,809.0)
Volume of Gd-enhancing lesions, ^c mm ³ , median (Q1, Q3)	80.0 (0.0, 300.0)	127 (0.0, 556.5)	93.0 (0.0, 422.5)
Volume of T2-weighted lesions, ^b mm ³ , median (Q1, Q3)	6,618.5 (3,896.0, 15,550.5)	10,128.9 (5,413.0, 15,881.0)	10,026.0 (5,504.0, 15,807.0)

Abbreviations: EDSS = Expanded Disability Status Scale; Gd = gadolinium; Q = quartile; RRMS = relapsing-relmitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis.

^aActive is defined as any new T1-Gd-enhancing lesions or new/enlarging lesions at month 2.

^bMeasure taken at screening (month 0).

^cMeasure taken at month 2.

patient had no enhancing lesions at screening; the ITT population thus contained 292 patients. Table 1 reports baseline demographic and clinical data, with no major differences between groups. Age and sex were similar across groups. The years since diagnosis of MS onset of clinical symptoms were higher in the treatment groups compared with the control group. In table 2, the baseline MRI findings among the 3 different treatment groups are shown. The placebo and 30-mg groups had a median number of 3 active lesions; in the 60-mg group, the median was 2.

MRI results. The primary MRI variable of cumulative active lesions over 12 months of treatment did not differ between treatment arms (30 mg/d vs placebo, $p = 0.76$; 60 mg/d vs placebo, $p = 0.74$; table 2). The cumulative volume of Gd-enhancing lesions over 12 months showed no effect either (30 mg/d vs placebo, $p = 0.56$; 60 mg/d vs placebo, $p = 0.09$).

For the entire study (table 3), no treatment arm distinguished itself when compared with the remaining arms (placebo vs 30 mg/d, $p = 0.33$; placebo vs 60 mg/d, $p = 0.16$; 30 mg/d, $p = 0.74$; 60 mg/d, $p = 0.83$), with respect to cumulative number of newly active lesions over 24 months. When treatment arms were compared in terms of cumulative enhancing volume, the placebo to 60 mg/d arm was marginally higher

when compared with the other treatment arms (placebo to 30 mg/d, $p = 0.37$; placebo to 60 mg/d, $p = 0.04$; 30 mg/d, $p = 0.91$; 60 mg/d, $p = 0.15$). Among the additional outcomes, no effect was seen on the volume of T2-hyperintense or T1-weighted hypointense lesions (black holes) at month 12 or month 24 (using baseline lesion volume as a covariate).

Percent brain volume change analysis. Over 12 months of treatment, the PBVC in the placebo group was higher (mean -1.20) compared with the 60-mg ibudilast group (mean -0.79 , $p = 0.04$); a dose-response effect was suggested with the 30-mg group being intermediate (mean -1.05 , $p = 0.36$). Over 2 years, the effect on PBVC was maintained, with the placebo switching to 60 mg comparing favorably to the group switching to 30 mg (figure 2). When the analysis was restricted to patients with relapsing-relmitting MS, the trend seemed have a more linear dose-dependent effect. Triggered by this favorable effect on PBVC, a post hoc analysis was performed on the evolution of active lesions to persistent black holes (PBHs).

Persistent black hole evolution analysis. In this post hoc analysis, predefined endpoints were the rates of evolution of newly active lesions at month 2 of the study into PBHs (hypointensity) or return to isoin-

Table 2 First-year MRI and clinical outcomes

	Placebo (n = 90)	Ibudilast 30 mg/d (n = 76)	Ibudilast 60 mg/d (n = 82)
Primary efficacy variable			
Cumulative active lesions^a			
Mean (SD)	26.2 (37.2)	24.6 (27.0)	21.1 (26.8)
Median	13.5	16.0	12.0
Secondary efficacy variable			
Time to first exacerbation, median	244	255	401
Relapse-free patients, n (%)	41 (41.0)	39 (41.5)	55 (56.1) ^b
Annualized relapse rate, mean (SD)	0.9 (1.0)	0.9 (1.0)	0.7 (1.0)
Cumulative volume of Gd-enhancing lesions, mean (SD)	2,128.0 (2,991.5)	2,425.2 (2,936.9)	1,756.6 (2,611.7)
Change in EDSS score, mean (SD)	-0.1 (0.9)	0.0 (0.7)	-0.2 (0.8)
Confirmed EDSS progression, %	8.0	5.3	4.1
PBVC, mean (SD)	-1.20 (1.15)	-1.05 (1.03)	-0.79 (1.02) ^b
Volume of T1-weighted hypointense lesions, mean (SD)	2,909.0 (4,516.8)	3,589.3 (4,131.9)	4,073.7 (6,024.0)
Volume of T2-weighted lesions, mean (SD)	10,965.1 (9,996.3)	14,000.2 (12,024.8)	15,882.1 (17,922.1)
Post hoc analysis: PBH rate			
	(n = 72)	(n = 64)	(n = 56)
No. of new lesions	426	338	315
No. of PBHs	98	58	47
Proportion evolving to PBH	0.24	0.17	0.14 ^c
Average PBH rate	0.24	0.20	0.16
Relative risk (95% CI)		0.735 (0.52-1.03)	0.630 (0.44-0.90)

Abbreviations: CI = confidence interval; EDSS = Expanded Disability Status Score; PBH = persistent black hole; PBVC = percent brain volume change.

^aActive is defined as any new T1-Gd-enhancing lesions.

^b $p < 0.05$.

^c $p < 0.01$.

tensity at month 10. All active lesions at month 2 were tracked by 1 rater (H.E.H.), blinded to treatment allocation, for their appearance after 8 months

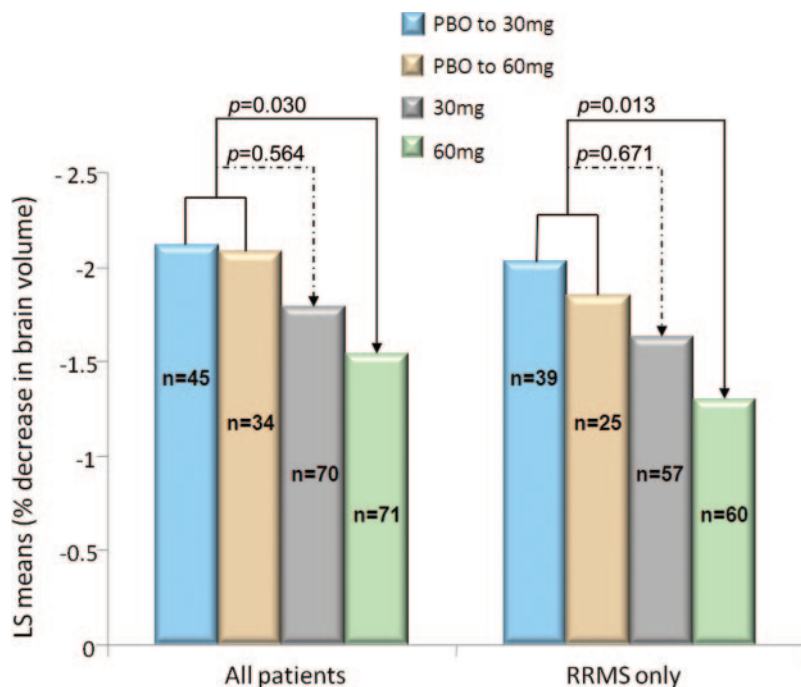
of follow-up: lesions that were hypointense at baseline and remained hypointense at month 10 were defined as PBHs.

Table 3 Second-year MRI and clinical outcomes

Additional efficacy variable	Placebo to ibudilast 30 mg/d	Placebo to ibudilast 60 mg/d	Ibudilast 30 mg/d	Ibudilast 60 mg/d
Cumulative no. of active lesions on MRI, mean (SD)	41.5 (55.9)	37.7 (34.2)	40.0 (50.8)	26.8 (29.6)
Time to first exacerbation, median	188	383	255	401
Relapse-free patients, n (%)	13 (25.5)	19 (38.8)	32 (34.0)	38 (38.8)
Annualized relapse rate, mean (SD)	0.9 (1.0)	0.6 (0.7)	0.8 (0.9)	0.8 (0.9)
Cumulative no. of Gd-enhancing lesions, mean (SD)	231.6 (454.6)	260.2 (736.6)	200.2 (345.1)	229.8 (413.0)
Cumulative volume of Gd-enhancing lesions, mean (SD)	232 (454)	266 (737)	200 (345)	230 (413)
Change in EDSS, mean (SD)	-0.2 (1.0)	0.0 (1.1)	0.0 (0.9)	-0.1 (0.9)
Confirmed EDSS progression, %	15.7	26.5	10.6	10.2
PBVC, mean (SD)	-2.26 (1.51)	-2.29 (2.09)	-1.97 (1.83)	-1.64 (1.67)
Volume of T1-weighted hypointense lesions, mean (SD)	2,677.8 (4,142.3)	3,306.2 (5,318.7)	3,638.3 (4,368.7)	3,796.7 (6,371.3)
Volume of T2-weighted lesions, mean (SD)	12,326.1 (14,099.2)	11,728.3 (10,498.9)	14,526.8 (12,427.3)	14,821.1 (17,915.4)

Abbreviations: EDSS = Expanded Disability Status Scale; Gd = gadolinium; PBVC = percent brain volume change.

Figure 2 Effect on percent brain volume change over 2 years



The blue and tan bars show the change in brain volume over 2 years in the placebo groups that changed to active treatment with ibudilast (either 30 or 60 mg) after 1 year. The gray and green bars show the results for the patients who received 30 mg or 60 mg ibudilast, respectively, for 2 years. The percent brain volume change was the least for patients who used 60 mg ibudilast during the whole study period. LS = least squares; PBO = placebo; RRMS = relapsing-remitting multiple sclerosis.

This analysis showed a reduction in the proportion of lesions that evaluated into PBHs for 60 mg (0.14, $p = 0.004$) and 30 mg (0.17, $p = 0.036$) compared with placebo (0.24). Analysis on a per-patient basis yielded similar results: the mean relative risk (RR) per patient for evolution to PBH was lower for the 60-mg/d ibudilast group (RR 0.63, CI 0.44–0.90, $p = 0.011$) compared with placebo. The comparison between the 30-mg/d treatment group and placebo showed intermediate results (RR 0.74, CI 0.52–1.03, $p = 0.074$). The evolution to isointensity (possibly indicating remyelination) did not differ among the treatment groups.

Clinical outcomes. During the first 12 months, 46.2% of all patients remained relapse-free, ranging from 41% in the placebo group to 56.1% in the 60 mg/d ibudilast group, with a trend favoring the 60-mg/d dose group ($p = 0.03$ vs placebo). There was a minor reduction in the annualized relapse rate (0.7 in the 60-mg group vs 0.9 for placebo). In the ITT population, time to first relapse increased from a median of 244 days in the placebo group to 255 days for the 30-mg group and 401 days for the 60-mg group (figure e-1 on the *Neurology*[®] Web site at www.neurology.org).

Over the entire study (months 1–24), there were no important differences found between the treatment arms in relapse rate (table 3); however, for the percentage of patients who were exacerbation-free, the 60-mg/d group and the placebo to 60 mg/d group were superior to the other dose groups (25.5% for placebo to 30 mg/d, 38.8% for placebo to 60 mg/d, 34% for 30 mg/d, and 38.8% for 60 mg/d).

In the first year, no significant differences were found with respect to confirmed progression on the EDSS scores. Over 2 years, there was less confirmed EDSS progression in those on active treatment throughout the study (10.4%) vs those initially on placebo (21%, $p = 0.026$).

Safety results. Treatment with ibudilast (both 30 and 60 mg/d) was safe and well tolerated. Fifty-four percent of the subjects experienced at least 1 AE during the core period, whereas 66% of subjects experienced at least 1 AE during the entire study. The percentage of subjects that experienced at least 1 AE was similar across treatment groups. The most frequently occurring AEs over the entire study were nasopharyngitis (20%), headache (14%), urinary tract infection (9%), pharyngitis (6%), and nausea (5%). Nausea, headache, and upper respiratory tract infection were the only treatment-related AEs with an incidence greater than 2%.

During the core period, there was a slight dose-related increase in the percentage of subjects with gastrointestinal AEs. The incidences of gastrointestinal AEs were 10% (placebo to 30 mg/d), 12% (placebo to 60 mg/d), 17% (30 mg/d), and 18% (60 mg/d) (table e-1).

The AE data indicated that the mild to moderate self-limiting nausea, vomiting, and diarrhea were dose related, with more subjects in the 60-mg/d dose experiencing these AEs compared with the other treatment groups. A possible increase in depression was observed in subjects treated with 60 mg/d during the latter part of the study.

Serious adverse events. For the entire study, there were slightly more subjects with at least 1 SAE in the 60-mg/d group (10%) compared with subjects in the other groups (range 4%–6%), although the SAEs were considered to be unlikely related to treatment with ibudilast. The SAEs did not show any discernable trends across system-organ classes.

DISCUSSION Ibudilast treatment did not demonstrate any effect on brain MRI lesion development or the volume of enhancing lesions in the present relapsing MS population. Ibudilast treatment also did not alter annualized relapse rate, even though the time to first relapse and percentage of patients relapse-free in the core (year 1) period was greater on

60 mg/d compared with placebo. Given the large sample size and the high level of on-study MRI activity, a type II error is unlikely. This study indicates that ibudilast does not have an important anti-inflammatory effect leading to suppression of disease activity.

By contrast, ibudilast may exert a neuroprotective effect. A reduction in brain atrophy rate was found, especially in the high-dose group. Post hoc analyses were confirmatory by showing a favorable effect on conversion of new lesions to PBHs, suggesting that ibudilast protects neurons in lesions from persistent damage after acute inflammation. The positive effects on sustained EDSS progression over 2 years may be a reflection of this possible neuroprotective effect, although caution should be paid here because both the patients and the raters were not blinded in the second year of the study.

The neuroprotective effect of ibudilast may not come as a surprise. Different studies performed in mice found that ibudilast significantly suppressed neuronal cell death induced by the activation of microglia with lipopolysaccharide and IFN- γ . Both TNF- α and nitric oxide, as well as the additional IL-1 β and IL-6, were suppressed by ibudilast, whereas the anti-inflammatory cytokine IL-10 was up-regulated.^{3,16} In one of these studies, an up-regulation of several neurotrophic factors (nerve growth factor, glia-derived neurotrophic factor, neurotrophin 4) was also found.³ Also, a pilot study in humans showed the same tendency for Th1 cytokine mRNA (IFN- γ and TNF- α) to be down-regulated, whereas the Th2 cytokine mRNA, such as IL-4 and IL-10, were found to be up-regulated.¹² Recently, a combination of lovastatin and rolipram (PDE4 inhibitor) was tested in the EAE model.^{17,18} A neuroprotective effect against inflammatory CNS demyelination was found in this study. The combination of both agents prevented the progression of the disease and promoted neurorepair. Importantly, the same effect was not found with either lovastatin or rolipram alone. In fact, the combination of another statin (atorvastatin) with interferon had a deleterious effect on inflammation, illustrating that combination treatment should be examined carefully.¹⁹

Ibudilast is safe and well tolerated, as expected. Previous reports on ibudilast in healthy subjects and patients with MS have not revealed safety problems at any of the dose levels tested. Moreover, ibudilast has been available in the Japanese and Korean markets for the treatment of asthma (20 mg/d) and cerebrovascular disorders (30 mg/d) for more than 15 years.

To further evaluate the potential neuroprotective effect of ibudilast, a trial is needed specifically aimed

at this property of the treatment. Such a study could also consider the combination of ibudilast and an anti-inflammatory drug to examine combined efficacy and safety.

AUTHOR CONTRIBUTIONS

The statistical analysis were completed by R. Landin, Medicinova Inc., San Diego, California.

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DISCLOSURE

Prof. Barkhof serves on scientific advisory boards for Lundbeck Inc., Roche, Bayer-Schering Pharma, sanofi-aventis, UCB, and Novartis; has served as a consultant for MediciNova, Inc.; and serves on the editorial boards of *Brain*, the *Journal of Neurology*, *Neurosurgery & Psychiatry*, *European Radiology*, the *Journal of Neurology*, and *Neuroradiology*. Mrs. Hulst reports no disclosures. Mrs. Drulovic serves as an Associate Editor for *BioMed Central Neurology*; and receives research support from Bayer-Schering Pharma and from the Ministry of Science, Republic of Serbia (grant no. 145045). Dr. Uitdehaag serves on a scientific advisory board for Merck Serono; served on the editorial board of *Tijdschrift voor Neurologie en Neurochirurgie*; receives royalties from the publication of *Evidence Based Neurology* (Blackwell Publishers, 2007); has served as a consultant for MediciNova, Inc. and Novartis; and has received research support from the Dutch MS Research Foundation. Mr. Matusda serves as a consultant for MediciNova, Inc. Dr. Landin was previously employed by MediciNova, Inc. and currently serves as an independent statistical consultant.

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