Miglustat in late-onset Tay-Sachs disease: a 12-month, randomized, controlled clinical study with 24 months of extended treatment

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Purpose: To evaluate the safety and efficacy of miglustat in patients with G_{M2} gangliosidosis. **Methods:** A randomized, multicenter, open-label, 12-month study involving patients aged 18 years or older, randomized 2:1 to miglustat (200 mg TID) or “no miglustat treatment.” This study was followed by 24 months of extended treatment during which all patients received miglustat. Primary efficacy endpoints were change in eight measures of isometric muscle strength in the limbs and isometric grip strength, evaluated at baseline, and months 12 and 36. Secondary efficacy endpoints included gait, balance, disability, and other neurological assessments. Safety evaluations included adverse event reporting. **Results:** Thirty patients (67% male, age range 18–56 years) with late-onset Tay-Sachs disease were enrolled; 20 were randomized to miglustat and 10 to “no miglustat treatment.” Muscle and grip strength generally decreased over the study period. No differences were observed between the two groups in any efficacy measure, either during the 12-month randomized phase or the full 36 months. The most common treatment-related adverse events were decrease in weight and diarrhea. **Conclusion:** Miglustat treatment was not shown to lead to measurable benefits in this cohort of patients with late-onset Tay-Sachs disease. The observed safety profile was consistent with that of the approved dose (100 mg TID) in type 1 Gaucher disease. *Genet Med* 2009;11(6):425–433.

Key Words: miglustat, G_{M2} gangliosidosis, Tay-Sachs disease, Sandhoff disease, clinical trial

G_{M2} gangliosidoses are inherited disorders of glycosphingolipid metabolism, associated with G_{M2} ganglioside storage in various tissues, particularly the neurons of the central nervous system. Several forms of G_{M2} gangliosidoses exist, including Tay-Sachs and Sandhoff disease. Tay-Sachs disease (TSD) is caused by a deficiency of β -hexosaminidase A; prevalence has been estimated to be 1 in 201,000 live births. Sandhoff disease is caused by a deficiency of β -hexosaminidase A and B and occurs once in every 384,000 live births.^{1,2} There are three clinical variants of TSD based on age of onset: infantile acute onset (type I),³ subacute (2–18 years, type II),^{4,5} and late-onset

(adulthood, type III) (LOTS).^{6,7} In the subacute form, an earlier age at onset of the disease is indicative of a more severe disease course.¹ Sandhoff disease is clinically indistinguishable from TSD.¹

Late-onset G_{M2} gangliosidosis is characterized by progressive neurological deterioration affecting motor and spinocerebellar function.^{1,8} Typically, the first symptoms to manifest are gait and balance problems.⁹ Progressive speech disturbance and muscle weakness are also frequent presenting complaints.¹ Psychiatric symptoms may also develop early, whereas dysphagia and behavioral problems tend to appear later in the disease course. In the “classic” infantile form of G_{M2} gangliosidosis, symptoms are evident before the age of 6 months, followed by rapid neurologic regression and death by 3–5 years. Visual loss, characterized by a “cherry-red” spot in the eye, is a common feature of the infantile form but is not seen in patients with subacute or chronic disease.¹ The subacute and chronic forms present later in childhood or adolescence and have a more protracted clinical course. These latter subtypes differ primarily in their neurologic features and course of disease.^{1,10} The subacute form is characterized by progressive spasticity with seizures and dementia, leading to a vegetative state by late childhood or mid-teens,^{5,9} whereas patients with the chronic form tend to suffer mild cognitive decline and psychiatric complaints and may live a normal lifespan.^{11,12} Often chronically affected patients become wheelchair bound.¹⁰ The heterogeneous nature of G_{M2} gangliosidosis is related to the wide spectrum of hexosaminidase mutations, and patients with chronic G_{M2} gangliosidosis exhibit residual enzyme activity.¹⁰

Currently, there is no treatment for G_{M2} gangliosidosis, and management is primarily supportive. Enzyme replacement therapy is not a viable option, as intravenous administration does not lead to adequate delivery across the blood-brain barrier. Bone marrow transplantation has been used in animal models and individual patients but has achieved mixed results.^{13–15} Miglustat is a reversible inhibitor of glucosylceramide synthase, the enzyme that catalyzes the first committed step in the synthesis of lacto- and globo-series glycolipids.¹⁶ Miglustat is licensed for the treatment of adult patients with mild-to-moderate type 1 Gaucher disease (GD1) for whom enzyme replacement therapy is unsuitable or not a therapeutic option.¹⁷ It has specific physicochemical properties that facilitate wide tissue distribution, including the brain.¹⁸ In vivo studies have demonstrated the ability of miglustat to prevent storage of G_{M2} ganglioside in the peripheral tissues and central nervous system of mouse models of TSD and Sandhoff disease.^{19,20} Case studies of miglustat in patients with infantile and subacute TSD have not detected slowing of neurological deterioration,^{15,21} but in patients with the infantile form, a high concentration of miglustat is achieved in the patient’s cerebrospinal fluid, associated with prevention of macrocephaly.²¹ To date, no studies of other therapies for G_{M2} gangliosidosis have been reported.

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Here, we report the results of a study of the efficacy, safety, and tolerability of miglustat in adult patients with G_{M2} gangliosidosis. As progressive muscle wasting is a common feature of G_{M2} gangliosidosis, efficacy of miglustat was primarily assessed by changes in limb muscle and grip strength. Changes in gait, balance, disability, and other neurological measures were also assessed.

MATERIALS AND METHODS

Study design

This was a Phase II, randomized, multicenter, open-label, controlled trial of miglustat in adult patients with G_{M2} gangliosidosis (LOTS [type III TSD] or Sandhoff disease [type II]). Patients were randomized 2:1 to miglustat or “no miglustat treatment” for 12 months. Subsequently, all patients were eligible to receive miglustat for two consecutive 12-month extension phases. Because of the low prevalence of G_{M2} gangliosidosis, a sample size of 30 patients was chosen on pragmatic grounds.

The protocol and all materials provided to the patient were reviewed and approved by the sites’ Institutional Review Board. Written informed consent was obtained from each individual participating in the study. The study was conducted in accordance with the Declaration of Helsinki, as revised in 2000.

Patients

Patients were recruited by investigators at two study centers in the United States (New York and Cleveland). Patients aged 18 years or older, with a confirmed diagnosis of G_{M2} gangliosidosis and who had stable renal function were included in the study. Diagnosis was based on deficient hexosaminidase A and/or B activity, and genotype was established for all patients. Patients who had suffered from clinically significant diarrhea (>three liquid stools per day for >7 days) without definable cause within 3 months of a screening visit, or who had a history of significant gastrointestinal disorders, were excluded. Patients with a current medical condition that rendered them unsuitable for the study, such as human immunodeficiency virus or hepatitis infection, or those with an adjusted creatinine clearance of <70 mL/minute/1.73 m² (CrCl < 70), were also excluded.

After the initial screening visit, patients were evaluated on four occasions during the 12-month randomized period, specifically at months 3, 6, 9, and 12. During the extension phase, clinic visits took place at months 15, 18, 21, 24, 28, 32, and 36. All patients from both randomization groups underwent the same assessment schedule.

Randomization procedure

Subjects were enrolled by the investigators and assigned to their treatment groups based on a randomization allocation sequence that was computer-generated using SAS® by the contract research organization’s biostatistics group. The randomization ratio of miglustat to “no miglustat treatment” was 2:1. As this was an open-label study, there was no blinding of patients or clinical staff.

Treatment

Patients receiving miglustat were given a starting dose of 200 mg orally TID (twice the dose usually prescribed to GD1 patients). This dose was selected as G_{M2} gangliosidosis is primarily a neurological condition, and higher drug concentrations may be required to reach the central nervous system. A similar dosing regimen has been used in studies of miglustat in

other neurological disorders.^{22,23} The starting dose was also the highest dose that was tolerated by patients in GD1 studies. Treatment dose could be reduced at the discretion of the treating physician.

Patients whose body surface area (BSA) was less than a normal adult’s (<1.8 m²) on entry to either the randomized period (if randomized to miglustat treatment) or extension phase had their dose adjusted according to BSA, based on the following formula: (BSA (m²)/1.8) × adult dose. Patients were continually monitored to ensure the correct dose of miglustat was taken at regular intervals.

Patients randomized to “no miglustat treatment” received the standard care for patients with G_{M2} gangliosidosis during the randomized phase, and started miglustat treatment upon entry into the extension phase of the study.

Endpoints

The primary efficacy endpoints were mean change in eight measures of isometric muscle strength (shoulder abduction, elbow flexion, elbow extension, finger extension, hip flexion, knee extension, knee flexion, and foot dorsiflexion) and isometric grip strength, evaluated at baseline, month 12 (end of randomized phase) and month 36 (end of full study period). Muscle and grip strength were chosen as the primary endpoints, because progressive muscle wasting is a common feature of chronic G_{M2} gangliosidosis. For each muscle group, a force transducer was placed distally to the joint of the segment being studied. The force transducer registered (in kg) the isometric force generated when performing a particular maneuver. Grip strength was assessed by dynamometry.

Secondary endpoints included change from baseline to month 12 and month 36 in gait, balance, and overall disability. A timed walk test (nonwheelchair bound patients only) was used to measure gait speed, and the Standard Ambulation Index (range 0–9)²⁴ was used to determine the time and degree of assistance required to walk a set distance (overall and for the nonwheelchair bound patients). The Modified Falls Efficacy Scale total score²⁵ (range 0–140) was used to assess patients’ fear of falling, and the Tinetti Scale balance (range 0–16) and gait (range 0–12) scores²⁶ were determined to assess the risk of future falls. The overall functional disability throughout the study was measured using the Amyotrophic Lateral Sclerosis Functional Rating Scale (range 0–44).²⁷

Neurological status was also a secondary endpoint and was evaluated using the Mini-Mental State Examination to assess cognition (range 0–30),²⁸ Purdue Pegboard Test total score to assess manual dexterity (range 0–100),²⁹ Archimedes Spiral mean score³⁰ to measure tremor (range 0–10), and speech diadochokinetic rate (number of PA-TA syllables in a 5-second interval) to assess speech performance.³¹

Safety assessments included adverse event reporting, biochemistry, hematology and urine analyses, and full physical examinations. Adverse events were evaluated for their severity (intensity), seriousness, and causal relationship to the study medication. Vital signs, including oral temperature, blood pressure, respiratory rate, and heart rate, were also assessed. Nerve conduction velocity studies were also performed at each clinic visit (peroneal and ulnar motor, sural and ulnar sensory).

Data analysis

For the initial 12-month randomized phase of the study, changes from baseline to month 12 in patients on miglustat were compared with those in the “no miglustat treatment” arm. For the overall 36-month study, patients who completed 36 months of miglustat treatment were compared with those who com-

pleted 12 months on “no miglustat treatment” and were then given miglustat for 24 months.

All endpoints were summarized with descriptive statistics (mean actual values with standard deviations and change from baseline with 95% confidence intervals). For the primary endpoints, the two treatment groups were compared with respect to changes from baseline to month 12 and month 36 using an analysis of covariance adjusted for baseline value and gender. The same analysis of covariance was also performed for each interim timepoint (months 3, 6, 9, 15, 18, 21, 28, and 32).

To account for patient withdrawals, an intention-to-treat analysis (change from baseline to last value) was also performed. The last value was the last valid postbaseline assessment recorded in the extended period (excluding the month 12 visit) up to and including the final day of the month 36 visit. All patients who withdrew from the study completed a follow-up visit.

Three analysis populations were defined. The “all randomized patients” population included all randomized patients regardless of whether those assigned to miglustat actually received treatment. Baseline data are presented for the “all randomized patients” population. The efficacy population included all randomized patients who had at least one postbaseline efficacy assessment for the given parameter during the randomized period (month 12 assessments) or the extension phases (month 36 and last value assessments). The safety population included all randomized patients who received at least one dose of miglustat during the study period and had at least one postbaseline value of safety assessment after the start of miglustat treatment. Data from patients originally randomized to “no miglustat treatment” were only included from the date the first dose of miglustat was taken (i.e., the first 12-month extension period).

RESULTS

Patients and treatment

Thirty patients were randomized to receive either miglustat ($n = 20$) or “no miglustat treatment” ($n = 10$) for 12 months. Fifteen patients were enrolled from each center. All patients presented with TSD; no patients with Sandhoff disease were enrolled. The first patient was enrolled in November 2002, and the last patient completed the study on July 31, 2006.

Patient demographics and baseline characteristics are presented in Table 1. The mean age was 38.2 years (SD 10.4 years), and the age range was 18–56 years. All patients had at least one manifestation of G_{M2} gangliosidosis at baseline. The most common manifestations were muscle weakness (19 patients from the miglustat group and 10 patients from the “no miglustat treatment” group), tremor (18 and 10 patients, respectively), and dysarthria (18 and 9 patients). A greater proportion of patients initially randomized to miglustat than to “no miglustat treatment” reported dysidiadochokinesis (90% vs. 60%), skeletal muscle cramps (85% vs. 70%), and ambulation difficulties (85% vs. 70%). A greater proportion of patients initially randomized to “no miglustat treatment” than to miglustat reported learning difficulties (50% vs. 25%), psychosis (60% vs. 20%), and bipolar disorder (60% vs. 10%). Three (15%) patients from the miglustat group and two (20%) patients from the “no miglustat treatment” group were wheelchair bound.

Patient disposition is shown in Figure 1. All patients from the “no miglustat treatment” group and 19 patients from the miglustat group completed the first 12 months and entered the first extension phase; one patient from the miglustat group withdrew

Table 1 Baseline demographics and characteristics

Characteristic	Miglustat ($n = 20$)	No miglustat treatment ($n = 10$)	Overall ($N = 30$)
Gender			
Male, n (%)	13 (65)	7 (70)	20 (67)
Age (yr)			
Mean (SD)	37.3 (11.9)	40.0 (6.5)	38.2 (10.4)
Age group (yr)			
18–30, n (%)	7 (35)	1 (10)	8 (27)
31–45, n (%)	7 (35)	6 (60)	13 (43)
46–65, n (%)	6 (30)	3 (30)	9 (30)
>65, n (%)	0	0	0
Race			
White, n (%)	20 (100)	10 (100)	30 (100)
Weight (kg)			
Mean (SD)	72.4 (21.4)	68.2 (15.2)	71.0 (19.4)
Height (cm)			
Mean (SD)	170.6 (12.8)	169.4 (7.9)	170.2 (11.3)
Body mass index (kg/m^2)			
Mean (SD)	24.6 (6.1)	23.8 (5.0)	24.4 (5.7)

Analysis population: all randomized patients.

from the randomized phase due to an adverse event (weight decrease).

During the first 12-month extension, four patients from the original miglustat group withdrew (two because of patient request and two because of an adverse event of intermittent diarrhea) and two from the original “no miglustat treatment” group withdrew (one patient request, one death; the cause of death was arrhythmia, which was considered unrelated to study treatment by the investigator).

During the second 12-month extension, three patients from the original miglustat group withdrew. In total, 11 patients from the original miglustat group and eight from the original “no miglustat treatment” group completed the full 36-month study period. Overall, more patient withdrawals were seen in the group of patients who received 36-months’ miglustat treatment compared with the group receiving “no miglustat treatment” followed by 24 months of miglustat. This may have been due to the higher proportion of patients in an advanced stage of disease in the miglustat group, as evidenced by ambulation difficulties at baseline.

Primary endpoints: Isometric muscle and grip strength

No group differences were detected in changes in isometric muscle strength and grip strength, either during the 12-month randomized phase, or over the whole 36-month study (Table 2). Similarly, no group differences in change from baseline to last value, or to any of the interim timepoints, were seen (data not shown). Changes from baseline to the interim timepoints were

Fig. 1. Patient disposition during the randomized study and two extension phases.

generally consistent with the primary analysis in both treatment groups. A general decrease in all measures of isometric muscle and grip strength was seen in both treatment groups over the 36-month study period.

Secondary endpoints

No clinically meaningful between-group differences were observed for any of the secondary efficacy endpoints in either the 12-month randomized trial or the full 36-month study period. The Tinetti scale (balance and gait) and disability (Amyotrophic Lateral Sclerosis Functional Rating Scale) scales decreased and the timed walk increased over the study duration for both groups, with no between-group differences at any time point (Table 3). The Modified Falls Efficacy Scale initially increased during the randomized phase in both treatment groups but decreased over the full study period (Table 3). The standard ambulation index (for all patients and for wheelchair-bound patients only) increased slightly more in patients who received 24-month miglustat treatment compared with those who received 36-month miglustat treatment (Table 3). Similar results were seen for change from baseline to last value (data not shown).

Mini-Mental State Examination scores remained stable in both groups over the study period, whereas Purdue Pegboard scores increased after 12 months treatment but decreased from baseline to month 36 in both groups (Table 4). Speech diadochokinetic rate stabilized or increased slightly in both groups over the 36-month period. From baseline to month 36, no change in tremor was seen in the 36-month miglustat group, whereas an increase in tremor was observed in the group receiving “no miglustat treatment” followed by 24 months’ miglustat (Table 4). Similar results were seen for change from baseline to last value for all neurological measures (data not shown).

Safety and tolerability

The combined safety population comprised 29 patients who had received miglustat and had safety assessments performed

during treatment. All 29 patients in the safety population experienced at least one treatment-related adverse event during the study. Overall, the median duration of exposure to miglustat was 736 days (range 274–1228 days).

During the randomized phase, weight decrease, diarrhea, flatulence, paresthesia, and dizziness were reported at a higher incidence in the miglustat group compared with the “no miglustat treatment” group. The other commonly reported events (including tremor aggravated, balance impaired, upper respiratory tract infection, appetite decreased) were generally reported by a similar proportion of patients in each treatment group. Falls were more commonly reported in the “no miglustat treatment” group.

During the 36-month study, the most frequently reported adverse events were falls (90%), weight decrease (79%), and diarrhea (76%) (Table 5). Tremor was aggravated in 31% patients. Fourteen patients had abnormal nerve conduction studies (sensory or motor or both) during the study; in 11 of these patients, the event was assessed as related to study drug. However, it should be noted that 13 (43%) of the patients who entered this study had abnormal nerve conduction studies at baseline, before exposure to the study drug.³² Peripheral neuropathy and weakness, resulting in abnormal sensory or motor nerve conduction studies, are known manifestations of late-onset TSD.³²

Most adverse events were mild or moderate in severity. During the 36-month study, serious adverse events were experienced by 10 patients (34%) while receiving miglustat; however, none of these events were considered to be related to miglustat treatment. No unexpected abnormal laboratory findings were detected.

The most frequently reported concomitant therapies were gastrointestinal medications, including loperamide. Overall, 21 (72%) of the 29 patients in the safety population received at least one gastrointestinal therapy during the study. Loperamide, the most commonly received gastrointestinal therapy, was taken by 19 (66%) patients overall.

Table 2 Mean (SD) isometric muscle and grip strength (kg) at baseline, mean (95% CI) change from baseline to end of randomized phase (12 mo) and end of full study period (36 mo), and estimated treatment difference (95% CI)

	Randomized phase (12 mo)				Full study period (36 mo)			
	12 mo miglustat (n = 19)		12 mo "no miglustat treatment" (n = 10)		36 mo miglustat (n = 10)		12 mo "no miglustat treatment" + 24 mo miglustat (n = 8)	
	Baseline	Change from baseline	Baseline	Change from baseline	Baseline	Change from baseline	Baseline	Change from baseline
Shoulder abduction (kg)	7.9 (2.8)	-1.0 (-2.2 to 0.2)	8.5 (5.6)	-0.5 (-2.9 to 1.9)	7.7 (3.1)	-1.9 (-3.7 to -0.2)	9.6 (5.8)	-2.6 (-6.0 to 0.9)
Elbow flexion (kg)	11.3 (3.1)	-0.4 (-1.9 to 1.1)	12.0 (4.3)	0.8 (-1.0 to 2.7)	11.1 (3.7)	-2.0 (-4.6 to 0.5)	13.0 (3.7)	-2.9 (-4.0 to -1.7)
Elbow extension (kg)	5.9 (3.6)	-1.0 (-1.8 to -0.3)	7.6 (6.0)	-1.3 (-3.4 to 0.8)	6.0 (3.3)	-2.9 (-4.1 to -1.6)	8.9 (6.0)	-3.3 (-5.7 to -1.0)
Finger extension (kg)	3.3 (1.4)	-0.5 (-1.1 to 0.2)	3.6 (1.7)	-0.6 (-1.9 to 0.8)	2.8 (1.2)	-0.4 (-1.2 to 0.5)	3.6 (1.7)	-1.0 (-2.0 to -0.1)
Hip flexion (kg)	6.3 (3.6)	-1.5 (-2.8 to -0.2)	8.2 (6.1)	-1.2 (-4.3 to 1.9)	6.7 (3.6)	-2.7 (-4.5 to -1.0)	8.8 (6.5)	-3.7 (-6.8 to -0.6)
Knee extension (kg)	4.4 (6.3)	-1.1 (-2.3 to 0.0)	6.0 (7.5)	-1.5 (-3.1 to 0.1)	4.7 (5.8)	-3.4 (-7.0 to 0.3)	7.2 (7.9)	-4.5 (-8.9 to -0.2)
Knee flexion (kg)	8.2 (4.0)	1.1 (-1.7 to 4.0)	11.3 (5.8)	1.1 (-2.2 to 4.3)	8.6 (4.4)	-1.7 (-7.0 to 3.5)	12.0 (6.0)	-3.0 (-5.7 to -0.3)
Foot dorsiflexion (kg)	8.4 (5.2)	-0.5 (-2.1 to 1.2)	8.4 (7.4)	-0.1 (-1.6 to 1.5)	7.2 (4.2)	-3.0 (-4.4 to -1.5)	9.5 (7.9)	-4.1 (-8.2 to -0.1)
Grip strength (kg)	18.4 (8.1)	-6.2 (-9.4 to -2.9)	18.7 (7.7)	-4.2 (-9.6 to 1.2)	18.2 (9.3)	-8.1 (-11.4 to -4.7)	19.1 (7.2)	-7.4 (-12.1 to -2.7)

Analysis population: efficacy.
*Based on least squares means from ANCOVA analysis adjusted for baseline value and gender. Mean isometric muscle strength scores (kg) in healthy individuals aged 20–80 yr (female and male, respectively): shoulder abduction: 11.3, 21.9; elbow flexion: 17.0, 28.8; elbow extension: 10.2, 17.4; hip flexion: 25.1, 38.0; knee extension: 32.5, 53.3; knee flexion: 18.9, 30.0.⁴⁰ Mean grip strength scores in healthy individuals aged 20–95 yr 27 kg (female), 49 kg (male).⁴¹ Normative values for finger extension and foot dorsiflexion are not available.

Table 3 Mean (SD) baseline gait, balance and disability assessment scores, and mean (95% CI) change from baseline to end of randomized phase (12 mo) and end of full study period (36 mo)

	Randomized phase (12 mo)			Full study period (36 mo)		
	12 mo miglustat (n = 19)		12 mo “no miglustat treatment” (n = 10)	36 mo miglustat (n = 10)		12 mo “no miglustat treatment” + 24 mo miglustat (n = 8)
	Baseline, mean (SD)	Change from baseline, mean (95% CI)		Baseline, mean (SD)	Change from baseline, mean (95% CI)	
Timed walk (s) ^a	11.0 (12.2)	4.6 (−0.8 to 9.9)	7.7 (3.2)	7.1 (1.6)	25.0 (−13.4 to 63.4)	6.1 (1.5)
Ambulation index ^b (range 0–9)	4.0 (2.4)	0.8 (0.2 to 1.3)	4.0 (3.0)	3.5 (2.4)	2.3 (0.8 to 3.8)	3.1 (2.6)
Ambulation index ^b (nonwheelchair) (range 0–9)	3.5 (1.9)	0.9 (0.3 to 1.5)	2.8 (1.7)	2.9 (1.5)	2.6 (1.0 to 4.1)	2.3 (1.1)
MFES score ^a (range 0–144)	89.3 (32.4)	1.2 (−12.1 to 14.4)	81.8 (40.7)	92.1 (34.0)	−37.5 (−61.4 to −13.6)	88.0 (43.7)
Tinetti balance score ^a (range 0–16)	8.3 (4.4)	−1.1 (−2.1 to 0.0)	7.5 (5.4)	8.4 (4.9)	−3.7 (−5.8 to −1.6)	8.4 (5.5)
Tinetti gait score ^a (range 0–12)	7.7 (3.2)	−0.8 (−1.9 to 0.3)	7.0 (4.3)	7.7 (3.4)	−1.9 (−4.0 to 0.2)	8.0 (3.9)
ALSFERS score ^a (range 0–44)	29.9 (4.7)	−0.3 (−1.5 to 0.9)	27.4 (5.9)	31.2 (4.8)	−3.9 (−5.8 to −2.0)	28.6 (6.0)

Analysis population: efficacy.

^aA lower score indicates greater impairment.

^bA lower score indicates better ambulation.

ALSFERS, Amyotrophic Lateral Sclerosis Functional Rating Scale; MFES, Modified Falls Efficacy Scale.

Table 4 Mean (SD) baseline score in neurological endpoints, and mean (95% CI) change from baseline to end of randomized phase (12 mo) and end of full study period (36 mo)

	Randomized phase (12 mo)				Full study period (36 mo)			
	12 mo miglustat (n = 19)		12 mo "no miglustat treatment" (n = 10)		36 mo miglustat (n = 10)		12 mo "no miglustat treatment" + 24 mo miglustat (n = 8)	
	Baseline, mean (SD)	Change from baseline, mean (95% CI)	Baseline, mean (SD)	Change from baseline, mean (95% CI)	Baseline, mean (SD)	Change from baseline, mean (95% CI)	Baseline, mean (SD)	Change from baseline, mean (95% CI)
Purdue pegboard test total score ^a (range 0–100)	19.5 (6.7)	0.7 (–1.0 to 2.4)	17.1 (8.1)	0.6 (–1.0 to 2.2)	19.8 (6.7)	–2.5 (–6.2 to 1.2)	21.3 (5.2)	–2.7 (–5.9 to 0.5)
MMSE score ^a (range 0–30)	27.4 (3.1)	0.2 (–0.7 to 1.0)	26.7 (3.7)	0.6 (–2.1 to 3.3)	26.3 (3.8)	0.8 (–1.0 to 2.6)	25.9 (3.8)	1.5 (–0.9 to 3.9)
Speech diadochokinetic rate ^a (No. of syllables in 5 second interval)	9.9 (2.4)	–0.5 (–1.4 to 0.5)	9.8 (2.5)	0.3 (–1.3 to 1.8)	9.5 (2.7)	0.6 (–0.6 to 1.8)	9.7 (2.8)	0.5 (–1.8 to 2.8)
Tremor (Archimedes spiral mean score) ^b (range 0–10)	2.5 (0.9)	0.1 (–0.4 to 0.6)	2.4 (1.5)	0.1 (–0.8 to 0.9)	2.6 (1.0)	–0.5 (–1.4 to 0.5)	1.9 (1.0)	1.3 (0.1 to 2.6)

Analysis population: efficacy.
^aA lower score indicates greater impairment.
^bA lower score indicates less tremor.
MMSE, Mini-Mental State Examination.

Table 5 Most commonly reported adverse events^a

Adverse event	No. (%) patients (N = 29)
Fall	26 (90)
Weight decreased	23 (79)
Diarrhea	22 (76)
Motor nerve conduction studies abnormal	13 (45)
Paresthesia	12 (41)
Laceration	11 (38)
Fatigue	11 (38)
Sensory nerve conduction studies abnormal	10 (34)
Abdominal pain	10 (34)
Flatulence	10 (34)
Vomiting	9 (31)
Tremor aggravated	9 (31)
Nasopharyngitis	9 (31)
Appetite decreased	9 (31)

Analysis population: safety.
^aReported by >30% patients.

DISCUSSION

This study was the first randomized, controlled trial to evaluate the efficacy of miglustat in patients with G_{M2} gangliosidosis. Preclinical studies have indicated that miglustat may prevent storage of G_{M2} ganglioside in mouse models of TSD and Sandhoff disease.^{19,20} In the current study, there were neither differences in the primary endpoints of isometric muscle and grip strength nor in the secondary neurological endpoints involving gait and disability assessments, between patients treated with miglustat and those receiving standard of care during the initial 12-month randomized phase of the study. As there were no other available treatments for patients with G_{M2} gangliosidosis, and it was possible that longer term miglustat therapy might have beneficial effects, it was felt that miglustat therapy should be made available to all patients involved in the randomized trial for a longer period, for compassionate reasons. However, after 36 months, no differences in any outcome measure were detected between patients who had received miglustat from the start and those who were initially randomized to “no miglustat treatment” and then given miglustat for 24 months. All patients showed a general deterioration in most endpoints. This likely represents the natural course of the disease rather than any effect of miglustat.

There is currently no recognized quantitative clinical endpoint validated for assessment of therapeutic effect in G_{M2} gangliosidosis. The primary endpoint of isometric muscle and grip strength was selected for this study as progressive muscle weakness is a known and common feature of LOTS, and was hypothesized to be a measurable outcome of therapeutic intervention. However, our observations suggest that neurological deficits in patients with TSD might be irreversible; specifically, muscle weakness may be evident only after significant neuronal damage has occurred. In an *in vivo* study using a mouse model of G_{M2} gangliosidosis, administration of miglustat before the

development of clinical symptoms increased life expectancy, whereas administration after symptoms developed did not result in any delay in disease progression.²⁰ In the current study, several patients were already at an advanced stage of disease at enrolment, as indicated by baseline standard ambulation index scores. Muscle weakness may therefore not have been a suitable measure for detecting therapeutic benefits in this patient cohort. Recent studies have suggested that ophthalmologic measures³³ or neuropsychological measures³⁴ might be useful in the assessment of therapeutic interventions of patients with G_{M2} gangliosidosis. In particular, memory and executive functioning (e.g., problem solving and planning) impairments have been shown to occur frequently in LOTS patients, thus neuropsychological tests might be an alternative method of measuring the effect of treatment on cortical involvement.^{34,35} Magnetic resonance imaging for cerebellar atrophy can also be used to measure progression in G_{M2} gangliosidosis and may be useful for detecting treatment effects. Further, proton spectroscopy can be used to measure specific cerebral metabolites that may be used to indicate disease severity³⁶; for example, *N*-acetylhexosamine has been shown to be a specific marker of Sandhoff disease.³⁷ Future studies of G_{M2} gangliosidosis might benefit from employing such assessments.

G_{M2} gangliosidosis is a very rare disease, and as mentioned above, there is currently no recognized quantitative clinical endpoint validated for assessing therapeutic effects. As only a few patients were available for the study, the sample size was selected on pragmatic grounds. We cannot eliminate the possibility that a small treatment effect might not have been detected, due to lack of statistical power and the inherent variation of the measures used as outcomes.

The safety and tolerability profile of 200 mg TID miglustat in the current study was consistent with the approved dose in GD1 (100 mg TID).¹⁷ Consistent with previous studies,^{38,39} the most frequently reported treatment-related adverse events were gastrointestinal, particularly diarrhea and weight decrease. In general, these events were of mild or moderate severity and decreased in frequency over time and were well controlled by medications such as loperamide. Although tremor seemed to decrease over time with miglustat treatment, as measured by the Archimedes Mean Spiral score, there were some incidences of aggravated tremor in patients receiving miglustat. Tremor has been reported as a side effect of miglustat in clinical trials of patients with GD1 but tends to reduce spontaneously while on continued therapy or with lowering of the miglustat dose.¹⁷ A recent study involving 30 patients with LOTS who underwent clinical and electrophysiologic examination found evidence of a predominantly axon loss polyneuropathy affecting distal nerve segments in the lower and upper extremities in eight patients (27%), and abnormal sensory or motor nerve conduction studies in 43%.³² Thus, the observed changes in nerve conduction noted in our patients are likely due to disease progression rather than an effect of the miglustat treatment.

In conclusion, this trial of miglustat in LOTS did not show benefits of treatment on the measured outcomes, either over 12 months randomized treatment (12 months miglustat versus “no miglustat treatment”) or over the full 36-month study (36 months miglustat vs. 12 months “no miglustat treatment” followed by 24 months miglustat). These findings do not support the use of miglustat for treatment of LOTS.

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