Lancet Neurology 2007; 6:765-72

Miglustat for treatment of Niemann-Pick C disease: a randomised controlled study

Marc C Patterson, Darleen Vecchio, Helena Prady, Larry Abel, James E Wraith

Summary

Background **Niemann-Pick type C disease (NPC) is an inherited neurodegenerative disorder characterised by an intracellular lipid-trafficking defect with secondary accumulation of glycosphingolipids. Miglustat, a small iminosugar, reversibly inhibits glucosylceramide synthase, which catalyses the first committed step of glycosphingolipid synthesis. Miglustat is able to cross the blood-brain barrier, and is thus a potential therapy for neurological diseases. We aimed to establish the effect of miglustat on several markers of NPC severity.**

Methods **Patients aged 12 years or older who had NPC (n=29) were randomly assigned to receive either miglustat 200 mg three times a day (n=20) or standard care (n=9) for 12 months. 12 children younger than 12 years of age were included in an additional cohort; all received miglustat at a dose adjusted for body surface area. All participants were then treated with miglustat for an additional year in an extension study. The primary endpoint was horizontal saccadic eye movement (HSEM) velocity, based on its correlation with disease progression. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN26761144.**

Findings **At 12 months, HSEM velocity had improved in patients treated with miglustat versus those receiving standard care; results were significant when patients taking benzodiazepines were excluded (p=0·028). Children showed an improvement in HSEM velocity of similar size at 12 months. Improvement in swallowing capacity, stable auditory acuity, and a slower deterioration in ambulatory index were also seen in treated patients older than 12 years. The safety and tolerability of miglustat 200 mg three times a day in study participants was consistent with previous trials in type I Gaucher disease, where half this dose was used.**

Interpretation **Miglustat improves or stabilises several clinically relevant markers of NPC. This is the first agent studied in NPC for which there is both animal and clinical data supporting a disease modifying benefit.**

Published Online August 2, 2007 DOI:10.1016/S1474-4422(07)70194-1

Departments of Neurology and Pediatrics, Columbia University, NY, USA (M C Patterson FRACP, D Vecchio); **Royal Manchester Children's Hospital, Biochemical Genetic Unit, Manchester, UK** (H Prady, J E Wraith FRCPCH); **Department of Optometry and Vision Sciences, University of Melbourne, VIC, Australia** (L Abel PhD)

Correspondence to: Marc C Patterson, Division of Child and Adolescent Neurology, Mayo Clinic, Rochester MN 55905, USA
patterson.marc@mayo.edu

Introduction

Niemann-Pick type C disease (NPC) is an autosomal recessive disease linked to dysregulation of intracellular lipid trafficking.[1,2] There is currently no treatment available for this disease aside from palliative care.

The birth incidence of NPC has been estimated at 1 in 150 000 in western Europe,[3] with a higher incidence in certain genetically isolated populations.[4,5] Most patients with NPC harbour mutations in the genes encoding the NPC1 (95%) and HE1/NPC2 (5%) proteins.[6,7]

Dysregulated lipid transport in NPC is associated with excess accumulation of free cholesterol and glycosphingolipids in many tissues including the brain.[2,8] Raised concentrations of GM2 and GM3 gangliosides are seen in many diseased neurons, by contrast with their virtual absence in healthy mature neurons.[9] GM2 ganglioside accumulation is invariably associated with neuron-specific ectopic dendritogenesis.[10] Neurons seem selectively vulnerable to NPC1 protein deficiency, although the mechanisms by which NPC1 and NPC2 sustain normal neuronal function are yet to be established.[11]

Although the lesions of NPC occur throughout the CNS, certain regions are susceptible to early and severe injury. Purkinje cell loss begins early and progresses rapidly, correlating with gait ataxia, dysarthria, and dysphagia.[12] Neurofibrillary tangles, ectopic dendritogenesis, and meganeurite formation in the cortex provide an anatomic substrate for dementia and seizures.[12] Severe cell loss has also been reported in the rostral interstitial nucleus of the medial longitudinal fasciculus, a crucial premotor area for vertical gaze, with lesser degeneration in the paramedian pontine reticular formation, the corresponding centre for horizontal saccades.[13]

Neurological findings in NPC include vertical and horizontal supranuclear gaze palsy, ataxia, dysarthria, dysphagia, dystonia, seizures, progressive dementia, psychiatric syndromes, and gelastic cataplexy.[14–17] Hepatosplenomegaly is frequently, but not invariably, present in NPC, and its absence does not exclude the diagnosis, particularly in late-onset cases.[18] Vertical supranuclear gaze palsy has been described in all but a handful of cases of NPC, irrespective of the age of onset.

Separate systems control vertical and horizontal saccades, providing an anatomical basis for the onset of vertical before horizontal saccadic palsy in NPC.[13,19] Saccadic recordings in individuals with NPC show an early, marked slowing of vertical saccadic eye movements, followed later by similar changes in horizontal saccadic eye movements (HSEM).[13,19–21] Vertical saccadic eye movements are often completely lost by the time NPC is diagnosed.

To date, there is no disease-modifying therapy for NPC.[22] Substrate reduction therapy is a novel therapeutic

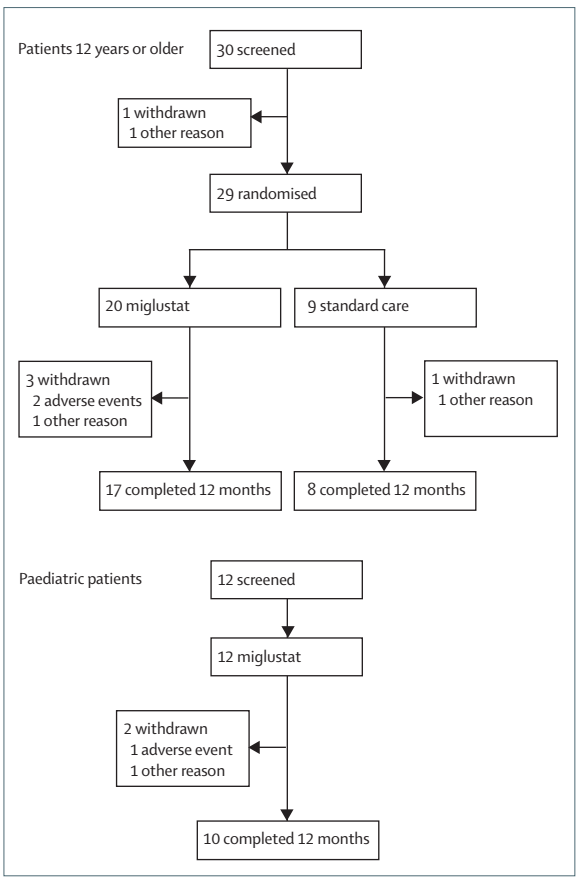

Figure 1: **Trial profile**

strategy for lysosomal storage diseases[23] that uses inhibitors, such as miglustat, to diminish glycolipid biosynthesis. Miglustat, a small iminosugar molecule, reversibly inhibits glucosylceramide synthase, which catalyses the first committed step of glycosphingolipid synthesis.[24] Its ability to cross the blood-brain barrier renders miglustat a suitable agent for treating CNS disease in NPC.[25] Administration of miglustat has ameliorated glycosphingolipid accumulation in neurons and prolonged survival in murine models of lysosomal storage disorders,[26] including NPC. Miglustat treatment of mice and cats with NPC resulted in reduced ganglioside accumulation, delayed onset of neurological dysfunction, and increased survival.[27] In people, depletion of glycosphingolipids by miglustat in an NPC patient reduced pathological lipid storage, improved endosomal uptake, and normalised lipid trafficking in peripheral blood B lymphocytes.[28]

Miglustat is currently approved for the treatment of selected patients with Type I Gaucher disease, the most prevalent lysosomal storage disorder. The efficacy, safety, and tolerability of miglustat in individuals with Gaucher disease have been shown in several clinical studies.[29–31] Patients with the disease who were treated with miglustat for up to 3 years showed improvement in key clinical markers of the disease.[30] The preceding data provided a strong rationale for the investigation of miglustat as a treatment for patients with NPC.

We aimed to assess the effects of miglustat as a treatment for NPC in adult, adolescent, and paediatric patients, over a 24-month treatment period. The first 12 months' data are presented in this report.

Methods

Participants

The efficacy, safety, and tolerability of miglustat in NPC were assessed in patients 12 years and older and paediatric patients (age 4–11 years). Patients with NPC confirmed by reduced cholesterol esterification and abnormal filipin staining in cultured fibroblasts who were capable of cooperating with the physical examination and other testing were considered eligible for participation. The major exclusion criteria included clinically significant diarrhoea (more than three liquid stools per day for more than 7 days) without definable cause within 3 months before enrolment, significant gastrointestinal disorders, or other intercurrent illnesses. Patients were enrolled between March, 2002, and April, 2004. Patient recruitment is shown in figure 1.

This study was done in accordance with the Declaration of Helsinki and complied with US Food and Drug Administration regulations and ICH Good Clinical Practice guidelines. All study documentation was submitted and approved by the local Institutional Review Board or Independent Ethics Committee before the study commenced. All patients or their legal representatives provided written informed consent.

Procedures

Patients aged 12 years or older were randomly assigned in a 2:1 ratio to either miglustat 200 mg taken orally three times a day for 12 months or to standard symptomatic care (no study drug) as a control group. Standard care included pharmacotherapy, physical, speech, and occupational therapy prescribed for accepted indications in each patient by his or her primary paediatrician or neurologist.

Both miglustat-treated and standard care groups received other concomitant medications for standard indications throughout the study. All children received miglustat in a dose adjusted according to body surface area. We assessed all patients 1 week after commencing miglustat therapy and monthly thereafter with dose modification as clinically indicated.

The study aimed to establish the effect of miglustat on several markers of NPC severity. Based on known mechanisms of action and animal data, we postulated that patients in the treatment group would show slower rates of decline or stabilisation in one or more markers of the disease compared with the standard care group.

The primary efficacy endpoint of this study was change from baseline in HSEM-α: a measure of HSEM velocity.

http://neurology.thelancet.com **Published online August 2, 2007 DOI:10.1016/S1474-4422(07)70194-1**

This endpoint was selected because of its characteristic impairment in NPC.[13,32] HSEM-α is the estimated slope of the linear regression line of peak duration (amplitude/peak velocity, ms) versus amplitude (deg) of HSEM. When peak velocity is plotted directly against amplitude, the result usually has the form of a saturating exponential.[19] The technique here allows for the replacement of this nonlinear equation with a straight line.[33] HSEM-α corresponds to the asymptotic peak velocity in the conventional equation and thus is driven by changes in larger saccades. A reduction in the slope (HSEM-α, ms/deg) and intercept (β, ms) of the regression line represents improvement of HSEM velocity. One eye was selected for HSEM measurement, and data for right and left directions were combined.

Every saccade was analysed for amplitude and peak velocity. Peak duration for each individual's saccades for a given test condition (eg, 12 months, horizontal) was obtained by dividing each saccade's amplitude by its peak velocity. This result was then plotted against amplitude for each saccade and linear regression was done, which yielded the alpha (slope) and beta (intercept) values which represented that particular patient under that test condition. Saccadic eye movement (SEM) velocity was assessed at screening and month 12 by established video-based and scleral search coil techniques and Matlab (version 7.04)/Rex and associated software to analyse saccadic data from oculographic recordings. Two assessments were done at each time point separated by a break of at least 1 hour. Patients had a general ophthalmologic assessment before assessment of SEM, to exclude other causes of visual impairment. The local assessors were masked to the patients' treatment status. Data for both study sites were sent to a blinded central assessor for final evaluation.

Secondary efficacy endpoints for all patients included HSEM-β, assessments of swallowing, auditory acuity, ambulatory ability (standard ambulation index), and cognition (mini-mental status examination [MMSE]). These outcome measures were assessed by the same investigator at each site.

Swallowing assessments were done at screening and at months 6 and 12. Patients were asked to swallow the following substances (in increasing level of difficulty): 5 mL of water, 1 teaspoon of purée, 1 teaspoon of soft lumps (tinned spaghetti or noodles), or a third of a cookie. Three attempts were made for each substance and the study assessment was done on the final attempt. The assessor evaluated the patient's swallowing ability using a five-degree category scale: "no problems swallowing", "mild", "moderate", "severe", or "could not swallow the substance at all". Assessments of auditory acuity and ambulation were done as part of a full neurological examination at screening and months 3, 6, 9, and 12. Auditory acuity was measured in each ear by assessing the ability of the participant to hear a ticking watch (US site) or Manchester rattle (Ewing Foundation, Manchester, UK) and a C^1 256 tuning fork (UK site) at 30 cm (or less) from the external auditory meatus. Patients able to hear the sound source at 30 cm were classified as normal; those able to hear the sound source at distances 0–30 cm as abnormal, and those unable to hear at 0 cm as deaf. Ambulatory ability was characterised with the Standard Ambulation Index. Patients aged 12 years or older also completed the MMSE at screening visit 1 or 2 and months 3, 6, 9, and 12 (or at the withdrawal or follow-up visit if not tested at month 12). Adverse events were assessed at each study visit by direct questioning.

41 patients were enrolled, including 29 patients older than 12 years and 12 paediatric patients. The planned sample size was selected on pragmatic grounds, since limited longitudinal data for HSEM changes was available for this patient population and the number of potential participants was likewise limited. For randomisation, the Investigator faxed an enrolment form to the Clinical Project Manager, who then selected the next available treatment allocation scratch card from a set that had been

	Age 12 years or older (miglustat)	Age 12 years or older (standard care)	Age younger than 12 years (miglustat)
Sex			
Male, n (%)	9 (45%)	5 (56%)	5 (42%)
Female, n (%)	11 (55%)	4 (44%)	7 (58%)
Age (years)			
Mean (SD)	25·4 (9·8)	22·9 (7·5)	7·2 (2·5)
Range	12–42	13–32	4–11
2–11	0	0	12 (100%)
12–17	5 (25%)	4 (44%)	0
≥ 18	15 (75%)	5 (56%)	0
Weight (kg)			
Mean (SD)	74·8 (22·3)	64·8 (13·5)	27·9 (10·5)
Height (cm)			
Mean (SD)	168·6 (15·7)	167·8 (10·4)	124·3 (19·9)

Table 1: **Baseline characteristics of patients**

	Age 12 years or older (miglustat) n=20	Age 12 years or older (standard care) n=9	Age younger than 12 years (miglustat) n=12
Vertical supranuclear gaze palsy	20 (100%)	7 (78%)	12 (100%)
Cognitive impairment	18 (90%)	7 (78%)	8 (67%)
Ataxia	20 (100%)	5 (56%)	10 (83%)
Speech difficulties	18 (90%)	4 (44%)	7 (58%)
Dystonia	14 (70%)	4 (44%)	5 (42%)
Swallowing difficulties	12 (60%)	6 (67%)	4 (33%)
Pyramidal tract dysfunction	10 (50%)	3 (33%)	5 (42%)
Splenomegaly	7 (35%)	5 (56%)	10 (83%)
Hepatomegaly	6 (30%)	4 (44%)	7 (58%)
Seizures	1 (5%)	1 (11%)	0
Cataplexy	1 (5%)	0	4 (33%)

Data are n (%).

Table 2: **Baseline clinical manifestations of NPC**

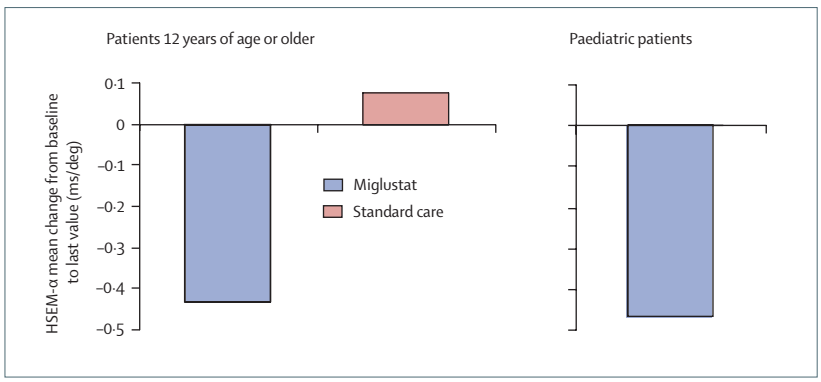

***Figure 2*: Mean changes in HSEM-α from baseline to last available value in patients receiving miglustat versus standard care**

Negative changes represent an improvement and positive changes represent a deterioration. 12 years or over: miglustat group n=18, mean (SE) –0·431 (0·221), standard care n=8, 0·074 (0·291). Paediatric group n=12, –0·465 (0·127).

prepared to provide the required ratio. The Clinical Project Manager then wrote the treatment allocation on the enrolment form and faxed this back to the Investigator. The randomisation scheme was constructed using a block size of 6, but was not stratified, to keep the chances of the Investigators predicting the next treatment assignment to a minimum. Each patient identifier was a concatenation of study number, patient number, sex, and age.

Statistical analysis

Analysis of the primary endpoint was done on the Efficacy Set, which included all randomised patients who received at least one dose of study medication and who had at least one post-baseline efficacy assessment for SEM. In the population aged 12 years or older, the two study groups (miglustat *vs* standard care) were compared using analysis of covariance (ANCOVA model) with baseline and centre as covariates. The test was done for values obtained from baseline, month 12, or the last available value on drug. An exploratory analysis of the SEM velocity was also done in a subgroup of patients excluding those patients who were taking benzodiazepine medications (which are known to affect SEM).[34] The paediatric group was compared with those aged 12 years or older using descriptive statistics on the baseline data and on the change from baseline to month 12 or to last available value.

The analyses of the secondary study endpoints were also done on the Efficacy Set. Analysis of HSEM-β was done using the same procedure as described for the primary endpoint. A stratified Wilcoxon test was used to compare the study groups with regard to a patient's ability to swallow the four substances. For each substance, the test was done for values obtained at month 12 or the last available value on drug. Data at each time point were stratified with the baseline data. The Standard Ambulation Index was compared between the standard care and the miglustat-treated group using descriptive statistics on change from baseline to month 12 or to last available value. The proportion of patients with normal and abnormal results for each category of the auditory acuity was summarised at month 12 or the last available value. The MMSE data was summarised with descriptive statistics on change from baseline to month 12 or to last available value. The proportion of patients with change in MMSE score of 2 or more was also summarised, as change of 2 or more points was regarded to be clinically meaningful. Adverse events were analysed using descriptive statistics

For a **list of concomitant medications** http://www.actelion.com/uninet/www/www_main_p.nsf/content/Phase+III+trial+concomitant+therapy+usage+in+patients+with+Niemann+Pick+type+C+disease+treated+with+miglustat/$FILE/ConcomitantTherapy.pdf

Role of funding source

Data analysis was made by a clinical research organisation paid by the study sponsor. The first draft of the manuscript was written by a medical writer. The manuscript was then revised and rewritten by the first author and was submitted to all authors for review.

Results

29 patients aged 12 years or older (20 receiving miglustat, nine receiving standard care) and 12 children were enrolled in the study (table 1). Baseline characteristics were similar for the standard care and miglustat-treated patients. The mean age for patients aged 12 years or older receiving miglustat was 25·4 years (SD 9·8), for those on standard care was 22·9 years (7·5), and for the paediatric group receiving miglustat was 7·2 years (2·5). In the study group aged 12 years or older, three patients in the miglustat-treatment group withdrew from the study (two because of adverse events, and one because of disease progression). One patient in the standard care group withdrew to restart treatment with an alternative therapy. One child also had adverse events which led to withdrawal from the study, and one withdrew for other reasons.

Table 2 shows the clinical manifestations of NPC at study entry. A greater proportion of patients in the miglustat-treatment group than in the standard care group reported clinical manifestations of NPC at baseline. Most patients had severe clinical manifestations.

Study participants could continue to take medications prescribed by their principal care physician. These included analgesics, antibiotics, anti-diarrhoeal agents, sedative or hypnotics, antiepileptic drugs, drugs used to treat dystonia, or other agents used to treat the symptoms of NPC. Supplements, whose actions or indications were unknown or not generally accepted in medical practice, were specifically excluded.

The primary efficacy endpoint was the change in HSEM-α velocity (figure 2). A decrease (indicating improvement) from baseline to month 12 or last available value was seen in patients treated with miglustat versus the group receiving standard care (figure 2). Those patients receiving miglustat showed a mean (SE) decrease of –0·431 (0·221) ms/deg versus +0·074 (0·291) ms/deg for patients receiving standard care. ANCOVA adjusted for baseline and centre did not show a significant

 Published online August 2, 2007 DOI:10.1016/S1474-4422(07)70194-1

difference between the two groups (mean treatment difference: –0·518; 95% CI –1·125 to 0·089; p=0·091). Paediatric patients showed a mean decrease of –0·465 (0·127) ms/deg (figure 2). Further exploratory analysis (ANCOVA adjusted for baseline and centre) of the primary endpoint in the group aged 12 years or older, excluding patients who were taking benzodiazepine medications (known to impair SEM[34]), revealed a significant treatment difference in favour of the miglustat-treated group; –0·485 ms/deg in the miglustat-treated group versus +0·234 ms/deg in the standard care group (treatment difference –0·718; 95% CI –1·349 to –0·088; p=0·028). Six patients taking benzodiazepines were excluded (five from the miglustat-treated group and one from the standard care group).

Increases in HSEM-β were seen for patients aged 12 years or older but were smaller in the miglustat-treated group than in the standard care group. ANCOVA adjusted for baseline and centre did not show a significant treatment difference (–0·722, 95% CI –7·781 to 6·337; p=0·834). None of the patients in either study group had severe swallowing difficulties at baseline. However, improvements in swallowing ability were seen in those aged 12 years or older treated with miglustat compared with those in the standard care group (figure 3). Improvements were seen in the ability to swallow water for six patients (30%), purée for three patients (15%), soft lumps for three patients (15%), and a third of a cookie for seven patients (35%). For the most difficult substance to swallow, namely a third of a cookie, differences between treatment groups was significant at 12 months (p=0·044; figure 3). Since more than 80% of paediatric patients swallowed all four substances easily at baseline, improvement was not anticipated. At baseline, auditory acuity was normal in 15 (75%) of 20 and 16 (80%) of 20 patients aged 12 years or older in the miglustat-treated group, for the right and the left ears, respectively. All nine patients in the standard care group had normal auditory acuity at baseline. At the last assessment, one additional patient had normal auditory acuity for the right and left ears in the miglustat-treated group, whereas two (22%) of nine patients had abnormal results in the standard care group.

At baseline, the patients in the miglustat treatment group aged 12 years or older had more impaired ambulation than patients in the standard care group (table 3). ANCOVA at month 12 or last available value, adjusted for baseline and centre, showed a treatment difference in favour of the miglustat-treated group (mean treatment difference –0·715, 95% CI –1·438 to 0·007, p=0·052). A slight improvement in the mean MMSE scores was seen in miglustat-treated individuals aged 12 years or older compared with the standard care group (MMSE mean [SD] change from baseline to month 12 was 1·2 [2·5] versus –0·3 [2·8], respectively, p=0·165; table 4). In the miglustat-treated group, 11 (58%) of the 19 patients had an increase in total score of 2 or more from baseline to last visit, whereas three (16%) of the 19 patients had a decrease in total score of 2 or more points. By contrast, only two (22%) of the nine control patients had a total score increase of 2 or more.

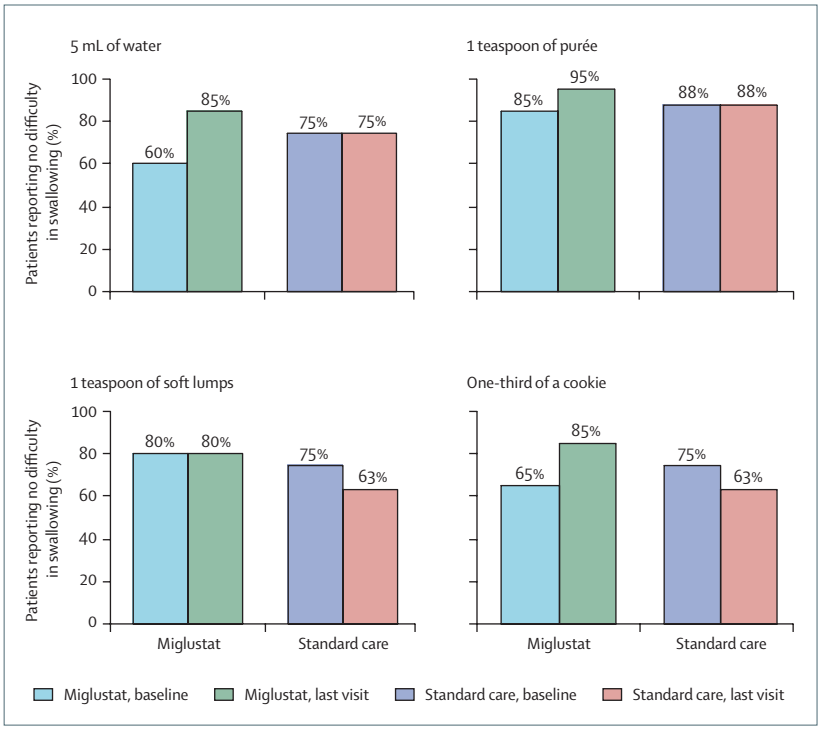

***Figure 3*: Effect of miglustat on swallowing ability in adult patients at month 12 or last available value**
Patients were asked to swallow the following substances (in increasing level of difficulty): 5 mL of water, 1 teaspoon of purée, 1 teaspoon of soft lumps (tinned spaghetti or noodles), or a third of a cookie. Three attempts were made for each substance and the study assessment done on the final attempt.

Duration of miglustat exposure in the group aged 12 years or older ranged from 180 to 429 days, with a

	n	Baseline (SD)	Last value (SD)	Change (SD)
Miglustat	20	2·4 (1·7)	2·6 (1·9)	0·2 (0·7)
Standard care	9	0·9 (1·1)	1·6 (1·7)	0·7 (0·9)

Scores range from 0 (fully active) to 9 (restricted to wheelchair). A lower score indicates better ambulation.Mean changes were in favour of miglustat group over the standard care group. Estimated treatment difference –0·715, (95% CI –1·438 to 0·007; p=0·052).

***Table 3*: Effects of miglustat on ambulatory index in patients aged 12 years or older**

	n	Baseline	Last value	Change
Miglustat	19	22·8 (5·2)	24·0 (5·6)	1·2 (2·5)
Standard care	9	23·4 (4·9)	23·1 (5·7)	–0·3 (2·8)

Data are mean (SD). Higher score indicates better mental status; a total score of 24 or above is considered normal. p=0·165 for change.

***Table 4*: Effects of miglustat on mini-mental status examination (MMSE) scores in patients aged 12 years or older**

	Patients treated with miglustat (n=20)	Patients receiving standard care (n=9)	Paediatric patients receiving miglustat (n=12)
Number of patients with at least one treatment-emergent AE during time interval	20 (100%)	9 (100%)	12 (100%)
Diarrhoea	17 (85%)	4 (44%)	8 (67%)
Flatulence	14 (70%)	0	4 (33%)
Weight decrease	13 (65%)	0	3 (25%)
Abdominal pain	10 (50%)	0	0
Headache	9 (45%)	3 (33%)	0
Tremor	8 (40%)	2 (22%)	0
Nausea	7 (35%)	0	0
Nasopharyngitis	7 (35%)	3 (33%)	4 (33%)
Fatigue	7 (35%)	0	5 (42%)
Vomiting	6 (30%)	0	4 (33%)
Insomnia	6 (30%)	0	0
Gait spastic	5 (25%)	0	0
Appetite decrease	5 (25%)	0	0
Depression	4 (20%)	0	0
Tremor aggravated	5 (25%)	0	0
Paresthesia	4 (20%)	0	0
Dysphagia	4 (20%)	4 (44%)	3 (25%)
Abdominal distension	4 (20%)	0	0
Laceration	4 (20%)	0	0
Gait abnormal	0	4 (44%)	4 (33%)
Dizziness	0	3 (33%)	0
Fall	0	2 (22%)	0
Pain in limb	0	2 (22%)	0
Eyelid ptosis	0	2 (22%)	0
Deafness	0	2 (22%)	0
Cough	0	0	4 (33%)
Ataxia	0	0	3 (25%)
Hyperreflexia	0	0	3 (25%)
Sinusitis	0	0	3 (25%)

Data are n (%).

Table 5: **Adverse events**

median of 364·5 days (range 180–429). Median exposure was similar in the paediatric patients (371 days; range 71–400).

Adverse events seen in the 12 years or older and paediatric groups treated with miglustat are shown in table 5. The most frequently reported adverse events in the miglustat-treated group aged 12 years or older were diarrhoea (17/20; 85%), flatulence (14/20; 70%), weight loss (13/20; 65%), and abdominal pain (10/20; 50%). The incidence of diarrhoea, flatulence, abdominal pain, vomiting, and tremor decreased over time. This decrease was most apparent for diarrhoea and flatulence, which were reported for 85% and 65% of patients, respectively, at between 0–13 weeks and for 39% and 50% of patients at more than 39 weeks. In the standard care group, the incidence of diarrhoea was 4 (44%) of 9 patients, with no cases of flatulence, weight decrease, or abdominal pain. Gastrointestinal problems were reported less frequently in the paediatric group, with diarrhoea reported in eight (67%) of 12 and flatulence in four (33%) of 12 patients. Weight loss occurred in three (25%) of 12 paediatric patients. No alteration of the growth curve was seen in the paediatric patients. Two cases of peripheral neuropathy were described: one adult patient in the miglustat group had a worsening of peripheral neuropathy, not considered to be treatment-related, and one patient in the standard care group.

Serious adverse events were seen in two patients in the group aged 12 years or older and two patients in the paediatric group, all receiving miglustat. None were considered to be related to the study medication. One of the patients in the group aged 12 years or older had a severe confusional state roughly 6 months after entering the study, and another patient had salivary hypersecretion. One child had severe dehydration and another patient had severe respiratory syncytial virus infection.

During the 12-month study, two aged 12 years or older and one child receiving miglustat had an adverse event that led to withdrawal. One patient in the group aged 12 years or older was withdrawn because of insomnia and confusional state, and the other because of severe diarrhoea attributable to Crohn disease. One paediatric patient had lethargy, memory impairment, and depression. No deaths were reported in this study.

Discussion

Overall, patients receiving miglustat for treatment of NPC showed consistent improvement or stabilisation in several clinically relevant endpoints compared with standard care. This trial is the first clinical controlled study to our knowledge that has assessed miglustat as a potential treatment for patients with NPC. Patients with progressive neurodegenerative disorders such as NPC might show apparent improvement or stabilisation if manifestations including seizures, malnutrition, and sleep disorders are effectively treated. However, we saw no evidence that such effects accounted for the changes seen in our treatment group as opposed to the standard care controls.

The observed improvement in HSEM-α in the miglustat group is clinically significant. Impairment of voluntary eye movements impairs reading, interpretation, and navigation of the visual environment generally and social interactions. An improvement or stabilisation in this aspect would probably improve or maintain patients' quality of life. Ideally, treatment would begin before vertical saccades were lost, as had generally occurred in our patients.

Progressive dysphagia, leading eventually to malnutrition and aspiration, is characteristic of NPC.[35] Improvement in swallowing ability was seen in patients aged 12 years or older treated with miglustat compared with the standard care group. Since most paediatric patients had no difficulties in swallowing at baseline, no improvement in swallowing was expected in this group. An improvement

For a list of **adverse events over time** see http://www.actelion.com/uninet/www/www_main_p.nsf/Content/Phase+III+trial+Adverse+events+reported+in+patients+with+Niemann+Pick+type+C+disease+treated+with+miglustat/$FILE/NiemannPickTypeC.pdf

http://neurology.thelancet.com **Published online August 2, 2007 DOI:10.1016/S1474-4422(07)70194-1**

or stabilisation in swallowing ability might be expected to improve quality of life and increase longevity.

Auditory acuity remained stable in patients aged 12 years or older treated with miglustat, compared with the standard care group. Hearing impairment is easily overlooked in NPC and other progressive dementias, and its recognition and management has obvious benefits in improving quality of life.

Although patients aged 12 years or older in the miglustat-treated group were more severely impaired at baseline than patients in the standard care group in terms of ambulation, treatment with miglustat was associated with slower deterioration in ambulation than in the standard care group. Such patients treated with miglustat also showed an improvement in MMSE scores, suggesting a beneficial effect of miglustat on cognitive function.

Previous studies in patients with Gaucher disease used miglustat doses of 100 mg three times a day.[29] The dosage of miglustat used in this study (200 mg three times a day) was twice that used in previous studies. Safety and tolerability results from the present study were consistent with those seen in patients with Gaucher disease. No unexpected side-effects were seen in patients with NPC treated with miglustat.

The study of rare diseases poses unique challenges. There are, by definition, few patients who, in the case of NPC, have highly variable manifestations and are dispersed over large geographic areas. This study was open-label, and there was no control group for the paediatric study arm. Patient clinical manifestations at baseline were heterogeneous both in terms of prevalence and severity. Because the effect of the study drug on NPC clinical manifestations could not be predicted in the absence of previous exposure of this population to the drug, a comprehensive panel of endpoints was selected. Additionally, the studied parameters, in particular those related to SEM, had a high inter-patient variability. In an attempt to keep the limitations to a minimum, in particular the open-label study design, measurements of the primary and secondary endpoints were done in a blinded manner when possible and assessments were done centrally. The study design was considered the most appropriate based on the available natural history data at study implementation.

The clinical manifestations of NPC indicate the loss of functioning neurons, consisting of those that have been lost and viable but functionally impaired cells. The primary biological goal of substrate reduction therapy is to limit the rate of toxic glycosphingolipid accumulation in the remaining viable neurons. The results of this study are consistent with the ability of miglustat to cross the blood-brain barrier[28,36] in individuals with NPC and to partly inhibit synthesis and limit accumulation of glycosphingolipid in neurons, consistent with murine studies.[27]

This study provides evidence that pharmacologic therapy can favourably affect the course of human NPC. Miglustat treatment improved or stabilised HSEM velocity, in both 12 years or older and paediatric patients. Swallowing capacity was also improved in patients in the group aged 12 years or older, auditory acuity remained stable, and a slower deterioration of ambulation index and improvement of MMSE scores were recorded. Miglustat administered at 200 mg three times a day in patients with NPC was well tolerated.

The 12-month study results are presented here; analyses of the final data are currently underway and will be presented in a separate manuscript. Follow-up data from this study will provide additional information on the long-term efficacy, safety, and tolerability of miglustat as a treatment for NPC patients. Miglustat is a promising therapy for patients with NPC, for which there has been no disease-modifying treatment available to date.

Contributors

The main investigators in this study were MCP and JEW. DV and HP had important roles in patient recruitment and management. LA provided the final blinded assessment of all data from both centres. The study was done at two centres (MCP at Columbia University College of Physicians and Surgeons, New York, USA and JEW at The Royal Manchester Children's Hospital, Pendlebury, Manchester, UK).

Conflicts of interest

MCP received funding support from Actelion Pharmaceuticals, and has received honoraria and travelling expenses from Actelion Pharmaceuticals, Amicus Therapeutic, and Stem Cells. Honoraria were not retained. JEW has received travelling expenses to attend meetings and has also done paid and unpaid consulting for Actelion Pharmaceuticals. DV, HP, and LA declare they have no conflicts of interest.

Acknowledgments

The authors wish to thank the patients and families who participated in the study. The study was initially supported by Oxford GlycoSciences, the original manufacturer of miglustat (OGT 918). During the study the Sponsor changed from Oxford GlycoSciences, a wholly-owned subsidiary of Celltech R&D Ltd, to Actelion Pharmaceuticals Ltd, Gewerbestrasse 16, CH-4123, Allschwil, Switzerland (August, 2004). The authors thank Dr Karen Yeow (PHOCUS Medical Communications, Güterstrasse 144, 4053 Basel, Switzerland) for assistance in the preparation of the first draft of the manuscript. The study was sponsored by Actelion Pharmaceutical, Allschwil, Switzerland.

References

1 Pentchev PG, Comly ME, Kruth HS, et al. Group C Niemann-Pick disease: faulty regulation of low-density lipoprotein uptake and cholesterol storage in cultured fibroblasts. *Faseb J* 1987; **1:** 40–45.

2 Liscum L, Sturley SL. Intracellular trafficking of Niemann-Pick C proteins 1 and 2: obligate components of subcellular lipid transport. *Biochim Biophys Acta* 2004; **1685:** 22–27.

3 Millat G, Marcais C, Rafi MA, et al. Niemann-Pick C1 disease: the I1061T substitution is a frequent mutant allele in patients of Western European descent and correlates with a classic juvenile phenotype. *Am J Hum Genet* 1999; **65:** 1321–29.

4 Wenger DA, Barth G, Githens JH. Nine cases of sphingomyelin lipidosis, a new variant in Spanish-American Children. Juvenile variant of Niemann-Pick Disease with foamy and sea-blue histiocytes. *Am J Dis Child* 1977; **131:** 955–61.

5 Winsor EJ, Welch JP. Genetic and demographic aspects of Nova Scotia Niemann-Pick disease (type D). *Am J Hum Genet 1978*; **30:** 530–38.

6 Carstea ED, Morris JA, Coleman KG, et al. Niemann-Pick C1 disease gene: homology to mediators of cholesterol homeostasis. *Science* 1997; **277:** 228–31.

7 Naureckiene S, Sleat DE, Lackland H, et al. Identification of HE1 as the second gene of Niemann-Pick C disease. *Science* 2000; **290:** 2298–301.

8 Frolov A, Srivastava K, Daphna-Iken D, Traub LM, Schaffer JE, Ory DS. Cholesterol overload promotes morphogenesis of a Niemann-Pick C (NPC)-like compartment independent of inhibition of NPC1 or HE1/NPC2 function. *J Biol Chem* 2001; **276:** 46414–21.

9 Walkley SU. Secondary accumulation of gangliosides in lysosomal storage disorders. *Semin Cell Dev Biol* 2004; **15:** 433–44.

10 Walkley SU, Siegel DA, Dobrenis K. GM2 ganglioside and pyramidal neuron dendritogenesis. *Neurochem Res* 1995; **20:** 1287–99.

11 Karten B, Campenot RB, Vance DE, Vance JE. The Niemann-Pick C1 protein in recycling endosomes of presynaptic nerve terminals. *J Lipid Res* 2006; **47:** 504–14.

12 Walkley SU, Suzuki K. Consequences of NPC1 and NPC2 loss of function in mammalian neurons. *Biochim Biophys Acta* 2004; **1685:** 48–62.

13 Solomon D, Winkelman AC, Zee DS, Gray L, Buttner-Ennever J. Niemann-Pick type C disease in two affected sisters: ocular motor recordings and brain-stem neuropathology. *Ann N Y Acad Sci* 2005; **1039**: 436–45.

14 Patterson MC. A riddle wrapped in a mystery: understanding Niemann-Pick disease, type C. *Neurologist* 2003; **9:** 301–10.

15 Sullivan D, Walterfang M, Velakoulis D. Bipolar disorder and Niemann-Pick disease type C. *Am J Psychiatry* 2005; **162:** 1021–22.

16 Walterfang M, Fietz M, Fahey M, et al. The neuropsychiatry of Niemann-Pick type C disease in adulthood. *J Neuropsychiatry Clin Neurosci* 2006; **18:** 158–70.

17 Oyama K, Takahashi T, Shoji Y, et al. Niemann-Pick disease type C: cataplexy and hypocretin in cerebrospinal fluid. *Tohoku J Exp Med* 2006; **209:** 263–67.

18 Patterson MC, Vanier MT, Suzuki K, et al. Niemann-Pick disease, type C: a lipid trafficking disorder. In: Scriver CR, Beaudet AL, Sly WS, et al, eds. The Metabolic and Molecular Bases of Inherited Disease, 8th edn. New York: McGraw-Hill, 2001: 3611–33

19 Rottach KG, von Maydell RD, Das VE, et al. Evidence for independent feedback control of horizontal and vertical saccades from Niemann-Pick type C disease. *Vision Res* 1997; **37:** 3627–38.

20 Garbutt S, Harris CM. Abnormal vertical optokinetic nystagmus in infants and children. *Br J Ophthalmol* 2000; **84:** 451–55.

21 Neville BG, Lake BD, Stephens R, Sanders MD. A neurovisceral storage disease with vertical supranuclear ophthalmoplegia, and its relationship to Niemann-Pick disease. A report of nine patients. *Brain* 1973; **96:** 97–120.

22 Patterson MC, Platt F. Therapy of Niemann-Pick disease, type C. *Biochim Biophys Acta* 2004; **1685:** 77–82.

23 Platt FM, Jeyakumar M, Andersson U, Dwek RA, Butters TD. New developments in treating glycosphingolipid storage diseases. *Adv Exp Med Biol* 2005; **564:** 117–26.

24 Platt FM, Neises GR, Dwek RA, Butters TD. N-butyldeoxynojirimycin is a novel inhibitor of glycolipid biosynthesis. *J Biol Chem* 1994; **269:** 8362–65.

25 Brady RO. Emerging strategies for the treatment of hereditary metabolic storage disorders. *Rejuvenation Res* 2006; **9:** 237–44.

26 Jeyakumar M, Dwek RA, Butters TD, Platt FM. Storage solutions: treating lysosomal disorders of the brain. *Nat Rev Neurosci* 2005; **6:** 713–25.

27 Zervas M, Somers KL, Thrall MA, Walkley SU. Critical role for glycosphingolipids in Niemann-Pick disease type C. *Curr Biol* 2001; **11:** 1283–87.

28 Lachmann RH, te Vruchte D, Lloyd-Evans E, et al. Treatment with miglustat reverses the lipid-trafficking defect in Niemann-Pick disease type C. *Neurobiol Dis* 2004; **16:** 654–58.

29 Cox T, Lachmann R, Hollak C, et al. A novel oral treatment of Gaucher's disease with N-butyldeoxynojirimycin (OGT 918) to decrease substrate biosynthesis. *Lancet* 2000; **355:** 1481–85.

30 Elstein D, Hollak C, Aerts JM, et al. Sustained therapeutic effects of oral miglustat (Zavesca, N-butyldeoxynojirimycin, OGT 918) in type I Gaucher disease. *J Inherit Metab Dis* 2004; **27:** 757–66.

31 Pastores GM, Barnett NL, Kolodny EH. An open-label, noncomparative study of miglustat in Type I Gaucher disease: efficacy and tolerability over 24 months of treatment. *Clin Ther* 2005; **27:** 1215–27.

32 Lengyel D, Weissert M, Schmid L, Gottlob I. [Eye movement abnormalities as a sign for the diagnosis in Niemann-Pick disease type C]. *Klin Monatsbl Augenheilkd* 1999; **214:** 50–52.

33 Inchingolo P, Spanio M. On the identification and analysis of saccadic eye movements—a quantitative study of the processing procedures. *IEEE Trans Biomed Eng* 1985; **32:** 683–95.

34 Roy-Byrne PP, Cowley DS, Radant A, Hommer D, Greenblatt DJ. Benzodiazepine pharmacodynamics: utility of eye movement measures. *Psychopharmacology (Berl)* 1993; **110:** 85–91.

35 Imrie J, Dasgupta S, Besley GT, et al. The natural history of Niemann-Pick disease type C in the UK. *J Inherit Metab Dis* 2007; **30:** 51–59.

36 Treiber A, Morand O, Clozel M. The pharmacokinetics and tissue distribution of the glucosylceramide synthase inhibitor miglustat in the rat. *Xenobiotica* 2007; **37:** 298–314.