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Miglustat in adult and juvenile patients with Niemann–Pick disease type C: Long-term data from a clinical trial

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ABSTRACT

A randomized, controlled trial of miglustat indicated that miglustat (Zavesca®) stabilized neurological disease over 12 months in adult and juvenile patients with Niemann–Pick disease type C (NP-C). We report data from a non-controlled, open-label extension to this initial randomized trial. All patients completing the randomized trial were allowed to continue treatment in a 12-month, non-controlled open-label extension. Those completing 12 months of extension therapy could continue further on miglustat in a 'continued extension' phase. From a total of 29 patients in the randomized phase (mean [±SD] age 24.6 ± 9.1 years; 52% female), 21 completed 12 months of therapy with miglustat (17 of whom received miglustat in the initial randomized phase, and four in the extension phase), and 15 patients (all from the miglustat-randomized group) completed 24 months on miglustat. Mean horizontal saccadic eye movement velocity (HSEM-α) indicated improvement in the 12-month miglustat group, and stabilization in the 24-month group; swallowing was improved or stable in 86% and in up to 93%, respectively. Ambulation was stabilized in both the 12- and 24-month groups. In an exploratory disease stability analysis of prospective data on key parameters of disease progression (HSEM-α, swallowing, ambulation and cognition), 13/19 (68%) patients receiving ⩾12 months' miglustat therapy had stable disease. Among all patients receiving ⩾1 dose of miglustat ($n = 28$), the most frequent adverse events were diarrhoea, weight decrease, flatulence and tremor. Overall, these data suggest that long-term miglustat therapy stabilizes neurological disease and is well tolerated in adult and juvenile patients with NP-C.

1. Introduction

Niemann–Pick disease type C (NP-C) is a panethnic, progressive neurovisceral disease that is estimated to occur in 1 in every 150,000 live births in Western Europe [1]. NP-C is an autosomal recessive disease; 95% of diagnosed patients possess mutations in the *NPC1* gene, while approximately 5% have mutations in the *NPC2*/*HE1* gene [2]. The protein products of these genes are involved in the intracellular transport and sorting of lipids [3]. *NPC1* and *NPC2/HE1* gene mutations give rise to severely impaired intracellular transport of LDL-derived cholesterol, glycosphingolipids and sphingosine [4], leading to accumulation of these lipids in a number of organs and tissues, particularly the liver, spleen and brain [5,6].

NP-C is characterized by progressive, disabling neurological symptoms and a variety of systemic manifestations [7]. While the clinical phenotypes of NP-C are highly heterogeneous [8], patients at the terminal stage of the disease are typically incapable of voluntary movement, tube-fed, and intellectually impaired. Data suggest that age at disease onset exerts a strong influence on disease symptomatology and rates of progression [9]. NP-C is frequently characterized as early-childhood (younger than 6 years of age) [6]; late childhood (6–11 years) [10,11]; and juvenile or adult presentation (12 years or older) forms [12,13]. In general, if symptoms arise early in life, the rate of deterioration is faster and premature death occurs earlier [10,11].

Until recently there was no disease-specific treatment capable of altering the clinical course of NP-C, although supportive therapy has been available for the alleviation of symptoms. Miglustat (Zavesca®; Actelion Pharmaceuticals Ltd.) was recently approved in

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Europe for the treatment of progressive neurological manifestations in adult and paediatric patients with NP-C [14]. Miglustat is a small iminosugar molecule that reversibly inhibits glucosylceramide synthase, the enzyme catalyzing the first committed step of glycosphingolipid synthesis [15]. It is able to cross the blood–brain barrier [16], and was shown to reduce brain ganglioside levels, delay neurological symptom onset and prolong survival in animal models of NP-C [17].

Findings from the first 12 months of a clinical trial have demonstrated that miglustat can stabilize key parameters of neurological disease progression in children, juveniles and adults with NP-C over 12 months [18]. Here, we report data on the long-term efficacy and safety of miglustat in juvenile and adult patients participating in a subsequent non-controlled, open-label extension phase.

2. Methods

2.1. Patients/design

Male and female juvenile/adult patients (aged $\geqslant$12 years) who had a diagnosis of NP-C confirmed by abnormal cholesterol esterification and filipin staining in cultured fibroblasts were enrolled between March 2002 and April 2004 in two study centres in Manchester, UK, and New York, USA. All patients completing the initial 12-month randomized, open-label, controlled trial of miglustat *versus* standard care [18] were given the option to continue treatment in a 12-month, open-label, non-controlled extension phase. Patients previously randomized to miglustat continued with their ongoing therapy, and patients previously randomized to standard care commenced miglustat. All patients completing 12 months of non-controlled extension therapy could continue with further miglustat treatment in a 'continued extension' phase.

The study was conducted in accordance with the Declaration of Helsinki (1964) and subsequent revisions, in compliance with US Food and Drug Administration regulations and ICH Good Clinical Practice guidelines, and subject to full institutional review board review and approval. Written, informed consent was obtained from all patients or their legal guardians.

2.2. Treatment

During the initial controlled trial, patients were randomized 2:1 to receive either miglustat 200 mg t.i.d. or standard care (symptomatic pharmacotherapy and physical, speech and/or occupational therapy prescribed for accepted indications by the patients' primary neurologist) [18]. Patients received other concomitant medications for standard indications throughout the initial 12-month randomized trial and during extension therapy.

2.3. Assessments

The primary efficacy measure, main-sequence horizontal saccadic eye movement asymptotic peak velocity (HSEM-α) [19], was evaluated at screening, baseline, Month 12 and Month 24. Eye movement recordings were assessed using computerized methods, as described previously [18], with evaluations by both a local investigator and a blinded independent central assessor. Patients underwent a general ophthalmologic assessment before SEM evaluations to exclude other causes of visual impairment.

Secondary efficacy endpoints assessed at Months 12 and 24 included: HSEM-β (main-sequence HSEM initial peak velocity–amplitude slope) [19], swallowing, ambulation and neuropsychological status. HSEM-β was calculated at the same time as HSEM-α as described previously [18]. Swallowing, ambulation and cognition were all assessed as described previously in the initial randomized, controlled trial [18], using individual swallowing evaluations, the standard ambulation index (SAI) and mini-mental status examination, respectively. No formal efficacy assessments were performed beyond Month 24, although further exploratory assessments were performed in some patients, based on physicians' judgment of need, for monitoring purposes.

Safety assessments were conducted up to 66 months and included adverse event monitoring, routine laboratory analyses, standardized neurological assessments, and tremor and nerve conduction velocity (NCV) tests.

2.4. Data analysis

The planned sample size for the initial randomized, controlled trial was selected on pragmatic grounds [18], since the number of potential participants was low owing to the rarity of NP-C and there were limited longitudinal data for changes in HSEM in this patient population. Efficacy findings based on prospective data are described for all patients completing 12 months of miglustat therapy ($n = 21$) and those completing 24 months of miglustat therapy ($n = 15$). Safety data are reported for all patients receiving at least one dose of miglustat ($n = 28$).

No statistical significance testing was undertaken. Efficacy data were analyzed based on complete cases using descriptive statistics. Mean and 95% confidence intervals (CIs) were calculated for primary and secondary efficacy parameters (HSEM-α, HSEM-β, SAI, and MMSE). For swallowing, the proportion of patients improved/stable was calculated, together with the 95% exact binomial CIs. Descriptive safety and tolerability data for the entire study period are presented.

An exploratory analysis of disease stability (based on prospective efficacy data) assessed individual patient responses to miglustat therapy based on key parameters of neurological disease progression in patients receiving at least 12 months of miglustat. While no formal efficacy analyses were conducted beyond 24 months of treatment, efficacy parameter data from patients assessed on an *ad hoc* basis, according to clinicians' judgment of need, were collected up to Month 48; no efficacy data were collected beyond this time point. Patients were classified as having 'stable disease' if there was no deterioration in swallowing, SAI and MMSE, or if only HSEM-α deteriorated. Deterioration (*versus* baseline) was defined for each parameter as follows: HSEM-α (increase >20%), swallowing function (any down-grading), SAI (increase >1 point), MMSE (decrease >2 points). Stable parameters were defined as follows: HSEM-α (change within ±20%); swallowing function (no change); SAI (no change or change within ±1 point); MMSE (change within ±2 points). The proportions of stable patients were calculated with 95% exact binomial CIs.

3. Results

3.1. Patients

The first patient visit was on 18th May 2002, and last patient, last visit was on 30th January 2008. Among 30 patients screened there was one screening failure. A total of 29 patients participated in the 12-month randomized, controlled phase (mean ± SD age, 24.6 ± 9.1 years; range 12–42 years; Table 1) [18]. A total of 21 patients completed 12 months of miglustat therapy (17 of whom received miglustat in the initial randomized phase, and four in the extension phase), and 15 patients, all initially randomized to miglustat, completed 24 months on miglustat (Fig. 1). A total of nine discontinuations were related to patient/investigator request, two patients were lost to follow up, and one patient was withdrawn due to non-compliance (Fig. 1). Overall, 13 patients completed the

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Table 1
Demographic and baseline characteristics ($n = 29$).

	Characteristic
Gender	
Male, *n* (%)	14 (48)
Female, *n* (%)	15 (52)
Age (years)	
Mean ± SD	24.6 ± 9.1
Median	25.0
Range	12–42
Age group (years)	
12–17, *n* (%)	9 (31)
⩾18, *n* (%)	20 (69)
Weight (kg)	
Mean ± SD	71.5 ± 20.3
Median	67.1
Range	41.1–119.0
Height (cm)	
Mean ± SD	169 ± 14
Median	166
Range	141–195
Body surface area (BSA) (cm^2)	
Mean ± SD	18,076 ± 3064
Median	17,794
Range	12,602–24,203

entire study period. All treated patients exhibited at least one characteristic manifestation of NP-C (Table 2) [18].

3.2. Treatment

The median (range) exposure to miglustat among all patients who received at least one dose of therapy ($n = 28$) was 714 (34–745) days. At least 80% of patients received miglustat at the recommended dose of 200 mg t.i.d. for up to 24 months. Among a total of 16 patients who received miglustat during the continued extension phase, the median (range) miglustat exposure was 1465 (825–2056) days.

3.3. Efficacy

3.3.1. HSEM

The mean (95% CI) absolute HSEM-α value decreased (indicating improvement) from baseline among patients completing 12 months of miglustat therapy, and was stable *versus* baseline among patients completing 24 months on miglustat (Table 3). There was considerable overlap between 95% CIs for mean HSEM-α at baseline, Month 12 and Month 24 for both 12- and 24-month completers. Mean (95% CI) HSEM-β values increased

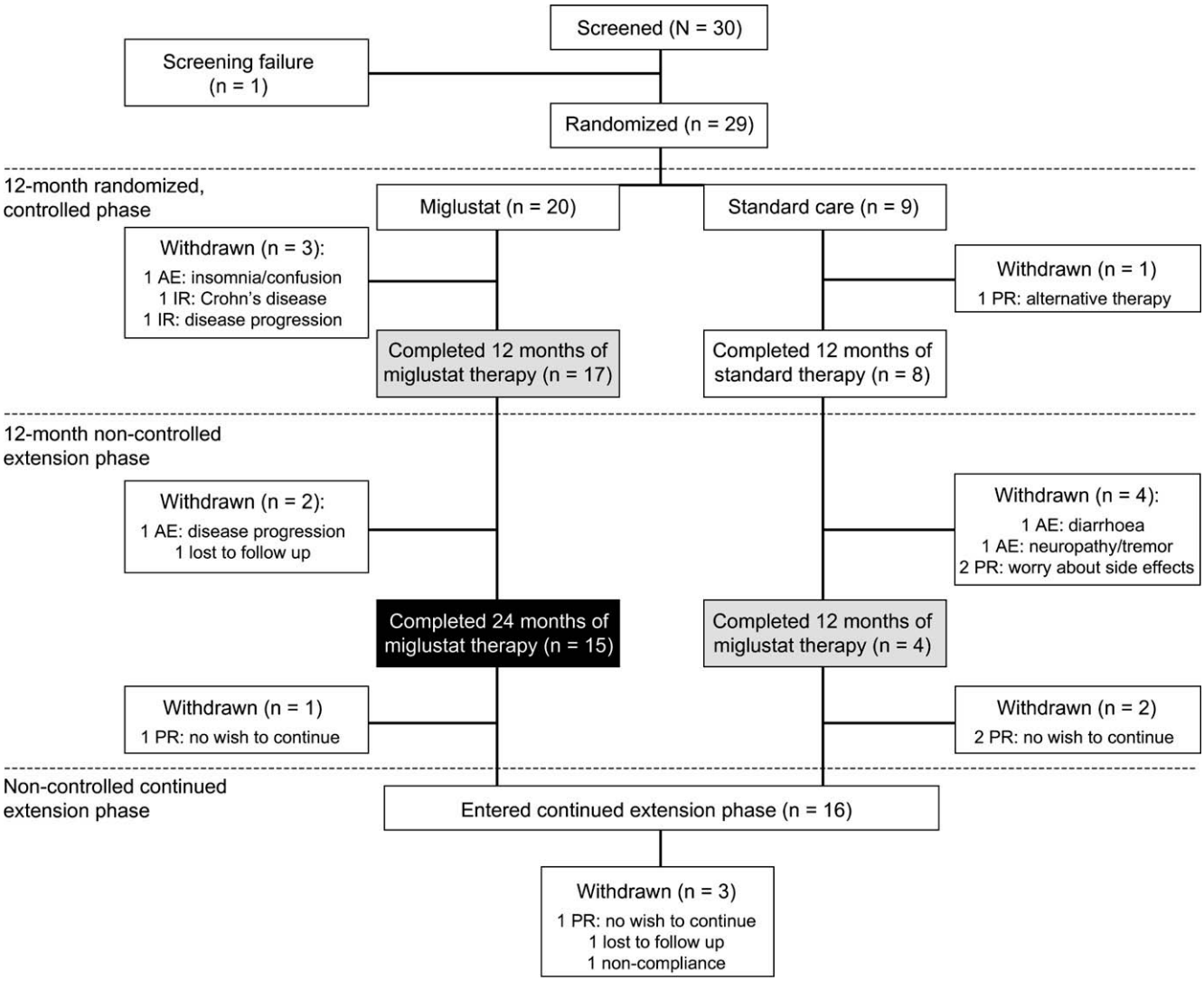

Fig. 1. Patient disposition (grey boxes, patients completing 12 months on miglustat ($n = 21$); black box, patients completing 24 months on miglustat ($n = 15$); AE, adverse event; PR, patient request; IR, investigator request. *Note:* One withdrawal related to patient request (alternative therapy; bone marrow transplantation), was an NPC2 patient).

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Table 2
Baseline manifestations of NP-C ($n = 29$).

	Number of patients (%)
Patients with ⩾1 manifestation of NP-C	29 (100)
Vertical supranuclear gaze palsy	27 (93)
Cognitive impairment	25 (86)
Ataxia	25 (86)
Speech	22 (76)
Difficulty in positioning of limbs	18 (62)
Swallowing difficulties	18 (62)
Pyramidal tract dysfunction	13 (45)
Splenomegaly	12 (41)
Hepatomegaly	10 (34)
Seizures	2 (7)
Cataplexy	1 (3)
Other[a]	26 (90)

[a] The category 'Other' includes NP-C manifestations not captured in the remaining categories (e.g., balance problems, tremor).

Table 3
HSEM-α and HSEM-β values in patients completing 12 and 24 months on miglustat.

	Mean (95% CI) values[a]	
	12-month miglustat completers ($n = 21$)	24-month miglustat completers ($n = 15$)
HSEM-α (ms/deg)		
Baseline	3.06 (2.09–4.04)	3.04 (1.74–4.34)
Month 12	2.87 (2.03–3.71)	2.57 (1.65–3.49)
Month 24	–	3.27 (1.22–5.31)
HSEM-β (ms/deg)		
Baseline	22.42 (17.47–27.38)	19.51 (13.81–25.20)
Month 12	25.95 (20.09–31.81)	22.98 (17.24–28.73)
Month 24	–	24.85 (17.75–31.94)

[a] A decrease in values indicates improvement.

slightly (indicating mild deterioration) from baseline among patients completing 12 months of miglustat therapy as well as those completing 24 months on miglustat (Table 3). Once again, 95% CIs showed considerable overlap across time-points in both 12- and 24-month completers.

3.3.2. Swallowing

Between 71% and 86% of patients who completed 12 months of miglustat therapy and 64–86% of patients completing 24 months on miglustat could swallow each of the four substances at baseline. Swallowing was improved or stable (*versus* baseline) in 86% of patients completing 12 months of miglustat therapy (Fig. 2). Among patients completing 24 months on miglustat, swallowing was improved or stable in 79–93% of patients, depending on the substance assessed (Fig. 2).

3.3.3. Ambulation

There was no difference between mean (95% CI) SAI scores at baseline and Month 12 among patients completing 12 months of miglustat therapy. Similarly, mean (95% CI) SAI scores showed only minimal change from baseline at Months 12 and 24 among patients completing 24 months on miglustat (Table 4).

3.3.4. Cognition

Among 18 patients with available data who completed 12 months of miglustat therapy, mean (95% CI) MMSE scores were 22.94 (20.28–25.61) at baseline and 24.06 (21.18–26.93) at Month 12. Among six patients with available data who completed 24 months of miglustat therapy, mean (95% CI) scores were 19.50 (12.21–26.79) at baseline, 21.17 (13.94–28.39) at Month 12, and 19.33 (9.98–28.69) at Month 24.

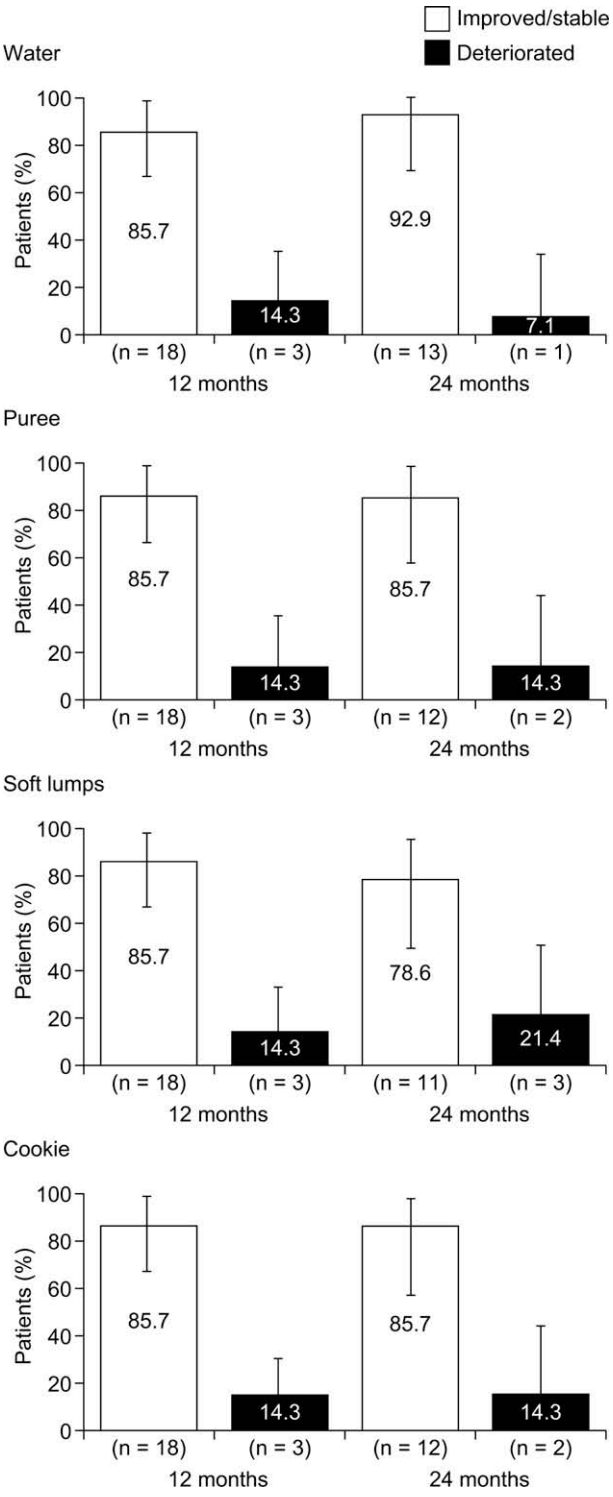

Fig. 2. Improved/stable or deteriorated swallowing in patients* completing 12 and 24 months on miglustat (*21 patients evaluated at Month 12 and 14 patients evaluated at Month 24; no swallowing evaluation in one patient completing 24 months on miglustat; error bars represent 95% exact binomial CIs of proportions).

3.3.5. Disease stability

A total of 19 adult/juvenile patients who received at least 12 months of miglustat therapy were included in an analysis of disease stability. Overall, 13/19 patients (68.4%; 95% CI, 43.5%, 87.4%) were categorized as having stable disease after treatment. HSEM-α was improved or stable in 11/18 (61.1%; 95% CI, 35.8%,

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Table 4
Standard ambulation index (SAI) scores in patients completing 12 and 24 months on miglustat.

	Mean (95% CI) scores[a]	
	12-Month miglustat completers ($n = 21$)	24-Month miglustat completers ($n = 15$)
Baseline	2.38 (1.59–3.18)	2.13 (1.51–2.76)
Month 12	2.57 (1.61–3.53)	2.20 (1.47–2.93)
Month 24	–	2.40 (1.49–3.31)

[a] Lower scores indicate better ambulation.

82.7%) of patients with evaluable HSEM data. Swallowing was improved or stable in 15/19 (78.9%; 95% CI, 54.4%, 94.0%) patients, ambulation (SAI) in 17/19 (89.5%; 95% CI, 66.9%, 98.7%) patients, and cognition (MMSE) in 14/18 (77.8%; 95% CI, 52.4%, 93.6%) patients. Overall, six patients were categorized as having deteriorated, among whom three were classed as having severe disease at baseline, two had mild disease and one had moderate disease. One patient showed only deterioration of swallowing and one showed only deterioration of cognition, two patients (both severe at baseline) showed deterioration of three of the four parameters, and one patient deteriorated in two parameters. One patient showed deterioration in swallowing but had stable ambulation; data for cognition and HSEM-α were not evaluable for this patient.

3.4. Safety and tolerability

Twenty-eight patients received at least one dose of miglustat and represent the safety population. The most frequently reported adverse events in terms of overall incidence were diarrhoea (in 89.3% of patients), weight decrease (75.0%), flatulence (64.3%) and tremor (57.1%) (Table 5). Among all recorded adverse events, diarrhoea, flatulence, abdominal pain and body weight decrease were most commonly considered as related to study medication. The majority of these gastrointestinal adverse events were rated as mild or moderate in severity. Over the entire course of the study, 12 patients (42.9%) received at least one gastrointestinal medication, mainly loperamide. Diarrhoea was reported in 24/28 (85.7%) patients during the first 6 months of therapy, 11/21 (52.4%) after 1 year, 8/17 (47.1%) after 2 years and 6/11 (54.5%) beyond 3 years. Weight decrease occurred in 75% of patients overall and was mainly mild or moderate. The overall mean (SD) change from baseline in weight during the first 24 months was −2.81 (±6.02) kg. During the continued extension phase, the mean (SD) change in weight was −2.76 (±3.52) kg at 48 months. Evaluation of growth curves among juvenile patients between baseline and Month 24 showed no deterioration.

Table 5
Overall incidence of treatment-emergent adverse events (safety population; $n = 28$).

Adverse event[a]	Incidence	
	n	%
Diarrhoea	25	89.3
Weight decrease	21	75.0
Flatulence	18	64.3
Tremor	16	57.1
Fatigue	13	46.4
Nasopharyngitis	12	42.9
Upper abdominal pain	11	39.3
Headache	11	39.3
Insomnia	9	32.1
Nausea	9	32.1
Vomiting	9	32.1
Confusional state	8	28.6
Abnormal NCV[b]	8	28.6
Abdominal pain	7	25.0
Cough	7	25.0
Dysphagia	7	25.0
Dystonia	7	25.0
Fall	7	25.0
Paraesthesia	7	25.0
Sleep disorder	7	25.0

[a] Occurring in ⩾25% of patients.
[b] NCV, nerve conduction velocity.

Tremor was reported in a total of 16 patients (57.1%) over the entire course of the study, and was generally mild or moderate in intensity. Two patients exhibited severe tremor, which was assessed to be related to study medication.

A total of six patients experienced serious adverse events during the entire study period. No serious adverse events were considered related to miglustat therapy. One patient had elective gastrointestinal tube insertion, one patient experienced confusional state, one patient had a wrist fracture and subsequent wound infection necessitating hospitalization, one patient experienced aspiration (on saliva) followed by pulmonary congestion, one patient experienced a viral infection requiring hospitalization, and one patient died in a road traffic accident.

During the entire study period, four patients discontinued miglustat treatment due to adverse events. One patient was withdrawn due to confusional state (defined as a serious adverse event and not considered as related to miglustat) together with insomnia and paranoia, one was withdrawn due to diarrhoea, one due to disease progression, and one due to axonal neuropathy and tremor.

There was no pattern of clinically relevant abnormal laboratory findings. The mean change from baseline to last visit for platelet counts was approximately 10% (-17.9×10^9/L). Baseline platelet counts were low in 11/28 (39.3%) patients and remained low up to Month 24, but no patients had a platelet count $<100 \times 10^9$/L.

4. Discussion and conclusions

These data indicate that the beneficial effects of miglustat on neurological disease in adult and juvenile patients with NP-C, as observed in the initial randomized controlled trial [18], were sustained during extension therapy up to 24 months. Horizontal saccadic eye movement velocity, swallowing and ambulation function were stable throughout the non-controlled extension phase. Cognitive function also appeared to be stabilized, although limited conclusions can be drawn regarding cognition due to the paucity of long-term follow-up data. Overall, more than two-thirds of patients were categorized as having 'stable' disease in the disease stability analysis of key parameters of neurological disease progression. Similar findings were observed in paediatric patients with NP-C, in which neurological disease progression was stabilized in 80% of patients after 24 months' treatment [20]. Our data provided no explanation for the progression of neurologic disease in six of the 19 patients receiving miglustat in the current study. No measures, including disease severity at baseline, clearly distinguished these patients from those who showed stabilization.

While there are limited data with miglustat in NP-C, beneficial effects on key measures of neurological disease progression have been reported outside of formal clinical trials. In a multicentre retrospective observational cohort study of 66 patients treated with miglustat, stabilization of neurological disease was observed in all age groups, although the magnitude of the effect was greater in patients diagnosed in late childhood and in juveniles and adults [21]. Improved swallowing and ambulation were reported in a 14-year old Taiwanese patient treated with miglustat over 6–12 months [22]. Improved ambulation and reduced functional disability were reported in a Brazilian case study following 12 months on miglustat [23]. General clinical improvement/stabilization and

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improved brain function have been described in three French adults, based on magnetic resonance spectroscopy [24].

Although quality of life data were collected during this study, few patients returned their questionnaires, leading to a high number of non-evaluable patients resulting in inconclusive findings. However, in our own clinic, we have a number of patients who have achieved disease stabilization on miglustat to the satisfaction of both the patients and their parents. A positive impact of miglustat upon social behaviour, depression and affective and attention problems, potentially leading to improved quality of life, was observed in the Brazilian case study [23], and a case series of two Taiwanese patients demonstrated both patient and carer satisfaction with miglustat treatment [22].

The safety and tolerability profile of miglustat 200 mg t.i.d. over 66 months was similar to that seen during the 12-month randomized trial [18], and consistent with trials with miglustat 100 mg t.i.d. in type 1 Gaucher disease [14]. Gastrointestinal adverse events are likely related to the inhibition of disaccharidases by miglustat in the gastrointestinal tract. Dietary modification (reduced intake of high-lactose or other high carbohydrate-content foods) and/or the use of anti-propulsive medications (e.g., loperamide) can reduce the occurrence of gastrointestinal adverse events [14].

No unexpected safety or tolerability issues were raised in patients with NP-C during long-term treatment with miglustat. Tremor (usually in the hands) is often seen during the initial months following commencement of miglustat therapy, but tends to decrease over time. The slight reduction in mean platelet count on therapy was not considered clinically relevant. Reduced platelet counts are often seen in untreated NP-C patients, mostly attributable to splenomegaly.

The absence of a control group in this study limits the full assessment of long-term treatment effects of miglustat. Maintaining patients on symptomatic treatment over the long term was not considered ethical in light of possible disease-altering benefits with miglustat. Further, there are no historical control data that are directly comparable with the current data set. Nonetheless, the stabilization of neurological disease with miglustat in this study contrasts with the continuous, unhindered progression of neurological manifestations seen in NP-C patients receiving only palliative therapy in observational cohort studies [9,13,25].

The absence of validated clinical markers for monitoring disease progression in NP-C further limits the interpretation of our findings. However, we selected efficacy endpoints on the basis of their clinical relevance and specificity for NP-C. The deterioration of HSEM in NP-C, particularly in terms of peak saccadic velocities (HSEM-α), has been correlated with progressive neurological dysfunction in affected areas of the brain including regions of both the frontal cortex and the brainstem [19,26]. In a recent case series, HSEM-α values were notably higher (indicating greater impairment) in NP-C patients than in control subjects, and NP-C patients with more severe biochemical, cognitive, and symptom deficits performed most poorly on ocular motor measures including HSEM-α [26]. However, the sensitivity of HSEM-α as therapeutic efficacy parameter is still under debate, as there are limited longitudinal data on the progression of saccadic abnormalities; the same is true for the secondary efficacy measure, HSEM-β. Our data indicate that HSEM-α may not fully detect treatment effects as it could not be correlated against other clinical parameters.

Regarding other efficacy measures, progressive dysphagia is an important functional manifestation of NP-C [7], and progressive impairments in ambulation/movement lead to disabling functional limitations over time [10–12]. In particular, swallowing and ambulation function have been shown to correlate strongly with progression of overall disease severity when assessed as part of a composite disability scale [25]. Further, a previous study of the natural history of NP-C has demonstrated that both ambulation and swallowing ability can be expected to deteriorate in a significant proportion of patients with NP-C over approximately 5 years [9]. However, while these studies provide a contrast against which 'stabilization' can be gauged, there are no solid historical control data that can be compared directly with the longitudinal functional assessments included in our data set.

Irreversible neuronal damage or loss is likely to be present in patients with NP-C by the time they are diagnosed, and improvement of neurological function is not expected. There is general consensus that stabilization of neurological disease can be considered the best attainable therapeutic goal in NP-C [27]. While supportive measures have traditionally been employed to alleviate clinical problems associated with the disease, they do not treat the underlying cause of the disease [9,25]. To date, only miglustat has been shown to provide quantifiable clinical benefits in terms of stabilized or improved patient function [18]. These findings are in line with preclinical evidence of the effects of miglustat on intracellular lipid transport and surrogate markers of clinical benefit [17]. Recent evidence also suggests that miglustat may indirectly affect the pathogenesis of NPC1 – by far the most common disease phenotype – through modulation of intracellular calcium homeostasis [28].

In conclusion, miglustat appears to provide therapeutic benefits in the long-term treatment of NP-C, as evidenced by stabilization of key parameters of neurological disease progression, in most patients.

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