Original Article

DOI: 10.5582/irdr.2024.01056

Evaluation of the safety and efficacy of miglustat for the treatment of Chinese patients with Niemann-Pick disease type C: A prospective, open-label, single-arm, phase IV trial

Huiwen Zhang[1,*], Hui Xiong[2,*], Cuijie Wei[2], Mengni Yi[1], Yufang Che[3], Jianmin Zhuo[4], Xueyu Li[3]

[1] Department of Pediatric Endocrinology/Genetics, Shanghai Institute For Pediatric Research, Xinhua Hospital affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China;
[2] Department of Pediatrics, Peking University First Hospital, Beijing, China;
[3] Medical Affairs, Xi'an Janssen Pharmaceutical Ltd., Beijing, China;
[4] Statistics & Decision Science, Janssen China R&D, Shanghai, China.

SUMMARY Niemann-Pick disease type C (NPC) is a rare, autosomal recessive, neurodegenerative disease associated with a wide variety of progressive neurological manifestations. Miglustat has demonstrated efficacy to delay progressive neurological deterioration in patients with NPC. We conducted a multicenter, open-label, single-arm, phase IV, post-approval commitment study to evaluate the efficacy and safety of miglustat among Chinese patients with NPC. Eligible patients were aged ≥ 4 years with an established diagnosis of NPC with two type C1 or C2 pathogenic markers or one marker with a positive biomarker (oxysterol, lysosphingolipids, or bile acids) and high clinical suspicion of NPC. Patients received oral miglustat ranging from 100 mg twice daily to 200 mg three times daily. The primary outcome was change in horizontal saccadic eye movement parameters from baseline to week 52. Seventeen patients were enrolled (median age: 14.0 years). From baseline to week 52, mean saccadic peak acceleration and velocity increased by 19.2% and 12.5%, respectively, while mean peak duration and linear regression decreased by 6.5% and 15.6%, respectively. By week 52, ambulation, manipulation, language, swallowing, and ocular movements had improved or stabilized versus baseline. All patients experienced treatment-emergent adverse events (TEAEs). Treatment-related TEAEs were reported in 12 patients with the most common being diarrhea (n = 12). Two patients died due to accidental death and asphyxia unrelated to miglustat treatment. This study demonstrated disease stabilization in Chinese patients with NPC receiving miglustat. Safety findings were consistent with miglustat's known safety profile. The study was registered at *ClinicalTrials.gov* (NCT03910621).

Keywords horizontal saccadic eye movement, lysosomal lipid storage disorder, China

1. Introduction

Niemann-Pick disease is an autosomal recessive, genetic, lysosomal lipid storage disorder caused by the deposition of a group of sphingomyelins (*1*). Niemann-Pick disease type C (NPC) is characterized by intracellular lipid transport defects and secondary pathological accumulation of free cholesterol, sphingomyelin, and glycosphingolipids within lysosomes/endosomes in various tissues and organs, but most widely in the brain (*1,2*). The clinical presentation of NPC is heterogenous; the liver, spleen, lungs, and nervous system are often involved in NPC, and the disease symptoms commonly include mental and motor regression, ataxia, and cataplexy (*1*). Clinical neurological manifestations of NPC include vertical supranuclear gaze palsy, ataxia, dysarthria, dysphagia, dystonia, epileptic seizures, progressive dementia, psychotic symptoms, and cataplexy (*1*). The clinical manifestations of the disease in the nervous system are continuously progressive without interruption (*1*).

Individuals with NPC can be categorized according to the type and age of onset of first neurological symptoms, *i.e.*, neonatal (≤ 2 months), early infantile (> 2 months to 2 years old), late infantile (> 2-6 years old), juvenile (> 6-15 years old), and adolescent/adult

(> 15 years old) (*1*). In newborns, the disease will often result in death within a short period of time (*1*). Compared with the late-infantile neurologic onset form, pediatric individuals with the severe neurologic early-infantile form experience rapid disease progression (*1*). Individuals with juvenile neurologic onset typically survive until adolescence or later (*1*), but individuals with advanced-stage disease are often disabled, suffer from dementia, and require tube feeding. This form of the disease is associated with a significant mental and economic burden to the individuals themselves, and their caregivers, families, and society (*1,3,4*). In Europe, NPC has an estimated incidence of between 1:100,000-120,000 live births (*1,5-7*), while in the United States, the prevalence is approximately one case per million people (*8*). However, currently there are no reports on the incidence rate of NPC in the Chinese population (*9*).

Miglustat is currently the only approved therapy in the European Union (EU)/European Economic Area (EEA) and China for the management of progressive neurological deterioration in adults and children with NPC (*10-12*). There are no alternative treatments available for NPC in China beyond those which provide symptomatic relief. Miglustat is a competitive and reversible inhibitor of the glucosylceramide synthase enzyme (involved in the synthesis of most glycosphingolipids) (*11,13*), α-glucosidases I and II (key enzymes involved in intracellular processing of glycoproteins), non-lysosomal β-glucocerebrosidase, and intestinal disaccharidases (*11,14*). Moreover, miglustat can pass through the blood-brain barrier, reversibly inhibiting glucosylceramide synthetase, thus preventing the accumulation of glycosphingolipids in lysosomes (*11,13*). Miglustat received approval based on the data of an international, non-blinded, randomized controlled phase III clinical trial involving 29 patients with NPC. This study showed that miglustat could improve the horizontal saccadic eye movement (HSEM) velocity, and improve or delay deterioration of neurological symptoms in cognitive function, swallowing function, and walking ability (*13*). A retrospective observational cohort study conducted in 12 countries (excluding China) also showed an improvement or stabilization of neurological symptoms in 66 individuals with NPC who were treated with miglustat (*15*). In addition, clinical studies and case reports have shown that some individuals with early neurological signs of NPC who were treated with miglustat achieved either stabilized or delayed progressive neurological symptoms (*16-19*).

This post-approval commitment study was conducted to further evaluate the efficacy and safety of miglustat among Chinese individuals with NPC over a 12-month treatment period.

2. Patients and Methods

2.1. Study design and patients

This was a prospective, multicenter, open-label, single-arm, 52-week, phase IV confirmatory study (Figure 1A). The primary objective was to evaluate the safety and effectiveness of miglustat on the rate of disease progression and disease stabilization, by measuring changes in HSEM parameters that are highly correlated with disease progression in patients with NPC.

The inclusion criteria for patients included: aged ≥ 4 years; an established diagnosis of NPC (with two type C1 or C2 pathogenic markers or one marker with a positive biomarker [oxysterol, lysosphingolipids, or bile acids]) and high clinical suspicion of NPC; ability to perform the tests for the HSEM and vertical saccadic eye movements; and ability to swallow the study drug. Patients were permitted to receive any prior concomitant therapies, with the exception of concomitant eliglustat, benzodiazepines, any other drugs potentially influencing eye movements or any of the secondary outcome measures, or any other potentially disease-modifying investigational drug. A full list of inclusion and exclusion criteria are in the Supplemental Material (*https://www.irdrjournal.com/action/getSupplementalData.php?ID=224*). Patients received oral miglustat ranging from 100 mg twice daily to 200 mg three times daily. The recommended dose was 200 mg three times daily based on previous studies of individuals with NPC and other neuronopathic glycosphingolipid storage disorders (*13*). The starting dose for patients with mild or moderate renal impairment was 200 mg twice daily or 200 mg once daily, respectively. For patients aged < 12 years, the starting dose was calculated according to body surface area.

This study was conducted in accordance with the ethical principles that originate from the Declaration of Helsinki, consistent with the International Council for Harmonization Good Clinical Practice guidelines (*20*), and all applicable local laws and regulations. The study protocol and amendments were reviewed by an Independent Ethics Committee at each study center (Supplemental Table S1, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=224*). All adult patients and the parents or legally designated representatives of pediatric patients (and assent from developmentally capable children) provided written informed consent to participate in the study.

2.2. Study endpoints

The primary outcome measure was the change in HSEM parameters from baseline to the end of treatment visit (week 52). Secondary outcome measures included the change in Pineda Disability Scale scores from baseline to week 52, the safety and tolerability of miglustat, and changes in height and body weight for pediatric patients.

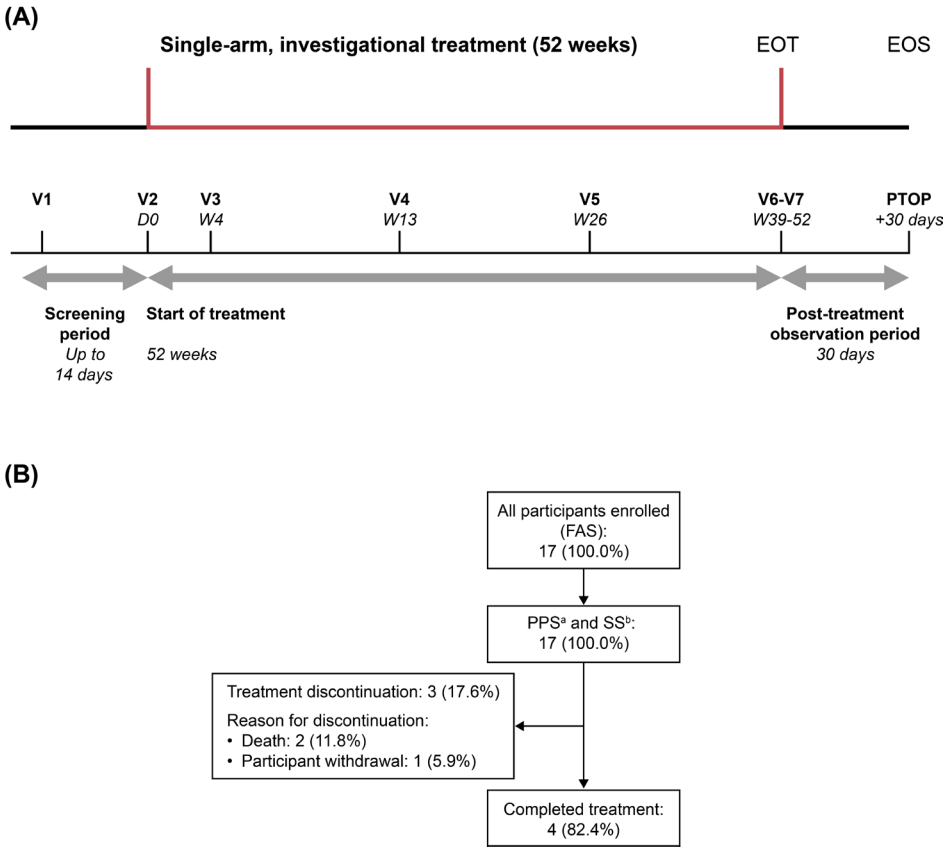

Figure 1. (A), Study design; (B), CONSORT flow diagram. Patients who prematurely discontinued the study treatment entered a PTOP, which lasted for at least 30 days after the last study drug intake. Expected duration of participation of each participant was up to 56 weeks (52 weeks treatment period + 30 days of PTOP). [a]All patients who received study treatment and had not presented with a protocol deviation that could affect the assessment of the primary endpoint. [b]All patients who received at least one dose of study medication. D: day; EOS: end of study; EOT: end of treatment; FAS: full analysis set; PPS: per protocol analysis set; PTOP: post-treatment observation period; SS: safety analysis set; V: visit; W: week.

2.3. Assessments

All efficacy parameters were measured from baseline to each visit (to weeks 13, 26, 39, and 52). A visit window of ± 7 days was allowed for all visits and a follow-up safety visit was performed 30 ± 2 days after the date of the last treatment dose. In case of premature discontinuation of treatment, the end of treatment visit was scheduled at the earliest opportunity, but no later than 7 days after the last dose of treatment. The absolute change and percentage change in HSEM parameters were assessed from baseline to each visit, including saccadic peak acceleration, mean velocity, peak duration, linear regression slopes, and line slopes of the ocular motor parameters. The HSEM parameter values were calculated by EyeSeeCam software (EyeSeeTec GmbH, Germany) and were then entered into the electronic data capture system. The change in Pineda Disability Scale score was a total additive score of six items of ambulation (scored from 0 to 5), manipulation (scored from 0 to 4), language (scored from 0 to 5), swallowing (scored from 0 to 4), seizures (scored from 0 to 3), and ocular movements (scored from 0 to 3). The total score ranged from 0 to 24, with a higher score indicating poorer condition. An item score of zero indicated no symptom or an absence of abnormalities. Body weight was measured at Screening and at each visit, and height was measured at Screening, week 26, and week 52.

Adverse events (AEs) were monitored and treatment-emergent AEs (TEAEs) were defined as AEs with onset date/time ≥ start date/time of study medication and ≤ 30 days after end of treatment, whether or not considered by the investigator as related to study medication. In cases where it could not be determined whether an AE was treatment-emergent, the AE was categorized as treatment-emergent. Other safety assessments included physical examinations, vital signs, and laboratory parameters.

2.4. Statistical methods

Approximately 19 patients with NPC were planned for enrollment in this study to ensure that 15 patients were treated with miglustat for a duration of 12 months (considering a possible 20% drop-out rate), as requested by the Chinese National Medical Products Administration. This single-arm study was descriptive in nature, and no formal statistical hypothesis or inference was made. The 95% confidence intervals (CIs) were estimated for the absolute mean change from baseline

and the percentage change mean from baseline on all efficacy variables. No imputation was made for the missing efficacy data.

The efficacy analysis was based on the full analysis set (FAS) that was defined as all enrolled patients who completed the Screening period. The per protocol analysis set (PPS), that comprised all patients who received study treatment who did not present a protocol deviation that could affect the assessment of the primary endpoint, supported the efficacy analysis. The safety analysis set (SS) included all patients who received at least one dose of study treatment.

3. Results

3.1. Patients

A total of 17 patients were enrolled between April 3, 2020, and March 29, 2022, at two centers in China. The FAS, PPS, and SS in this analysis comprised 17 patients with NPC who received at least one dose of miglustat, as none of these patients had any protocol deviations that affected the primary endpoint assessment. The majority of patients (n = 12, 70.6%) had one pathogenic mutation in *NPC1* with a positive biomarker test and high clinical suspicion of NPC, while the remaining five patients (29.4%) had two pathogenic mutations in *NPC1*. Median age was 14.0 (range, 6.0-33.0) years, 47.1% of patients were female, and all patients were from China (Table 1). At Screening, four patients (23.5%) reported a history of medical conditions and three (17.6%) patients had received prior therapy.

Table 1. Participant demographics and baseline characteristics (FAS)

Characteristics	Total (n = 17)
Age, years	
Mean (SD)	15.1 (6.6)
≤ 6 years	1 (5.9)
> 6 and ≤ 15 years	9 (52.9)
> 15 years	7 (41.2)
Sex	
Male	9 (52.9)
Female	8 (47.1)
Race	
Asian	17 (100.0)
Pathogenic mutation	
Two pathogenic mutations in *NPC1*	5 (29.4)
One pathogenic mutation in *NPC1* + a positive biomarker + high clinical suspicion of NPC	12 (70.6)
Prior medication	3 (17.7)
Concomitant medication	17 (100.0)
Any medical history	4 (23.5)
Hyperuricemia	2 (11.8)
Epilepsy	2 (11.8)
Hypothyroidism	1 (5.9)
Medical history of special interest	
Epilepsy	2 (11.8)

Data are reported as n (%) unless otherwise specified. FAS: full analysis set; NPC: Niemann-Pick disease type C; *NPC1*: Niemann-Pick disease type C1 gene; SD: standard deviation.

3.2. Treatment exposure

In total, 14 (82.4%) patients completed the 52-week treatment period and three patients (17.7%) discontinued miglustat early. The primary reasons for early discontinuation were death (n = 2, 11.8%) and participant withdrawal (n = 1, 5.9%; Figure 1B). During the study, 70.6% (n = 12) of the patients received miglustat 200 mg three times daily, and the remainder received 100 mg three times daily (n = 4, 23.5%), 200 mg twice daily (n = 2, 11.8%), or 100 mg twice daily (n = 1, 5.9%). Overall, 82.4% (n = 14) of patients received 80-120% of the planned dose. The overall median duration of miglustat exposure was 370 (range, 110-373) days, with most patients (n = 14, 82.4%) having > 360 days of exposure.

3.3. Efficacy

3.3.1. HSEM parameter analysis

The following HSEM parameter measures include those from the FAS population while the PPS population showed a similar trend to the FAS population (Supplemental Table S2, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=224*).

3.3.1.1. Saccadic peak acceleration

An increase in mean saccadic peak acceleration was observed from baseline in the patients completing 52 weeks of miglustat therapy (Figure 2A and 2B). The mean saccadic peak acceleration increased by 20.7% across the treatment period (95% CI: 7.2 to 34.3%; absolute mean change: 2,594.1 [standard deviation (SD): 2,943.7] deg/sec^2) at week 13 (n = 16); 6.9% (95% CI: -15.2 to 29.0%; absolute mean change: 1,029.2 [SD: 4,528.5] deg/sec^2) at week 26 (n = 14); 10.6% (95% CI: -7.1 to 28.4%; absolute mean change: 1,748.1 [SD: 4,415.3] deg/sec^2) at week 39 (n = 14); and 19.2% (95% CI: 11.7 to 26.74%; absolute mean change: 2,900.4 [SD: 1,923.4] deg/sec^2) at week 52 (n = 13) from the mean baseline value of 14,555.7 (95% CI: 11,786.2 to 17,325.3) deg/sec^2 (n = 17).

3.3.1.2. Mean velocity

The mean velocity values increased from baseline during the 52-week treatment period (Figure 2C and 2D). The mean velocity increased by 17.88% across the treatment period (95% CI: -5.3 to 41.0%; absolute mean change: 9.0 [SD: 30.0] deg/sec) at week 13 (n = 16); 11.3% (95% CI: -17.0 to 39.7%; absolute mean change: 3.7 [SD: 33.3] deg/sec) at week 26 (n = 14); 14.3% (95% CI: -6.0 to 34.6%; absolute mean change: 7.9 [SD: 25.0] deg/sec)

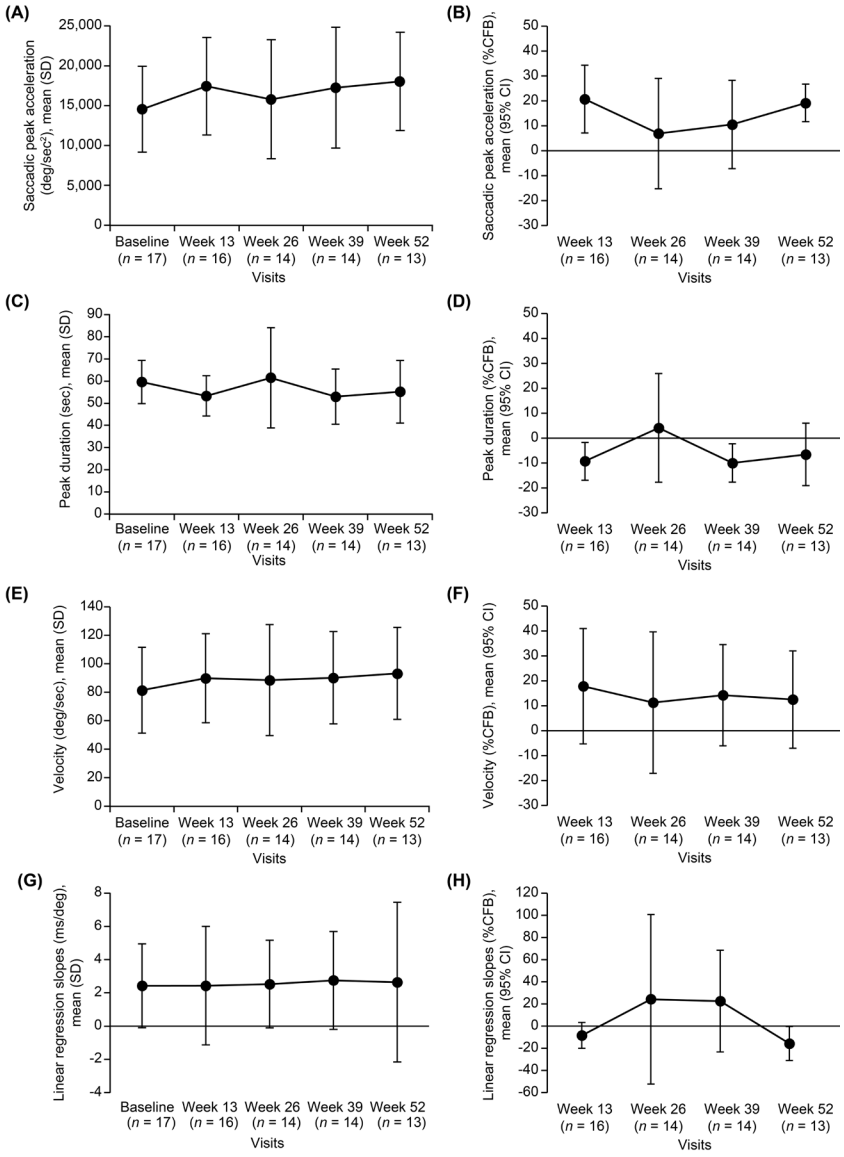

Figure 2. Mean HSEM parameters (left panels) and percentage change (right panels) from baseline to week 52 (including all time points). (A,B), Saccadic peak acceleration; **(C,D)**, velocity; **(E,F)**, Peak duration; **(G,H)**, Linear regression slope. %CFB: percentage change from baseline (FAS); CI: confidence interval; FAS: full analysis set; HSEM: horizontal saccadic eye movement; SD: standard deviation.

at week 39 (*n* = 14); and 12.5% (95% CI: -7.0 to 32.0%; absolute mean change: 8.8 [SD: 21.4] deg/sec) at week 52 (*n* = 13) in comparison with the mean baseline value of 81.5 (95% CI: 66.0 to 97.0) deg/sec (*n* = 17).

3.3.1.3. Peak duration

A decrease in mean peak duration parameter was observed from baseline to all visits (except at week 26) across the 52-week treatment period (Figure 2E and 2F). The mean change in peak duration was -9.3% (95% CI: -16.8% to -1.7%; absolute mean change: -6.1 [SD: 9.0] sec) at week 13 (*n* = 16); 4.1% (95% CI: -17.7 to 25.9%; absolute mean change: 2.0 [SD: 21.6] sec) at week 26 (*n* = 14); -9.9% (95% CI: -17.6% to -2.2%; absolute mean change: -5.8 [SD: 8.2] sec) at week 39 (*n* = 14); and -6.5% (95% CI: -19.0 to 6.0%; absolute mean change: -4.1 [SD: 11.3] sec) at week 52 (*n* = 13) from a mean baseline value of 59.6 (95% CI: 54.6 to 64.6) sec (*n* = 17).

3.3.1.4. Linear regression slopes

A reduction in mean linear regression slopes was observed from post-baseline during the 52-week treatment period; however, this was not consistent across all assessment visits (Figure 2G and 2H). The mean percentage change in linear regression slope was -8.2% (95% CI: -19.9 to 3.5%; absolute mean change: -0.01 [SD: 1.2] ms/deg) at week 13 (*n* = 16); 24.3% (95% CI: -52.2 to 100.82%; absolute mean change: 0.1 [SD: 3.2] ms/deg) at week 26 (*n* = 14); 22.7% (95% CI: -23.2 to 68.6%; absolute mean change: 0.4 [SD: 1.5] ms/deg) at week 39 (*n* = 14); and -15.6% (95% CI: -30.9% to -0.2%;

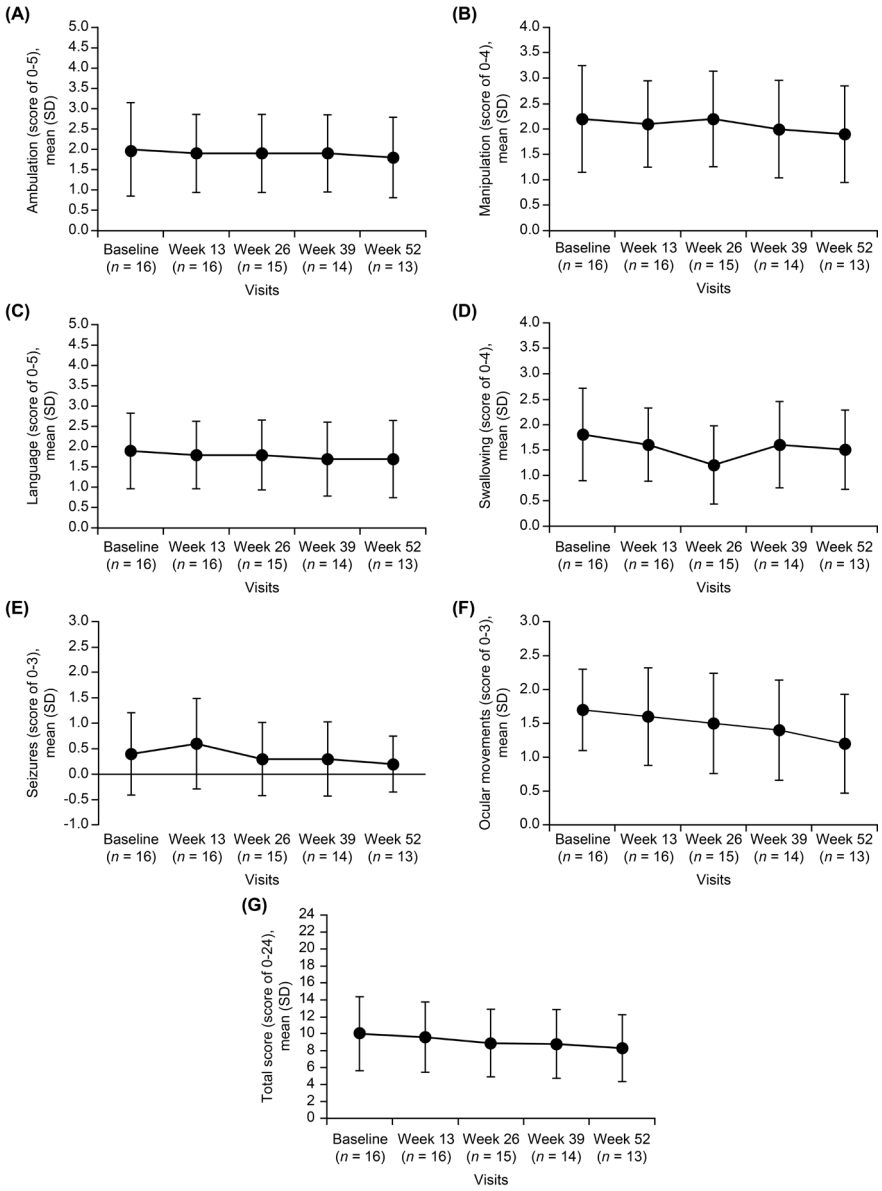

Figure 3. Mean of Pineda Disability Scale scores. (A), Ambulation; **(B)**, Manipulation; **(C)**, Language; **(D)**, Swallowing; **(E)**, Seizure; **(F)**, Ocular movements; **(G)**, Total score from baseline to week 52 (including all time points) (FAS). Mean (± SD) values are shown. Fourteen patients completed week 52 of treatment; however, Pineda Disability Scale data for one patient are missing. FAS: full analysis set; SD: standard deviation.

absolute mean change: 0.2 [SD: 2.0] ms/deg) at week 52 (n = 13), when compared with the mean baseline value of 2.4 (95% CI: 1.1 to 3.7) ms/deg (n = 17).

3.3.2. Pineda Disability Scale analysis

The Pineda Disability Scale score had a numerical improvement in ocular movements with a mean decrease of 0.4 (on a scale of 0-3) at week 52 from baseline (Figure 3). Other components of the Pineda Disability Scale also showed sustained response or minor numerical improvements in manipulation, language, swallowing, and seizures, although the changes in scores (range of changes from 0.1 to 0.4 on scales from 0-3 to 0-4) were less than those observed in ocular movements.

3.3.3. Height and body weight among pediatric patients

Among the 12 (70.6%) patients aged < 18 years, the mean values for height showed an increase during post-baseline periods when compared with the baseline period (Supplemental Table S3, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=224*). The mean height was 149.2 cm (SD: 22.7; absolute mean change: 1.2 [SD: 1.0] cm) at week 26 (n = 10) and 153.3 cm (SD: 21.3; absolute mean change: 2.6 [SD: 1.8] cm) at week 52 (n = 9), compared with the mean baseline value of 147.3 (SD: 21.8) cm (n = 12). For weight, the changes were minimal during post-baseline periods when compared with the baseline period (Supplemental Table S3, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=224*).

3.4. Safety

All 17 patients (100.0%) experienced at least one TEAE during the study. The most commonly reported TEAE was diarrhea (*n* = 12, 70.6%). Other commonly (≥ 2 patients) reported TEAEs were upper respiratory tract infection (*n* = 7, 41.2%), hyperuricemia (*n* = 4, 23.5%), and epistaxis (*n* = 3, 17.6%); abdominal pain, anal incontinence, large intestine infection, tremor, pyrexia, weight reduction, insomnia, leukocytosis, aggravation of NPC, and abnormal hepatic function were each reported in two patients [11.8%] (Table 2). Severe TEAEs occurred in four (23.5%) patients and these included pneumonia, asphyxia, accidental death, and Henoch-Schönlein purpura (each reported in one participant [5.9%]). Serious TEAEs were reported in five patients (29.4%); asphyxia, accidental death, malnutrition, pneumonia, and Henoch-Schönlein purpura were reported in one participant each and none were considered related to miglustat treatment. Two patients died due to accidental death and asphyxia, which were not considered to be related to miglustat treatment.

In total, 12 (70.6%) patients experienced TEAEs that were considered related to miglustat treatment, the most common of which were diarrhea (*n* = 12; 70.6%) and insomnia (*n* = 2, 11.8%; Table 2). Overall, five patients (29.4%) had TEAEs leading to interruption of miglustat treatment, of which four events were deemed treatment-related. The percentage of patients with TEAEs leading to discontinuation of miglustat treatment was 11.8% (*n* = 2); these two patients experienced fatal TEAEs (accidental death and asphyxia) that were not considered related to miglustat treatment per investigator's assessment.

There was a small mean change in hematological parameters between baseline and post-baseline periods (Supplemental Table S4, *https://www.irdrjournal.com/action/getSupplementalData.php?ID=224*). During the study, no marked differences in the mean changes of chemistry parameters were observed.

Table 2. Summary of TEAEs by relationship to miglustat (preferred term) reported by at least two patients (SS)

TEAEs	Related to miglustat	Not related to miglustat
Any cause	12 (70.6)	17 (100.0)
Diarrhea	12 (70.6)	3 (17.6)
Anal incontinence	0	2 (11.8)
Upper respiratory tract infection	0	7 (41.2)
Hyperuricemia	1 (5.9)	4 (23.5)
Tremor	0	2 (11.8)
Pyrexia	0	2 (11.8)
Epistaxis	0	3 (17.6)
Insomnia	2 (11.8)	0
Leukocytosis	0	2 (11.8)
Niemann-Pick disease	0	2 (11.8)
Hepatic function abnormal	0	2 (11.8)

Data are reported as *n* (%). SS: safety analysis set; TEAE: treatment-emergent adverse events.

4. Discussion

This post-approval commitment study assessed the safety and efficacy of miglustat in 17 individuals with NPC. Without treatment, the manifestations of the disease continuously worsen without interruption (*1*). Results from the current study showed consistent findings with previous studies, suggesting that miglustat delays the progression of NPC and has manageable toxicity (*13,16,18*).

In neurometabolic disorders such as NPC, where multiple organ involvement is frequently seen, ocular motor problems can help demonstrate the severity or clinical progression (*13*). The choice of HSEM as the primary outcome measure in this study was dictated by knowledge of the disease evolution in NPC, in which, typically, vertical saccadic eye movements are affected earlier than HSEM (*21*). As demonstrated in previous studies, vertical saccadic eye movements are usually already severely affected at the time of diagnosis, and vertical gaze palsy is frequently present (*13*). In the present study, the mean saccadic peak acceleration and velocity increased by 19.2% and 12.5%, respectively, between baseline and week 52, while the mean peak duration and mean linear regression slope decreased by 6.5% and 15.6%, respectively, during the same period. Overall, this suggests that patients who received miglustat treatment experienced an improvement in HSEM, although this was not statistically evaluated. The mean ambulation, manipulation, language, swallowing, seizure, and ocular movement scores improved or stabilized between baseline and week 52. These data are consistent with the findings of the international, non-blinded, randomized controlled clinical study, which recruited 29 individuals with NPC and showed that miglustat could improve the individuals' HSEM velocity and improve or delay the deterioration of neurological symptoms in cognitive function, swallowing function, and walking ability (*13*). Data from an observational retrospective cohort study of 66 patients, across 25 expert centers, similarly demonstrated the stabilization and improvement of neurological symptoms as measured by four key parameters of neurological disease progression in NPC (ambulation, manipulation, language, and swallowing) following miglustat treatment (*12,13,15*). Similar findings were also observed in a prospective study of five children who received miglustat treatment for up to 6 years, although there was a trend towards deterioration after 5 years of treatment (*18*).

The TEAEs reported in this study were generally consistent with the known safety profile of miglustat (*13*), with the most prevalent TEAE of diarrhea being reported in 70.6% of patients. Sporadic occurrences of diarrhea were also observed in previous studies of miglustat and

it has been theorized that this occurs when sweets and/or milk-based foods are consumed (*12,18,19*). However, information on the diet of patients was not recorded in this study. Most patients could tolerate treatment (the majority of TEAEs were mild [100.0%] or moderate [76.5%] in intensity), with only 11.8% discontinuing miglustat due to TEAEs unrelated to miglustat treatment.

The safety profile of miglustat observed in the present study is consistent with that reported from 11 clinical trials of 247 patients, including 40 individuals with NPC, who received miglustat doses of 50-200 mg three times daily for an average duration of 2.1 years (*12*). Taken together, evidence from the current and previous studies shows that AEs following miglustat treatment are generally of mild-to-moderate severity (*12*). Weight loss, which is a frequent well-known side effect of miglustat treatment, was only reported in 11.8% of patients in the present study, whereas in the previous studies 55% of patients experienced TEAEs of weight loss 6–12 months after treatment initiation (*12*). The reason for this discrepancy is uncertain but it is likely that after more than a decade's worth of clinical experience, weight management practices for individuals receiving miglustat treatment have improved.

The selected study design was based on the best available knowledge and guidance from previously conducted studies, and the study evaluations used a broad approach with careful assessment of a large number of variables. Due to the progressive nature of NPC and its severity, together with the unblinding effect anticipated from the characteristic gastrointestinal side effects of miglustat and the use of objective endpoint measures, an open-label design was considered appropriate. These data should be considered in the context of the limited sample size and short duration of observation.

Currently, miglustat is the only approved disease-modifying treatment for NPC (*22,23*). No other approved therapies reverse the progressive deterioration of the nervous system that characterizes NPC (*22*), and health authority guidelines have not provided advice on suitable efficacy criteria or outcome measures to be tested in clinical studies. To the best of our knowledge, our study is the first clinical study to evaluate miglustat in patients with NPC in China. A search on both major English and Chinese medical literature databases for miglustat in Chinese patients with NPC only returned case studies. This further highlights that the results from our study provide more evidence for clinical practice in China by demonstrating that miglustat is efficacious and has a well-established and manageable safety profile.

Acknowledgements

Medical writing support was provided by Russell Craddock, PhD, and Shao-Hua Chin, PhD, of Parexel. The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at *https://www.janssen.com/clinical-trials/transparency*. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at *http://yoda.yale.edu*.

Funding: This study was sponsored by Actelion Pharmaceuticals Trading (Shanghai) Co., Ltd.

Conflict of Interest: Yufang Che and Xueyu Li are employees of Xi'an Janssen Pharmaceutical Ltd. and Jianmin Zhuo is an employee of, and owns stocks in, Janssen. Huiwen Zhang, Hui Xiong, Cuijie Wei, and Mengni Yi have no conflicts of interest to disclose.

References

1. Vanier MT. Niemann-Pick disease type C. Orphanet J Rare Dis. 2010; 5:16.
2. Mengel E, Klunemann HH, Lourenco CM, Hendriksz CJ, Sedel F, Walterfang M, Kolb SA. Niemann-Pick disease type C symptomatology: An expert-based clinical description. Orphanet J Rare Dis. 2013; 8:166.
3. Imrie J, Galani C, Gairy K, Lock K, Hunsche E. Cost of illness associated with Niemann-Pick disease type C in the UK. J Med Econ. 2009; 12:219-229.
4. Mengel E, Patterson MC, Chladek M, Guldberg C, Í Dali C, Symonds T, Lloyd-Price L, Mathieson T, Crowe J, Burbridge C. Impacts and burden of Niemann Pick type-C: A patient and caregiver perspective. Orphanet J Rare Dis. 2021; 16:493.
5. Patterson MC, Hendriksz CJ, Walterfang M, Sedel F, Vanier MT, Wijburg F, NP-C Guidelines Working Group. Recommendations for the diagnosis and management of Niemann-Pick disease type C: An update. Mol Genet Metab. 2012; 106:330-344.
6. Wassif CA, Cross JL, Iben J, Sanchez-Pulido L, Cougnoux A, Platt FM, Ory DS, Ponting CP, Bailey-Wilson JE, Biesecker LG, Porter FD. High incidence of unrecognized visceral/neurological late-onset Niemann-Pick disease, type C1, predicted by analysis of massively parallel sequencing data sets. Genet Med. 2016; 18:41-48.
7. Patterson MC, Mengel E, Vanier MT, Moneuse P, Rosenberg D, Pineda M. Treatment outcomes following continuous miglustat therapy in patients with Niemann-Pick disease type C: a final report of the NPC Registry. Orphanet J Rare Dis. 2020; 15:104.
8. Burton BK, Ellis AG, Orr B, Chatlani S, Yoon K, Shoaff JR, Gallo D. Estimating the prevalence of Niemann-Pick disease type C (NPC) in the United States. Mol Genet Metab. 2021; 134:182-187.
9. Liang H, Zhan X, Wang Y, Maegawa GHB, Zhang H. Development and validation of a new genotype-phenotype correlation for Niemann-Pick disease type C1. J Inherit Metab Dis. 2024; 47:317-326.
10. European Medicines Agency. Miglustat. Summary of product characteristics. *https://www.ema.europa.eu/en/documents/product-information/zavesca-epar-product-information_en.pdf* (accessed October 7, 2024).
11. Lyseng-Williamson KA. Miglustat: A review of its use in Niemann-Pick disease type C. Drugs. 2014; 74:61-74.
12. Actelion Pharmaceuticals. Investigator's Brochure JNJ-

66674140 Zavesca® (miglustat). 2020; pp. 123.
13. Patterson MC, Vecchio D, Prady H, Abel L, Wraith JE. Miglustat for treatment of Niemann-Pick C disease: A randomised controlled study. Lancet Neurol. 2007; 6:765-772.
14. Platt FM, Neises GR, Dwek RA, Butters TD. N-butyldeoxynojirimycin is a novel inhibitor of glycolipid biosynthesis. J Biol Chem. 1994; 269:8362-8365.
15. Pineda M, Wraith JE, Mengel E, Sedel F, Hwu WL, Rohrbach M, Bembi B, Walterfang M, Korenke GC, Marquardt T, Luzy C, Giorgino R, Patterson MC. Miglustat in patients with Niemann-Pick disease type C (NP-C): A multicenter observational retrospective cohort study. Mol Genet Metab. 2009; 98:243-249.
16. Karimzadeh P, Tonekaboni SH, Ashrafi MR, *et al.* Effects of miglustat on stabilization of neurological disorder in Niemann-Pick disease type C: Iranian pediatric case series. J Child Neurol. 2013; 28:1599-1606.
17. Fecarotta S, Amitrano M, Romano A, Della Casa R, Bruschini D, Astarita L, Parenti G, Andria G. The videofluoroscopic swallowing study shows a sustained improvement of dysphagia in children with Niemann-Pick disease type C after therapy with miglustat. Am J Med Genet A. 2011; 155A:540-547.
18. Chien YH, Peng SF, Yang CC, Lee NC, Tsai LK, Huang AC, Su SC, Tseng CC, Hwu WL. Long-term efficacy of miglustat in paediatric patients with Niemann-Pick disease type C. J Inherit Metab Dis. 2013; 36:129-137.
19. Heron B, Valayannopoulos V, Baruteau J, Chabrol B, Ogier H, Latour P, Dobbelaere D, Eyer D, Labarthe F, Maurey H, Cuisset JM, de Villemeur TB, Sedel F, Vanier MT. Miglustat therapy in the French cohort of paediatric patients with Niemann-Pick disease type C. Orphanet J Rare Dis. 2012; 7:36.
20. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice *https://database.ich.org/sites/default/files/ICH_E6%28R3%29_DraftGuideline_2023_0519.pdf* (accessed June 28, 2024).
21. Patterson MC, Di Bisceglie AM, Higgins JJ, Abel RB, Schiffmann R, Parker CC, Argoff CE, Grewal RP, Yu K, Pentchev PG, Brady RO, Barton NW. The effect of cholesterol-lowering agents on hepatic and plasma cholesterol in Niemann-Pick disease type C. Neurology. 1993; 43:61-64.
22. Cariati I, Masuelli L, Bei R, Tancredi V, Frank C, D'Arcangelo G. Neurodegeneration in Niemann-Pick type C disease: An updated review on pharmacological and non-pharmacological approaches to counteract brain and cognitive impairment. Int J Mol Sci. 2021; 22:6600.
23. Tirelli C, Rondinone O, Italia M, Mira S, Belmonte LA, De Grassi M, Guido G, Maggioni S, Mondoni M, Miozzo MR, Centanni S. The genetic basis, lung involvement, and therapeutic options in Niemann-Pick disease: A comprehensive review. Biomolecules. 2024; 14:211.

Received November 1, 2024; Revised November 21, 2024; Accepted November 26, 2024.

**Address correspondence to:*
Huiwen Zhang, Xinhua Hospital affiliated to Shanghai Jiao Tong University School of Medicine, 1665 Kongjiang Road, Yanpu District, Shanghai, China.
E-mail: zhanghuiwen@xinhuamed.com.cn

Hui Xiong, Department of Pediatrics, Peking University First Hospital, 8 Xishiku Street, Xicheng District, Beijing, China.
E-mail: xh_bjbj@163.com

Released online in J-STAGE as advance publication November 30, 2024.