

MIGLUSTAT IN NIEMANN-PICK TYPE C (NPC) DISEASE: A 1-YEAR INTERIM ANALYSIS

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INTRODUCTION

- Niemann-Pick type C (NPC) disease is a fatal neurovisceral disorder linked to dysregulation in lipid trafficking¹⁻³
- No treatment exists for this disease aside from palliative care
- Clinical features include pulmonary infiltrates and liver disease in infancy, and progressive neurodegeneration in later onset cases
- The disease is characterised by accumulation of unesterified cholesterol and glycosphingolipids (GSLs) in the lysosomal compartments of many tissues⁴
- The abnormal storage of GSLs is associated with ectopic dendritogenesis and meganeurite formation, characteristic features of NPC⁵
- Miglustat (Zavesca®) is a small iminosugar molecule which can reversibly inhibit glucosylceramide synthase, the enzyme that catalyses the first committed step of GSL synthesis⁶
- Its physico-chemical properties allow miglustat to cross the blood-brain barrier⁷. As such, it may have potential as a therapeutic agent for NPC disease, including the neurological symptoms
- This study is the first to test a potential medication for NPC disease in juveniles and adults, as well as in children

OBJECTIVES

- This study aims to evaluate the safety and efficacy of miglustat as a treatment for NPC disease.

PATIENTS & METHODS

- The main study included juvenile/adult patients randomised to receive either miglustat or standard care. In the paediatric study, all patients received miglustat
- The study cohort comprised male or female patients with NPC (confirmed by abnormal cholesterol esterification and abnormal filipin staining), with normal renal function, who were able to ingest a capsule, and who did not suffer from clinically significant diarrhoea
- Patients <4 years, and those with medical conditions or who were on concomitant medications that would render them unsuitable for the study were excluded
- Patients were assessed for the primary endpoint, horizontal saccadic eye movement (HSEM- α) during the screening period and at Month 12. On each occasion, assessments of eye movement velocity were performed twice within 24 hours
- Swallowing ability was assessed at screening, Months 6 and 12
- Neurological examinations and quality of life assessments (for juveniles/adults) were performed at screening, Months 3, 6, 9, and 12, and at follow-up
- Safety assessments were performed at screening, every 3 months, and at follow-up. Adverse events (AEs) were recorded at each post-screening visit
- Measurements presented in the figures were taken at baseline and at Month 12 (last value)
- The two treatment groups (miglustat vs. standard care) were compared using an analysis of covariance (ANCOVA) model. A non-parametric stratified Wilcoxon test was used to compare the treatment groups with respect to patients' swallowing ability. Data from the paediatric group were compared to those from the juvenile/adult group (descriptive statistics were used for the analysis)

Juvenile/Adult Study

- This was a randomised, controlled phase I/II study in 29 juveniles and adults (≥ 12 years) with NPC
- Patients were randomised 2:1 to 200 mg miglustat three times daily (t.i.d.) or standard care for 12 months
- Patients were given the option to enter or continue active treatment for an additional year after the initial 12-month trial period

Paediatric Study

- This was a non-randomised phase I/II study
- The study involved 12 children (<12 years old) with NPC
- Miglustat dose was adjusted according to body surface area

Criteria for evaluation

- Efficacy:** HSEM measurements, swallowing assessment, neurological tests (including neurological examination and neuropsychological tests), and quality of life assessment. Juveniles/adults also underwent tremor and organ volume assessments
- Safety:** AEs, laboratory analysis, vital signs, concomitant medications, and physical examination

RESULTS

PATIENTS

- The demographics and characteristics of the juvenile/adult and paediatric patients at baseline are summarised in Table 1
- At baseline, all patients suffered from various neurological manifestations, including vertical supranuclear gaze palsy, cognitive impairment, ataxia, dystonia, dysarthria, and swallowing difficulties. The proportion of patients from each treatment group manifesting these neurological symptoms at baseline is summarised in Table 2

Table 1. Summary of patient demographics and baseline characteristics

Characteristic	Juvenile/Adult		Paediatric
	Miglustat (n=20)	Standard care (n=9)	
Gender			
Male	9	5	5
Female	11	4	7
Age (years)			
Mean (SD)	25.4 (9.8)	22.9 (7.5)	7.2 (2.5)
Range	12-42	13-32	4-11
4-11 years	0	0	12
12-17 years	5	4	0
≥ 18 years	15	5	0
Weight (kg)			
Means (SD)	73.3 (22.0)	64.4 (11.1)	27.9 (10.6)
Height (cm)			
Means (SD)	168.7 (15.7)	166.7 (12.4)	124.3 (19.9)

Table 2. Neurological manifestations at baseline in juvenile/adult and paediatric patients

Manifestation of NPC	Juvenile/Adult		Paediatric
	Miglustat (n=20)	Standard care (n=9)	
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)
Dystonia	14 (70)	4 (44)	5 (42)
Dysarthria	18 (90)	4 (44)	7 (58)
Swallowing difficulties	12 (60)	6 (67)	4 (33)

EFFICACY

Horizontal saccadic eye movement HSEM- α

- Primary analysis of miglustat treatment vs. standard care shows an improvement in HSEM- α both in juvenile/adult and paediatric patients (Fig. 1)
- Exclusion of patients who were on benzodiazepines (known to affect HSEM velocity) showed statistically significant improvements between miglustat treatment vs. standard care (Fig. 1)

- In paediatric patients, an improvement in HSEM- α was seen after 12 months of miglustat treatment (Fig. 1). This result was comparable to that of the juvenile/adult patients

Swallowing and auditory acuity

- Miglustat was found to improve measures of swallowing in juveniles/adults in nearly all cases, with no overall deteriorations (Fig. 2)
- Miglustat had no effect on swallowing ability in paediatric patients. However, over 80% of paediatric patients swallowed all test substances easily at baseline, in contrast to the juvenile/adult population, which showed impaired swallowing at baseline
- An overall trend of improved auditory acuity was seen in juveniles/adults treated with miglustat, while the standard care group showed overall worsening (Fig. 3)

Figure 1. Improvements in HSEM- α in juvenile/adult (L) and paediatric (R) patients

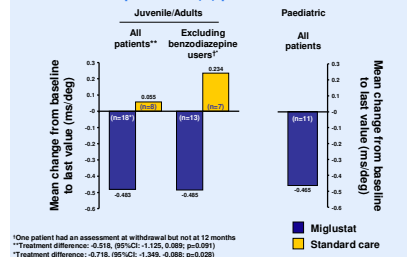
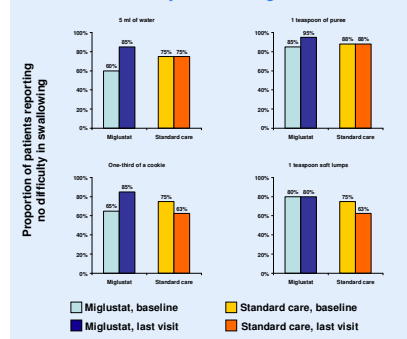


Figure 2. Proportion of juvenile/adult patients reporting no difficulty in swallowing



Effects of miglustat on other secondary endpoints

- Miglustat treatment resulted in improvements in Mini Mental Status Exam (MMSE) scores in juveniles/adults (Table 3)
- Slower deterioration of Standard Ambulatory Index scores with miglustat treatment (+0.2) vs. standard care (+0.7) in juveniles/adults was observed. No changes were observed in the paediatric group
- Neurological examination and neuropsychological testing did not reveal any notable changes from baseline or shifts from normal to abnormal
- Improvement of several quality of life domains were observed with miglustat treatment, as compared to standard care, including bodily pain, general health, social functioning, mental health and physical component parameters

Figure 3. Proportion of juvenile/adult patients reporting normal auditory acuity

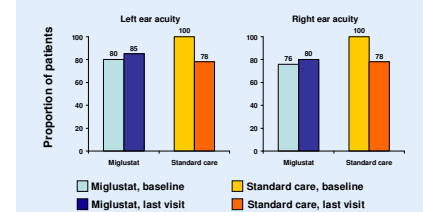


Table 3. Treatment with miglustat improves Mini Mental State Examination (MMSE) score in juveniles/adults

	n	Baseline (SD)	Last value (SD)	Change (SD)
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)

A higher score indicates better mental status, a total score of 24 or above is considered normal

Adverse Events (AEs)

- In adults, the most frequently-occurring individual AEs were diarrhoea (85%), flatulence (70%), and weight loss (65%). A summary of adverse events is given in Table 4
- The most frequently-occurring AEs were diarrhoea (67%) and flatulence (33%) in paediatric patients
- Discontinuation due to AEs were reported in 3 patients: in 1 paediatric patient due to memory impairment and in 2 adult patients due to confusional state (1 patient) and diarrhoea (1 patient)
- No deaths were reported

Table 4. Summary of adverse events

	Juveniles/Adults		Paediatrics
	Miglustat (n=20)	Standard care (n=9)	
Diarrhoea	17 (85%)	4 (44%)	8 (67%)
Flatulence	14 (70%)	0	4 (33%)
Weight loss	13 (65%)	0	3 (25%)
Headache	9 (45%)	3 (33%)	2 (17%)
Tremor	8 (40%)	2 (22%)	2 (17%)
Appetite decrease	5 (25%)	0	1 (8%)
Dysphagia	4 (20%)	4 (44%)	3 (25%)
Abnormal gait	2 (10%)	4 (44%)	4 (33%)

DISCUSSION & CONCLUSIONS

- Treatment with miglustat resulted in improvements in the primary endpoint, HSEM- α , in miglustat-treated patients compared to standard care
- Miglustat treatment showed trends for improved swallowing capacity and auditory acuity, compared to standard care in adult/juvenile patients
- Slower deterioration in Standard Ambulatory Index was observed in miglustat-treated juvenile/adult patients (untreated patients showed a greater worsening)
- Miglustat had a positive effect on cognitive function in juvenile/adult patients (assessed by MMSE score)
- No unexpected miglustat toxicity was found
- Results indicate that miglustat favourably influences function in some neuronal populations based on improvements in several clinically relevant parameters
- Miglustat is a potential treatment option for patients with NPC, a disease with unmet medical needs

REFERENCES

- Carstea ED et al. Science 1997;277:228-231.
- Liscum L and Sturley SL. Biochim Biophys Acta 2004;1685:22-27.
- Sturley SL et al. Biochim Biophys Acta 2004;1685:83-87.
- Ganley IG and Pfeiffer SR. J Biol Chem 2005;280:17869-17899.
- Walley SJ and Suzuki K. Biochim Biophys Acta 2004;1685:48-62.
- Lachmann RH. Drugs Today (Barc). 2006;42:29-38.
- Platt FM et al. Science 1997;276:428-431.