FDA ADVISORY BRIEFING BOOK

FOR MIGLUSTAT (OGT 918, Zavesca®) IN NIEMANN-PICK TYPE C DISEASE

NDA 021-348/S-007

Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC)

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Actelion Pharmaceuticals Ltd,
Gewerbestrasse 16,
CH-4123 Allschwil, Switzerland

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1 LIST OF ABBREVIATIONS AND ACRONYMS

ADR	Adverse drug reaction
AE	Adverse event
ANCOVA	Analysis of covariance
AUC	Area under the concentration-time curve
AZT	Zidovudine
b.i.d.	*bis in die* (twice a day)
BSA	Body surface area
CI	Confidence interval
C_{max}	Maximum blood/plasma concentration
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computed tomography
CV	Coefficient of variation
EDX	Electrodiagnostic
ERT	Enzyme replacement therapy
GD-1	Type 1 Gaucher disease
GD-3	Type 3 Gaucher disease
GlcCer	Glucosylceramide
GSL	Glycosphingolipid(s)
HSEM	Horizontal saccadic eye movements
IC_{50}	Half maximal inhibitory concentration
IS^3	Intensive Safety Surveillance Scheme
K_i	Inhibitory constant
LFT	Liver function test(s)
LDL	Low-density lipoprotein
LOTS	Late onset Tay-Sachs disease
LSD	Lysosomal storage disorder

MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NA	Not available/ Not applicable
NAA	N-acetyl aspartate
NLSD	Neuronopathic LSD
NP-A/B	Niemann-Pick type A/B disease
NP-C	Niemann-Pick type C disease
o.d.	Once a day
PK	Pharmacokinetic(s)
PMS	Post-marketing surveillance
QoL	Quality of life
SAE	Serious adverse event
SAI	Standard ambulation index
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SEM	Saccadic eye movement
SEMV	Saccadic eye movement velocity
SRT	Substrate reduction therapy
t½	Terminal elimination half-life
t.i.d.	*Ter in die* (three times daily)
t_{max}	Time of maximum blood/plasma concentration
USPI	US package insert
VFS	Videofluoroscopic
VSEM	Vertical saccadic eye movement(s)
VSGP	Vertical supranuclear gaze palsy

2 INTRODUCTION

Miglustat (OGT 918, *N*-butyl-deoxynojirimycin) is an imino sugar (molecular weight: 219 daltons) developed for the treatment of progressive neurological manifestations in adult and pediatric patients with Niemann-Pick type C disease (NP-C). Miglustat is an orally-administered drug that crosses the blood-brain barrier. The primary pharmacological activity of miglustat is inhibition of the enzyme glucosylceramide synthase, catalyzing the first step in the biosynthesis of glycosphingolipids (GSL), i.e., the formation of glucosylceramide (GlcCer). Reduced formation of GlcCer will lead to decreased biosynthesis of more complex GSL. This therapeutic principle, called substrate reduction therapy (SRT), may be useful in disorders of intracellular (predominantly lysosomal) accumulation of GSL either due to their deficient breakdown or intracellular transport/trafficking.

Miglustat, as Zavesca® 100 mg t.i.d., was approved by the FDA in 2003 for the treatment of adult patients with mild to moderate type 1 Gaucher disease (GD-1) when enzyme replacement therapy (ERT) is not a therapeutic option. GD-1 is caused by lysosomal accumulation of GlcCer due to deficient activity of the enzyme glucocerebrosidase that catalyzes its breakdown. In GD-1, miglustat acts through the principle of SRT, reducing formation of GlcCer to an extent that allows its removal by the deficient enzyme. Zavesca is also approved for use in GD-1 in the European Union, Canada, Switzerland, Russia, Brazil, Australia, Turkey, Israel, South Korea and New Zealand.

The principle of SRT is also the basis for the use of miglustat in NP-C, a very rare and previously untreatable disorder of intracellular GSL and cholesterol trafficking resulting in endosomal/lysosomal accumulation and predominant manifestations of progressive neurodegeneration. In this situation, reduced formation of GlcCer will, secondarily, lead to reduced formation of more complex GSL.

The indication targeted in the application is:

Zavesca is indicated for the treatment of progressive neurological manifestations in adult patients and pediatric patients with Niemann-Pick type C disease.

On 26 January 2009 the European Commission approved the use of Zavesca 200 mg t.i.d. (adjusted to body surface area in children) for the treatment of progressive neurological manifestations in adult patients and pediatric patients with NP-C. Zavesca is also approved for this indication in Russia, Brazil and South Korea.

Recently published consensus statements provide clinical guidelines on the diagnosis and management of NP-C and include recommendations on treatment with miglustat [Wraith 2009].

The scope of this Briefing Book is to provide an overview of the documentation for miglustat treatment in NP-C supporting the favorable benefit/risk ratio in the targeted indication.

- The background section [Section 3] describes NP-C, the complex clinical picture and the consequences of the disease to the patients. The rationale for the utility of miglustat in the treatment of NP-C, based on the preclinical evidence is also presented.
- The pharmacokinetics of miglustat and the dose rationale for its use in the target population are discussed in the section on clinical pharmacology [Section 4]. This section of the document also includes information previously submitted to the FDA that was generated in patients with GD-1.
- The efficacy section [Section 5] discusses the efficacy of miglustat as substantiated by a prospective controlled clinical trial in NP-C, a retrospective study in patients with NP-C treated with miglustat in clinical practice, as well as recent publications and case reports. Data from a retrospective natural history study in NP-C are provided for comparison.
- Because of the rarity of NP-C, the safety section [Section 6] includes and discusses the safety experience with miglustat across studies in several lysosomal storage disorders and other studied indications. Therefore, data are included from studies that were previously submitted to the FDA, but for which study reports are not included in the current application. The cumulative post-marketing safety experience with Zavesca is summarized.

Zavesca is commercially available as hard gelatine capsules for oral use containing miglustat100 mg and the marketed formulation was used in the clinical trials discussed in this Briefing Book. The biopharmaceutical information, as well as other data relevant to the currently approved indication (GD-1), is detailed in the approved US Package Insert (USPI) for Zavesca® [Appendix 3].

3 DISEASE BACKGROUND AND SCIENTIFIC RATIONALE

3.1 Niemann-Pick type C disease

Niemann-Pick type C disease (NP-C) is a very rare, autosomal-recessive disorder primarily affecting children and teenagers. The estimated incidence is 1:150,000 live births. NP-C is a disorder of intracellular lipid trafficking leading to cytotoxic lysosomal/endosomal accumulation of lipids, particularly glycosphingolipids (GSL), and cholesterol in tissues throughout the body, including the central nervous system (CNS). The disease is dominated clinically by progressive and disabling neurological signs and symptoms such as dysphagia, dysarthria, dystonia, seizures, abnormal saccadic eye

movements, as well as learning, cognitive and psychiatric abnormalities. In the later stages of the disease, patients become bedridden, in need of naso-gastric tube feeding, demented and in need of care for all aspects of daily life. Ultimately, the outcome is premature death. Currently, there is no specific treatment for NP-C available in the US.

3.1.1 Genetics and molecular defect in NP-C

Niemann-Pick type C disease results from mutations in one of two genes called *NP-C1* and *NP-C2*. Approximately 95% of individuals with NP-C have mutations in the *NP-C1* gene located at chromosome 18q11-q12, the remainder having mutations in the *NP-C2* gene located at chromosome 14q24.3 [Steinberg 1994, Vanier 1996a].

In neurons and other cell types, parts of the plasma membrane containing GSL and cholesterol are internalized as coated pits, transported through the endosomal compartment, and are sorted either for recycling to the plasma membrane, or delivered to the lysosome for degradation [Schulze 2009]. The NP-C1 and NP-C2 proteins present in the late endosome/lysosome compartment work in conjunction to ensure the recycling of GSL and cholesterol to the membrane. Hence, defective NP-C1 and NP-C2 proteins result in impaired recycling and endosomal/lysosomal accumulation of GSL and cholesterol.

NP-C is a disorder entirely distinct from Niemann-Pick type A (NP-A) and Niemann-Pick type B (NP-B) diseases, which are characterized by a genetic defect in the lysosomal enzyme acid sphingomyelinase [Blanchette 2000, Patterson 2001].

3.1.2 Neuropathophysiology of NP-C

3.1.2.1 Lipid storage

The pattern of lipids stored intracellularly in NP-C is different between visceral tissues (e.g., liver and spleen) and the CNS. In visceral organs, unesterified cholesterol, sphingomyelin, and bis(monoacylglycero)phosphate are the predominant compounds, although levels of GSL (glucosylceramide, lactosylceramide, G_{M2} and G_{M3} gangliosides) are also increased [Vanier 1996b].

Neuronal storage of GSL is the most conspicuous cerebral pathology, with elevated concentrations of glucosylceramide, lactosylceramide, G_{M2} and G_{M3} gangliosides [Vanier 1999, Zervas 2001b, Gondré-Lewis 2003]. Although GSL are components of the plasma membranes of all eukaryotic cells, it is notable that G_{M2} and G_{M3} gangliosides are virtually absent in healthy mature neurons. Excess G_{M2} ganglioside in neurons in NP-C correlates well with ectopic dendritogenesis and meganeurite formation, which are characteristic neuronal features in NP-C [Figure 1] [Walkley 1998, Zervas 2001a]. A similar correlation is seen in several other GSL storage diseases [Walkley 1998].

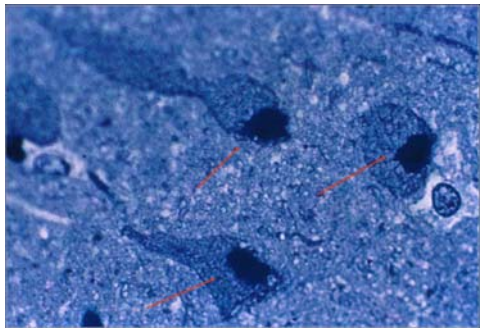
3.1.2.2 Neuropathology

The brain in NP-C is often atrophic, especially in patients with a slowly progressive clinical course [Walkley 1998, Walkley 2000]. Cerebral cortical neurons, in particular large pyramidal neurons in the deep cortical layers, are distended with GSL ("balloon cells") [Figure 1]. In the basal ganglia and thalamus, the larger neurons also tend to be the most affected. Neuroaxonal dystrophy (swelling of distal portions of axons) is found throughout the neuraxis, in particular in the thalamus, dentate nucleus, and midbrain, including the *substantia nigra*. The cerebellum is variably affected. The perikarya of both anterior and posterior horn neurons in the spinal cord are distended with lipid storage material. The cerebral white matter is usually normal, although demyelination with perivascular collections of macrophages has been reported [Walkley 2000, Sarna 2003]. Additionally, more recent studies have shown that, similar to the observations in Alzheimer's disease, so-called neurofibrillary tangles are consistently found in the brains of NP-C patients with a prolonged clinical course [Suzuki 1995, Yamazaki 2001, Saito 2002, Tamboli 2005]. The distribution of neurofibrillary tangles generally parallels that of storage neuronal GSL storage.

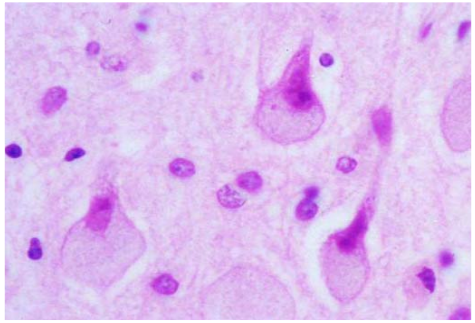
In summary, NP-C is characterized by abnormal neuronal morphology and membrane organization, resulting in abnormal neuronal responses, metabolism and homeostasis, as well as defects in myelination and neuron-glia interactions, leading to disturbed neuronal activity [Paul 2004].

Figure 1 Neuropathological changes in NP-C neurons

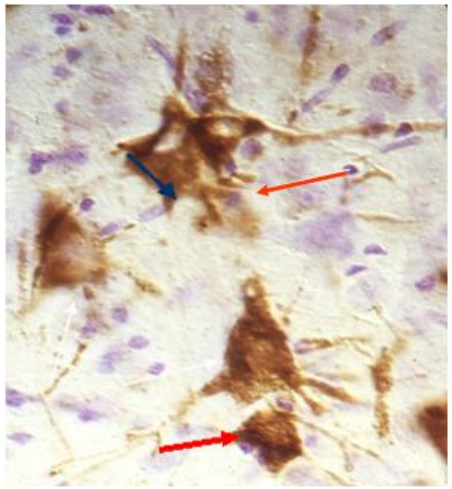
Meganeurites



Balloon cells



Ectopic dendritogenesis



3.1.3 NP-C clinical presentation

Typical clinical manifestations of NP-C according to age at onset are summarized in Table 1.

Table 1 Clinical picture at disease onset of NP-C

Age at onset	Systemic manifestations	Neurological manifestations
Pre-/perinatal period (≤ 3 months)	Fetal hydrops Hepatosplenomegaly Fetal ascites Prolonged cholestasis (frequent) Pulmonary infiltration Respiratory and/or hepatic failure	Usually none seen
Early infantile period (3 months to < 2 years)	Hepatosplenomegaly	Delayed developmental motor milestones Central hypotonia; hearing loss Vertical Supranuclear Gaze Palsy (VSGP), usually not recognized
Late infantile period (2 to < 6 years)	Splenomegaly (usually present)	Frequent falls; ataxia, dystonia, dysphagia, dysarthria Central hypotonia; hearing loss Seizures (partial or generalized); cataplexy VSGP (usually present)
Juvenile (classical) (6–15 years)	Splenomegaly (rarely present)	School failure; behavioral problems Frequent falls; ataxia, dysarthria, dystonia, dysphagia Seizures (focal and/or generalized); cataplexy Myoclonus; VSGP (usually present)
Adolescent and adult (> 15 years)	Splenomegaly (rarely present)	Clumsiness; frequent falls Difficulties in further education or work Slowly progressing neurological symptoms Seizures (partial and/or generalized); cataplexy Dementia; psychiatric signs Myoclonus; VSGP (almost always present)

*VSGP, vertical supranuclear gaze palsy – increased latency in the initiation of vertical saccades, with gradual slowing and eventual loss of saccadic movements.
Adapted from Patterson 2001

Especially during the first years of life, the presentation of NP-C may be non-specific and go unrecognized by clinicians. Severely affected babies may have ascites *in utero* and severe liver disease with hepatosplenomegaly, jaundice, and persistence of ascites after birth. However, organomegaly is not present in many NP-C cases. Some neonates present with prolonged but reversible jaundice, others have early hypotonia and delayed psychomotor development with minimal or absent hepatic dysfunction. Extensive pulmonary infiltration can also occur as a presenting feature, and may lead to respiratory

failure. Very young children usually do not exhibit vertical supranuclear gaze palsy (VSGP) at diagnosis.

The "classic" form of NP-C, that represents 60–70% of cases, manifests in middle-to-late childhood with clumsiness and gait disturbance evolving into ataxia. Impairment of vertical gaze movements (up or down) is a frequent initial neurological finding, and progresses to VSGP, and later also horizontal gaze palsy, leading to marked visual impairment. Gelastic cataplexy, with manifestations varying from head nods to complete collapse provoked by emotional stimuli, is characteristic of childhood-presentation NP-C, occurring in 20–50% of cases. Partial and/or generalized seizures develop in 30–50% of patients, and can be difficult to control. Disturbed sleep is a frequent complaint. As the disease progresses, most children develop dystonia, typically beginning as action dystonia in one limb, and gradually spreading to involve all limb and axial muscles. Progressive dysphagia and dysarthria are prominent manifestations, leading to gradual disruption of swallowing and speech until, eventually, oral feeding becomes impossible due to frequent food aspiration.

Late-onset presentations, sometimes with partial phenotypes, are now being recognized. Adolescents and adults may present with subtle symptoms of apparent psychiatric illness (e.g., psychosis, depression, schizophreniform pathology). Patients may also present with neurological deficits similar to those seen in childhood-onset NP-C, but with a slower rate of progression, which may be overshadowed by psychiatric problems. In particular, the presence of VSGP is an important clue in the diagnosis. Visceral signs or symptoms are frequently absent in late childhood and adult-onset patients.

In summary, NP-C is a disorder with a wide variety of manifestations that can present from intrauterine life to adulthood. Patients with NP-C may thus present to perinatologists, pediatricians, family practitioners, hematologists, gastroenterologists, neurologists, internists, or psychiatrists.

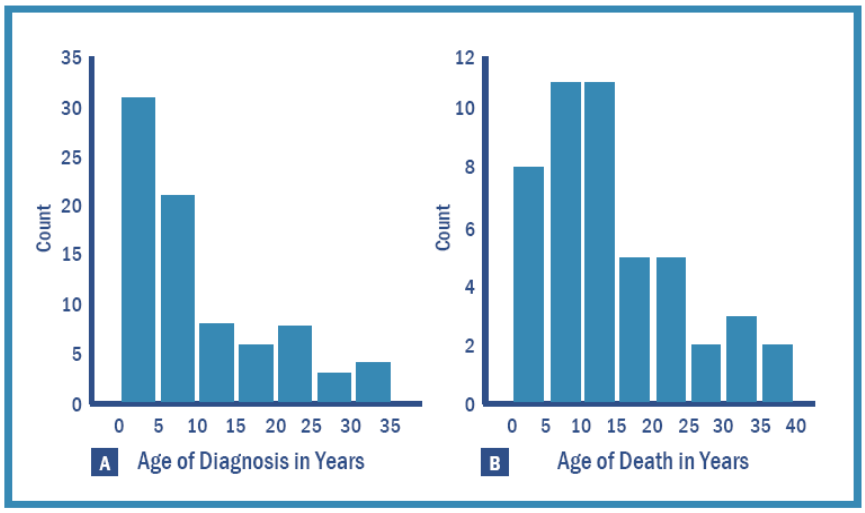
3.1.3.1 Evaluation of neurological disability in NP-C

In order to monitor disease progression and evaluate response to treatment, it is important to quantify the degree of patient disability, especially that resulting from neurological impairment. As a means to achieve this, Iturriaga et al. [Iturriaga 2006] formulated a scale based on impairments in four key neurological domains typically affected in NP-C, i.e., ambulation, manipulation, language and swallowing [Table 15]. Deficits in each of these domains were assigned numeric scores ranging from best to worst. Assessments of functional disability in patients with NP-C using this scale provide useful longitudinal, long-term follow up information. As with any score-based clinical assessment, patient performance is subject to normal variation. Scale scores should therefore, be recorded in order to reflect the patient's best level of performance in the preceding week or month [Wraith 2009].

3.1.4 Prognosis of NP-C

The majority of patients with NP-C die prematurely, although disease progression rates and life expectancy vary, primarily dependent on the age at onset of neurological symptoms. A survey conducted in the US involving the families of 87 NP-C patients showed a median age at diagnosis of 6.9 years and a median age at death of 12.5 years [Garver 2007]. Estimates of age at onset and prognosis based on studies conducted in the US and France are summarized in Figure 2 and Table 2, respectively.

Figure 2 Age at diagnosis and age at death in US patients



Reference: Garver 2007.

Table 2 Age at diagnosis and age at death in French patients

Onset of neurological manifestations	Mean age (range) at diagnosis	Mean age (range) at death
Early infantile	1.3 years (1 month–3.5 years)	3.8 years (1.6–6.5 years)
Late infantile	4 years (1 month–7 years)	10 years (6.5–14 years)
Juvenile	9 years (8 months–16 years)	19 years (13–34 years)
Adult	27 years (3 months–58 years)	44 years (28–49 years)

Reference: Wraith 2009.

3.1.5 Epidemiology of NP-C

The prevalence of NP-C may have been underestimated due to factors such as confusing terminology, insufficient availability of specific biochemical or genetic tests, varied pathology, or variant clinical manifestations. Epidemiological data on NP-C are very sparse but the incidence has been estimated at 1:150,000 live births in Western Europe based on the number of cases identified over a 15-year period in France, Germany and the UK [Pinto 2004, Poorthuis 1999, Meikle 1999]. The estimated number of patients with an established diagnosis of NP-C is approximately 400 overall in the US and Europe.

3.1.6 Confirmation of diagnosis of NP-C

The accurate diagnosis requires awareness of the heterogeneity of the clinical picture, narrowing of differential diagnosis by ancillary testing, and final confirmation by biochemical testing. NP-C disease has a unique cellular phenotype of visceral cell endosomal/lysosomal accumulation of unesterified cholesterol together with delayed and diminished homeostatic responses to exogenous low-density lipoprotein (LDL) cholesterol loading. Following skin biopsy and cell culture of fibroblasts, the diagnosis is confirmed by the concomitant demonstration of (i) intralysosomal accumulation of unesterified cholesterol as shown by a characteristic pattern of intense perinuclear fluorescence after challenge with LDL-enriched medium and filipin staining, and (ii) abnormal intracellular cholesterol homeostasis as defined by impaired LDL-induced cholesterol esterification [Vanier 1991]. Molecular genetic testing is generally used to confirm the diagnosis in individuals with variant biochemical findings and is also essential for prenatal diagnosis.

3.1.7 Treatment of NP-C

No disease-modifying treatment is currently approved for NP-C in the US. Supportive therapies are variably effective for the alleviation of symptoms and can improve patients' quality of life [Patterson 2006, Patterson 1993, Erickson 2000, Gartner 1986, Hsu 1999].

Palliative pharmacotherapy is usually offered to alleviate common neurological symptoms of NP-C. For example, tricyclic antidepressants or CNS stimulants may control cataplexy, anti-epileptic drugs can control or diminish the frequency of seizures, dystonia and tremor may respond to anticholinergic drugs, and botulinum toxin can be effective in selected cases. Melatonin has been used to treat insomnia.

Patients with NP-C frequently become malnourished as swallowing difficulties progress. Feeding and swallowing ability should be carefully monitored as patients are at risk of silent aspiration. Secondary lung involvement due to aspiration is a frequent complication. Most patients with NP-C eventually require a gastrostomy tube. Impaired swallowing is often associated with drooling and this can sometimes be controlled by small doses of orally administered atropine, or parotid and submandibular glandular injections of botulinum toxin.

Bone marrow or liver transplantation have been shown to partially normalize tissue storage of cholesterol and sphingomyelin in pre-clinical and clinical studies: however these therapies were not effective in treating neurological symptoms in NP-C. Cholesterol-lowering agents reduce hepatic and plasma cholesterol levels without amelioration of neurological disease.

3.2 Scientific rationale and preclinical evidence for miglustat treatment in Niemann-Pick type C disease

Treatment goals of a disease-modifying therapy for NP-C should take into account the known neuropathology of the disease. Overall neurological function may be considered proportional to the sum pool of CNS neurons in networks that retain functional capacity. This pool would form the primary therapeutic target in a progressive neurodegenerative disorder such as NP-C. Because a fraction of this neuronal pool will likely be irreversibly damaged or lost by the time the diagnosis is made and disease-specific treatment initiated, disease stabilization or a reduced rate of disease progression are likely the best attainable goals for long-term therapy.

3.2.1 Scientific rationale

The core structure of all GSL is ceramide, to which different carbohydrate moieties are added. The first (and committed) step in the synthesis of GSL involves the transfer of glucose from its UDP-glucose donor to ceramide to form glucosylceramide (GlcCer), the 'backbone' of all GSL. This step is catalyzed by the enzyme GlcCer synthase on the cytosolic surface of the Golgi apparatus. The more complex GSL, including neutral GSL and gangliosides, are formed by the sequential addition of monosaccharides to the terminal sugar in the growing oligosaccharide chain, with each synthetic step catalyzed by a specific enzyme [Figure 3]. All GSL are eventually degraded by the sequential hydrolytic removal by lysosomal enzymes of terminal sugars in the oligosaccharide chain to the less complex GSL and, ultimately, to the basic moieties of glucose and ceramide.

Since intracellular (lysosomal) GSL accumulation represents an imbalance between the rate of synthesis and the rate of degradation or recycling through trafficking of a particular substrate, the approach of limiting GSL synthesis by blocking a step in the synthetic pathway was proposed as a means of reducing GSL accumulation in LSD [Vunnam 1980, Inokuchi 1987]. This principle has been termed substrate reduction therapy (SRT).

Miglustat (*N*-butyl-deoxynojirimycin) is an iminosugar that inhibits GlcCer synthase. The inhibitory constant, K_i, of miglustat was found to be 7.4 μM for GlcCer synthase derived from microsomes from a human promyelocytic leukemia cell line [Platt 2008]. Biochemical studies showed that miglustat is competitive with ceramide but non-competitive with UDP-glucose, and therefore could act as a ceramide mimic in this reaction.

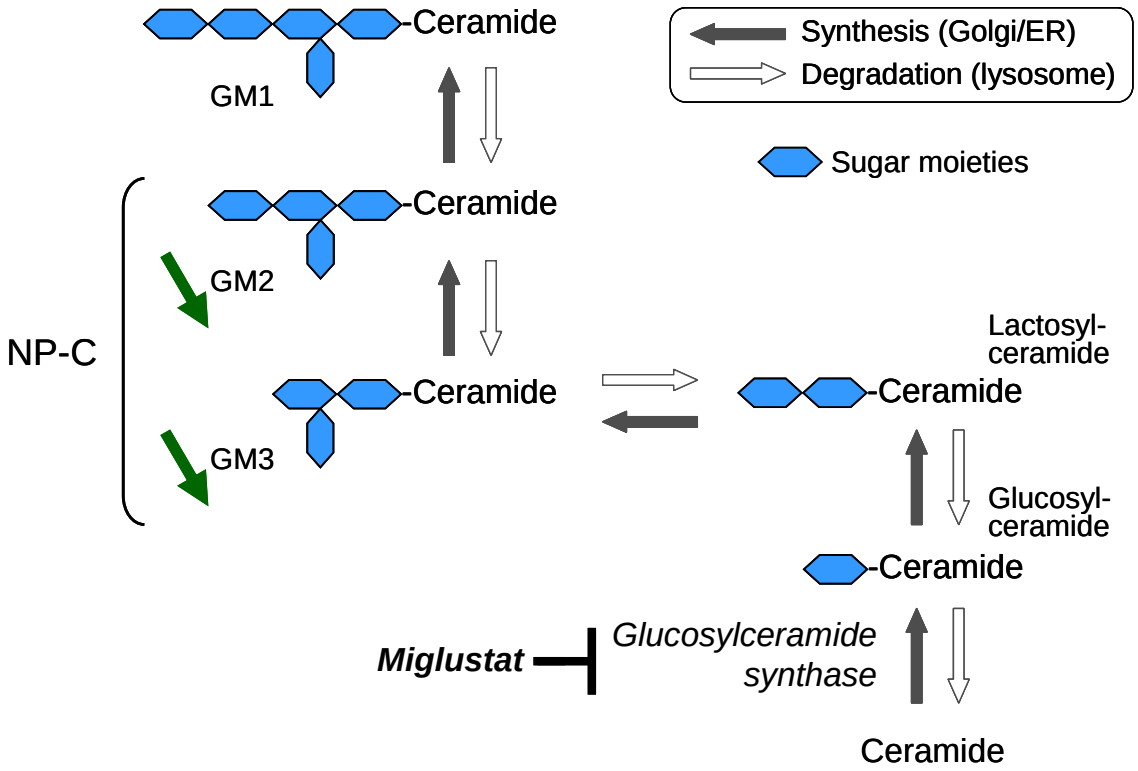
Through its action as a competitive and reversible inhibitor of GlcCer synthase, miglustat acts through the principle of SRT, reducing the formation of the substrate of complex GSL, i.e., GlcCer, and subsequently the further synthesis of GSL including G_{M2} and G_{M3} gangliosides.

The effect of miglustat on GSL formation has been examined in a variety of human and murine cell lines using radiolabeled lipids. Miglustat was found to inhibit the biosynthesis of all glucose-based GSL species, but not galactose-based species, or sphingomyelin, which are key components of myelin [Platt 1994].

Type 1 Gaucher disease (GD-1) is a genetic disorder linked to a functional deficiency of lysosomal glucocerebrosidase, the enzyme responsible for the breakdown of GlcCer. The experience with miglustat in this disease has shown that the concept of SRT in LSD is effective. The clinical utility of miglustat as a treatment for GD-1 has been documented in both treatment-naïve patients and in patients after switch from enzyme replacement therapy (ERT) [Elstein 2005, Elstein 2007]. Miglustat, as Zavesca 100 mg t.i.d., is currently approved in the United States for the treatment of adult patients with mild to moderate GD-1 for whom enzyme replacement therapy is not a therapeutic option.

The rationale for the development of miglustat in NP-C is to reduce the neuronal accumulation of complex GSL in the CNS that is responsible for the progressive neurological manifestations of the disease. An important attribute of miglustat in the treatment of NP-C is its ability to cross the blood-brain barrier.

Figure 3 Biochemical pathways of GSL metabolism and point of action of miglustat



Green arrows indicate miglustat-induced reduction.
GM1 = G_{M1} ganglioside; GM2 = G_{M2} ganglioside; GM3 = G_{M3} ganglioside; ER = endoplasmic reticulum.

3.2.2 Preclinical evidence with miglustat in animal models of NP-C disease

The demonstration that miglustat ameliorates clinical neurological disease in mouse and cat models of NP-C indicates that the inhibition of GSL synthesis may constitute an effective and beneficial approach to therapy for this disorder.

Miglustat has been tested in the BALB/c npc^{nih} mouse, a murine model of NP-C that shares many of the clinical abnormalities observed in NP-C patients. The defect in the npc^{nih} mouse arose as a spontaneous mutation that has been localized to mouse chromosome 18 in a region syntenic to the human NP-C1 locus [Loftus 1997]. The npc^{nih} mouse exhibits foamy macrophages, neuronal vacuoles, focal axonal swelling and decreased Purkinje cell numbers in the brain [Sarna 2003, Loftus 1997]. Pathological examination shows hepatosplenomegaly, cerebral atrophy, leucodystrophy and evidence of lipid storage in peripheral tissues and the brain, including sphingomyelin, cholesterol, sphingosine and GSL. The npc^{nih} mouse develops symptoms by 28–35 days of age.

Tremor is usually the first clinical sign and is followed by hind limb paralysis, impaired grooming, and death by inanition at between 70 and 80 days of age.

When npc^{nih} mice were treated with miglustat 1,200 mg/kg/day in food admix starting at 3.5 weeks of age, there was a delay in the onset of symptoms [Zervas 2001b]. By 63 to 75 days of age, clinical neurological disease and deaths were observed in all untreated mice. In contrast, 100% of miglustat-treated mice of the same age range were alive and only 56% displayed abnormal motor function. The average lifespan of treated mice was 89 days, versus 67 days for untreated mice [Zervas 2001b].

As compared to untreated animals, miglustat-treated mice displayed reduced spheroid formation in the granule cell layer, preserved Purkinje cell architecture throughout the extent of cerebellar folia, and persistence of many Purkinje cells in the cerebellum. This probably resulted from a slower rate of G_{M3} and G_{M2} ganglioside accumulation, leading to a prolongation of the pre-symptomatic phase and a slower rate of symptomatic progression [Zervas 2001b].

In another study, npc^{nih} mice were treated with miglustat 600 mg/kg/day food admix starting at 3 weeks of age [Smith 2009]. Miglustat as monotreatment prolonged survival by 5 weeks compared to untreated mice, completely prevented the onset of tremor and delayed the loss in motor function. Miglustat also protected against Purkinje cell loss. The effects of miglustat on survival in npc^{nih} mice were confirmed in a later study where miglustat 300 mg/kg/day was administered by the intraperitoneal route between Day 10 and Day 23, followed by oral administration as food admix at 1,200 mg/kg/day [Davidson 2009].

Miglustat was also tested in a cat model. The cat strain of NP-C disease has an *NP-C1* missense mutation, and is less severely affected than the *npc*^{nih} mouse [Brown 1994]. NP-C cats treated with miglustat at doses ranging from 50 to 150 mg/kg/day showed a delay in the progression of intention tremor, and in the onset of ataxia with falling [Zervas 2001b]. These effects seemed more pronounced in young animals. Miglustat reduced the levels of G_{M2} and G_{M3} gangliosides in the cerebral cortex of NP-C cats compared to age-matched untreated NP-C-affected cats [Zervas 2001b].

4 CLINICAL PHARMACOLOGY

4.1 Pharmacokinetics of miglustat

The pharmacokinetics (PK) of miglustat have previously been characterized in healthy subjects, in patients with GD-1, Fabry disease, and in subjects with HIV/AIDS. A cross-study population PK analysis of data from a total of 71 GD-1 and Fabry disease subjects provided additional information on the PK of miglustat. Miglustat showed very consistent PK across the different subject and patient groups. All of these data are reflected in the approved USPI of Zavesca [Appendix 3] and are summarized below.

Following oral administration, miglustat is rapidly absorbed with a median time to reach maximum concentration (t_{max}) of approximately 2.5 h. A standard high-fat breakfast eaten no more than 30 min before administration significantly reduced (by 36%) the peak plasma concentration, but not the extent of systemic exposure to miglustat (decrease of 14%). Given this small effect on exposure, the effects of food intake on the PK of miglustat are not considered to be of clinical relevance.

After peaking, concentrations show a biexponential decline, characterized by a short and shallow distribution phase and a longer elimination phase. Accordingly, concentration-time data could be well fitted to a two-compartment model with a short lag time for absorption. Absolute measures of distribution volume and clearance have not been obtained because an intravenous formulation of miglustat has not been studied in man. However, in view of its negligible metabolism and excretion by the kidney, mainly as unchanged drug, accurate indirect measures could be obtained and allowed estimation of PK parameters. The apparent volume of distribution and apparent oral clearance were, on average, 83–105 L and 12–14 L/h, respectively. Therefore, the drug distributes into extravascular tissues and has the characteristics of a low-clearance compound, i.e., is not sensitive to changes in liver blood flow. Miglustat does not show any binding to plasma proteins and distributes freely into erythrocytes.

The elimination half-life of miglustat is approximately 6–7 h and steady-state conditions upon multiple dosing are attained within 1 day. With t.i.d. dosing regimens, the degree of accumulation of miglustat at steady state is approximately 2-fold and independent of the duration of treatment (up to 12 months). The PK are dose-proportional over a wide dose range and show a low degree of intersubject variability (coefficient of variation [CV] approximately 20%). Following administration of a single dose of 100 mg [^{14}C]-miglustat to healthy subjects, 83% of the radioactivity was recovered in urine and 12% in feces. Several metabolites were identified in urine and feces. The most abundant metabolite in urine was miglustat glucuronide, which accounted for 5% of the dose. The terminal half-life of radioactivity in plasma was longer than that of miglustat suggesting the presence of one or more metabolites with a longer half-life. Data in rats did not provide evidence of retention in any tissue. The very low extent of miglustat metabolism *in vivo* is

in accordance with *in vitro* data, which show that the drug does not undergo any detectable metabolism by any of the cytochrome P450 enzymes.

Based on available data, the PK of miglustat are not influenced by demographic (age, sex, ethnic origin, body mass index) or disease (GD-1, Fabry disease, HIV/AIDS) variables. Exposure to miglustat is increased in renal impairment but not affected by liver impairment.

4.1.1 Pharmacokinetic studies

In comparison to the 100 mg t.i.d. dosing regimen used in GD-1, the NP-C dosing regimen of 200 mg t.i.d. and the adaptation to body surface area (BSA) in the pediatric population are of particular note. The data presented below are considered important for understanding the PK of miglustat dosed at 200 mg t.i.d.

The PK data of miglustat in pediatric (< 12 years), juvenile (≥ 12–17 years), and adult patients (≥ 18 years) to support the NP-C indication were generated from three clinical studies. Additional supportive data that were not included in the submitted documentation are also provided from one recent publication [Maegawa 2009].

4.1.1.1 Clinical studies

- NP-C patients (sub-study to OGT 918-007)
- GD-3 patients (sub-study to OGT 918-006)
- Adult G_{M2} gangliosidosis (LOTS) patients (sub-study to OGT 918-009)

Studies OGT 918-006 and OGT 918-009 also investigated whether miglustat can cross the blood-brain barrier.

The multiple-dose PK studies in patients with NP-C and GD-3, and G_{M2} gangliosidosis (both adult and pediatric) are detailed in Table 3.

Some caveats to the interpretation of the PK data should be noted: The administration time of the dose prior to the one following which blood samples were collected was absent or inaccurate, leading to fluctuations in the predose drug concentrations. In addition, blood samples for all dosing regimens were only collected up to 8 h after drug administration, which complicates comparisons among once a day, b.i.d., and t.i.d. regimens. For the same reason, the apparent terminal elimination half-life could not be estimated in these studies. Limitations to the interpretations of the PK results were also posed by the small number of patients available for study in these rare disorders. However, recently published data [Maegawa 2009] provide additional information in these respects.

Table 3 Summary of Actelion-sponsored pharmacokinetic studies

Study	Disease	N	Duration	Miglustat Dose	Design
OGT 918-007	Niemann-Pick type C	10	12 months	300–600 mg/day	Non-comparative, open-label
OGT 918-006	Type 3 Gaucher	13	12 months	100–600 mg/day	Non-comparative, open-label
OGT 918-009	G_{M2} gangliosidosis, adults	6	12 months	600 mg/day	Non-comparative, open-label

4.1.1.2 Recently published data

- pediatric G_{M2} gangliosidosis patients [Maegawa 2009]

The publication provides multiple-dose PK data in patients with G_{M2} gangliosidosis (both juvenile and pediatric) [Table 4]. In contrast to the three studies listed above, these publication data provide information on the elimination half-life after both single- and multiple-dose administration.

Table 4 Summary of publication data

Study	Disease	N	Duration	Miglustat Dose	Design
Maegawa 2009	G_{M2} gangliosidosis, pediatric	11*	6–24 months	90–600 mg/day	Non-comparative, open-label

* 10 patients were evaluable.

4.1.1.3 Pharmacokinetics in NP-C patients

In a substudy to OGT 918-007 the PK of miglustat were studied in six patients of at least 12 years, who received miglustat 200 mg t.i.d., and in four patients younger than 12 years who received miglustat at a dose adjusted for BSA [Table 9]. The aim of adjusting the dosing regimen to BSA was to reach miglustat concentrations similar to those in adult patients treated with 200 mg t.i.d. The PK parameters were determined after 1 month of treatment. The mean plasma concentration-time profiles for the different dosing regimens are presented in Figure 4. The derived PK parameters are given in Table 5. Although the patient numbers in most subgroups were small, there were no apparent differences in the exposure to miglustat between patients of at least 12 years of age and those of less than 12 years of age or due to the different dosing regimens used. Interpatient variability in exposure to miglustat was low.

Figure 4 **Study OGT 918-007: Mean plasma concentration-time profiles of miglustat following repeated oral administration to patients ≥ 12 years and < 12 years of age**

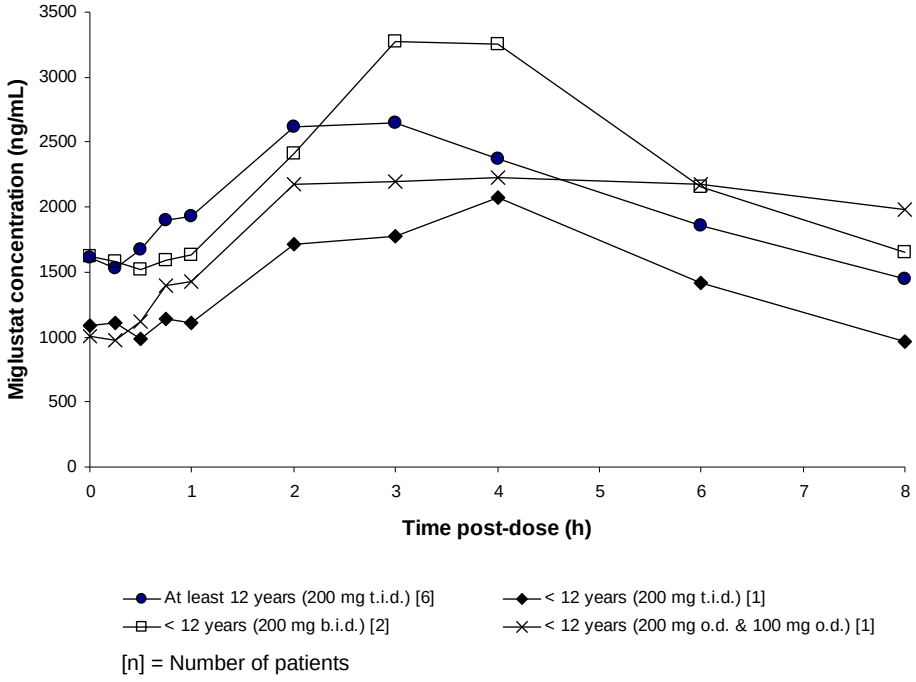


Table 5 **Study OGT 918-007: Mean PK parameters of miglustat following repeated oral administration to patients ≥ 12 years and < 12 years of age**

Age Group (years)	Dose Regimen	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-8h} (ng.h/mL)
≥ 12	200 mg t.i.d.	2698 [6] (22.9)	3.00 [6] (0.75–4.00)	16412 [6] (19.5)
< 12	200 mg t.i.d.	2075 [1] (NA)	4.00 [1] (NA)	11975 [1] (NA)
	200 mg b.i.d.	3289 [2] (9.03)	3.54 [2] (3.08–4.00)	18792 [2] (13.9)
	200 mg o.d. (a.m.) 100 mg o.d. (p.m.)	2223 [1] (NA)	4.00 [1] (NA)	15866 [1] (NA)

Data are presented as geometric mean (%CV) except for t_{max} which is presented as median (range).
[n] = Number of patients
AUC = area under the concentration-time curve; b.i.d. = *bis in die* (twice-daily); C_{max} = maximum blood/plasma concentration; CV = coefficient of variation; h = hours; NA = not applicable; o.d. = once daily; t.i.d. = *ter in die* (three times daily); t_{max} = time of maximum blood/plasma concentration.

4.1.1.4 Pharmacokinetics in type 3 Gaucher disease patients

In a substudy to OGT 918-006, the PK of miglustat were studied in seven patients of at least 12 years (four on 200 mg t.i.d. and three on 200 mg b.i.d.) and in six patients younger than 12 years who received a dose regimen adjusted for BSA [Table 9]. The PK were determined after 1 month of treatment. The mean plasma concentration-time profiles for the different dosing regimens are presented in Figure 5. The derived PK parameters are given in Table 6. Although the patient numbers in most subgroups were small, there were no apparent differences in the exposure to miglustat between patients of at least 12 years of age and those who were younger, or due to the different dosing regimens used. Interpatient variability in exposure to miglustat was low.

Figure 5 Study OGT 918-006: Mean plasma concentration-time profiles of miglustat following repeated oral administration to patients ≥ 12 years and < 12 years of age

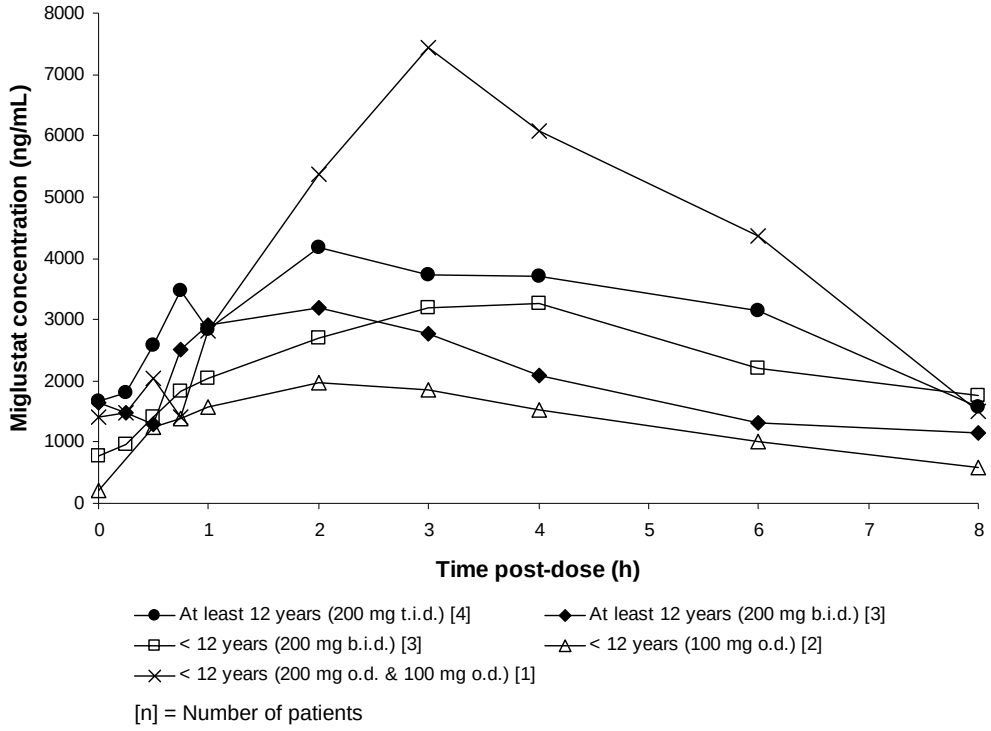


Table 6 Study OGT 918-006: Mean PK parameters of miglustat following repeated oral administration to patients ≥ 12 years and < 12 years of age

Group	Dose Regimen	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0–8h}$ (ng.h/mL)
≥ 12 years	200 mg t.i.d.	5248 [4] (11.9)	2.00 [4] (1.00–6.00)	25188 [4] (13.0)
	200 mg b.i.d.	3529 [3] (17.1)	2.00 [3] (1.00–2.00)	16072 [3] (16.8)
< 12 years	200 mg b.i.d.	3428 [3] (24.8)	4.00 [3] (3.00–6.00)	18928 [3] (26.1)
	200 mg o.d. (a.m.) 100 mg o.d. (p.m.)	7437 [1] (NA)	3.00 [1] (NA)	35326 [1] (NA)
	100 mg o.d.	2011 [2] (4.03)	2.50 [2] (2.00–3.00)	10405 [2] (3.36)

Data are presented as geometric mean (%CV) except for t_{max} which is presented as median (range).
[n] = Number of patients
AUC = area under the concentration-time curve; b.i.d. = *bis in die* (twice-daily); C_{max} = maximum blood/plasma concentration; CV = coefficient of variation; h = hours; NA = not applicable; o.d. = once daily; t.i.d. = *ter in die* (three times daily); t_{max} = time of maximum blood/plasma concentration.

4.1.1.5 Pharmacokinetics in adult patients with G_{M2} gangliosidosis

In a substudy to OGT 918-009, the PK of miglustat were studied in 6 adult patients who received 200 mg t.i.d and the PK parameters were determined after 1 month of treatment. The individual plasma concentration-time profiles are presented in Figure 6. The derived PK parameters are given in Table 7. Interpatient variability in exposure to miglustat was low.

Figure 6 **Study OGT 918-009: Individual plasma concentration-time profiles of miglustat following repeated three times daily oral administration of 200 mg miglustat for 1 month to six patients**

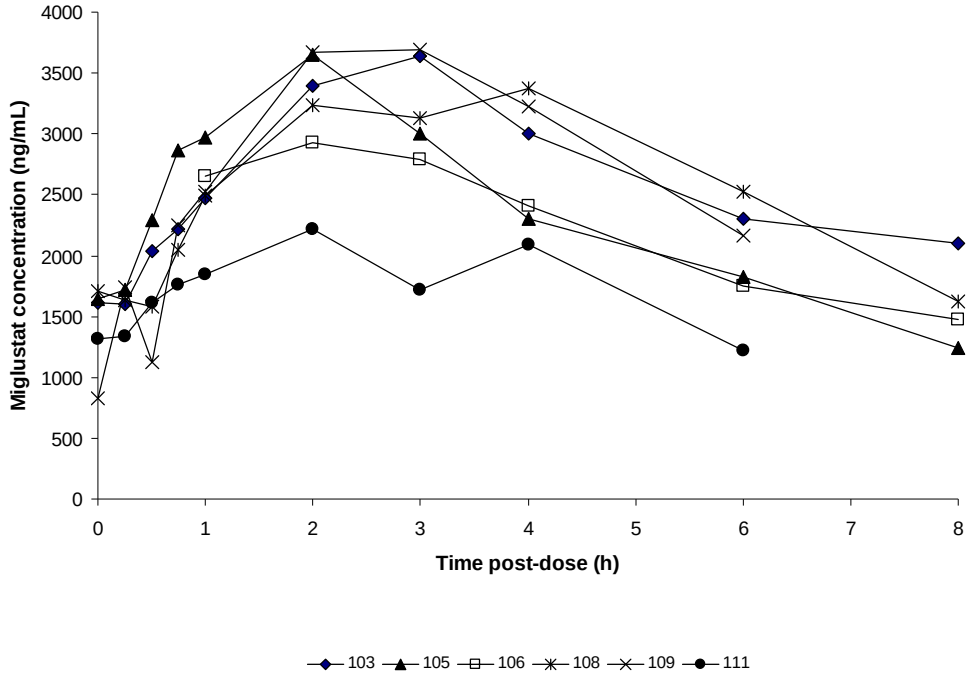


Table 7 **Study OGT 918-009: Mean PK parameters of miglustat following repeated three-times daily oral administration of 200 mg for 1 month to six patients**

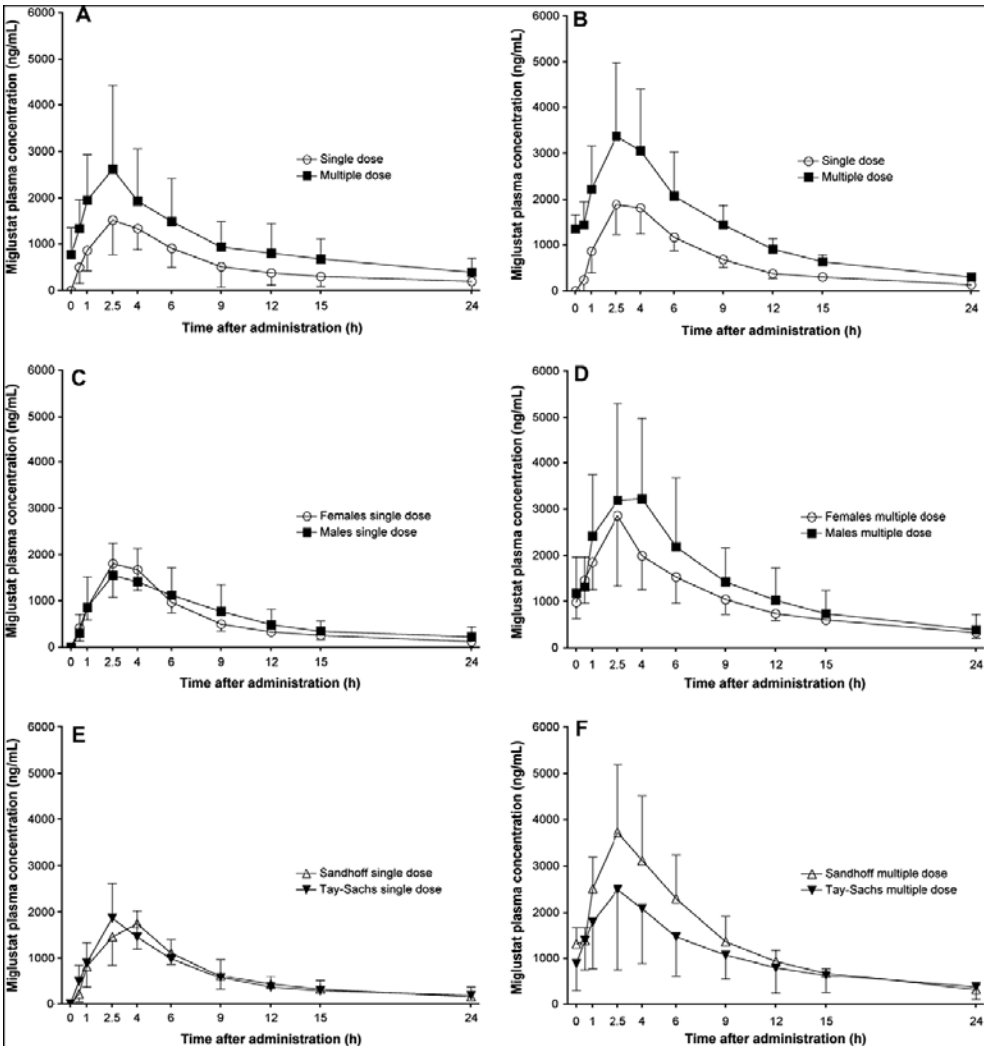
Sampling Time	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-8h} (ng.h/mL)
Month 1	3200 (20.1)	2.50 (2.00, 4.00)	18457 (17.5)

Data are presented as geometric mean (%CV) except for t_{max} which is presented as median (range).
AUC = area under the concentration-time curve; C_{max} = maximum blood/plasma concentration; CV = coefficient of variation; h = hours; t_{max} = time of maximum blood/plasma concentration.

4.1.1.6 Recently published PK data in pediatric patients with G_{M2} gangliosidosis

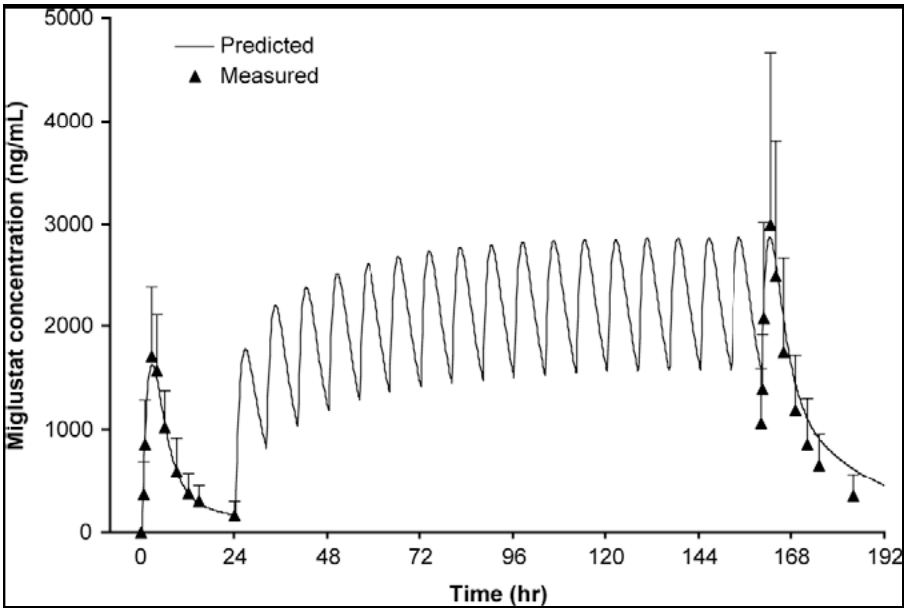
A recent publication [Maegawa 2009] reports on the PK of miglustat given as single and multiple doses to five pediatric patients (1.0–5.0 years) and five juvenile patients (8.7-20.1 years) with G_{M2} gangliosidosis. The population included patients of both genders and with different variants of G_{M2} gangliosidosis, i.e., Tay-Sachs disease and Sandhoff disease. The miglustat dosing regimen was 30–200 mg t.i.d. adjusted to BSA to correspond to an adult dose regimen of 200 mg t.i.d. [Table 9]. Patients underwent PK assessments on Day 1 and at Month 3 (on these days only one dose was administered). The mean plasma concentration-time profiles are presented in Figure 7. The derived PK parameters are given in Table 8. The PK parameters were time-independent and did not differ between pediatric and juvenile cohorts. As described previously [Section 4.1], the PK of miglustat can be described by a two-compartment model. On the basis of this model, the multiple-dose concentration-time profile (Month 3) could be reliably predicted from the single-dose data (Day 1). This is illustrated in Figure 8.

Figure 7 Mean concentration-time profiles of miglustat after single- and multiple-dose administration in pediatric/juvenile patients with Tay-Sachs disease and Sandhoff disease by age group, gender and disease variant



Pediatric (A, n = 5) and juvenile (B, n = 5) patients with G_{M2} gangliosidosis. The single- and multiple-dose analyses of the mean plasma concentrations are also depicted by sex (C and D, n = 5 for both sexes) and disease variants, Tay-Sachs disease (n = 6) or Sandhoff disease (n = 4) disease (E and F, respectively).

Figure 8 Simulation of the multiple-dose profile of miglustat using a two-compartment PK model with a lag time



Data extracted from both infantile (n = 5) and juvenile (n = 5) patient groups. The measured data (± standard deviation) are shown by the closed triangles.

Table 8 Descriptive statistics of PK parameters of miglustat in infantile and juvenile patients with G_{M2} gangliosidosis after single- and multiple-dose administration (n = 10)

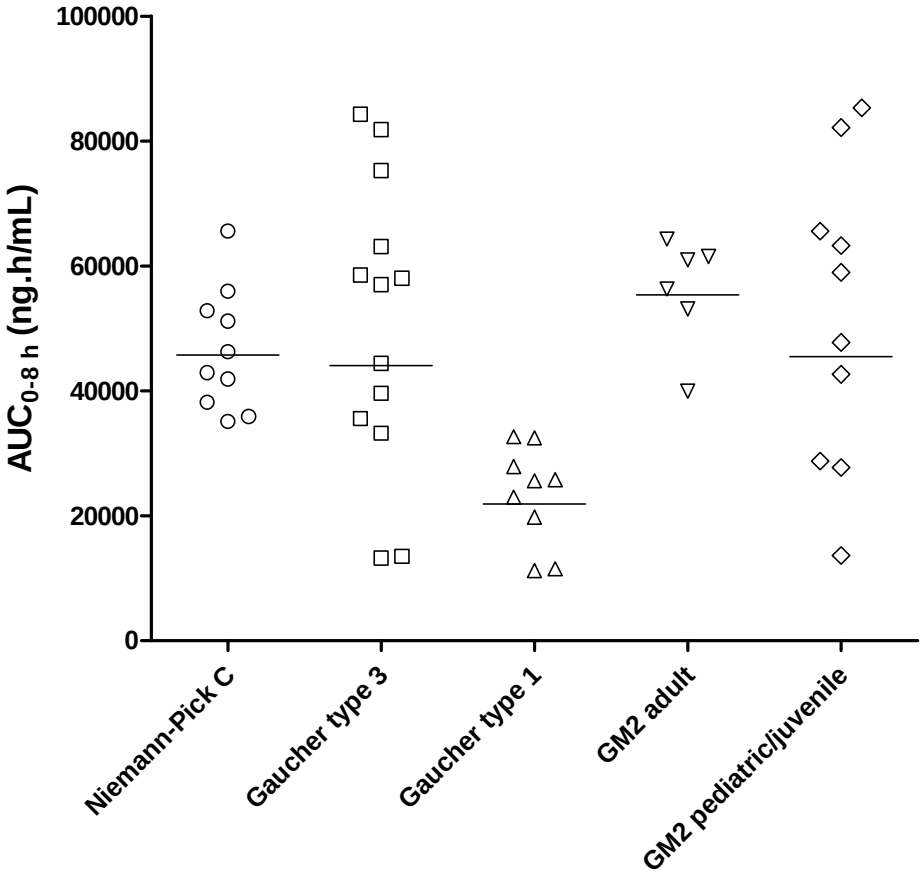
Parameter	Single dose (Day 1)	Multiple dose (Month 3)
C_{max} (ng/mL)	1822 (1436–2311)	2771 (1785–4302)
t_{max} (h)	2.5 (2.5–6.0)	2.5 (1.0–4.0)
AUCo–∞ (ng.h/mL)	15920 (11635–21783)	
AUC_{τ} (ng.h/mL)		15167 (10058–22869)
AUC_{τ}/AUCo–∞		0.95 (0.71–1.3)
Accumulation index		1.7 (1.2–2.5)
$t_{½}$ (h)	8.3 (7.0–9.8)	10.0 (7.3–13.9)

Data are presented as geometric means (95% confidence intervals), with exception of t_{max}, which is presented as median (range).
AUC = area under the concentration-time curve; C_{max} = maximum blood/plasma concentration; CV = coefficient of variation; h = hours; NA = not applicable; PK = pharmacokinetic; $t_{½}$ = terminal elimination half life; t_{max} = time of maximum blood/plasma concentration.

4.1.1.7 Comparison of pharmacokinetics across studies

Figure 9 provides a comparison of exposure to miglustat in the four studies described above, as well as in GD-1 patients. A historical comparison of studies should be conducted with caution in view of the small cohorts of patients included and the heterogeneity of included patients with respect to disease variant/intensity and age. AUCτ values in the four studies using a miglustat dose of 200 mg t.i.d. (adjusted to BSA in pediatric patients) were approximately two-fold greater than those observed in adult GD-1 patients administered miglustat 100 mg t.i.d., consistent with the dose-proportional PK of miglustat. The PK of miglustat appeared consistent across the different diseases studied, as well as between different age categories. In general, the interpatient variability in the exposure to miglustat was low with a CV of approximately 20%. As shown previously in GD-1 patients and also in the studies presented here, the median t_{max} was 2.5 h, the $t_{½}$ approximately 8 h, the ratio $AUC_{\tau}/AUC_{0-\infty}$ was close to 1, and only slight accumulation occurred upon multiple dosing.

Figure 9 Comparison of exposure to miglustat in GD-1, NP-C, GD-3 and G_{M2} gangliosidosis in both adult/juvenile and pediatric patients

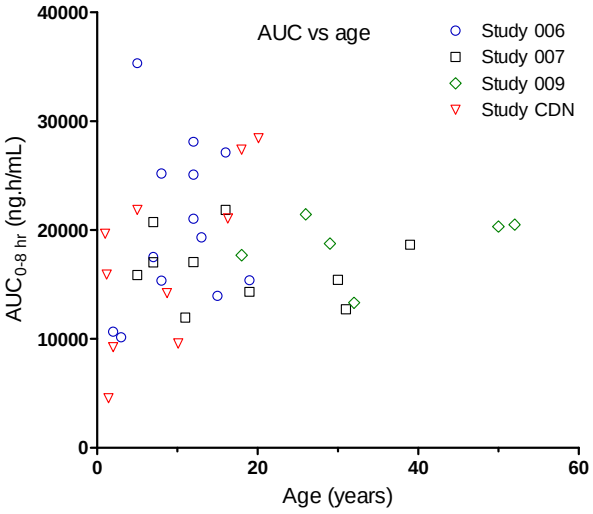


Data are shown as individual AUC_{τ} values (ng.h/mL). The geometric means as indicated by the horizontal lines were 16285, 19044, 7288, 18457, and 15166 ng.h/mL, in Niemann-Pick type C, GD-3, GD-1 adult, G_{M2} adult and G_{M2} pediatric patients, respectively.
Data are from studies OGT 918-007 (NP-C), OGT 918-006 (GD-3), OGT 918-009 (G_{M2} adults), Maegawa 2009 (G_{M2} pediatrics), OGT 918-001 and OGT 918-005 (GD-1).
Dose regimen was 200 mg t.i.d. (adjusted by BSA for pediatric patients) for all indications except GD-1, in which a 50-100 mg t.i.d. regimen was used.
AUC = area under the concentration-time curve; BSA = body surface area; t.i.d. = *ter in die* (three times daily).

4.1.1.8 Influence of demographic variables on the pharmacokinetics of miglustat

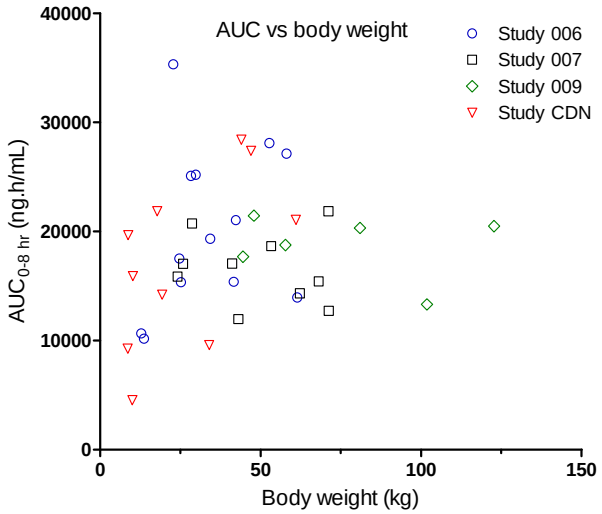
Figure 10, Figure 11 and Figure 12 present the exposure to miglustat, expressed as $AUC_{0\text{-}8h}$, as a function of age, body weight, and BSA from the four PK studies described above. No clear trends for an influence of any of these variables on the PK of miglustat could be discerned. This provides further support that the recommended dose reduction according to BSA in pediatric patients is justified from a PK viewpoint [Section 4.3].

Figure 10 Relationship between AUC_{0-8h} and age



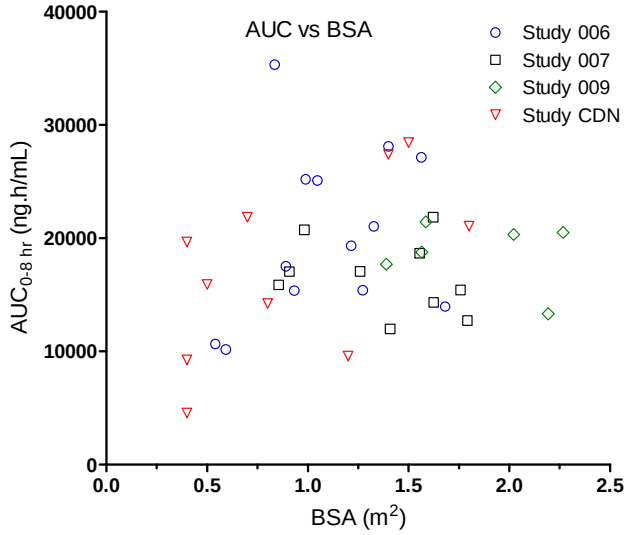
Studies OGT 918-006, OGT 918-007, and OGT 918-009 are represented by 006, 007, and 009, respectively. CDN refers to Maegawa 2009.
AUC = area under the concentration-time curve.

Figure 11 Relationship between AUC_{0-8h} and body weight



Studies OGT 918-006, OGT 918-007, and OGT 918-009 are represented by 006, 007, and 009, respectively. CDN refers to Maegawa 2009. AUC = area under the concentration-time curve.

Figure 12 Relationship between AUC_{0-8h} and BSA



Studies OGT 918-006, OGT 918-007, and OGT 918-009 are represented by 006, 007, and 009, respectively. CDN refers to Maegawa 2009. AUC = area under the concentration-time curve; BSA = body surface area.

4.1.2 Penetration of miglustat into the central nervous system

Since the site of action of miglustat in NP-C is the CNS [Section 3.1.2.2], concentrations of the drug in cerebrospinal fluid (CSF) were assessed in two of the studies described above (OGT 918-006 and OGT 918-009). CSF represents a compartment which is usually in rapid equilibrium with different brain structures. The frequency at which CSF samples can be collected is limited and, therefore, no complete CSF concentration-time profiles could be obtained.

4.1.2.1 CSF concentrations in type 3 Gaucher disease patients (study OGT 918-006)

Pre-dose CSF samples were taken by lumbar puncture from seven patients: from three patients of at least 12 years during Month 1, 6 or 12, and from four patients less than 12 years during Month 1, 3, 6 or 9 (each patient provided only one CSF sample). A plasma sample was taken at the same time point as the CSF sample. CSF concentrations of miglustat in patients of at least 12 years were 37–42% of those in plasma and in patients less than 12 years, were 31–67% of those in plasma.

4.1.2.2 CSF concentrations in adult patients with G_{M2} gangliosidosis (study OGT 918-009)

Pre-dose CSF samples were taken by lumbar puncture from two patients at Month 1. Plasma samples were taken at the corresponding time point. The CSF/plasma concentration ratios measured in the two patients were 29% and 46%.

4.2 Pharmacodynamics

No pharmacodynamic studies were performed in humans in the intended indication.

Established pharmacological effects of miglustat are reflected in the USPI for Zavesca [Appendix 3]. In addition to the target activity of inhibition of GlcCer synthase, miglustat also inhibits the activities of α-glucosidases I and II, non-lysosomal glucosylceramidase, sucrase, and isomaltase, and is a weak inhibitor of lactase. The inhibition of disaccharidases provides a reasonable explanation for the gastrointestinal adverse events that are particularly prevalent during the early phases of treatment with miglustat [Section 6.6.2].

4.3 Rationale for dosing regimen of miglustat in Niemann-Pick type C disease

Progressive neurodegeneration dominates the manifestations of NP-C [Section 3.1.3]. In order to counteract CNS manifestations of the disease, a therapeutically efficacious drug should penetrate the blood-brain barrier and reach effective concentrations in the CNS.

The dose in the approved indication, GD-1, is 100 mg t.i.d. Miglustat administered at 100 mg t.i.d. results in peak plasma concentrations in the range of 1–2 μg/mL and trough

concentrations of approximately 0.8 µg/mL. In this concentration range, miglustat was shown to be effective at both a biochemical and clinical level.

Miglustat penetrates the blood-brain barrier and attains CSF concentrations 41 ± 12% (mean ± SD) of those in plasma of patients with GD-3 and G_{M2} gangliosidosis under steady-state conditions. Therefore, as CSF is in rapid equilibrium with brain tissue, miglustat is expected to reach concentrations in relevant brain structures which are approximately half of those in plasma. To achieve concentrations in the CNS that have previously been shown effective in peripheral tissues in GD-1, the dosing regimen of miglustat 200 mg t.i.d was selected for clinical studies in NP-C and other neuronopathic LSD (GD-3 and G_{M2} gangliosidosis). For pediatric patients (< 12 years), the dose regimen was adjusted according to BSA [Table 9].

Table 9 Dosing regimen on the basis of BSA in clinical trials

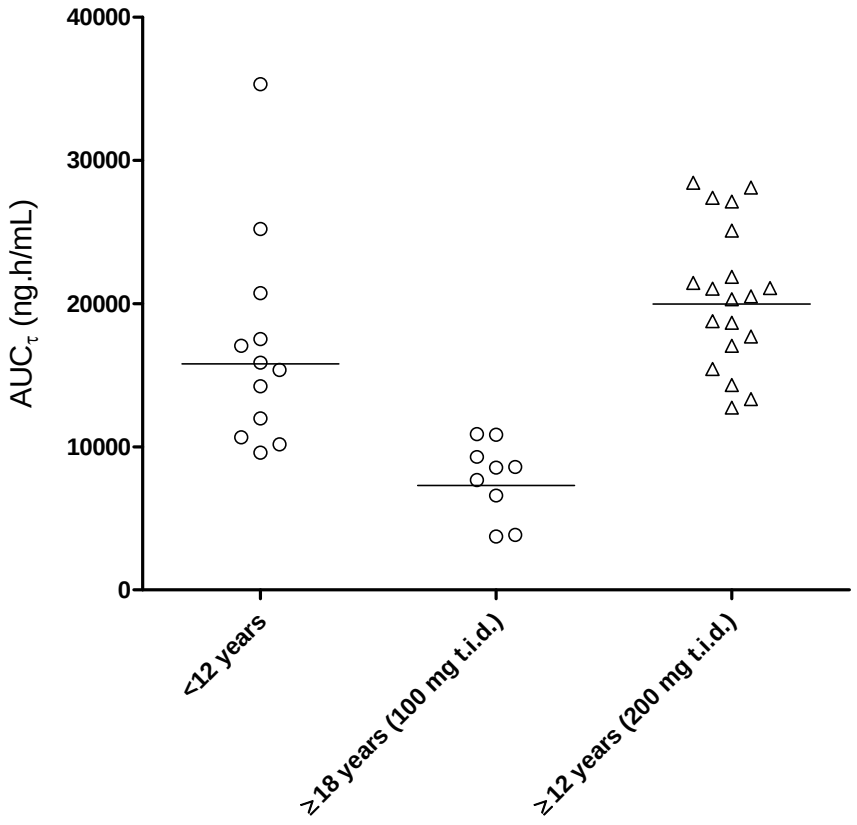
BSA (m^2)	Recommended dose regimen
> 1.25–1.8 (juvenile/adult)	200 mg t.i.d.
> 0.88–1.25	200 mg b.i.d.
> 0.73–0.88	200 mg a.m. and 100 mg p.m.
> 0.47–0.73	100 mg b.i.d.
≤ 0.47	100 mg o.d.

b.i.d. = *bis in die* (twice daily); BSA = body surface area; o.d. = once daily; t.i.d. = *ter in die* (three times daily).

In PK terms, the appropriateness of these BSA adjustments is supported by the data from studies OGT 918-007 (NP-C) and OGT 918-006 (GD-3). The results are described in Section 4.1.1 and show that these dose recommendations lead to similar exposures to miglustat across different studies, disease entities, and age categories.

Figure 13 presents a comparison of exposure to miglustat in subjects of at least 12 years and those younger than 12 years. In the latter group, the dose was adapted according to BSA. Irrespective of the age category and the dose adaptation, the exposure to miglustat in NP-C, GD-3, and G_{M2} gangliosidosis (based on 200 mg t.i.d.) is approximately double the exposure in GD-1 patients ≥ 12 years (100 mg t.i.d.).

Figure 13 Comparison of exposure to miglustat in GD-1, NP-C, GD-3, and G_{M2} gangliosidosis in patients ≥ 12 years and < 12 years of age



Data are shown as individual AUC_τ values (ng.h/mL). The geometric means as indicated by the horizontal lines were 15773 ng.h/mL in NP-C, G_{M2} gangliosidosis, and GD-3 patients < 12 years of age treated with a dosing regimen aimed at exposure similar to that on 200 mg t.i.d. but adapted to BSA, 7288 ng.h/mL in GD-1 patients ≥ 12 years (100 mg t.i.d.), and 19973 ng.h/mL in NP-C, G_{M2} gangliosidosis, and GD-3 patients ≥ 12 years.
Data are from studies OGT 918-007 (NP-C), OGT 918-006 (GD-3), OGT 918-009 (G_{M2} adults), [Maegawa 2009] (G_{M2} pediatrics), OGT 918-001, and OGT 918-005 (GD-1).
AUC = area under the concentration-time curve; BSA = body surface area; t.i.d. = *ter in die* (three times daily).

5 EFFICACY OF MIGLUSTAT IN NIEMANN-PICK TYPE C DISEASE

The datasets supporting the efficacy of miglustat in Niemann-Pick type C disease are listed in Table 10 to Table 13.

Data are presented from a prospective clinical trial (study OGT 918-007) and from a retrospective analysis of NP-C patients treated with miglustat as Zavesca in clinical practice and not included in clinical trials (Stage I survey). The natural history of neurological disease progression among NP-C patients who were not treated with

miglustat was investigated in a further retrospective analysis (Stage II survey). All datasets include pediatric, juvenile and adult patients. Additional efficacy data were also obtained from individual patient case reports and recent publications.

Study OGT 918-007 included:

- A prospective, parallel-group, controlled, open-label efficacy 1-year study conducted in 29 adult/juvenile patients with NP-C (Main study) and two optional extension periods.
- A prospective, open-label, 1-year study involving 12 NP-C patients less than 12 years of age (Pediatric sub-study) and two optional extension periods.

An additional, *post hoc*, individual patient responder analysis was performed for the 29 patients from the Main study (n = 19) and the Pediatric Sub-study (n = 10) of OGT 918-007 who had received at least 12 months of miglustat treatment.

Given the heterogeneous presentation and course of NP-C disease, a confirmatory study on a traditional clinical endpoint would have to be a long-term placebo-controlled study.

The data from study OGT 918-007 have been in the public domain since 2005 [Patterson 2005, Patterson 2007] and the overall data on miglustat in NP-C have now resulted in consensus statements on the diagnosis and management of NP-C [Wraith 2009]. In this situation, and with Zavesca on the market, undertaking any additional prospective, controlled clinical studies would not be feasible in a very rare disorder such as NP-C, for which no other disease course-modifying intervention is available or known to be under investigation. Therefore retrospective studies were conducted.

The Stage I survey was a retrospective study of neurological disease progression (neurological outcome) prior to and during treatment with miglustat. It was conducted in 66 patients with NP-C treated with miglustat as Zavesca in clinical practice and not included in a clinical trial. These patients comprised a sizable proportion (more than 60%) of patients estimated to have been undergoing treatment for NP-C with commercially available miglustat at the time of data collection. The patients served as their own controls, providing data before and during treatment with miglustat.

The Stage II survey was a retrospective natural history study that included data on neurological disease progression at multiple time points for 57 patients prior to any miglustat exposure.

Overall, 104 individual patients were included in the surveys, with data for 19 patients included in both. Analysis of the data for the subset of 19 patients who were included in both surveys, allowed a further, detailed comparison of disease progression during the natural history of the disease and during treatment with miglustat. Since the results were similar to the observations of Survey I, they have not been separately displayed.

Data are also provided from 15 case reports in the form of individual reports, publications or attestations of treatment and outcome provided by treating physicians for patients with NP-C [Bembi 2008, Chien 2007, Hartung 2008, Patterson 2008, Rolfs 2008].

In addition to the above case reports, recently published data that were not included in the documentation submitted to the FDA are discussed for 23 patients with NP-C treated with miglustat in a non-Actelion sponsored study [Fecarotta 2009]. Additional data are also provided for three patients with NP-C, for whom quantitative evaluation of miglustat treatment was performed using brain spectroscopy [Galanaud 2008].

Table 10 Summary of clinical trial OGT 918-007 datasets providing efficacy data in NP-C patients

Study OGT 918-007	Study design	Treatment arms and dose	Treatment duration	Number of patients
Main study (adult/juvenile patients)	Comparative, open-label, randomized controlled study	Miglustat 200 mg t.i.d. No Treatment	12 months	29 patients: 20 miglustat 9 No-Treatment
Extended study (adult/juvenile patients)	Open-label, uncontrolled	Miglustat 200 mg t.i.d.	12 months (up to 24 months in total)	25 miglustat patients (17 of the 20 treated with miglustat; 8 of the 9 No-Treatment patients)
Continued treatment extension period (adult/juvenile patients)	Open-label, uncontrolled	Miglustat 200 mg t.i.d.	From Month 24 to study close: 31 December 2007 Up to 68 months	16 miglustat patients
Pediatric sub-study	Open-label, uncontrolled	Miglustat 200 mg t.i.d. equivalent according to BSA	12 months	12 miglustat patients
Pediatric extended study	Open-label, uncontrolled	Miglustat 200 mg t.i.d. adapted according to BSA	12 months (up to 24 months in total)	10 miglustat patients
Pediatric continued treatment extension period	Open-label, uncontrolled	Miglustat 200 mg t.i.d. equivalent according to BSA	From Month 24 to study close: 31 December 2007 (efficacy evaluated up to Month 24)	10 miglustat patients
OGT 918-007 studies Individual patient responder analysis	All patients from the Main and the Pediatric sub-study who were exposed to miglustat for at least 12 months	Miglustat 200 mg t.i.d. or dose equivalent according to BSA	From 13–68 months	29 miglustat patients (19 from Main study, 10 from Pediatric sub-study)

BSA = body surface area; t.i.d. = *ter in die* (three times daily).

Table 11 Summary of efficacy datasets based on retrospective studies in NP-C patients

Report	Study design	Treatment arms and dose	Duration of observation	Number of patients
Survey of neurological outcomes (Stage I survey)	Retrospective	Standard care followed by miglustat	Mean ± SD of 3.1 ± 3.4 years (max 15.2 years) pre-miglustat Mean ± SD of 1.5 ± 1.1 years (max 4.5 years) on miglustat treatment. Overall mean duration of observation of 4.6 years (max 15.4 years).	66 miglustat-treated patients
Survey of natural history of neurological disease (Stage II survey)	Retrospective	Standard care	Mean ± SD of 5.5 ± 4.8 years (max 29.9 years)	57 patients not treated with miglustat
Subset of patients who participated in both surveys	Retrospective	Standard care followed by miglustat	Mean 4.9 years (max 14.6 years) pre-miglustat Mean 1.2 years (max 4.5 years) on miglustat-treatment) Overall mean duration of observation of 6.2 years (max 15.4 years).	19 miglustat-treated patients

BSA = body surface area; SD = standard deviation.

Table 12 Summary of efficacy datasets based on case reports of NP-C patients

Report	Study design	Treatment arms and dose	Treatment duration	Number of patients
Individual patient case studies [Bembi 2008, Chien 2007, Hartung 2008, Patterson 2008, Rolfs 2008]	Observational	Miglustat (plus one non-treated patient control)	Up to 6 years	15 patients

Table 13 Recently published data from studies in NP-C patients

Report	Study design	Treatment arms and dose	Treatment duration	Number of patients
Multicenter study in adult/juvenile and pediatric patients treated with miglustat [Fecarotta 2009]	Open-label, uncontrolled	Miglustat	6-42 months	23 miglustat-treated patients
24-month follow-up of adult patients treated with miglustat [Galanaud 2008]	Open-label, uncontrolled	Miglustat	24 months	3 miglustat-treated patients

5.1 Methodology

5.1.1 Prospective clinical trial (OGT 918-007)

Study OGT 918-007 represented the first controlled study of pharmacological treatment for neurological disease progression in NP-C. Its aim was to investigate the efficacy of miglustat in affecting the underlying disease process in a population of adult/juvenile and pediatric patients.

The study design and selection of variables to evaluate efficacy was based on extensive discussions with experts in the field of GSL storage disorders, including careful assessment of variables considered relevant to the pharmacological rationale for miglustat and to the neurological disease progression of NP-C. In view of those discussions and the natural history of NP-C (as shown also in the Stage II survey), both reduction of the rate of disease progression or disease stabilization were considered appropriate treatment goals. Variables were chosen to allow evaluation of effects of miglustat on several levels of CNS function, using quantitative assessment of changes that could be related to progressive organ damage and clinical benefit.

Patient selection criteria were based on confirmed disease status (abnormal cholesterol esterification and abnormal filipin staining with additional confirmation of NP-C disease by genotyping), safety factors and the ability of the patients to ingest the study medication in the form of a capsule.

The study was conducted at the two largest US and European (UK) centers for NP-C. For adult patients, a randomized, parallel group, controlled, open-label study design was selected. The control arm selected was No-Treatment, i.e., standard care, which was provided to all patients. In view of the unblinding effect anticipated from the gastrointestinal side effects of miglustat, an open-label design was considered appropriate. This decision also took into consideration the use of objective parameters for the assessment of treatment effect and the constraints related to administration of oral placebo medication to a patient population with frequent swallowing problems.

The Pediatric sub-study was of an open-label, non-comparative design.

Due to the absence of previous data from clinical studies, the very limited natural history data and the small size of the available patient population, it was not possible to power the study for any specific variable. The selection of variables was based on clinical considerations and the selection of sample size was based on feasibility. All available data were evaluated, so as not to discount any therapeutic effect.

5.1.1.1 Design of OGT 918-007 Main (adult/juvenile) controlled study and uncontrolled extension phases

This was a prospective, randomized, controlled, 12-month efficacy and safety study conducted in adult/juvenile patients (≥ 12 years of age). Patients were randomized in a 2:1 ratio to receive either miglustat 200 mg t.i.d. or No-Treatment.

Patients who completed the 12-month randomized period were given the option of participating in a 12-month extension phase. All patients who entered this 12-month extension phase received miglustat 200 mg t.i.d.

Patients who completed the 12-month extension phase were given the option of participating in a continued treatment extension phase. Patients who entered this phase continued to receive miglustat until study closure at a dose of 200 mg t.i.d. or their previously established dose, if this was different due to tolerability reasons.

5.1.1.1.1 Study variables

The primary variable was the change from baseline to Month 12 for horizontal saccadic eye movement (HSEM) velocity, defined as HSEM-α. A summary of the efficacy variables defined in the study protocol and the methods used to assess them is shown in Table 14. More details are provided in the respective results sections.

Table 14 Efficacy variables assessed in study OGT 918-007, adult/juvenile and pediatric patients

Primary variable		**Instrument/evaluation method**
SEMV	HSEM-α	Infrared system (Center 1), scleral search coil (Center 2)
Other variables		**Instrument/evaluation method**
Swallowing assessment		4-food item ease of swallowing semiquantitative asessment
Ambulation function		Standard Ambulation index (Hauser)
Neuropsychological testing		MMSE*, Purdue peg board*
SEMV	HSEM-β	Infrared system (Center 1), scleral search coil (Center 2)
	VSEM	Infrared system (Center 1), scleral search coil (Center 2)
Quality of life		SF-36 and CHQ-PF50 questionnaires
Liver volume*		MRI or CT
Spleen volume*		MRI or CT
Cerebellar volume**		MRI
Neurological assessments	Clinical neurological examination	Cranial nerves and fundoscopy, visual acuity and auditory function, ocular movements, muscle tone, bulk and strength, balance and coordination sensory testing.
	Tremor assessment	Archimedes Spiral score*
Biochemical assessments	Biochemical marker of NP-C activity	Chitotriosidase analysis*

* Performed only in adult/juvenile patients
** Performed only in adult/juvenile patients at one center
CT = computerized tomography; HSEM = horizontal saccadic eye movement; MMSE = Folstein mini-mental state examination; MRI = magnetic resonance imaging; SEMV = saccadic eye movement velocity; VSEM = vertical saccadic eye movement.

5.1.1.1.2 Statistical methods

All patients who received at least one dose of study drug and had at least one post-baseline efficacy observation were included in the Efficacy set, which was the primary analysis set. Analyses were performed on observed data, with last post-baseline value carried forward in the case of a missing end of study value. Where there was no post-baseline value, no imputation for a missing end-of-study value was performed in the planned analyses. No correction for multiplicity was performed. Efficacy was evaluated up to Month 24. In the continued treatment extension period of the study, only limited efficacy data were collected.

Saccadic eye movement velocity (SEMV) data comprised saccadic peak duration (ms) versus saccade amplitude (deg), with a linear regression fitted to these data points. The slope (α, ms/deg) and intercept (β, ms) of the regression line were estimated using ordinary least squares [Inchingolo 1985] by the central assessor (treatments were blinded) and were forwarded to the study statistician to perform the statistical analyses that incorporated other study data.

For the analysis of the primary variable (HSEM-α), data were summarized descriptively at baseline, Month 12, Month 24 and last value, and similarly for change from baseline. For patients who discontinued prematurely during a study period, the last value for the patient in that study period was used in the analysis. The two treatment groups (miglustat and No-Treatment) were compared at Month 12 using an analysis of covariance (ANCOVA) model with terms for (i) baseline, age and treatment group and (ii) baseline, center and treatment group. An estimate of the adjusted treatment difference was presented, together with the corresponding 95% confidence interval (CI). Descriptive summaries by age group and center, as well as ANCOVA including age as a covariate, were prospectively planned. A supplementary *post hoc* ANCOVA analysis using center instead of age was performed and the treatment-by-center interaction was also examined.

Results of blinded central assessment of the SEMV plots were reported in the Main study report but no statistical analysis of the response data (deterioration, no change or improvement) was performed. A *post hoc* analysis of the response data (deterioration or no deterioration) is reported in this Briefing Book, in terms of risk and relative risk, together with the two-sided 95% CIs (exact binomial). Fisher's exact test was performed to compare the two treatment groups.

Standard Ambulation Index (SAI) and MMSE were summarized descriptively by treatment group and visit, and data were analyzed using an ANCOVA model with terms for baseline, center and treatment group.

Analysis of swallowing data in the SAP included descriptive summary by visit, as well as cross-tabulation of shift from baseline, for each type of food substance. A non-parametric stratified Wilcoxon test was used to compare the two treatment groups with regard to a patient's ability to swallow. A *post hoc* analysis of swallowing response (deterioration or no deterioration) across all four substances was performed. For this analysis, a conservative approach was adopted, where deterioration in swallowing of one or more substances by one score point constituted overall deterioration in swallowing at that visit. The method of analysis is similar to that mentioned above for HSEM-α response using Fisher's exact test to compare the two treatment groups.

Safety data were presented for all patients who received at least one dose of miglustat during the study. Treatment exposure time was used in the summary of treatment-emergent AEs.

5.1.1.2 OGT 918-007 Pediatric sub-study and extension phases

The non-comparative Pediatric sub-study examined the efficacy and safety of miglustat in children above 4 years and below 12 years of age. All children received treatment with miglustat. The starting dose was adjusted according to BSA for equivalence to the 200 mg t.i.d. adult dose, using the following formula:

BSA of patient (m^2)/1.8 × adult dose (200 mg t.i.d).

The actual dose administered varied from 100 mg o.d. to 200 mg t.i.d.

Pediatric patients could remain on miglustat therapy after completion of the initial 12-month study in the optional 12-month extension phase and a further continued treatment extension phase.

The efficacy of miglustat was evaluated similarly as for the adult/juvenile patients but with a reduced number of variables [Table 14]. For example, cognitive assessment with MMSE was not performed in pediatric patients, as it is not validated in this population. Efficacy was evaluated up to Month 24.

5.1.1.3 OGT 918-007 Individual patient efficacy analysis (responder analysis)

The analysis set for this *post hoc* analysis included 19 adult/juvenile patients enrolled in the Main study and 10 pediatric patients from the Pediatric sub-study who had received at least 12 months treatment with miglustat in study OGT 918-007. Baseline was defined as the timepoint at which miglustat therapy was initiated.

For the Main study, baseline corresponded to the value recorded at screening for patients randomized to miglustat. For patients initially randomized to No-Treatment and who subsequently received treatment with miglustat during the extension phases, baseline was the value recorded at Month 12 of the comparative, randomized, controlled phase. For the Pediatric sub-study, baseline corresponded to the value recorded at screening for all patients.

The efficacy variables considered in this responder analysis were swallowing function, SAI and MMSE (adult/juvenile patients only).

5.1.2 Retrospective studies

5.1.2.1 Stage I survey of neurological outcomes

The 38 world-wide sites/physicians identified by the coordinating investigator as prescribing miglustat (Zavesca) for NP-C disease were invited to participate. Physicians were asked to complete a data collection form for each NP-C patient at their site who was currently receiving, or had previously been treated with commercially-available miglustat and who had not been enrolled in a clinical trial. A web-based data collection form [Appendix 4] was designed to collect available data, with an emphasis on neurological

progression/outcomes. As in the Stage II survey, the period for which data were collected was generally 1992–2008.

The dose regimen of miglustat in this retrospective study had been selected by the participating physicians at their own discretion. However dosing was overall comparable between the Stage I survey and study OGT 918-007, both in adult/juvenile and pediatric patients.

The aim was to collect data for as many NP-C patients as possible in order to corroborate the results generated in study OGT 918-007. As NP-C is so rare, a relatively large sample size could only be achieved through this retrospective collection of data from physicians' medical records.

5.1.2.1.1 Study variables

The investigators assessed neurological disease progression by using a published NP-C disability scale [Section 3.1.3.1, Iturriaga 2006] that was slightly modified in order to consistently assign a score ranging from 0 (the best grade) to 1 (the worst grade) to each of the four clinically-relevant domains that were assessed at each time point of evaluation (i.e., ambulation, manipulation (dysmetria/dystonia), language function/articulation and swallowing). This was designed to give equal weight to each of the four domains that comprise the composite score [Table 15]. A composite score was calculated for each patient, as the mean of the four individual domain scores, provided at least three out of the four individual scores were available. Domain and composite scores were calculated at three time points, i.e., at the time of diagnosis, at the start of miglustat treatment and at last clinical contact or discontinuation of miglustat.

Table 15 NP-C Disability Scale

	Original scale[a]	Modified scale (score)
Ambulation		
Normal	1	0
Autonomous ataxic gait	2	0.25
Outdoor assisted ambulation	3	0.50
Indoor assisted ambulation	4	0.75
Wheelchair-bound	5	1
Manipulation		
Normal	1	0
Slight dysmetria/dystonia (allows autonomous manipulation)	2	0.33
Mild dysmetria/dystonia (requires help for several tasks; able to feed himself)	3	0.67
Severe dysmetria/dystonia (requires assistance in all activities)	4	1
Language function/articulation		
Normal	1	0
Mild dysarthria (understandable)	2	0.25
Severe dysarthria (only comprehensible to some members of the family)	3	0.50
Non-verbal communication	4	0.75
Absence of communication	5	1
Swallowing		
Normal	1	0
Occasional dysphagia	2	0.33
Daily dysphagia	3	0.67
Nasogastric tube or gastric button feeding	4	1

[a] Source: Iturriaga 2006.

5.1.2.1.2 Statistical methods

The composite disability score (the mean of the four individual scores) was calculated if at least three out of four individual scores were available at each time point. No imputation was performed. In order to provide an estimate of the rate of disease progression, the change in each of the four domain scores and in the composite disability score were determined as absolute change in each score per year of observation. A treatment effect of miglustat on disease progression rate was defined as the difference in annual progression rate during and prior to miglustat treatment. Statistical inference was performed using a paired t-test. All statistical analyses were exploratory.

In addition, the effects of age at diagnosis on progression rate of the disease before and after treatment with miglustat were evaluated. For the assessment of overall disease progression (composite disability score), patients were stratified into three groups: those diagnosed during early childhood (< 6 years), late childhood (6–11 years), and juvenile/adulthood (≥ 12 years).

Additional analyses for treatment response included the subgroup of patients with documented progressive neurological disease manifestations before starting miglustat, defined as those with increasing disability score in at least one functional domain or incident/worsened seizure activity between diagnosis and treatment initiation.

5.1.2.2 Stage II survey of natural history

This NP-C natural history study was conducted to investigate the course of neurological disease progression in untreated NP-C disease and to provide a comparison with the disease progression data before and during treatment with miglustat in the Stage I survey. Of the 38 centers worldwide approached for the Stage I survey, 14 that had long-term clinical experience in the management of NP-C patients were identified and invited by the coordinating investigator to enter data. Seven sites/physicians from six countries entered demographic and clinical data from multiple (at least three) time points of observation for all of their NP-C patients, using a secure website, as in the Stage I survey. As in the Stage I survey, the period for which data were collected was generally 1992–2008.

The disability rating scale used was identical to that in the Stage I survey [Table 15] and scores were calculated in an identical manner. Analysis of the annual rate of progression was performed using the same methods as in the Stage I survey to assess domain and composite score changes over time since diagnosis for all patients and according to age group at diagnosis.

5.1.2.3 Patients included in both surveys

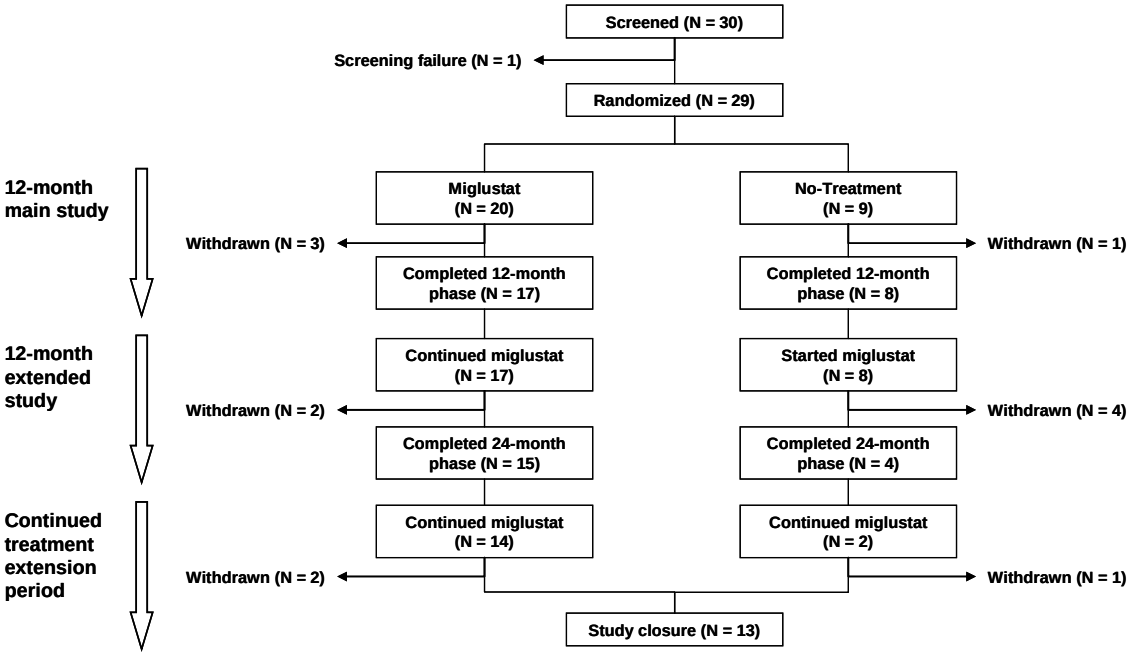
Nineteen patients provided data at multiple time points on pre-treatment disease progression in the Stage II survey and also provided information on disease progression during miglustat therapy in the Stage I survey.

5.2 Patient disposition

5.2.1 Main study OGT 918-007 (adult/juvenile patients)

The disposition of the patients who enrolled in the OGT 918-007 Main study is presented in Figure 14. Reasons for study withdrawal are presented in Table 16.

Figure 14 Study OGT 918-007: Disposition of adult/juvenile patients by study phase



Reasons for withdrawals are presented in Table 16.

Table 16 Study OGT 918-007: Reason for withdrawal of adult/juvenile patients by study phase

Study phase	Patient No.	Reason for withdrawal	Duration on study (months)
12-month comparative			
Miglustat	007-102	NP-C Disease progression	5.9
	007-103	NP-C Disease progression	11.0
	007-109	Diarrhea, Crohn's disease	6.6
No-Treatment	007-213	Patient's family requested withdrawal to return to alternative therapy	3.1
12-month extended study			
Continued miglustat treatment	007-104	Axonal neuropathy	12.7
	007-212	Patient requested withdrawal due to difficulty in scheduling travel (needed to travel with two companions)	23.5
No-Treatment switched to miglustat after 12 months	007-101	Hemorrhagic diarrhea	22.1 (10.6 on miglustat)
	007-108	Patient requested withdrawal as he considered that the risks of side-effects were not worth taking (patient experienced AEs of abdominal pain, diarrhea and flatulence that were considered to be treatment-related).	13.5 (1.1 on miglustat)
	007-113	Patient requested withdrawal as he was worried about side-effects (patient experienced AEs of abdominal pain, diarrhea, nausea, flatulence and aggrevated tremor that were considered to be treatment-related).	16.4 (4.7 on miglustat)
	007-208	Tremor	20.3 (8.7 on miglustat)
Continued treatment extension			
Miglustat	007-210	Non-compliance (patient refused to take drug)	30.7 (18.7 on miglustat)
	007-105	Lost to follow-up	59.2 (47.5 on miglustat)
No-Treatment switched to miglustat after 12 months	007-112	Patient requested withdrawal	38.7 (27.0 on miglustat)

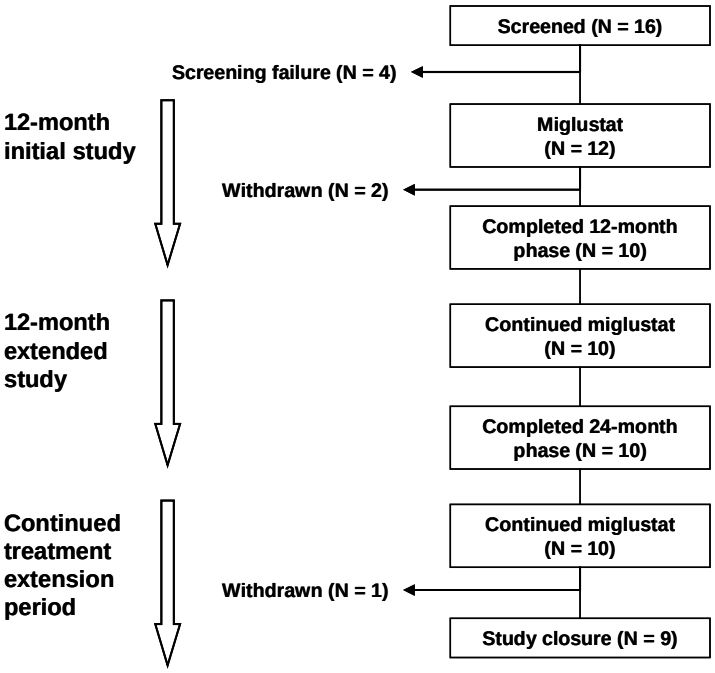
AE = adverse event.

5.2.2 Pediatric sub-study OGT 918-007

The disposition of the pediatric patients who enrolled in study OGT 918-007 is presented in Figure 15. Reasons for study withdrawal are presented in Table 17.

One patient (007-227) did not have at least one post-baseline efficacy assessment and was excluded from the efficacy set.

Figure 15 Study OGT 918-007: Disposition of pediatric patients by study phase



Reasons for withdrawals are presented in Table 17.

Table 17 Study OGT 918-007: Reason for withdrawal of pediatric patients by study phase

Study phase	Patient No.	Reason for withdrawal	Duration on study (months)
12-month initial study	007-221	Depression, memory loss, lethargy	5.7
	007-227	Patient requested withdrawal (refused to swallow miglustat)	2.3*
Continued treatment extension period	007-122	Diarrhea, painful defecation (subsequent diagnosis of Crohn's disease)	44.0

*Time on study and duration of exposure were calculated from withdrawal visit date since date of last administration was not recorded on the case report form.

5.3 Patient demographics and disease characteristics

5.3.1 Baseline demographic and disease characteristics in study OGT 918-007

Summaries of baseline demographic and disease characteristics are shown in Table 18. In the adult/juvenile and pediatric populations of study OGT 918-007, all patients had at least one manifestation of NP-C disease at baseline, and all but two patients (in the No-Treatment group of the Main study) had vertical supranuclear gaze palsy (VSGP). In the adult/juvenile population, a greater proportion of patients reported the various manifestations of NP-C disease (in particular neurological symptoms) in the miglustat group than in the No-Treatment group. As expected from the natural history of the disease, a greater proportion of pediatric patients had splenomegaly, hepatomegaly, and cataplexy, and a smaller proportion had swallowing difficulties compared to the adult/juvenile patients.

Table 18 Summary of patient demographics and disease characteristics at baseline in study OGT 918-007

	OGT 918-007 Main study Adult/juvenile		OGT 918-007 Pediatric Sub-study
	No-Treatment	Miglustat	Miglustat
Number of patients	**N = 9**	**N = 20**	**N = 12**
Gender			
Male n (%)	5 (56%)	9 (45%)	5 (42%)
Female n (%)	4 (44%)	11 (55%)	7 (58%)
Age (years) Mean (SD)	22.9 ± 7.5	25.4 ± 9.8	7.2 ± 2.5
Range	13–32	12–42	4–11
Age group (years)			
4–11 n (%)	0	0	12 (100%)
12–17 n (%)	4 (44%)	5 (25%)	0
≥ 18 n (%)	5 (56%)	15 (75%)	0
NP-C disease manifestations			
Number of patients with at least one manifestation of NP-C disease	9 (100%)	20 (100%)	12 (100%)
Vertical supranuclear gaze palsy	7 (78%)	20 (100%)	12 (100%)
Ataxia	5 (56%)	20 (100%)	10 (83%)
Cognitive impairment	7 (78%)	18 (90%)	8 (67%)
Speech impairment	4 (44%)	18 (90%)	7 (58%)
Difficulty in positioning of limbs	4 (44%)	14 (70%)	5 (42%)
Swallowing difficulties	6 (67%)	12 (60%)	4 (33%)
Pyramidal tract dysfunction	3 (33%)	10 (50%)	5 (42%)
Splenomegaly	5 (56%)	7 (35%)	10 (83%)
Hepatomegaly	4 (44%)	6 (30%)	7 (58%)
Seizures	1 (11%)	1 (5%)	0
Cataplexy	0	1 (5%)	4 (33%)

NT = No-Treatment; SD = standard deviation.

5.3.2 Demographic and disease characteristics in Stage I and Stage II surveys

A summary of patient characteristics and duration of disease is shown for the retrospective surveys in Table 19. In the Stage I retrospective survey, patients had been under observation for a mean of 3.1 ± 3.4 years between diagnosis of NP-C disease and start of treatment with miglustat and had then been on treatment with miglustat for a mean of 1.5 ± 1.1 years, giving a total time of observation of 4.6 ± 3.5 years. In the Stage II survey of natural history, patients had been under observation for a mean of 5.5 ± 4.8 years between diagnosis and last reported visit.

Table 19 Patient characteristics and duration of disease – retrospective studies

Number of patients		Stage I retrospective survey of neurological outcomes N = 66*	Stage II retrospective survey of natural history N = 57*	Patients who participated in both surveys N = 19
Gender	Male	31	25	11
	Female	35	32	8
Age (years) at diagnosis	Mean (SD)	9.7 (7.6)	10.7 (9.6)	13.6 (5.9)
	Range	< 1–32	< 1–41	3–26
Age (years) at treatment start	Mean (SD)	12.8 (9.5)	–	18.7 (8.0)
	Range	0.6–43	–	7–37
Age group (years) at diagnosis				
< 12	n (%)	44 (67%)	35 (61%)	7 (37%)
≥ 12	n (%)	22 (33%)	22 (39%)	12 (63%)
Age group (years) at treatment start				
< 12	n (%)	36 (55%)	–	4 (21%)
≥ 12	n (%)	30 (45%)	–	15 (79%)
Time interval between diagnosis and treatment start (years)	Mean (SD)	3.1 (3.4)	–	4.9 (4.1)
Range		0–15.2	–	0.2–14.6
Time interval between diagnosis and last visit (years)	Mean (SD)	4.6 (3.5)	5.5 (4.8)	6.2 (3.8)
Range		0.2–15.4	0.2–29.9	1.0–15.4
Duration of treatment (years) Mean (SD)		1.5 (1.1)	–	1.2 (0.8)
Range		(0.05–4.5)		0.2–4.5
Ambulation at diagnosis				
Evaluable patients (N)		64	57	19
Patients with normal function (n, %)		22 (34%)	22 (39%)	6 (32%)
Mean (SD) score at diagnosis		0.18 (0.16)	0.19 (0.18)	0.17 (0.12)
Manipulation at diagnosis				
Evaluable patients (N)		64	57	19
Patients with normal function (n, %)		24 (38%)	28 (49%)	7 (37%)
Mean (SD) score at diagnosis		0.26 (0.23)	0.20 (0.22)	0.23 (0.19)
Language at diagnosis				
Evaluable patients (N)		64	57	19
Patients with normal function (n, %)		24 (38%)	33 (58%)	6 (32%)
Mean (SD) score at diagnosis		0.17 (0.16)	0.14 (0.22)	0.21 (0.22)
Swallowing at diagnosis				
Evaluable patients (N)		62	56	19
Patients with normal function (n, %)		42 (68%)	45 (80%)	12 (63%)
Mean (SD) score at diagnosis		0.13 (0.21)	0.10 (0.22)	0.14 (0.20)
Composite score at diagnosis				
Evaluable patients		64	57	19
Mean (SD) score at diagnosis		0.18 (0.14)	0.16 (0.16)	0.19 (0.12)

*19 patients participated in both surveys
SD = standard deviation.

5.4 Results

5.4.1 Saccadic eye movement velocity – study OGT 918-007

Saccadic eye movements (SEM) are rapid eye movements, which are usually conjugate (i.e., both eyes move together in the same direction) and under voluntary control. The main function of SEM is to focus visual images onto the fovea, where there is greatest visual acuity. Abnormal SEM, resulting in blurred vision, are a typical early-onset manifestation in NP-C disease, and are attributed to brainstem dysfunction. Typically, vertical SEM (VSEM) are affected earlier than horizontal SEM (HSEM) during the course of NP-C [Patterson 1993]. As a result, by the time of diagnosis of NP-C, VSEM are usually already severely affected, and vertical saccadic gaze palsy (VSGP) is frequently present, leaving little room for assessment of change of this variable [Table 18].

Relentless deterioration of SEM velocity (SEMV), progressing to gaze palsy is a hallmark of brainstem involvement in NP-C disease. Gaze palsy is associated with highly relevant visual and educational handicap and spontaneous improvement in SEMV is unknown in the natural course of the disorder. The degree of impairment in SEMV appears closely related to the severity of other illness variables as assessed by MMSE and the NP-C disability scale [Abel 2009, Iturriaga 2006]. Given this relationship to the underlying disease process, SEMV should be considered an appropriate pharmacodynamic variable for the assessment of treatment effect in NP-C. In addition, it was considered that SEMV would be adequately sensitive to distinguish between miglustat and No-Treatment in a small population, whereas the other clinically relevant variables might require a larger number of patients to detect a treatment effect.

It is acknowledged that no published data are available to support a direct relationship between a specific change in SEMV and a change in disease burden perceived by the patient. Therefore, a positive effect on SEMV alone cannot be considered as a full demonstration of clinical benefit against the neurological manifestations of NP-C.

SEMV was only evaluated in study OGT 918-007, due to the practical limitations of retrospectively collecting such data. Focus was on HSEM velocity, since the vast majority of patients had established VSGP at screening. Horizontal SEMV was assessed at screening and Month 12, Month 24 and last value by established video-based or scleral search coil techniques and associated software. The local assessors were blinded to the patients' treatment status. Data for both study sites were sent to a central assessor for blinded final evaluation.

5.4.1.1 Horizontal Saccade α

The primary variable was the mean change from baseline to Month 12 for the larger horizontal saccadic eye movements, described as HSEM-α. HSEM-α is estimated from the slope of the linear regression line of peak duration (amplitude/peak velocity, ms)

versus amplitude (degrees) of HSEM. HSEM-α was selected as the primary variable because it is an objective measure and is characteristically impaired in NP-C [Solomon 2005]. Normal values for HSEM-α have been estimated as 1.66 ± 0.36 (SD) ms/deg (N = 10) [Abel 2009].

The HSEM variable β, which reflects smaller horizontal saccades and is subject to greater variability than α, was evaluated as a secondary variable [Section 5.4.6].

Results

In the adult/juvenile population of OGT 918-007, a mean decrease in HSEM-α (improvement) was observed at Month 12 in the miglustat group, whereas an increase (deterioration) was seen in the No-Treatment group. The difference between the treatment groups was not statistically significant in the planned analysis (p = 0.327) [Table 20]. Nevertheless, the p-value for the change from baseline in the miglustat group was 0.047 in the framework of the main analysis using ANCOVA with terms for baseline HSEM-α, age and treatment group. The age effect was not statistically significant. Since different SEM measurement techniques were used at the two centers (infrared limbus tracker used at Center 1 and the more noise-free scleral search coil technique used at Center 2; both are current, standard methods). An additional *post hoc* analysis including center as a covariate instead of age was performed. The observed treatment difference was greater in this analysis, (p = 0.091) [Table 20].

Table 20 HSEM-α (ms/deg) in adult/juvenile patients: Descriptive statistics and analysis of covariance on change from baseline to last value in the 12-month main controlled study, Efficacy set

HSEM-α (ms/deg)	Statistic	No Treatment (N = 9)	Miglustat (N = 20)
Descriptive and inferential statistics	Baseline		
	n	8[a]	18[b]
	Mean ± SD	2.483 ± 1.425	3.021 ± 2.166
	95% CI	(1.292, 3.675)	(1.943, 4.098)
	Min, max	0.79, 4.81	0.87, 9.46
	Last Value		
	n	8	18
	Mean ± SD	2.558 ± 1.734	2.590 ± 1.585
	95% CI	(1.108, 4.007)	(1.802, 3.378)
	Min, max	0.79, 5.30	1.07, 6.82
	Change from baseline		
	n	8	18
	Mean ± SD	0.074 ± 0.823	–0.431 ± 0.938
	95% CI	(–0.614, 0.762)	(–0.897, 0.036)
	Min, max	–0.79, 1.95	–2.64, 0.91
Main analysis: ANCOVA with terms for baseline, age and treatment group	Change from baseline		
	Mean (adjusted) ± SE	–0.050 ± 0.269	–0.376 ± 0.179
	95% CI	(–0.608, 0.509)	(–0.746, –0.005)
	p-value	0.855	0.047
	Treatment difference (estimated)		
	Mean ± SE	–0.326 ± 0.325	
	95% CI	(–1.000, 0.348)	
	p-value (primary analysis)	0.327	
Supplementary analysis: ANCOVA with terms for baseline, center and treatment group*	Change from baseline (adjusted)		
	Mean (adjusted) ± SE	0.055 ± 0.240	–0.463 ± 0.161
	95% CI	(–0.443, 0.553)	(–0.796, –0.129)
	p-value	0.821	0.009
	Treatment difference (estimated)		
	Mean ± SE	–0.518 ± 0.293	
	95% CI	(–1.125, 0.089)	
	p-value	0.091	

Baseline is the data recorded at Screening Visit 1 and Last Value is the last post-baseline value up to Month 12. Only patients with a baseline value are summarized. Increase from baseline indicates worsening.
[a] One patient in the No-Treatment group had no post-baseline assessment and was excluded from the analysis.
[b] Two patients in the miglustat group had no post-baseline assessment and were excluded.
*Model including treatment group-by-center interaction term gave the corresponding p-value of 0.389.
CI = confidence interval; SD = standard deviation; SE = standard error.

It is well known that benzodiazepines impair SEM [Kroboth 1998]. An additional *post hoc* analysis that excluded patients on confounding benzodiazepine medication supported a

difference between treatment groups at Month 12 [Table 21]. Overall, six patients (four of whom were evaluable for SEM measurement) in the miglustat group and one patient in the No-Treatment group received benzodiazepines during the study and were excluded from this analysis. A statistically significant p-value of 0.028 was obtained for the treatment difference between miglustat and No-Treatment.

Table 21 HSEM-α (ms/deg) in adult/juvenile patients excluding those receiving benzodiazepines: Descriptive statistics and analysis of covariance on change from baseline to last value in the 12-month main controlled study, Efficacy set

HSEM-α (ms/deg)	Statistic	No Treatment (N = 8)	Miglustat (N = 14)
Descriptive summary	Baseline		
	n	7[a]	14
	Mean ± SD	2.429 ± 1.530	3.114 ± 2.423
	95% CI	(1.014, 3.844)	(1.715, 4.513)
	Min, max	0.79, 4.81	0.87, 9.46
	Last Value		
	n	7	14
	Mean ± SD	2.626 ± 1.861	2.678 ± 1.663
	95% CI	(0.905, 4.348)	(1.717, 3.638)
	Min, max	0.79, 5.30	1.12, 6.82
	Change from baseline		
	n	7	14
	Mean ± SD	0.197 ± 0.806	–0.436 ± 0.976
	95% CI	(–0.548, 0.942)	(–1.000, 0.127)
	Min, max	–0.35, 1.95	–2.64, 0.66
Supplementary ANCOVA analysis with terms for baseline, centre and treatment group	Change from baseline		
	Mean (adjusted) ± SE	0.234± 0.237	–0.485 ± 0.167
	95% CI	–0.267, 0.734	–0.837, –0.133
	p-value	0.339	0.01
	Treatment difference (estimated)		
	Mean ± SE	–0.718 ± 0.299	
	95% CI	(–1.349, –0.088)	
	p-value	0.028	

Baseline is the data recorded at Screening Visit 1 and Last Value is the last post-baseline value up to Month 12. Only patients with a baseline value are summarized. Increase from baseline indicates worsening.
Note: Three patients in the miglustat group were not assessable for SEMV and so were also excluded in addition to the patients who received benzodiazepines.
[a] Patient 007-213 did not have at least one post-baseline HSEM-α value and was excluded from the analysis.
CI = confidence interval; SD = standard deviation; SE = standard error.

The change from baseline to Month 12 in the Pediatric sub-study was consistent with the data for the adult/juvenile population of the Main study. Pediatric patients [Table 22] showed mean decreases (improvement) in HSEM-α to Month 12/last value that were of

similar magnitude to those observed in the adult/juvenile patients [Table 20]. The ratio of mean change to standard error (t-test statistic) and the associated 95% CIs indicated that the within-patient comparison was statistically significant at Month 12 in the pediatric patients, i.e., showed improvement (p = 0.005).

Table 22 HSEM-α (ms/deg) in pediatric patients: Analysis change from baseline to last value in the 12-month sub-study, Efficacy set

Pediatric 12-month Substudy	Statistic	Miglustat (N = 11)
Descriptive and inferential analysis	Baseline (last screening value)	
	n	10[a]
	Mean ± SD	2.201 ± 1.217
	95% CI	(1.331, 3.072)
	Min, max	0.94, 4.68
	n	10
	Mean ± SD	1.736 ± 1.025
	95% CI	(1.003, 2.470)
	Min, max	0.54, 3.98
	Change from baseline	
	n	10
	Mean ± SD	–0.465 ± 0.401
	95% CI	(–0.752, –0.178)
	Min, max	–1.37, 0.04
	p-value	0.005

Baseline is the data recorded at screening; Last value is the last post-baseline value.
[a] One patient did not have a Month-12 assessment and was excluded from the analysis.
SD = standard deviation, CI = confidence interval.

A pre-planned responder assessment of SEMV was performed by an external expert, who was blinded to treatment allocation. This provided an evaluation of the main sequence scatter plots and regression slopes from the 26 NP-C patients (18 in the miglustat-treated group and 8 in the No-treatment group) in the Main study with evaluable data at both baseline and Month 12 or at last visit. Among the 16 miglustat-treated patients with interpretable results, 14 (88%) were stable or improved (seven improved, seven no change), two deteriorated. Among the six patients in the No-Treatment group with interpretable results, three (50%) were stable or improved (one improved, two no change), and three deteriorated [Table 23]. Consistent results were found in the Pediatric sub-study, with a degree of qualitative improvement observed in 9/10 patients, and no change seen in the remaining patient.

Table 23 SEMV blinded central assessment: Responder analysis of adult/juvenile patients in the 12-month main controlled study

SEMV Response (Adult/Juvenile Main study)	No Treatment (N = 9)	Miglustat (N = 20)
n	6[a]	16[b]
Deterioration	3 (50.0%)	2 (12.5%)
95% CI	(11.81, 88.19)	(1.55, 38.35)
Relative risk	0.25	
95% CI	0.05, 1.15	
n	6[a]	16[b]
No Deterioration*	3 (50.0%)	14 (87.5%)
95% CI	(11.81, 88.19)	(61.65, 98.45)
Relative risk	1.75	
95% CI	0.77, 3.98	
Treatment Group Comparison p-value (Fisher's Exact Test)	p = 0.101	

[a] Patient 007-213 was not assessed, as there were no-post baseline data. Patients 007-112 and -208 had ambiguous results and were excluded.
[b] Patients 007-102 and -103 were not assessed, as there were no post-baseline plots. Patient 007-202 and -212 had ambiguous plots and were excluded.
* No deterioration comprises unchanged or improved response according to the Central Assessor's evaluation of the SEMV plots.
CI = confidence interval; SEMV = saccadic eye movement velocity.

In the second year of miglustat treatment, there was some resumption of deterioration of mean HSEM-α in both adult/juvenile and pediatric patients [Table 24]. Nonetheless, 24 months of miglustat treatment appears to be compatible with essentially maintained horizontal SEMV as assessed by HSEM-α.

Table 24 HSEM-α (ms/deg) in adult/juvenile and pediatric patients: Descriptive statistics on change from baseline to last value in the 24-month open-label extension study, Efficacy set

HSEM-α (ms/deg)	Statistic	Adult/juvenile patients (N = 17)	Pediatric patients (N = 10)
Descriptive summary	Baseline (last screening value)		
	n	15[a]	9[b]
	Mean ± SD	3.040 ± 2.353	2.181 ± 1.289
	95% CI	(1.738, 4.343)	(1.190, 3.171)
	Min, max	0.87, 9.46	0.94, 4.68
	Last Value (during the extension period)		
	n	15[a]	9[b]
	Mean ± SD	3.267 ± 3.687	2.106 ± 1.213
	95% CI	(1.225, 5.309)	(1.173, 3.038)
	Min, max	0.95, 15.66	1.25, 5.07
	Change from baseline		
	n	15[a]	9[b]
	Mean ± SD	0.226 ± 1.756	–0.075 ± 1.235
	95% CI	(–0.746, 1.199)	(–1.024, 0.874)
	Min, max	–1.46, 6.20	–2.52, 1.60

Baseline is the last value up to and including final day of Screening (Visit 2) at study start and Last Value is the last post-baseline value recorded in the 12-month extension period (excluding the Month-12 visit) up to and including the final day of the Month-24 visit. Only patients with a baseline value are summarized. Increase from baseline indicates worsening.

[a] Two adult/juvenile patients did not have SEMV data at Month 24 or withdrawal and were excluded from the analysis.

[b] One pediatric patient did not have SEMV data at Month 24 or withdrawal and was excluded from the analysis.

CI = confidence interval; SD = standard deviation; SEMV = saccadic eye movement velocity.

Discussion

Overall, the findings in the controlled phase of study OGT 918-007 indicated that, during an observation period of 12 months, there was detectable deterioration in horizontal SEMV in untreated patients, consistent with the anticipated progression of the disease. In miglustat-treated patients, the pattern of horizontal SEMV progression, measured as HSEM-α, was different, with a mean observed initial improvement versus baseline and a generally stable situation over 24 months of treatment.

After 12 months of miglustat treatment there was a reduction (improvement) from baseline in HSEM-α for both adult/juvenile (0.431°ms/deg, 14% improvement versus baseline) and pediatric patients (0.465 ms/deg, 21% improvement versus baseline), while a mean increase of 0.074 ms/deg (3% deterioration versus baseline) was seen in the adult/juvenile No-Treatment group. Taking in consideration a normal HSEM-α ± SD of 1.66 ± 0.36 ms/deg [Abel 2009] the degree of improvement may be considered meaningful and supportive of activity of miglustat in the functional improvement of a dysfunctional but

potentially salvageable neuronal cell pool. The consistent response between adult/juvenile and pediatric populations as well as the responder assessment performed by an external expert blinded to treatment allocation supports this conclusion.

5.4.2 Swallowing function – study OGT 918-007, Stage I and II surveys

Disturbed co-ordination of swallowing results from brainstem involvement and represents a disabling and distressing component of the symptomatology of NP-C. With time, it becomes a constant finding, especially in patients with childhood and juvenile onset of symptomatology. Progressive deterioration of swallowing may lead to malnutrition and pulmonary complications secondary to food aspiration, an important, direct cause of death in NP-C [Zafeiriou 2003, Chien 2007, Patterson 2001].

The clinical relevance of an effect of therapy on this type of dysfunction is evident. Thus, swallowing function was assessed both in study OGT 918-007 and in the retrospective studies.

All patients in study OGT 918-007 underwent a standardized swallowing assessment by the same trained observer at screening and at subsequent visits. In this assessment, patients were asked to try to swallow the following substances:

- 5 mL of water from a small cup
- One teaspoon of puree
- One teaspoon of soft lumps
- One-third of a cookie/biscuit

During the administration of these food substances, the patients were asked to position themselves in their optimum swallowing position. The assessor began with the food substance with the easiest consistency as chosen by the patient and the patient's ease of swallowing for each substance was evaluated using the following grading: swallowed easily, mild swallowing problems, moderate swallowing problems, severe swallowing problems, could not swallow.

In both the Stage I and Stage II retrospective surveys, swallowing dysfunction was assessed within the NP-C disability scale [Iturriaga 2006, Table 15]. Swallowing function was graded as 'normal', 'occasional dysphagia', 'daily dysphagia', or 'nasogastric tube or gastric button feeding'.

Results

Study OGT 918-007: In study OGT 918-007, 18/29 (62%) of adult/juvenile patients had clinical findings of swallowing difficulties at baseline, while in the pediatric population included in the study, few patients (4/12) had, as yet, developed this complication.

Among patients with both baseline and at least one post-baseline swallowing assessment for up to 12 months, stable swallowing function for all four food substances was seen in 16/20 patients (80%) on miglustat, with four patients (20%) showing deterioration for at least one substance. For the No-Treatment group, the corresponding numbers were 4/8 (50%) for both stable swallowing function and deterioration [Table 25].

After 24 months of miglustat treatment, stable swallowing function compared with baseline was seen for 11 (73%) of the 15 patients with data.

At the end-of-study visit, 10 of the 14 patients with available data (71%) showed stable swallowing function, after 30–42 months of treatment with miglustat.

Table 25 Swallowing function in adult/juvenile patients: Responder analysis in the 12-month main controlled study, Efficacy set

Swallowing function (Adult/Juvenile Main study)	No Treatment (N = 9)	Miglustat (N = 20)
n	8[a]	20
Deterioration*	4 (50.0%)	4 (20%)
95% CI	(15.7, 84.3%)	(5.7, 43.7%)
Relative risk	0.4	
95% CI	(0.13, 1.22)	
n	8[a]	20
No Deterioration**	4 (50.0%)	16 (80%)
95% CI	(15.7, 84.3%)	(56.3, 94.3%)
Relative risk	1.6	
95% CI	(0.77, 3.31)	
Treatment Group Comparison p-value (Fisher's Exact Test)	p = 0.17	

[a] Patient 007-213 had no-post baseline value for swallowing assessments.
* Deterioration for at least one substance was defined as overall deterioration.
** No Deterioration was defined as no change or improvement for all four substances.
CI = confidence interval.

Pediatric patients were generally able to swallow all substances easily at baseline. Among patients with both baseline and at least one post-baseline swallowing assessment for up to 12 months, stable swallowing function for all four food substances was seen in 8/11 patients (73%), with three patients (27%) showing deterioration for at least one substance [Table 26].

After 24 months of miglustat treatment, stable swallowing function was seen for 9/10 pediatric patients (90%) with available data. No patient experienced severe swallowing problems over the 24-month assessment period

Table 26 Swallowing function in pediatric patients: Responder analysis in the 12-month study, Efficacy set

Swallowing function (Pediatrics)	Miglustat (N = 11)
n	11
Deterioration*	3 (27.3%)
95% CI	(6.0, 61.0%)
n	11
No Deterioration**	8 (72.7%)
95% CI	(39.0, 94.0%)

* Deterioration for at least one substance was defined as overall deterioration.
** No deterioration was defined as no change or improvement for all four substances.
CI = confidence interval.

Stage I and II surveys: The natural course of deterioration of swallowing function in patients with NP-C was assessed in the Stage II survey [Table 27] over a mean observation time of 5.5 years. At the time of diagnosis of NP-C, abnormal swallowing function was described for 18% of patients. This increased to 77% during the period of observation. Overall, 39/56 evaluable patients (70%) showed progressive deterioration of swallowing and no patient showed spontaneous improvement. Deterioration was continuous, occurring at an average rate of 0.10 score units/year in the modified NP-C disability scale score [Table 15].

Table 27 Frequency of patients with either 'improved', 'stable' or 'progressed' swallowing function – Stage II natural history survey

Stage II retrospective survey	N = 57 n (%)
Evaluable patients	56
Improved	0 (0)
Stable	17 (30.4)
Progressed	39 (69.6)
Progression rate – score units/year (95% CI)	0.10 (0.07, 0.13)

CI = confidence interval.

In the pre-treatment period of the Stage I survey, the average rate of swallowing deterioration was similar (0.08 score units/year) to the Stage II survey results, with no patient showing improvement. During treatment with miglustat for a mean of 1.5 years, swallowing function was at least stable in 51 patients (81%). Improvement was recorded in some patients. Only 12 patients (19%) had progressive deterioration [Table 28].

Progression of the swallowing score before and during miglustat treatment is illustrated in Figure 16. The annual rate of change on miglustat in the modified NP-C disability scale was –0.06 score units/year, indicating at least stable disease. The difference in progression

rate between the miglustat treatment and pre treatment phases (treatment effect) was –0.14 (95% CI –0.25 –0.04) score units/year, indicating a statistically significant, beneficial impact of miglustat on swallowing dysfunction. This effect was further accentuated in the population with documented progressive neurological disease (in any domain) before treatment with miglustat [Figure 16].

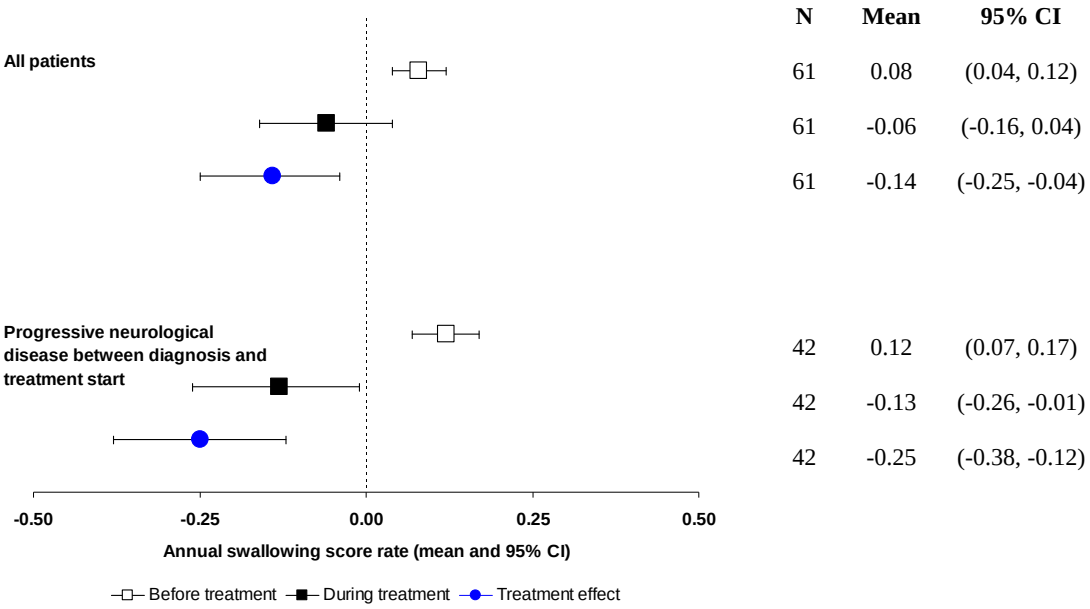
These findings of disease stabilization when patients were treated with miglustat corroborate the observations from study OGT 918-007, where 73% and 71% of patients showed stable swallowing function after 24 months and 30–42 months (end of study) of miglustat therapy, respectively, and contrast markedly with the relentless deterioration of swallowing function shown in the retrospective natural history survey, where 70% showed progressive deterioration during the period of observation.

Table 28 Frequency of patients with either 'improved', 'stable' or 'progressed' swallowing function on miglustat treatment – Stage I retrospective survey

Stage I retrospective survey	**N = 66 n (%)**
Evaluable patients	63
Improved	12 (19.0)
Stable	39 (61.9)
Progressed	12 (19.0)
Progression rate – score units/year (95% CI) (n = 61)	
Prior to start of miglustat treatment	0.08 (0.04, 0.12)
After start of miglustat treatment	–0.06 (–0.16, 0.04)

CI = confidence interval.

Figure 16 Comparison of the annual progression rate of the swallowing score prior to and during miglustat treatment – Stage I survey



Discussion

The findings for swallowing function from both Stage I and Stage II retrospective surveys indicated a high incidence of ongoing, continuous deterioration and an absence of spontaneous improvement in the observation period between diagnosis and start of miglustat treatment (last observation in the natural history survey). These observations are consistent with clinical experience and with published data [Patterson 2001], and reveal the expected pattern of continuous progression of swallowing impairment over the natural course of NP-C.

Treatment with miglustat in study OGT 918-007 and the Stage I survey resulted in at least stabilization of swallowing function in the majority of both juvenile/adult and pediatric patients. Improvement was described in some patients, a finding not observed during the natural course of the disease. The observed treatment effect (difference in progression rate between miglustat treatment and pre-treatment phases) was statistically significant.

These findings provide strong support for miglustat efficacy in a distressing, potentially life-threatening complication of the disease. The consistency of the findings between the prospective study OGT 918-007 and the Stage I and II surveys argues against bias being an important confounder to the interpretation of the results from the retrospective studies.

5.4.3 General motor disability / ambulation impairment – study OGT 918-007, Stage I and II surveys

Progressive motor disability is a cardinal manifestation of NP-C, with the patient eventually becoming wheel-chair bound or bed-ridden. Considering the obvious clinical relevance of a treatment effect on this type of dysfunction, motor disability/ambulation was assessed both in study OGT 918-007 and in the retrospective studies.

In study OGT 918-007, general motor disability was evaluated through the Hauser Standard Ambulation Index (SAI) [Table 29], which assesses mobility by evaluating the time and degree of assistance required to walk 25 feet. Scores range from 0 (fully active) to 9 (restricted to a wheelchair). The index has been validated in other progressive, neurodegenerative disorders as a measure of ambulatory ability, and is also considered applicable to the assessment of overall physical performance in NP-C disease. The deterioration of overall neuro-motor function, with progressive loss of independent mobility, is an integral and clinically relevant feature of NP-C.

Table 29 Hauser Standard Ambulation Index

0	Asymptomatic; fully active.
1	Walks normally but reports fatigue which interferes with athletic or other demanding activities.
2	Abnormal gait or episodic imbalance; gait disorder is noticeable to family and friends. Able to walk 25 feet in 10 seconds or less.
3	Walks independently; able to walk 25 feet in 20 seconds or less.
4	Requires unilateral support (cane, single crutch) to walk; uses support more than 80% of the time. Walks 25 feet in 20 seconds or less.
5	Requires bilateral support (canes, crutches, walker) and walks 25 feet in greater than 20 seconds.
6	Requires bilateral support and walks 25 feet in greater than 20 seconds. May use wheelchair on occasion.
7	Walking limited to several steps with bilateral support; unable to walk 25 feet. May use wheelchair for most activities.
8	Restricted to wheelchair; able to transfer independently.
9	Restricted to wheelchair; unable to transfer independently.

In the Stage I and Stage II retrospective surveys, ambulation was assessed within the NP-C disability scale [Table 15]. Ambulation function was assessed as ‘normal’, ‘autonomous ataxic gait’, ‘outdoor assisted ambulation’, ‘indoor assisted ambulation’, or ‘wheelchair-bound’.

Results

Study OGT 918-007: Among the 41 adult/juvenile and pediatric patients enrolled in study OGT 918-007, only nine were fully active at baseline (index = 0) and the Hauser SAI was abnormal (score > 2) for 29 patients (71%).

In the adult/juvenile patients in study OGT 918-007 (Main study), baseline ambulatory score was, on average, higher (i.e., indicating more severe disability) in patients randomized to miglustat than in patients randomized to No-Treatment. The observed mean change from baseline during the controlled phase of the study was smaller in the miglustat group indicating less deterioration than in the No-treatment group [Table 30]. In a supplemental analysis (ANCOVA with terms for baseline, center and treatment group), the differences between the groups in the change from baseline to Month 12 showed a trend in favor of the miglustat group ($p = 0.052$).

At the responder level, 13/20 patients (65%) in the miglustat group had no change in index value from baseline, one patient improved (5%) and 6/20 patients (30%) worsened. Of the six patients who worsened, five worsened by one grade. In comparison, in the No-Treatment group 6/9 patients (67%) had no change and 3/9 patients worsened (33%). Of the three patients who worsened, two patients worsened by two grades.

Table 30 Standard Ambulation Index in adult/juvenile patients: Descriptive statistics and analysis of covariance on change from baseline to last value in the 12-month main controlled study, Efficacy set

	Statistic	No-Treatment (N = 9)	Miglustat (N = 20)
Descriptive summary	Baseline		
	n	9	20
	Mean ± SD	0.9 ± 1.1	2.4 ± 1.7
	95% CI	(0.1, 1.7)	(1.6, 3.2)
	Min, max	0, 2	1, 8
	Last Value		
	n	9	20
	Mean ± SD	1.6 ± 1.7	2.6 ± 1.9
	95% CI	(0.2, 2.9)	(1.6, 3.5)
	Min, max	0, 4	0, 9
	Change from baseline		
	n	9	20
	Mean ± SD	0.7 ± 0.9	0.2 ± 0.7
	95% CI	(0.0, 1.3)	(–0.2, 0.5)
	Min, max	0, 2	–2, 1
ANCOVA with terms for baseline, center and treatment group*	Change from baseline		
	Mean (adjusted) ± SE	0.802 ± 0.283	0.087 ± 0.181
	95% CI	(0.220, 1.385)	(–0.287, 0.461)
	p-value	0.009	0.636
	Treatment difference (estimated)		
	Mean ± SE	–0.715 ± 0.351	
	95% CI	(–1.438, 0.007)	
	p-value	0.052	

Baseline is the last value up to and including final day of Screening Visit 2 and Last Value is the last post-baseline value up to Month 12. Only patients with a baseline value are summarized. A lower score indicates better ambulation (Score 0-9).
*Model including treatment group-by-center interaction term gave the corresponding p-value of 0.093.
CI = confidence interval; SD = standard deviation; SE = standard error.

For the Pediatric sub-study, the small increases in ambulation index scores over time were similar to those seen in the miglustat treatment arm in the adult/juvenile patients in the Main study at 12 months [Table 31].

Table 31 Standard Ambulation Index in pediatric patients: Analysis change from baseline to last value in the 12-month substudy, Efficacy set

Pediatric 12-Month Substudy	Statistic	Miglustat (N = 11)
Descriptive and inferential analysis	Baseline (last screening value)	
	n	11
	Mean ± SD	2.1 ± 2.0
	95% CI	(0.8, 3.4)
	Min, max	0, 7
	Last Value	
	n	11
	Mean ± SD	2.5 ± 2.6
	95% CI	(0.7, 4.2)
	Min, max	0, 9
	Change from baseline	
	n	11
	Mean ± SD	0.4 ± 0.7
	95% CI	(–0.1, 0.8)
	Min, max	0, 2
	p-value	0.104

Data are only presented for patients with a valid baseline and post-baseline assessment.
Scores range from 0 (fully active) to 9 (restricted to wheelchair). A lower score indicates better ambulation.
CI = confidence interval; SD = standard deviation.

After 24 months of miglustat therapy, there was only minimal further increase in mean ambulation index, indicating disease stabilization during long-term miglustat therapy [Table 32].

Table 32 Standard Ambulation Index in adult/juvenile and pediatric patients: Descriptive statistics on change from baseline to last value in the 24-month open-label extension study, Efficacy set

24-month open-label extension study	Statistic	Adult/juvenile patients (N = 17)	Pediatric patients (N = 10)
Descriptive summary	Baseline (last screening value)[a]		
	n	15[c]	10
	Mean ± SD	2.1 ± 1.1	2.0 ± 2.1
	95% CI	(1.5, 2.8)	(0.5, 3.5)
	Min, max	1, 6	0, 7
	Last Value (during the extension period)[b]		
	n	15	10
	Mean ± SD	2.4 ± 1.6	2.6 ± 3.0
	95% CI	(1.5, 3.3)	(0.4, 4.8)
	Min, max	0, 7	0, 9
	Change from baseline		
	n	15	10
	Mean ± SD	0.3 ± 1.0	0.6 ± 1.3
	95% CI	(–0.3, 0.8)	(–0.4, 1.6)
	Min, max	–2, 3	0, 4

[a] Baseline is the last value up to and including final day of Screening Visit 2; [b] Last Value is the last post-baseline value recorded in the 12-month extension period (excluding the Month-12 visit) up to and including the final day of the Month-24 visit; [c] Patients 007-104 and 007-212 did not have at least one post-Month 12 ambulation index value and were excluded from the analysis.
CI = confidence interval; SD = standard deviation; SE = standard error.

Stage I and II surveys: In the retrospective studies, ambulation was assessed within the NP-C disability scale as 'normal', 'autonomous ataxic gait', 'outdoor assisted ambulation', 'indoor assisted ambulation', or 'wheelchair-bound' [Table 15].

At the time of diagnosis of NP-C disease, ambulatory disability was reported for 66% of patients in the Stage I survey and 61% of patients in the Stage II survey. During the period between diagnosis of NP-C disease and start of treatment with miglustat (Stage I survey) or last observation (Stage II survey), there was an uninterrupted increase in the number of patients showing any degree of ambulatory disability, as well as in the mean severity of ambulatory disability. Similarly, progression of ambulatory disability was observed in 77% of patients during a mean observation period of 5.5 years in the Stage II survey. Spontaneous improvement was not observed in any patient. [Table 33]. Deterioration was continuous, occurring at an average rate of 0.10 score units/year in the modified NP-C disability scale score [Table 15].

Table 33 Frequency of patients with either 'improved', 'stable' or 'progressed' ambulation – Stage II survey

	N = 57
Stage II retrospective survey	**n (%)**
Evaluable patients	57
Improved	0 (0)
Stable	13 (22.8)
Progressed	44 (77.2)
Progression rate – score units/year (95% CI)	0.10 (0.07, 0.14)

CI = confidence interval.

In the pre-treatment period of the Stage I survey, the average rate of ambulation deterioration was similar (0.07 score units/year) to the Stage II survey results, with no patient showing improvement. During treatment with miglustat for a mean of 1.5 years in the Stage I survey, ambulation function was at least stable in 49 patients (77%). Improvement was recorded in some patients. Only 15 patients (23%) had progressive deterioration [Table 34].

Progression of the ambulation disability score before and during miglustat treatment is illustrated in Figure 17. The annual rate of change on miglustat was –0.02 score units, indicating at least stable disease. The difference in progression rate between the miglustat treatment and pre-treatment phases (treatment effect) was –0.09 (95% CI –0.18, –0.01) score units/year, indicating a statistically significant, beneficial effect of miglustat on ambulatory dysfunction. This effect was even more apparent in the population with documented progressive neurological disease (in any domain) before treatment with miglustat [Figure 17].

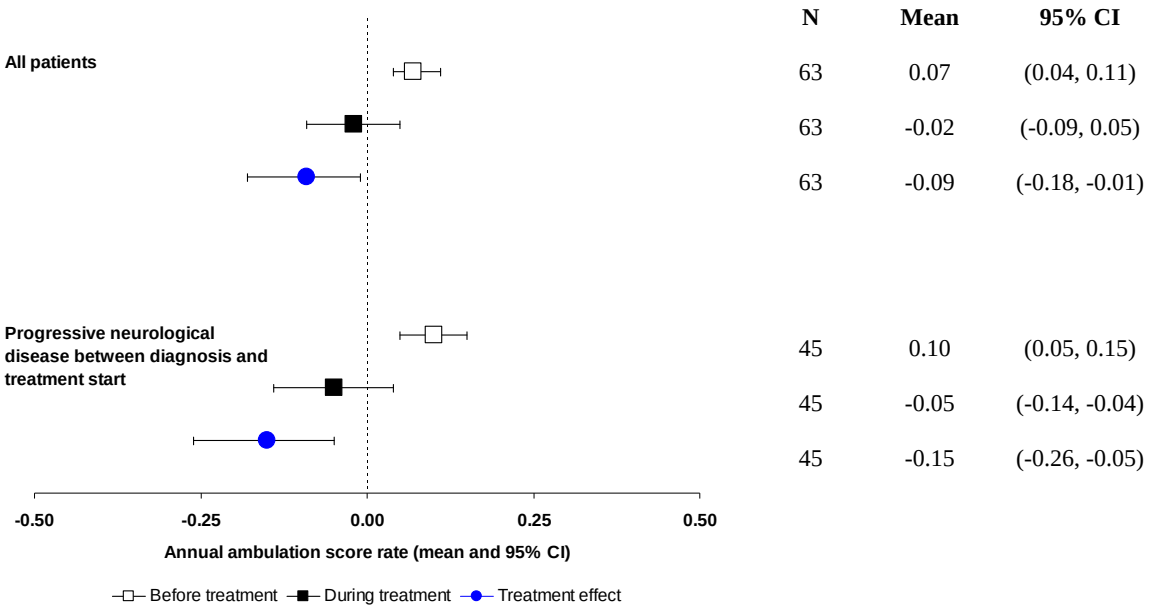
These findings of disease stabilization when patients were treated with miglustat corroborate the observations from trial OGT 918-007, where 11/17 (65%) and 8/12 (67%) showed stable ambulation function over 24 months and 47 months (end of study) of miglustat therapy, respectively, and contrast markedly with the relentless deterioration of ambulation function shown in the retrospective natural history survey, where 77% showed progressive deterioration during the period of observation.

Table 34 Frequency of patients with either 'improved', 'stable' or 'progressed' ambulation on miglustat treatment – Stage I survey

	N = 66
Stage I retrospective survey	**n (%)**
Evaluable patients	64
Improved	9 (14.1)
Stable	40 (62.5)
Progressed	15 (23.4)
Progression rate – score units/year (95% CI) (n = 63)	
Prior to start of miglustat treatment	0.07 (0.04, 0.11)
After start of miglustat treatment	–0.02 (–0.09, 0.05)

CI = confidence interval.

Figure 17 Comparison of the annual progression rate of the ambulation score prior to and during miglustat treatment – Stage I survey



Discussion
The findings for ambulation function from both retrospective studies indicated a high incidence of ongoing deterioration and an absence of spontaneous improvement in the observation period between diagnosis and start of miglustat treatment (last observation in the natural history survey). These observations are consistent with clinical experience and with published data, and reveal the expected pattern of continuous deterioration of ambulation function over the natural course of NP-C.

In contrast, treatment with miglustat in study OGT 918-007 and the Stage I survey resulted in at least stabilization in ambulation function in the majority of both adult/juvenile and pediatric patients. Improvement was described in some patients, a finding not observed during the natural course of the disease. The observed treatment effect (difference in progression rate between the miglustat treatment and pre treatment phases) in the Stage I survey reached statistical significance and was even more pronounced in the target population of patients with documented progressive neurological disease prior to miglustat treatment. These findings provide strong and consistent evidence of miglustat efficacy in a debilitating complication of the disease.

5.4.4 Cerebellar dysfunction

Various aspect of cerebellar dysfunction cause progressive and clinically relevant disability in NP-C. Findings indicating ataxia were assessed in study OGT 918-007, while dysmetria/dystonia was explored in the retrospective surveys.

5.4.4.1 Ataxia – study OGT 918-007

In study OGT 918-007, cerebellar dysfunction (ataxia) was evaluated by measures of gait balance and coordination within the clinical neurological examination. The patient's ability to walk in a straight line, walk in tandem, hop, and skip were assessed at screening and at follow-up visits. Findings were classified as 'spastic', 'dystonic', 'atactic', 'other', and were graded by severity.

Results
During the controlled 12-month phase of study OGT 918-007 (adult/juvenile patients), there was little change from baseline to last visit in the proportion of patients in each group with abnormal results. A higher proportion of patients in the miglustat group than in the No-Treatment group had abnormal results for these assessments at baseline. After 24 months of treatment with miglustat, some deterioration of the co-ordination of walking was described in 2/15 patients for whom data were available for the full treatment period. Neither of these patients experienced changes in their ambulation index scores that reflected these findings.

Pediatric patients were assessed mainly for the ability to walk in a straight line and for hopping. During a period of up to 24 months of miglustat treatment, some degree of abnormality in straight-line walking was observed in 82% of pediatric patients, compared

with 64% at baseline. In contrast, the percentage of pediatric patients with some degree of abnormality in the hopping test was the same at baseline and 24 months (63%).

5.4.4.2 Dysmetria/dystonia (Manipulation domain) – Stage I and II surveys

In the retrospective surveys, cerebellar dysfunction was assessed as dysmetria/dystonia, within the NP-C disability scale domain 'manipulation', and categorized as 'normal', 'slight dysmetria/dystonia', 'mild dysmetria/dystonia', or 'severe dysmetria/dystonia' [Table 15].

Results

Progressive deterioration of dysmetria/dystonia was seen over the 5.5 years of observation in the Stage II survey of natural history, at an average rate of 0.09 score units/year. At the time of diagnosis of NP-C, dysmetria/dystonia was present in 51% of patients and was predominantly categorized as 'slight'. This increased to 86% at the end of the period of observation, with almost half of the patients (47%) showing severe dysmetria/dystonia [Table 35]. No patient showed spontaneous improvement. Overall, 41 patients (72%) showed progressive deterioration in the manipulation domain during the natural course of the disease.

Table 35 Frequency of patients with either 'improved', 'stable' or 'progressed' manipulation – Stage II survey

Stage II retrospective survey	**N = 57 n (%)**
Evaluable patients	57
Improved	0 (0)
Stable	16 (28.1)
Progressed	41 (71.9)
Progression rate – score units/year (95% CI)	0.09 (0.06, 0.12)

CI = confidence interval.

In the pre-treatment period of the Stage I survey, the average rate of deterioration in dysmetria/dystonia (0.08 score units/year) was similar to the Stage II survey results, again with no patient showing improvement. During treatment with miglustat for a mean of 1.5 years, dysmetria/dystonia was at least stable in 48 patients (76%). Improvement was recorded in some patients. Only 15 patients (24%) had progressive deterioration [Table 36].

Progression in the manipulation domain score before and after miglustat treatment is illustrated in Figure 18. The annual rate of change in the modified NP-C disability scale on miglustat was 0.02 score units, indicating a reduction in the rate of deterioration. This reduction or treatment effect (–0.06, 95% CI –0.16, 0.05) was substantial, and was statistically significant in the population of patients with documented progressive

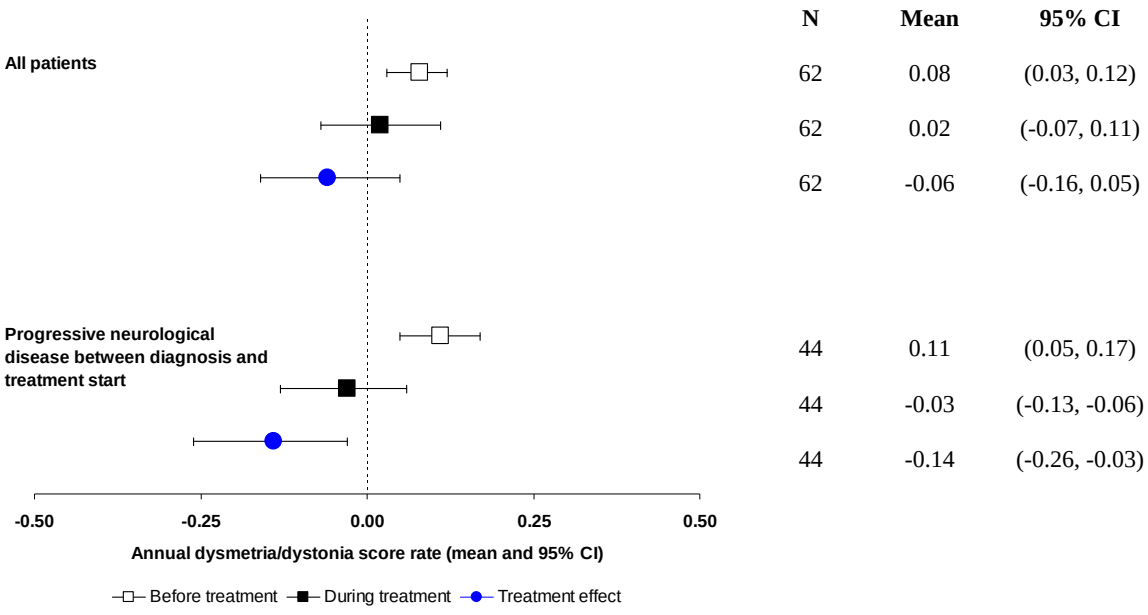
neurological disease (in any domain) before treatment with miglustat [Figure 18]. These findings contrast markedly with the relentless deterioration shown in the retrospective natural history survey, where 72% showed progressive deterioration during the period of observation.

Table 36 Frequency of patients with either 'improved', 'stable' or 'progressed' dysmetria/dystonia on miglustat treatment – Stage I survey

Stage I retrospective survey	**N = 66 n (%)**
Evaluable patients	63
Improved	8 (12.7)
Stable	40 (63.5)
Progressed	15 (23.8)
Progression rate – score units/year (95% CI) (n = 62)	
Prior to start of miglustat treatment	0.08 (0.03, 0.12)
After start of miglustat treatment	0.02 (–0.07, 0.11)

CI = confidence interval.

Figure 18 Comparison of the annual progression rate of the dysmetria/dystonia score prior to and during miglustat treatment – Stage I survey



Discussion

In the evaluation of ataxia, as defined in study OGT 918-007, no clear evidence of benefit of miglustat could be established. Cerebellar dysfunction was evaluated as dysmetria/dystonia in the retrospective studies with findings of a high incidence of ongoing deterioration and an absence of spontaneous improvement in the observation period between diagnosis and start of miglustat treatment (last observation in the natural history survey). During miglustat treatment, dysmetria/dystonia was reported as stable or improved in 76% of patients with available data, markedly contrasting with the relentless deterioration shown in the retrospective natural history survey, where 72% showed progressive deterioration during the period of observation. The observed treatment effect (difference in progression rate between the miglustat treatment and pre treatment phases) in the Stage I survey was substantial and, as for other domains, was largest and reached statistical significance among the patients with documented progressive neurological disease prior to miglustat treatment.

5.4.5 Cognitive and language function - study OGT 918-007, Stage I and II surveys

In the Main study of OGT 918-007, the Folstein Mini-Mental State Examination (MMSE) was performed to assess cognitive function. The MMSE is a brief cognitive test designed for the quantification of cognitive potential and screening of possible functional disorders. It assesses orientation to time and place, attention, immediate and recall memory, calculation, language, and constructional ability. The total score has a maximum of 30 points, and a score below 24 points indicates cognitive disorders. Although it has not been specifically validated for NP-C disease, it was chosen as a general easy-to-use tool for assessing cognitive function in adult and juvenile NP-C patients.

In the retrospective surveys, the NP-C disability scale evaluated language as a composite of articulation and communication ability, thereby incorporating components of cognition. The function was assessed as ‘normal’, ‘mild dysarthria’, ‘severe dysarthria’, ‘non-verbal communication’, or ‘absence of communication’.

Results

Study OGT 918-007: In the Main study of OGT 918-007, MMSE was performed at screening and at Months 3, 6, 9 and 12. Few assessments were made during the extension phase.

At Screening, 13 patients (45%) showed an MMSE score below 24 (indicating cognitive impairment) and only 5 patients (17%) showed a fully normal MMSE (from 28 to 30). After treatment with miglustat, patients showed a mean improvement in MMSE score over the initial 12-month study period, whereas patients in the No-Treatment group deteriorated [Table 37].

Table 37 Mini mental state examination (MMSE) in adult/juvenile patients: Descriptive statistics and analysis of covariance on change from baseline to last value in the 12-month main controlled study, Efficacy set

(Adult/Juvenile Main study)	Statistic	No-Treatment (N = 9)	Miglustat (N = 20)
Descriptive summary	Baseline		
	n	9	19[a]
	Mean ± SD	23.4 ± 4.9	22.8 ± 5.2
	95% CI	(19.7, 27.2)	(20.3, 25.3)
	Min, max	14, 29	11, 28
	Last Value		
	n	9	19
	Mean ± SD	23.1 ± 5.7	24.0 ± 5.6
	95% CI	(18.8, 27.5)	(21.3, 26.7)
	Min, max	15, 30	13, 30
	Change from baseline		
	n	9	19
	Mean ± SD	–0.3 ± 2.8	1.2 ± 2.5
	95% CI	(–2.5, 1.8)	(0.0, 2.4)
	Min, max	–5, 4	–5, 4
ANCOVA with terms for baseline, center and treatment group	Change from baseline		
	Mean (adjusted) ± SE	–0.352 ± 0.902	1.219 ± 0.620
	95% CI	(–2.213, 1.510)	(–0.060, 2.498)
	p-value	0.700	0.061
	Treatment difference (estimated)		
	Mean ± SE	1.571 ± 1.097	
	95% CI	(–0.692, 3.834)	
	p-value	0.165	

[a] Patient 007-212 did not have at least one post-baseline MMSE.
Baseline is the last value up to and including final day of Screening Visit 2 and Last Value is the last post-baseline value up to Month 12. Only patients with a baseline value are summarized. A higher score indicates better mental status: a total score of 24 or above is considered normal.
CI = confidence interval; SD = standard deviation; SE = standard error.

Only nine patients in total had post-baseline MMSE data recorded in the Extended Study and six patients for the continued treatment extension period. There was a small numerical decrease in mean MMSE score observed from baseline to last value in the extension periods.

MMSE evaluation was not performed in children enrolled in the Pediatric sub-study. Neuropsychological testing was performed according to the Wechsler and Vineland Adaptive Behavior Scales during the first 12 months of the study. Very small mean changes were observed for scores on the Wechsler Scale. Increases (i.e., improvements) in score were noted for verbal IQ, information, arithmetic, digit span, comprehension, picture

completion, and object assembly. In contrast, mean decreases (i.e., worsening) in scores were observed for the Vineland Adaptive Behavior Scale scores. Due to the paucity of data, the clinical relevance of these findings is uncertain.

Stage I and II surveys: In these retrospective studies, language skills were assessed within the domain language function/articulation as 'normal', 'mild dysarthria', 'severe dysarthria', 'non-verbal communication', or 'absence of communication' using the NP-C disability scale [Table 15].

In the Stage II survey of natural history, language function/articulation was already abnormal (predominantly mild dysarthria) in 42% of patients at the time of diagnosis of NP-C. This increased to 86% during the period of observation, with 49% of patients having severe dysarthria or worse; no patient showed spontaneous improvement. Deterioration was continuous, at a rate of 0.07 score units/year. Table 38 shows a summary of change in language function/articulation from diagnosis to last contact.

Table 38 Frequency of patients with either 'improved', 'stable' or 'progressed' language function/articulation – Stage II survey

Stage II retrospective survey	**N = 57** **n (%)**
Evaluable patients	57
Improved	0 (0)
Stable	21 (36.8)
Progressed	36 (63.2)
Progression rate – score units/year (95% CI)	0.07 (0.05, 0.09)

CI = confidence interval.

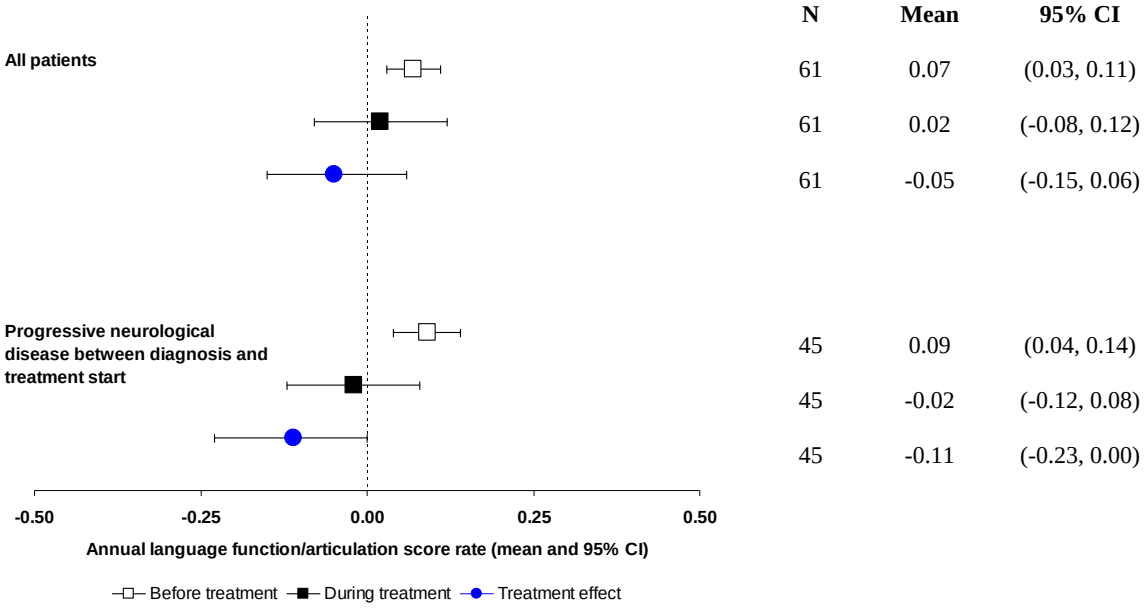
In the pre-treatment period of the Stage I survey, the average rate of deterioration in language function/articulation (0.07 score units/year) was the same as in the Stage II survey results, again with no patient showing improvement. During treatment with miglustat for a mean period of 1.5 years, language function/articulation was at least stable in 47 patients (77%). Improvement was recorded in some patients. Only 14 patients (23%) had progressive deterioration [Table 39]. The mean annual rate of deterioration decreased to 0.02 score units/year during miglustat treatment. Progression of the language function/articulation score before and after miglustat treatment is illustrated in Figure 19. As for the other domains, the treatment effect was defined as the difference in progression rate between the period on miglustat and the pre-treatment period. This effect was –0.05 (95% CI –0.15, 0.06) and reached statistical significance in the population of patients with documented progressive neurological disease (in any domain) before treatment with miglustat [Figure 19].

Table 39 Frequency of patients with either 'improved', 'stable' or 'progressed' language function/articulation on miglustat treatment – Stage I survey

Stage I retrospective survey	N = 66 n (%)
Evaluable patients	61
Improved	7 (11.5)
Stable	40 (65.6)
Progressed	14 (23.0)
Progression rate – score units/year (95% CI) (n = 61)	
Prior to start of miglustat treatment	0.07 (0.03, 0.11)
After start of miglustat treatment	0.02 (–0.08, 0.12)

CI = confidence interval.

Figure 19 Comparison of the annual progression rate of the language function/articulation score prior to and during miglustat treatment – Stage I survey



Discussion

Overall, the findings provide additional evidence of activity of miglustat on CNS symptomatology in the targeted population, supporting an effect of miglustat to reduce progression of cognitive dysfunction and language impairment in NP-C disease. The Stage I survey findings of a reduction in the rate of disease progression when patients were

treated with miglustat contrast markedly with the relentless deterioration shown in the natural history Stage II survey and support a relevant effect of miglustat on this aspect of CNS involvement in NP-C. Based on the difference in progression rate between the miglustat treatment and pre-treatment phases in the Stage I survey, a treatment effect of miglustat was observed, reaching statistical significance among patients with documented progressive neurological disease prior to miglustat treatment.

5.4.6 Additional evaluated variables

As listed in Table 14, a number of other assessments were included in study OGT 918-007. The findings for these variables, although not providing clear, additional indications of activity of miglustat, are summarized here for completeness.

5.4.6.1 Horizontal Saccade β

Horizontal Saccade β (HSEM-β) was evaluated as a secondary endpoint in study OGT 918-007. HSEM-β measurements were associated with much higher variability than those for HSEM-α and no beneficial (or detrimental) effect of miglustat could be demonstrated in either adult/juvenile or pediatric patients. There was no indication that the relative improvement observed in HSEM-α was counterbalanced by any opposite effect on HSEM-β.

5.4.6.2 Vertical saccadic eye movement

As described for baseline characteristics in study OGT 918-007 [Table 18], 27/29 adult/juvenile patients (Main study) and 12/12 pediatric patients (Pediatric sub-study) had established vertical gaze palsy at study entry and could not contribute any useful measurements of VSEM.

5.4.6.3 Organ volumes

Liver and spleen volumes were evaluated by magnetic resonance imaging (MRI) or computed tomography (CT) up to Month 12 in the OGT 918-007 Main study (adult/juvenile patients) and did not indicate clinically relevant differences between the miglustat and No-Treatment groups. Considering the adult/juvenile population studied, and the pattern of visceral lipid storage in NP-C, this finding is not surprising [Section 3.1.2.1 and Section 3.1.3].

Cerebellar volume (MRI) was assessed up to Month 12 at only one center in OGT 918-007 Main study (adult/juvenile patients). Data are available for only seven patients in the miglustat group and five patients in the No-Treatment group. A small mean increase in cerebellar volume was observed in patients on miglustat, compared with a decrease in the No-Treatment group (1.76 versus −7.55 cm^3, p = 0.321). The relevance is unclear. There

was no interpretable relationship between change in cerebellar volume and ambulatory function.

5.4.6.4 Clinical neurological examination

In study OGT 918-007, patients were subjected to 3-monthly standardized neurological and neuropsychological examinations.

The neurological variables assessed included cranial nerves and fundoscopy, visual acuity and auditory function, ocular movements, muscle tone, bulk and strength, and balance and coordination sensory testing.

For vibratory sense, the proportion of patients with abnormal results increased more notably in the miglustat group than in the No-Treatment group. Peripheral nervous system effects are discussed further in the section on Safety, in relation to findings from prospective neurophysiological evaluation [Section 6.6.1].

Tongue muscles were normal for all but one patient (5%) in the miglustat group at baseline. However, at the last visit, 3/9 patients in the No-Treatment group (33%) had abnormal tongue muscles, compared with no patients in the miglustat group.

Clinical auditory function testing during the first 12 months of study OGT 918-007 showed that at baseline 5/20 and 4/20 patients in the miglustat group in the Main study had abnormal results for the right and left ears, respectively, but at the last assessment 4/20 patients and 3/20 patients, respectively had abnormal results. In the No-Treatment group, no patient had abnormal results for either ear at baseline, but at the last assessment 2/9 patients had abnormal results. Pediatric NP-C patients had no changes in hearing over the 12 months of miglustat treatment. Only one patient had abnormal hearing at both baseline and last assessment.

There were no obvious patterns in the shifts from normal to abnormal for patients in the miglustat treatment group or the No-Treatment group for any of the other variables assessed.

5.4.6.5 Neurological tests

The Purdue Peg Board Test was used in OGT 918-007 Main study (adult/juvenile patients) to measure two types of dexterity: cross movements of the fingers, hands and arms, and fine fingertip dexterity necessary in assembly tasks. Patients in the miglustat treatment group had lower scores at baseline than patients in the No-Treatment group and demonstrated a slight decrease from baseline of 1.7 (indicating a worsening in dexterity) compared to very little change in the No-Treatment group (0.1). It is likely that these observations are confounded by treatment-related tremor in the miglustat group.

Tremor was assessed quantitatively through the Archimedes spiral score in OGT 918-007 Main study (adult/juvenile patients). This assessment involved asking patients to draw

'Archimedes spirals', which were then graded from 0 (least severe tremor) to 10 (most severe tremor). An increase in score was seen in the miglustat group, compared to the No-Treatment group. Miglustat-induced tremor is discussed further in the section on safety [Section 6.6.1].

5.4.6.6 Biochemical markers

Plasma chitotriosidase levels are elevated in NP-C patients, although to a far lesser extent than in Gaucher disease. Chitotriosidase activity was measured as an exploratory variable during the first 12 months of the OGT 918-007, Main Study (adult/juvenile patients). The median baseline level of chitotriosidase was lower in the miglustat treatment group (199 nmol/mL.hour) than in the No-Treatment group (241 nmol/mL.hour). During the study, an increase from baseline in chitotriosidase levels was seen in the miglustat group, reaching 306 nmol/mL.hour at 12 months, whereas levels remained stable in the No-Treatment group. It is likely that the low degree of elevation of chitotriosidase activity in NP-C renders this measure of little use for assessment of disease activity or response to treatment, and that no specific relevance can be assigned to the finding. During the initial 12-month period, both treatment groups remained within the range described in the literature for patients with NP-C (median 925 nmol/h per mL, interquartile range 319–1215) [Ries 2006]. These values are much lower than those observed in Gaucher patients with a median chitotriosidase activity of 12,655 nmol/h per mL (interquartile range 4693–20982) [Ries 2006].

5.4.6.7 Quality of life

In study OGT 918-007, patients aged 14 years and over completed the SF-36 QoL questionnaire, and the guardians of patients aged 13 years and under were to complete the CHQ-PF50 QoL questionnaire. Ultimately, very few CHQ-PF50 questionnaires were completed. In the results of the SF-36 QoL assessment, patients in the miglustat group demonstrated an improvement from baseline to Month 12 in mean scores for the domains bodily pain, general health, social functioning, mental health and physical component summary, whereas patients in the No-Treatment group had a worsening in mean scores. However, no consistent, statistically significant differences in the changes from baseline to last value were observed between the groups.

5.4.7 Overall disease progression assessment – study OGT 918-007, Stage I and II surveys

As introduced in Section 5.1.1.3 and Section 5.1.2.1], respectively, an assessment of overall disease progression, based on a composite evaluation of clinically-relevant neurological variables was performed both within the prospective trial OGT 919-007 and the retrospective Stage I and II surveys.

Results

Study OGT 918-007, Individual patient (responder) analysis: In study OGT 918-007 a *post hoc* responder analysis of selected efficacy variables was performed for those patients from the Main study and Pediatric sub-study (N = 29; 19 from the Main study and 10 from the Pediatric sub-study) who had been exposed to miglustat for at least 12 months. The mean duration of exposure to miglustat in these patients was 42 months for those from the Main study and 37 months for those from the Pediatric sub-study. The baseline for each patient was the timepoint of starting miglustat treatment. The evaluation criteria are summarized in Table 40.

Table 40 Criteria for definition of disease change in individual patient efficacy analysis

Variable	Improvement	Stabilization	Deterioration
Swallowing function	Any up-grading compared to baseline	No change from baseline	Any down-grading compared to baseline
Ambulation index	Decrease from baseline by > 1 point	No change from baseline or change ± 1 point	Increase from baseline of > 1 point
MMSE*	Increase from baseline of > 2 points	Change from baseline of ± 2 points	Decrease from baseline by > 2 points

* Main (adult/juvenile) study only.
MMSE = Mini Mental State Examination.

At least stable swallowing function was observed in 24 patients (83%) and deterioration in five patients (17%).

At least stable ambulatory ability was reported in 25/29 patients (86%).

Cognitive performance was assessed on the basis of change in MMSE score in adult/juvenile patients. Overall, 14 (78%) patients showed at least stable cognitive function.

For an overall responder analysis, each patient's condition was defined as stable if there was no deterioration in swallowing function, ambulation index and MMSE (swallowing function and ambulation index only in children). On the basis of this analysis, in the adult/juvenile population, 13 patients showed disease stabilization and six patients showed deterioration. In the Pediatric sub-study, eight patients showed overall disease stabilization and two patients showed deterioration. In total, 72% of patients (N = 21) had stable disease and 28% of patients (N = 8) showed deterioration during treatment with miglustat. A clear relationship between disease severity at baseline and treatment response could not be established.

Stage I and II surveys: In the Stage I and II retrospective surveys, a composite disability score was calculated for each patient, as the mean of the four individual domain scores

(swallowing, ambulation, manipulation, and language function/articulation) at each time point of assessment (if values were available for at least three of the four domain scores). Thus, each patient was assigned a composite score value between 0 (all variables normal) and 1 (all variables at their most abnormal) at each time point. In order to estimate the rate of overall disease progression, the absolute changes over time were adjusted for the time intervals between assessments.

In the Stage II survey of natural disease history, the mean composite disability score and all four functional domain scores increased progressively and substantially from the time of diagnosis to last visit, with a mean deterioration rate of 0.09 score units/year in the composite score.

Table 41 NP-C composite disability score progression – Stage II survey

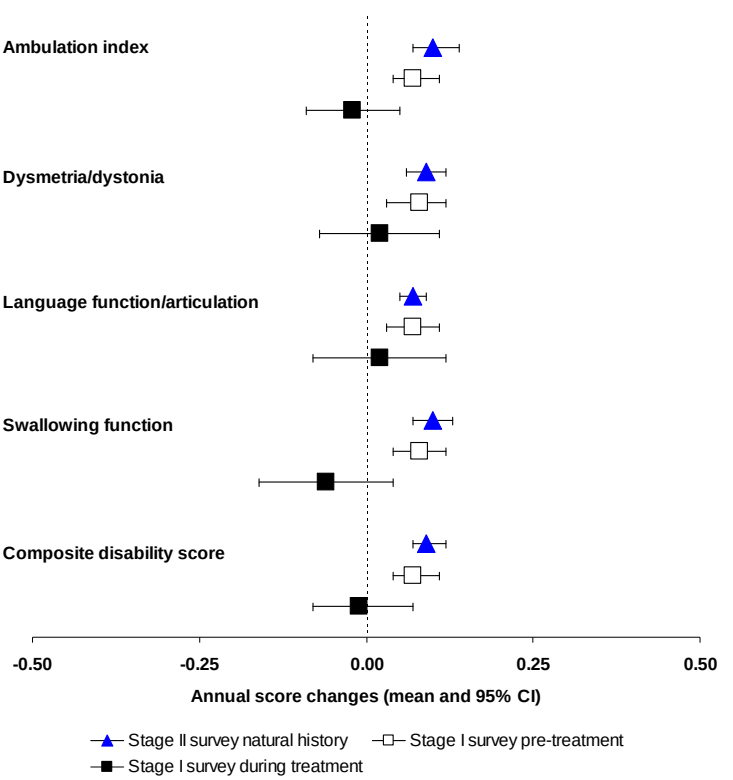
Stage II retrospective survey of natural history	**N = 57**
Evaluable patients	57
Progression rate - score units/year (95% CI)	0.09 (0.07, 0.12)

CI = confidence interval.

During the pre-treatment period of the Stage I survey, the average rate of deterioration in composite disability score (0.07 score units/year) was very similar to the Stage II survey results, again with no patient showing improvement. As discussed above, during treatment with miglustat for a mean period of 1.5 years, no further mean progression was observed for swallowing or ambulation, and there was only a marginal change for language function and manipulation. The annual progression of the functional domain scores before miglustat treatment (Stage I and II surveys) and during miglustat treatment (Stage I survey) are again summarized in Figure 20, which also provides the same information for the composite disability score.

As seen in Figure 20 and also summarized in Table 42, the mean annual rate of change in the composite score during miglustat treatment was –0.01 score units/year, indicating at least stable disease. The findings of disease stabilization during treatment with miglustat corroborate the individual patient responder analysis from trial OGT 918-007, where 72% of patients showed stable disease over the mean 42 months for those from the Main study and 37 months for those from the Pediatric sub-study, and contrast markedly with the relentless deterioration shown in the retrospective natural history survey.

Figure 20 Comparison of the annual progression rates across domains and in composite score in the retrospective studies – Stage I survey and Stage II survey



	N	Mean	95% CI
Ambulation index	57	0.1	(0.07, 0.14)
	63	0.07	(0.04, 0.11)
	63	-0.02	(-0.09, 0.05)
Dysmetria/dystonia	57	0.09	(0.06, 0.12)
	62	0.08	(0.03, 0.12)
	62	0.02	(-0.07, 0.11)
Language function/articulation	57	0.07	(0.05, 0.09)
	61	0.07	(0.03, 0.11)
	61	0.02	(-0.08, 0.12)
Swallowing function	57	0.1	(0.07, 0.13)
	61	0.08	(0.04, 0.12)
	61	-0.06	(-0.16, 0.04)
Composite disability score	57	0.09	(0.07, 0.12)
	63	0.07	(0.04, 0.11)
	63	-0.01	(-0.08, 0.07)

Table 42 NP-C composite disability score progression – Stage I survey

	N = 66	
Stage I retrospective survey of neurological outcomes	**Mean**	**95% CI**
Evaluable patients	63	
At diagnosis	0.18	0.14, 0.21
At initiation of miglustat therapy	0.40	0.33, 0.46
At last clinical contact or discontinuation of miglustat	0.44	0.36, 0.51
Progression rate – score units/year (95% CI) (n = 63)		
Prior to start of miglustat treatment	0.07 (0.04, 0.11)	
After start of miglustat treatment	–0.01 (–0.08, 0.07)	

CI = confidence interval.

Figure 21 summarizes the mean annual changes in composite disability score and the treatment effect of miglustat on the composite disability score progression rate (defined as the difference in progression rate between the miglustat treatment and pre-treatment

phases) in the Stage I survey, in all patients and according to age group (pediatric, juvenile or adult) at the time of diagnosis. The treatment effect of miglustat was -0.08 score units/year (95% CI –0.16, –0.00) in the overall Stage I survey population. Although the treatment effect of miglustat was apparent across the range of age at diagnosis, it was smaller (–0.01 score units/year) in the youngest age group (< 6 years at diagnosis). Both Stage II and Stage I survey results indicated that age at diagnosis is a predictor of overall disease progression rate in untreated patients, progression being more rapid in patients diagnosed at an early age. These findings are also supported by published data [Higgins 1992].

Figure 22 provides the same information for the subgroup of patients with documented progressive neurological disease (in at least one domain) between diagnosis and start of miglustat treatment. A substantial and comparable effect of miglustat treatment on composite disability score progression rate was seen across the age ranges. The treatment effect in the whole subgroup reached statistical significance at –0.16 score units/year (95% CI –0.25, –0.06).

Figure 21 Comparison of the annual progression rate in the composite disability score prior to and during miglustat treatment in all patients and by age at diagnosis – Stage I survey

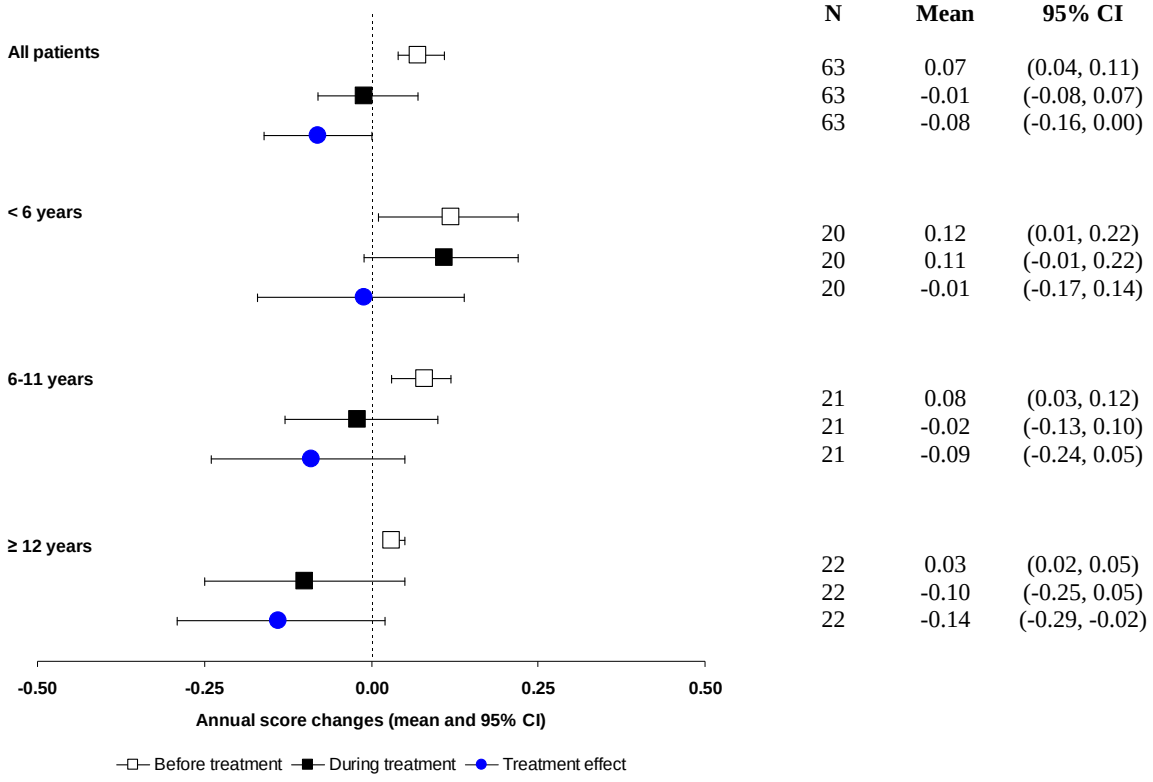
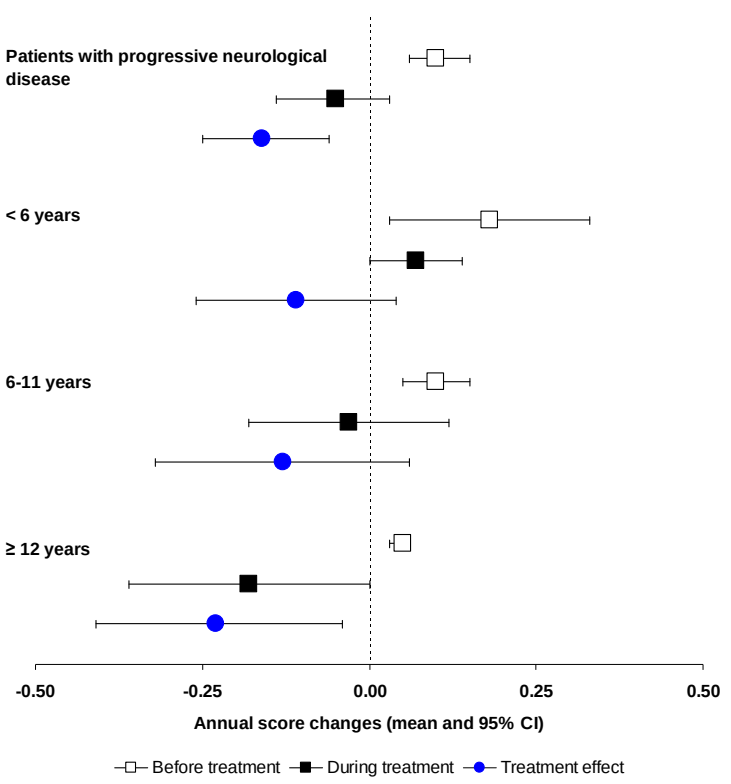


Figure 22 **Comparison of the annual progression rate in the composite disability score prior to and during miglustat treatment in patients with progressive neurological disease and by age at diagnosis – Stage I survey**



	N	Mean	95% CI
Patients with progressive neurological disease	45	0.10	(0.06, 0.15)
	45	-0.05	(-0.14, 0.03)
	45	-0.16	(-0.25, -0.06)
< 6 years	13	0.18	(0.03, 0.33)
	13	-0.07	(0.00, 0.14)
	13	-0.11	(-0.26, 0.04)
6-11 years	16	0.10	(0.05, 0.15)
	16	-0.03	(-0.18, 0.12)
	16	-0.13	(-0.32, 0.06)
≥ 12 years	16	0.05	(0.03, 0.06)
	16	-0.18	(-0.36, 0.00)
	16	-0.23	(-0.41, -0.04)

Discussion

Based on the difference in progression rate between the miglustat treatment and pre-treatment phases in the Stage I survey, a significant treatment effect of miglustat to induce disease stabilization was observed for overall disease progression rate, evaluated as a composite disability score. As for the individual domains, this effect was even more pronounced in patients with documented progressive neurological disease prior to miglustat treatment and was comparable across the age ranges. Long-term data from study OGT 918-007 indicate a sustained effect of miglustat treatment in terms of neurological disease stability and are concordant with those from the Stage I survey. Overall, treatment with miglustat in NP-C disease induces neurological disease stabilization in the great majority of patients.

5.4.8 Additional information from case reports and publications for patients not included in study OGT 918-007

Data are also provided from case reports for 15 patients (14 treated with miglustat) in the form of individual reports, publications or attestations of treatment and outcome provided by physicians treating NP-C patients [Bembi 2008, Chien 2007, Hartung 2008, Patterson 2008, Rolfs 2008].

As described in one of these experts' case narratives, videofluoroscopic (VFS) assessments of swallowing were performed in two children with NP-C treated with miglustat. The report documents significant improvement in one patient with great difficulties in swallowing prior to therapy and stable disease in a second patient who had no significant swallowing problems prior to therapy [Chien 2007].

Stabilization or improvement in terms of motor function was observed in the majority of patients included in the case reports. In the 14 case reports, there was only one case of a patient (a 46-year-old man with NP-C symptoms for 10 years) where an absence of improvement or stabilization was reported [Rolfs 2008].

A recent study [Galanaud 2008] provided quantitative measurements of 24-month miglustat treatment effects in three adult NP-C patients using the non-invasive techniques of MRI and magnetic resonance spectroscopy (MRS). For each patient, the choline:creatine ratio (a marker of neuronal dysfunction) and the N-acetyl aspartate (NAA):creatine ratio (a marker of neuronal viability) were measured in the white matter of the brain at baseline and at intervals up to 24 months. It was anticipated that disease progression would result in an increase in the choline/creatine ratio and a decrease in the NAA/creatine ratio. However, the results revealed a sustained decrease in the choline/creatine ratio for all three patients, with the mean choline/creatine ratio decreasing from 1.3 at baseline to approximately 1.0 at 18 and 24 months. The achieved ratios were similar to those expected in healthy control subjects (approximately 1.1). During the same period, the mean NAA:creatine ratio remained stable. Clinically, the patients showed mild improvement or stabilization of their neurological disease, according to assessment using the NP-C disability scale [Iturriaga 2006]. The authors concluded that miglustat had a beneficial effect on brain dysfunction and suggested on the basis of the findings in one of the patients, who had more advanced disease, that some of the dysfunction may be reversible even in the advanced stages of NP-C.

A multicenter, non-Actelion sponsored, uncontrolled study was conducted in 23 patients with NP-C treated with miglustat in Italy and was recently reported [Fecarotta 2009]. The study included patients aged 7 months to 44 years treated for 6–42 months with miglustat. None of these patients had been included in any of the studies described in this Briefing Book. Genotyping showed that 22 of the patients had mutations of *NP-C1* and one patient had a mutation of *NP-C2*. Clinical evaluation included neurological signs assessed using a

severity score and swallowing function assessed by the methods of Patterson 2007 and also by VFS for four pediatric patients.

The results showed that the majority of patients showed stabilization or improvement across swallowing function [Table 43] and different neurological variables [Table 44]. The swallowing findings were validated in the four pediatric patients who were assessed by VFS. In this evaluation, three patients with severe swallowing abnormalities at baseline had minimal abnormalities at 36 months and the patient with normal swallowing at baseline showed no deterioration at 36 months. The patient with the *NP-C2* mutation showed sustained improvement in psychomotor development following treatment for 36 months.

Table 43 Results of swallowing assessments for NP-C patients treated with miglustat in the study of Fecarotta et al.

	Substance			
	Water	**Puree**	**Pasta**	**Cookie**
Evaluable patients (n)	20	20	20	20
Stable (%)	75	85	85	75
Improved (%)	10	5	10	10

Table 44 Results of neurological assessments for NP-C patients treated with miglustat in the study of Fecarotta et al.

	Neurological assessment				
	Gait	**Dystonia**	**Dysmetria**	**Dysarthria**	**Cognitive/ psychometric ability**
Evaluable patients (n)	16	20	19	16	20
Stable (%)	81	80	74	63	85
Improved (%)	13	5	5	25	5

5.5 Efficacy conclusions

Niemann-Pick type C disease is a very rare disorder, dominated by progressive, disabling, and ultimately fatal nervous system involvement. As substantiated by the 104 patients included in the two retrospective studies on the natural history of NP-C disease and neurological outcomes following miglustat treatment (Stage I and II surveys), the progression of neurological disease in NP-C is continuous and uninterrupted for the clinically important measures of ambulatory disability, dysmetria/dystonia, language function/articulation and swallowing dysfunction.

In the US, there is currently no approved therapy for the treatment of NP-C disease. From a pathology perspective, the pool of viable neurons, including those that are dysfunctional but potentially salvageable, should be considered as the primary target for a therapeutic

agent in an ongoing, progressive neurodegenerative disorder such as NP-C. During long-term therapy, disease stabilization or a reduction in the rate of disease progression is probably the most realistic goal. Given the relentlessly progressive nature of the disease, a safe treatment that could favorably modify neurological function, by halting the progression or reducing the rate of neurological deterioration, would represent a substantial advancement in the clinical management of the disease, which is currently based on supportive measures only.

There are multiple and consistent indications that miglustat is active on the progression of neurological manifestations in NP-C disease, and that this activity translates into beneficial effects both in individual endpoints of clear clinical relevance and in responder analyses assessing the benefit at the patient level.

Given its relationship to the underlying disease process in NP-C, saccadic eye movement velocity (SEMV) can be considered an appropriate pharmacodynamic variable for the assessment of treatment effect in this disease. Changes in horizontal SEMV in clinical trial OGT 918-007 reflect a direct effect on a central pathway of the brainstem that is dysfunctional in NP-C disease. The observations from study OGT 918-007, although not statistically significant in the predefined analysis of this intrinsically insufficiently powered study, indicate a positive effect of miglustat on the progression of horizontal SEMV deterioration.

For swallowing dysfunction and general motor disability, observations from study OGT 918-007 indicate a clinical benefit of long-term treatment with miglustat in slowing disease progression, both in comparison with No-Treatment for 12 months and in relation to baseline over long-term therapy for a mean of 42 months. The findings were strongly supported by the data collected in the Stage I survey from 66 additional patients treated with commercially-available miglustat in a non-clinical trial setting. These data showed a clear reduction of the progression rate after the initiation of miglustat, compared with the pre-treatment phase in these patients. The treatment effect of miglustat, defined as the difference in progression rate between the miglustat treatment and pre-treatment phases was statistically significant in both domains. The majority of patients achieved at least stabilization of swallowing and general motor function during miglustat therapy for a mean of 1.5 years (51/63 [81.0%] for swallowing and 49/64 [77%] for ambulation). Data from the natural history Stage II survey further support the continuously progressive nature of neurological deterioration in NP-C disease, that spontaneous improvement is not seen, and that the observed disease stabilization with miglustat therapy both in the clinical trial OGT 918-007 and the Stage I survey cannot simply be explained by a naturally occurring plateau in disease progression.

Dysmetria/dystonia was assessed in both the Stage I and II surveys within the manipulation domain of the disability scale. The Stage I survey showed that manipulation was at least stabilized in 76% of patients during a mean duration of treatment with miglustat of 1.5 years, a pattern clearly distinct from that during the pre-treatment period

in these patients. The treatment effect of miglustat on annual progression rate was substantial and, as for other domains was largest and reached statistical significance among patients with documented progressive neurological disease prior to miglustat treatment. Data from the natural history Stage II survey of NP-C further strengthen these findings, showing a continuous progression of the severity of dysmetria/dystonia during the natural course of the disease.

The assessment of cognitive ability, measured through the MMSE score, indicated a difference in favor of miglustat over No-Treatment during the controlled phase of study OGT 918-007 in adult/juvenile patients. Further support for these observations was provided by the findings in the Stage I survey that showed at least stable language function/articulation (globally evaluating pertinent disease components such as dysarthria and impaired communication skills) in the majority of patients during treatment with miglustat. Based on the difference in progression rate between the miglustat treatment and pre-treatment phases, a treatment effect of miglustat was observed and was statistically significant among patients with documented progressive neurological disease prior to miglustat treatment. The natural history characteristics of this domain, as shown in the Stage II survey, are again fully supportive of a continuous worsening in untreated patients and thus of relevant therapeutic benefit of miglustat treatment.

At an integrated, 'responder' level there is clear evidence that a clinically identifiable, meaningful and sustained benefit to maintain at least stable disease status is provided to a large majority of the targeted population with NP-C disease. In the Stage I survey, a treatment effect of miglustat was observed for overall disease progression rate, evaluated using the composite disability score. As for the individual domains, this effect was even more pronounced and statistically significant in patients with documented progressive neurological disease prior to miglustat treatment and comparable across the age ranges. Long-term data from study OGT 918-007 indicate a sustained effect of miglustat treatment in terms of neurological disease stability and are concordant with those from the Stage I survey. There were no signs of detrimental effect (e.g., no acceleration of disease progression rate) in those remaining patients who showed no clear response to miglustat treatment.

Collectively, these findings provide consistent evidence for an effect of miglustat on cardinal aspects of CNS involvement in NP-C disease. Importantly, the data from treatment with miglustat of pediatric patients with NP-C disease fully corroborate the findings in the controlled study in adult and juvenile patients. Moreover, data from the Stage I survey patients treated with commercially-available miglustat and from the natural history Stage II survey fully support the clinical trial data. Altogether, the consistency of the findings between the prospective study OGT 918-007 and the Stage I and II surveys argues against bias being an important confounder to the interpretation of the results of the retrospective studies. Overall, treatment with miglustat in NP-C disease induces at least neurological disease stabilization in the great majority of patients.

6 SAFETY

6.1 Introduction

Due to the extreme rarity of the disease, the number of NP-C patients available for prospective clinical study is limited. In order to provide the most comprehensive evaluation of the safety of miglustat possible, this assessment includes the 206 patients treated with miglustat in clinical trials in LSD, including the currently approved indication in the US, GD-1 [Table 45].

Special emphasis is given to the discussion of the safety profile of miglustat in NP-C and the other conditions (GD-3 and G_{M2} gangliosidosis) where patients were treated with miglustat 200 mg t.i.d., twice the currently approved 100 mg t.i.d. dose. In addition, the safety profile of miglustat in pediatric patients is described.

Table 45 Summary of clinical trials that contributed safety data

Indication	Dose Regimen	Number of patients treated with miglustat	Exposure (years)	
			Mean	Maximum
All patients treated with miglustat		206	2.2	6.6
Type 1 Gaucher disease (GD-1)				
All GD-1		90	2.2	6.6
OGT 918-001 + extension	100 mg t.i.d.	28 (8)*	2.6	6.6
OGT 918-003 + extension	50–100 mg t.i.d.#	18 (8)*	2.7	5.2
OGT 918-004 + extension	100 mg t.i.d.	34 (7)*	1.8	4.9
OGT 918-005 + extension	100 mg t.i.d.	10	1.5	2.0
OGT 918-016	100 mg t.i.d.	(23)*	1.5	2.6
Neuronopathic LSD		100	2.3	5.4
Niemann-Pick type C (NP-C)				
All NP-C		40	2.6	5.4
OGT 918-007 + extension (Main)	200 mg t.i.d.	28	2.6	5.4
OGT 918-007 + extension (Pediatric)	(adjusted for BSA in pediatric patients)	12	2.7	4.4
Type 3 Gaucher disease (GD-3)				
OGT 918-006 + extension	200 mg t.i.d. (adjusted for BSA in pediatric patients)	30	2.0	4.0
G_{M2} gangliosidosis				
OGT 918-009 + extension	200 mg t.i.d.	30	2.2	3.4
Other LSD		16	0.8	1.2
Fabry disease				
OGT 918-002	100 mg o.d.–100 mg b.i.d.	16	0.8	1.2

All data are included from studies OGT 918-001, -002, -003, -004, -005, -006, -007 and -009.
Data up to the 24 months visit are included for study -016.
50 mg t.i.d. for first 6 months followed by 100 mg t.i.d.
* Study -016 included patients previously enrolled in studies 001, -003 and -004. These patient counts are displayed in parentheses and are not included in the N counts.
BSA = body surface area; LSD = lysosomal storage disorder.

6.1.1 Descriptions of clinical trials in non-NP-C indications included in the integrated safety analysis

6.1.1.1 Type 1 Gaucher disease

OGT 918-001 (12 months, uncontrolled) and extension: Total exposure up to 6.6 years.

This was a non-comparative study in 28 adult patients with mild to moderate GD-1, unable or unwilling to be treated with ERT. The targeted dose of miglustat was 100 mg t.i.d. The

main study lasted for 12 months. Patients who completed the initial 12-month period, were invited to enter the extension phase of the study (OGT 918-001X) for an additional 12 (22 patients) or 24 months (18 patients) and up to a maximum exposure of 79.2 months.

OGT 918-003 (6 months, uncontrolled) and extension: Total exposure up to 5.2 years.

This study evaluated miglustat 50 mg t.i.d. over 6 months, followed by an extension period of 6 months, in which the dose could be increased to 100 mg t.i.d. The patients enrolled in this study were similar to those enrolled in study OGT 918-001 and, except for the dose, the study followed an identical protocol. There were 18 patients in the main study (the first 6 months), with 16 of these patients continuing to 12 months.

OGT 918-005 (12 months, uncontrolled) and extension: Total exposure up to 24 months.

This was a non-comparative study enrolling 12 adult patients with confirmed, mild to moderate GD-1 unwilling or unable to receive ERT. Treatment was miglustat 100 mg t.i.d. for 12 months in the main study (10 patients), with an extension of up to 24 months (7 patients).

OGT 918-004 (6 months, controlled) and uncontrolled extension: total exposure up to 4.9 years.

Study OGT 918-004 was a prospective, open-label, single-center study, in which 36 adult patients with GD-1, maintained on ERT for at least 2 years and on a stable dose for at least 6 months, were randomized to (i) treatment with miglustat 100 mg t.i.d. (n = 12), or (ii) continuation of their current dose regimen of ERT (n = 12), or (iii) the two treatments in combination for a period of 6 months (n = 12).

Of the 33 patients who completed the initial 6-month study phase, 29 (10 patients from each of the miglustat and ERT groups, and nine from the combination group) elected to enter an open-label extension phase for an initial 6 months, receiving miglustat alone. Of these 29 patients, 28 subsequently completed the first extension period, with all 28 electing to enter a second extension phase for a further 12 months.

OGT 918-016 (uncontrolled capture study).

This was an open-label safety and efficacy study of long-term miglustat treatment in adult patients with GD-1 who had been treated with miglustat in previous clinical trials. GD-1 patients who had completed a previous study with miglustat (studies OGT 918-001, OGT 918-003 or OGT 918-005) were given the opportunity to transfer into this protocol. A total of 23 patients entered this study.

The dose of miglustat was based on that in the last dosing interval of the previous study.

6.1.1.2 Type 3 Gaucher disease

OGT 918-006 (12 months, controlled) and extensions: total exposure up to 4.0 years.

This was a randomized, comparative open-label study in 30 adult/juvenile and pediatric patients with GD-3. Patients were randomized to receive either miglustat or No-Treatment (standard clinical care) for a 12-month treatment period, (miglustat N = 20, No-Treatment N = 10), followed by optional extended treatment periods during which all patients received miglustat. Patients aged 12 years or more received a miglustat starting dose of 200 mg t.i.d. For children 2–11 years, the dose administered varied from 100 mg o.d. to 200 mg t.i.d. according to BSA, using the same formula as in study OGT 918-007 [Section 5.1.1.2].

6.1.1.3 G_{M2} gangliosidosis

OGT 918-009 (12 months, controlled) and extensions: total exposure up to 3.4 years.

This was a randomized, comparative open-label study, in which 30 patients aged 18 years or older with a diagnosis of G_{M2} gangliosidosis (late-onset Tay-Sachs phenotype) were randomized (miglustat N = 20, No-Treatment N = 10) to receive either treatment with miglustat or No-Treatment (standard clinical care) for a 12-month treatment period. The recommended treatment dose was 200 mg t.i.d. The 12-month study was followed by a non-comparative extension period in which all patients received miglustat.

6.1.1.4 Fabry disease

OGT 918-002 (12 months, uncontrolled): total exposure up to 1.2 years.

This study was conducted in 16 adult patients with Fabry disease. These patients had significant renal impairment as a result of their disease. The study was a non-comparative, open-label, 12-month study. The patients received between 100 mg o.d. and 100 mg b.i.d. of miglustat.

6.2 Patient exposure

Within the overall dataset of 206 patients, 18 patients with GD-1 received miglustat 50 mg t.i.d. (in the initial 6 months of study OGT 918-003), 88 patients with GD-1 received miglustat 100 mg t.i.d., and 100 patients with neuronopathic LSD (NP-C, GD-3 and G_{M2} gangliosidosis) received miglustat 200 mg t.i.d. (adjusted for BSA in 29 pediatric patients) [Table 46]. Sixteen patients with Fabry disease were treated with miglustat 100 mg o.d. to 100 mg b.i.d. Altogether, 183/206 patients (88.8%) were exposed to miglustat for at least 6 months, and 98 patients (47.6%) were exposed for at least 2 years. This dataset represents 444 patient-years of exposure to miglustat, of which 105 patient-years relate to the use of miglustat in NP-C.

In study OGT 918-007, a total of 40 patients (28 adult/juveniles and 12 children) with NP-C received at least one dose of miglustat. Mean exposure was 2.6 years with 87.5% of the patients exposed for at least 6 months and 65.0% exposed for at least 2 years.

Table 46 Exposure to miglustat, overall and by selected indications, Safety set

		Indication		
	Overall	NP-C 200 mg tid	NLSD 200 mg tid	GD1 50-100 mg tid
	N=206[a] n %	N=40 n %	N=100 n %	N=90 n %
Duration of Exposure				
At least 1/2 year	183 88.8%	35 87.5%	92 92.0%	76 84.4%
At least 1 year	157 76.2%	31 77.5%	84 84.0%	66 73.3%
At least 1 1/2 years	128 62.1%	28 70.0%	75 75.0%	53 58.9%
At least 2 years	98 47.6%	26 65.0%	60 60.0%	38 42.2%
At least 2 1/2 years	71 34.5%	22 55.0%	44 44.0%	27 30.0%
At least 3 years	52 25.2%	15 37.5%	28 28.0%	24 26.7%
At least 3 1/2 years	38 18.4%	14 35.0%	15 15.0%	23 25.6%
At least 4 years	28 13.6%	11 27.5%	11 11.0%	17 18.9%
At least 4 1/2 years	17 8.3%	3 7.5%	3 3.0%	14 15.6%
At least 5 years	13 6.3%	2 5.0%	2 2.0%	11 12.2%
Exposure(years)				
n	206	40	100	90
Mean	2.2	2.6	2.3	2.2
SD	1.5	1.6	1.2	1.7
Median	2.0	2.9	2.2	1.8
Q1 , Q3	1.0 , 3.0	1.2 , 4.0	1.5 , 3.1	1.0 , 3.5
Min , Max	0.0 , 6.6	0.0 , 5.4	0.0 , 5.4	0.0 , 6.6

Qi = 25% quartile, Q3 = 75% quartile
[a] This number also includes 16 patients with Fabry disease treated within study OGT 918-002
NLSD = Neuronopathic lysosomal storage disorders (NP-C, GD-3, G_{M2} gangliosidosis

Miglustat exposure according to patient age and by selected indications is presented in Table 47. All of the data presented for juvenile and pediatric patients were generated in studies in NP-C (OGT 918-007) and GD-3 (OGT-918-006).

Table 47 Patients exposed to miglustat, by age group and selected indications

Disease Type	Overall N=206[a] n	%	Adults N=161 n	%	Juveniles N=16 n	%	Pediatrics N=29 n	%
NP-C	40	19.4%	21	13.0%	7	43.8%	12	41.4%
GD-1	90	43.7%	90	55.9%	-		-	
GD-3	30	14.6%	4	2.5%	9	56.3%	17	58.6%
GM2	30	14.6%	30	18.6%	-		-	
Fabry	16	7.8%	16	9.9%	-		-	

Pediatrics: 2–11 years, Juveniles: 12–17 years, Adults: >= 18 years
[a]This number also includes 16 patients with Fabry disease treated within study OGT 918-002
GM2 = G_{M2} gangliosidosis

6.3 Patient demographics

The age range of patients who received miglustat treatment in the studies was wide, including children from 2 years to elderly adults of 69 years [Table 48]. Both genders were well represented, with women comprising 47.1% of the overall population.

The demographic characteristics of the NP-C population in study OGT 918-007 are further described in Section 5.3.1 and presented in Table 18.

Table 48 Patient demographics in the miglustat-treated study population, overall and by selected indications, Safety set

		Indication		
	Overall N=206[a]	NP-C N=40	NLSD N=100	GD1 N=90
	n %	n %	n %	n %
Gender				
n	206	40	100	90
Male	109 52.9%	19 47.5%	51 51.0%	42 46.7%
Female	97 47.1%	21 52.5%	49 49.0%	48 53.3%
Age (years)				
n	206	40	100	90
Mean	32.6	19.8	22.6	41.5
SD	16.6	11.4	14.6	12.8
Median	33.0	18.0	18.5	42.0
Q1 , Q3	18.0 ,47.0	10.0 ,30.5	10.0 ,33.0	31.0 ,51.0
Min , Max	2.0 , 69.0	4.0 , 42.0	2.0 , 56.0	18.0 , 69.0

NLSD = Neuronopathic lysosomal storage disorders (NP-C, GD-3, G_{M2} gangliosidosis)
[a]This number also includes 16 patients with Fabry disease treated within study OGT 918-002

The age and gender distributions of the miglustat-treated population are shown in Table 49.

Table 49 Demographic characteristics of the miglustat-treated study population, overall and by age group, Safety set

	Overall N=206 n %	Adults N=161 n %	Juveniles N=16 n %	Pediatrics N=29 n %
Gender				
n	206	161	16	29
Male	109 52.9%	90 55.9%	8 50.0%	11 37.9%
Female	97 47.1%	71 44.1%	8 50.0%	18 62.1%
Age (years)				
n	206	161	16	29
Mean	32.6	39.0	13.9	7.2
SD	16.6	12.5	2.1	2.3
Median	33.0	39.0	13.5	7.0
Q1 , Q3	18.0 ,47.0	29.0 ,49.0	12.0 ,16.0	6.0 , 9.0
Min , Max	2.0 , 69.0	18.0 , 69.0	12.0 , 17.0	2.0 , 11.0

Pediatrics: 2–11 years, Juveniles: ≥ 12–17 years, Adults: >= 18 years

6.4 Adverse events

6.4.1 Overview of common adverse events in miglustat-treated patients

The overall adverse event (AE) profile in patients with NP-C was similar to that for patients with GD-1 (the approved indication) and the overall miglustat-treated population. Similarly to the AE profile in the overall miglustat-treated population, the most frequently reported AEs in NP-C patients were diarrhea, weight decrease, tremor, flatulence, fatigue and headache [Table 50]. The prevalences of diarrhea, weight loss and tremor appeared to decrease with time on treatment. In the overall miglustat-treated population, the prevalence of diarrhea was 78% over the first 6 months of treatment, subsequently decreasing to 46%−57% in each of the following 6 month periods up to 3 years. For weight decrease, the highest prevalence was 60%, observed between 6 and 12 months of treatment, subsequently decreasing to 39%−57% up to 3 years. Tremor was most prevalent in the first two 6-month periods of treatment (approximately 35%) declining to 26%−32% thereafter. In NP-C patients, a similar pattern was seen.

In the overall miglustat-treated population, a total of 38.8% of patients experienced at least one AE that was graded as severe. Among patients with neuronopathic LSD the incidence of severe AEs was 48.0%, and in NP-C patients 67.5% [Table 50]. Given the small overall number of patients and the differences between study populations regarding underlying disease, disease severity and demographic characteristics, as well as the open-label design of the studies, it is difficult to draw meaningful conclusions. Severe AEs in NP-C patients were varied and included gastrointestinal and neurological/psychiatric AEs.

A higher dose of miglustat (200 mg t.i.d.) was administered to patients in the neuronopathic LSD studies (including NP-C) compared to the GD-1 studies (50 or 100 mg t.i.d.), but there was no distinct pattern of incidences or severity of common AEs that would support a relationship with miglustat dose [Table 50]. It is acknowledged that

such evaluation is potentially confounded by differences in the manifestations of the underlying diseases and by different demographic characteristics in different studies. The types of AEs reported more frequently with miglustat 200 mg t.i.d. versus 100 mg t.i.d. were mainly those that could be anticipated in disorders with predominant nervous system involvement (e.g., depression and insomnia), or which might be partly elicited by prospective neurophysiological evaluation in disorders with high underlying prevalences of such disorders (e.g., nerve conduction studies abnormal, paresthesia). The recruitment of a high proportion of pediatric and juvenile subjects in studies of miglustat 200 mg t.i.d. and the potential impact on the overall incidence of AEs such as cough, pyrexia, nasopharyngitis and vomiting should also be considered. Additionally, in the high-dose (500–1,000 mg t.i.d.) HIV studies [Section 6.8], the administration of doses up to 5-fold higher than those proposed in the treatment of NP-C, did not indicate additional safety issues, in terms of a different pattern or increased severity of AEs, over those reported in the clinical trials in neuronopathic LSD.

Common AEs that were suspected by the investigator to be related to miglustat treatment were generally those associated with the gastrointestinal or nervous systems, such as diarrhea, decreased weight, flatulence, tremor and abdominal pain.

Given the small number of Black, Asian and Other patients in the studies, evaluation by ethnic origin was not performed. The proportions of males and females in the overall miglustat-treated population and in the NP-C population who experienced at least one AE were similar [Section 6.4.4].

The pattern of AEs in pediatric patients was generally similar to that in the overall population. However, in comparison to the overall population, diarrhea was reported less commonly in children and cough, pyrexia and vomiting were reported more commonly (Section 6.4.3, Table 53).

Table 50 AEs and severe AEs with an incidence > 10% in the miglustat-treated study population, overall and by selected indications, Safety set

Preferred Term Intensity	Overall N=206[a] n	%	Indication: NP-C N=40 n	%	Indication: NLSD N=100 n	%	Indication: GD1 N=90 n	%
Total patients with at least one AE	203	98.5%	39	97.5%	97	97.0%	90	100%
Severe	80	38.8%	27	67.5%	48	48.0%	24	26.7%
DIARRHOEA	174	84.5%	33	82.5%	77	77.0%	82	91.1%
Severe	15	7.3%	6	15.0%	8	8.0%	5	5.6%
WEIGHT DECREASED	129	62.6%	24	60.0%	55	55.0%	63	70.0%
Severe	6	2.9%	1	2.5%	5	5.0%	1	1.1%
TREMOR	95	46.1%	23	57.5%	48	48.0%	34	37.8%
Severe	4	1.9%	2	5.0%	2	2.0%	-	
FLATULENCE	91	44.2%	22	55.0%	34	34.0%	48	53.3%
Severe	3	1.5%	-		-		3	3.3%
FATIGUE	61	29.6%	18	45.0%	32	32.0%	25	27.8%
Severe	1	0.5%	-		-		1	1.1%
HEADACHE	60	29.1%	17	42.5%	30	30.0%	29	32.2%
Severe	6	2.9%	1	2.5%	2	2.0%	4	4.4%
ABDOMINAL PAIN	56	27.2%	9	22.5%	24	24.0%	30	33.3%
Severe	2	1.0%	-		1	1.0%	1	1.1%
NASOPHARYNGITIS	56	27.2%	16	40.0%	31	31.0%	22	24.4%
Severe	0	0.0%	0	0.0%	0	0.0%	0	0.0%
VOMITING	46	22.3%	14	35.0%	30	30.0%	11	12.2%
Severe	4	1.9%	1	2.5%	2	2.0%	1	1.1%
ABDOMINAL PAIN UPPER	43	20.9%	13	32.5%	21	21.0%	21	23.3%
Severe	2	1.0%	-		-		2	2.2%
NAUSEA	43	20.9%	10	25.0%	22	22.0%	17	18.9%
Severe	1	0.5%	-		1	1.0%	-	
FALL	42	20.4%	10	25.0%	37	37.0%	5	5.6%
Severe	1	0.5%	1	2.5%	1	1.0%	-	
COUGH	39	18.9%	12	30.0%	26	26.0%	12	13.3%
Severe	2	1.0%	-		2	2.0%	-	
ARTHRALGIA	36	17.5%	5	12.5%	16	16.0%	16	17.8%
Severe	1	0.5%	-		-		1	1.1%
DIZZINESS	33	16.0%	3	7.5%	14	14.0%	17	18.9%
Severe	0	0.0%	0	0.0%	0	0.0%	0	0.0%
MUSCLE SPASMS	33	16.0%	2	5.0%	11	11.0%	21	23.3%
Severe	1	0.5%	-		-		1	1.1%
PAIN IN EXTREMITY	32	15.5%	5	12.5%	15	15.0%	15	16.7%
Severe	0	0.0%	0	0.0%	0	0.0%	0	0.0%
PARAESTHESIA	32	15.5%	7	17.5%	19	19.0%	11	12.2%
Severe	1	0.5%	-		1	1.0%	-	
INFLUENZA	30	14.6%	3	7.5%	11	11.0%	12	13.3%
Severe	1	0.5%	-		-		-	
PYREXIA	30	14.6%	5	12.5%	21	21.0%	7	7.8%
Severe	1	0.5%	-		1	1.0%	-	
BACK PAIN	28	13.6%	3	7.5%	12	12.0%	14	15.6%
Severe	2	1.0%	-		1	1.0%	1	1.1%
CONSTIPATION	24	11.7%	5	12.5%	11	11.0%	13	14.4%
Severe	1	0.5%	-		1	1.0%	-	
CONTUSION	24	11.7%	6	15.0%	16	16.0%	8	8.9%
Severe	1	0.5%	1	2.5%	1	1.0%	-	
DECREASED APPETITE	24	11.7%	6	15.0%	15	15.0%	9	10.0%
Severe	0	0.0%	0	0.0%	0	0.0%	0	0.0%
NERVE CONDUCTION STUDIES ABNORMAL	24	11.7%	8	20.0%	24	24.0%	-	
Severe	5	2.4%	5	12.5%	5	5.0%	-	
UPPER RESPIRATORY TRACT INFECTION	23	11.2%	3	7.5%	10	10.0%	13	14.4%
Severe	0	0.0%	0	0.0%	0	0.0%	0	0.0%
DEPRESSION	22	10.7%	7	17.5%	13	13.0%	6	6.7%
Severe	3	1.5%	-		1	1.0%	-	
INSOMNIA	21	10.2%	9	22.5%	14	14.0%	7	7.8%
Severe	3	1.5%	3	7.5%	3	3.0%	-	

[a] This number also includes 16 patients with Fabry disease treated within study OGT 918-002
AE = adverse event, NLSD = Neuronopathic lysosomal storage disorders (NP-C, GD-3, G_{M2} gangliosidosis)

6.4.2 Comparison of adverse events in patients with neuronopathic LSD who received miglustat versus No-Treatment

Comparative data (miglustat versus No-Treatment) on the safety of miglustat are available from the initial 12-month periods of studies OGT 918-007, OGT 918-006 and OGT 918-009, providing information from 72 and 29 patients on miglustat and No-Treatment, respectively. The incidences of reported AEs are given in Table 51.

A similar comparison of the incidences of reported AEs in the adult/juvenile NP-C patients who were randomized to either miglustat or No-Treatment over the first 12 months of study OGT 918-007 is presented in Table 52. In both cases it should be taken into consideration that the studies were of open-label design.

In keeping with the previous experience in the approved indication GD-1 (see USPI, Appendix 3), gastrointestinal events of diarrhea, flatulence, abdominal pain, nausea and vomiting were reported at clearly higher incidences in the miglustat group compared to the No-Treatment group, both in the overall population of patients with neuronopathic LSD and in patients with NP-C. The same was true for decreased appetite and decreased weight. On the other hand, dysphagia, a symptom typically associated with NP-C disease, was less common in the miglustat group of study OGT 918-007.

Also in accordance with the experience in GD-1, there was a higher incidence of tremor/aggravated tremor, and headache reported as an AE in the miglustat treatment group. Paresthesia, insomnia, spastic gait and fatigue, as well as some psychiatric disorders were also reported more frequently on miglustat. It should be considered that such symptoms are also part of the manifestations of the underlying disease.

Table 51 Treatment-emergent adverse events occurring in at least 10% of patients in either group in the controlled phases of the NLSD studies, Safety set

	Miglustat N = 72	No-Treatment N = 29
Exposure (years)		
Mean (SD)	1.0 (0.2)	1.0 (0.1)
Median	1.0	1.0
Maximum	1.2	1.2
Preferred term	**n (%)**	**n (%)**
Number of patients with at least one treatment-emergent[a] AE	71 (98.6)	27 (93.1)
Diarrhoea	59 (81.9)	9 (31.0)
Weight decreased	39 (54.2)	2 (6.9)
Tremor	33 (45.8)	2 (6.9)
Flatulence	28 (38.9)	-
Vomiting	19 (26.4)	1 (3.4)
Headache	19 (26.4)	4 (13.8)
Fatigue	17 (23.6)	3 (10.3)
Nasopharyngitis	16 (22.2)	5 (17.2)
Abdominal pain upper	14 (19.4)	-
Pyrexia	14 (19.4)	2 (6.9)
Nausea	13 (18.1)	3 (10.3)
Fall	12 (16.7)	10 (34.5)
Cough	12 (16.7)	2 (6.9)
Abdominal pain	11 (15.3)	2 (6.9)
Gait disturbance	11 (15.3)	5 (17.2)
Paraesthesia	10 (13.9)	1 (3.4)
Ataxia	8 (11.1)	2 (6.9)
Dizziness	8 (11.1)	5 (17.2)
Arthralgia	8 (11.1)	2 (6.9)
Pain in extremity	8 (11.1)	2 (6.9)
Gait spastic	7 (9.7)	1 (3.4)
Influenza	7 (9.7)	1 (3.4)
Depression	7 (9.7)	2 (6.9)
Insomnia	7 (9.7)	-
Contusion	7 (9.7)	3 (10.3)
Decreased appetite	7 (9.7)	1 (3.4)
Dysphagia	6 (8.3)	4 (13.8)
Excoriation	6 (8.3)	3 (10.3)
Upper respiratory tract infection	5 (6.9)	3 (10.3)
Balance disorder	5 (6.9)	4 (13.8)
Intention tremor	5 (6.9)	3 (10.3)
Aspartate aminotransferase increased	3 (4.2)	3 (10.3)
Skin laceration	2 (2.8)	3 (10.3)
Sensory disturbance	1 (1.4)	3 (10.3)
Angiotensin converting enzyme increased	1 (1.4)	3 (10.3)
Diplopia	-	3 (10.3)

[a] Study emergent for the No-Treatment group.
Includes the 12-month comparative periods of Studies OGT 918-006, OGT 918-007 and OGT 918-009.
AE = adverse event.

Table 52 Treatment-emergent adverse events occurring in at least 10% of adult/juvenile patients in either group in study OGT 918-007, controlled phase, Safety set

	Number (%) of patients	
	Miglustat (N = 20)	**No-Treatment (N = 9)**
Exposure (years)		
Mean (SD)	1.0 (0.2)	0.9 (0.2)
Median	1.0	1.0
Maximum	1.2	1.0
Preferred term	**n (%)**	**n (%)**
Number of patients with at least one treatment-emergent[a] AE	20 (100)	9 (100)
Diarrhoea	17 (85)	4 (44)
Flatulence	14 (70)	0
Weight decreased	13 (65)	0
Abdominal pain	10 (50)	0
Headache	9 (45)	3 (33)
Tremor	9 (45)	2 (22)
Nausea	7 (35)	1 (11)
Nasopharyngitis	7 (35)	3 (33)
Fatigue	7 (35)	1 (11)
Insomnia	6 (30)	0
Vomiting	6 (30)	0
Gait spastic	5 (25)	1 (11)
Appetite decreased	5 (25)	0
Paraesthesia	4 (20)	1 (11)
Tremor aggravated	4 (20)	0
Dysphagia	4 (20)	4 (44)
Abdominal distension	4 (20)	0
Laceration	4 (20)	1 (11)
Gait abnormal	2 (10)	4 (44)
Pain in limb	2 (10)	2 (22)
Fall	2 (10)	2 (22)

[a] Study emergent for the No-Treatment group.
AE = adverse event.

6.4.3 Evaluation of adverse events by age

The incidences of AEs according to age group (pediatric, juvenile and adult) are presented in Table 53.

There were 29 children (aged 2–11) in the pooled dataset, representing 14% of the 206 patients. All pediatric patients were enrolled in studies OGT 918-007 (NP-C) and OGT 918-006 (GD-3) and treated with miglustat 200 mg t.i.d, adjusted according to BSA.

The pattern of AEs in children was generally similar to that in adults and the small group of juvenile patients, although in comparison to the other age groups, diarrhea, flatulence, nausea, decreased appetite and decreased weight were reported at lower incidences in children. Weight changes in pediatric patients are discussed in detail in Section 6.6.3.1. Insomnia, muscle spasm and arthralgia were reported less frequently in children than in juveniles and adults. Conversely, ataxia and gait disturbance were reported at incidences < 10% in the overall miglustat population (4.3% and 2.5%, respectively), but with higher incidences in children (24.1% and 27.6%, respectively) and in juveniles (12.5% and 12.5%, respectively). It is plausible that the higher incidence of these AEs in the younger age groups is because the pediatric/juvenile population comprised GD-3 and NP-C patients only and such neurological signs/symptoms are known manifestations of the underlying diseases.

The dataset for juvenile patients (aged 12–17) included 16 patients, representing 7.8% of the 206 patients in the overall pooled dataset. All juvenile patients were enrolled in studies OGT 918-007 (NP-C) and OGT 918-006 (GD-3) and treated with a target dose of miglustat of 200 mg t.i.d. With the small number of patients available it is difficult to draw meaningful conclusions but the pattern of AEs in juvenile patients appeared generally similar to that in adults. However, some AEs including headache, nasopharyngitis and cough were reported at higher incidences than in adults.

Table 53 Summary of adverse events occurring in > 10% of patients in the miglustat-treated study population overall, by age group, Safety set

	Overall N=206[a] n %	Adults N=161 n %	Juveniles N=16 n %	Pediatrics N=29 n %
Exposure (years)				
Mean (SD)	2.2 (1.5)	2.1 (1.5)	2.3 (1.5)	2.4 (1.1)
Median	2.0	1.9	2.2	2.4
Maximum	6.6	6.6	5.4	4.4
Preferred term				
ALL SYSTEM ORGAN CLASSES				
Total patients with at least one AE	203 98.5%	161 100%	15 93.8%	27 93.1%
Total number of AEs	3051	2342	299	410
DIARRHOEA	174 84.5%	142 88.2%	13 81.3%	19 65.5%
WEIGHT DECREASED	129 62.6%	114 70.8%	9 56.3%	6 20.7%
TREMOR	95 46.1%	74 46.0%	7 43.8%	14 48.3%
FLATULENCE	91 44.2%	80 49.7%	7 43.8%	4 13.8%
FATIGUE	61 29.6%	51 31.7%	4 25.0%	6 20.7%
HEADACHE	60 29.1%	42 26.1%	9 56.3%	9 31.0%
ABDOMINAL PAIN	56 27.2%	42 26.1%	5 31.3%	9 31.0%
NASOPHARYNGITIS	56 27.2%	42 26.1%	8 50.0%	6 20.7%
VOMITING	46 22.3%	33 20.5%	4 25.0%	9 31.0%
ABDOMINAL PAIN UPPER	43 20.9%	34 21.1%	7 43.8%	2 6.9%
NAUSEA	43 20.9%	35 21.7%	6 37.5%	2 6.9%
FALL	42 20.4%	36 22.4%	3 18.8%	3 10.3%
COUGH	39 18.9%	21 13.0%	7 43.8%	11 37.9%
ARTHRALGIA	36 17.5%	34 21.1%	2 12.5%	-
DIZZINESS	33 16.0%	30 18.6%	2 12.5%	1 3.4%
MUSCLE SPASMS	33 16.0%	33 20.5%	-	-
PAIN IN EXTREMITY	32 15.5%	25 15.5%	4 25.0%	3 10.3%
PARAESTHESIA	32 15.5%	28 17.4%	2 12.5%	2 6.9%
INFLUENZA	30 14.6%	27 16.8%	2 12.5%	1 3.4%
PYREXIA	30 14.6%	18 11.2%	4 25.0%	8 27.6%
BACK PAIN	28 13.6%	25 15.5%	2 12.5%	1 3.4%
CONSTIPATION	24 11.7%	17 10.6%	3 18.8%	4 13.8%
CONTUSION	24 11.7%	20 12.4%	2 12.5%	2 6.9%
DECREASED APPETITE	24 11.7%	22 13.7%	2 12.5%	-
NERVE CONDUCTION STUDIES ABNORMAL	24 11.7%	20 12.4%	3 18.8%	1 3.4%
UPPER RESPIRATORY TRACT INFECTION	23 11.2%	18 11.2%	2 12.5%	3 10.3%
DEPRESSION	22 10.7%	21 13.0%	-	1 3.4%
INSOMNIA	21 10.2%	20 12.4%	1 6.3%	-

The pediatric population comprised 12 patients with NP-C from study OGT 918-007 and 17 patients with GD-3 from study OGT 918-006
The juvenile population comprised 9 patients with NP-C from study OGT 918-007 and 7 patients with GD-3 from study OGT 918-006
[a]This number also includes 16 patients with Fabry disease treated within study OGT 918-002
AE = adverse event, NLSD = Neuronopathic lysosomal storage disorders (NP-C, GD-3, G_{M2} gangliosidosis)

6.4.4 Evaluation of adverse events by gender

The proportions of males and females in the overall miglustat-treated population and in the NP-C population who experienced at least one AE were similar.

In both the overall miglustat-treated population and the NP-C population, the incidences of diarrhea and flatulence were somewhat higher in males than in females. Conversely, decreased weight was reported at a higher incidence in females than in males. Tremor occurred at a similar incidence in both genders in the overall population, but in the NP-C population this AE, as well as headache, appeared more common in females [Table 54].

The preferred term “Nerve conduction studies abnormal” was more commonly reported in males than in females, particularly in NP-C patients.

Table 54 Summary of adverse events occurring in > 10% of patients in the miglustat-treated study population, overall, NP-C indication and by gender, Safety set

	Overall		NP-C	
	Male N=109 n %	Female N=97 n %	Male N=19 n %	Female N=21 n %
ALL SYSTEM ORGAN CLASSES				
Total patients with at least one AE	108 99.1%	95 97.9%	19 100%	20 95.2%
Total number of AEs	1529	1522	353	456
DIARRHOEA	97 89.0%	77 79.4%	17 89.5%	16 76.2%
WEIGHT DECREASED	62 56.9%	67 69.1%	10 52.6%	14 66.7%
FLATULENCE	57 52.3%	34 35.1%	12 63.2%	10 47.6%
TREMOR	53 48.6%	42 43.3%	9 47.4%	14 66.7%
FATIGUE	36 33.0%	25 25.8%	10 52.6%	8 38.1%
NASOPHARYNGITIS	24 22.0%	32 33.0%	6 31.6%	10 47.6%
ABDOMINAL PAIN	23 21.1%	33 34.0%	6 31.6%	3 14.3%
HEADACHE	23 21.1%	37 38.1%	4 21.1%	13 61.9%
ABDOMINAL PAIN UPPER	22 20.2%	21 21.6%	5 26.3%	8 38.1%
FALL	22 20.2%	20 20.6%	2 10.5%	8 38.1%
VOMITING	21 19.3%	25 25.8%	7 36.8%	7 33.3%
INFLUENZA	19 17.4%	11 11.3%	1 5.3%	2 9.5%
NAUSEA	19 17.4%	24 24.7%	5 26.3%	5 23.8%
NERVE CONDUCTION STUDIES ABNORMAL	19 17.4%	5 5.2%	6 31.6%	2 9.5%
DIZZINESS	18 16.5%	15 15.5%	2 10.5%	1 4.8%
MUSCLE SPASMS	17 15.6%	16 16.5%	1 5.3%	1 4.8%
ARTHRALGIA	16 14.7%	20 20.6%	1 5.3%	4 19.0%
DECREASED APPETITE	16 14.7%	8 8.2%	2 10.5%	4 19.0%
COUGH	15 13.8%	24 24.7%	4 21.1%	8 38.1%
PAIN IN EXTREMITY	15 13.8%	17 17.5%	1 5.3%	4 19.0%
PARAESTHESIA	15 13.8%	17 17.5%	4 21.1%	3 14.3%
DEPRESSION	14 12.8%	8 8.2%	5 26.3%	2 9.5%
PYREXIA	14 12.8%	16 16.5%	1 5.3%	4 19.0%
INSOMNIA	13 11.9%	8 8.2%	5 26.3%	4 19.0%
ASTHENIA	12 11.0%	8 8.2%	1 5.3%	-
OEDEMA PERIPHERAL	12 11.0%	5 5.2%	2 10.5%	1 4.8%
BACK PAIN	11 10.1%	17 17.5%	2 10.5%	1 4.8%
EPISTAXIS	11 10.1%	8 8.2%	3 15.8%	2 9.5%
UPPER RESPIRATORY TRACT INFECTION	11 10.1%	12 12.4%	2 10.5%	1 4.8%

AE = adverse event, NLSD = Neuronopathic lysosomal storage disorders (NP-C, GD-3, G_{M2} gangliosidosis)

6.5 Deaths, serious adverse events, and adverse events leading to discontinuation of study treatment

6.5.1 Deaths

During the clinical trials, one patient with G_{M2} gangliosidosis died during miglustat treatment (Day 276) due to suspected cardiac arrhythmia, and an NP-C patient died 2 weeks after miglustat discontinuation due to NP-C progression with respiratory distress. An additional three deaths (two patients with NP-C and one GD-1 patient) occurred 6-8 months after discontinuation of miglustat treatment. None of the deaths were attributed as related to miglustat treatment by the investigator. The cases are summarized in Table 55. Narratives are provided in Appendix 2.

Table 55 Summary of deaths in the miglustat-treated study population, Safety set

Treatment Group Patient No. Age, Gender Treatment duration	Cause of death preferred term	Comments	Investigator-attributed relationship to study drug
During study treatment period			
[**OGT 918-009 - 104**] 48-year-old male with G_{M2} gangliosidosis Died Day 276 of miglustat treatment.	Suspected cardiac arrhythmia	History of atrial fibrillation treated with digoxin. Miglustat dose was reduced from 200 mg t.i.d. to 100 mg t.i.d. on Day 156 due to weight loss	Not suspected
After cessation of treatment			
[**OGT 918-007 - 205**] 22-year-old female with NP-C Died 2 weeks after discontinuation, following 13 months of miglustat treatment	NP-C progression with respiratory distress	Patient had swallowing difficulties, dementia, progressive dystonia and respiratory distress	Not suspected
[**OGT 918-001 - 203**] 39-year-old female with GD-1 Died Day 181 (permanently discontinued study on Day 5)	Hepatocellular carcinoma	Withdrew from study on Day 5 due to partial hepatic portal vein thrombosis. Retrospective analysis of stored samples revealed presence of tumor markers prior to start of study treatment .	Not suspected
[**OGT 918-007 - 112**] 20-year-old male with NP-C Died 6 months after withdrawing at his own request after > 3 years treatment.	Road traffic accident	The cause of the accident was unknown; the patient was driving alone.	Not suspected
[**OGT 918-007 - 122**] 11-year-old female with NP-C Died 8 months after last dose	Pneumonia, NP-C disease progression and Crohn's disease	Withdrew from study after approximately 4 years due to painful defecation and Crohn's disease	Not suspected

6.5.2 Serious adverse events

Of the 206 patients included in the overall safety dataset, 41 patients (19.9%) experienced an SAE [Table 56]. The most commonly reported SAE was viral infection, reported in three patients (1.5%). All other SAEs were reported in one to two patients only. In the NP-C population two patients experienced a viral infection SAE. All other SAEs in this population were experienced by one patient only.

Table 56 Summary of serious adverse events in the miglustat-treated study population, overall and by selected indications, Safety set

Preferred Term	Overall N=206[a] n	%	Indication: NP-C 200 mg tid N=40 n	%	NLSD 200 mg tid N=100 n	%	GD1 50-100 mg tid N=90 n	%
ALL SYSTEM ORGAN CLASSES								
Total patients with at least one SAE	41	19.9%	11	27.5%	28	28.0%	13	14.4%
Total number of SAEs	71		23		52		19	
VIRAL INFECTION	3	1.5%	2	5.0%	3	3.0%	-	
ASPIRATION	2	1.0%	1	2.5%	2	2.0%	-	
CONSTIPATION	2	1.0%	-		2	2.0%	-	
POSTOPERATIVE WOUND INFECTION	2	1.0%	1	2.5%	1	1.0%	1	1.1%
PSYCHOTIC DISORDER	2	1.0%	-		2	2.0%	-	
TIBIA FRACTURE	2	1.0%	-		2	2.0%	-	
ABDOMINAL PAIN	1	0.5%	-		1	1.0%	-	
ACCIDENTAL OVERDOSE	1	0.5%	-		1	1.0%	-	
ANAL SKIN TAGS	1	0.5%	1	2.5%	1	1.0%	-	
ANALGESIC THERAPY	1	0.5%	-		1	1.0%	-	
ARRHYTHMIA	1	0.5%	-		1	1.0%	-	
ASTHENIA	1	0.5%	-		1	1.0%	-	
BONE PAIN	1	0.5%	-		-		1	1.1%
BREAST CANCER	1	0.5%	-		-		1	1.1%
BREAST MASS	1	0.5%	-		-		1	1.1%
BRONCHITIS	1	0.5%	-		1	1.0%	-	
CELLULITIS	1	0.5%	1	2.5%	1	1.0%	-	
CEREBRAL HAEMORRHAGE	1	0.5%	-		-		1	1.1%
CHEMICAL POISONING	1	0.5%	-		-		1	1.1%
CHOKING	1	0.5%	-		1	1.0%	-	
CHOLECYSTECTOMY	1	0.5%	-		-		1	1.1%
CHOLELITHIASIS	1	0.5%	-		-		1	1.1%
CONFUSIONAL STATE	1	0.5%	1	2.5%	1	1.0%	-	
CROHN'S DISEASE	1	0.5%	1	2.5%	1	1.0%	-	
DEHYDRATION	1	0.5%	1	2.5%	1	1.0%	-	
DEPRESSION	1	0.5%	-		1	1.0%	-	
DIARRHOEA	1	0.5%	1	2.5%	1	1.0%	-	
DISINHIBITION	1	0.5%	-		1	1.0%	-	
DYSPNOEA	1	0.5%	-		1	1.0%	-	
ELECTIVE PROCEDURE	1	0.5%	-		-		1	1.1%
GAIT DISTURBANCE	1	0.5%	1	2.5%	1	1.0%	-	
GASTROINTESTINAL TUBE INSERTION	1	0.5%	1	2.5%	1	1.0%	-	
GENERAL ANAESTHESIA	1	0.5%	1	2.5%	1	1.0%	-	
HIP ARTHROPLASTY	1	0.5%	-		-		1	1.1%
LOBAR PNEUMONIA	1	0.5%	-		-		1	1.1%
MANIA	1	0.5%	-		1	1.0%	-	
NEPHROLITHIASIS	1	0.5%	-		1	1.0%	-	
NEUROPATHY PERIPHERAL	1	0.5%	-		-		1	1.1%
NIEMANN-PICK DISEASE	1	0.5%	1	2.5%	1	1.0%	-	
OTITIS MEDIA	1	0.5%	-		1	1.0%	-	
PAINFUL DEFAECATION	1	0.5%	1	2.5%	1	1.0%	-	
PERINEAL ABSCESS	1	0.5%	1	2.5%	1	1.0%	-	
PERINEAL PAIN	1	0.5%	1	2.5%	1	1.0%	-	
PNEUMONIA	1	0.5%	-		1	1.0%	-	
PNEUMOTHORAX	1	0.5%	-		1	1.0%	-	
PORTAL VEIN THROMBOSIS	1	0.5%	-		-		1	1.1%
POST LUMBAR PUNCTURE SYNDROME	1	0.5%	-		1	1.0%	-	
PROSTATOMEGALY	1	0.5%	-		-		1	1.1%
PULMONARY CONGESTION	1	0.5%	1	2.5%	1	1.0%	-	
PULMONARY FUNCTION TEST	1	0.5%	-		-		1	1.1%
RENAL STONE REMOVAL	1	0.5%	-		1	1.0%	-	
RESPIRATORY SYNCYTIAL VIRUS INFECTION	1	0.5%	1	2.5%	1	1.0%	-	
RESPIRATORY TRACT INFECTION VIRAL	1	0.5%	-		1	1.0%	-	
SPINAL OSTEOARTHRITIS	1	0.5%	-		1	1.0%	-	
SURGERY	1	0.5%	-		-		1	1.1%
THORACIC CAVITY DRAINAGE	1	0.5%	-		1	1.0%	-	
TONSILLECTOMY	1	0.5%	-		-		1	1.1%
TRAUMATIC ARTHROPATHY	1	0.5%	-		-		1	1.1%
UPPER RESPIRATORY TRACT INFECTION	1	0.5%	-		-		1	1.1%
UTERINE LEIOMYOMA	1	0.5%	-		1	1.0%	-	
VOMITING	1	0.5%	1	2.5%	1	1.0%	-	
VULVAL ABSCESS	1	0.5%	1	2.5%	1	1.0%	-	
WRIST FRACTURE	1	0.5%	1	2.5%	1	1.0%	-	
WRIST SURGERY	1	0.5%	1	2.5%	1	1.0%	-	

[a] This number also includes 16 patients with Fabry disease treated within study OGT 918-002
NLSD = Neuronopathic lysosomal storage disorders (NP-C, GD-3, GM2 gangliosidosis), SAE = serious adverse event

SAEs reported during the first 12 months in studies OGT 918-007, OGT 918-006 and OGT 918-009, including 72 patients on miglustat versus 29 on No-Treatment, are given in Table 57. The incidence of patients with at least one SAE was similar between treatment groups. There was no pattern of SAEs suggesting a relationship to miglustat treatment.

Table 57 Treatment-emergent serious adverse events occurring in the controlled phases of the NLSD studies (OGT 918-007, -006, -009), Safety set

System Organ Class Preferred Term	Miglustat N = 72 n (%)	No-Treatment N = 29 n (%)
Total No. of patients with at least one SAE	8 (11.1)	4 (13.8)
Exposure (years)		
Mean (SD)	1.0 (0.2)	1.0 (0.1)
Median	1.0	1.0
Maximum	1.2	1.2
Viral infection	1 (1.4)	-
Bronchitis	1 (1.4)	-
Otitis media	1 (1.4)	-
Respiratory syncytial virus	1 (1.4)	-
Post lumbar puncture syndrome	1 (1.4)	-
Psychotic disorder	1 (1.4)	-
Confusional state	1 (1.4)	-
Aspiration	1 (1.4)	-
Dehydration	1 (1.4)	-
Femur fracture	-	1 (3.4)
Depression	-	1 (3.4)
Mania	-	1 (3.4)
Dyspnoea	-	1 (3.4)
Uterine leiomyoma	-	1 (3.4)

SAE = serious adverse event; SD = standard deviation.

6.5.3 Discontinuations due to adverse events

Of the 206 patients included in the safety dataset, 37 patients (18.0%) experienced an AE that resulted in discontinuation of study treatment [Table 58]. The most common reasons for discontinuation were diarrhea (eight patients, 3.9%), tremor (five patients, 2.4%), flatulence, and weight loss (four patients each, 1.9%). In the NP-C population, nine patients (22.5%) experienced an AE leading to discontinuation. In this patient group there was a higher incidence of psychiatric events (three patients, 7.5%) leading to discontinuation. The overall incidence of psychiatric AEs was also higher in NP-C

patients, and included depression, insomnia, confusional state, sleep disorder and agitation [Table 54]. All these types of events also represent known disease manifestations of NP-C.

Further discussion of neurological and gastrointestinal AEs is provided in Section 6.6.1 and Section 6.6.2, respectively.

Table 58 Summary of adverse events leading to discontinuation in the miglustat-treated study population, overall and by selected indications, Safety set

	Overall	Indication		
		NP-C 200 mg tid	NLSD 200 mg tid	GD1 100 mg tid
Preferred Term	N=206[a] n %	N=40 n %	N=100 n %	N=90 n %
ALL SYSTEM ORGAN CLASSES				
Total patients with at least one AE leading to discontinuation	37 18.0%	9 22.5%	14 14.0%	18 20.0%
Total number of AEs leading to discontinuation	54	17	22	25
DIARRHOEA	8 3.9%	1 2.5%	2 2.0%	4 4.4%
TREMOR	5 2.4%	-	-	2 2.2%
FLATULENCE	4 1.9%	-	-	4 4.4%
WEIGHT DECREASED	4 1.9%	-	2 2.0%	1 1.1%
AXONAL NEUROPATHY	2 1.0%	1 2.5%	1 1.0%	1 1.1%
DEPRESSION	2 1.0%	2 5.0%	2 2.0%	-
FATIGUE	2 1.0%	-	-	2 2.2%
MEMORY IMPAIRMENT	2 1.0%	-	-	2 2.2%
NEUROPATHY PERIPHERAL	2 1.0%	-	1 1.0%	1 1.1%
PARAESTHESIA	2 1.0%	-	-	2 2.2%
AMNESIA	1 0.5%	1 2.5%	1 1.0%	-
ANOREXIA	1 0.5%	1 2.5%	1 1.0%	-
ARRHYTHMIA	1 0.5%	-	1 1.0%	-
CEREBRAL HAEMORRHAGE	1 0.5%	-	-	1 1.1%
CONFUSIONAL STATE	1 0.5%	1 2.5%	1 1.0%	-
CONVULSION	1 0.5%	1 2.5%	1 1.0%	-
CROHN'S DISEASE	1 0.5%	1 2.5%	1 1.0%	-
DIARRHOEA HAEMORRHAGIC	1 0.5%	1 2.5%	1 1.0%	-
DISTURBANCE IN ATTENTION	1 0.5%	-	-	1 1.1%
DYSPHAGIA	1 0.5%	1 2.5%	1 1.0%	-
EPSTEIN-BARR VIRUS INFECTION	1 0.5%	-	-	1 1.1%
HYPOAESTHESIA	1 0.5%	-	-	1 1.1%
INSOMNIA	1 0.5%	1 2.5%	1 1.0%	-
LETHARGY	1 0.5%	1 2.5%	1 1.0%	-
PAINFUL DEFAECATION	1 0.5%	1 2.5%	1 1.0%	-
PARANOIA	1 0.5%	1 2.5%	1 1.0%	-
POLLAKIURIA	1 0.5%	1 2.5%	1 1.0%	-
PORTAL VEIN THROMBOSIS	1 0.5%	-	-	1 1.1%
PRURITUS	1 0.5%	-	-	1 1.1%
RENAL FAILURE	1 0.5%	-	-	-
TEARFULNESS	1 0.5%	1 2.5%	1 1.0%	-

[a] This number also includes 16 patients with Fabry disease treated within study OGT 918-002
AE = adverse event, NLSD = Neuronopathic lysosomal storage disorders (NP-C, GD-3, G_{M2} gangliosidosis)

6.6 Safety areas of special interest

6.6.1 Discussion of the neurological safety of miglustat

The initial clinical trials in GD-1 raised concerns regarding a potential association of miglustat to peripheral neuropathy. The USPI for Zavesca [Appendix 3] recommends that all patients receiving Zavesca treatment should undergo baseline and repeat neurological evaluations at approximately 6-month intervals. Patients who develop symptoms such as

numbness and tingling should have a careful re-assessment of the benefit/risk of Zavesca therapy and that cessation of treatment may be considered.

The assessment of a relationship of reported peripheral nervous system AEs to miglustat is complicated by the progressive neurological signs and symptoms inherent to the underlying disorders studied, and is also hampered by the open-label design of the clinical trials. Although symptoms/signs compatible with peripheral nerve conduction disturbance/peripheral neuropathy have been reported in all of the conditions studied, it should be noted that those studies that have implemented prospective neurophysiological (EDX) evaluation have not supported a causal relationship to miglustat. Thus, a clinical trial in GD-1 (OGT 918-005) did not indicate a detrimental effect of miglustat on peripheral nerve function measured by EDX. Moreover, an ongoing observational study of miglustat-naïve patients with GD-1 (OGT 918-018), has shown that the prevalence and incidence of peripheral neuropathy is markedly increased in patients with GD-1 [Biegstraaten 2008].

Prospective EDX assessment was implemented in all the clinical studies in neuronopathic LSD (OGT 918-007, OGT 918-006, OGT 918-009) and identified high baseline prevalences of nerve conduction abnormalities as part of the underlying disease process in NP-C, GD-3 and G_{M2} gangliosidosis. The association between NP-C disease and polyneuropathy is also suggested by literature reports [Zafeiriou 2003].

Specifically, the EDX evaluation within study OGT 918-007 (Main study in adult and juvenile patients with NP-C) found evidence for a mild sensory-motor polyneuropathy with or without symptoms in 12/29 (41%) patients with data at baseline. At 12 months (data for 25 patients), one patient (randomized to the No-Treament group) had emergent EDX signs of developing polyneuropathy. One additional such case was found among the 12 patients examined at 24 months. Some patients with asymptomatic EDX evidence of polyneuropathy at baseline developed symptoms during the course of the trial. Overall the data from prospective EDX evaluation in patients with NP-C and other neuronopathic LSD do not seem to indicate that miglustat relevantly increases the risk of neuropathy in these patients.

Nevertheless, an apparent over-representation of AEs consistent with peripheral nervous system effects (mainly paresthesia) in the miglustat treatment arm during the controlled phases of the trials in neuronopathic LSD including NP-C is recognized. Monitoring of such events is part of the general clinical follow-up of patients with NP-C and is covered by the recommendation already included in the current USPI for Zavesca.

Treatment with miglustat was associated with increased incidences of headache and tremor across the spectrum of conditions investigated. These events were generally of mild to moderate intensity and there were no cases reported as SAEs.

Tremor in patients treated with miglustat was generally reported as fine, bilateral hand tremor, beginning within the first month of treatment, and sometimes resolving during continued treatment. Several patients had pre-existing tremor, exacerbated during treatment with miglustat. New-onset or worsening tremor responded to dose reduction, and resolved in all cases after withdrawal of miglustat. Tremor resulted in the discontinuation of five patients (2.4%) from the overall miglustat-treated population. New-onset tremor was not reported as an AE leading to discontinuation for any patient in the NP-C population. One adult NP-C patient experienced worsening of previous tremor during study OGT 918-007 and had her dose reduced as a result. She subsequently discontinued study medication and withdrew from the study due to this AE after approximately 9 months of miglustat treatment.

As described in previous sections, a number of other nervous system events were reported, especially among patients enrolled in the clinical trials of neuronopathic LSD, including NP-C. Generally, the types of events were those expected as manifestations of the underlying disease. The comparative phases of the studies did not suggest effects of miglustat on the incidence of important nervous system AEs [Table 50, Table 51, Table 52] or SAEs other than those discussed above [Table 56]. In contrast, as discussed in the sections on clinical efficacy in this Briefing Book [Section 5.4], study OGT 918-007 and the retrospective surveys gave clear indications of beneficial effects of miglustat for CNS involvement in NP-C disease.

In summary, the available data from concluded clinical trials do not indicate nervous system impairment of miglustat that would influence the benefit/risk evaluation in NP-C disease. Post-marketing experience, including follow-up within the IS^3 Post-Marketing Surveillance program (PMS) in the EU supports this conclusion [Section 6.7].

6.6.2 Discussion of the gastrointestinal safety of miglustat

Miglustat is associated with a high incidence of events related to gastrointestinal intolerance in the form of diarrhea, flatulence, abdominal pain and nausea, especially during the early phases of treatment. This is likely due to the inhibitory effect of miglustat on intestinal disaccharidases, resulting in carbohydrate maldigestion and osmotic diarrhea. In clinical studies in GD-1, gastrointestinal intolerance appeared to occur at similar frequencies and intensities at doses of 50 mg t.i.d. and 100 mg t.i.d. The majority of patients tolerated long-term therapy with miglustat. Tolerability appeared to improve over time on treatment and based on clinical experience, it may also be helped by diet modification (i.e., avoiding high carbohydrate content foods), taking miglustat away from meal times, and/or the use of antidiarrheal medications. Diarrhea and other gastrointestinal complaints consistently responded to cessation of therapy.

Gastrointestinal AEs were also reported frequently in the three studies in neuronopathic LSD. Importantly, and across studies, gastrointestinal tolerability did not appear different

with miglustat 200 mg t.i.d. than with 100 mg t.i.d. and appeared better in the pediatric subset of the target population of NP-C patients, compared to juvenile and adult patients.

Four patients (1.9%) in the overall dataset experienced gastrointestinal disorder AEs that were serious. Two of these were NP-C patients. One of the NP-C patients experienced an SAE of Crohn's disease and diarrhea. The patient discontinued study treatment as a result of Crohn's disease and painful defecation. For the second NP-C patient, the SAE was vomiting (associated with an SAE of viral infection). The other two patients were GD-3 patients with SAEs of constipation, one with associated abdominal pain. There were no deaths associated with gastrointestinal AEs.

Overall, 14 patients (6.8%) discontinued miglustat treatment due to gastrointestinal disorders. Four patients with NP-C discontinued due to gastrointestinal disorders, one of these was the patient who discontinued due to Crohn's disease and another was a patient who discontined due to diarrhea and was subsequently diagnosed with Crohn's disease. One further patient with NP-C treated with miglustat in general practice was diagnosed with Crohn's disease [Section 6.7]. Available data suggest a potential association between NP-C and Crohn's disease, as indicated by two published reports [Steven 2005, Jolliffe 1983] and by an unpublished report of three other cases [Wraith E personal communication] of patients with NP-C who were diagnosed with Crohn's disease but who had not received miglustat treatment. The remaining two patients discontinued due to AEs of hemorrhagic diarrhea and dysphagia.

As described in the USPI for Zavesca [Appendix 3], miglustat was associated with adenocarcinomas of the large intestine in a 2-year study in CD-1 mice. The changes observed in this study occurred at estimated intestinal exposures in excess of those possible at clinical doses. The histopathological findings in mice consisted primarily of inflammatory lesions associated with regenerative hyperplasia. The treatment-related life-long persistence of this condition in mice led to an increased incidence of adenocarcinomas in the large intestine. The findings were not observed in rats at similar dose levels. The particular situation in mice cannot be compared with the clinical situation in which patients show either a spontaneous or intended (diet modification) adaptation towards Zavesca-induced intestinal side effects. Additional data are discussed in [Section 6.7].

Considering the relatively small database available in the rare diseases investigated, the USPI for Zavesca recommends that patients with persistent gastrointestinal events that continue during treatment with Zavesca, and who do not respond to usual interventions (e.g. diet modification), should be evaluated to determine whether significant underlying gastrointestinal disease is present. As the safety of treatment with Zavesca has not been evaluated in patients with significant gastrointestinal disease, such as inflammatory bowel disease, continued treatment of these patients with Zavesca should occur only after consideration of the risks and benefits.

6.6.3 Weight and height development in pediatric and juvenile patients

Failure to thrive (gain height and weight) is a well-described manifestation of NP-C disease in children [Coleman 1998]. Since treatment with miglustat is associated with weight loss, growth in pediatric and juvenile patients was recorded in clinical studies that included such patients. Full details of the weight and height analyses from the clinical studies in NP-C are provided in Appendix 1. The proposed USPI for Zavesca includes information to prescribers that growth should be monitored in pediatric and adolescent patients during treatment with Zavesca and that the benefit/risk balance should be re-assessed for continuation of therapy on an individual basis.

6.6.3.1 Weight

There was no clear indication of any long-term impact of miglustat on weight gain in pediatric or juvenile patients.

An analysis of long-term (up to 3 years) body weight evolution in pediatric and juvenile miglustat-treated patients was performed [Appendix 1A]. A decrease in age-adjusted weight percentile was observed during the first year of treatment of pediatric and juvenile NP-C patients. Thereafter, median weight remained stable at the same percentile for the following 2 years. Following miglustat treatment for 2.5–3 years, the median weight was between the 40^{th} and 50^{th} percentile.

An analysis of individual weight data for juvenile and pediatric NP-C patients indicated that in most cases, although patients lost weight during the first year of therapy, they subsequently gained weight.

6.6.3.2 Height

In pediatric and juvenile patients treated with miglustat, some decline in the average rate of height gain was seen over the first year of treatment. Subsequently, median height percentiles remained stable, indicating maintained growth at an expected rate during long-term treatment up to three years. No long-term height growth issues were observed in individual growth charts for pediatric and juvenile patients during treatment with miglustat in the extension periods to study OGT 918-007 in NP-C disease [Appendix 1B].

6.6.4 Effects of miglustat on platelet counts in NP-C

The safety evaluation in all clinical trials included routine hematology, clinical chemistry and urinalysis tests. The only abnormality that could constitute a potential safety concern relates to reduced platelet counts in patients with NP-C disease. In patients with GD-1 miglustat increases platelet counts as part of the treatment effect. No impact on platelet counts was seen in trials in GD-3 (OGT 918-006) or G_{M2} gangliosidosis (OGT 918-009).

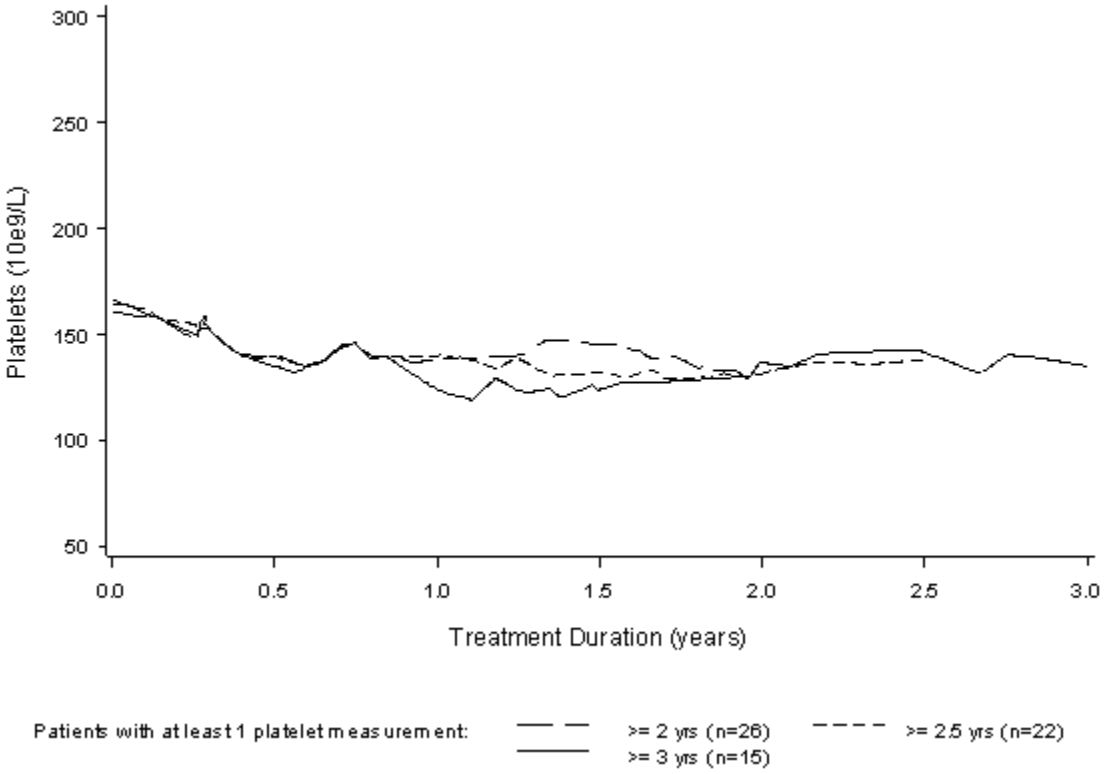
Reduced platelet counts are a common finding in NP-C disease, most likely related to residual splenomegaly, an assumption that is supported by a higher incidence of this finding in pediatric patients [Wraith 2009]. In study OGT 918-007, 31% of the adult/juvenile and 42% of the pediatric patients had platelet counts below the lower limit of normal (150×10^9/L) at screening.

During the study, moderate reductions in median platelet counts from approximately 160×10^9/L at treatment start to approximately 130×10^9/L were observed in adult/juvenile and pediatric patients [Figure 23]. There was no indication of progressive platelet count reduction over time in patients on long-term treatment for up to 3 years. No patient developed progressive thrombocytopenia and no patient had a documented platelet count $< 50 \times 10^9$/L during treatment with miglustat. There were no reports of bleeding with any apparent relationship to low platelet counts in the clinical studies. Additionally, in a study conducted in 60 HIV patients administered miglustat 1,000 mg t.i.d. (NS8-93-06-004, see Section 6.8), there was a mean reduction from baseline in platelet count of less than 5% for the 34 patients who received 24 weeks of treatment. No AEs of thrombocytopenia were reported. Post-marketing data are discussed in Section 6.7.

The effects of miglustat on platelet counts in patients with NP-C are not considered to relevantly affect the benefit/risk balance of treatment with miglustat in this indication. The proposed USPI includes appropriate information to prescribers and advice on monitoring. The information states that in a clinical trial, mild reductions in platelet counts without association with bleeding were observed in some patients with NP-C disease treated with Zavesca. It is recommended that platelet counts are monitored in these patients.

Figure 23 Median platelet values over time in patients with NP-C, Safety set

1st degree Lagrange interpolation
OGT 918, Protocol/extension: OGT 918-007/-007X
Analysis set: Safety, Overall Miglustat



6.6.5 Potential safety concerns arising from preclinical data

In addition to what has been discussed above, the following could be noted:

6.6.5.1 Potential effects on testicular function

Treatment of rats with miglustat up to small multiples of human exposure induced reversible changes in late spermiogenesis (spermatid degeneration and retention). Treatment at higher multiples of human exposure was associated with tubular atrophy. The findings correlated with reversible effects on epididymal sperm parameters (mainly motility and morphology) and fertility. The same reversible effects on sperm parameters were shown in juvenile rats treated from mid-term lactation until adulthood. The findings were seen in rats and in mice (Bone 2007), but not in non-rodent species (dog, monkey).

An increased incidence of Leydig cell adenomas was seen in the 2-year rat carcinogenicity study. The mechanism of this finding relates to a decreased production of prolactin,

sustained luteinizing hormone stimulation and finally Leydig cell adenomas in the rat. This prolactin-based mechanism is considered rat-specific without relevance to humans [Clegg 1997].

In a study in seven healthy human subjects, oral administration of miglustat 100 mg b.i.d. for 6 weeks had no apparent effect on sperm concentration, motility or sperm morphology, and there were no changes in acrosome structure or function [Amory 2007].

The current USPI for Zavesca advises that male patients should maintain reliable contraceptive methods while taking miglustat and that before seeking to conceive, male patients should cease miglustat and maintain reliable contraceptive methods for 3 months thereafter.

6.6.5.2 Potential teratogenicity

In studies in pregnant rats exposed to miglustat during gestation and lactation, dystocia and delayed parturition were observed at a systemic exposure similar to the human therapeutic systemic exposure. In the absence of clinical data, miglustat is contraindicated in women who are or may become pregnant.

6.7 Post-marketing experience

Zavesca was first registered in the EU on 20 November 2002 for the treatment of mild to moderate type 1 Gaucher disease. A post-marketing surveillance system for solicited AE reporting (the Intensive Safety Surveillance Scheme, IS^3 PMS) has been in place in the EU since that time. Zavesca was approved in the US on 31 July 2003 and post-marketing experience has been reported periodically to the FDA in line with regulations since approval.

In the 7 years (up to 19 October 2009) following first registration (in Europe), it is estimated that 998 patients have been exposed to miglustat. Of these patients, 811 received miglustat as commercially available Zavesca and 187 received miglustat in sponsored trials. With regard to age, 584 of the patients were adult/juvenile and 229 were pediatric; age was not reported for 184 patients. The IS^3 program included data for 343 of the patients, of whom 112 were NP-C patients and 155 were GD-1 patients. In addition three Zavesca-treated patients were enrolled into a newly initiated NPC Registry.

Over the post-marketing period, 415 case reports, including 62 from patients in clinical trials, were received. This included 261 reports of adverse drug reactions (ADR), of which 13 were received for patients enrolled in clinical trials.

The most frequently reported AEs from post-marketing sources, irrespective of causality and seriousness, were diarrhea (135 cases), flatulence (30 cases), abdominal distension (16 cases), dysphagia (18 cases), abdominal pain (14 cases), nausea (14 cases), and vomiting (13 cases). In addition, there were 82 cases of decreased weight reported. An

intestinal polyposis (histopathologically benign) was diagnosed in a 63-year-old female GD-1 patient (study OGT 918-016), 6.5 years after miglustat initiation. In addition, there was a post-marketing case of Crohn's disease reported in a 5-year-old, female NP-C patient treated with miglustat for 2 years (see Section 6.9.2). In both cases, a causal relationship to miglustat appeared unlikely due to the presence of confounding age and disease factors.

A total of 25 post-marketing reports containing at least one event of 'neuropathy' and/or a sign or symptom potentially suggesting peripheral neuropathy have been received. Of these cases, 14 were reported for GD-1 patients, four were reported for NP-C patients and seven were reported for other neuronopathic LSD disorders.

Peripheral neuropathy in GD-1 patients was either pre-existing or not confirmed or occurred in the presence of confounding factors such as vitamin B_{12} deficiency, monoclonal gammopathy or nerve root or spinal cord compression. Peripheral neuropathy is difficult to interpret in neuronopathic LSD patients due to the high background prevalence of neuropathy and other neurological manifestations in this population. Overall, there is no convincing evidence that Zavesca contributed to the events.

Of note, a 22-year-old, female GD-1 patient (genotype N370S/ L444P) with pre-existing neurological signs, and vitamin B_{12} deficiency, experienced symptoms of dysdiadochokinesia, dysmetria and hyperreflexia diagnosed as cerebellar syndrome after 4 months of miglustat use in the ongoing study OGT 918-011. The causal relationship between miglustat and these events is difficult to establish due to the patient's neurological condition that was present prior to initiation miglustat therapy.

There were 11 post-marketing case reports of decreased platelet count/thrombocytopenia. Of these events, eight were reported in patients with GD-1, two were reported in patients with NP-C, and the remaining case was reported in a patient with mucopolysaccharidosis. For eight of the 11 patients (most of whom had values below the lower limit of normal at baseline) mild to moderate reductions/fluctuations of platelet count were reported (lowest value 65×10^9/L). In one GD-1 patient, platelet count increased from 47×10^9/L at baseline to 75×10^9/L during Zavesca treatment. Subsequently, platelet count decreased again to 48×10^9/L. No laboratory values were provided for two patients.

Eight deaths were reported for NP-C patients treated with miglustat in general practice. Of these patients, five were female and three were male. At the time of death, seven patients were below the age of 14 years and one patient was 20 years old. None of the deaths were attributed by the treating physician as related to Zavesca, but due to progression of the patient's underlying disease. The reported causes of death were: NP-C progression (two patients), bronchopneumonia and NP-C progression (two patients), respiratory failure secondary to NP-C (one patient), pseudomonas respiratory infection and airway obstruction (one patient), asphyxiation (one patient) and hepatic failure in an 11-month-old male (one patient). All of these patients were exposed to miglustat for less than 1 year.

Based on review of the post-marketing experience, the safety profile of Zavesca is consistent with that described for the miglustat clinical trials.

6.8 Safety data from indications unrelated to LSD

Miglustat was initially developed to inhibit the replication and infectivity of the HIV virus through its activity on the oligosaccharide-processing enzymes α-glucosidase I and II. The substance concentrations needed for inhibition *in vitro*, suggested the use of very high daily doses of miglustat. These were investigated in a series of small Phase-1 studies of short duration, and in two Phase-2 studies conducted by GD Searle in 185 HIV-infected subjects. The mean age of the subject groups ranged from 33 to 38 years, and the majority of patients were Caucasian males. The studies were submitted to the FDA as part of the original Zavesca NDA. The safety experience in the two Phase-2 studies is summarized below.

Study NS8-93-06-004 consisted of an open-label, dose escalation phase, followed by a 24-week phase in which 60 subjects were randomized to miglustat 1,000 mg t.i.d. in combination with zidovudine (AZT), and 58 to placebo and AZT. Diarrhea was the most common AE and was reported for 92% of patients on miglustat compared to 36% of patients on placebo. Other gastrointestinal complaints were also frequently reported. Weight decrease was reported for 8% and 3% of patients on miglustat and placebo, respectively. As in other studies, headache was reported more frequently on miglustat than on placebo (52% versus 35%). Paresthesia was reported for 12% of subjects treated with miglustat versus 3% treated with placebo. The reported incidence of tremor was low for subjects on miglustat and on placebo (3% and 0%, respectively). Granulocytopenia was reported in 15% of subjects on miglustat compared to 7% on placebo. However, there was no difference between the groups regarding the incidence of severe granulocytopenia, and there were no other hematological AEs.

Study NS8-94-06-009 was an open-label, randomized, factorial design study conducted in 67 subjects assigned to treatment with miglustat 0, 500 or 1,000 mg t.i.d., with or without concomitant AZT for 12 weeks. In an extension phase, a total of 18 subjects continued treatment with miglustat 500 or 1,000 mg with or without AZT for up to 24 weeks. The incidence of diarrhea was 67% and the incidence of headache was 20%. Tremor and hypoesthesia/paresthesia were reported at respective incidences of 6%, and 3%. There were two reports of leukopenia (3%), but no other hematological AEs were reported.

In summary, the experience in these studies does not indicate additional safety issues with daily doses of miglustat up to 5-fold higher than those proposed in the treatment of NP-C.

6.9 Safety conclusions

The safety observations with miglustat have been consistent over the clinical development program and in post-marketing reporting, and no qualitatively new clinical observations

have been made since the initial studies. The findings made in the previous clinical development program are also reflected in the studies in neuronopathic LSD, especially NP-C as discussed in this Briefing Book. The potential safety issues therefore relate to two main areas: neurological safety and gastrointestinal safety.

6.9.1 Neurological safety

There is evidence that miglustat is associated with tremor or worsening of previous tremor, and with an increased incidence of headache. These reactions have typically been of mild intensity, tend to improve with time on therapy, and are reversible upon discontinuation of miglustat. Adverse events indicating a potential association of miglustat to peripheral neuropathy were reported in the first registration studies in GD-1 but have not been confirmed in additional studies with prospective neurophysiological evaluation or in the post-marketing experience. Peripheral neuropathy was either pre-existing or not confirmed or occurred in the presence of confounding factors such as vitamin B_{12} deficiency, monoclonal gammopathy or nerve root or spinal cord compression following vertebral body collapse. Taking into account the high prevalence of neurological involvement in neuronopathic LSD patients (including those with NP-C), there appears to be no clear evidence that miglustat is a contributory factor.

6.9.2 Gastrointestinal safety

Miglustat is associated with gastrointestinal intolerance, manifesting mainly as diarrhea, likely related to the inhibition by miglustat of intestinal disaccharidases. Clinical experience indicates that dietary advice, including a low carbohydrate diet and not taking miglustat around meal times, may prevent or ameliorate diarrhea, which also responds to symptomatic antidiarrheal therapy. The gastrointestinal tolerability to miglustat improves over time of use, and diarrhea and other gastrointestinal complaints consistently respond to cessation of therapy. Consistent with the proposed mechanism, miglustat has not been causally associated with the development of inflammatory bowel disease. In the three studies in neuronopathic LSD, including NP-C, the great majority of patients tolerated long-term treatment with miglustat at 200 mg t.i.d. (adjusted according to BSA in pediatric patients) and there were no indications that this higher dose was associated with a gastrointestinal safety profile that is relevantly different from the dose (100 mg t.i.d.) approved for the treatment of GD-1.

As in studies in GD-1, transient weight loss, usually temporally associated to diarrhea, was observed in half of the patients with neuronopathic LSD treated with miglustat. Weight stabilized over the first year of treatment. In pediatric patients, there was no indication of negative long-term effects of miglustat on body growth. Patients on miglustat should, however, be appropriately monitored for body weight changes during treatment, and growth should be followed in pediatric patients.

6.9.3 Overall conclusion

Overall, the data generated corroborate the conclusion that the safety profile of miglustat in pediatric and adult patients with neuronopathic LSD (including NP-C) is comparable with that in the approved indication in adult patients with GD-1. Neither the higher dose of miglustat of 200 mg t.i.d., nor the use of miglustat in pediatric or juvenile patients have raised important new safety concerns.

7 BENEFIT/RISK EVALUATION

7.1 Summary of benefits

Niemann-Pick type C disease is a very rare disorder, dominated by disabling and ultimately fatal nervous system involvement. The neurological disease is invariably progressive, without spontaneous remission or natural plateau, as shown also by the evolution in untreated patients and patients observed prior to miglustat treatment, as described in this Briefing Book.

There has been no therapy with proven efficacy in NP-C. Given the relentlessly progressive nature of the disease, a tolerable treatment that could favorably modify neurological function would represent a highly relevant advancement in the clinical management of the disease, which is currently based on supportive measures. In this context, halting the progression of the neurological disease or reducing its rate of deterioration should be considered beneficial.

As discussed in this Briefing Book, there is consistent evidence that miglustat is active on the progression of neurological involvement in patients with NP-C disease, and that this activity translates into benefit for patients both in individual, clinically relevant endpoints, as well as responder and progression rate analyses that assess the benefit at the patient level.

Data from study OGT 918-007 support a positive effect of miglustat on the progression of deterioration of horizontal saccadic eye movement velocity, an important and characteristic sign of brainstem involvement in patients with NP-C. This should eventually translate into a delay of the development of established gaze palsy, which is associated with marked visual handicap.

Both the data from the prospective clinical trial OGT 918-007 and the findings in the Stage I survey have indicated long-term benefit of miglustat treatment on major and clinically highly relevant aspects of neurological disability in NP-C patients, such as swallowing impairment and ambulatory disability. Disease stabilization was achieved by the majority of patients during treatment with miglustat and appeared maintained over long-term treatment for a mean of 42 months in study OGT 918-007. These findings are clinically important and in marked contrast to the natural course of the disease, as shown by both the pre-treatment evolution among patients in the Stage I survey and during

long-term observation of untreated patients in the Stage II survey of natural disease history. In the Stage I survey there was a clear reduction of the progression rate after the initiation of miglustat, compared with the pre-treatment phase in these patients. The treatment effect of miglustat, defined as the difference in progression rate between the miglustat treatment and pre-treatment phases, was statistically significant in both domains. The majority of patients achieved at least stabilization of swallowing and general motor function during miglustat therapy for a mean of 1.5 years.

Miglustat treatment also prevented progressive deterioration of dysmetria/dystonia, a relevant manifestation of cerebellar dysfunction in NP-C, in a high proportion of patients in the Stage I survey. The observed treatment effect of miglustat on the rate of disease progression was substantial and significant in the group of patients with documented progressive neurological disease prior to treatment. Again, this is in contrast with the uninterrupted worsening of dystonia and dysmetria during the natural course of the disease.

Both clinical trial data and the retrospective surveys also indicated a therapeutic effect of miglustat on cognitive ability, measured through the MMSE in the OGT 918-007 Main study, and through the assessment of the language function/articulation domain in the Stage I and II surveys.

At the responder level, a clinically meaningful benefit in stabilization of disease was provided to the targeted NP-C patient population, both in the prospective study OGT 918-007 and in the retrospective Stage I survey, where a clear treatment effect of miglustat on the progression rate of composite disability was observed. Among patients with documented progressive neurological disease prior to the initiation of miglustat treatment, the magnitude of the effect on neurological disease progression rate appeared the largest and was statistically significant, and comparable across patients with different ages of disease onset. This included those patients with early-childhood onset, known to be associated with rapid disease progression.

Taking the totality of the information into account, miglustat treatment provides clinically relevant effects on the progression of CNS involvement in patients with NP-C disease. The datasets have limitations regarding size and methodology. Nevertheless, a degree of robustness is created by the fact that long-term findings in 160 NP-C patients (120 treated with miglustat and 40 untreated), representing nearly 50% of the entire estimated number of approximately 400 patients diagnosed with NP-C disease in the US and in the EU, have been considered, with fully consistent findings.

7.2 Summary of risks

The findings in the previous clinical development program in GD-1 and in the post-marketing experience were also reflected in the studies in neuronopathic LSD discussed in this Briefing Book. Neither the higher dose of miglustat of 200 mg t.i.d., nor

the use of miglustat in juvenile and pediatric patients have raised important new safety issues.

Miglustat is associated with gastrointestinal intolerance, manifesting as diarrhea, flatulence, abdominal discomfort/pain, nausea, or combinations thereof. All available data indicate that these symptoms are due to the inhibitory effect of miglustat on intestinal disaccharidases, resulting in osmotic diarrhea. Overall, the gastrointestinal side effects of miglustat tend to improve with time on treatment, and the experience in the approved indication GD-1 has shown them to be manageable in clinical practice. The studies of patients with neuronopathic LSD, including NP-C, at the adult dose of 200 mg t.i.d. (adjusted for BSA in children) showed that the great majority of patients tolerated long-term treatment with miglustat at this dose and with a similar gastrointestinal safety profile as in patients with GD-1 at 100 mg t.i.d.

Consistent with previous findings in GD-1, and as described in the USPI for Zavesca, weight loss was observed in the majority of patients with NP-C and other neuronopathic LSD. Similar to gastrointestinal tolerability, weight stabilized over time.

As weight loss may be an area of special interest in growing individuals, the long-term data on weight and height development available from pediatric and juvenile patients exposed to miglustat for up to 3 years were scrutinized in detail. The findings do not suggest that the use of miglustat in children would introduce any risk for growth impairment that would outweigh benefit. Patients on miglustat should, however, be monitored as appropriate for body weight changes during treatment, and growth characteristics should be followed in pediatric and juvenile patients.

Another area of special interest with miglustat has been nervous system safety. As discussed in this Briefing Book, there are indications that miglustat is causally associated with fine tremor or worsening of previous tremor and headache. These reactions have typically been of mild intensity, and reversible upon discontinuation of miglustat. A potential association of miglustat with peripheral neuropathy was raised by AEs reported in the first registration studies in GD-1. This finding has not been confirmed by data from additional patients, either in clinical studies with prospective neurophysiological evaluation, or in post-marketing data.

Study OGT 918-007 in NP-C disease showed a modest and non-progressive reduction in platelet counts in patients treated with miglustat. This finding was not accompanied by bleeding events and was not seen in other studies with miglustat. Considering the mild nature of the change and that it is easily monitored in clinical practice, the impact on the benefit/risk ratio of miglustat in NP-C is considered minor.

Finally, previous preclinical studies raised potential issues regarding reversible testicular effects of miglustat. No clinical data are available to define any relevance of these findings specifically for the population of juvenile/adult or pediatric male patients with NP-C. In

the benefit/risk assessment, the progressive and eventually fatal course of untreated NP-C disease should be taken into account.

Overall, the data support the conclusion that the safety profile of miglustat in pediatric and adult/juvenile patients with neuronopathic LSD, and especially in patients with NP-C disease, is comparable with that in the approved indication in adult patients with GD-1.

7.3 Overall benefit/risk

The available data consistently support favorable activity of miglustat on several cardinal neurological manifestations of NP-C, both in a clinical trial and in the clinical practice setting. The evidence provided shows a relevant clinical benefit of miglustat treatment in patients with this currently untreatable and invariably progressive disorder. The magnitude of the treatment effect and the consistency of the impact of miglustat treatment on the neurological disease appear even more relevant when NP-C patients with progressive neurological disease are considered. Both patients with early onset of the disease during childhood and those with onset during late childhood/adolescence and adulthood appear to benefit from miglustat treatment.

There are no specific safety concerns associated with miglustat in the population of patients with NP-C disease with neurological involvement that could not be monitored and managed in clinical use or that would outweigh a benefit of miglustat in the treatment of NP-C.

The use of miglustat should be managed and monitored by physicians knowledgeable and experienced in the care of patients with NP-C disease. As discussed above, the USPI, as amended, is considered to provide adequate advice on monitoring and precautionary measures.

7.4 NP-C disease registry

To ensure the continued generation of data on the disease course and the effectiveness of treatment in the very rare disease of NP-C, a disease registry has been implemented by Actelion in the EU and will be extended to other countries where Zavesca is approved for this indication, including the US. The registry is a multicenter, prospective, observational program designed to collect data in patients with NP-C disease, and is open to patients with NP-C, irrespective of whether they receive treatment with miglustat. The objectives of the registry are to follow, from the time of enrolment, the long-term natural history and disease course of NP-C in patients in the real-world clinical setting and to collect safety data for patients treated with Zavesca.

A registry approach has been selected due to the severe limitations imposed by the rarity of NP-C on the evaluation of miglustat in formal clinical trials. Currently, a major proportion of the known population of patients with NP-C (estimated at approximately 400 in Europe and the US) is either receiving treatment with miglustat in clinical practice, or

has received treatment in clinical trials. Given the heterogeneous presentation and course of NP-C disease, a confirmatory study on a traditional clinical endpoint would have to be a long-term placebo-controlled study. The data from study OGT 918-007 have been in the public domain since 2005 [Patterson 2005, Patterson 2007] and the overall data on miglustat in NP-C have resulted in consensus statements on the diagnosis and management of NP-C [Wraith 2009].

7.5 Conclusion

Based on thorough assessment of the available data, and taking into account the current complete lack of treatment options and, thus, the level of unmet medical need, the benefit/risk ratio for Zavesca is favorable in the proposed indication:

Zavesca is indicated for the treatment of progressive neurological manifestations in adult patients and pediatric patients with Niemann-Pick type C disease.

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APPENDIX 1 PEDIATRIC AND JUVENILE WEIGHT AND HEIGHT DATA

A. Weight

Of the 206 patients in the overall dataset, including both adult and juvenile/pediatric patients, 129 (62.6%) reported AEs for weight decrease. The incidence of weight decrease as an AE was similar across the indications, and reported in 60% of NP-C patients. Decreased appetite and anorexia were, respectively, reported by 12% and 5% of the overall miglustat-treated population and 15% and 8% of the NP-C population.

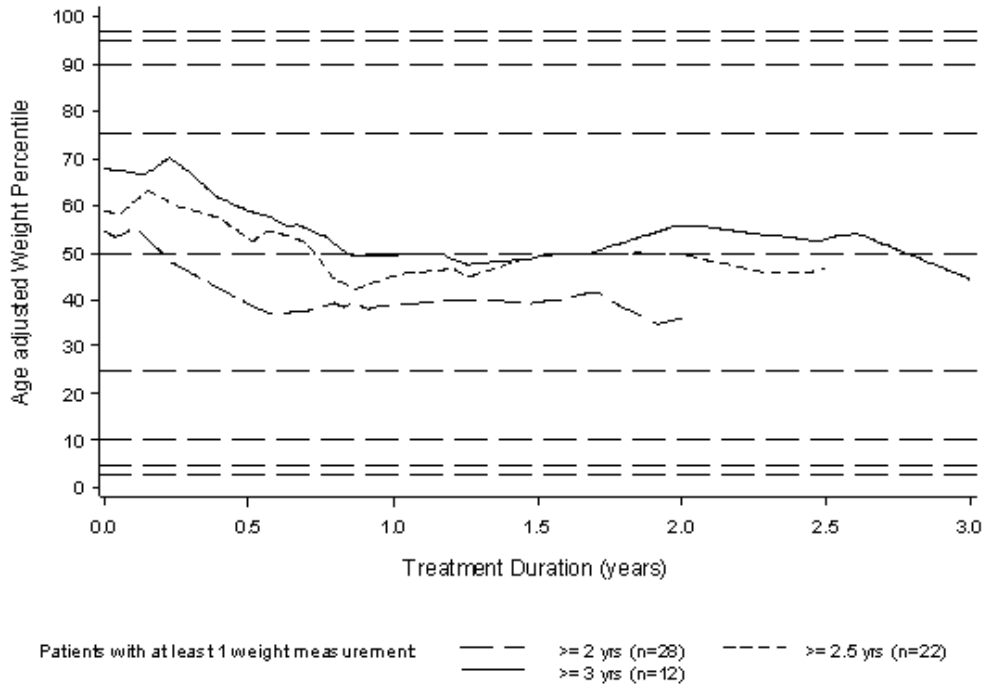
In the overall miglustat-treated population, the period prevalence of weight decrease peaked at 60% between Months 6 and 12, and subsequently decreased in every 6-month period thereafter up to 3 years. From 2.5–3 years, the prevalence was 39%.

None of the events of weight decrease were reported as SAEs. However, four patients discontinued study treatment as a result of decreased weight. These cases occurred in one GD-1 patient, one Fabry disease patient and two G_{M2} gangliosidosis patients, one of whom experienced weight decrease assessed as severe. No NP-C patient discontinued miglustat treatment as a result of a weight decrease AE.

Body weight decrease may be of special concern in growing patients in the pediatric and adolescent age range. A separate analysis of long-term (up to 3 years) body-weight evolution during miglustat treatment was performed [Figure 1]. This analysis focused on the evolution of weight percentile (i.e., adjusted by age and gender) in patients aged < 20 years at treatment start. A decrease in weight percentile was observed during the first year of treatment. Thereafter, median weight remained stable at the same percentile for the following 2 years. Patients were generally above the 50^{th} percentile at baseline and the medians at 2.5–3 years were between the 40^{th} and 50^{th} percentile. No long-term weight decrease was observed during treatment with miglustat.

Figure 1 Median weight percentile values over time (1st degree Lagrange interpolation), overall miglustat pediatric and juvenile population

Protocols/extensions: OGT 918-004/-004X, OGT 918-006/-006X, OGT 918-007/-007X and OGT 918-009/-009X

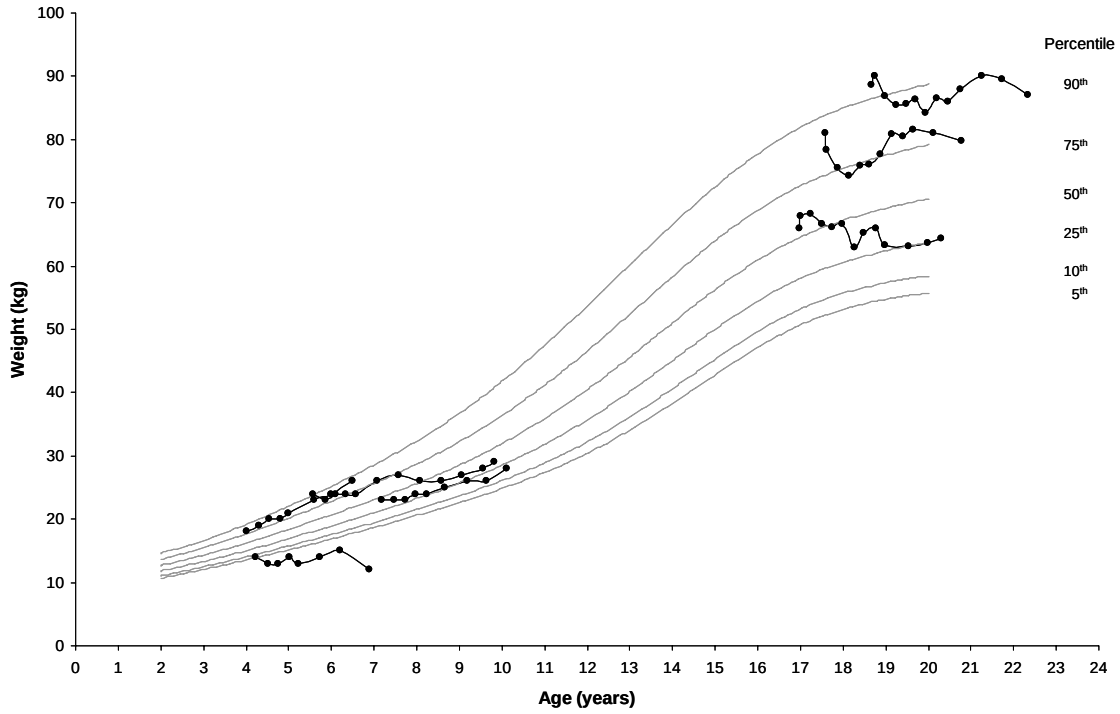


Individual weight curves in male patients with NP-C

One pediatric male patient (226) who commenced miglustat treatment at the age of 4.2 years failed to gain weight over the 2.5 years that he was on miglustat treatment [Figure 2], although he did gain height [Figure 5]. This patient suffered persistent diarrhea and had mild swallowing problems throughout most of the study. Further, he had a medical history of frequent respiratory infections and allergies and suffered ear, sinus and respiratory tract infections on a number of occasions during the study.

Three other male pediatric patients continued to gain weight over the treatment period [Figure 2]. Three patients, aged 17.0, 17.6 and 18.7 years at baseline, initially lost weight. Overall, these patients lost up to 2.4% of bodyweight over the duration of study treatment.

Figure 2 Weight changes in male pediatric and juvenile patients treated with miglustat (study OGT 918-007)



Individual patient data (bold lines with data points) and percentiles (fine lines) [www.cdc.gov]

Individual weight curves in female patients with NP-C

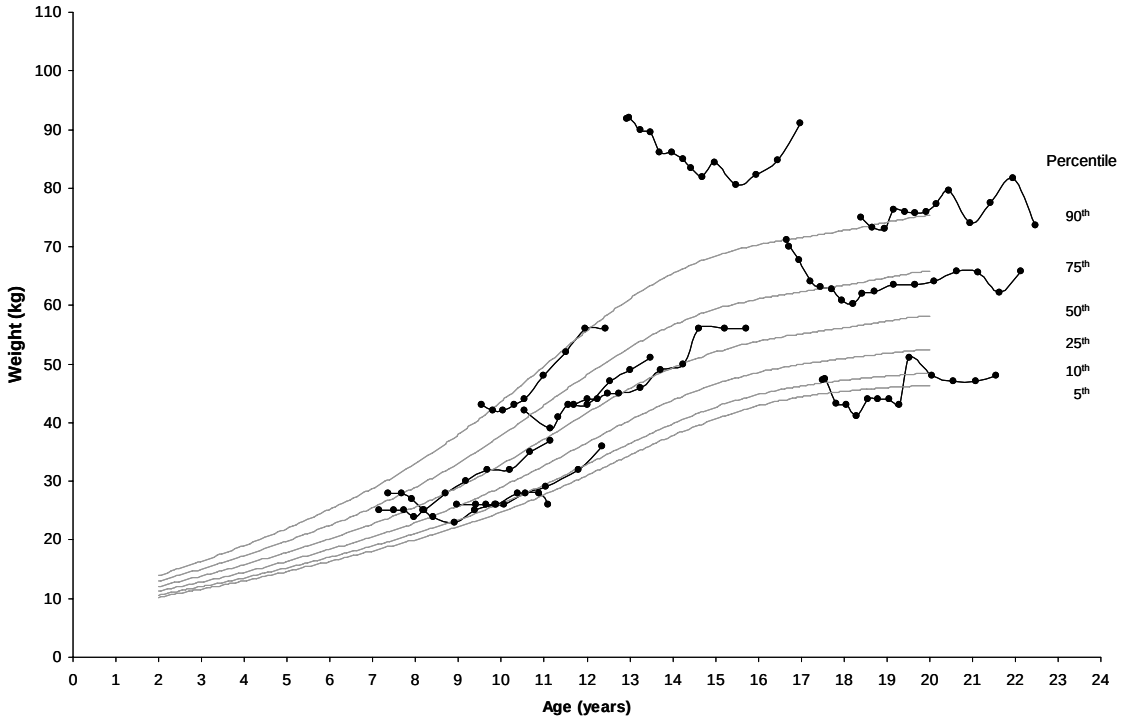
Patient 122 who was 7.3 years old at baseline experienced a decrease in weight from the 12th percentile at baseline to below the 1st percentile at last visit [Figure 3]. During the same period, she gained height. During the study, she suffered diarrhea but had no or only mild difficulty swallowing.

The other five pediatric female patients all gained weight over the study, although during the first year of treatment they either gained little weight or lost some weight.

One juvenile patient aged 12.9 years at baseline lost weight over the first 2 years of study treatment. However, she had already achieved a height that exceeded the 90th percentile for an 18-year-old female at baseline, did not increase in height during the study and her weight exceeded the 97th percentile throughout the study. In addition, her weight at last value was similar to her baseline weight.

Three female patients aged 16.7, 17.5 and 18.4 years at baseline initially lost weight but two returned to within 2% of baseline weight by last value, while the third had an overall weight loss of 7.3% from baseline.

Figure 3 Weight changes in female pediatric and juvenile patients treated with miglustat (study OGT 918-007)



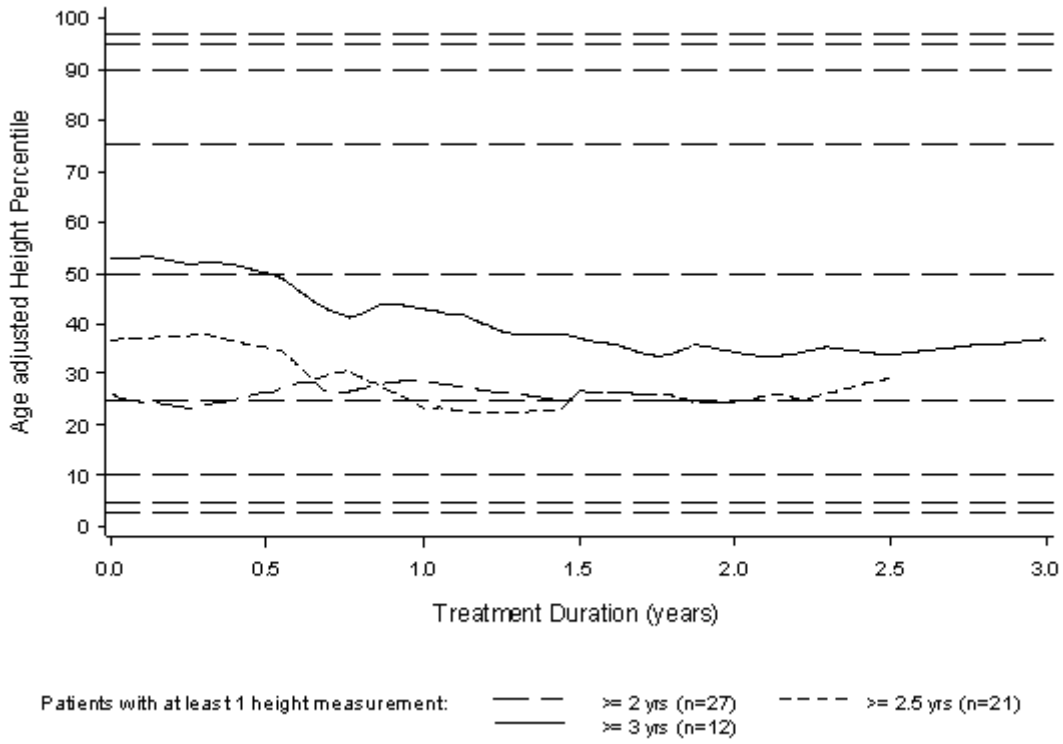
Individual patient data (bold lines with data points) and percentiles (fine lines) [www.cdc.gov]

B. Height

Figure 4 shows the evolution of height percentile (i.e., adjusted by age and gender) in patients aged < 20 years at baseline. A small decline in the rate of height growth was seen over the first year of treatment. Subsequently, median height percentiles remained stable, indicating maintained growth, at an expected rate. No other long-term height growth issues were observed in individual growth charts for pediatric and juvenile patients during treatment with miglustat in the extension periods to study OGT 918-007 in NP-C disease [Figure 5 and Figure 6].

Figure 4 Median height percentile values over time (1st degree Lagrange interpolation), overall miglustat pediatric and juvenile population

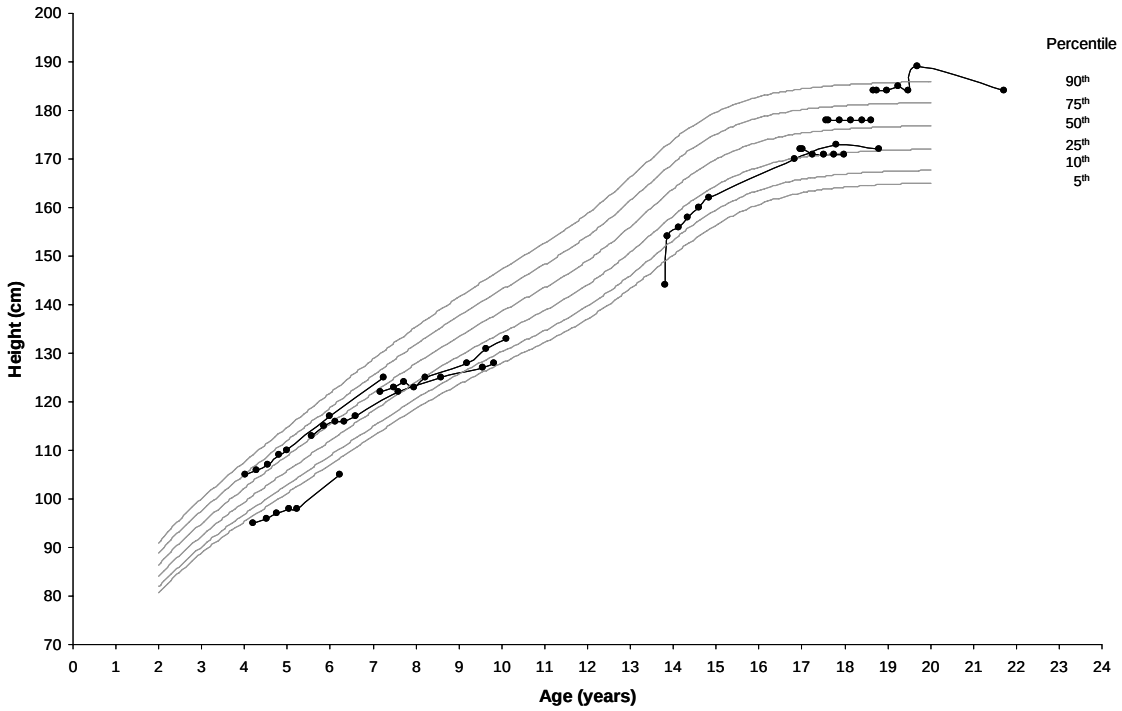
Protocols/extensions: OGT 918-004/-004X, OGT 918-006/-006X, OGT 918-007/-007X and OGT 918-009/-009X



Individual height curves in male patients with NP-C

Two male patients commenced miglustat treatment at heights that were below the 5th percentile. One of these patients (13.8 years at baseline) achieved a height at the 25th percentile at the age of 18.8 years, the other patient who was 4.2 years at baseline, grew steadily but remained below the 5th percentile at 6.2 years. Three male patients did not gain height, but were 17.0, 17.6 and 18.7 years old at baseline. The other patients gained height over the assessment period and there was no clear indication of any long-term impact on height growth in pediatric or juvenile males [Figure 5].

Figure 5 Height changes in male pediatric and juvenile patients treated with miglustat (study OGT 918-007)

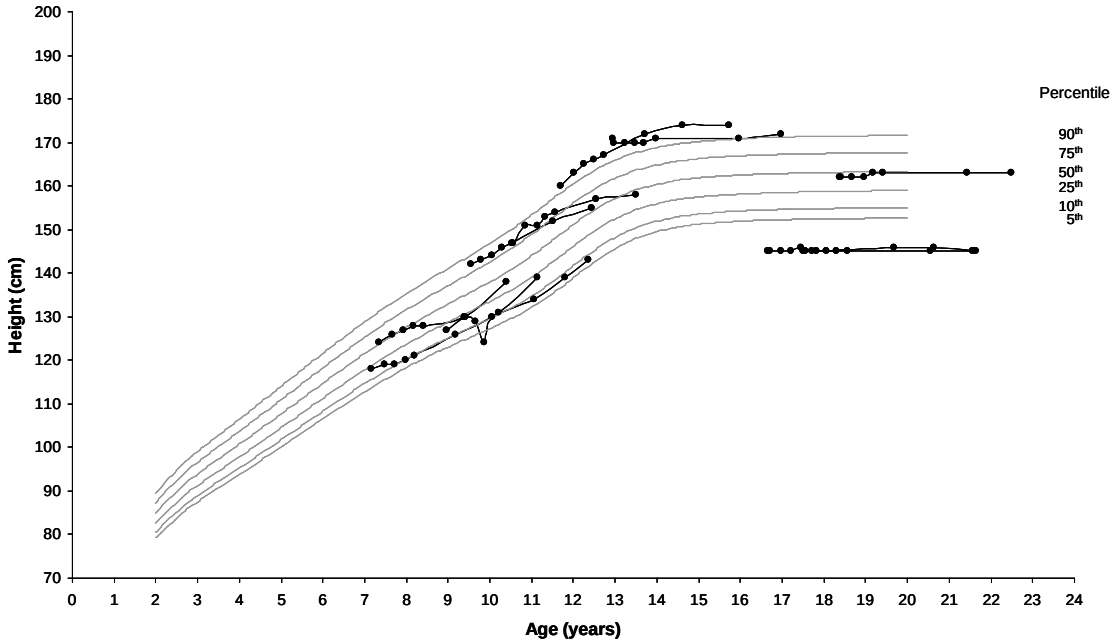


Individual patient data (bold lines with data points) and percentiles (fine lines) [www.cdc.gov]

Individual height curves in female patients with NP-C

There were two female patients who were below the 5% percentile at each measurement point, but they were 16.7 and 17.5 years of age at baseline and, therefore, had probably achieved their maximum height prior to start of miglustat treatment. Two other female patients failed to grow, but one was 18.4 years at baseline and the other had already exceeded the 90th percentile for an 18-year-old at the age of 12.9 years. The other patients gained height over the assessment period and there was no clear indication of any long-term impact on height growth in pediatric or juvenile females [Figure 6].

Figure 6 Height changes in female pediatric and juvenile patients treated with miglustat (study OGT 918-007)



Individual patient data (bold lines with data points) and percentiles (fine lines) [www.cdc.gov]

APPENDIX 2 NARRATIVES FOR DEATHS IN MIGLUSTAT CLINICAL TRIALS

A. Study 918-009, Patient 009-104

This 48-year-old male patient with G_{M2} gangliosidosis and a medical history that included supraventricular tachycardia, commenced treatment with miglustat 200 mg t.i.d. on 11 February 2004. Concomitant medication included digoxin, propranolol, levothyroxine, valproate, lithium, quetiapine, Reguloid, lactulose, ascorbic acid, omega-3, cetirizine and potassium. His miglustat dose was down-titrated to 100 mg t.i.d. on an unknown date due to poor appetite and weight loss.

At 10:30 pm on 6 October 2004, immediately after taking his quetiapine and valproate medications and having felt unwell for the entire day, the patient fell back and stopped breathing. Resuscitation attempts were unsuccessful. His mother reported that the paramedics observed an orange fluid in his lungs. The patient's primary physician attributed the death to cardiac arrhythmia. No autopsy was performed. The investigator assessed the death as unrelated to miglustat.

B. Study 918-007, Patient 007-205

This 22-year-old female patient with NP-C disease commenced treatment with miglustat 200 mg t.i.d. on 16 April 2004. Concomitant medication included guaifenesin, citalopram, diazepam, baclofen, and chloral hydrate.

Exacerbation of the patient's NP-C was reported on 4 May 2005. She had swallowing difficulties, dementia, progressive dystonia and respiratory distress. Miglustat treatment was stopped on 15 August 2005 due to swallowing difficulties. The patient died on 29 August 2005 due to disease progression with respiratory distress. No autopsy was performed. The investigator assessed the death as unrelated to miglustat.

C. Study 918-001, Patient 001-203

This 39-year-old female patient with Gaucher disease commenced treatment with miglustat 100 mg t.i.d. on 15 December 1998. Previous treatment for Gaucher disease included Ceredase and Cerezyme (before May 1998). Medical history included fitting of a port-a-cath on an unknown date and a splenectomy in 1977. No concomitant medications were reported.

On 18 December 1998, the patient was hospitalized with abdominal pain in the liver region (right lower quadrant) that had commenced 3 days earlier. She had a slight fever (38 °C), nausea, anorexia and constipation. Her miglustat treatment was stopped the same day. A CT-scan was consistent with partial thrombosis of the portal vein but revealed no tumor. The patient also had massive inhomogenous hepatomegaly (usual in Gaucher disease). Her port-a-cath was removed because of chronic infection that was considered to

be a potential trigger for further deterioration of her condition. The patient was started on enzyme therapy but developed portal hypertension and liver failure. Alpha-fetoprotein levels were highly elevated and hepatocellular carcinoma complicated by portal thrombosis was diagnosed. A retrospective analysis of stored serum samples revealed that her alpha-fetoprotein levels were already very high in May 1998, 6 months prior to initiation of miglustat treatment. The patient died on 12 June 1999 after a possible septic episode. An autopsy was refused. The investigator assessed the event as unrelated to miglustat.

D. Study 918-007, Patient 007-112

This 20-year-old male patient with NP-C disease commenced treatment with miglustat 200 mg t.i.d. on 22 January 2004. No medical history or concomitant medication were detailed.

The patient withdrew from the study on 3 May 2007 at his own request. On 27 November 2007, he died in a road traffic accident. The cause of the accident is unknown. The patient was driving alone and no other cars were thought to be involved. The investigator assessed the death as unrelated to miglustat.

E. Study 918-007, Patient 007-122

This 11-year-old female patient with NP-C disease commenced treatment with miglustat 200 mg b.i.d.on 14 August 2003 with the dose increased to 200 mg t.i.d. on 23 February 2007. A current condition of cataplexy was reported and concomitant medications included clonazepam and imipramine.

She was hospitalized with painful bowel motions, profuse diarrhea, perianal tags (acrochordon), genital pain, and pyrexia after 3.5 years on miglustat treatment. A vulval abscess was suspected. A stool culture was negative, but a sigmoidoscopy showed congested erythematous mucosa in the rectosigmoid and colorectal biopsies revealed moderate stromal inflammatory infiltrate including microgranulomas (no foam cells). Mild mucin depletion was apparent, but there was no dysplasia, malignancy, or cryptitis. The appearance was consistent with Crohn's disease. The results of a barium swallow test were normal. The patient was treated with oral prednisolone, naso-gastric feeding, i.v. and oral antibiotics. Miglustat treatment was discontinued, and her condition improved. The investigator could not rule out the possibility that miglustat could have worsened the symptoms of Crohn's disease, however, he noted that he knew of three other patients with NP-C who had concurrent Crohn's disease and had never been treated with miglustat. The investigator assessed the SAEs of Crohn's disease, anal skin tags, painful defecation and perianal abscess as unrelated to miglustat and the event of profuse diarrhea as unrelated to study medication; however, the sponsor considered the case to be related because the contribution of miglustat to the diarrhea could not be excluded.

Approximately 8 months after discontinuation of miglustat treatment, the patient died due to bilateral pneumonia, NP-C disease, scoliosis, and Crohn's disease.

APPENDIX 3 CURRENT ZAVESCA USPI

PACKAGE INSERT

ZAVESCA®

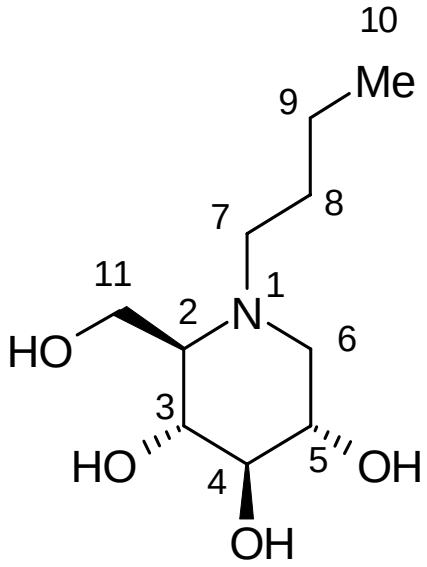
[miglustat]

Capsules, 100mg

DESCRIPTION

ZAVESCA® (miglustat capsules, 100mg) is an inhibitor of the enzyme glucosylceramide synthase, which is a glucosyl transferase enzyme responsible for the first step in the synthesis of most glycosphingolipids. ZAVESCA® is an N-alkylated imino sugar, a synthetic analogue of D-glucose.

The chemical name for miglustat is 1,5-(butylimino)-1,5-dideoxy-D-glucitol with the chemical formula $C_{10}H_{21}NO_4$ and a molecular weight of 219.28.



Miglustat is a white to off-white crystalline solid and has a bitter taste. It is highly soluble in water (>1000mg/mL as a free base).

ZAVESCA® is supplied in hard gelatin capsules each containing 100 mg miglustat for oral administration. Each ZAVESCA® 100 mg capsule also contains sodium starch glycollate, povidone (K30), and magnesium stearate. Ingredients in the capsule shell include gelatin and titanium dioxide, and the shells are printed with edible ink consisting of black iron oxide and shellac.

CLINICAL PHARMACOLOGY

Background

Type 1 Gaucher disease is caused by a functional deficiency of glucocerebrosidase, the enzyme that mediates the degradation of the glycosphingolipid glucosylceramide. The failure to degrade glucosylceramide results in the lysosomal storage of this material within tissue macrophages leading to widespread pathology. Macrophages containing stored glucosylceramide are typically found in the liver, spleen, and bone marrow and occasionally in lung, kidney, and intestine. Secondary hematologic consequences include severe anemia and thrombocytopenia in addition to the characteristic progressive hepatosplenomegaly. Skeletal complications include osteonecrosis and osteopenia with secondary pathological fractures. Enzyme replacement therapy is the standard of care for most patients who require treatment for type 1 Gaucher disease.

Mode of Action

Miglustat functions as a competitive and reversible inhibitor of the enzyme glucosylceramide synthase, the initial enzyme in a series of reactions which results in the synthesis of most glycosphingolipids. The goal of treatment with ZAVESCA® is to reduce the rate of glycosphingolipid biosynthesis so that the amount of glycosphingolipid substrate is reduced to a level which allows the residual activity of the deficient glucocerebrosidase enzyme to be more effective (substrate reduction therapy). *In vitro* and *in vivo* studies have shown that miglustat can reduce the synthesis of glucosylceramide-based glycosphingolipids. In clinical trials, ZAVESCA® improved liver and spleen volume, as well as hemoglobin concentration and platelet count.

Pharmacokinetics

Absorption

After a 100 mg oral dose, the time to maximum observed plasma concentration of miglustat (t_{max}) ranged from 2 to 2.5 hours in Gaucher patients. Plasma concentrations show a biexponential decline, characterized by a short distribution phase and a longer elimination phase. The effective half-life of miglustat is approximately 6 to 7 hours, which predicts that steady-state will be achieved by 1.5 to 2 days following the start of three times daily dosing.

Miglustat, dosed at 50 and 100 mg in Gaucher patients, exhibits dose proportional pharmacokinetics. Miglustat's pharmacokinetics were not altered after repeated dosing three times daily for up to 12 months.

Co-administration of ZAVESCA® with food results in a decrease in the rate of absorption of miglustat (maximum serum concentration [C_{max}] was decreased by 36% and t_{max} delayed 2 h) but has no statistically significant effect on the extent of absorption of miglustat (area-under-the-plasma-concentration curve [AUC] was decreased by 14%).

The mean oral bioavailability of a 100-mg miglustat capsule is about 97% relative to an oral solution administered under fasting conditions.

Distribution

Miglustat does not bind to plasma proteins. Mean apparent volume of distribution of miglustat is 83-105 liters in Gaucher patients, indicating that miglustat distributes into extravascular tissues.

Elimination

The major route of excretion of miglustat is renal. Miglustat is excreted unchanged in the urine. Renal impairment has a significant effect on the pharmacokinetics of miglustat resulting in increased systemic exposure of miglustat in such patients. There is no evidence that miglustat is metabolized in humans.

Special Populations

Geriatric Patients

ZAVESCA® has not been evaluated in geriatric patients over 65 years. (See **PRECAUTIONS**; **Geriatric Use**)

Pediatric Patients

ZAVESCA® has not been evaluated in patients under the age of 18 years. (See **PRECAUTIONS; Pediatric Use**)

Gender

There was no statistically significant gender difference in miglustat pharmacokinetics, based on pooled data analysis.

Race

Ethnic differences in miglustat pharmacokinetics have not been evaluated in Gaucher patients. However, apparent oral clearance of miglustat in patients of Ashkenazi Jewish descent was not statistically different to that in others (1 Asian and 15 Caucasians), based on a cross-study analysis.

Hepatic Insufficiency

No studies have been performed to assess the pharmacokinetics of miglustat in patients with hepatic impairment, since miglustat is not metabolized in the human liver.

Renal Insufficiency

Limited data in patients with Fabry disease and impaired renal function indicate that clearance (CL/F) of miglustat decreases with decreasing renal function. While the number of subjects with mild and moderate renal impairment was very small, the data suggest an approximate decrease in CL/F of 40% and 60%, respectively, in mild and moderate renal impairment, justifying the need to decrease the dosing of miglustat in such patients dependent upon creatinine clearance levels (see **DOSAGE AND ADMINISTRATION**).

Data in severe renal impairment are limited to two patients with creatinine clearances in the range 18-29 mL/min and cannot be extrapolated below this range. These data suggest a decrease in CL/F by at least 70% in patients with severe renal impairment. Treatment with miglustat in patients with severe renal impairment is therefore not recommended (see sections on **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Drug Interactions (See also PRECAUTIONS, Drug Interactions)

Miglustat does not inhibit or induce various substrates of cytochrome P450 enzymes; consequently significant interactions are unlikely with drugs that are substrates of cytochrome P450 enzymes.

Drug interaction between ZAVESCA® (miglustat 100 mg orally three times daily) and Cerezyme® (imiglucerase; 7.5 or 15 U/kg/day) was assessed in Cerezyme stabilized patients after one month of co-administration. There was no significant effect of Cerezyme on pharmacokinetics of miglustat, with the co-administration of Cerezyme and miglustat resulting in a 22% reduction in C_{max} and a 14% reduction in the AUC for miglustat. While ZAVESCA® appeared to increase the clearance of imiglucerase by 70%, these results are not conclusive because of the small number of subjects studied and because patients took variable doses of Cerezyme (see **PRECAUTIONS, Drug Interactions**).

Concomitant therapy with loperamide during clinical trials did not appear to significantly alter the pharmacokinetics of miglustat.

Clinical Studies

The efficacy of ZAVESCA® in type 1 Gaucher disease has been investigated in two open-label, uncontrolled studies and one randomized, open-label, active-controlled study with enzyme replacement given as Cerezyme. Patients who received ZAVESCA® were treated with doses ranging from 100 to 600 mg a day, although the majority of patients were maintained on doses between 200 to 300 mg a day. Efficacy parameters included the evaluation of liver and spleen organ volume, hemoglobin concentration, and platelet count. A total of 80 patients were exposed to ZAVESCA® during the three studies and their extensions.

Open-Label Uncontrolled Monotherapy Studies

In Study 1, ZAVESCA® was administered at a starting dose of 100 mg three times daily for 12 months (dose range of 100 once-daily -200 mg three times daily) to 28 adult patients with type 1 Gaucher disease, who were unable or unwilling to take enzyme replacement therapy, and who had not taken enzyme replacement therapy in the preceding 6 months. Twenty-two patients completed the study. After 12 months of treatment, the results showed significant mean percent reductions from baseline in liver volume of 12% and spleen volume of 19%, a non-significant increase from baseline in mean absolute hemoglobin concentration of 0.26 g/dL and a mean absolute increase from baseline in platelet counts of 8 x 10^9/L (See Tables 1-4).

In Study 2, ZAVESCA® was administered at a dose of 50 mg three times daily for 6 months to 18 adult patients with type 1 Gaucher disease who were unable or unwilling to take enzyme replacement therapy and who had not in the preceding 6 months. Seventeen patients completed the study. After 6 months of treatment, the results showed significant mean percent reductions from baseline in liver volume of 6% and spleen volume of 5%. There was a non-significant mean absolute decrease from baseline in hemoglobin concentration of 0.13 g/dL and a non-significant mean absolute increase from baseline in platelet counts of 5 x 10^9/L (See Tables 1-4).

Extension period

Eighteen patients were enrolled in a 12-month extension to Study 1. A subset of patients continuing in the extension had somewhat larger mean baseline liver volumes, and lower mean baseline platelet counts and hemoglobin concentrations than the original study population. After a total of 24 months of treatment, there were significant mean decreases from baseline in liver and spleen organ volume of 15% and 27%, respectively, and significant mean absolute increases from baseline in hemoglobin concentration and platelet counts of 0.9 g/L and 14 x 10^9/L, respectively (See Tables 1-4).

Sixteen patients were enrolled in a 6-month extension to Study 2. After a total of 12 months of treatment, there was a mean decrease from baseline in spleen organ volume of 10%, whereas the mean percent decrease in liver organ volume remained at 6%. There were no significant changes in hemoglobin concentrations or platelet counts (See Tables 1-4).

Liver volume results from Studies 1 and 2 and their extensions are summarized in Table 1:

Table 1: Liver Volume Changes in 2 Open-Label Uncontrolled Monotherapy Studies of ZAVESCA® with Extension Phases

	n	Liver Volume	
		Absolute Mean (L) (2-sided 95% CI)	**Percent Mean (%) (2-sided 95% CI)**
Study 1 (starting dose ZAVESCA® 100 mg three times daily)			
Baseline (Month 0)	21	2.39	
Month 12 Change from baseline		-0.28 (-0.38, -0.18)	-12.1% (-16.4, 7.9)
Study 1 Extension Phase			
Baseline (Month 0)	12	2.54	
Month 24 Change from baseline		-0.36 (-0.48, -0.24)	-14.5% (-19.3, 9.7)
Study 2 (ZAVESCA® 50 mg three times daily)			
Baseline (Month 0)	17	2.45	
Month 6 Change from baseline		-0.14 (-0.25, -0.03)	-5.9% (-9.9, -1.9)
Study 2 Extension Phase			
Baseline (Month 0)	13	2.35	
Month 12 Change from baseline		-0.17 (-0.3, -0.0)	-6.2% (-12.0, -0.5)

Spleen volume results from Studies 1 and 2 and their extensions are summarized in Table 2:

Table 2: Spleen Volume Changes in 2 Open-Label Uncontrolled Monotherapy Studies of ZAVESCA® with Extension Phases

	n	Spleen Volume	
		Absolute Mean (L) (2-sided 95% CI)	**Percent Mean (%) (2-sided 95% CI)**
Study 1 (starting dose ZAVESCA® 100 mg three times daily)			
Baseline (Month 0)	18	1.64	
Month 12 Change from baseline		-0.32 (-0.42, -0.22)	-19.0% (-23.7, -14.3)
Study 1 Extension Phase			
Baseline (Month 0)	10	1.56	
Month 24 Change from baseline		-0.42 (-0.53, -0.30)	-26.4% (-30.4, -22.4)
Study 2 (ZAVESCA® 50 mg three times daily)			
Baseline (Month 0)	11	1.98	
Month 6 Change from baseline		-0.09 (-0.18, -0.01)	-4.5% (-8.2, -0.7)
Study 2 Extension Phase			
Baseline (Month 0)	9	1.98	
Month 12 Change from baseline		-0.23 (-0.46, 0.00)	-10.1% (-20.1, -0.1)

Hemoglobin concentration results from Studies 1 and 2 and their extensions are summarized in Table 3:

Table 3: Hemoglobin Concentration Changes in 2 Open-Label Uncontrolled Monotherapy Studies of ZAVESCA® with Extension Phases

	n	Hemoglobin Concentration	
		Absolute Mean (g/dL) (2-sided 95% CI)	**Percent Mean (%) (2-sided 95% CI)**
Study 1 (starting dose ZAVESCA® 100 mg three times daily)			
Baseline (Month 0)	22	11.94	
Month 12 Change from baseline		0.26 (-0.05, 0.57)	2.6% (-0.5, 5.7)
Study 1 Extension Phase			
Baseline (Month 0)	13	11.03	
Month 24 Change from baseline		0.91 (0.30, 1.53)	9.1% (2.9, 15.2)
Study 2 (ZAVESCA® 50 mg three times daily)			
Baseline (Month 0)	17	11.60	
Month 6 Change from baseline		-0.13 (-0.51, 0.24)	-1.3% (-4.4, 1.8)
Study 2 Extension Phase			
Baseline (Month 0)	13	11.94	
Month 12 Change from baseline		0.06 (-0.73, 0.85)	1.2% (-5.2, 7.7)

A more pronounced improvement in hemoglobin concentrations was seen at 18 and 24 months in patients with baseline (Month 0) hemoglobin concentrations <11.5 g/dL.

Platelet count results from Studies 1 and 2 and their extensions are summarized in Table 4:

Table 4: Platelet Count Changes in 2 Open-Label Uncontrolled Monotherapy Studies of ZAVESCA® with Extension Phases

	n	Platelet Count	
		Absolute Mean (10^9/L) (2-sided 95% CI)	**Percent Mean (%) (2-sided 95% CI)**
Study 1 (starting dose ZAVESCA® 100 mg three times daily)			
Baseline (Month 0)	22	76.58	
Month 12 Change from baseline		8.28 (1.88, 14.69)	16.0% (-0.8, 32.8)
Study 1 Extension Phase			
Baseline (Month 0)	13	72.35	
Month 24 Change from baseline		13.58 (7.72, 19.43)	26.1% (14.7, 37.5)
Study 2 (ZAVESCA® 50 mg three times daily)			
Baseline (Month 0)	17	116.47	
Month 6 Change from baseline		5.35 (-6.31, 17.02)	2.0% (-6.9, 10.8)
Study 2 Extension Phase			
Baseline (Month 0)	13	122.15	
Month 12 Change from baseline		14.0 (-3.4, 31.4)	14.7% (-1.4, 30.7)

Open-Label Active-Controlled Study

Study 3 was an open-label, randomized, active-controlled study of 36 adult patients with type 1 Gaucher disease, who had been receiving enzyme replacement therapy with Cerezyme for a minimum of 2 years prior to study entry. Patients were randomized 1:1:1 to one of three treatment groups, as follows:

- ZAVESCA® 100 mg three times daily alone
- Cerezyme (patient's usual dose) alone
- ZAVESCA® 100 mg three times daily + Cerezyme (usual dose)

Patients were treated for 6 months, and 33 patients completed the study. At Month 6, the results showed a significant decrease in mean percent change in liver volume in the combination treatment group compared to the Cerezyme alone group. There were no significant differences between the groups for mean absolute changes in liver and spleen volume and hemoglobin concentration. However, there was a significant difference between the ZAVESCA® alone and Cerezyme alone groups in platelet counts at Month 6, with the ZAVESCA® alone group having a mean absolute decrease in platelet count of 21.6 x 10^9/L and the Cerezyme alone group having a mean absolute increase in platelet count of 10.1 x 10^9/L (see Tables 5-8).

Extension period

Twenty-nine patients were enrolled in a 6-month extension to Study 3. In the extension phase, all 29 patients had withdrawn from Cerezyme and received open-label ZAVESCA® 100 mg three times daily monotherapy. At Month 12, the results showed non-significant decreases in platelet counts from baseline in all three treatment groups (by original randomization). There were significant decreases in platelet counts from Month 6 to Month 12 in the 2 groups originally randomized to treatment with Cerezyme and to combination therapy, and a continued decrease in platelet counts in the group originally randomized to ZAVESCA® alone. There were no significant changes in any treatment group for liver volume, spleen volume, or hemoglobin concentration (see Tables 5-8).

Liver volume results from Study 3 and extension are summarized in Table 5:

Table 5: Liver Volume Changes from Study 3 and Extension Phase

	Cerezyme alone	ZAVESCA® alone	Combination
Study 3	n=11	n=10	n=9
Month 0	1.81	1.58	2.01
Month 6 Change (L)	0.04	-0.05	-0.09
Month 6 % Change	3.6%	-2.9%	-4.9%
Adjusted mean Difference from Cerezyme (95% CI)		-4.5% (-13.2, 4.2)	-8.4% (-16.6, -0.1)
Extension Phase*	n=10	n=8	n=8
Month 0	1.94	1.60	2.04
Month 12 Change (L)	-0.05	-0.01	-0.08
Month 12 % Change	-0.7%	-0.8%	-4.0%

*All patients received ZAVESCA® 100 mg three times daily monotherapy from Month 6 to Month 12

Spleen volume results from Study 3 and extension are summarized in Table 6:

Table 6: Spleen Volume Changes from Study 3 and Extension Phase

	Cerezyme alone	ZAVESCA® alone	Combination
Study 3	n=8	n=7	n=7
Month 0	0.61	0.69	0.76
Month 6 Change (L)	-0.02	-0.03	-0.08
Month 6 % Change	-2.1%	-4.8%	-8.5%
Adjusted % Difference from Cerezyme (95% CI)		-5.8% (-22.1, 10.5)	-6.4% (-21.0, 8.2)
Extension Phase*	n=7	n=6	n=6
Month 0	0.83	0.57	0.84
Month 12 Change (L)	0.04	-0.05	-0.05
Month 12 % Change	1.5%	-6.1%	-4.8%

*All patients received ZAVESCA® 100 mg three times daily monotherapy from Month 6 to Month 12

Hemoglobin concentration results from Study 3 and extension are summarized in Table 7:

Table 7: Hemoglobin Concentration Changes from Study 3 and Extension Phase

	Cerezyme alone	ZAVESCA® alone	Combination
Study 3	n=12	n=10	n=11
Month 0	13.18	12.44	12.38
Month 6 Change (g/L)	-0.15	-0.31	-0.10
Month 6 % Change	-1.2%	-2.4%	-0.5%
Adjusted % Difference from Cerezyme (95% CI)		-1.9% (-6.4, 2.6)	-0.6% (-4.8, 3.5)
Extension Phase*	n=10	n=9	n=9
Month 0	13.39	12.46	12.20
Month 12 Change (g/L)	-0.48	-0.13	-0.13
Month 12 % Change	-3.1%	-1.1%	-0.8%

*All patients received ZAVESCA® 100 mg three times daily monotherapy from Month 6 to Month 12

Platelet count results from Study 3 and extension are summarized in Table 8:

Table 8: Platelet Count Changes from Study 3 and Extension Phase

	Cerezyme alone	ZAVESCA® alone	Combination
Study 3	n=12	n=10	n=11
Month 0	165.75	170.55	152.14
Month 6 Change (10^9/L)	15.29	-21.60	2.73
Month 6 % Change	10.1%	-9.6%	3.2%
Adjusted % Difference from Cerezyme (95% CI)		-17.1% (-32.9, -1.3)	-4.6% (-19.9, 10.7)
Extension Phase*	n=10	n=9	n=9
Month 0	170.05	184.83	136.33
Month 12 Change (10^9/L)	-3.75	-27.39	-12.22
Month 12 % Change	-3.2%	-10.4%	-8.3%

*All patients received ZAVESCA® 100 mg three times daily monotherapy from Month 6 to Month 12

In patients with platelet counts above 150 x 10^9/L at baseline, there were significant decreases in platelet counts at Month 12 in patients randomized to ZAVESCA® treatment.

Summary of clinical studies

Treatment with ZAVESCA® as monotherapy at a starting dose of 100 mg three times daily (dosage range 100 mg once daily to 200 mg three times daily) in adult type 1 Gaucher disease patients who were either treatment naïve or who had not taken enzyme replacement therapy in the previous 6 months resulted in decreases in liver and spleen volume after 12 months of treatment, and increases in platelet counts and hemoglobin concentration after 24 months of treatment. However, in adult type I Gaucher disease

patients who had been treated with enzyme replacement therapy for at least 2 years, switching to ZAVESCA® as monotherapy was associated with decreases in platelet counts after discontinuation of enzyme replacement therapy. Platelet counts also declined after discontinuation of enzyme replacement therapy in patients treated with combination therapy.

The efficacy and safety of ZAVESCA® has not been evaluated in patients with severe type 1 Gaucher disease, defined as a hemoglobin concentration below 9 g/dL or a platelet count below 50 x 10^9/L or active bone disease.

INDICATIONS AND USAGE

ZAVESCA® is indicated for the treatment of adult patients with mild to moderate type 1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option (e.g. due to constraints such as allergy, hypersensitivity, or poor venous access).

CONTRAINDICATIONS

ZAVESCA® is contraindicated in patients who have demonstrated hypersensitivity to the active substance or any of the excipients.

Pregnancy Category X

Miglustat may cause fetal harm when administered to a pregnant woman. In female rats given miglustat by oral gavage at doses of 20, 60, 180 mg/kg/day beginning 14 days before mating and continuing through gestation day 17 (organogenesis), decreased live births including complete litter loss and decreased fetal weight was observed in the mid- and high-dose groups (systemic exposures ≥2 times the human therapeutic systemic exposure based on body surface area comparison). In pregnant rats given miglustat by oral gavage at doses of 20, 60, 180 mg/kg/day from gestation day 6 through lactation (postpartum day 20), dystocia and delayed parturition were observed in the mid- and high-dose groups (systemic exposures ≥2 times the human therapeutic systemic exposure, based on body surface area comparison), in addition decreased live births and pup body weights were observed at >20 mg/kg/day (systemic exposures less than the human therapeutic systemic exposure, based on body surface area comparison).

In pregnant rabbits given miglustat by oral gavage at doses of 15, 30, 45 mg/kg/day during gestation days 6-18 (organogenesis), maternal death and decreased body weight gain were observed at 15 mg/kg/day (systemic exposures less than the human therapeutic systemic exposure, based on body surface area comparisons).

ZAVESCA® is contraindicated in women who are or may become pregnant. If this drug is administered to a woman with reproductive potential, the patient should be apprised of the potential hazard to a fetus.

WARNINGS

Peripheral Neuropathy

Cases of peripheral neuropathy have been reported in patients treated with ZAVESCA®. All patients receiving ZAVESCA® treatment should undergo baseline and repeat neurological evaluations at approximately 6-month intervals. Patients who develop symptoms such as numbness and tingling should have a careful re-assessment of the risk/benefit of ZAVESCA® therapy and cessation of treatment may be considered.

PRECAUTIONS

General

Therapy should be directed by physicians knowledgeable in the management of patients with Gaucher disease.

Tremor

Approximately 30% of patients have reported tremor or exacerbation of existing tremor on treatment. These tremors were described as an exaggerated physiological tremor of the hands. Tremor usually began within the first month of therapy and in many cases resolved between 1 to 3 months during treatment. Dose reduction may ameliorate the tremor usually within days but discontinuation with treatment may sometimes be required.

Diarrhea and Weight Loss

Diarrhea and weight loss were common in clinical studies of patients treated with ZAVESCA®, with approximately 85% and up to 65% of treated patients, respectively, reporting these conditions. Diarrhea appears to be the result of the disaccharidase inhibitory activity of ZAVESCA®, with a resultant osmotic diarrhea. It is unclear if weight loss results from the diarrhea and associated gastrointestinal complaints, a decrease in food intake, or a combination of these or other factors. The incidence of weight loss was most evident in the first 12 months of treatment. The incidence of diarrhea was noted to decrease over time with continued ZAVESCA® treatment, and was noted to result in an increase in the use of anti-diarrheal medications, most commonly loperamide. Patients may be instructed to avoid high carbohydrate content foods during treatment with ZAVESCA® if they present with diarrhea.

Patients with persistent gastrointestinal events that continue during treatment with Zavesca, and who do not respond to usual interventions (e.g. diet modification), should be evaluated to determine whether significant underlying gastrointestinal disease is present. The safety of treatment with Zavesca has not been evaluated in patients with significant gastrointestinal disease, such as inflammatory bowel disease, and continued

treatment of these patients with Zavesca should occur only after consideration of the risks and benefits of continued treatment.

Male Fertility

Male patients should maintain reliable contraceptive methods while taking ZAVESCA®. Studies in the rat have shown that miglustat adversely affects spermatogenesis and sperm parameters, thereby reducing fertility. Until further information is available, it is advised that before seeking to conceive, male patients should cease ZAVESCA® and maintain reliable contraceptive methods for 3 months thereafter (see **Carcinogenesis, Mutagenesis, and Impairment of Fertility**).

Information for Patients

Patients should be informed of the potential risks and benefits of ZAVESCA® and of alternative modes of therapy. Patients should be advised that diarrhea, gastrointestinal complaints, and weight loss are common side effects of ZAVESCA® therapy, and to adhere to dietary instructions. Patients should also be advised to promptly report any numbness, pain, or burning in the hands and feet, and the development of tremor or worsening in an existing tremor.

Drug Interactions

While co-administration of ZAVESCA® appeared to increase the clearance of Cerezyme by 70%, these results are not conclusive because of the small number of subjects studied and because patients took variable doses of Cerezyme. Combination therapy with Cerezyme (imiglucerase) and ZAVESCA® is not indicated (see **CLINICAL PHARMACOLOGY, Drug Interactions**).

Animal Toxicology

Histopathology findings in the absence of clinical signs in the central nervous system of the monkey (brain, spine) that included vascular mineralization, in addition to mineralization and necrosis of white matter were observed at >750 mg/kg/day (4 times the human therapeutic systemic exposure based on area-under-the-plasma-concentration curve [AUC] comparisons) in a 52-week oral toxicity study using doses of 750 and 2000 mg/kg/d. Vacuolization of white matter was observed in rats dosed orally by gavage at ≥ 180 mg/kg/d (6 times the human therapeutic exposure based on surface area comparisons, mg/m^2) in a 4-week study using doses of 180, 840, and 4200 mg/kg/d. Vacuolization can sometimes occur as an artifact of tissue processing. Findings in dogs included tremor and absent corneal reflexes at 105 mg/kg/day (10 times the human therapeutic systemic exposure, based on body surface area comparisons mg/m^2) after a 4-week oral gavage toxicity study using doses of 35, 70, 105, and 140 mg/kg/d. Ataxia, diminished/absent pupillary, palpebral, or patellar reflexes were observed in a dog at ≥495 mg/kg/day (50 times the human therapeutic systemic exposure based on body surface area comparisons,

mg/m^2), in a 2-week oral gavage toxicity study using doses of 85, 165, 495, and 825 mg/kg/d.

Cataracts were observed in rats at ≥180 mg/kg/day (4 times the human therapeutic systemic exposure, based on AUC) in a 52-week oral gavage toxicity study using doses of 180, 420, 840, and 1680 mg/kg/d.

Gastrointestinal necrosis, inflammation, and hemorrhage were observed in dogs at ≥ 85 mg/kg/day (9 times the human therapeutic systemic exposure based on body surface area comparisons, mg/m^2) after a 2-week oral (capsule) toxicity study using doses of 85, 165, 495, and 825 mg/kg/d. Similar GI toxicity occurred in rats at 1200 mg/kg/day (7 times the human therapeutic systemic exposure, based on AUC) in a 26-week oral gavage toxicity study using doses of 300, 600, and 1200 mg/kg/d. In monkeys, similar GI toxicity occurred at ≥750 mg/kg/day (6 times the human therapeutic systemic exposure based on AUC) following a 52-week oral gavage toxicity study using doses of 750 and 2000 mg/kg/d.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Two year carcinogenicity studies have been conducted with miglustat in CD-1 mice at oral doses up to 500 mg/kg/day and in Sprague Dawley rats at oral doses up to 180 mg/kg/day. Oral administration of miglustat for 104 weeks produced mucinous adenocarcinomas of the large intestine at 210, 420 and 500 mg/kg/day (about 3, 6 and 7 times the recommended human dose, respectively, based on the body surface area) in male mice and at 420 and 500 mg/kg/day (about 6 and 7 times the recommended human dose, respectively, based on the body surface area) in female mice. The adenocarcinomas were considered rare in CD-1 mice and occurred in the presence of inflammatory and hyperplastic lesions in the large intestine of both males and females. In rats, oral administration of miglustat for 100 weeks produced increased incidences of interstitial cell adenomas of the testis at 30, 60 and 180 mg/kg/day (about 1, 2 and 5 times the recommended human dose, respectively, based on the body surface area).

Miglustat was not mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays including the bacterial reverse mutation (Ames), chromosomal aberration (in human lymphocytes), gene mutation in mammalian cells (Chinese hamster ovary), and mouse micronucleus assays.

Male rats, given 20 mg/kg/day miglustat by (systemic exposure less than the human therapeutic systemic exposure based on body surface area comparisons, mg/m^2) oral gavage 14 days prior to mating, had decreased spermatogenesis with altered sperm morphology and motility and decreased fertility. Decreased spermatogenesis was reversible following 6 weeks of drug withdrawal. A higher dose of 60 mg/kg/day (2 times the human therapeutic systemic exposure based on body surface area comparison, mg/m^2) resulted in seminiferous tubule and testicular atrophy/degeneration.

Female rats were given oral gavage doses of 20, 60, 180 mg/kg/day beginning 14 days before mating and continuing through gestation. Effects observed at 20 mg/kg/day (systemic exposure less than the human therapeutic systemic exposure, based on body surface area comparisons) included decreased corpora lutea, increased postimplantation loss, and decreased live births.

Pregnancy Category X. See **CONTRAINDICATIONS** section.

There are no adequate and well-controlled studies of miglustat in pregnant women. ZAVESCA® should not be used during pregnancy.

Labor and Delivery

Studies in pregnant rats exposed to ZAVESCA® during gestation through lactation are associated with dystocia and delayed parturition at systemic exposure 2 times the human therapeutic systemic exposure, based on body surface area comparisons.

Nursing Mothers

It is not known whether miglustat is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from miglustat, ZAVESCA® should not be used in nursing mothers unless the potential benefit justifies the potential risk to the infant. A decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the lactating woman.

Pediatric Use

The safety and effectiveness of ZAVESCA® have not been evaluated in patients under the age of 18. Treatment with ZAVESCA® is associated with diarrhea and weight loss in approximately 85% and up to 65%, respectively, of adult patients. The effects of ZAVESCA® on growth and development in children have not been evaluated.

Geriatric Use

Clinical studies of ZAVESCA® did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, and cardiac function and of concomitant disease or other drug therapy.

Renal Impairment

Miglustat is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. The clearance of miglustat is decreased by 40 to 60% in patients with mild to moderate renal impairment, and up to 70% in patients with severe renal impairment. As a result of this,

dose reductions are recommended for those patients with mild to moderate renal impairment, the reduction being dependent upon the level of their creatinine clearance adjustment. For those patients with severe renal impairment, treatment with miglustat is not recommended. Since elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

ADVERSE REACTIONS

The most common serious adverse reaction reported with Zavesca treatment in clinical studies was peripheral neuropathy (see **WARNINGS: Peripheral Neuropathy**).

The most common treatment-emergent adverse events reported in clinical studies with Zavesca were weight loss, diarrhea, and tremor (see **PRECAUTIONS: Tremor, and Diarrhea and Weight Loss**). Other common adverse reactions were flatulence, abdominal pain, headache, and influenza-like symptoms.

The most common adverse reaction requiring intervention was diarrhea (see **PRECAUTIONS: Diarrhea and Weight Loss**). Most episodes of diarrhea were ameliorated by the use of anti-diarrheal medications, and/or the avoidance of high carbohydrate content foods, or were noted to decrease over time with continued Zavesca treatment. The next most common adverse reaction requiring intervention was tremor (see **PRECAUTIONS: Tremor**). In many cases, tremor resolved despite continued Zavesca treatment. Dose reduction of Zavesca may ameliorate tremor, but discontinuation of Zavesca was required in some patients.

The data described below reflect exposure of 80 adult type 1 Gaucher disease patients to Zavesca in two open-label, uncontrolled, monotherapy trials, and one open-label, active-controlled trial. Patients were ages 18 to 69 years at first treatment. The population was nearly evenly distributed by gender.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In two open-label, uncontrolled monotherapy trials, adult type 1 Gaucher disease patients were treated with ZAVESCA® at a starting dose of 100 mg three times daily (dose range 100 to 200 mg three times daily) for up to 12 months in 28 patients [Study 1], or at a dose of 50 mg three times daily for up to 6 months in 18 patients [Study 2]. Table 9 below enumerates adverse events that occurred during the trials in ≥5% of patients. Reported adverse events have been classified using standard WHOART terms.

Table 9: Adverse Reactions in ≥5% of Patients in Two Open-Label, Uncontrolled Monotherapy Trials of ZAVESCA®		
	Incidence of adverse reaction	
	Study 1 (starting dose 100 mg three times daily)	**Study 2 (50 mg three times daily)**
Patients entered in Study (n)	28	18
Body System - Preferred Term	% of patients reporting	% of patients reporting
Gastrointestinal System		
Diarrhea	89	89
Flatulence	29	44
Abdominal Pain	18	50
Nausea	14	22
Vomiting	4	11
Bloating	0	6
Anorexia	7	0
Dyspepsia	7	0
Epigastric pain not food-related	0	6
Metabolic and Nutritional Disorders		
Weight Decrease	39	67
Central and Peripheral Nervous System		
Headache	21	22
Tremor	11	11
Dizziness	0	11
Cramps legs	4	11
Paresthesia	7	0
Migraine	0	6
Vision Disorders		
Visual Disturbance	0	17
Musculoskeletal Disorders		
Cramps	0	11
Platelet, Bleeding, and Clotting Disorders		
Thrombocytopenia	7	6
Reproductive disorders, female		
Menstrual disorder	0	6

In an open-label, active-controlled study (versus Cerezyme; imiglucerase), 36 adult type 1 Gaucher disease patients were treated with ZAVESCA®, Cerezyme, or ZAVESCA® + Cerezyme (Study 3) for up to 12 months. Table 10 enumerates adverse events that occurred during the trial in ≥5% of patients. Reported adverse events have been classified using standard WHOART terms.

Table 10: Adverse Reactions in ≥5% of Patients in Open-Label Active Controlled Study			
	Incidence of adverse reaction		
	ZAVESCA® alone	Cerezyme alone	ZAVESCA® + Cerezyme
Patients entered in Study (n)	12	12	12
Body System - Preferred Term	% of patients reporting	% of patients reporting	% of patients reporting
Gastrointestinal System			
Diarrhea	100	0	83
Abdominal Pain	67	0	58
Flatulence	50	0	42
Constipation	8	0	25
Nausea	8	0	8
Mouth dry	8	0	0
Body as a Whole			
Influenza-Like Symptoms	0	0	8
Pain	0	8	8
Pain legs	0	0	8
Weakness generalized	17	0	8
Abdominal distension	8	0	8
Back pain	8	0	0
Abdominal distension gaseous	8	0	0
Chills	0	0	8
Heaviness in limbs	8	0	0
Metabolic and Nutritional Disorders			
Weight Decrease	67	0	42
Central and Peripheral Nervous System			
Tremor	17	0	33
Dizziness	8	0	25
Cramps legs	8	0	0
Gait unsteady	8	0	0
Numbness localized	0	0	8
Shaking	0	0	8
Psychiatric disorders			
Appetite absent	0	0	8
Jitteriness	0	0	8
Memory loss	8	0	0
Vision Disorders			
Eye abnormality	0	0	8
Visual disturbance	0	0	8
Reproductive disorders, female			
Menstrual irregularity	0	0	8

Overdosage

In the clinical development program for ZAVESCA®, no patient experienced an overdose of study drug. However, ZAVESCA® has been administered at doses of up to 3000 mg/day (approximately 10 times the recommended starting dose administered to Gaucher patients) for up to six months in Human Immunodeficiency Virus (HIV)-positive patients. Adverse events observed in the HIV studies included granulocytopenia, dizziness, and paresthesia. Leukopenia and neutropenia have also been observed in a similar group of patients receiving 800 mg/day or above.

DOSAGE AND ADMINISTRATION

Instructions for Administration

Therapy should be directed by physicians who are knowledgeable in the management of Gaucher disease.

The recommended dose for the treatment of adult patients with type 1 Gaucher disease is one 100 mg capsule administered orally three times a day at regular intervals.

It may be necessary to reduce the dose to one 100 mg capsule once or twice a day in some patients for adverse effects, such as diarrhea or tremor.

Patients with Renal Insufficiency

In patients with mild renal impairment (adjusted creatinine clearance 50-70 mL/min/1.73 m^2), ZAVESCA® administration should commence at a dose of 100 mg twice per day. In patients with moderate renal impairment (adjusted creatinine clearance of 30-50 mL/min/1.73 m^2), ZAVESCA® administration should commence at a dose of one 100mg capsule per day. Use of ZAVESCA® in patients with severe renal impairment (creatinine clearance of <30 mL/min/1.73 m^2) is not recommended.

STORAGE

Store at 20ºC to 25ºC (68ºF to 77ºF). Brief exposure to 15ºC to 30ºC (59ºF to 86º F) permitted (see USP Controlled Room Temperature).

HOW SUPPLIED

ZAVESCA® is supplied in hard gelatin capsules containing 100 mg miglustat. ZAVESCA® 100 mg capsules are white opaque with “OGT 918” printed in black on the cap and “100” printed in black on the body.

ZAVESCA® 100 mg capsules are packed in blister cards. Five blister cards of 18 capsules are supplied in each carton.

NDC 66215-201-90: carton containing 90 capsules.
NDC 66215-201-18: blister card containing 18 capsules

Rx only

Manufactured by:

Almac Pharma Services Ltd.
22 Seagoe Industrial Estate
BT63 5QD, UK

Marketed and Distributed by:

Actelion Pharmaceuticals US Inc

South San Francisco, CA 94080, US
(650) 624 6900

Patient Information

ZAVESCA® (zah-VEHS-kah) (miglustat) 100 mg Capsules

Read the Patient information that comes with ZAVESCA® before you start using it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your healthcare provider about your condition or your treatment.

What is ZAVESCA®?

ZAVESCA® is a prescription medicine taken by mouth for adults with mild to moderate type 1 Gaucher disease. ZAVESCA® is used only in patients who cannot be treated with enzyme replacement therapy.

ZAVESCA® has not been studied in children under 18 years of age.

What is type 1 Gaucher disease?

Type 1 Gaucher disease is an inherited disease that you get from both your parents. People with type 1 Gaucher disease are missing an enzyme that breaks down a chemical in the body called glucosylceramide. Too much glycosylceramide causes liver and spleen enlargement, changes in the blood, and bone disease. ZAVESCA® may stop glucosylceramide from forming.

Who should not take ZAVESCA®?

Do not take ZAVESCA® if you are allergic to any of its ingredients. The active ingredient is miglustat. See the end of this leaflet for a complete list of ingredients.

Tell your doctor before taking ZAVESCA®:

- **If you are pregnant or planning to become pregnant.** ZAVESCA® may harm your baby. You should use effective birth control while taking ZAVESCA®. **ZAVESCA® may also harm a man's sperm.** All men should use effective birth control during treatment with ZAVESCA® and for 3 months after stopping ZAVESCA®. Do not use ZAVESCA® if you plan to become pregnant, or if your partner can become pregnant.

- **If you are breast-feeding.** It is not known if ZAVESCA® passes into your milk and if it can harm your baby. You should decide either to breast feed or take ZAVESCA®, but not both.

- **If you have kidney problems**

- **About all of your medical conditions**

- **About all the medicines you take including prescription and non-prescription medicines, vitamins and other dietary supplements.** Some medicines may affect ZAVESCA®. ZAVESCA® may affect other medicines.

How should I take ZAVESCA®?

- Take ZAVESCA® exactly as your doctor has prescribed. Check with your doctor or your pharmacist if you are not sure.

- Take ZAVESCA® at the same time or times each day. Your doctor will prescribe the dose that is right for you.

- Swallow ZAVESCA® capsules whole with water. ZAVESCA® may be taken with or without food.

- If you miss a dose of ZAVESCA®, skip that dose. Take the next ZAVESCA® capsule at the usual time.

- If you take too much ZAVESCA® or overdose, call your doctor or local poison control center right away.

What should I avoid while taking ZAVESCA®?

Do not get pregnant while taking ZAVESCA®. Men and women should use effective birth control during treatment with ZAVESCA®. Men should keep using effective birth control for 3 months after treatment with ZAVESCA® stops.

What are the possible side effects of ZAVESCA®?

ZAVESCA® can cause problems affecting your nerves (neurologic problems):

- **Hand tremors (shaky movements) or worsen a hand tremor that you already have.** Tremors may begin within the first month of starting treatment. Sometimes the tremors may go away between 1 to 3 months with continued treatment. Sometimes a lower dose or stopping ZAVESCA® is needed to help the tremors go away. Call your doctor if you get hand tremors while taking ZAVESCA® or the hand tremors you already have get worse.

- **Numbness and tingling in your hands, arms, legs, or feet (peripheral neuropathy).** Call your doctor right away if you get numbness or tingling in your arms or legs.

Your doctor may test your nerves (neurological exam) before you start ZAVESCA® and may repeat this procedure at a later time.

Diarrhea is the most common side effect for people taking ZAVESCA®. Your doctor may give you another medicine (anti-diarrheal) to treat diarrhea if it is a problem for you, and may recommend changes to your diet. You may also lose weight when you start treatment with ZAVESCA®.

Some of the other side effects with ZAVESCA® are:

- Gas
- Stomach pain
- Headache
- Dizziness
- Nausea
- Constipation
- Muscle cramps
- Weakness
- Cramps
- Do not feel like eating
- Vision problems
- Low platelet count

Call your doctor if you get any side effect that bothers you. Sometimes the side effects will go away. Sometimes a lower dose of ZAVESCA® will help side effects go away.

These are not all the side effects with ZAVESCA®. For more information, ask your doctor or your pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at **1-800-FDA 1088.**

How do I store ZAVESCA®?

- Store ZAVESCA® between 20ºC to 25ºC (68ºF to 77ºF)
- Do not use ZAVESCA® that has expired.
- **Keep ZAVESCA® and all medicines out of the reach of children.**

General information about ZAVESCA®

Medicines are sometimes prescribed for conditions that are not mentioned in Patient Information leaflets. Do not use ZAVESCA® for a condition for which it was not prescribed. Do not give ZAVESCA® to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about ZAVESCA®. If you would like more information, talk with your doctor. You can ask you doctor or pharmacist for information about ZAVESCA® that is written for health professionals. For more information about ZAVESCA® contact:

Medical Information Department
Actelion Pharmaceuticals US Inc.
5000 Shoreline Court, Suite 200
South San Francisco, CA 94080 US
Tel: toll-free (866) 228 3546

What are the ingredients of ZAVESCA®?

Active Ingredient: miglustat

Inactive Ingredients: sodium starch glycollate, povidone (K30) and magnesium stearate in the capsule; the capsule shell contains gelatin and titanium dioxide; the edible printing ink contains, black iron oxide and shellac.

RX Only

February 2008

APPENDIX 4 NIEMANN-PICK TYPE C DISEASE STAGE I AND STAGE II SURVEY DATA COLLECTION FORMS

A. Stage I Survey: Retrospective survey of neurological outcomes in patients with Niemann-Pick Type C disease treated with miglustat – Data Collection Form

NPC-Survey

Demographics

Year of birth (YYYY) ☐

Gender ☐ Female ☐ Male

Weight ☐ kg ☐ lb

Height ☐ cm ☐ ft ☐ in

NPC diagnosis

Date of diagnosis (YYYY) ☐

Method of NPC diagnosis:

Abnormal cholesterol esterification assessed? ☐ Yes ☐ No

Filipin staining assessed? ☐ Yes ☐ No

Genotype assessment available? ☐ Available ☐ Not available

If available, please describe:

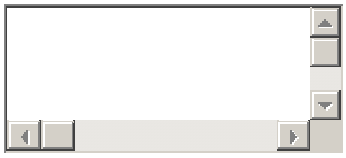
Miglustat Treatment

Currently treatment is:
- ☐ On-going
- ☐ Discontinued

Please provide the reason(s) for miglustat discontinuation:

Death	☐ Yes	☐ No
Pregnancy	☐ Yes	☐ No
Adverse event / Drug reaction	☐ Yes	☐ No
Patient lost to follow up	☐ Yes	☐ No
Lack of efficacy	☐ Yes	☐ No
Non-medical reason	☐ Yes	☐ No
Other	☐ Yes	☐ No

If other, please specify:



Miglustat treatment history

Start YYYY-MM-DD	End YYYY-MM-DD	Dose		Frequency	
- -	- -	200 mg 100 mg 50 mg Other	If 'Other', please specify dose mg	Three times daily (TID) Two times daily (BID) One time daily (QD) Other	If 'Other', please specify frequency
- -	- -	200 mg 100 mg 50 mg Other	If 'Other', please specify dose mg	Three times daily (TID) Two times daily (BID) One time daily (QD) Other	If 'Other', please specify frequency
- -	- -	200 mg 100 mg 50 mg Other	If 'Other', please specify dose mg	Three times daily (TID) Two times daily (BID) One time daily (QD) Other	If 'Other', please specify frequency
- -	- -	200 mg 100 mg 50 mg Other	If 'Other', please specify dose mg	Three times daily (TID) Two times daily (BID) One time daily (QD) Other	If 'Other', please specify frequency

Other therapies:

Other NPC treatment?	☐ Yes	☐ No
Vitamins or supplement?	☐ Yes	☐ No
Symptomatic drug therapies?	☐ Yes	☐ No
Physical therapy?	☐ Yes	☐ No
Speech therapy?	☐ Yes	☐ No

Patient Assessment

You are asked to provide information on the presence and severity of NPC neurological manifestations for a minimum of three time points:

1) at the time of diagnosis
2) at initiation of miglustat therapy
3) at the last clinical contact or at discontinuation of miglustat as appropriate

Ambulation		
At diagnosis ☐ Normal ☐ Autonomous ataxic gait ☐ Outdoor assisted ambulation ☐ Indoor assisted ambulation ☐ Wheelchair-bound	**Upon initiation of miglustat therapy** ☐ Normal ☐ Autonomous ataxic gait ☐ Outdoor assisted ambulation ☐ Indoor assisted ambulation ☐ Wheelchair-bound	**Last clinical contact or at discontinuation of miglustat** ☐ Normal ☐ Autonomous ataxic gait ☐ Outdoor assisted ambulation ☐ Indoor assisted ambulation ☐ Wheelchair-bound

Manipulation		
At diagnosis ☐ Normal ☐ Slight dysmetria/dystonia (allows autonomous manipulation) ☐ Mild dysmetria/dystonia (requires help for several tasks but is able to feed himself) ☐ Severe dysmetria/dystonia (requires assistance in all activities)	**Upon initiation of miglustat therapy** ☐ Normal ☐ Slight dysmetria/dystonia (allows autonomous manipulation) ☐ Mild dysmetria/dystonia (requires help for several tasks but is able to feed himself) ☐ Severe dysmetria/dystonia (requires assistance in all activities)	**Last clinical contact or at discontinuation of miglustat** ☐ Normal ☐ Slight dysmetria/dystonia (allows autonomous manipulation) ☐ Mild dysmetria/dystonia (requires help for several tasks but is able to feed himself) ☐ Severe dysmetria/dystonia (requires assistance in all activities)

Language		
At diagnosis ☐ Normal ☐ Mild dysarthria (understandable) ☐ Sever dysarthria (only comprehensible to some members of the family) ☐ Non-verbal communication ☐ Absence of communication	**Upon initiation of miglustat therapy** ☐ Normal ☐ Mild dysarthria (understandable) ☐ Sever dysarthria (only comprehensible to some members of the family) ☐ Non-verbal communication ☐ Absence of communication	**Last clinical contact or at discontinuation of miglustat** ☐ Normal ☐ Mild dysarthria (understandable) ☐ Sever dysarthria (only comprehensible to some members of the family) ☐ Non-verbal communication ☐ Absence of communication

Swallowing		
At diagnosis ☐ Normal ☐ Occasional dysphagia ☐ Daily dysphagia ☐ Nasogastric tube or gastric button feeding	**Upon initiation of miglustat therapy** ☐ Normal ☐ Occasional dysphagia ☐ Daily dysphagia ☐ Nasogastric tube or gastric button feeding	**Last clinical contact or at discontinuation of miglustat** ☐ Normal ☐ Occasional dysphagia ☐ Daily dysphagia ☐ Nasogastric tube or gastric button feeding

Seizure Activity		
At diagnosis ☐ Partial ☐ Global ☐ Both	**Upon initiation of miglustat therapy** ☐ Partial ☐ Global ☐ Both	**Last clinical contact or at discontinuation of miglustat** ☐ Partial ☐ Global ☐ Both

Seizure Frequency		
At diagnosis ☐ < 1 per 3 month period ☐ ≥ 1 per 3 month - < 1 per month ☐ ≥ 1 per month - < 1 per week ☐ ≥ 1 per week	**Upon initiation of miglustat therapy** ☐ < 1 per 3 month period ☐ ≥ 1 per 3 month - < 1 per month ☐ ≥ 1 per month - < 1 per week ☐ ≥ 1 per week	**Last clinical contact or at discontinuation of miglustat** ☐ < 1 per 3 month period ☐ ≥ 1 per 3 month - < 1 per month ☐ ≥ 1 per month - < 1 per week ☐ ≥ 1 per week

Was the patient receiving antiepileptic drugs prior to miglustat start?

☐ Yes

☐ No

If 'yes', please list drug name, dose and frequency:

General health

Prior to miglustat start, the patient's general health was:	☐ Very Good ☐ Good ☐ Fair ☐ Poor ☐ Very Poor
Can you evaluate the change of patient's general health since treatment start?	☐ Yes ☐ No
If 'yes', please specify:	☐ Much better ☐ Somewhat better ☐ About the same ☐ Somewhat worse ☐ Much worse

Physician's overall assessment

In your opinion, how would you assess the patient's benefit from miglustat treatment?	☐ Excellent ☐ Good ☐ Fair ☐ Poor ☐ None
Is it your intention to continue treating this patient with miglustat?	☐ Yes ☐ No

Free comments:

B. Stage II Survey: Natural history of neurological disease in patients with Niemann-Pick type C disease: a retrospective survey – Data Collection Form

Year of birth (YYYY) ☐

Gender
O Female
O Male

Weight ☐ kg ☐ lb

Height ☐ cm ☐ ft ☐ in

NPC diagnosis

Date of diagnosis (taken from patient assessment)

Method of NPC diagnosis:

Abnormal cholesterol esterification assessed?
O Yes
O No

Filipin staining assessed?
O Yes
O No

Genotype assessment available?
O Available
O Not available

If available, please describe:

You are asked to provide information on the presence and severity of NPC neurological manifestations for a minimum of three time points:

A) at the time of diagnosis
B) at the time of visit 1
C) at the time of visit 2
D) at the time of visit 3

Date

At diagnosis YYYY-MM-DD	**At Visit 1 YYYY-MM-DD**	**At Visit 2 YYYY-MM-DD**	**At Visit 3 YYYY-MM-DD**
☐☐☐☐-☐☐-☐☐	☐☐☐☐-☐☐-☐☐	☐☐☐☐-☐☐-☐☐	☐☐☐☐-☐☐-☐☐

Ambulation

At diagnosis	**At Visit 1**	**At Visit 2**	**At Visit 3**
O Normal	O Normal	O Normal	O Normal
O Autonomous ataxic gait	O Autonomous ataxic gait	O Autonomous ataxic gait	O Autonomous ataxic gait
O Outdoor assisted ambulation	O Outdoor assisted ambulation	O Outdoor assisted ambulation	O Outdoor assisted ambulation
O Indoor assisted ambulation	O Indoor assisted ambulation	O Indoor assisted ambulation	O Indoor assisted ambulation
O Wheelchair-bound	O Wheelchair-bound	O Wheelchair-bound	O Wheelchair-bound

Manipulation

At diagnosis	At Visit 1	At Visit 2	At Visit 3
O Normal	O Normal	O Normal	O Normal
O Slight dysmetria/dystonia (allows autonomous manipulation)	O Slight dysmetria/dystonia (allows autonomous manipulation)	O Slight dysmetria/dystonia (allows autonomous manipulation)	O Slight dysmetria/dystonia (allows autonomous manipulation)
O Mild dysmetria/dystonia (requires help for several tasks but is able to feed himself)	O Mild dysmetria/dystonia (requires help for several tasks but is able to feed himself)	O Mild dysmetria/dystonia (requires help for several tasks but is able to feed himself)	O Mild dysmetria/dystonia (requires help for several tasks but is able to feed himself)
O Severe dysmetria/dystonia (requires assistance in all activities)	O Severe dysmetria/dystonia (requires assistance in all activities)	O Severe dysmetria/dystonia (requires assistance in all activities)	O Severe dysmetria/dystonia (requires assistance in all activities)

Language

At diagnosis	At Visit 1	At Visit 2	At Visit 3
O Normal	O Normal	O Normal	O Normal
O Mild dysarthria (understandable)	O Mild dysarthria (understandable)	O Mild dysarthria (understandable)	O Mild dysarthria (understandable)
O Severe dysarthria (only comprehensible to some members of the family)	O Severe dysarthria (only comprehensible to some members of the family)	O Severe dysarthria (only comprehensible to some members of the family)	O Severe dysarthria (only comprehensible to some members of the family)
O Non-verbal communication	O Non-verbal communication	O Non-verbal communication	O Non-verbal communication
O Absence of communication	O Absence of communication	O Absence of communication	O Absence of communication

Swallowing

At diagnosis	At Visit 1	At Visit 2	At Visit 3
O Normal	O Normal	O Normal	O Normal
O Occasional dysphagia	O Occasional dysphagia	O Occasional dysphagia	O Occasional dysphagia
O Daily dysphagia	O Daily dysphagia	O Daily dysphagia	O Daily dysphagia
O Nasogastric tube or gastric button feeding	O Nasogastric tube or gastric button feeding	O Nasogastric tube or gastric button feeding	O Nasogastric tube or gastric button feeding

Seizure Activity

At diagnosis	At Visit 1	At Visit 2	At Visit 3
O Partial	O Partial	O Partial	O Partial
O Global	O Global	O Global	O Global
O Both	O Both	O Both	O Both

Seizure Frequency

At diagnosis	At Visit 1	At Visit 2	At Visit 3
O < 1 per 3 month period	O < 1 per 3 month period	O < 1 per 3 month period	O < 1 per 3 month period
O ≥ 1 per 3 month - < 1 per month	O ≥ 1 per 3 month - < 1 per month	O ≥ 1 per 3 month - < 1 per month	O ≥ 1 per 3 month - < 1 per month
O ≥ 1 per month - < 1 per week	O ≥ 1 per month - < 1 per week	O ≥ 1 per month - < 1 per week	O ≥ 1 per month - < 1 per week
O ≥ 1 per week	O ≥ 1 per week	O ≥ 1 per week	O ≥ 1 per week

Was the patient receiving antiepileptic drugs prior to miglustat start?

O Yes
O No

If 'yes', please list drug name, dose and frequency:

Please note the following:

1. **We are looking for *additional data* between Diagnosis and Start of Treatment to enable us to see *more assessments* during the *natural history* of your patient.**
2. **If you have *already* inserted information during Stage I, *YOUR* data (e.g. Year of diagnosis") will be *automatically* inserted by the system in the box about "At diagnosis" and the "Start of miglustat treatment" will *pop up* for your information.**
3. **If you have *wrongly* inserted data after the "Start of miglustat treatment", you will get a *notification* from the system if you want to save the additional assessments.**
4. **If you start with *new patients* - not previously documented - you only have to fill in the data requested on the web-based questionnaire.**

Thank you for your support.

End of form
