European Medicines Agency

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ASSESSMENT REPORT
FOR
ZAVESCA

International non-proprietary name/Common name: miglustat

PROCEDURE No: EMEA/H/C/000435/II/0029

Variation Assesment Report as adopted by the CHMP with All information of a commercially confidential nature deleted

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3.1 Introduction

Zavesca is a competitive inhibitor of the enzyme glucosylceramide synthase, which catalyzes the first and committed step in the synthesis of glycosphingolipids. Treatment with Zavesca can be considered as a substrate reduction therapy. Zavesca was authorised by the centralised procedure (EU/1/02/238/001) under exceptional circumstances in November 2002, for the oral treatment (100 mg t.i.d.) of mild to moderate type 1 Gaucher disease in patients for whom enzyme replacement therapy is unsuitable.

On 16 February 2006, Zavesca was granted designation as an Orphan Medicinal Product for the indication 'Treatment of Niemann-Pick Disease, type C' (EU/3/06/351).

The MAH submitted this type II variation application to extend the indication for Zavesca in the "treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C disease (NP-C disease)."

3.2 Non-clinical aspects

The non-clinical documentation for the new indication consists of an addendum to the non-clinical overview, an update to the pharmacokinetics written summary, and an update to the toxicology written summary. The proposed new indication, "treatment of progressive neurological manifestations in adult patients and paediatric patients with NP-C disease" involves a dose of 200 mg thrice daily (t.i.d.) to be compared with previously approved dose of 100 mg t.i.d. in Gaucher's disease.

The addendum to the non-clinical overview reviews the data available for miglustat also taking into account the new clinical dose that is twice as high as for Gaucher's disease. All toxicological data have been previously submitted. Studies include a 13 week mouse study completed in 2002 and a study report from a 13 week oral study dealing with investigations of rat brain glycolipids. A series of literature references is also provided.

The pharmacological rationale for treatment of Niemann-Pick disease Type C is based on substrate reduction therapy, reducing the amount of glucosylceramide by acting on the first step on glycosphingolipid biosynthesis. In some non-clinical models of lipid storage disease, miglustat has been shown to have the potential to reduce storage of glycosphingolipids and enhance survival. Two murine models of Niemann-Pick C have been described in the literature, but no specific studies with miglustat using these models appear available. In other mouse models, such as the Sandhoff mouse, of neurodegenerative disease, miglustat induced a significant reduction of glycosphingolipids. Data indicate though that CNS storage burden is not the only factor in clinical disease onset.

The preclinical pharmacokinetics of miglustat has been previously characterised. Distribution into brain has been shown in mouse, rat and monkey.

The toxicology of miglustat was assessed at the time of the application for MA for treatment in Gauchers disease. The main target organs for toxicity are the gastrointestinal system and male reproductive tract. A NOEL could be established in only two of the repeated dose toxicity studies and corresponded to x1 and x5 the estimated exposure in humans. The application to extend the indication to Niemann-Pick Disease, type C' involves a dose twice as high (200 mg t.i.d.) and margins of exposure may thus be expected to be even lower, if identifiable at all. However, considering the clinical particulars these issues might not have an impact on the overall risk benefit assessment.

A 13 week mouse study (GLP, QA) was completed in 2002. Groups of 10 male and 10 female rats were administered miglustat by gavage 3 times daily at levels of 0, 100, 420 and 840 mg/kg/day. Clinical signs, body weights, haematology, clinical chemistry and necropsy were recorded for all animals. Histopathology was conducted on a comprehensive list of tissues from control and high dose animals. Clinical signs consisted of hunched posture, subdued behaviour, rolling gait, piloerection, weight loss and respiratory signs. Increases in AST were recorded for the high dose group with no histological correlate. Statistically significant increases in weight of liver (males from 420 mg/kg/d), spleen (female high dose) and brain (from 420 mg/kg/d in females) were noted. Minimal splenic megakaryocytosis in all treated male animals and increased lymphocytolysis in

thymus in males and females was noted. A NOEL was not identified. Toxicokinetic data showed supraproportional increases in systemic exposure with dose on day 1, but there was no evidence of accumulation from day 1 to week 13. In females, reduced platelet counts seemed to correlate with the incidence of splenic megakaryocytosis and this was considered a regenerative response to reduced platelet counts.

Miglustat penetrates the blood-brain barrier and distributes to the cerebrospinal fluid. Rat brain glycolipids were analysed from a 13 week study in male rats given doses of 180, 340 or 420 mg/kg/day. No consistent effects of miglustat on gangliosides, sulfatide glycolipids or galactosylceramide were reported. In neutral brain glycolipid subfractions, a band comigrating with the glucosylceramide band doublet was evident. In brains from recovery and control animals no such band was detected. It was estimated that miglustat caused an approximately 2 fold increase in a glycolipid band and limited analysis was consistent with the band being glucosylceramide. The increase appeared reversible and it is suggested that a difference in sensitivity of glucosylceramide synthase and non-lysosomal glucosylceramidase towards inhibition by miglustat may play a role in this. It is of interest to note that in nonclinical models of GM2 diseases interventions such as bone marrow transplant, although having no effect on brain glycolipids, appeared to have an increased effect on survival compared with substrate reduction therapy regimens. The relevance of these data for the human disease is unknown.

The identification of appropriate parameters for comparison animal and human data is not straightforward. However, many of the effects seen in animal studies have already been identified in the clinic and strategies proposed for their management and these are considered resolved from the non-clinical point of view and considered in the current revised SPC. One issue concerns male fertility and effects on sperm which is an identified effect and is considered adequately addressed in section 5.3.

In one study, results showed a potential of miglustat to inhibit non-lysosomal glucosylceramidase (later identified as β-glucosidase 2) with an IC_{50} of 200 nM to compare with an IC_{50} of 20 to 50 μM for inhibition of glucosylceramide synthesis. This data, although limited and including uncertainties as to threshold values at which effects became apparent, also indicated that the text in 5.1 should be revised.
It is concluded that from the non-clinical point of view there are no new issues that should be addressed in relation to an extension of indication to include Niemann-Pick Type C disease.

CHMP conclusions
The CHMP concluded that the revision of sections 5.1 and 5.3 and overall the changes proposed are considered acceptable.

Environmental Risk Assessment (ERA)

The CHMP concluded that an ERA according to the current guideline was not presented. Therefore the MAH was asked to justify the absence of the ERA or to conduct an environmental risk assessment according to the guideline on the environmental risk assessment of the medicinal products for human use.
A further commitment is made by the MAH to provide a revised ERA for Zavesca no later than middle of February 2009.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

3.3. Clinical aspects

3.3.1. Clinical pharmacology

New pharmacokinetic information on miglustat comes from three recently performed clinical studies. In these studies (OGT 918-006, OGT 918-007, and OGT 918-009) miglustat was given at a dose of 200 mg t.i.d., i.e., twice the currently approved dose for the treatment of adult type 1 Gaucher patients. Paediatric patients were also included in studies OGT 918-006 and OGT 918-007, and were dosed based on body surface area (BSA).

Study OGT 918-007
In this study, 4 children (ages ranging from 5 to 11) and 6 adolescents/adults (ages ranging from 12 to 39) with NP-C disease provided blood samples for pharmacokinetic evaluation after 1 month of treatment with miglustat. Adolescent/adult patients received 200 mg TID OGT 918, and juvenile patients received doses that were adjusted according to their BSA.

BSA (m^2)	Recommended dose
> 1.25 - 1.8 (adolescent/adult)	200 mg TID
> 0.88 - 1.25	200 mg BID
> 0.73 - 0.88	200 mg a.m. 100 mg p.m.
> 0.47 - 0.73	100 mg BID
≤0.47	100 mg OD

OD = Once daily; BID = Twice daily; TID = Thrice daily.

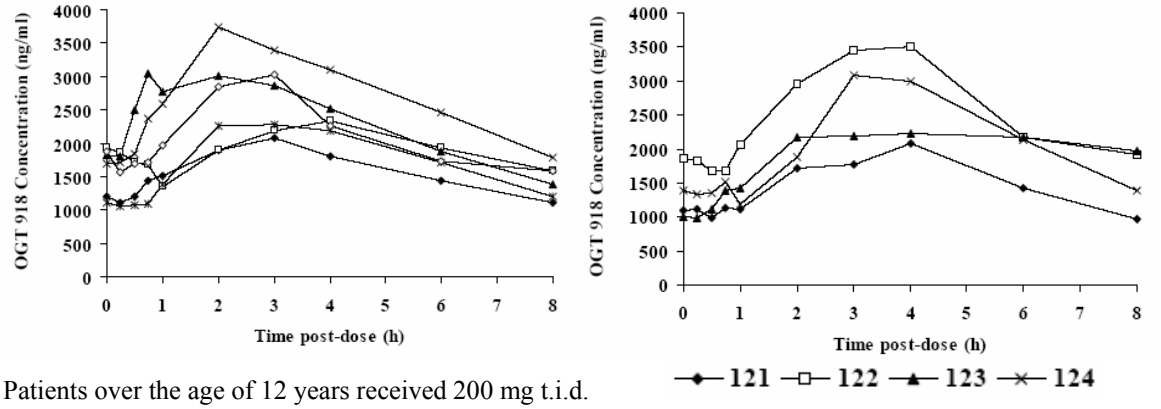
Blood samples were taken during Month 1 at pre-dose and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6 and 8 h post-dose. The plasma analyses of OGT 918 were performed using a previously validated LC-MS method. Pharmacokinetic parameters were determined by non-compartmental analysis.

The geometric mean (geometric mean coefficients of variation in parentheses) pharmacokinetic parameters of OGT 918 are summarised below:

Age Group (years)	Dose Regimen	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-8h} (ng.h/mL)	C_{trough} (ng/mL)
Over 12	200 mg TID	2698 [6] (22.9)	3.00 [6] (0.750-4.00)	16412 [6] (19.5)	1427 [6] (18.3)
Under 12	200 mg TID	2075[1] (NA)	4.00 [1] (NA)	11975 [1] (NA)	962
	200 mg BID	3289 [2] (9.03)	3.54 [2] (3.08-4.00)	18792 [2] (13.9)	NA
	200 mg OD (a.m.) 100 mg OD (p.m.)	2223 [1] (NA)	4.00 [1] (NA)	15866 [1] (NA)	NA

[n] = Number of patients included in mean
tmax values are median with range of values in parentheses
NA = Not applicable

Individual plasma concentrations of OGT 918 following repeated oral administration of OGT 918 to patients over the age of 12 years (left) and patients under the age of 12 years (right)



Patients over the age of 12 years received 200 mg t.i.d.
Patient 121 received 200 mg TID.
Patients 122 and 124 received 200 mg BID .
Patient 123 received 200 mg OD (a.m.) and 100 mg OD (p.m.).

Study OGT 918-006

In this study, 6 children (ages ranging from 2 to 8) and 7 adolescents/adults (ages ranging from 12 to 19) with type 3 Gaucher disease (GD-3) provided blood samples for pharmacokinetic evaluation after 1 month of treatment with miglustat. In addition, pre-dose (trough) samples of cerebrospinal fluid (CSF) and blood were taken at Months 1, 3, 6, 9, and 12, for comparison of miglustat concentrations in CSF relative to that in plasma. Patients over and under 12 years were to receive 200 mg TID OGT 918. However, doses were adjusted according to their BSA.

BSA (m^2)	**Recommended dose**
> 1.25 - 1.8 (adolescent/adult)	200 mg TID
> 0.88 - 1.25	200 mg BID
> 0.73 - 0.88	200 mg a.m. 100 mg p.m.
> 0.47 - 0.73	100 mg BID
≤0.47	100 mg OD

OD = Once daily; BID = Twice daily; TID = Thrice daily.

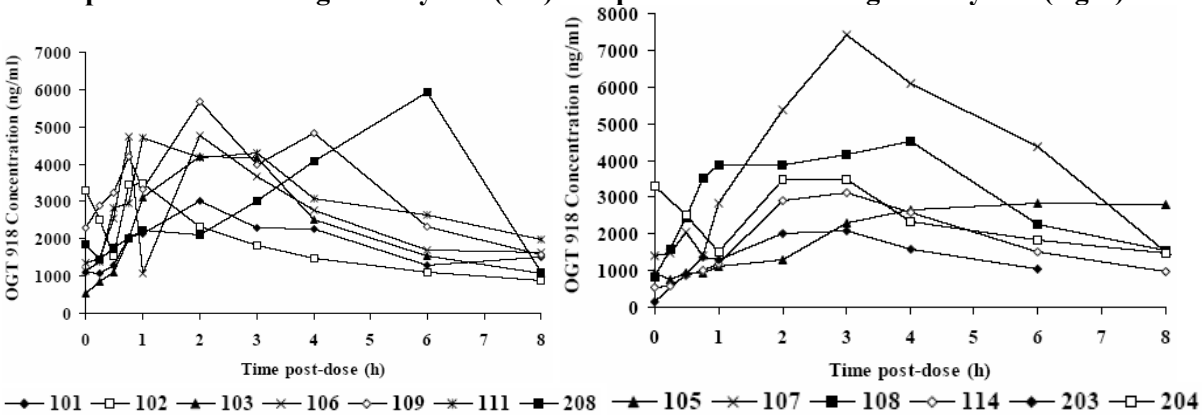
Blood samples (4 mL from patients over 12 years or 2 mL from patients under 12 years) were taken during Month 1 at pre-dose and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6 and 8 h post-dose. Additional trough samples were taken during Months 3, 6, 9 or 12. Seven patients also had a CSF taken: from 3 patients over 12 years during Months 1, 6 and 12, and from 4 patients under 12 years during Months 1, 3, 6 and 9, for the determination of trough CSF concentrations. The CSF and plasma analyses of OGT 918 were performed using previously validated LC-MS methods. The pharmacokinetic parameters were derived by non-compartmental analysis.

The geometric mean (geometric mean coefficients of variation in parentheses) pharmacokinetic parameters of OGT 918 are summarised below:

Group	Dose Regimen	C_{max} (ng/mL)	t_{max} (h)	AUC_{0-8h} (ng.h/mL)	C_{trough}
Over 12 years	200 mg TID	5248 [4] (11.9)	2.00 [4] (1.00-6.00)	25188 [4] (13.0)	1535 [4] (25.4)
	200 mg BID	3529 [3] (17.1)	2.00 [3] (1.00-2.00)	16072 [3] (16.8)	NA
Under 12 years	200 mg BID	3428 [3] (24.8)	4.00 [3] (3.00-6.00)	18928 [3] (26.1)	NA
	200 mg OD (a.m.) 100 mg OD (p.m.)	7437 [1] (NA)	3.00 [1] (NA)	35326 [1] (NA)	NA
	100 mg OD	2011 [2] (4.03)	2.50 [2] (2.00-3.00)	10405 [2] (3.36)	NA

t_{max} values are median with range of values in parentheses. All other values are geomean with CV in parentheses
[n] = Number of patients included in mean NA = Not applicable

Individual plasma concentrations of OGT 918 following repeated oral administration of OGT 918 to patients over the age of 12 years (left) and patients under the age of 12 years (right)



Patients 106, 109, 111 and 208 received 200 mg TID
Patients 101, 102 and 103 received 200 mg BID

Patients 105, 108 and 114 received 200 mg BID.
Patient 107 received 200 mg (a.m.) and 100 mg (p.m.).
Patients 203 and 204 received 100 mg OD

Concentrations of miglustat in CSF ranged from 201 to 512 ng/ml (37% to 42% of that in plasma) for patients aged 12 and over and from 365 to 677 ng/ml (31% to 67% of that in plasma) for patients aged less than 12 years. This observation indicates that miglustat is able to cross the blood-brain barrier.

Study OGT 918-009

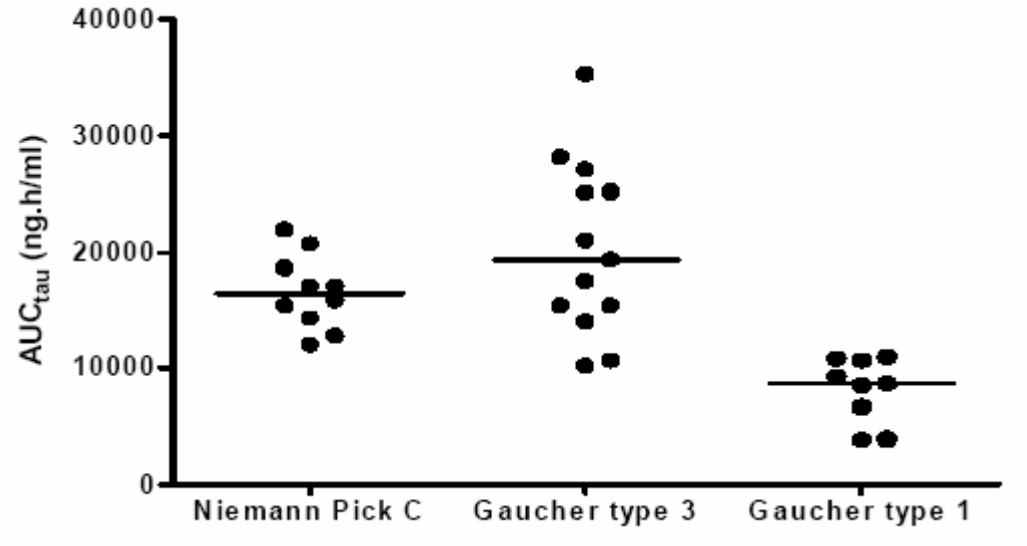
In this study, 6 adult patients with late onset Tay Sachs disease (LOTS) provided blood samples for pharmacokinetic evaluation after 1 month of treatment with miglustat 200 mg t.i.d. In addition, in 2 of these 6 patients, trough CSF samples were taken at Month 1 for comparison of miglustat concentrations in CSF relative to that in plasma. The exposure to miglustat as measured by AUC_{0-8h} and C_{max} was similar in this study when compared to exposure reached in studies OGT 918-006 and OGT 918-007. The mean (geometric mean coefficients of variation in parentheses) pharmacokinetic parameters of OGT 918 are summarised below (n = 6; unless otherwise stated [n]):

C_{max} (ng/mL)	t_{max} (h)	AUC_{0-8h} (ng.h/ml)	C_{trough} (ng/mL)
3200 (20.1)	2.50 (2.00, 4.00)	18457 (17.5)	1582 [4] (22.4)

In the 2 patients who provided CSF samples, concentrations of miglustat in CSF were 382 and 747 ng/ml (29% and 42% of that in plasma), indicating that miglustat is able to cross the blood-brain barrier.

Consistent with the higher dose given, the plasma concentrations of miglustat were higher in the GD-3 and NP-C disease patients than in type 1 Gaucher disease patients. C_{max} and AUC_{τ} values were approximately two-fold those observed in adult type 1 Gaucher disease patients administered miglustat 100 mg t.i.d., consistent with the linear pharmacokinetics of miglustat.

Comparison of exposure to miglustat in adult type 1 Gaucher subjects and paediatric subjects with type 3 Gaucher disease or Niemann-Pick type C disease



Data are shown as individual AUC_{tau} values (ng.ml/h). The geometric means as indicated by the horizontal lines were 16,285, 19,044, and 7,556 ng.ml/h, in Niemann Pick C, Gaucher type 3 and Gaucher type 1 patients, respectively. Data are from studies OGT 918-007 (Niemann-Pick type C), OGT-918-006 (type 3 Gaucher) and OGT 918-001 and -005 (type 1 Gaucher).

In addition, as mentioned above, in the study in GD-3 disease patients (OGT 918-006), it was shown that the concentration of miglustat in CSF ranged from 31.4% to 67.2% of that in plasma, indicating good penetration across the blood-brain barrier.

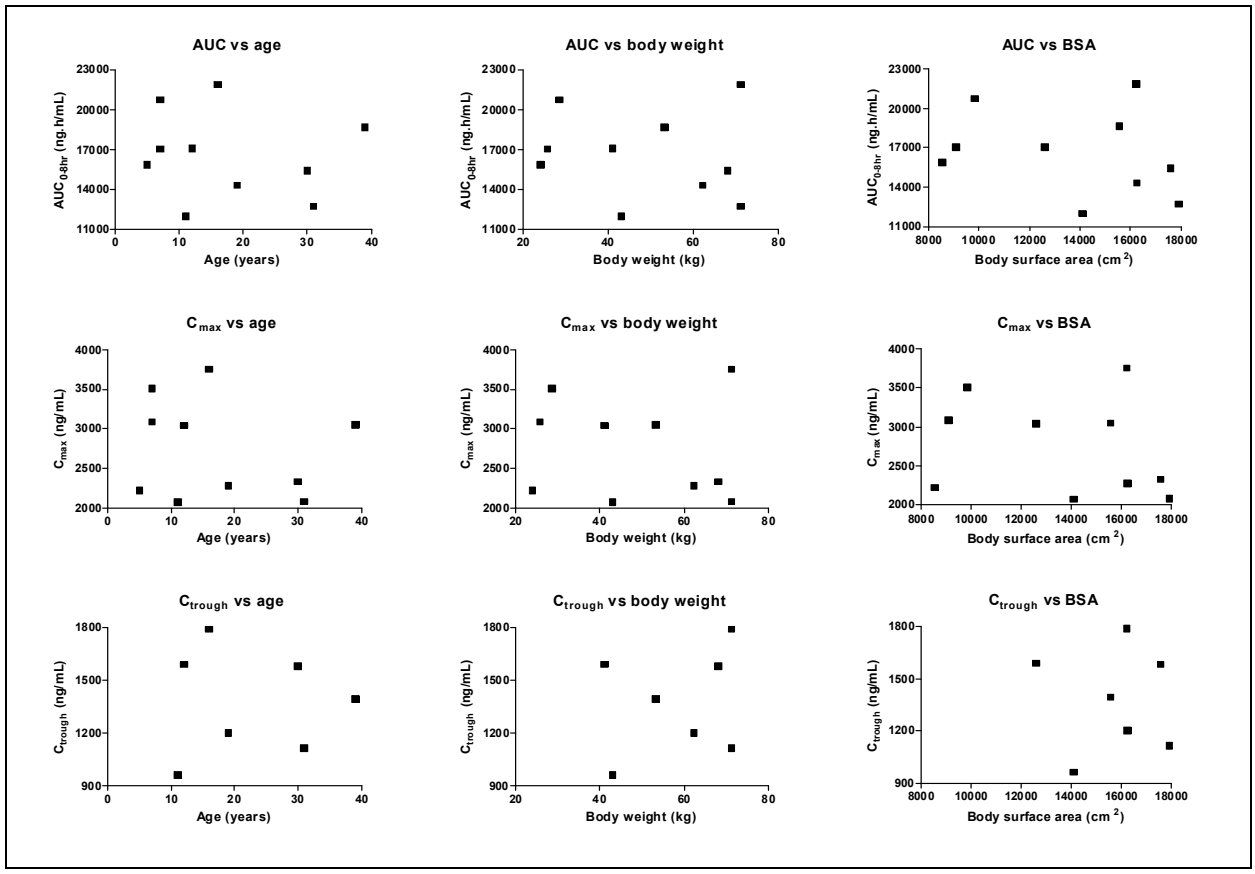
The average exposure to miglustat was 18475 ng.h/ml in the LOTS patient population, which was similar to that observed in GD-3 and NP-C patients treated with the same dose. Also, the limited data available indicate that the CSF penetration of miglustat in LOTS patients was similar to that observed in GD-3 patients.

Together, these new data indicate that dosing of miglustat with the adult target dose of 200 mg t.i.d., with adjustment based on body surface area in paediatric patients, and as used in the clinical trials, yields exposure values to miglustat which are comparable over a wide age range in paediatric and adult patients. The concentration of miglustat obtained in the CSF of subjects treated with this regimen is comparable to that in plasma of adult type 1 Gaucher disease patients treated with miglustat 100 mg t.i.d. It may, thus, be expected that at the proposed dosing regimen of 200 mg t.i.d., sufficient quantities of miglustat cross the blood-brain barrier to inhibit the target enzyme glucosylceramide synthase in the brain.

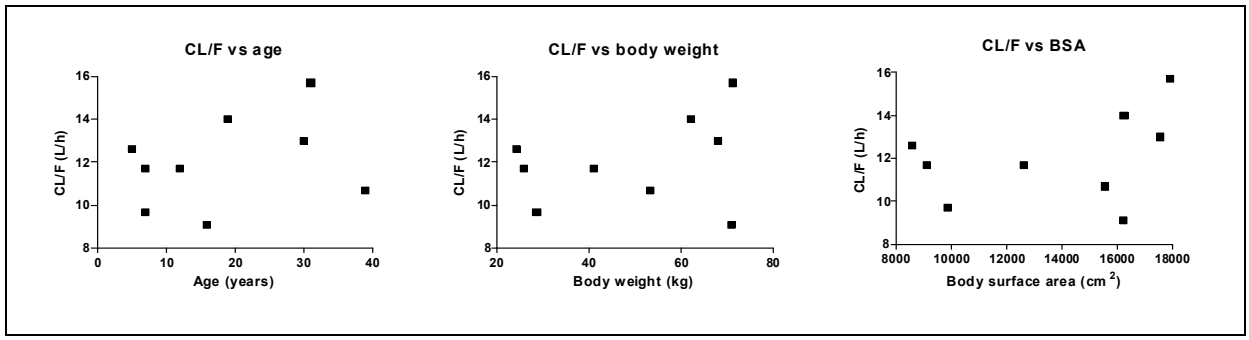
To further substantiate the pharmacokinetic adequacy of the dosing recommendation, analyses were produced of $AUC_{0\text{-}8h}$, C_{max} and C_{min} (or pre-dose concentration) vs age, BSA and body weight. CL/F (calculated as dose/$AUC_{0\text{-}8hr}$) plotted vs age, BSA and body weight.

No clear trends for an influence of any of the demographic variables on the pharmacokinetics of miglustat could be discerned. Together with the rather small variability in exposure of only about 2-fold across the paediatric age range studied, this would support that the chosen dosing is appropriate.

Plots of $AUC_{0\text{-}8h}$, C_{max} and C_{min} (or pre-dose concentration) vs age, body surface area, and body weight



CL/F plotted vs age, body surface area, and body weight



It is acknowledged that the calculations suffer from the weakness that for those patients receiving miglustat twice a day, $AUC_{0\text{-}8hr}$ does not properly reflect exposure to miglustat. For these patients an $AUC_{0\text{-}12hr}$ should have been calculated (but was not possible due to the limited blood-sampling scheme), and for all patients the AUC should have been normalised to a 24-hour AUC for proper comparison between patients who received miglustat b.i.d. or t.i.d.

Finally, although a dosing regimen based on body surface area may not be ideal, the observed low variability in exposure in the tested patient population indicates that the dosing regimen investigated is appropriate based on PK considerations.

Conclusions on pharmacological data

Additional pharmacokinetic data for miglustat was obtained in paediatric/adolescent and adult patients with NP-C disease, paediatric /adolescents patients with GD-3 disease and in adults patients with LOTS. Adults received 200 mg t.i.d., i.e. twice the dose presently recommended for patients with type

1 Gaucher disease. Children and adolescents received doses adjusted according to their BSA, corresponding to the doses proposed in the SPC. Plasma samples for PK evaluation were taken during 8 h after one month's treatment. $AUC_{0\text{-}8h}$ was calculated by trapezoidal methodology. As dosing scheduled differed from once to three times daily, use of $AUC_{0\text{-}8h}$ has its limitations but provides a rough comparison of exposure. Differences between dosing schedules is likely somewhat larger than that observed in the comparison of $AUC_{0\text{-}8h.}$

Ten children in the age range 2-11 years and 13 adolescent/adults in the age range 12-39 years were included in studies -006 and -007. The provided plots of $AUC_{0\text{-}8h}$, C_{max} and C_{min} (or pre-dose concentration) vs age, body surface area and body weight show that the PK parameters each vary within an approximate 2-fold range, and there seem to be no relationship between the PK parameters and age, body weight or BSA. As the data represent a mixture of different dosage regimens (BID and TID dosing) and the AUC_{τ} for BID dosing is underestimated, it would have been useful if different symbols had been used for the different treatment regimens. The MAH has presented data only from study 007. Given the low number of patients, it would have been useful if also data from study 006 had been included.

The data presented showed no trends for influence on CL/F by age, weight or BSA. However, CL/F was calculated as dose /$AUC_{0\text{-}8h}$, which is not an accurate estimate of CL/F for BID dosing. In patients with BID dosing (3 subjects with BSA<1.25 m^2), CL/F has been overestimated. With a lower CL/F in these subjects, there could be a trend for a relationship between all PK parameters and CL/F, with lower CL/F in the lower BSA / age / weight range (assuming that the 3 subjects with BSA<1.25 m^2 receiving BID dosing are the youngest subjects of lowest weight).

The MAH claimed that the BSA based dosing is adequate as the exposure varies between a 2-fold range and miglustat does not have a narrow therapeutic window. Unfortunately it is a bit difficult to evaluate this as the MAH had not provided CL/F estimates and as AUC_{τ} had been underestimated in the smaller children. However, C_{max} is fairly well described and the presented AUC and CL/F data vary within a fairly narrow range. Also, dosing by BSA in children on average seems to result in fairly similar exposure as 200 mg TID in adolescents / adults. Therefore, the lack of a more detailed evaluation is accepted. The presented data suggest no clear trends for age or body weight being better predictors of exposure than BSA, suggesting that dosage by BSA is appropriate.

Concentrations of miglustat in CSF of between 200 and 677 ng/ml were obtained. The MAH claimed that these concentrations are similar to those observed in plasma at 100 mg TID in type 1 Gaucher disease. Simulations made by the MAH during the approval procedure for Zavesca indicated that the plasma concentration on average fluctuates between about 800 and 2000 ng/ml. Hence, CSF concentrations obtained with 200 mg TID dosing seem to be lower than those observed in plasma at 100 mg TID in type 1 Gaucher disease. It can be concluded that miglustat is able to cross the blood-brain barrier. However, based on these data, it is difficult to determine if sufficient quantities of miglustat cross the blood-brain barrier to inhibit the target enzyme glucosylceramide synthase in the brain.

3.3.2. Clinical efficacy

The studies/surveys listed below comprise the main data supporting the current application. Furthermore, as supportive data, the MAH has submitted study protocols for 2 additional studies including 30 patients with GD-3 (OGT 918-006), and 30 patients with LOTS disease (OGT 918-009).

Overview of clinical studies in NP-C disease

Protocol (Report No.)	Study design	Treatment arms and dose	Treatment duration	Number of patients
OGT 918-007 Main study	Comparative, open-label, controlled study	Miglustat 200 mg t.i.d. No Treatment	12 months	29 patients: 20 miglustat 9 No Treatment
OGT 918-007 Main study: Optional Extended Study	Open-label, non-controlled	Miglustat 200 mg t.i.d.	12 months (up to 24 months in total)	25 miglustat patients (17 from miglustat; 8 from No Treatment)
OGT 918-007 Main study: Optional continued treatment extension period	Open-label, non-controlled	Miglustat 200 mg t.i.d.	From Month 24 to study close: 31 December 2007	16 miglustat patients
OGT 918-007 Pediatric sub-study	Open-label, non-controlled	Miglustat 200 mg t.i.d. equivalent according to BSA	12 months	12 miglustat patients
OGT 918-007 Pediatric sub-study Optional continued treatment extension period	Open-label, non-controlled	Miglustat 200 mg t.i.d. equivalent according to BSA	12 months (24 months in total) reported separately	10 miglustat patients
OGT 918-007 Pediatric sub-study Optional continued treatment extension period	Open-label, non-controlled	Miglustat 200 mg t.i.d. equivalent according to BSA	From Month 24 to study close: 31 December 2007	10 miglustat patients
Individual OGT 918 007 studies patient efficacy analysis	Subgroup of patients from the Main and the Pediatric sub-study	Miglustat 200 mg t.i.d. or dose equivalent according to BSA	From 387 days to 2056 days	29 miglustat patients (19 from Main study 10 from Pediatric sub-study)
Survey of neurological outcomes (Stage I survey)	Retrospective	Miglustat	From 18 days to 1646 days (4.5 years)	66 miglustat patients
Survey of natural history of neurological disease (Stage II survey)	Retrospective	No planned treatment arms	-	57 patients (19 from Stage I survey)
Individual patient case studies	Retrospective	Miglustat (plus one non-treated patient control)	-	14 miglustat patients 1 control
OGT 918-006	Open-label	Miglustat 200 mg t.i.d. or according to BSA if < 12 y No Treatment	12 months	21 miglustat patients 9 No Treatment
OGT 918-009	Open-label	Miglustat 200 mg t.i.d. No Treatment	12 months	20 miglustat patients 10 No Treatment

- BSA = body surface area, t.i.d. = three times daily.

Study OGT 918-007

Study Design

This was a randomized, parallel group, open-label, controlled study conducted at two sites: one in the United Kingdom (UK) and one in the United States (USA). Since there are no available therapies for NP-C, the control arm selected was No Treatment, i.e., standard care.

Patients randomized to miglustat received a dose of 200 mg t.i.d. for 12 months while patients randomized to No Treatment received standard care. Patients were randomized in a 2:1 ratio to miglustat or No Treatment using a blocked central randomization but were not stratified by center to limit the chances of the investigating site being able to predict the treatment assignment. Both randomized groups followed an identical visit schedule. Inclusion criteria were based on confirmed disease (abnormal cholesterol esterification and abnormal filipin staining) and the ability of the patients to ingest the study medication in the form of capsule.

1) The Main study was designed to have a 12-month controlled, comparative period (miglustat versus No Treatment) during which patients were evaluated every 3 months, with a ≤ 28-day screening period. The study period was completed when all patients completed the 12-month study.

2) The 12-month optional Extended Study was designed to offer 12 months therapy to patients who were randomized to No Treatment in the 12-month randomized period and to offer a further 12 months therapy to those patients originally randomized to miglustat. The Extended Study had an open-label, non-comparative study design. Patients were evaluated every 3 months to Month 24.

3) The optional continued treatment extension period permitted all patients to continue with therapy beyond 24 months if it was considered by the Investigator to be in the best interests of the patient.

4) The Pediatric sub-study was performed to investigate the efficacy of miglustat in paediatric patients with NP-C younger than 12 years. The Pediatric sub-study had an open-label, non-comparative design. All paediatric patients received treatment with miglustat (at a starting dose equivalent to 200 mg t.i.d.). The miglustat dose was adjusted according to BSA. This study was followed by an extension period of 12 months.

5) The individual patient efficacy analysis from study OGT 918-007 was an exploratory analysis of individual efficacy data for a sub-group of 29 patients: 19 from the Main study and 10 patients from the Pediatric sub-study. The analysis was undertaken in order to explore any possible association between disease severity at baseline and treatment response.

Study population

Of the 29 patients in the original study, 14 were male and 15 were female. The mean age of the patients was 24.6 years (standard deviation [SD] = 9.1). There was a higher proportion of patients aged 12–17 years in the No Treatment group (44%) when compared with the miglustat group (25%). A greater proportion of patients in the miglustat group reported the various manifestations of NP-C (in particular neurological symptoms). The pediatric study included patients above 4 years and under 12 years of age, with a mean age of 7.2 ± 2.5.

Summary of patient demographics

		OGT 918-007 Adult/juvenile			OGT 918-007 Sub-study Pediatric	
		12 Month		EOS	12 Month	EOS
Number of patients		Miglustat N = 20	NT N = 9	Miglustat N = 16	Miglustat N = 12	Miglustat N = 10
Gender	Male	9 (45%)	5 (56%)	9 (56%)	5 (42%)	4 (40%)
	Female	11 (55%)	4 (44%)	7 (44%)	7 (58%)	6 (60%)
Age (years)	Mean (SD)	25.4 ± 9.8	22.9 ± 7.5	22.6 ±9.4	7.2 ± 2.5	7.2 ± 2.5
	Range	12-42	13-32	12-42	4-11	4-11
Age group (years)						
2–11	n (%)	0	0	0	12 (100%)	10 (100%)
12–17	n (%)	5 (25%)	4 (44%)	6 (38%)	0	0
≥ 18	n (%)	15 (75%)	5 (56%)	10 (63%)	0	0
Race						
White	n (%)	15 (75%)	8 (89%)	13 (81%)	9 (75%)	7 (70%)
Black	n (%)	2 (10%)	0	1 (6%)	1 (8%)	1 (10%)
Asian (Oriental)	n (%)	0	0	0	0	0
Asian (Other)	n (%)	2 (10%)	0	1 (6%)	0	0
Hispanic	n (%)	1 (5%)	1 (11%)	1 (6%)	2 (17%)	2 (20%)

12 Month = First 12 months or Main study period; EOS = end of study or final results from continued treatment extension period.

NT = No Treatment, SD = standard deviation.

Efficacy measurements

The primary efficacy assessment of the study was the measurement of saccadic eye movements, based on expert consideration. The primary analysis endpoint was the mean change from baseline to Month 12 for Horizontal saccadic eye movements (HSEM-α).

The following secondary endpoints were assessed in the studies: Swallowing, evoked potentials, physical performance assessments, neuropsychological tests, neurological examination, nerve conduction velocity and tremor, organ volumes, isometric muscle strength, speech tests, pulmonary tests, biochemical markers of disease burden and quality of life measures.

Patient disposition

A total of 29 juvenile/adult NP-C patients were randomized, 20 to miglustat and 9 to No Treatment in addition to standard care. Three patients receiving miglustat withdrew from the 12-month study prematurely. Two withdrew due to AEs while one patient withdrew for other reasons (unacceptable disease progression and evidence of progressive neuro-degeneration). In the No Treatment group, one patient withdrew to start treatment with an alternative therapy. A total of 25 patients completed the 12-month controlled period and entered the 12-month non-controlled Extended Study (17 from the miglustat group and 8 from the No Treatment group). Nineteen patients completed the 12-month Extended Study (15/17 patients from the miglustat group (24 months miglustat therapy) and 4/8 patients from the No Treatment group (12 months miglustat therapy).

Of the 19 patients who completed the 24-month visit, 16 patients (14 from the original miglustat group and 2 from the original No treatment group) entered the continued treatment extension period. All 16 patients completed at least 6 months of the extension period (to Month 30) and 13 completed the study. At this point, patients had received treatment up to a maximum of 66 months (adults/juveniles) or 48 months (pediatrics). Three patients were withdrawn prior to study closure. All patients who were in the study at the closure date continued to receive miglustat after the closure date.

The pediatric sub-study included 12 patients.

Patient withdrawals in studies OGT 918-007

Number of patients	OGT 918-007 Adult/juvenile					OGT 918-007 Sub-study Pediatric		
	12 Month		24 Month		EOS	12 Month	24 Month	EOS
	Mig	NT	Mig/Mig	NT/Mig	Mig	Mig	Mig	Mig
Number of patients	20	9	17	8	16	12	10	10
Number of patient withdrawals	3	1	2	4	3	2	0	1
Reasons for withdrawal[a]								
Adverse event	3		1	2		1		1
Lost to follow-up	1		1		1			
Non-compliant			1		1			
Patient requested withdrawal		1	1	2	1	1		
Investigator requested withdrawal	3		1	1				

[a] more than one reason for withdrawal could be recorded.
12 Months = First 12 months or Main study period; 24 Months = Extended study (adults/juveniles) or second year of miglustat treatment for continued treatment extension period of pediatric study; EOS = end of study or final results from continued treatment extension period.
Mig = miglustat, NT = No Treatment

Retrospective survey of neurological outcomes (Stage I survey)

Methods

The Stage I retrospective survey of neurological outcomes was conducted between July 2007 and July 2008. The survey was designed to collect available data, particularly on neurological outcomes, physician's global assessment of the utility of treatment, and main reasons for discontinuation of treatment in NP-C patients treated with miglustat. Furthermore data on seizure activity and frequency was included in the survey.

Using a web-based survey, 38 sites/physicians were invited to enter demographic and clinical data from NP-C patients treated with miglustat. Twenty-five physicians had entered data at the time of the summary report. Physicians were asked to complete a questionnaire for each patient who had been treated with miglustat . Data collection was via a secure website.

Sixty-six patients were included in the analysis. Patients had been on treatment with miglustat for a mean of 543 days. At the time of the questionnaire, treatment was ongoing in 54 of the 66 patients and had been discontinued in 10 patients.

Data were available for 36 pediatric patients and 30 adult/juvenile patients. Mean age at treatment start was 12.8 years overall, range 0.6 to 43 years. The mean age at diagnosis was 9.7 years, range 0 to 32 years. Patients had been under observation for a mean of 3.1 years between diagnosis of NP-C disease and start of treatment with miglustat and had been on treatment with miglustat for a mean of 543 days (approximately 1½ years).

For patients in the Stage I survey and those included in both survey I and II, treatment duration is summarized below.

Summary of exposure (weeks) to miglustat in retrospective surveys

	N	≤ 26 weeks (≤6 months)	> 26 - 52 weeks (>6 - 12 months)	> 52 - 104 weeks (>12 - 24 months)	> 104 weeks (>24 months)
Stage I retrospective survey	66	16 (24%)	11 (17%)	21 (32%)	18 (27%)
Patients in both surveys	19	7 (37%)		9 (47%)	3 (16%)

Overall, dosing was comparable between the survey and the study OGT 918-007 with 41 of 61 patients with dosing data available (67%) receiving at least 300 mg per day of miglustat.

Retrospective survey of natural history of neurological disease (Stage II survey)

Methods

The Stage II retrospective survey of the natural history of neurological disease in NP-C patients was conducted between June 2007 and August 2008. The web-based survey was conducted in order to corroborate the robustness of findings from the Stage I survey and to better understand the pattern of neurological disease progression in NP-C patients. The survey was aimed at retrospectively evaluating the natural course of the disease, and, when possible, to compare it with changes of neurological disease progression rate after treatment with miglustat, as analyzed also in the Stage I survey. By completing a questionnaire on a secure website, seven physicians had provided data relating to 57 patients (35 pediatric and 22 adult/juvenile). This included data for 19 patients who had previously been included in the Stage I survey and had received miglustat treatment. The mean (SD) time interval between the first visit at diagnosis and the last visit was 5.5 (4.8) years.

The rating scale used in the survey of natural history was the same as that used in the Stage I survey and was applied in an identical manner. The scale was used to score the severity of disturbance in the parameters ambulation, manipulation, language articulation and swallowing at each visit.

Results

Study OGT 918-007

Primary endpoint

A mean improvement in the primary endpoint, HSEM-α, was shown in adult and juvenile patients receiving miglustat relative to No Treatment in the 12-month randomized period. Increases (i.e., worsening) from baseline in HSEM-α were observed for both groups at Month 24 and at the last visit (last value). Differences between treatment groups were not statistically significant.

Secondary endpoints

- Swallowing

A statistically significant shift towards improvement was observed with miglustat compared with the No Treatment group ($p = 0.044$) for swallowing the one-third cookie at the end of the main, controlled study. For other substances, the shifts were not statistically different between the treatment groups at last value or Month 12. At Month 6, a significant shift was observed with miglustat compared with the No Treatment group ($p = 0.043$) for swallowing the puree.

Summary of shifts in swallowing ability from baseline to last value (Efficacy set)

	OGT 918 (N = 20)				No Treatment (N = 10)*			
	Water	Puree	Lumps	Cookie	Water	Puree	Lumps	Cookie
Improvement								
Moderate to easy	2 (10%)	1 (5%)	1 (5%)	3 (15%)	0	0	0	0
Moderate to mild	0	0	0	2 (10%)	0	0	0	0
Mild to easy	4 (20%)	2 (10%)	2 (10%)	2 (10%)	1 (13%)	0	1 (13%)	1 (13%)
Worsening								
Easy to mild	1 (5%)	1 (5%)	3 (15%)	1 (5%)	1 (13%)	0	2 (25%)	2 (25%)
Mild to moderate	1 (5%)	0	0	0	0	0	0	0

Overall, among patients with both baseline and Month 12 data, improved or stable swallowing functions were seen in 15/17 patients (88%) on miglustat, with 2 patients (12%) showing deterioration.

For the No Treatment group, 5/8 patients (62%) showed deterioration and 3 patients (38%), improved.
At the last value assessment in the 12-month extension period the ability to swallow water, puree, soft lumps and one-third of a cookie had improved or remained stable compared to baseline for a higher proportion of patients in the 24 months miglustat group than in the 12 months miglustat group. At the last value assessment, the ability to swallow water, puree, soft lumps and one-third of a cookie had improved or remained stable compared to baseline for 13 (87%), 12 (80%), 11 (73%) and 13 (87%) of the 15 patients in the 24 months miglustat group. Improved or stable ability to swallow water, puree, and one-third of a cookie were seen for two (40%) of the five patients in the 12 months miglustat group and improved or stable ability to swallow soft lumps in two of four patients (50%).

Most of the ten pediatric patients in the efficacy set swallowed all four substances (water, puree, soft lumps and one-third of a cookie) easily at baseline, therefore, few patients had scope for improvement. This was the same for the last value assessment.

- Physical performance tests

Standard Ambulation Index (SAI) scores increased during the 12-month, controlled period, but the increase (i.e., deterioration) was less in patients on miglustat than in the No Treatment group.

SAI: analysis of changes from baseline to Month 12 and last value (Efficacy set)

	Adjusted mean change from baseline				
Standard Ambulation Index	**OGT 918**	**No Treatment**	**Estimated treatment difference**	**95% confidence interval**	**p-values[a]**
Month 12	0.023	0.793	–0.770	(–1.610, 0.071)	0.071, 0.070
Last Value	0.087	0.802	–0.715	(–1.438, 0.007)	0.052, 0.039

Paediatric NP-C patients showed a small mean increase (deterioration) in SAI score over12 months of miglustat treatment which was similar to that observed in miglustat-treated juvenile/adult patients.
In the assessment of the SAI after 24 months of treatment, there was a smaller increase from baseline to last value in the patients in the 24 months miglustat group (0.3) compared with the 12 months miglustat group (1.2) (estimated treatment difference: –1.377; 95% CI: –2.720, –0.034; p = 0.045; ANCOVA).

- Neuropsychological tests

NP-C patients treated with miglustat showed a mean improvement in Mini Mental Status Examination (MMSE) score over the 12-month study period, whereas patients in the No Treatment group deteriorated.

NP-C patients treated with miglustat had a mean decrease (deterioration) in the Purdue Pegboard Test score over the 12-month study period, whereas patients in the No Treatment group had a relatively stable score.

- Quality of Life assessments

Most of the NP-C patients in the main analysis were ≥ 14 years of age and completed the SF-36 questionnaire. In four of the eight domains (bodily pain, general health, social functioning, mental health) and the physical component summary score, mean improvements from baseline to the last value were observed with miglustat compared with deterioration in the No Treatment group.
A smaller deterioration was observed in the miglustat group compared with the No Treatment group in two other domains (vitality, role physical). Patients on miglustat fared less well than those in the No Treatment group in the domains of physical functioning and role emotional, and in the mental component summary score. However, none of these differences between treatment groups were statistically significant in *post-hoc* analyses.
Three paediatric NP-C patients completed the Children's Health Questionnaire – Parent form-50 questionnaire (CHQ-PF50). Substantial mean increases (i.e., improvements) from baseline to last value were observed in the domains role social behaviour, role physical, bodily pain, self-esteem, and family cohesion.

Continued treatment extension period

On completion of Month 24 (Extended Study) an option of continued treatment with miglustat was provided. This was a prospective, open-label, study design and the efficacy analysis was exploratory. In the assessment of swallowing, eleven (> 75%) of the 14 patients with available data showed improvement or stability in swallowing ability. Three patients (21%) showed deterioration in swallowing in the 5 mL of water; two patients (14%) worsened in swallowing the 1-teaspoon of soft lumps and in the 1-teaspoon of puree assessments; one patient worsened in swallowing 1/3 of a cookie.
Mean ambulatory index score showed a slight deterioration from baseline to last value. The majority of patients (8 out of 12, 67%) showed no change in score.

Individual patient analysis

A total of 29 patients were included in the individual patient efficacy analysis: 19 from study OGT 918-007 and 10 from the Pediatric sub-study. All patients had received at least 12 months of treatment with miglustat.
For the overall response analysis, each patient was defined as stable if none of the variables swallowing function, ambulation index and MMSE was deteriorated. Patients were considered stable also if only deterioration of HSEM-α occurred whilst the other three clinical parameters were either stable or improved. Alternatively, patients were defined as deteriorated.

Criteria for definition of disease change in individual patient efficacy analysis

Variable	Improvement	Stabilization	Deterioration
HSEM-α	Decrease from baseline higher than 20%	Change from baseline within ±20%	Increase from baseline higher than 20%
Swallowing function	Any up-grading compared to baseline	No change from baseline	Any down-grading compared to baseline
Ambulation index	Decrease from baseline > 1 point	No change from baseline or change ± 1 point	Increase from baseline >1 point
MMSE*	Increase from baseline of > 2 points	Change from baseline of ± 2 points	Decrease from baseline by > 2 points

* Main study only

In the Main study, 13 patients showed overall disease stabilization and 6 patients showed deterioration. Of the 6 patients with deterioration, one patient showed only deterioration of swallowing

function and one showed only deterioration of cognitive performance as shown by MMSE changes. In the paediatric study, 8 patients showed overall disease stabilization and 2 patients showed deterioration. Overall, among 29 patients assessed, 21 patients (72.4%) showed overall disease stabilization, 8 (27.6%) patients showed disease deterioration.

The analysis of the relationship between disease severity at baseline and treatment response was not conclusive. Although the highest (100%) and the lowest (33%) response rates were observed among patients with the mildest (n = 4) and the most severe (n = 3) disease at baseline, respectively, the confidence intervals were wide. The response rate in nine patients with moderate disease at baseline (77.8%) was comparable to that (75.0%) in 12 patients with mild disease at baseline.

Retrospective survey of neurological outcomes (Stage I survey)

Efficacy was assessed using a disability scale measuring the status of ambulation, manipulation, language articulation and swallowing function at three distinct time points, i.e., at the time of diagnosis, at treatment start and at last clinical contact or discontinuation of miglustat.

- Neurological parameters

At the time of diagnosis of NP-C, some degree of ambulatory disability was described for 66% of patients. During the period between diagnosis of NP-C and start of treatment with miglustat, this increased to 89%; no patient showed spontaneous improvement. During treatment with miglustat, ambulation was reported as improved in 9/64 patients with data available (14%) and was stable in 40/64 patients (62%). Fifteen patients (23%) showed progressive deterioration of ambulatory function during treatment with miglustat.

Ambulation – status at assessment time points by number and frequency (Stage I survey)

	Patients	
Status	**N**	**%**
At time of diagnosis		
Normal	22	34.4%
Autonomous ataxic gait	39	60.9%
Outdoor assisted ambulation	1	1.6%
Indoor assisted ambulation	2	3.1%
Wheelchair-bound	0	0.0%
Total	64	
Missing values	2	
At initiation of miglustat therapy		
Normal	7	10.8%
Autonomous ataxic gait	30	46.2%
Outdoor assisted ambulation	10	15.4%
Indoor assisted ambulation	9	13.8%
Wheelchair-bound	9	13.8%
Total	65	
Missing values	1	
At last clinical contact or at discontinuation of miglustat		
Normal	8	12.5%
Autonomous ataxic gait	27	42.2%
Outdoor assisted ambulation	7	10.9%
Indoor assisted ambulation	4	6.3%
Wheelchair-bound	18	28.1%
Total	64	
Missing values	2	

Manipulation was abnormal in 65% of patients at the time of diagnosis. This increased to 83% during the period of observation prior to start of miglustat; no patient showed spontaneous improvement. During treatment with miglustat, manipulation was reported as improved in 8/63 patients with data

available (13%) and was stable in 40/63 patients (64%). Fifteen patients (24%) showed progressive deterioration of manipulation during treatment with miglustat.

Manipulation – status at assessment time points by number/frequency (Stage I survey)

	Patients	
Status	**N**	**%**
At diagnosis		
Normal	22	35.5%
Slight dysmetria/dystonia (allows autonomous manipulation)	28	45.2%
Mild dysmetria/dystonia (requires help for several tasks but is able to feed himself)	12	19.4%
Severe dysmetria/dystonia (requires assistance in all activities)	0	0.0%
Total	62	100.0%
Missing values	4	
At initiation of miglustat therapy		
Normal	11	17.2%
Slight dysmetria/dystonia (allows autonomous manipulation)	23	35.9%
Mild dysmetria/dystonia (requires help for several tasks but is able to feed himself)	18	28.1%
Severe dysmetria/dystonia (requires assistance in all activities)	12	18.8%
Total	64	100.0%
Missing values	2	
At last clinical contact or at discontinuation of miglustat		
Normal	9	14.1%
Slight dysmetria/dystonia (allows autonomous manipulation)	24	37.5%
Mild dysmetria/dystonia (requires help for several tasks but is able to feed himself)	14	21.9%
Severe dysmetria/dystonia (requires assistance in all activities)	17	26.6%
Total	64	100.0%
Missing values	2	

Concerning articulation, abnormal findings were described for 62% of patients. During the period between diagnosis of NP-C and start of treatment with miglustat, this increased to 87%; no patient showed spontaneous improvement. During treatment with miglustat, language articulation was reported as improved in 7/61 patients with data available (11%) and was stable in 40/61 patients (66%). Fourteen patients (23%) showed progressive deterioration of language skills during treatment with miglustat.

Language articulation – status at assessment time points by number/frequency (Stage I survey)

	Patients	
Status	**N**	**%**
At diagnosis		
Normal	24	38.1%
Mild dysarthria (understandable)	38	60.3%
Severe dysarthria (only comprehensible to some members of the family)	0	0.0%
Non-verbal communication	0	0.0%
Absence of communication	1	1.6%
Total	63	100.0%
Missing values	3	
At initiation of miglustat therapy		
Normal	8	12.7%
Mild dysarthria (understandable)	39	61.9%
Severe dysarthria (only comprehensible to some members of the family)	9	14.3%
Non-verbal communication	5	7.9%
Absence of communication	2	3.2%
Total	63	100.0%
Missing values	3	
At last clinical contact or at discontinuation of miglustat		
Normal	7	11.3%
Mild dysarthria (understandable)	34	54.8%
Severe dysarthria (only comprehensible to some members of the family)	10	16.1%
Non-verbal communication	6	9.7%
Absence of communication	5	8.1%
Total	62	100.0%
Missing values	4	

Abnormal swallowing function was described for 31% of patients. During the period between diagnosis of NP-C and start of treatment with miglustat, this increased to 64%; no patient showed spontaneous improvement. During treatment with miglustat, swallowing function was reported as improved in 12/63 patients (19%) and was at least stable in 39/63 patients with data available (62%). Twelve patients (19%) showed progressive deterioration of swallowing during treatment with miglustat.

Swallowing – status at assessment time points by number/frequency (Stage I survey)

Status	Patients	
	N	%
At diagnosis		
Normal	41	68.3%
Occasional dysphagia	16	26.7%
Daily dysphagia	2	3.3%
Nasogastric tube or gastric button feeding	1	1.7%
Total	60	100.0%
Missing values	6	
At initiation of miglustat therapy		
Normal	23	35.9%
Occasional dysphagia	19	29.7%
Daily dysphagia	14	21.9%
Nasogastric tube or gastric button feeding	8	12.5%
Total	64	100.0%
Missing values	2	
At last clinical contact or at discontinuation of miglustat		
Normal	20	31.7%
Occasional dysphagia	23	36.5%
Daily dysphagia	12	19.0%
Nasogastric tube or gastric button feeding	8	12.7%
Total	63	100.0%
Missing values	3	

- Individual parameter score

An individual score was calculated for each of the four parameters based on a published disease-specific disability scale. The scale was used to score the severity of disturbances in the parameters. For the purpose of the analysis, the original scale was slightly modified in order to consistently assign to each of the four parameters a score ranging from 0 (the best grade) to 1 (the worst grade).

NP-C disability scale scores, all patients (Stage I survey)

	Ambulation (n = 63)		Manipulation (n = 61)		Language (n = 61)		Swallowing (n = 59)	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
At diagnosis	0.18	0.16 -0.20	0.27	0.24 -0.30	0.16	0.14 -0.18	0.12	0.10 -0.15
At initiation of miglustat therapy	0.43	0.39 -0.47	0.48	0.43 -0.52	0.31	0.28 -0.34	0.36	0.32 -0.41
At last clinical contact or discontinuation of miglustat	0.48	0.43 -0.53	0.52	0.48 -0.56	0.37	0.33 -0.40	0.37	0.32 -0.41

- Composite score

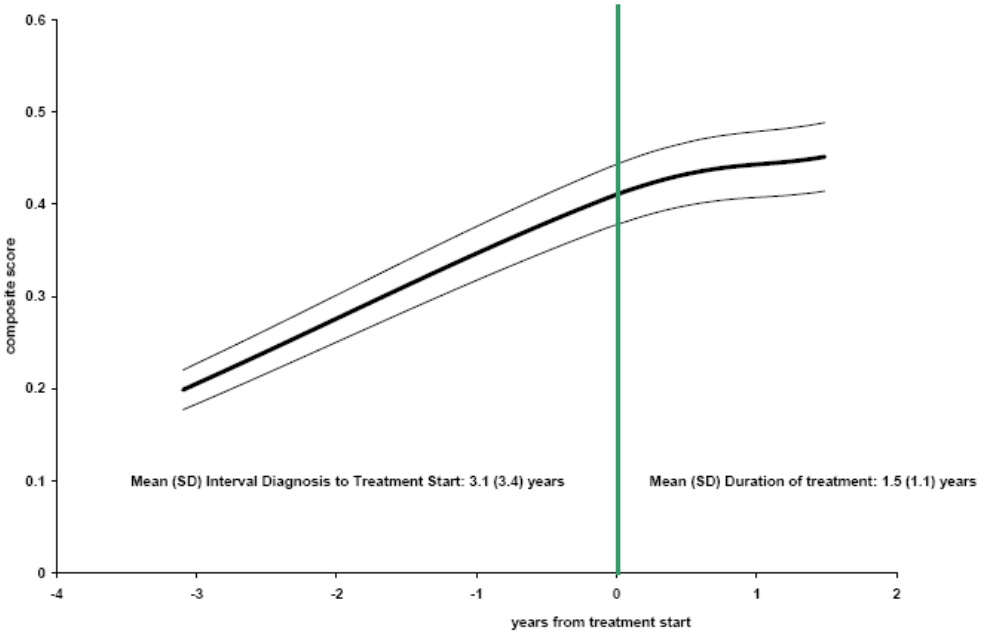
For the purpose of quantitative analysis, a composite score was calculated for each patient as the mean of the 4 individual scores at each of the 3 assessment time-points.

Disability scale composite score - retrospective survey (Stage I survey)

	N	Mean	95% C.I.	
At diagnosis	65	0.20	0.24	0.16
At initiation of miglustat therapy	66	0.41	0.47	0.35
At last clinical contact or discontinuation of miglustat	65	0.45	0.52	0.38

In order to provide an estimate of the rate of overall disease progression, the absolute changes of the composite score over time were adjusted for the time intervals between the three time points.
The progression rate decreased significantly from 0.11 score units/year between diagnosis and treatment start to −0.01 units/year after miglustat initiation (paired sample test comparison by Wilcoxon signed rank test Z = −3.03; p = 0.002).

Progression rate during observation and treatment periods



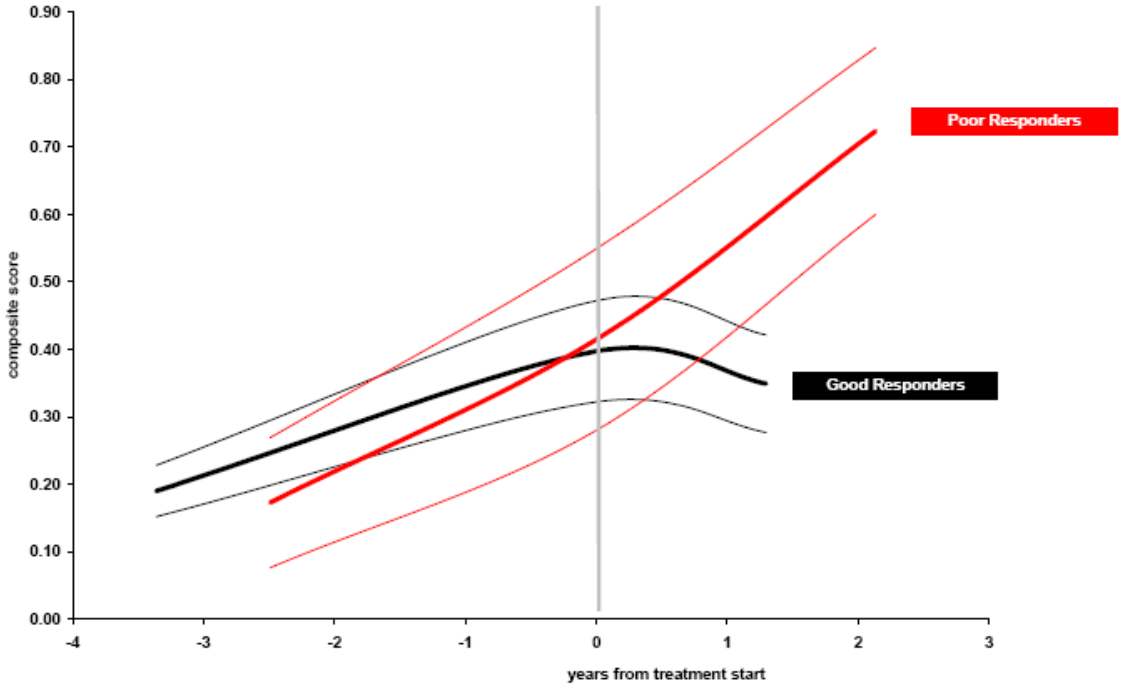
- Responder analysis

Patients were stratified according to the number of worsened parameters after initiation of miglustat treatment. Subjects were classified either as "good responders" if none or only one out of four parameters worsened after treatment, and as "poor responders" if two or more parameters worsened: 75% of patients were classified as "good responders" and 25% as "poor responders".

Distribution of patients per number of worsened parameters after miglustat treatment (Stage I survey)

	N	**%**	
None	40	61.5	**Good responders**
1	9	13.8	
2	6	9.2	**Poor responders**
3	5	7.7	
All 4	5	7.7	
Unknown	1		

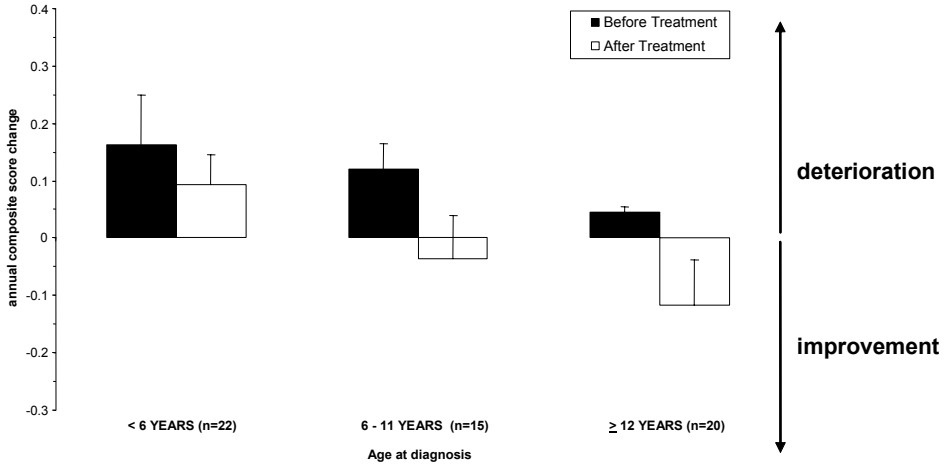
Progression rates during observation and treatment periods in 'good responders' and 'poor responders' (Mean and 95% CI)



An analysis was conducted to compare the characteristics of the "good responders" compared with the "poor responders". The mean age at diagnosis and at treatment start was lower in the poor responder group. Disease severity (as indicated by the composite score) at diagnosis and at treatment start was similar in "good" and "poor responders". However, disease progression rate prior to miglustat was 2.5 times higher in "poor responders" than in "good responders". In 'poor responders' annual progression rate was 0.21 (95% C.I. -0.10-0.51) between diagnosis and treatment start and 0.24 (95% C.I. 0.09-0.39) after treatment. A multivariate stepwise logistic regression analysis indicated that age at diagnosis was the most significant predictor of response.
Patients were therefore stratified in three groups, based on age at diagnosis: the "early childhood" group of those aged less than 6 years at diagnosis, "late childhood" of those aged between 6 and 11, and the "juveniles/adults" of those aged 12 years or older.

The progression rate of neurological disease before treatment initiation was fastest in the early childhood group and lowest among juveniles/adults. After treatment, the disease progression rate appeared to decrease across all age groups. Overall, the annual disease progression rate seemed reduced in the youngest group, became slightly negative (indicating disease stability) in the late childhood group, and was clearly reversed (indicating improvement) in the juvenile-adult patients.

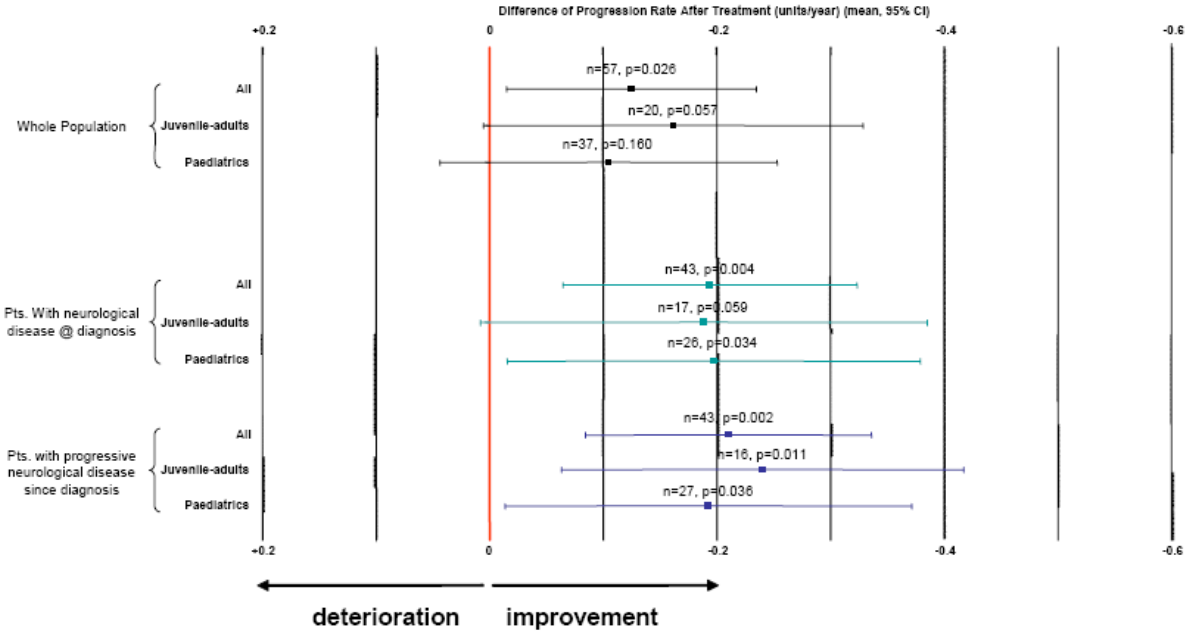
Annual progression rate between diagnosis and treatment start, and after treatment according to categories of age at diagnosis (Stage I survey)



Treatment difference			
Mean	-0.070	-0.157	-0.162
95% CI	-0.275, 0.136,	-0.394, 0.080,	-0.329, 0.006
Sig. (2-tailed)	0.488	0.177	0.057

An analysis was performed also in the subgroups of patients with neurological disease at diagnosis (n = 49), and patients with progressive neurological disease between diagnosis and treatment start (n = 44). In both subgroups, after treatment with miglustat, the progression rate became negative (indicating a general improvement): the treatment difference was statistically significant and numerically larger than observed in the whole population.

Age at diagnosis, neurological disease pattern and treatment effect



- Physician's global assessment

Patients' general health was considered improved (much or somewhat better, 37%) or stable (40%) for 77% of patients. The overall assessment of patients' benefit from miglustat treatment was good (41%) or fair (33%) in 74% of patients. Physicians indicated their intention to continue miglustat in 52 (96%) out of 54 patients who were on treatment with miglustat at the time of the last visit.

- Reasons for discontinuation

At the time of the questionnaire, miglustat treatment was ongoing in 54 of the 66 patients and had been discontinued in 10 patients.

Distribution of reasons for discontinuation in the survey population

Reason for discontinuation	**N**	**Cases ID**
Death:	4	(case 14, 18, 28, 30)
Adverse Event/ Drug Reactions:	4	(case 15, 30, 41, 42)
Lost to follow up:	1	(case 15)
Lack of efficacy:	3	(case 22, 30, 46)
Other:	3	(case 13, 15, 41)

- Seizure activity and frequency

Participating physicians were asked to report seizure activity and frequency at diagnosis, at treatment initiation, and at last clinical contact. At the time of diagnosis of NP-C disease, seizure activity was present in 13% of patients. During the period between diagnosis of NP-C disease and start of treatment with miglustat, this fraction increased to 25%. At start of miglustat treatment, 47 patients were free of seizures, of whom 7developed seizures while on miglustat treatment. Of the 16 patients with seizures at treatment start, one was reported to have no seizure activity at last contact.
The 7 patients who developed seizures over treatment with miglustat were younger at diagnosis and treatment start, showed a larger annual change of the composite score after treatment start, and a higher number of worsened parameters of the disability scale. Seizure activity at treatment start was not associated with a higher discontinuation rate.

Retrospective survey of natural history of neurological disease (Stage II survey)

At the time of diagnosis of NP-C, some degree of ambulatory disability was described for 61% of patients. This increased to 89% during the period of observation. Forty-four patients overall (77%) showed progressive deterioration of ambulatory function between diagnosis and last visit.

For manipulation, at the time of diagnosis of NP-C, manipulation was abnormal in 51% of patients. This increased to 86% during the period of observation. Forty-one patients (72%) showed progressive deterioration of manipulation during the natural course of the disease as measured from diagnosis to last visit.

Language articulation was abnormal in 42% of patients at time of diagnosis, which increased to 86% of patients during the period of observation. Thirty-six patients (63%) showed progressive deterioration of language skills from diagnosis to last visit.

Abnormal swallowing function was described for 18% of patients at diagnosis and deteriorated during the period of observation and a total of 77% of patients had abnormal swallowing function at the last visit. Thirty-nine patients (70%) showed progressive deterioration of swallowing over the observation period.

The composite score (as described above) increased substantially, indicating considerable deterioration of neurological function, from 0.15 at the time of diagnosis to 0.58 at the last visit.

The annual rate of progression was analyzed for patients with a time interval of at least 1 year between diagnosis and last visit and was similar across the 4 different parameters. The composite score progressed by 0.11 units/year. This rate was the same as observed in the Stage I survey between diagnosis and treatment start. In the Stage II survey, the pattern of progression of the composite score did not show any sign of plateau or even partial deceleration over the natural course of the disease. For each of the four parameters, the progression rate appeared continuous, without any apparent spontaneous decline of its average rate or any individual remission. Progression rate was consistently faster among patients with the lowest age-at-diagnosis.

Concerning seizure activity and frequency seizure activity was present in three patients (5%) at the time of diagnosis. During the period between diagnosis of NP-C disease and last visit, the proportion of patients with seizure activity rose to 32% (18 patients).

Using the rating scale, subjects were classified either as with ‘stable’ disease if none or only one out of four parameters had worsened during the period of observation, or with ‘progressed’ disease if at least two parameters had worsened: among patients (N = 49) with a time interval of at least 1 year between the first visit at diagnosis and the last visit, 14% of patients had ‘stable’ disease and 86% ‘progressed’. No patients showed ‘improvement’.

Retrospective survey of neurological outcomes (Stage I +II survey)

Nineteen patients in the natural history survey dataset had also been included in the previous Stage I survey. The use of the same scale for the evaluation of the neurological disease progression allowed a comparison of the time changes of the four single scores and of the composite score before treatment (for a mean time interval of 4.9 years) and after miglustat treatment (for a mean duration of 1.2 years).

Progression of disease as seen in the increase in ambulation, manipulation and language articulation score, which was continuous over the natural course of the disease, was halted after treatment with miglustat. The swallowing score, which was the most rapidly progressive before treatment start, decreased after treatment.

Progression of all four parameters and of the composite score during the natural course of the disease and after miglustat treatment

		N	Mean	95% C.I.	
Ambulation	Natural history: diagnosis	19	0.17	0.12	0.22
	Natural history: 2nd visit[1]	19	0.24	0.17	0.31
	Natural history: 3rd visit[2]	19	0.38	0.29	0.47
	Natural history: last visit-pretreatment[3]	19	0.54	0.41	0.67
	After miglustat treatment[4]	19	0.53	0.36	0.69
Manipulation	Natural history: diagnosis	19	0.23	0.14	0.32
	Natural history: 2nd visit[1]	19	0.28	0.19	0.37
	Natural history: 3rd visit[2]	19	0.39	0.28	0.49
	Natural history: last visit-pretreatment[3]	19	0.56	0.42	0.70
	After miglustat treatment[4]	19	0.53	0.38	0.67
Language	Natural history: diagnosis	19	0.21	0.11	0.31
	Natural history: 2nd visit[1]	19	0.26	0.17	0.36
	Natural history: 3rd visit[2]	19	0.28	0.19	0.37
	Natural history: last visit-pretreatment[3]	19	0.36	0.25	0.46
	After miglustat treatment[4]	19	0.34	0.26	0.43
Swallowing	Natural history: diagnosis	19	0.12	0.03	0.21
	Natural history: 2nd visit[1]	19	0.19	0.07	0.32
	Natural history: 3rd visit[2]	19	0.25	0.11	0.38
	Natural history: last visit-pretreatment[3]	19	0.46	0.32	0.59
	After miglustat treatment[4]	19	0.37	0.25	0.49
Composite score	Natural history: diagnosis	19	0.18	0.13	0.23
	Natural history: 2nd visit[1]	19	0.24	0.18	0.31
	Natural history: 3rd visit[2]	19	0.32	0.25	0.40
	Natural history: last visit-pretreatment[3]	19	0.48	0.39	0.57
	After miglustat treatment[4]	19	0.44	0.34	0.55

[1] Mean (95% C.I.) Interval between visit at diagnosis and visit 2: 1.34 (0.74-1.94) years.
[2] Mean (95% C.I.) Interval between visit at diagnosis and visit 3: 2.61 (1.82-3.39) years.
[3] Mean (95% C.I.) Interval between visit at diagnosis and last visit pre-treatment: 4.93 (3.07-6.79) years.
[4] Mean (95% C.I.) Interval between visit at diagnosis and visit after miglustat treatment: 6.17 (5.82-6.52) years.

Additional patient case reports

Data were additionally provided for 14 miglustat treated patients and one control. These were retrospective case summaries provided by the treating physicians.

Study OGT 918-006 (GD-3)

The primary endpoint was the change from baseline to Month 12 in Vertical saccadic eye movements (VSEM α), and results indicated a general worsening with no statistically significant difference between treatment groups. No significant differences between treatment groups were observed in other Saccadic eye movements (SEM) or in most other secondary efficacy variables, including evoked potentials, neuropsychological tests, neurological examination results, liver and spleen volumes, and pulmonary function variables.

Most patients completed the CHQ-PF50 questionnaire, quality of life instrument. Global health and global behaviour worsened from baseline in both groups.

Overall, the study was unable to demonstrate a consistent beneficial effect of miglustat as add-on to Enzyme replacement therapy (ERT) on VSEM or the other markers of GD-3 assessed.

Study OGT 918-009 (LOTS)

Variables of primary interest included muscle and grip strength measures, and the Rainbow Passage Test (speech), none of which showed a statistically significant treatment effect with miglustat over the first 12 months of treatment. No statistically significant treatment effects were observed in secondary variables. In general, LOTS patients in this study showed deterioration over time with or without miglustat treatment.

Conclusions on efficacy

The pivotal study for the indication (Study OGT 918-007 main study, 12 months extension and paediatric sub-study) was submitted as part of the application for the NP-C extension of indication.The current application also includes an optional extension of the pivotal study in which 16 patients received treatment up to a maximum of 66 months (adults/juveniles) or 48 months (pediatrics). Efficacy analyses were only explorative and due to the open-label, uncontrolled design and the limited number of patients, it is difficult to draw any conclusions concerning long term efficacy.

In addition, the MAH presented data from 66 patients in a retrospective survey of patients treated off-label with miglustat. In this survey ambulation, manipulation, articulation and swallowing were assessed at diagnosis, at the time of treatment initiation and at last clinical contact/treatment discontinuation. The results for the parameters were rather similar. There was a deterioration of an additional 20-25 % of the patients between the time of diagnosis until treatment start with miglustat, without any improvements, resulting in 65-90% of the patients having abnormal assessments for the different parameters respectively, at the time of treatment initiation. In spite of the treatment with miglustat, 20-25 % of the patients deteriorated further, but an improvement was reported in approximately 15% of the patients. The results were also presented as individual and composite scores. Even though composite scores may not be fully validated, they could be of use for the purpose of further trying to evaluate the findings. The MAH had calculated an annual rate of deterioration of the composite score and based on these calculations, the results in the survey show a slowing of progression after initiation of miglustat.

The score was also used in the second retrospective survey with the purpose to evaluate the natural course of NP-C disease. The results indicate that there is a continuous progression of the disease for a majority of the patients and that improvement seems to be unlikely.

Data are also presented for 19 patients who were included in both surveys. Compared to time before treatment, a stabilisation of the disease for these patients after treatment initiation with miglustat was reported. These results are based on few patients, and considering the intended long-term treatment, 1.2 years of treatment duration must be considered as rather short. However, the results support the fact that at least some patients benefit from the treatment. In the SPC it is stated that the benefit of treatment should be evaluated on regular basis, e.g. every 6 months and that continuation of therapy should be re-appraised after at least 1 year of treatment with miglustat. This may be a way to limit the treatment to those who really benefit from it.

Considering the retrospective, uncontrolled, non-randomised design of the surveys, the results should be interpreted with care. The results do however support the fact that the activity seen in the main study could translate into clinically relevant benefits for some patients.

Although efforts were made to identify patient characteristics that could predefine responders to the treatment, due to the limited numbers of patients, this was not easily done. However, there were some indications that patients with early onset of disease and/or rapidly progressing disease are less likely to respond to the treatment. In the survey, data indicates that age at treatment start may be an indicator of treatment result as younger patients may have a less favourable outcome. However, the data are too limited to draw any firm conclusions concerning subgroups with an expected higher/lower benefit.

In addition, since up to now there are no data available, regarding the number of the patients who might benefit most from treatment with miglustat, ongoing patient evaluation after beginning of treatment is mentioned in the SPC.

Overall the data showed that treatment with Zavesca can reduce the progression of clinically relevant neurological symptoms in patients with Niemann-Pick type C disease.

3.3.3. Clinical safety

Miglustat is associated with a high incidence of diarrhoea, flatulence, abdominal discomfort/pain, nausea, or combinations thereof. The pharmacological mechanism is most likely the inhibitory effect of miglustat on intestinal disaccharidases, resulting in carbohydrate maldigestion and consequent osmotic diarrhoea with related symptoms and signs.

The other area of potential concern with miglustat has been the nervous system. There is evidence that miglustat is associated with tremor or worsening of previous tremor and is also likely to be associated with an increased incidence of headache and dizziness.
In the early phase of treatment with miglustat, reduced growth has been reported in some paediatric patients with NP- C disease. Growth should be monitored in paediatric and adolescent patients during treatment with Zavesca and the benefit/risk balance should be re-assessed on an individual basis for continuation of therapy.
The potential association of miglustat with peripheral neuropathy and/or cognitive disturbance generated in the first registration studies in type 1 Gaucher disease have been analysed and discussed in detail in previous submissions. There have been no further signals of these serious events either in studies or post-marketing experience.

3.3.3.1. Patient exposure

Patient exposure to miglustat in trials OGT 918-006, -007, -009 and their respective extensions, is summarised below. The mean duration of exposure to miglustat was 2.0 years in study OGT 918-006, 2.6 years (adult/juvenile patients) and 2.7 years (paediatric patients) in study OGT 918-007, and 2.2 years in study OGT 918-009.

Number of patients exposed per indication, protocol and study drug

Indication	Dose Regimen	Number of Patients	Mean Exposure (years)
All		100	2.3
Type 3 Gaucher disease			
OGT 918-006 and -006X	200 mg t.i.d.	30	2.0
Niemann-Pick type C disease			
OGT 918-007 and -007X (Main)	200 mg t.i.d.	28	2.6
OGT 918-007 and -007X (Pediatric)	(equiv adult dose)	12	2.7
G_{M2} gangliosidosis			
OGT 918-009 and -009X	200 mg t.i.d.	30	2.2

3.3.3.2. Adverse events (AE)

Study OGT 918-007 (NP- C)

Adverse events occurring in ≥ 20% of patients with Niemann-Pick type C, overall or in paediatric patients (Safety set)

System organ class Preferred term	Number (%) of patients			
	Miglustat by ICH E11 age category			
	Paediatric (2–11 y) (n = 12)	Juvenile (12–17 y) (n = 5)	Adult (≥ 18 y) (n = 15)	No Treatment (juv/adult)† (n = 9)
Patients with at least one AE	12 (100%)	5 (100%)	15 (100%)	9 (100%)
Nervous system disorders	9 (75%)	5 (100%)	15 (100%)	8 (89%)
Headache NOS	2 (17%)	3 (60%)	6 (40%)	3 (33%)
Tremor	2 (17%)	3 (60%)	6 (40%)	2 (22%)
Gait spastic	2 (17%)	1 (20%)	4 (27%)	1 (11%)
Gait abnormal NOS	4 (33%)	1 (20%)	1 (7%)	4 (44%)
Ataxia	3 (25%)	0	2 (13%)	1 (11%)
Hyperreflexia	3 (25%)	0	1 (7%)	1 (11%)
Gastrointestinal disorders	8 (67%)	5 (100%)	15 (100%)	6 (67%)
Diarrhoea NOS	8 (67%)	4 (80%)	13 (87%)	4 (44%)
Flatulence	4 (33%)	4 (80%)	10 (67%)	0
Abdominal pain NOS	2 (17%)	5 (100%)	5 (33%)	0
Vomiting NOS	4 (33%)	1 (20%)	5 (33%)	0
Dysphagia	3 (25%)	0	4 (27%)	4 (44%)
Nausea	0	2 (40%)	5 (33%)	1 (11%)
Infections and infestations	10 (83%)	4 (80%)	8 (53%)	5 (56%)
Nasopharyngitis	4 (33%)	2 (40%)	5 (33%)	3 (33%)
Sinusitis NOS	3 (25%)	0	0	0
General disorders and administration site conditions	8 (67%)	3 (60%)	7 (47%)	4 (44%)
Fatigue	5 (42%)	2 (40%)	5 (33%)	1 (11%)
Investigations	3 (25%)	5 (100%)	10 (67%)	0
Weight decreased	3 (25%)	5 (100%)	8 (53%)	0
Respiratory, thoracic and mediastinal disorders	6 (50%)	3 (60%)	3 (20%)	4 (44%)
Cough	4 (33%)	1 (20%)	0	1 (11%)

Common adverse events

- Gastrointestinal intolerance

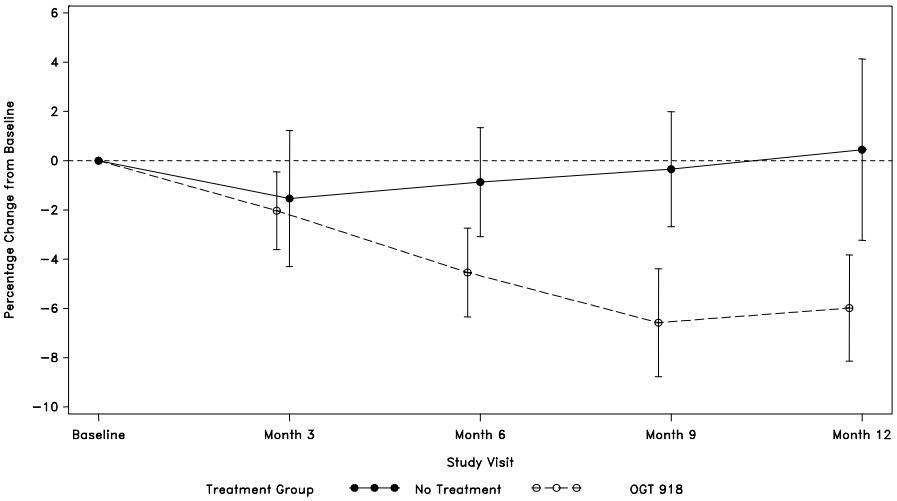
High incidences of diarrhoea and other gastrointestinal complaints were reported in miglustat treated patients. Diarrhoea, in particular, was frequent and considered severe and/or reached NCI toxicity grade 3 in several cases. However, there was only one premature withdrawal due to diarrhoea. Gastrointestinal complaints appeared to be less frequent among paediatric than juvenile and adult NP-C patients. The incidence of diarrhoea over time appeared to decrease, which may have been related to the use of loperamide and/or improved tolerance to miglustat.

- Weight and Height

Among NP-C patients, weight decrease was reported for 65% of juvenile/adult miglustat-treated patients (versus none in the No Treatment group) and in 25% of treated paediatric patients. All except one of the patients with decreased weight also experienced diarrhoea during the study. In most cases, weight loss was < 20%, however one juvenile/adult patient had a ≥ 20% decrease in body weight. No NP-C patient had miglustat discontinued because of weight loss.

In juvenile/adult patients, mean body weight decreased with miglustat treatment but appeared to stabilise after 9 months, whereas the mean body weight of paediatric NP-C patients increased slightly over 12 months of miglustat treatment. Associated with the miglustat-related weight loss, a few patients had a downward shift in BMI category, but few patients in the program were considered underweight.

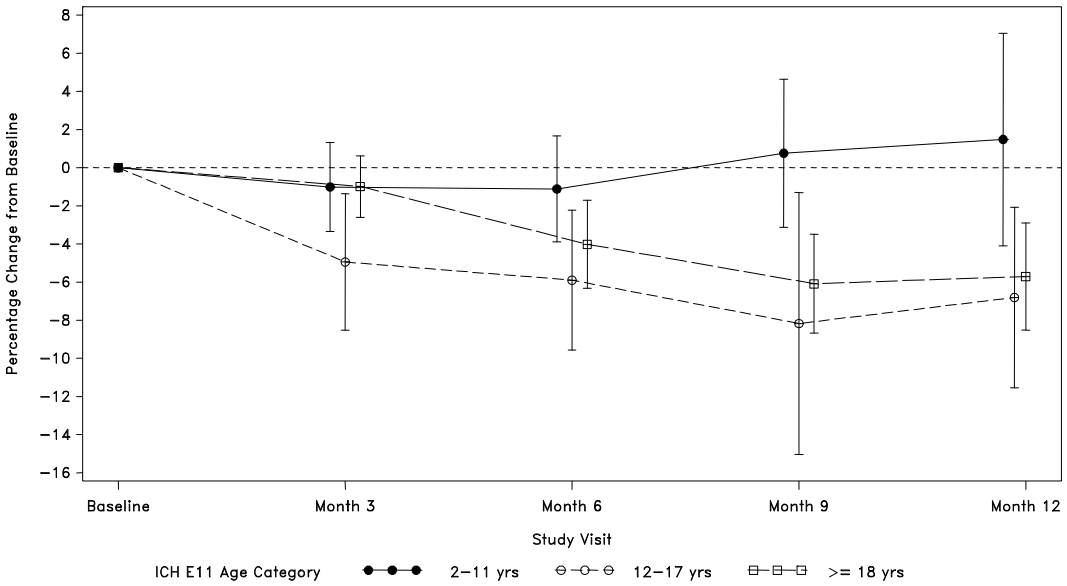
Body weight: Mean percentage changes from baseline over time – OGT 918-007



Produced: August 17, 2005, version 1.
Source: Data for this figure can be derived from Table 32.2.1.

Note: Baseline is the last value up to and including final day of Screening Visit 2.
For the OGT 918 group, n=19 at Month 3, n=18 at Month 6, n=17 at Month 9 and n=16 at Month 12.
For the No Treatment group, n=9 at Month 3 and n=8 at all other visits.
Confidence intervals are based on the t−distribution with n−1 degrees of freedom.

Body weight: mean percentage changes from baseline over time by 1 age category– OGT 918-007 (paediatric sub-study)

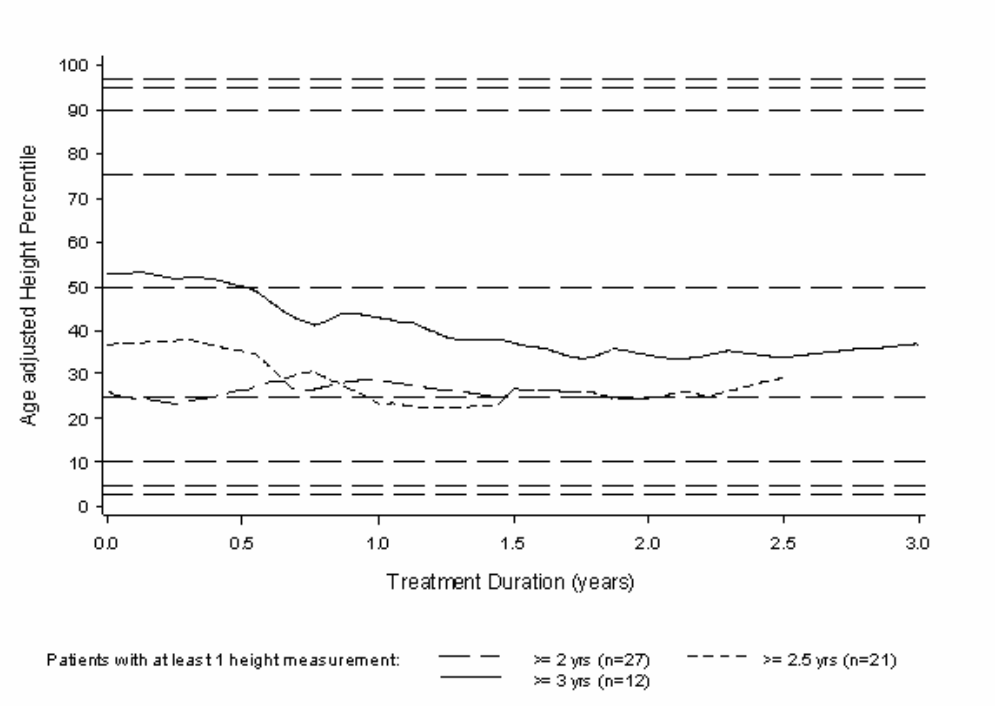


Produced: November 3, 2005, version 1.
Source: Data for this figure can be derived from Table 29.2.1.

Note: Baseline is the last value up to and including final day of Screening Visit 2.
For the 2−11 yrs age category, n=10 at all visits.
For the 12−17 yrs age category, n=5 at Months 3 and 6 and n=4 at all other visits.
For the >=18 yrs age category, n=14 at Month 3, n=13 at Months 6 and 9 and n=12 at Month 12.
Confidence intervals are based on the t−distribution with n−1 degrees of freedom.

Next figure shows the evolution of height percentile (adjusted by age and gender) in patients aged ≤ 20 years at treatment start. A decline in height growth rate was seen at 6 months and at 1 year of treatment. After that, median height remained stable at the same percentile.

Evolution of height over time



- Neurological safety

Tremor was reported in nine miglustat-treated juvenile/adult NP-C patients (45%) and two paediatric patients (17%), but 14 juvenile/adult (70%) and three paediatric patients (25%) experienced at least one AE denoting tremor (preferred terms tremor, aggravated tremor, and/or intention tremor). All cases of tremor were of mild or moderate intensity.
An independent analysis of the data concluded that tremor was present at baseline in 23 of 28 evaluated patients. Of the 26 cases with at least two available assessments over time, 3 patients had a tremor emerge where previously there was none (all on miglustat), 3 had a worsening of tremor over time (all on miglustat), and 1 patient showed an improvement in tremor (No Treatment group).

In juvenile/adult NP-C patient, AEs of paraesthaesia or sensory loss were reported in 35% of miglustat-treated patients compared with 11% in the No Treatment group, and peripheral neuropathy or polyneuropathy was reported as an AE in 2 (10%) vs 0 patients, respectively. Periodical neurological evaluation found that the proportion of patients with abnormal vibratory sense was higher in the miglustat than the No Treatment group (30% vs 11% at last value compared with 10% vs 0 at baseline
Prospective studies of nerve conduction velocity were performed as part of the efficacy assessments. In OGT 918-007, a mild sensory-motor polyneuropathy was present at baseline in 9 of 27 patients with data at baseline (5/18 patients in the miglustat group; 4/9 patients in the No Treatment group), and in 11 of 28 patients with data at Month 12 (6/19 patients in the miglustat group; 5/9 patients in the No Treatment group). Of the 23 patients with assessments at baseline and Month 12, 2 patients were noted to have findings compatible with an emergent sensory-motor axonal polyneuropathy.

Two patients with NP-C disease reported clonic convulsions after 3–6 months on miglustat, versus no patients in the No Treatment group. In the paediatric sub-study, two patients reported tonic or clonic convulsions after 6–9 months on miglustat. None of the affected patients had a medical history of seizures.

Serious adverse events and deaths

- Deaths

No patients died during the 12-month controlled study.

- Serious adverse events

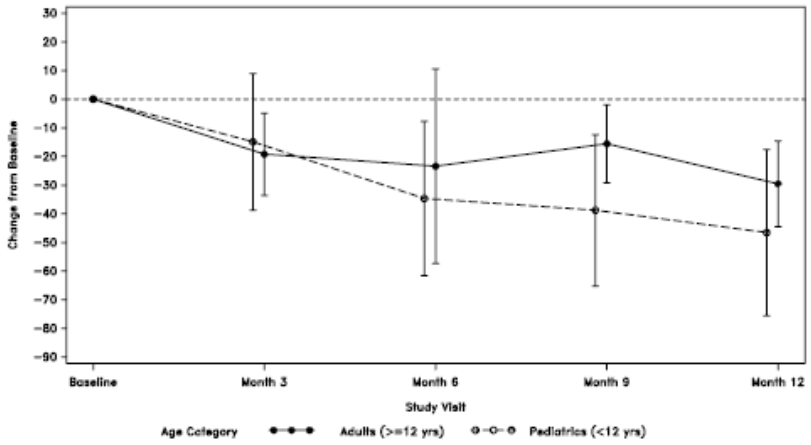
Eleven patients reported a total of 23 SAEs. The most frequent SAEs were infections and infestations and gastrointestinal disorders. Seven patients withdrew because of AEs in the Main study and two in the Paediatric Sub-study. None of the SAEs leading to discontinuation was considered related to miglustat treatment.

Laboratory findings

- Haemoglobin concentration and platelet count

The small mean decrease in haemoglobin concentration observed in miglustat-treated NP-C patients compared with the increase in the No Treatment group was not statistically significant.
The 12% mean decrease in platelet count among miglustat-treated NP-C patients compared with the small mean increase in the No Treatment group approached statistical significance in the analysis ($p = 0.060$).The mean baseline value was higher in the miglustat group, and the greater decrease in platelets was not associated with clinically significant thrombocytopenia. The majority of the decrease in platelets occurred during the first 3 months of treatment, with relatively stable counts thereafter.
In paediatric NP-C patients, the decrease in platelets with miglustat was greater than in juvenile/adult patients (-41.0 vs -23.3×109/L), as counts continued to decrease after the 3-month assessment. Nine of the 12 paediatric patients had at least one value that was below the normal range, but decreases in platelets were not associated with AE reports of thrombocytopenia, bruising, or bleeding except for two mild cases of epistaxis.

Platelet count: Mean changes over time (Efficacy set)– OGT 918-007 (paediatric sub-study)



Postmarketing data

The safety profile of miglustat has been further evaluated during the post-marketing period using the IS[3] post-marketing surveillance programme in the EU. At present, marketing approval for miglustat has been obtained from health authorities in the Australia, Brazil, Canada, the European Union, Israel, Switzerland, Turkey and United States.

An estimated 595 patients have been exposed to Zavesca since its introduction. Of these patients, 141 were in clinical trials and 454 were exposed to commercial Zavesca, comprising 246 adults and elderly (54.2%), 143 children/infants (31.5%) and 60 adolescents (13.2%). The age was not reported for 5 patients (1.1%).

A total of 273 AE reports were received since International Birth Date (IBD), with 162 cases considered to be related to miglustat, and 58 ADR reports assessed as 'serious'. Of the total number of reports, 66% originated through post-marketing surveillance, and 18.7% originated through spontaneous reporting. Gastrointestinal disorders (22.9%) and Nervous system/psychiatric disorders (21.5% and 4.6%) accounted for almost half of all reported events. Nervous system/psychiatric disorders (26.1%), General disorders (10.4%), Investigations (11.2%), and Musculoskeletal disorders (6.4%) also reflect the underlying conditions of the patients taking Zavesca.

The estimated cumulative 'post-marketing' reporting rate was 49%, and 34% for reports assessed as related to Zavesca. Since IBD (excluding clinical trial reports) 454 case reports have been received for commercial Zavesca. The reporting rate for the most commonly reported events was 18.5% (84/454) for diarrhoea, 8.6% (39/454) for tremor, 4.4% (20/454) for unspecified neurological symptoms, 12.3% (56/454) for weight decrease, 3.3% (15/454) for memory impairment, and 2.6% (12/454) for convulsions.

Eleven reports with fatal outcome have been received since IBD outside of clinical trials. One of these 11 patients was treated for type 1 Gaucher disease, with the remainder being treated for other indications. All fatal events were reported as unrelated to Zavesca, and most patients died of disease progression.

In conclusion, the safety profile of miglustat in the post-marketing period is similar to that observed in clinical studies with respect to gastrointestinal disturbances, weight loss, and tremor.

Conclusions on safety

The CHMP concluded that overall, the side effect profile of miglustat is known (gastrointestinal side effects, tremor, weight loss, impaired growth and low platelet count) and adequately addressed in the SPC. Furthermore, the CHMP concluded that special problems will be further evaluated in the NP-C disease registry (platelet count, weight and growth, risk of polyneuropathy or seizures, etc.).

3. 4 Pharmacovigilance

Risk Management Plan
The MAH submitted a Risk Management Plan (RMP).

Summary of the EU Risk Management Plan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
• Diarrhoea and other gastrointestinal ADRs	Routine pharmacovigilance Monitoring through IS[3] and NP-C disease registry Conducting a survey of colonoscopies performed on patients who have been on long-term treatment with Zavesca	Information in SmPC in section 4.4 to investigate further in case of chronic diarrhoea or persistent gastrointestinal symptoms. Educational material as prescribing kit for prescribers. Controlled distribution.
• Central nervous system AEs such as tremor, peripheral neuropathy (numbness, tingling),	Routine pharmacovigilance Monitoring through IS[3] and NP-C disease registry	Information in sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the SmPC. Educational material as prescribing kit for prescribers. Controlled distribution.
• Use in paediatric patients	Routine pharmacovigilance Monitoring within NP-C registry	Information in SmPC, section 4.2, about limited experience in patients under the age of 3 years. Information package to prescribers.
• Seizure activity in patients with NP-C disease treated with miglustat	Routine pharmacovigilance Specific monitoring within NP-C registry	Information in SmPC, section 4.8 and PIL. Information package to prescribers.
• Growth disturbance in paediatric patients with NP-C disease treated with miglustat	Routine pharmacovigilance Specific monitoring within NP-C registry	Information in SmPC, section 4.4 and PIL, regarding the need for monitoring of growth characteristics in paediatric patients. Information package to prescribers.
• Reduced platelet counts in patients with NP-C disease treated with miglustat	Routine pharmacovigilance Specific monitoring within NP-C registry	Information in SmPC, sections 4.4, 4.8 and PIL. Information package to prescribers.

The Annex II has been updated accordingly.
The CHMP concluded that the RMP is well structured and comprehensive. There is an already existing post-marketing safety surveillance programme IS[3]. Furthermore, the MAH has presented a new registry concerning the specific diagnosis of NP-C disease. This registry can produce valuable data involving safety aspects but also efficacy data with regard to the use of miglustat. The initiation of the NP-C registry is essential for the approval of the new indication.
The CHMP, having considered the data submitted with the application, is of the opinion that no additional risk minimisation activities are necessary for the safe and effective use of the medicinal product. The RMP was acceptable to the CHMP.

Conclusions and Benefit / Risk Assessment

The CHMP acknowledged that there is currently no treatment available for NP-C disease.
The pharmacological rationale for treatment of NP-C disease is based on substrate reduction therapy. In some non-clinical models of lipid storage disease, miglustat has been shown to have the potential to reduce storage of glycosphingolipids and enhance survival.
Available data show that miglustat treatment can have a clinically relevant ability to slow down the progression of neurological symptoms of NP-C disease in some patients.
The main safety issues (gastrointestinal side effects, reduced growth, CNS effects and decrease of platelets) are considered as covered in the product information and RMP.
There is limited data concerning long term treatment both concerning efficacy and safety. The initiation of the NP-C registry is essential for the approval of the new indication and a further commitment is made by the MAH to provide the final documents concerning the NP-C disease registry for Zavesca no later than middle of February 2009.

IV. CONCLUSION

On 18 December 2008 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.

Follow-up measures undertaken by the Marketing Authorisation Holder

As requested by the CHMP, the MAH agreed to submit the follow-up measures as listed below and to submit any variation application which would be necessary in the light of compliance with these commitments (see Letter of Undertaking attached to this report):

Area[1]	Description	Due date[2]
Pharmacovigilance	The MAH should establish a Niemann-Pick type C disease Registry. The Registry should be submitted for assessment and endorsement by the CHMP including the following: 1. Efficacy parameters. 2. Characteristics of "responders" / "non responders". 3. Analysis of long-term efficacy results.	15/02/2009
Non-clinical	The MAH should justify the absence of the ERA or conduct an environmental risk assessment according to the guideline on the environmental risk assessment of the medicinal products for human use.	15/02/2009

1. Areas: Quality, Non-clinical, Clinical, Pharmacovigilance
2. Due date for the follow-up measure or for the first interim report if a precise date cannot be committed to.