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This product was later resubmitted to the EMEA. See here for information on the outcome of the resubmission.

WITHDRAWAL ASSESSMENT REPORT
FOR
ZAVESCA

International Nonproprietary Name:
miglustat

Procedure No. EMEA/H/C/000435/II/0021

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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I. SCIENTIFIC DISCUSSION

1.1. Scope of the variation

Zavesca is a competitive inhibitor of the enzyme glucosylceramide synthase, which catalyzes the first and committed step in the synthesis of glycosphingolipids. 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.

The MAH submitted this type II variation application to extend the indication for Zavesca in "the treatment of neurological manifestations in patients with Niemann Pick type C disease."

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).

1.2. Non clinical aspects

The non clinical documentation for the current application consists of an addendum to the non clinical overview, update to the pharmacokinetic written summary and the toxicology written summary. All toxicological data have been previously submitted with the exception of a 13 week mouse study and a study report from a 13 week oral study dealing with investigations of rat brain glycolipids. A series of literature references dating from 1994 to 2006 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 MAA (Marketing Authorisation Application) 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 current application 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.

The 13 week mouse study 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.

1.2.1. Conclusion on non-clinical aspects

Miglustat has not been directly tested in animal models of Niemann-Pick Type C, but in other non-clinical models of lipid storage disease the compound has been shown to have the potential to decrease glycosphingolipids and enhance survival. The toxicological profile of miglustat has been previously assessed and the main target organs include the gastrointestinal system and male reproductive tract. Changes were noted at doses with low safety margins compared to exposure expected in humans and with the currently proposed higher dose (200 mg t.i.d.) these will be lower, if identifiable at all.
Two studies have been submitted; a 13 week mouse study where increases in organ weight (liver, spleen, brain), minimal splenic megakaryocytosis and increased lymphocytolysis in thymus were reported and an analysis of rat brain glycolipids from a 13 week study, showing no consistent effects of miglustat on gangliosides, sulfatide glycolipids or galactosylceramide, but a reversible increase of glucosylceramide seemed to occur. 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. The relevance of these data for the human disease is unknown.

1.3. Clinical aspects

1.3.1. 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, (studies are discussed under "Clinical efficacy") miglustat was given at a dose of 200 mg t.i.d. (three times a day), 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 the dose was adjusted in proportion to the body surface area.

Based on the pharmacokinetic data of these studies it can be concluded that miglustat is able to cross the blood-brain barrier, but 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. The pharmacokinetic data cannot fully support the chosen dose. However, it is acknowledged that this is an orphan indication and that the possibility to explore different doses is limited. Furthermore, the dose was not only selected based on the desirability of achieving CSF (cerebrospinal fluid) concentrations but also based on considerations of tolerability data in patients with other glycosphingolipid storage disorders. Considering dose-dependent gastro-intestinal adverse events, a higher dose would probably not be tolerated. Therefore the dose selection and dosage by BSA is considered acceptable.

1.3.2. Clinical efficacy

The development programme of miglustat (OGT 918) in neuronopathic glycosphingolipidoses includes three completed studies, conducted in a total of 101 patients (83 exposed to miglustat at doses ranging from 50 to 600 mg daily) including 29 juvenile/adult patients with NP-C disease (OGT 918-007), 30 patients with GD-3 (OGT 918-006), and 30 patients with LOTS disease (OGT 918-009), randomised in each study to open-label miglustat or a No Treatment group. Study OGT 918-007 included a paediatric sub-study that enrolled an additional 12 NP-C patients under 12 years of age.

Overview of the therapeutic studies in patients with neuronopathic glycosphingolipidoses

Protocol (Report No.)	Study objectives (Study design)	Treatment	Treatment duration	No. of patients enrolled
OGT 918-007	Efficacy and safety in Niemann-Pick type C disease (OL)	Miglustat 200 mg t.i.d. No Treatment	12 months	Miglustat 20 No Treatment 9
Paediatric sub-study	(As above)	Miglustat according to BSA in patients < 12 y	12 months	Miglustat 12
OGT 918-006	Efficacy and safety in type 3 Gaucher disease (OL)	Miglustat 200 mg t.i.d. or according to BSA if < 12 y No Treatment	12 months	Miglustat 21 No Treatment 9
OGT 918-009	Efficacy and safety in late onset Tay-Sachs disease (OL)	Miglustat 200 mg t.i.d. No Treatment	12 months	Miglustat 20 No Treatment 10
Optional extension	(As above)	Miglustat 200 mg t.i.d.	12 months	Miglustat 29

BSA = body surface area, OL = open-label, t.i.d. = three times daily, y = years, m = months.

1.3.2.1. Methods

Study design

The studies had a randomised, controlled, parallel-group design, with the duration of the controlled phase maximised to what was considered to be ethically acceptable for the patients, with optional following long-term extension phases. Patients were randomised to treatment with miglustat or No Treatment in addition to standard care. In view of the unblinding effect anticipated from the characteristic gastrointestinal side effects of miglustat and the use of objective endpoint measures, an open-label format was considered appropriate. This decision also took into consideration the ethical constraints related to administration of oral placebo medication to a patient population with frequent swallowing problems.

Each of the studies was designed to have a 12-month controlled, comparative period, with a ≤ 28-day screening period and a 12-month treatment/follow-up period during which patients were evaluated every 3 months. The study period was completed when all patients completed the 12-month study. An optional 12-month extension (all patients received miglustat, total follow-up 24 months), and a following 12-month extended-use period (all patients continue the miglustat dose received during the extension, total follow-up 36 months) were available for patients who completed the 12-month comparative period.

Trial treatments

The dose of 100 mg t.i.d. is the approved dose for the use of miglustat in type 1 Gaucher disease.
Miglustat distributes freely into the extravascular space and penetrates the blood-brain barrier, although it is at reduced concentrations in cerebrospinal fluid compared with plasma. To compensate for this, a dose of 200 mg t.i.d. was selected for adult patients in studies of miglustat in neuronopathic sphingolipidoses, reduced in proportion to body surface area in paediatric patients.

Efficacy endpoints

Endpoints of primary interest were planned in each study:

- OGT 918-007 (NP-C): Mean change from baseline to Month 12 in HSEM α (Horisontal saccadic eye movement velocity)
- OGT 918-006 (GD-3): Mean change from baseline to Month 12 and last value in VSEM α (vertical (up and down) saccadic eye movement)
- OGT 918-009 (LOTS): Mean changes from baseline to Month 12 in isometric muscle strengths

Efficacy variables
Variables were chosen to allow evaluation of potential effects of miglustat at several levels of the central nervous system and in visceral organs. Both a reduction in the rate of disease progression and improvement of function were considered worthwhile goals.

The following efficacy variables were assessed in the studies:
Saccadic eye movement velocity, 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, quality of life measures.

1.3.2.2. Results

Study OGT 918-007 (NP- C disease)

Horizontal saccadic eye movement
The change in HSEM α (left and right combined) from baseline to Month 12 was the primary endpoint in OGT 918-007. For SEM parameters, a reduction over time represents an improvement. Mean decreases in HSEM α were observed at both Month 12 and the last value with miglustat, whereas small increases were seen in the No Treatment group. The differences between treatment groups were not statistically significant in the planned analysis.

HSEM α: summary of mean values and changes from baseline (Efficacy set)

	OGT 918 (N = 20)				No Treatment (N = 9)			
	N	BL value (SD)	Actual value (SD)	Change from BL (SD)	N	BL value (SD)	Actual value (SD)	Change from BL (SD)
Baseline	19	–	3.038 (2.107)	–	9	–	2.432 (1.342)	–
Month 12	17	2.976 (2.225)	2.587 (1.634)	–0.389 (0.950)	8	2.483 (1.425)	2.558 (1.734)	0.074 (0.823)
Last value	18	3.021 (2.167)	2.590 (1.585)	–0.431 (0.938)	8	2.483 (1.425)	2.558 (1.734)	0.074 (0.823)

Because different measurement techniques were used at each centre an exploratory analysis including centre in addition to baseline and treatment group in the ANCOVA model was also performed.
Because the sedative effects of benzodiazepines could have potentially confounded results (i.e., artificially slowed saccades), an exploratory subgroup analysis was also performed in which patients who were taking benzodiazepines were excluded (5 patients in the miglustat group and 1 in the No Treatment group). In this patient group, a statistically significant difference was observed between the miglustat group and the No Treatment group at both Month 12 and last value ($p = 0.028$).

HSEM α: analyses of changes from baseline to Month 12 and last value (Efficacy set)

HSEM α (ms/deg)		Adjusted mean change from baseline		Estimated treatment difference	95% confidence interval	p-value
		OGT 918	No Treatment			
Planned analysis[a]	Month 12	–0.329	–0.055	–0.274	(–0.959, 0.411)	0.414
	Last value	–0.376	–0.050	–0.326	(–1.000, 0.348)	0.327
Including centre in the model[b]	Month 12	–0.450	0.066	–0.515	(–1.149, 0.118)	0.105
	Last value	–0.463	0.055	–0.518	(–1.125, 0.089)	0.091
Excluding pts on benzodiazapam[c]	Month 12	–0.485	0.234	–0.718	–1.349, –0.088	0.028
	Last value	–0.485	0.234	–0.718	–1.349, –0.088	0.028

Horizontal saccadic eye movement, paediatric study

Paediatric NP-C patients had mean decreases in HSEM α at Month 12 and last value which were of similar magnitude to those observed in juvenile/adult patients.

HSEM α: summary of mean values and changes from baseline on miglustat (Efficacy set) – paediatric sub-study

	Paediatric (< 12 years) (N = 11)				Juvenile/Adult (≥ 12 years) (N = 20)			
	N	BL value (SD)	Actual value (SD)	Change from BL (SE)	N	BL value (SD)	Actual value (SD)	Change from BL (SE)
Baseline	10	–	2.201 (1.217)	–	19	–	3.038 (2.107)	–
Month 12	9	2.181 (1.289)	1.692 (1.077)	–0.489 (0.139)	17	2.976 (2.225)	2.587 (1.634)	–0.389 (0.230)
Last value	10	2.201 (1.217)	1.736 (1.025)	–0.465 (0.127)	18	3.021 (2.166)	2.590 (1.585)	–0.431 (0.221)

The beneficial effects of miglustat in the treatment of NP-C disease as shown in study OGT 918-007, are considered very limited. The difference between miglustat treated patients and the No treatment group concerning the primary endpoint was not statistically significant even though patients on miglustat had a reduction in HSEM α while untreated patients had a slight increase. However, the clinical relevance of this difference is difficult to evaluate.

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. 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, the corresponding numbers were 5/8 patients (62%) and 3 patients (38%), respectively. Nearly all paediatric NP-C patients were able to swallow all substances easily at baseline.

The MAH provided a sensitivity analysis (responses RSI Jan 07) that counts for patients who improved during treatment.

The sensitivity analysis supported the view that treatment with miglustat showed a positive trend for "swallowing". However, the results are not very convincing and the clinical relevance of the observed results remains highly questionable, particularly taking into consideration unblinded assessment of swallowing.

Auditory acuity and brainstem evoked potentials
Auditory acuity was tested as part of the neurological examination. At baseline, abnormal hearing in the right and left ears was found in 5 and 4 patients respectively, among the 20 patients in the miglustat group. After 12 months of treatment with miglustat, an improvement was seen in one of each ear (4 and 3 patients, respectively, had abnormal hearing). In contrast, no patients in the No Treatment group had abnormal hearing at baseline, but after 12 months, abnormal hearing was found in 2 patients for each ear among the 9 patients in the group. Paediatric 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.

Physical performance tests
Standard Ambulation Index (SAI) scores increased during the 12-month 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 in SAI score over 12 months of miglustat treatment which was similar to that observed in miglustat-treated juvenile/adult patients.

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.

Miglustat treated patients had less deterioration in SAI compared to untreated patients. This could be considered as a reduction in the rate of disease progression. MMSE showed improvements while Purdue Pegboard Test showed deterioration. Thus, the effect of miglustat on neuropsycholgical parameters is difficult to assess.

Neurological examination
Among juvenile/adult NP-C patients, no major differences between treatment groups were observed in most of the neurological examination parameters.

Organ volumes

Summary of mean values and changes from baseline to last value for normalised liver and spleen organ volumes (Efficacy set)

	OGT 918 (N = 20)				No Treatment (N = 9)			
Parameter (normalised)	**N**	**BL value (SD)**	**Last value (SD)**	**Change from BL (SD)**	**N**	**BL value (SD)**	**Last value (SD)**	**Change from BL (SD)**
Liver volume (L)/height (cm) (× 100)	19	0.87 (0.26)	0.84 (0.27)	–0.03 (0.16)	7	0.94 (0.25)	0.84 (0.29)	–0.09 (0.10)
Liver volume (L)/BMI (kg/m^2) (× 100)	18	5.82 (1.63)	6.18 (2.29)	0.35 (1.15)	7	6.81 (1.64)	6.35(2.0)	–0.46 (0.78)
Liver volume (L)/BSA (cm^2) (× 100)	18	0.82 (0.20)	0.82 (0.26)	0.00 (0.14)	7	0.90 (0.22)	0.80 (0.25)	–0.10 (0.11)
Spleen volume (L)/height (cm) (× 100)	18	0.36 (0.22)	0.39 (0.27)	0.03 (0.10)	7	0.37 (0.20)	0.34 (0.16)	–0.03 (0.05)
Spleen volume (L)/BMI (kg/m^2) (× 100)	17	2.43 (1.38)	2.84 (1.86)	0.40 (0.70)	7	2.62 (1.22)	2.55 (1.15)	–0.07 (0.34)
Spleen volume (L)/BSA (cm^2) (× 100)	17	0.33 (0.18)	0.37 (0.23)	0.03 (0.09)	7			–0.03 (0.05)

Further post-hoc investigation and the analysis of unadjusted liver volume and liver volume adjusted for weight have been performed. It reveals that liver volume, liver volume/weight and liver volume/BMI in the OGT treatment group is statistically significantly different, from baseline to month 12, compared to the non –treatment group.

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 CHQ-PF50 (Child Health Questionnaire) questionnaire. 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.

Since the study was open-label the results of the Quality of Life assessments can not be adequately evaluated due to potential bias.

Individual patient data analysis

In order to further illustrate the effects of treatment with miglustat in NP-C disease, and to take into account the observed baseline imbalances for disease severity between treatment groups, a *post-hoc*, individual patient data analysis was made of patients from the main study that provided data at both baseline and Month 12. This analysis took into account changes from baseline in HSEM-α and -β,

Swallowing, Gait, Standard Ambulation Index, Auditory acuity, and MMSE, for an assessment of global patient outcome as regards neurological disease severity.

Summary of changes from baseline to Month 12 – Individual patient data analysis (juvenile/adult population)

Severity at baseline	Minimal		Mild or Mild – Moderate		Moderate or Moderate – Severe		Severe	
Disease status at Month 12	Miglustat	No Treatment	Miglustat	No Treatment	Miglustat	No Treatment	Miglustat	No Treatment
Stable – improvement	–	–	3	1	1	–	–	–
Stable	–	1	–	1	6	–	–	–
Stable – progression	–	–	2	2	4	–	–	–
Progression	–	–	–	–	–	3	1	–

Overall outcome of efficacy analysis by in patients with improvements on miglustat

Patient No./ gender/age	Severity Baseline/ Month 12	Main results	Overall outcome
007-104/F/39	Mild – Moderate Mild – Moderate	Improvement: HSEM-α, swallowing.	Stable – improvement
007-106/F/16	Mild – Moderate Mild – Moderate	Improvement: HSEM-α, swallowing, MMSE, Standard Ambulation Index.	Stable – improvement
007-110/M/26	Mild – Moderate Mild – Moderate	Improvement: HSEM-α, swallowing, MMSE. Deterioration: Standard Ambulation Index (one grade).	Stable – improvement
007-204/F/12	Moderate – Severe Moderate – Severe	Improvement: HSEM and MMSE (three scores) within the normal range. No other major changes.	Stable – improvement

The individual patient analysis gives the impression that patients with moderate disease activity may benefit from treatment with miglustat. Still, the results are not impressing and some of the efficacy variables may have been biased by the open label design. Furthermore, even if NP-C is a progressive disease, there seems to be a rather substantial variation in the speed of the progression between individuals. When comparing small groups of patients these individual differences may influence the results.

Case reports

In the assessment of treatment effects in rare disorders such as NP-C disease, case narratives from experts can be taken into account. The MAH provided case reports on 9 children and 3 adult patients with NP-C disease.

Overall, the case reports give a much more positive picture of miglustat treatment in NP-C disease compared to study OGT 918-007. It seems as if some patients may benefit from this treatment.

Study OGT 918-006 (GD-3)

The primary endpoint was the change from baseline to Month 12 in 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 SEM variables 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 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 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.

12 month extension study OGT 918-007, 24 Months

This study included male or female patients aged 12 years or over with confirmed NP-C disease. Twenty-nine patients entered the 12-month randomised period (20 randomised to miglustat and 9 randomised to a No Treatment group). Twenty-five of the 29 patients completed this period and entered the 12-month extension period (17/20 patients from the miglustat group [i.e., the 24-Months miglustat group] and 8/9 patients from the No Treatment group [i.e., the 12-Months miglustat group]). Nineteen of the 25 patients completed the 12-month extension period (15/17 patients from the 24-Months miglustat group and 4/8 patients from the 12-Months miglustat group). All patients received treatment with miglustat 200 mg t.i.d. in the extension period.

The primary interest variable was the change in horizontal saccadic eye movement (HSEM)-α from baseline to Months 12, 24 and last value. Secondary endpoints included change from baseline to Months 12, 24 and last value in: HSEM-β, swallowing, neurological examination, neuropsychological assessment, tremor and quality of life (QoL) assessment.

Analyses were performed on the efficacy set, which comprised all randomised patients who entered the 12-month extension period and who had at least one post-baseline efficacy assessment during the 12-month extension period. There was no imputation for missing data.

Saccadic eye movement

Summary of actual values and change from baseline for HSEM-α (ms/deg)

	24 Months OGT 918 (N = 17)				12 Months OGT 918 (N = 8)			
	N	Baseline value (SD)	Actual value (SD)	Change from baseline (SD)	N	Baseline value (SD)	Actual value (SD)	Change from baseline (SD)
Baseline	17	–	2.976 (2.225)	–	8	–	2.483 (1.425)	–
Month 12	17	2.976 (2.225)	2.587 (1.634)	–0.389 (0.950)	8	2.483 (1.425)	2.558 (1.734)	0.074 (0.823)
Month 24	15	3.040 (2.353)	3.267 (3.687)	0.227 (1.756)	4	2.940 (1.662)	4.056 (2.495)	1.116 (1.464)
Last value	15	3.040 (2.353)	3.267 (3.687)	0.227 (1.756)	6	2.975 (1.294)	3.717 (2.016)	0.742 (1.279)

Analysis of change from baseline in HSEM-α (ms/deg)

Parameter	Visit	Adjusted mean change from baseline		Estimated treatment difference	Standard error	95% confidence interval	P-value
		24 Months OGT 918	12 Months OGT 918				
HSEM-α	Month 12	–0.450	0.066	–0.515	0.305	–1.149, 0.118	0.105
	Month 24	0.155	1.150	–0.994	0.845	–2.796, 0.808	0.258
	Last value	0.166	0.761	–0.594	0.703	–2.078, 0.889	0.410

Source: Table 74a and 74b
ANCOVA model used for all analyses included terms for baseline, center and treatment group.

At M24 and last value, a nominal increase (i.e., worsening) from baseline in HSEM-α was observed for both the 12- and 24-Months miglustat groups. However, these increases were numerically smaller in patients in the 24-Months miglustat group.

Adjusted mean increases in HSEM-β from baseline to last value were observed in both the 12- and 24-Months miglustat groups.

Study OGT918-007 Paediatric Sub-study, 24 months

This prospective, non-controlled, open-label study in children 4-11 years old with NP-C disease had a 12-month core phase, followed by a 12-month Extended Use period. All patients received miglustat, with the dose adjusted for BSA, based on the adult target dose of 200 mg t.i.d. Altogether 12 patients were enrolled, 10 of whom completed the 12-month phase and continued into the Extended Use period. All 10 completed 24 months of treatment with miglustat.

Saccadic eye movement

Change from baseline in HSEM-α (ms/deg) and associated 95% confidence intervals (efficacy set)

Parameter	Visit	Pediatrics (< 12 years)		Adults (≥ 12 years)	
		Mean change from baseline (SE)	95% confidence interval	Mean change from baseline (SE)	95% confidence interval
HSEM-α	Month 12	–0.489 (0.139)	–0.810, -0.167	–0.389 (0.230)	–0.878, 0.099
(ms/deg)	Month 24	–0.075 (0.412)	–1.024, 0.874	0.226 (0.453)	–0.746, 1.199
	Last value	–0.093 (0.368)	–0.926, 0.741	0.152 (0.387)	–0.664, 0.968

From a qualitative review of SEMV data, it can be concluded that at Month 12, nine out of the ten paediatric patients improved and one patient was stable, and that at last value, three of the ten patients improved, one patient was stable, and six patients deteriorated.

1.3.2.3.Retrospective survey of patients with NP-C disease

To respond to CHMP major objections regarding the limited beneficial effect demonstrated in study OGT 918-007, the MAH presented at the oral explanation data from a retrospective survey of patients with Niemann-Pick type C disease currently or previously treated with miglustat.
The objectives of the survey were to assess retrospectively, available data on changes of neurological manifestations and overall utility of treatment with miglustat in NPC disease patients in the market from start of treatment to last available clinic visit. The MAH identified several patients with NP-C disease that have been identified world-wide as currently or previously treated with miglustat and not enrolled in MAH trials. Treating physicians have been asked to complete one questionnaire per patient treated with miglustat in order to collect retrospectively available data, specifically on changes of neurological manifestations, physician's global assessment of the utility of treatment, and main reasons for discontinuation of treatment in NPC patients treated off label.
At the time of the oral explanation, the survey was still ongoing and therefore only data from 23 patients were presented. Of these patients 59% (n=13, median treatment duration 24 months)) were considered to have at least a stable status for the four main neurogial parameters that were assessed. However, since these data are uncontrolled and considering the heterogenity in disease progression, it is difficult to assess the true benefit of the miglustat treatment given.
Overall, the findings support the fact that miglustat has some kind of activity in the treatment of NP-C patients but the clinical relevance of this activity is difficult to evaluate.
The information gained from these cases was not considered as robust evidence of the efficacy of miglustat in the treatment of patients with NP-C disease.

1.3.2.4. Conclusion on efficacy

Study 918-007 is the pivotal study for this application. After 12 months of treatment with miglustat there was a numerical but not statistically significant improvement in HSEM-ά of unknown clinical significance. After an additional 12 months of treatment (extension study) there was instead a worsening in this parameter compared to baseline. Even if the results of the primary endpoint could be interpreted as a slowing of disease progression compared to the untreated patients, changes of the primary endpoint can not directly be translated into clinical benefits for the patients. Results from secondary endpoints may be interpreted as stabilisation of the disease. However, for some parameters there is rather "less worsening" than improvement and the groups are often too small to draw any conclusions.
Similar results were found in the paediatric study. At Month 12, nine out of the ten paediatric patients improved and one patient was stable concerning the primary endpoint, and at last value (24 months), three of the ten patients improved, one patient was stable, and six patients deteriorated.
Based on the clinical data results the CHMP concluded that the beneficial effects of miglustat in the treatment of NP-C disease were considered as very limited. The data from a retrospective survey of patients with Niemann-Pick type C disease currently or previous treated with miglustat was not considered as robust evidence of the efficacy of miglustat in the treatment of patients with NP-C disease. The CHMP concluded that miglustat has some kind of activity in the treatment of these patients but the clinical relevance of this activity is still difficult to evaluate.

1.3.3. 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.
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 has been no further signals of these serious events either in studies or post-marketing experience.

1.3.3.1. Patient exposure

Overall, 90 patients with type 1 Gaucher disease have been exposed to miglustat for periods up to 48 months in clinical trials, while the total market exposure, including patients with other diseases, is estimated at 196 patients as of 19 October 2005.

The withdrawal rate in the pivotal study for this application (OGT 918-007) must be considered as rather low. However, even though NP-C disease is a rare condition, the number of subjects exposed for more than one year (n=14) must be considered as too low for an evaluation of long time efficacy and safety .

1.3.3.2. 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)

	Number (%) of patients			
	Miglustat by ICH E11 age category			
System organ class Preferred term	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%)

Study OGT918-007 Main study, 24 months

The analysis set for the evaluation of safety comprised all 28 patients who received at least one dose of miglustat. The mean duration of exposure was 531 days. The most frequent treatment-emergent AEs were associated with the system organ classes Nervous system disorders, Gastro-intestinal disorders, and Investigations (mainly weight decrease). The most common individual AEs were diarrhoea (25/28 patients; 89%), weight decreased (19/28 patients; 68%), tremor or aggravated tremor or intention tremor (19/28 patients, 68%), flatulence (18/28 patients; 64%), and abdominal pain (15/28 patients; 54%).

The majority of treatment-emergent AEs were mild or moderate in intensity. Nineteen patients experienced severe AEs. Severe events reported in more than one patient comprised diarrhoea and nerve conduction studies abnormal, each reported by five patients (18%) and tremor, ataxia and insomnia, each reported by two patients (7%).

Six patients discontinued the study due to AEs whilst receiving miglustat. In the 24-Months miglustat group, four patients were withdrawn due to AEs: one for confusional state together with AEs of insomnia and paranoia, one for diarrhoea, and another for unacceptable disease progression, all leading to withdrawal in the 12-month randomised period, and one for axonal neuropathy leading to withdrawal in the 12-month extension period. Two patients in the 12-Months miglustat group were withdrawn due to AEs during miglustat treatment in the 12-month extension period: one for diarrhoea and the other for tremor.

There was a mean decrease in platelet count of approximately 8% from baseline to last value.

Peripheral neuropathy was reported for two patients and led to discontinuation of study treatment in one. In this context, an independent central assessment of clinical neurological and neurophysiological (EDX) study data concluded that a sub-clinical polyneuropathy, defined as compatible EDX abnormalities without clinical neurological signs or symptoms, was present in 11 of 29 patients at baseline compared with eight of 25 patients at Month 12 and six of 12 patients at Month 24, respectively. A mild sensory polyneuropathy, defined by compatible clinical neurological signs and/or symptoms and EDX abnormalities was present in one of 29 patients at baseline, five (four treated and one untreated patient) of 25 patients at Month 12 (four patients of whom had sub-clinical polyneuropathy at baseline), and five of 12 patients at Month 24.

Study OGT918-007 Paediatric Sub-study, 24 months

The most common individual AEs in paediatric patients were diarrhoea and cough, reported by 67% and 50% of patients respectively. In general, the AE profile was comparable for paediatric, juvenile, and adult patients and the second 12-month period of treatment with miglustat did not identify any new or unexpected safety concerns.

Most treatment-emergent AEs reported during the Paediatric sub-study were mild or moderate in intensity. A total of five paediatric patients reported one or more severe treatment-emergent AEs (supranuclear gaze palsy, saccadic eye movement, clonic convulsion, vomiting, dehydration, respiratory syncytial virus infection, ataxia, gait abnormal and cataplexy). None of these were considered related to treatment with miglustat. The most common treatment-related AEs in paediatric patients were diarrhoea, flatulence, and weight decrease.

Tremor and/or aggravated tremor and/or intention tremor were experienced by 6 paediatric patients (50%), 3 juvenile patients (60%) and 13 adult patients (87%). There were no new-onset neurological AEs with long-term treatment and, especially, no reports of seizure/convulsion beyond 12 months.

One 10-year-old male patient experienced AEs of lethargy, memory impairment and depression, which resulted in his withdrawal from the initial 12-month treatment period. There were no other withdrawals due to AEs.

Mean decreases in platelets from baseline to last value of 20% were observed for paediatric patients.

Although a mean increase in weight from baseline to last value of 3.3 kg (mean percentage increase 11.4%) was noted for paediatric patients, mean weight initially decreased up to Month 6, before increasing from Month 9 onwards. On average, the paediatric patients did not continue along their predicted percentile growth path as mean body mass index (BMI), weight and height decreased by 20, 19 and 14 percentile points, respectively, from baseline to last visit.

Gastrointestinal side effects were common in miglustat treated patients as well as cases of weight decrease and thrombocytopenia in the 12 month study.
No new safety concerns were identified during the extension phase.

1.3.3.3. Serious adverse events and deaths

Deaths
No patients died during any of the 12-month controlled studies. One LOTS patient with a medical history of atrial fibrillation died during the 12-month extension of OGT 918-009. This 46-year-old male patient, initially randomised to the No Treatment group, experienced the SAE of cardiac arrhythmia, and died after 274 days of miglustat treatment (642 days after randomization). The investigator assessed the death as not related to miglustat treatment.

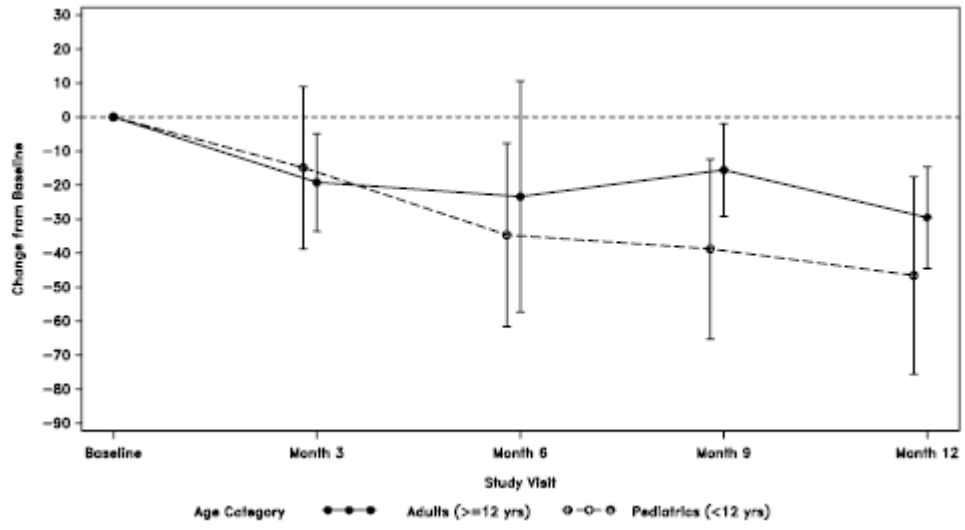
Serious adverse events
In the three studies, several isolated serious adverse events (SAE) affecting different body systems were reported, but only mania was reported for more than one patient on miglustat (two LOTS patients).
It is of course difficult to say if this AE is associated with miglustat or not since neuro-psychiatric conditions can be associated with the diseases themselves.

1.3.3.4. Laboratory findings

In all three studies, routine haematology, clinical chemistry, and urinalysis parameters were assessed every three months. In addition, fasting blood glucose and serum lipid profiles were assessed in OGT 918-007 (NP-C).

In OGT 918-007 and OGT 918-006, changes in haemoglobin concentration and platelet count from baseline to the last value were additionally analyzed as an efficacy variable.

Figure 6. Platelet count: Mean changes over time (Efficacy set)– OGT 918-007 (paediatric sub-study)



The decrease in platelets in paediatric patients is a serious safety issue, especially since the decrease continued during the entire study (12 M study).

The MAH presented additional data from the 12 month extension study. The reduction in platelets did not seem to progress during the 12 month extension phase. Platelet counts were below the lower limit of normal at one or more assessments in 75% in the 24-Months treatment group and in 100% in the 12-Months treatment group. However, these reductions did not seem to be associated with bleedings and no patient had platelet count measurement below 50×10^9/L .

1.3.3.5. Postmarketing data

The safety profile of miglustat has been evaluated during the post-marketing period using a post-marketing surveillance program in the EU known as the Intensive Safety Surveillance Scheme (IS3).
It is estimated (from both the IS3 and spontaneous reporting) that for the period from 20 November 2002 (the date of the first marketing authorisation) to 19 October 2005, 196 patients were exposed to miglustat world-wide in clinical practice. Serious or non-serious adverse reactions were reported in 53 patients (More than one reaction may have been reported in one patient). The most frequently reported adverse reactions belonged to the system organ class Gastrointestinal disorders, followed by Nervous system disorders.
For the 6 months following the cut-off date of the 5th PSUR, i.e. for the period from 20 October 2005 to 19 April 2006, 24 initial case reports (12 serious and 12 non-serious), representing 23 patients, were received.

The postmarketing data seem to confirm the spectrum of adverse events that has been seen in clinical studies.

1.3.3.6. Conclusion on 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. 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 has been no further signals of these serious events either in studies or post-marketing experience.
Gastrointestinal side effects were common in miglustat treated patients as well as cases of weight decrease and thrombocytopenia in the 12 month study.
No new safety concerns were identified during the extension phase.

II. BENEFIT/RISK

The CHMP acknowledged that there is currently no treatment available for NP-C disease. According to the MAH a considerable number of patients with NP-C disease are currently treated with Zavesca in off-label use. However the beneficial effects of miglustat in the treatment of patients with NP-C disease as shown in the pivotal study and the extension of this study are considered as very limited. After 12 months treatment, the difference between miglustat treated patients and the No treatment group concerning the primary endpoint was not statistically significant even though patients on miglustat had a reduction in HSEM α while untreated patients had a slight increase. The clinical benefit of this difference was however difficult to assess. After an additional 12 months treatment there was instead a worsening in this parameter compared to baseline. Even if the results could be interpreted as a slowing of disease progression in those patients that were treated for 24 months compared to those treated for 12 months, on the whole, the results are very limited. Furthermore the results of the secondary endpoints are difficult to interpret and do not conclusively support an effect of miglustat. Considering the common occurrence of gastrointestinal adverse events as well as cases of weight decrease and thrombocytopenia, the benefit/risk balance for Zavesca in the treatment of neurological manifestations in Niemann Pick type C disease can not be considered as positive.

III. CONCLUSION

On 18 October 2007 the CHMP considered this Type II variation not to be acceptable on the following grounds:

- The CHMP considered that the beneficial effects of Zavesca in the treatment of neurological manifestations in Niemann Pick type C disease as shown in the pivotal study OGT 918-007 were considered very limited with regards to the primary endpoint ; after 12 months treatment, the difference between miglustat treated patients and the No treatment group concerning the primary endpoint was not statistically significant. Data from additional 12 months treatment did not provide substantial support for a clinical relevant beneficial effect.
- The CHMP considered that the secondary endpoints of study OGT 918-007 do not conclusively support an effect of Zavesca in the treatment of neurological manifestations in Niemann Pick type C disease.
- The CHMP considered that there are safety issues associated with Zavesca treatment in Nieman-Pick type C patients mainly in relation to the common occurrence of gastrointestinal adverse events as well as cases of weight decrease and thrombocytopenia.
- The CHMP considered that in the view of the current available data which only demonstrated a limited efficacy of Zavesca in the treatment of neurological manifestations in Niemann Pick type C disease and the safety concerns, the benefit/risk is negative.