CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-348

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS: ADDENDUM

NDA:	21-348
Submission Date(s):	23-May-2003
Brand Name	Zavesca
Generic Name	Miglustat Capsule
Reviewers	Sang M. Chung, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation 2 (DPE-2)
OND division	Division of Metabolic and Endocrine (HFD-510)
Sponsor	Actelion
Submission Type	1S
Strength(s)	100 mg hard gelatin capsule
Indication	Treatment of Type I Gaucher disease

Executive Summary

The sponsor is seeking approval of Zavesca™ (miglustat) for the oral treatment of Type I Gaucher disease under [redacted] The original application (21-August-2001) received an NA letter by the Agency because balance of risk and benefit was not properly demonstrated to warrant the approval.

In this Amendment, there was no new information related to Clinical Pharmacology and Biopharmaceutics except the proposed specification on dissolution acceptance criterion. DPE-2 recommended Q=[redacted] at [redacted] minutes in the original review and the sponsor proposed Q=[redacted] at [redacted] minutes instead of the DPE-2's recommendation based on additional stability data.

Upon completing review on additional dissolution data, DPE-2 concluded that the specification of Q=[redacted] at [redacted] minutes is the most appropriate specification. With this specification, some lots have to go to stage 2 according to USP. The conclusion was conveyed through a tele-conference on June 05, 2003 to the sponsor. During the tele-conference, the sponsor explained that European Medicine Evaluation Agency (EMEA) does not permit a dissolution retesting and the sponsor wants to have the same dissolution specification for EMEA and USA. Considering the situations, DPE-2 proposed at the tele-conference a specification as **Q=[redacted] at 30 minutes** with concurrence of the

reviewing chemist and the sponsor agreed on that unless there is potential problem in stability test under the specification.

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/s/

Sang Chung
7/17/03 05:37:35 PM
PHARMACOLOGIST

Hae-Young Ahn
7/22/03 11:09:38 AM
BIOPHARMACEUTICS

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-348
Submission Date(s):	21-August-2001
Brand Name	Zavesca
Generic Name	Miglustat Capsule
Reviewers	Sang M. Chung, Ph.D.
	Wei Qiu, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation 2 (DPE-2)
OND division	Division of Metabolic and Endocrine (HFD-510)
Sponsor	Oxford GlycoSciences
Relevant IND(s)	60,197
Submission Type	1S
Strength(s)	100 mg hard gelatin capsule
Indication	Treatment of Type I Gaucher disease

1 Executive Summary

Oxford GlycoSciences (OGS) is seeking approval of Zavesca™ (miglustat) for the oral treatment of Type I Gaucher disease. Miglustat is a new molecular entity that is the first in therapeutic class.

Gaucher disease is an inherited glycosphingolipids catabolism disorder. Functional deficiency of β-glucocerebrosidase (β-glucosidase) leads to accumulation of glucocerebroside in tissues including spleen, liver, lung, and bone marrow. The glycosphingolipid storage disorder causes clinical symptoms of liver and spleen enlargement, anemia, bleeding due to low platelet, recurrent infection and repeated episodes of bone pain. Zavesca has obtained Orphan Product Designation Status.

Miglustat is an inhibitor of glucosylceramide synthase and thus will reduce synthesis of glycosphigolipids. The proposed dosing is 100 mg capsule three times daily and dose adjustment was indicated with effectiveness and safety factors. Current treatment option for Gaucher disease is surgery (i.e., splenectomy) or enzyme replacement therapy (i.e., bone marrow transplant or parenteral glucocerebrosidase). Miglustat is also shown to have activity against α-glucosidase I and anti-human immunodeficiency virus (HIV-1).

Clinical pharmacology and biopharmaceutics (CPB) of Zavesca™ was elucidated within 4 clinical trials. In addition, results of 5 studies from HIV patients and 4 in vitro studies were included as supportive data in Section 6 of NDA 21-348.

Human pharmacokinetic characteristics in brief is as follows:
Time to reach maximum concentration was approximately 2 to 2.5 hours. Miglustat does not bind to plasma proteins over a concentration range of 1.0 to 20.0 μg/ml and mean ratio of blood and

plasma concentration is 0.877. Mean peak plasma concentrations were about 860 ng/ml after 100 mg single dose and about 1920 ng/ml with 100 mg TID to Guacher subjects. Values of apparent volume of distribution (Vd/F) and clearance (CL/F) of miglustat were 83-105 liters and 196-230 ml/min, respectively. Degree of accumulation at steady-state following TID dosing was approximately 2- to 2.5-fold based on AUC ratio of multiple and single dosing. Pharmacokinetic characteristics appeared to be unchanged after chronic dosing.

The capsule formulation was bioequivalent to an oral solution under fasting conditions. Food decreased the extent of exposure (AUC_{0-inf}) and peak concentration (C_{max}) by 14% and 36%, respectively. Food also delayed the time to peak concentration (T_{max}) by 2 hours.

The AUC_{0-8hr} of miglustat during a dosing interval was approximately 16% greater when miglustat was administered alone than with miglustat and Cerezyme co-administration. The mean C_{max} of miglustat was approximately 29% higher when miglustat was administered alone than co-administration with Cerezyme. The mean apparent clearance of Cerezyme was increased 70% when miglustat was co-administered with Cerezyme.

Miglustat increased the AUC_{0-8hr} and C_{max} values of zidovudine by 41% and 45%, respectively.

Neither evident metabolism of miglustat nor significant inhibitory effect of miglustat on the metabolism of major cytochrome P450 isozymes was observed in human liver microsomes. Miglustat was not found to be a substrate or an inhibitor of the P-gp efflux system. However, a significant increase in the secretion of the P-gp substrate, cyclosporin A across the Caco-2 monolayer was observed in the presence of miglustat. It suggested that miglustat might increase the activity of P-gp.

The clinical trial formulation (CT) was identical to the to-be-marketed formulation (TBM). However, the CT used decompressed process while the TBM used compressed process. Although TBM has slower dissolution rates than CT, miglustat is highly soluble and dissolves in 0.1N HCl in 15 minutes. Based on Guidance for Industry, Dissolution testing of IR solid oral dosage forms, the bioavailability of the drug is not limited by dissolution.

Covariates of 6 demographic factors and 6 clinical laboratory parameters were analyzed for correlation with pharmacokinetics using cross-study population approach. Only adjusted creatinine clearance showed significant correlation with miglustat oral clearance indicating significant renal elimination mechanism. Also, of pharmacokinetic and pharmacodynamic analyses, diarrhea as a safety factor and spleen response as a 6-month efficacy measurement showed a significant relationship with steady-state concentrations.

According to the reviewing Medical officer, neurologic adverse events are the approvable issue. In addition, Zavesca treatment has been temporarily hold in Israel because there was an unexplained cognitive dysfunction in a patient who was on the Zavesca treatment but stopped it in October, 2001. The safety issue was remained unchanged but efficacy was reduced with 50 mg TID dosing compared to 100 mg TID dosing.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation-II (OCPB/DPE-II) has reviewed NDA21-348 (Zavesca™) submitted on 21-August-2001. Findings of CPB find it acceptable to OCPB/DPE-II. The Recommendation, Comment and Labeling Comments should be sent to the sponsor as appropriate.

1.2 Comment

1. The following dissolution method and specification is recommended:

   - Dissolution test conditions
     - Medium: 0.1 N HCl
     - Apparatus: USP Apparatus 1 (baskets) 100 rpm
     - Volume: 1000 ml
   - Dissolution specification
     - Q= — at —minute

2. The results of Caco-2 cells monolayer experiment indicated activation of P-gp by miglustat. Transporters become increasingly important as a mechanism of drug interaction. In this regard, OCPB/DPE-II recommends to provide confirmatory evidence that miglustat activate P-gp in Caco-2 cells using other substrate(s).

3. The sponsor has proposed the starting dose of 100 mg TID, and indicated that dosing should be adjusted (up or down). However, during the clinical trials there were only a few cases of dose adjustment; 2 for 50 mg BID, 7 for 100 mg BID, and 3 for 200 mg TID during the 50 or 100 mg TID dosing in Gaucher subjects. There may not be sufficient data to support dose adjustment. The sponsor primarily studied 100 mg TID as a maintenance dose in the clinical trials. A fixed dose for every patient may not be agreeable upon optimal dosing. Therefore, it is recommended that the sponsor consider the range of the doses in future clinical trial(s).

/S/

Sang M. Chung, Ph.D. -April-2002
Division of Pharmaceutical Evaluation II Date
Office of Clinical Pharmacology and Biopharmaceutics

/S/

Wei Qiu, Ph.D. -April-2002
Division of Pharmaceutical Evaluation II Date
Office of Clinical Pharmacology and Biopharmaceutics

Final version signed by Team Leader

/S/

Hae-Young Ahn, Ph.D. -April-2002
Date

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5 Summary of CPB Findings

Miglustat (M.W. 219.28) is a synthetic derivative of imino sugar with the following structure:

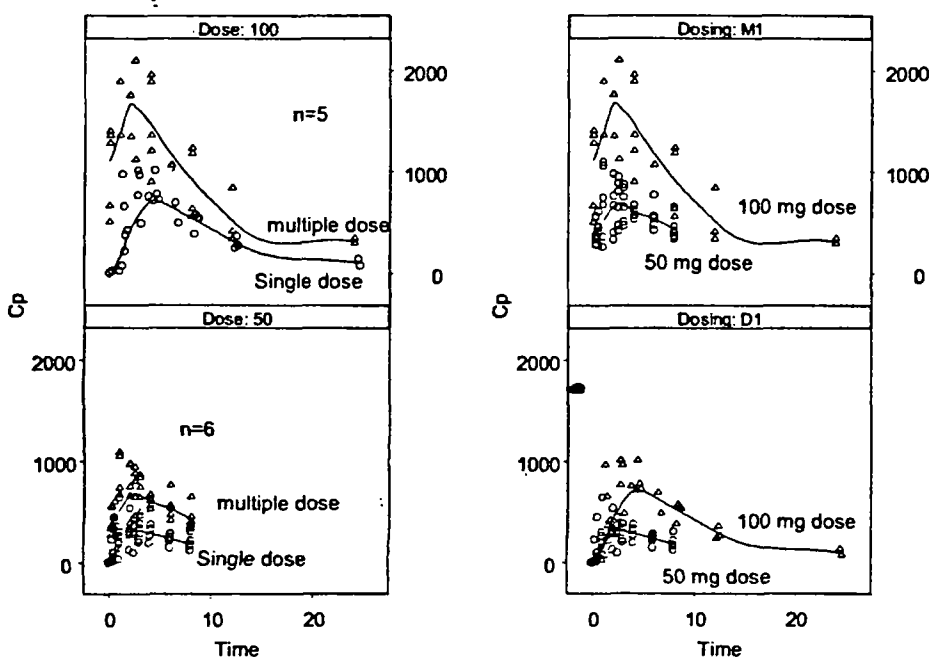
$C_{10}H_{21}NO_4$

Imino sugars were originally isolated from plants and microorganisms and showed potent inhibition on a number of hydrolytic enzymes.

G.D. Searle *initially* developed the compound as an anti-viral agent for acquired immune deficiency syndrome (*AIDS*). The development was not successful because high plasma concentration was required for anti-HIV effect but the doses that would reach the effective concentrations could not be given to patients due to poor tolerability with diarrhea.

- **Pharmacokinetics of miglustat in Gaucher subjects**

Pharmacokinetics of miglustat in Gaucher subjects was obtained based on two dosage regimens (100 mg TID for 12 months and 50 mg TID for 6 months). (note: The 100 mg TID is the proposed starting as well as maintenance dosing.) Results are shown in the following figures.



(A) (B)

Figure 1 Plasma concentration-time profiles of miglustat after 50 and 100 mg Zavesca oral administration (n=6 for 50 mg and n=6 for 100 mg). Panel (A) is for comparison between single and multiple dose at each dose, and panel (B) is for comparison between 50 and 100 mg at Day1 and at Month 1. Lines are LOESS smooth, a non-parametric and locally weighted scatter plot smooth to the data.

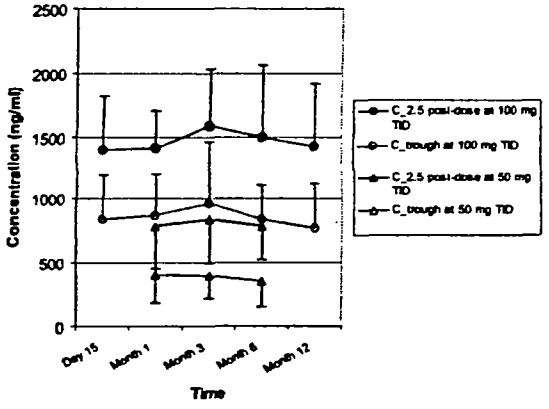


Figure 2 Concentrations of 2.5 hours post-dose and pre-dose (or trough) after 50 and 100 mg TID throughout treatments in Gaucher subjects (Study 001 and 003).

Maximum concentration of 862 ng/ml was reached at 2.0 to 2.5 hours post-dose and effective half-life was approximately 6 to 7 hours after 100 mg single dose. The degree of accumulation

was 2.25 on average based on AUC ratio of multiple (TID) and single doses during the dosing interval. Values of AUC during the dosing interval were the same as AUC_{0-inf} after single dose and thus average pharmacokinetics appeared to be unchanged during the treatments.

- **Pharmacokinetics of miglustat in Fabry subjects**

Fabry disease is also a glycosphingolipid biodegration disorder with α-galactosidase mutation. The patients generally exhibit mild to severe renal impairment. The disease is prevailing in male because the gene of enzyme is linked to X-chromosome.

Plasma sampling was similar to that in Gaucher subjects; extensive sampling in subset (n=6) and sparse sampling in all subjects (n=16). Results are shown in the following figures compared with Gaucher subjects.

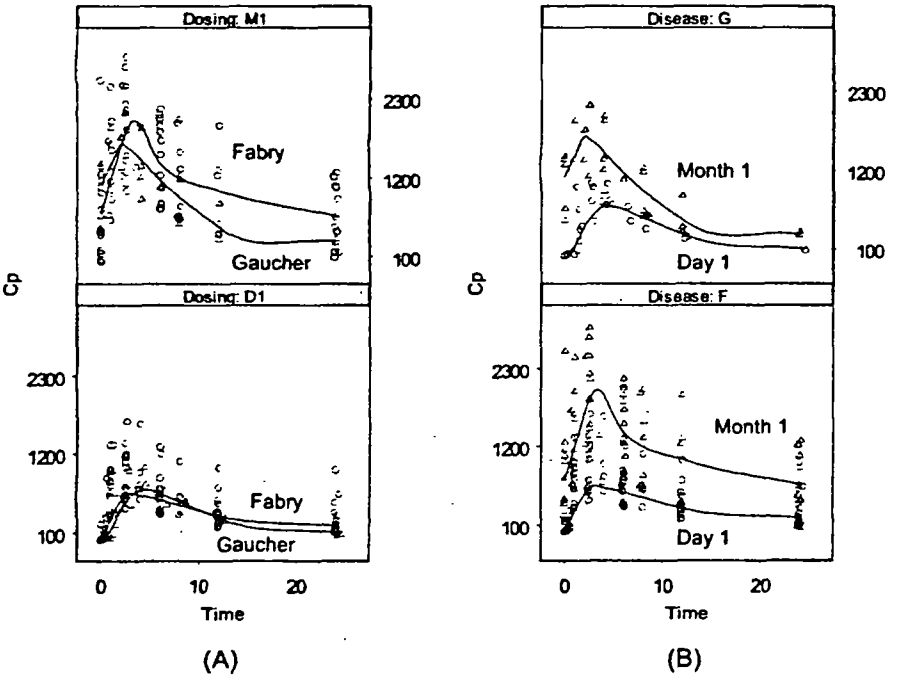


Figure 3 Plasma concentration-time profile after 100 mg QD Zavesca administration to Fabry subjects; Panel (A) is for comparison with Gaucher subjects at Day 1 and Month 1 and Panel (B) is for comparison between at Day 1 and at Month 1 in each disease categories.

Maximum concentration of 905 ng/ml was reached approximately 2.5 hours post-dose in Fabry subjects following 100 mg Zavesca oral dose. Effective half-life was 15.2 hours and degree of accumulation was 1.7 at Month 1 and 2.34 at Month 6, which was based on AUC ratio of multiple and single dosing.

Exposure was increased in Fabry subjects compared to that in Gaucher subjects. Impaired renal function in Fabry subjects appeared to be a major factor causing the exposure difference.

- **Food effect and relative bioavailability of miglustat capsule**

On average food decreased the C_{max} and $AUC_{0\text{-}inf}$ values by 36% and 14%, respectively. Food also tended to delay the T_{max} values by two hours. Relative bioavailability of a capsule to an oral solution was approximately 97%. The results of statistical analyses are provided in the following table.

Table I Summary of statistical analyses

Parameter	Comparison	Point Estimate	90% CI
$AUC_{0\text{-}inf}$	Non-fasted capsule vs. Fasted capsule	0.86	0.81, 0.91
	Fasted capsule vs. Fasted solution	0.97	0.91, 1.02
C_{max}	Non-fasted capsule vs. Fasted capsule	**0.64**	**0.57, 0.71**
	Fasted capsule vs. Fasted solution	0.92	0.82, 1.03

- **Drug interactions**

A randomized, open-label, multiple dose, Phase II study (OGT 918-004) was conducted to assess the tolerability and pharmacokinetics of miglustat and Cerezyme given in co-administration compared with Cerezyme and miglustat alone in 36 adult patients with Type I Gaucher disease. The results showed that the mean area under the miglustat plasma concentration-time curve during a dosing interval ($AUC_{0\text{-}8hr}$) and maximum plasma concentration (C_{max}) were approximately 16% and 29% greater when miglustat was administered alone than administration of miglustat and Cerezyme co-administration therapy, respectively. The mean apparent clearance of Cerezyme was 70% higher when Cerezyme was co-administered with miglustat than Cerezyme alone.

Two multicenter, randomized, placebo-controlled Phase II studies (NS8-93-06-004 and NS8-94-06-009) were conducted to assess the drug interaction between miglustat and zidovudine (AZT or ZDV). The results of study NS8-93-06-004 showed that the $AUC_{0\text{-}8hr}$ and C_{max} values of AZT for the miglustat treated group were approximately 41% and 45% greater than that of the placebo group. Further population pharamcokinetics analysis supported these findings. The population pharmacokinetic analyses of another study NS8-94-06-009 were inconsistent with these observations. The dosing regimens of miglustat in study NS8-93-06-004 were 300 mg to 1000 mg TID. As the dosing regimens of miglustat used in these studies was 3- to 10-fold higher than the proposed dosing regimen of 100 mg TID, it was less likely that miglustat would cause clinically relevant drug-drug interactions with zidovudine.

- **In vitro metabolism of miglustat and effect of miglustat on P450 isozymes and P-gp**

The metabolism of miglustat was examined in rat, primate, and human liver microsomal systems. Incubations were conducted in the presence of 20 µg/ml [^{14}C] miglustat and microsomal protein (1.0 and 2.0 mg/ml) in the presence and absence of NADPH-regenerating system. The results showed no evident metabolism of miglustat (20 µg/ml) in any of the in vitro microsomal systems.

The potential inhibitory effect of miglustat on a range of human hepatic cytochrome P450 (CYP) enzyme activities in vitro was investigated. Model substrates of CYP1A2 (0.4 µM ethoxyresorufin), CYP2A6 (5 µM coumarin), CYP2C9 (100 µM tolbutamide), CYP2C19 (100 µM S-mephenytoin), CYP2D6 (10 µM bufuralol), CYP2E1 (40 µM chlorzoxazone), CYP3A4 (65 µM testosterone), and CYP4A11 (20 µM lauric acid) were incubated with miglustat at a single

concentration of 20 µg/ml in pooled hepatic microsomes. No significant inhibitory effect of miglustat on the metabolism of the major cytochrome P450 isozymes was observed in human liver microsomes.

The effect of miglustat on P-gp activity was assessed by examining transport of radio-labeled and non radio-labeled marker compounds across Caco-2 monolayers in both the apical to basolateral and basolateral to apical directions in the presence and absence of a single concentration of miglustat (50 µM). Mannitol transport was evaluated as a paracellular marker, cyclosporin A was examined as a substrate for P-gp, and verapamil hydrochloride as an inhibitor of P-gp. miglustat was not found to be a substrate or an inhibitor of the P-gp efflux system based on the secretion ratios. However, a significant increase in the secretion of the P-gp substrate, cyclosporin A across the Caco-2 monolayer was observed in the presence of miglustat. It implied that miglustat might increase the P-gp activity.

- **Pharmacokinetics in Special Populations**

Cross-study population pharmacokinetics was performed for four studies using a single-stage nonlinear mixed-effects modeling approach.

Population pharmacokinetics was performed using extensive plasma samples in subsets and sparse plasma samples in all subjects. In brief, extensive samples were obtained after the first (Day 1) and the 1 month (Month 1) dosing within subsets; 5 out of 28 patients for Study 001, 6 out of 18 patients for Study 003, 6 out of 16 Study 002. In Study 004, extensive sampling was conducted at Month 1 in 6 subjects receiving Zavesca alone, and 5 subjects receiving Zavesca and Cerezyme together. Sparse sampling was conducted at pre-dose and at 2.5 hours post-dose in all the patients excluding Study 004.

The following major conclusions were made through cross-study analyses:

- Of a number of demographic and laboratory covariates studied, only adjusted creatinine clearance (standardized for body surface area) was found to have an effect on CL/F.
- The results of the analysis showed a pharmacokinetic difference between Gaucher and Fabry subjects.
- Individual CL/F estimates indicated that subjects with moderate to severe renal impairment have a 60 % to 70 % decrease in miglustat oral clearance, and would therefore require an adjustment in dose.
- The population estimate for CL/F (L/hr) in Gaucher subjects was

$$12.4\,(\mathrm{L/hr}) \times \frac{\text{adjusted } \mathrm{CL_{cr}}\ (\mathrm{ml/min/1.73\,m^2})}{125}$$

Also, the population estimate for V/F was

$$119\,(\mathrm{L}) \times \frac{\mathrm{Cr}\ (\mathrm{mg/dl})}{1.2}$$

- The parameter estimates from final covariate model are summarized in the following table.

Table II Parameter estimates in the final covariate model

Parameter	Estimate	95% CI
CL/F (θ_2, L/hr)	12.4	11.1-13.7
CL/F (θ_1 in Fabry subjects, L/hr)	9.9	5.2-14.6
V/F (θ_4, L)	140	114.4-165.6
V/F (θ_3 in Fabry subjects, L)	119	75.2-162.8

- Data from final 1-compartment oral covariate model, using dataset with outlier removed.
- Covariate on $\theta_1$and θ_2 is adjusted CLcr, and on θ_3 and θ_4 is Cr.

- Over the range of values present in the studies, no correlation was found between miglustat pharmacokinetics and laboratory markers of liver function.
- Of the adverse events (diarrhea and tremor) examined, only diarrhea showed a significant relationship with steady-state concentrations.
- Of the 6-month efficacy measurements evaluated (spleen and liver response, hemoglobin response, and platelet response), only spleen response showed a significant relationship with steady-state concentrations.

The results of cross-study analyses were consistent with clinical findings according to the Division clinical reviewer. Liver response seemed to be significant in the 12-month efficacy measurement, which was not included in the population pharmacokinetics.

6 QBR

6.1 General Attributes

6.1.1 Highlights of the physico-chemical properties

6.1.1.1 What are the highlights of physico-chemical properties of the product ?

Miglustat is highly soluble (> 1 g / ml) and 100 mg of Zavesca was completely dissolved in 250 ml of USP buffer solutions of pH 1.0, 3.0, 5.0, 5.9, 6.9, and 7.5. No degradation was observed at any of the pH tested.

6.1.1.2 What is the composition of Zavesca ?

G.D. Searle developed the formulation for 100 mg and 500 mg capsules for the anti-HIV program and OGS decided to proceed with the same 100 mg formulation, using essentially the same manufacturing method and specification developed by Searle. The formulation was transferred to two contract manufacturer, namely . for initial clinical trial supply (i.e., batch 0207N) and to Galen, Ltd. Craigavon, UK for clinical trials, stability, and commercialization (i.e., SB001-100 and SB003-100).

The names of the ingredients, % unit formulae, and functions are summarized in the following table.

Table III Ingredients and % unit formulae of Zavesca Capsules

	Names of Ingredients	Unit (% formula)	Function
Active Ingredients			
	miglustat	100 mg	
Other Ingredients			
	Sodium Starch Glycollate		
	Povidone (K30)		
	Magnesium Stearate		
	Capsule		

6.2 General Clinical Pharmacology

6.2.1 Highlights of the pharmacokinetic characteristics

6.2.1.1 What is the basic pharmacokinetic characteristics of Zavesca ?

Essential pharmacokinetic parameters were estimated with conventional as well as cross-study pharmacokinetic approaches within 4 clinical trials.

Extensive plasma samples were collected on the first day and at the first month dosing within subsets of Study OGT 918-001 (100 mg TID), 002 (100 mg QD in Fabry subjects), and 003 (50 mg TID). Sparse plasma samples were collected in all the subjects 2.5 hours after the dose and at pre-dose for Study OGT 918-001 (N=28), 002 (N=16), and 003 (N=18).

Also, extensive samples were collected at the first month after dosing for Study OGT 918-004 and control study data were included in the cross study comparison.

Pharmacokinetic parameters based on the conventional method for Gaucher subjects are summarized in the Table V to Table VIII.

In general, maximum concentration was reached between 2- to 2.5- hours after dose and after then plasma concentration profiles showed bi-exponential decay. Values of half-life in Table V and VIII were effective half-life, which is the measure of the time to reach steady-state for drugs having multiple compartment pharmacokinetic characteristics. The sponsor used the following approximation to calculate the effective half-lie:

$$\text{Half}-\text{life} = f_1 \times \frac{0.693}{\lambda_1} + f_2 \times \frac{0.693}{\lambda_2}$$

where $f_1 = (A/\lambda_1)/(A/\lambda_1+B/\lambda_2)$ and $f_2=1-f_1$, and A, B, λ_1, and λ_2 are constants of biexponential function. Terminal or elimination half-life can be calculated from the terminal elimination rate constants in Table VI and it ranged from 8.3 to 33.4 hour (arithmetic mean and S.D of 16.6 ± 11.36 hr) after the first dose in Gaucher subjects.

In this regarding, it is recommended that terminal half-life as well as effective half-life be in labeling.

Accumulation index was 2.25 for 100 mg and 2.48 for 50 mg after 1 month dosing and the results were based on AUC ratio of multiple and single dose during dosing interval.

Table IV Mean (CV%) miglustat pharmacokinetic parameters following single and multiple dosing at 100 mg TID (Study OGT 918-001)

	Day 1	Month 1
C_{max} (ng/ml)	862 (16)	1922 (9)
t_{max} (hr)	2.5 (2-4)	2.0 (1-2.5)
$AUC_{0\text{-}6h}$ (ng hr/ml)	3746 (23)	8911 (22)
$AUC_{0\text{-}24h}$ (ng hr/ml)	7683 (31)	NA
$AUC_{0\text{-}inf}$ (ng hr/ml)	9502 (22)	NA
$t_{1/2}$ (hr)	7.30 (17)	6.39
R_{lin}	NA	0.89 (7)
R	NA	2.25 (18)

n = 5
NA = not applicable
t_{max}: values are median with range of values in parentheses
The dosing interval (τ) was 6 hours.
R_{lin} = linearity ratio (comparison of $AUC_{0\text{-}inf}$ to $AUC_{0\text{-}\tau}$)
R_0 = observed degree of accumulation of miglustat in plasma at Month 1 (comparison of $AUC_{0\text{-}\tau}$ at Month 1 to $AUC_{0\text{-}\tau}$ on Day 1)

Table V Individual miglustat pharmacokinetic parameters from fit of 2-compartment oral model (Study OGT 918-001)

Subject

Table VI Pharmacokinetic parameters following multiple dosing at 100 mg TID with sparse sampling

		2.5 hours post-dose			Trough	
Time	*n*	Mean	SD	n	Mean	SD
Day 15	17	1403	418	17	836	356
Month 1	17	1418	285	18	861	337
Month 3	18	1590	445	18	954	513
Month 6	17	1504	559	16	832	275
Month 12	16	1428	491	16	767	357

Table VII Mean (CV%) miglustat pharmacokinetic parameters following single and multiple dosing at 50 mg TID (Study OGT 918-003)

	Day 1	Month 1
C_{max} (ng/ml)	382 (34)	827 (25)
t_{max} (hr)	2.5 (1-8)	1.75 (
AUC_{0-6h} (ng hr/ml)	NA	3668 (22)
AUC_{0-inf} (ng hr/ml)	3222 (18)	NA
$t_{1/2}$ (hr)	4.73 (12)	5.71 (15)
R_{lin}	NA	1.27 (36)
R	NA	2.48 (30)

n = 6
NA = not applicable
t_{max}: values are median with range of values in parentheses
The dosing interval (τ) was 6 hours.
R_{lin} = linearity ratio (comparison of AUC_{0-inf} to $AUC_{0-\tau}$)
R_0 = observed degree of accumulation of miglustat in plasma at Month 1 (comparison of $AUC_{0-\tau}$ at Month 1 to $AUC_{0-\tau}$ on Day 1)

Results of population pharmacokinetic approaches are summarized in the Section 6.3.1 of demographic factor. In brief, mean oral clearance (CL/F) of 100 mg in Gaucher subjects was 229.3 ml/min (S.D. 39.3). Also, mean values of V/F and K_a were 82.9 L and 1.027 h^{-1}, respectively. The mean values of CL/F and V/F were similar between conventional and population approaches.

Descriptive statistics of miglustat pharmacokinetic parameters for the population model were summarized in the following table. Data were from final 1-compartment oral covariate model estimated using FOCE with interaction using dataset with outlier removed.

Table VIII Miglustat pharmacokinetic parameters

PK parameter	Statistic	OGT918-001 (Gaucher) (N=26)	OGT918-002 (Fabry) (N=16)	OGT918-003 (Gaucher) (N=18)	OGT918-004 (Gaucher) (N=11)
CL/F (ml/min)	Mean (SD)	229.3 (39.3)	135.5 (57.9)	195.6 (34.5)	211.3 (32.2)
	Median	231.7	115.2	195.8	224.7
	Min, Max				
V/F (L)	Mean (SD)	82.9 (21.7)	112.7 (36.7)	104.7 (28.7)	86.1 (25.1)
	Median	84.8	101.6	101.2	83.0
	Min, Max				
Ka (h^{-1})	Mean (SD)	1.027 (0.164)	1.046 (0.306)	0.949 (0.285)	0.923 (0.164)
	Median	1.058	1.061	0.880	0.870
	Min, Max				

General pharmacokinetic characteristics of miglustat showed higher exposure in Fabry subjects (Table X) compared to that in Gaucher subjects. Also, accumulation index ranged from 1.66 to 2.34 at Month 1 to Month 6 after 100 QD dosing.

Table IX Mean (CV%) miglustat pharmacokinetic parameters following single and multiple dosing at 100 mg QD or BID in Fabry subjects (Study OGT 918-002)

100 mg Vevesca single dose								
Time of sampling	n	C_{max} (ng/ml)	t_{max} (hr)	AUC_{0-24h} (ng.hr/ml)	$AUC_{0-\infty}$ (ng.hr/ml)	$t_{1/2}$ (hr)	R_O	R_{lin}
Day 1	16	905 (39)	2.5 (1-6)	10316 (46)	17408 (74)	15.2 (99)	NA	NA
100 mg Vevesca once daily								
Time of sampling	n	C_{max} (ng/ml)	t_{max} (hr)	AUC_{0-24h} (ng.hr/ml)	$AUC_{0-\infty}$ (ng.hr/ml)	$t_{1/2}$ (hr)	R_O	R_{lin}
Month 1	15	1367 (48)	2.5 (1-6)	17589 (51)	NA	11.6 (51)	1.66 (32)	1.15 (41)
Month 3	9	1777 (28)	2.5 (1-2.5)	22110 (58)	NA	11.9 (46)	2.16 (48)	1.18 (28)
Month 6	9	1782 (30)	2.5 (0-2.5)	24004 (51)	NA	13.8 (63)	2.34 (31)	1.38 (29)
100 mg Vevesca twice daily								
Time of sampling	n	C_{max} (ng/ml)	t_{max} (hr)	AUC_{0-12h} (ng.hr/ml)	$AUC_{0-\infty}$ (ng.hr/ml)	$t_{1/2}$ (hr)	R_O	R_{lin}
Month 3	5	1872 (34)	2.5 (1-4)	15973 (42)	NA	8.85 (37)	1.97 (7)	1.28 (9)
Month 6	5	1933 (34)	2.5 (2.5-6)	16044 (37)	NA	8.58 (28)	1.92 (29)	1.29 (21)

NA=not applicable

t_{max} values are median with range of values in parentheses

The dosing interval, τ, was 24 and 12 hours for once daily and twice daily dosing, respectively

R_{lin} = Linearity ratio (comparison of $AUC_{0-\infty}$ to $AUC_{0-\tau}$)

R_O = Observed degree of accumulation of miglustat in plasma following multiple dosing (comparison of $AUC_{0-\tau}$ at Month 1, 3, or 6 to $AUC_{0-\tau}$ on Day 1)

6.2.1.2 Is miglustat pharmacokinetics different among diseases?

Pharmacokinetic characterization in various patients groups was performed throughout the miglustat development programs. Based on cross-study comparison, it was concluded that pharmacokinetics of miglustat was significantly different among Gaucher subjects, Fabry subjects, and AIDS patients. However, it should be noted that dose was significantly higher in AIDS than in others. The primary parameters from all the groups are summarized in the following table.

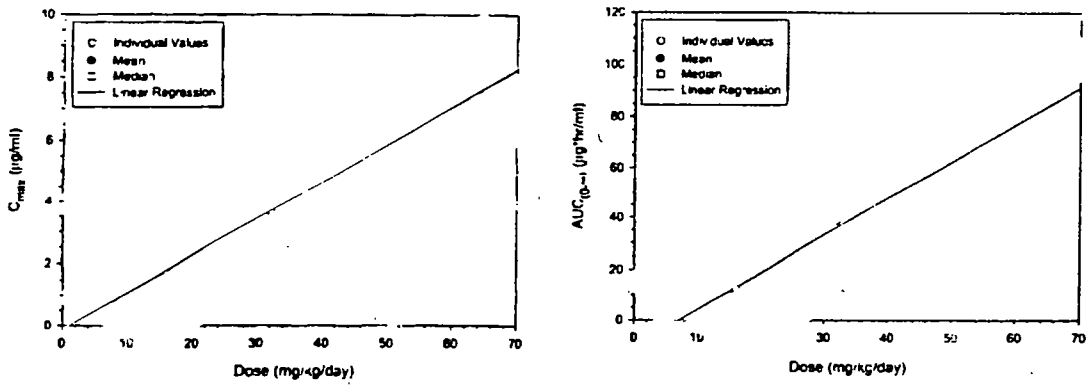
Table X Comparison of mean values of primary pharmacokinetic parameters (SE) between group*

	Gaucher subject	Fabry subject	AIDS patients
CL/F (L/hr)	12.4 (0.48)	9.9 (1.81)	19.0 (1.7)
V/F (L)	140 (9.93)	119 (17)	125 (21)

* The population means were estimated by NONMEM approach.

6.2.1.3 Is dose proportionality of Zavesca established ?

Dose proportionality was established within the trials with a supportive data. Dose normalized pharmacokinetic parameters were similar within the dosing of 50 mg and 100 mg based on Table V and Table VIII. Also, the sponsor included supportive data (Report NS8-93-06-001 studied by G.D. Searle) indicating dose linearity up to 64 mg/kg/day (QID regimen) for 2-8 subjects per treatment group. The supportive data are shown in the following figures.



(A) (B)

Figure 4 Values of Cmax (A) and AUC (B) as a function of dose following single dosing with miglustat in AIDS or advanced ARC subjects

Mean apparent oral clearance across all doses was estimated as 0.285 (0.117) L/hr/kg and mean apparent volume of distribution was 2.86 (1.78) L/kg.

6.2.1.4 Does pharmacokinetics change with time following chronic dosing ?

Mean AUC during the dosing interval after the multiple doses is same as AUC from time zero to infinity after the first dose. Also, in an attempt of modeling, the sponsor successfully predicted plasma concentration-time profiles after multiple doses using parameters after the first dose. The above results indicate the time average invariant of miglustat pharmacokinetics.

6.2.1.5 Is major route of elimination identified ?

The sponsor has not done a mass balance study or a study to determine major route of elimination for Zavesca.

Cross-study population pharmacokinetic analyses showed significant correlation between creatinine clearance and miglustat oral clearance. The results indicate that renal elimination may be an important factor for miglustat.

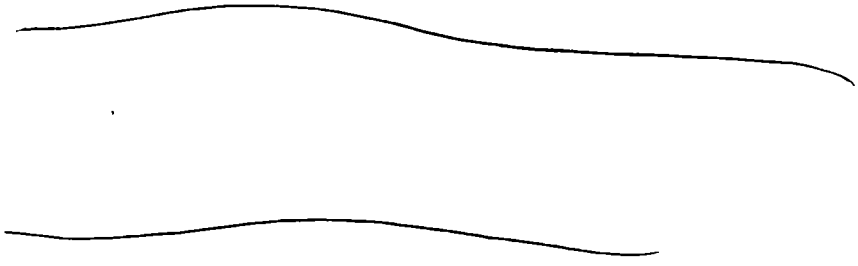
6.3 Intrinsic Factors

6.3.1 Demographic factors

6.3.1.1 Are demographic factors significant covariate for Zavesca pharmacokinetics ?

The effects of demographic factors on Zavesca pharmacokinetics were evaluated through cross-study population pharmacokinetic approach. The detailed method of the method was described in the Appendix. Demographic factors such as age, gender, weight, body mass index (BMI) and race were estimated as a covariate to explain random variability on miglustat pharmacokinetic parameters. Of demographic factors studied, no significant covariate was found to have an effect on miglustat pharmacokinetics.

In brief, 1466 data were entered including 548 from Study 001, 533 from Study 002, 297 from Study 003, and 88 from Study 004 for NONMEM analyses. Overall data structures are shown in the following figures and were summarized in Table XII.



(A) (B)

Figure 5 Histogram of sample distribution times (A) and plot of all the measured miglustat plasma concentrations (1466 measurements) through 4 clinical trials (Study OGT

918-001, 002, 003, and 004). In (B), units for TIME (time) and CONC (concentration) are hour and ng/ml, respectively.

Table XI Summary of Zavesca dosing and concomitant medications of interest in 4 clinical trials.

		OGT918-001	OGT918-002	OGT918-003	OGT918-004	All
Zavesca						
	50 mg BID	0	0	2	0	2
	50 mg TID	0	0	18	0	18
	100 mg QD	1	15	0	0	16
	100 mg BID	3	6	4	0	13
	100 mg TID	25	1	0	11	37
	200 mg TID	3	0	0	0	3
Loperamide Use						
	Yes	9	0	1	4	14
	No	17	16	17	7	57
Cerezyme Use						
	Yes	0	0	0	6	6
	No	26	16	18	5	65

Based on the structure model, pharmacokinetic parameters for individual subjects were estimated and statistical significance on correlation between covariates and the parameters were estimated. Of demographic factor and laboratory covariates studied, only creatinine clearance showed significant correlation with CL/F of miglustat. In addition, creatinine showed significant correlation with Vd/F.

Including significant covariates, final covariate model was established to estimate Bayesian posterior parameters.

The following figures are shown the final model prediction on observation.

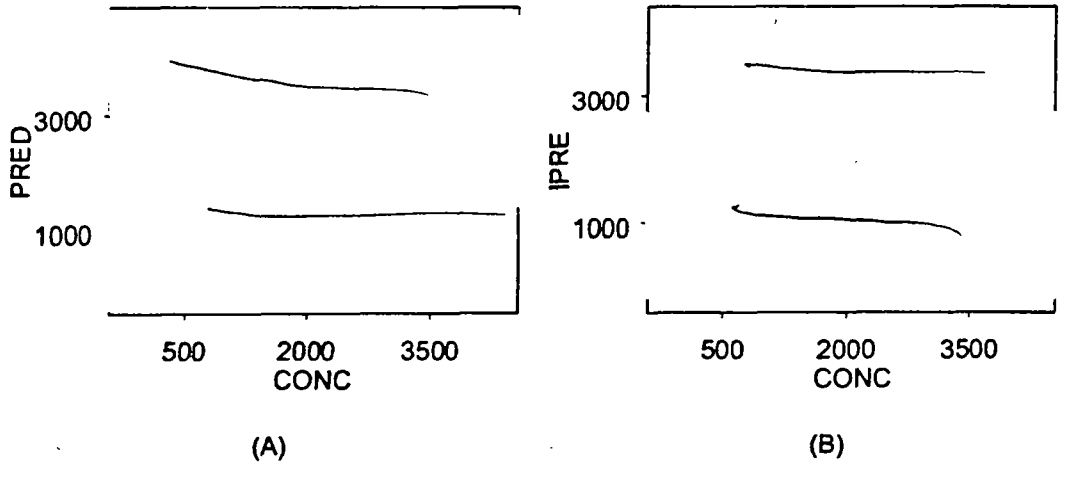


Figure 6 Observed vs. predicted (A) or individual predicted (B) concentrations under final covariate model.

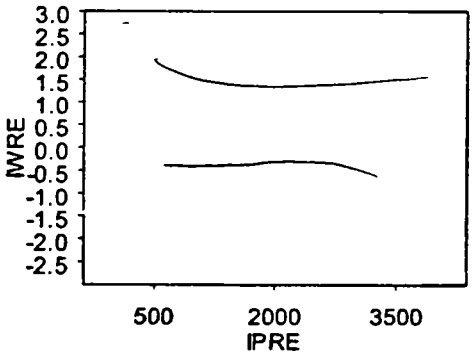
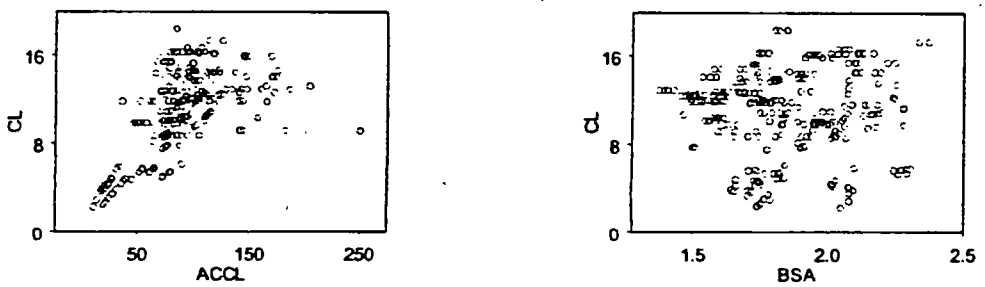


Figure 7 Individual predicted concentrations versus individual weighted residuals under final covariate model.

6.3.2 Renal function

6.3.2.1 Does the renal function affect Zavesca pharmacokinetics ?

There was significant correlation between adjusted (standardized for body surface area) creatinine clearance (ACCL) and CL/F as shown in the following figures. In contrast, there was no correlation between BSA and CL/F.



(A) (B)

Figure 8 Plot summary for correlation of ACCL (A) or BSA (B) to oral clearance.

Individual CL/F estimates indicated that subjects with moderate to severe renal impairment have a 60% to 70% decrease in miglustat oral clearance. Mean values of CL/F were 60.74 (N=2) and 88.70 (N=3) ml/min for severe and moderate renal impaired patients, respectively.

Therefore, it is concluded that there is significant effect of renal function on miglustat pharmacokinetics and dose adjustment is recommended with adjusted CLcr.

6.3.3 Liver function

6.3.3.1 Does the liver function affect Zavesca pharmacokinetics ?

Correlation between laboratory markers of liver function (ALT, AST, alkaline phosphatase, and bilirubin) was evaluated to pharmacokinetic parameters.

No significant effects were found with any of the liver function markers tested. However, it should be noted that the majority of subjects were within normal range for these parameters. For example, three of 71 subjects were above the upper limit of alkaline phosphatase (1.1- to 1.5-fold higher), six of 70 subjects with ALT data were above the upper limit (1.1- to 1.6-fold higher), five of the 64 subjects with AST value were above the upper limit (1.1- to 1.8-fold higher), and eight of 56 subjects with bilirubin data were above the upper limit (1.1- to 3.2-fold higher).

Therefore, the results are not conclusive though no correlation was found between miglustat pharmacokinetics and liver function markers over the range of values presented in the population studied.

6.4 Extrinsic Factors

6.4.1 Food Effect

6.4.1.1 Does food affect the bioavailability of miglustat? What was the relative bioavailability of 100 mg capsules of miglustat compared with an oral solution?

Food had no statistically significant effect on the extent of exposure (AUC_{0-inf}) but had significant mean reduction of 36% in peak concentration (C_{max}) and a median delay of two hours in the time to peak concentration (T_{max}). Under fasted conditions, the capsule formulation was 97% bioavailable relative to an oral solution.

A randomized, open-label, single dose, 3-way, crossover study was conducted to assess the effect of food on the pharmacokinetics of a 100 mg capsule of miglustat and compare the relative bioavailability of the capsule formulation with an oral solution of miglustat. Each dose was separated by a washout period of at least 6 days. Twenty-four healthy male and female subjects received 100 mg miglustat as a capsule formulation under fed and fasted conditions and as a solution under fasted conditions. Plasma concentrations for miglustat were determined using

Geometric mean pharmacokinetic parameters of miglustat following oral administration of a capsule formulation under fed and fasted conditions and as a solution under fasted conditions are summarized below:

Table XII Summary of food effect on miglustat pharmacokinetic parameters

PK parameters	Capsule Fed	Capsule Fasted	Solution Fasted
C_{max} (ng/ml)	843	1328	1442
T_{max} (h)	4.42	2.13	1.77
AUC_{0-t} (ng.h/ml)	8723	10382	10777
AUC_{0-inf} (ng.h/ml)	9320	10868	11255
λz (/h)	0.0866	0.0891	0.0887
$T_{1/2}$ (h)	8.00	7.78	7.82

The statistical analyses provided the following overall comparisons between the capsule under non-fasted and fasted conditions and between the fasted states for the capsule and solution:

Table XIII Summary of statistical analyses of food effect on miglustat pharmacokinetics

Parameter	Comparison	Point Estimate	90% CI
AUC_{0-inf}	Non-fasted capsule vs. Fasted capsule	0.86	0.81, 0.91
	Fasted capsule vs. Fasted solution	0.97	0.91, 1.02
C_{max}	Non-fasted capsule vs. Fasted capsule	0.64	0.57, 0.71
	Fasted capsule vs. Fasted solution	0.92	0.82, 1.03

The results of this study demonstrated that food significantly reduced peak exposure but did not significantly alter the extent of systemic exposure of miglustat. Following administration with food, the C_{max} and AUC_{0-inf} values were decreased by 36% and 14%, respectively. Ingestion of food with Zavesca also tended to delay the onset of C_{max}; with food, the median T_{max} value (4.5 h) tended to be longer than that under fasted conditions (2.5 h).

Under fasted conditions, the capsule formulation was bioequivalent to an oral solution. The average extent of exposure of miglustat (AUC_{0-inf}) from the capsule formulation was 97% (90% CI of 91-102%) and peak exposure (C_{max}) was 92% (90% CI of 82-103%), relative to that of the solution.

6.4.2 Drug-Drug Interaction

6.4.2.1 Is there pharmacokinetic drug-drug interaction between miglustat and Cerezyme?

The mean area under the miglustat plasma concentration-time curve during a dosing interval (AUC_{0-8hr}) was approximately 16% greater when miglustat was administered alone in comparison with miglustat and Cerezyme co-administration. The mean C_{max} was approximately 29% higher when miglustat was administered alone compared with co-administration with Cerezyme.

The co-administration of Cerezyme with miglustat in comparison to the administration of Cerezyme alone revealed significant differences in apparent clearance ($Dose/AUC_{0-t}$). The mean apparent clearance ($Dose/AUC_{0-t}$) was 70% higher when Cerezyme was co-administered with miglustat compared with Cerezyme alone.

A randomized, open-label, multiple dose, Phase II study (OGT 918-004) was conducted to assess the tolerability and pharmacokinetics of miglustat and Cerezyme given in co-administration compared with Cerezyme and miglustat alone. Thirty-six subjects were randomized into one of three study groups as follows: miglustat monotherapy; Cerezyme monotherapy; and miglustat and Cerezyme combination therapy. Subjects assigned to one of the miglustat arms received a dose of 100 mg TID miglustat for 6 months. Subjects assigned to one of the Cerezyme arms continued receiving their existing doses for the next 6 months. At Month 1, the first 6 available subjects produced PK profiles for their respective drug therapy.

The miglustat samples were collected pre-dose and at 1, 2, 2.5, 4, 6, and 8 hours post dose. The Cerezyme samples were collected pre-dose and at 10, 20, 30, 60, 90, 95, 100, 105, and 120 minutes relative to the start of the 90 minute infusion. Subjects in the combination group who underwent PK analysis for both miglustat treatment and Cerezyme infusion took the miglustat capsule immediately prior to the start of the Cerezyme infusion. At Month 1, a PK profile of miglustat and Cerezyme was obtained from 18 subjects, six from each randomized treatment

group. The plasma analyses of miglustat were performed using a validated — method. The methodology for the Cerezyme was to measure the glucocerebrosidase activity in plasma. The results are summarized in the following tables.

Table XIV Mean (SD) miglustat Pharmacokinetic Parameters

PK Parameter	miglustat alone (N=6)	miglustat and Cerezyme (N=5)
C_{max} (ng/ml)	1722 (330)	1340 (227)
$AUC_{0\text{-}8hr}$ (ng.h/ml)	9071 (2191)	7821 (1118)

Table XV Cerezyme PK Parameters

Subject	Dose (U/kg)	C_{max} (nmol.h/ml)	$AUC_{0\text{-}t}$ (nmol.h/ml).min	Dose/$AUC_{0\text{-}t}$
	Cerezyme alone			
101	7.5	411	36099	2.08×10^{-4}
107	7.5	311	31347	2.39×10^{-4}
113	15	417	35682	4.20×10^{-4}
116	7.5	489	30954	2.42×10^{-4}
117	7.5	345	23522	3.19×10^{-4}
137	15	250	16836	8.91×10^{-4}
Mean (SD)		389* (78)	30480* (5195)	3.86×10^{-4} (2.59×10^{-4})
	Cerezyme and miglustat co-administration therapy			
104	15	723	36249	4.14×10^{-4}
108	15	368	36762	4.08×10^{-4}
123	15	174	14221	1.05×10^{-3}
124	15	195	23140	6.48×10^{-4}
131	15	182	19919	7.53×10^{-4}
Mean (SD)		328 (235)	26058 (10059)	6.55×10^{-4} (2.67×10^{-4})

*. Subjects 113 and 137 were not included in the mean calculations.

The results showed that the mean area under the miglustat plasma concentration-time curve during a dosing interval ($AUC_{0\text{-}8hr}$) and maximum plasma concentration (C_{max}) were approximately 16% and 29% greater when miglustat was administered alone in comparison with administration of miglustat and Cerezyme co-administration therapy, respectively. However, the differences were not statistically significant ($p>0.05$).

Analysis on apparent clearance (Dose/$AUC_{0\text{-}t}$) showed that the mean apparent clearance was 70% higher when Cerezyme was co-administered with miglustat compared with Cerezyme alone. Thus, it can be concluded that miglustat decreased the extent of systemic availability of Cerezyme. Since the duration of infusion for Cerezyme was different in each subject (ranged from 73 to 163 minutes), C_{max} values were not directly comparable between subjects.

It was reported that all 36 subjects took at least one concomitant medication during the course of the study. The most frequent concomitant medications taken during the study were paracetamol, taken by 16 (44%) subjects, loperamide hydrochloride, taken by 13 (36%) subjects. The Cerezyme group took notably less loperamide hydrochloride (1 subject) during the study than the miglustat (6 subjects) and combination (7 subjects) groups. It should be noted that the loperamide hydrochloride was taken specifically to control the diarrhea experienced by the two treatment groups that took miglustat. Paracetamol was also taken by a higher proportion of the combination group (9 subjects) during the study than the miglustat and Cerezyme groups (5 and 2 subjects, respectively).

6.4.2.2 Does Zavesca alter the pharmacokinetics of Zidovudine in HIV patients?

Two studies were conducted to evaluate the effect of milglustat on the pharmacokinetics of zidovudine (AZT or ZDV) in HIV patients. The results of study NS8-93-06-004 showed that the $AUC_{0\text{-}8hr}$ and C_{max} values of AZT for the miglustat treated group were approximately 41% and 45% greater than those of the placebo group. The results of population pharmacokinetic analysis were consistent with these findings. The population pharmacokinetic analyses of another study NS8-94-06-009 predicted that there was no statistically significant pharmacokinetic interaction between ZDV and miglustat on the extent of absorption of either drug.

A multicenter, randomized, double-blind, placebo-controlled study (NS8-93-06-004) was conducted to compare the pharmacokinetics of zidovudine (AZT) given alone with combination with miglustat in HIV-1 infected patients. In the initial dose-escalation phase, patients received ascending doses (300 mg t.i.d., 700 mg t.i.d., 1000 mg t.i.d.) of miglustat or placebo orally in combination with 100 mg t.i.d. of AZT orally for successive periods of two weeks each. In the efficacy phase patients received either 1000-mg t.i.d. of miglustat or placebo orally in combination with 100-mg t.i.d. AZT orally for 24 weeks. A total of 118 patients were randomly assigned to receive either 3,000 mg/day miglustat in combination with 300 mg/day AZT (60 patients) or placebo in combination with 300 mg/day AZT (58 patients). The pharmacokinetics of AZT is summarized in the following table.

Table XVI Mean (SD) Pharamokinetics of AZT

PK parameter	Single dose 100 mg AZT		100 mg AZT (300 mg/day)	
	Placebo	300 mg miglustat Single dose	placebo	1000 mg miglustat (3000 mg/day)
$AUC_{0\text{-}8hr}$ (ng.hr/ml)	432 (100)	734 (126)	436 (93)	616 (160)
C_{max} (ng/ml)	303 (27)	580 (65)	385 (138)	559 (235)
Tmax (hr)	0.938 (0.258)	0.750 (0.112)	1.06 (0.33)	0.800 (0.184)

The extent of exposure ($AUC_{0\text{-}8hr}$) and peak plasma concentration (C_{max}) of AZT in patients receiving miglustat were increased in comparison to patients receiving placebo. This was true regardless of whether the first dose or steady-state was examined. The $AUC_{0\text{-}8hr}$ and C_{max} values of AZT after single dose were 70% and 91% higher with co-administration of miglustat compared with AZT alone. At steady state, the $AUC_{0\text{-}8hr}$ and C_{max} values of AZT were 41% and 45% higher with co-administration of miglustat compared with AZT alone. The effect appeared less pronounced at steady-state as compared to the single dose. Since miglustat is a sugar-like molecule, it is possible that it may interfere in the glucuronidation of AZT.

The firm also performed a population analysis on pharmacokinetics of miglustat and AZT. It was predicted that the AZT C_{max} for the miglustat treated group (524 ng/ml) was approximately 47% greater than that of the placebo group (356 ng/ml). It was also concluded that there was an evidence that both the clearance and extent of absorption were greater for the miglustat group than for the placebo group.

In addition, the pharmacokinetics of miglustat and ZDV given alone and in combination were assessed in another multicenter, open-label, randomized Phase II study (NS8-94-06-009). Miglustat was administered in doses of 0, 1500, and 3000 mg/day in combination with either 0, 300, or 600 mg/day of ZDV. Sixty-seven HIV-1 infected patients were enrolled in the study.

On Day 1, blood samples were obtained for pharmacokinetic assessment at 0, 0.25, 0.5, 1, 2, and 3 hours post-dosing. For patients treated with miglustat, a blood sample for pharmacokinetic analysis was drawn six hours following the morning dosing on any study day between Week 4 and Week 6. At Week 8, blood samples for the determination of pharmacokinetic assessment were drawn at 0, 0.25, 0.5, 1, 2, and 3 hours post-dosing. To investigate the potential pharmacokinetic interactions of miglustat and ZDV, population pharmacokinetic analyses were performed using the miglustat and ZDV pharmacokinetic data. The results of population pharmacokinetic analyses suggested that there was insufficient evidence to conclude a pharmacokinetic interaction between ZDV and miglustat.
In summary, the conventional pharmacokinetic analysis of the study NS8-93-06-004 clearly showed that miglustat increased the exposure of zidovudine. The results of population pharmacokinetic analysis of the two studies mentioned above were controversial. Since the miglustat doses used in these studies were 3- to 10-fold higher than the proposed to-be-marketed dose, it is less likely that miglustat would cause clinically significant drug interaction with zidovudine.

6.4.2.3 Is miglustat metabolized by rat, primate, and human liver microsomal systems? Does miglustat bind to plasma proteins and blood cells?

The metabolism of miglustat was examined in rat, primate and human liver microsomal systems. Incubations were conducted in the presence of 20 µg/ml [^{14}C]miglustat and microsomal protein (1.0 and 2.0 mg/ml) in the presence and absence of NADPH-regenerating system. Incubations were terminated at 1 and 2 hours. The metabolites of miglustat were measured by —— using on-line radiochemical detection. The results showed no evident metabolism of miglustat (20 µg/ml) in any of the in vitro incubation supernatants. It was concluded that rat, primate, and human liver microsomal preparations are incapable of metabolizing miglustat under the conditions in the present study.

The in vitro binding of [^{14}C] miglustat to plasma proteins and blood cells of rat, monkey, and man were determined using an ultrafiltration method. No binding to plasma proteins was observed in any of the three species analyzed across the target concentration range 1.0-20.0 µg/ml. Blood cell binding was measured, using centrifugation, on pooled blood samples from male rats, monkeys, and humans. The blood cell binding was moderate and the mean blood:plasma concentration ratios in rat, monkey, and human blood were 0.943 (range ——), 0.941 (range ——) and 0.877 (range ——) respectively.

6.4.2.4 Is miglustat an inhibitor of major cytochrome P450 (CYP) isozymes?

No significant inhibitory effect of miglustat on the metabolism of the major cytochrome P450 isozymes was observed in human liver microsomes.

The potential inhibitory effect of miglustat on a range of human hepatic cytochrome P450 (CYP) enzyme activities in vitro was investigated. Model substrates of CYP1A2 (ethoxyresorufin), CYP2A6 (coumarin), CYP2C9 (tolbutamide), CYP2C19 (S-mephenytoin), CYP2D6 (bufuralol), CYP2E1 (chlorzoxazone), CYP3A4 (testosterone), CYP4A11 (lauric acid) were incubated with miglustat at a single concentration of 20 µg/ml in pooled hepatic microsomes. The results are provided in the following table.

Table XVII Effect of miglustat on the activities of major P450 isozymes

CYP Isoform (metabolic pathway)	Sample ID	Activity (pmol.min-1.mg-1) mean ± S.D.	% activity remaining
CYP1A2 (7-Ethoxyresorufin o-deethylation)	Control	23.6 ± 0.340	
	MIGLUSTAT	21.6 ± 0.255	**91.6**
CYP2A6 (Coumarin 7-hydroxylation)	Control	242 ± 14.4	
	MIGLUSTAT	253 ± 26.4	**105**
CYP2C9 (Tolbutamide 4-hydroxylation)	Control	65.3 ± 8.28	
	MIGLUSTAT	74.4 ± 2.58	**114**
CYP2C19 (S-mephenytoin 4-hydroxylation)	Control	70.0 ± 0.408	
	MIGLUSTAT	70.0 ± 2.03	**100**
CYP2D6 (Bufuralol 1-hydroxylation)	Control	64.2 ± 5.74	
	MIGLUSTAT	72.7 ± 0.960	**113**
CYP2E1 (Chlorzoxazone 6-hydroxylation)	Control	459 ± 19.1	
	MIGLUSTAT	417 ± 26.4	**91.0**
CYP3A4 (Testosterone 6β-hydroxylation)	Control	1171 ±19.9	
	MIGLUSTAT	1217 ± 6.10	**104**
CYP4A11 (uric acid hydroxylation)	Control	496 ± 26.2	
	MIGLUSTAT	511 ± 24.0	**103**

Miglustat produced very slight inhibition of 7-ethoxyresorufin o-deethylase activity (CYP1A2) and chlorzoxazone 6-hydroxylase activity (CYP2E1) (91.6 and 91.0% of control activity remaining, respectively). Negligible inhibition of S-mephenytoin 4-hydroxylase (CYP2C19) was observed. A slight elevation in catalytic activity was observed with coumarin 7-hydroxylase (CYP2A6), tolbutamide 4-hydroxylase (CYP2C9), bufuralol 1-hydroxylase (CYP2D6), testosterone 6β-hydroxylase (CYP3A4) and lauric acid hydroxylase (CYP4A11) (between 3 and 14% increases). As the concentration of miglustat screened was 10-fold higher than peak plasma concentrations, it was less likely that miglustat would cause clinically relevant drug-drug interactions with the substrates of these P450 isozymes.

6.4.2.5 Is miglustat a substrate and/or an inhibitor of P-Glycoprotein (P-gp)?

Miglustat was not found to be a substrate or an inhibitor of the P-gp efflux system based on the secretion ratios. However, a significant increase in the secretion of the P-gp substrate, cyclosporin A across the Caco-2 monolayer was observed in the presence of miglustat. It suggested that miglustat increased the activity of P-gp in Caco-2 cell culture.

Transport of radiolabeled and nonradiolabeled marker compounds in the presence and absence of miglustat across Caco-2 monolayers was evaluated in both the apical to basolateral and basolateral to apical directions. Mannitol transport was evaluated as a paracellular marker, cyclosporin A was examined as a substrate for P-gp, and verapamil hydrochloride as an inhibitor of P-gp. A single concentration of miglustat (50 µM) was used to evaluate its interaction with P-gp. The results are summarized in the following table.

Table XVIII Summary of transepithelial permeability in Caco-2 cell monolayer

Marker	Co-solute	Apical to Basolateral Mean Papp (cm/second)	Basolateral to Apical Mean Papp (cm/second)	Mean Secretion
^{14}C-Mannitol	—	4.06×10^{-7}	NA	NA
^{3}H-Cyclosporine A	Control	1.73×10^{-6}	8.48×10^{-6}	4.95
	Verapamil	1.85×10^{-6}	4.10×10^{-6}	2.28
	MIGLUSTAT	1.26×10^{-6}	2.96×10^{-5}	23.4
MIGLUSTAT	Control	2.16×10^{-7}	1.59×10^{-7}	0.411
	Cyclosporin A	9.06×10^{-8}	1.41×10^{-7}	1.48
	Verapamil	1.20×10^{-7}	1.47×10^{-7}	1.23

Since the mean secretion ratio of miglustat was 0.411 and both Cyclosporine A and Verapamil did not affect the basolateral to apical mean apparent permeability (Papp), OGT was not a substrate of the P-gp efflux system. In contrast, both cyclosporine A and verapamil slightly decreased the apical to basolateral mean Papp.

It was found that miglustat significantly increased the secretion of the P-gp substrate, cyclosporin A across the Caco-2 monolayer. OGT increased the basolateral to apical mean Papp 2.5 fold with a minimum effect on apical to basolateral mean Papp. This result may be due to an increase in the activity of P-gp.

This study revealed an additional peak in the miglustat chromatograms. In the absence of the monolayers, miglustat was stable over a period of 2 hours at 37°C, however, in the presence of the monolayers, an average of 13% loss in miglustat was observed. This apparent loss in miglustat in part may be attributed to the appearance of an additional peak in the miglustat chromatograms at 3.5 minutes. This additional peak was observed in all samples taken from the receiver side of the cells, irrespective of whether miglustat was added to the apical or basolateral side. This finding suggested that miglustat might be metabolized in Caco-2 cell culture.

6.5 General Biopharmaceutics

6.5.1 Dissolution

6.5.1.1 What is acceptable dissolution test condition and specification for the product ?

Dissolution testing was carried out using USP Apparatus 1 (Baskets) at 100 rpm in —— of the media. Twelve dosage units from each of the drug product lots were tested. Samples were withdrawn at 10, 15, 20 and 30 minute intervals. The percentage of labeled claim dissolved at each specified testing interval was reported for each individual unit. The mean percent dissolved, range of dissolution and coefficient of variation (RSD) was reported.

The tested batches were

- 0207N; manufactured by —— for clinical trials
- SB001-100; manufactured by Galen for clinical trials, and
- OG001-100; manufactured by Galen for marketing.

Pre-compression step added in the encapsulation process to reduce the weight variation for OG001-100.

Results are summarized in the following tables.

Table XIX Dissolution data in various pH media

pH	Batch	Time (min) 10	%RSD	15	%RSD	20	%RSD	30	%RSD
6.8								94.6	2.5
								97.9	1.6
								98.9	6.6
4.5								94.1	2.4
								94.3	1.7
								92.3	2.8
0.1N HCl								98.5	1.5
								98.3	0.7
								95.1	2.9

Clinical trials (CT) batches (SB001-100 and 0207N) used ——— process while the to-be-marketed (TBM) used —— process. The TBM batches (OG001-100) seems to have slower dissolution rates than CT batches in the all three dissolution media. However, miglustat is highly soluble and dissolves in 0.1N HCl in 15 minutes. Based on Guidance for Industry, Dissolution testing of IR solid oral dosage forms, the bioavailability of the drug is not limited by dissolution. Therefore, slightly slower dissolution rate for the TBM batch should not be an issue.

The sponsor proposed the following dissolution method and it is acceptable:

- Dissolution test conditions
  - Medium: 0.1 N HCl
  - Apparatus: USP Apparatus 1 (baskets) 100 rpm
  - Volume: 1000 ml
  - Sampling times: — min (information only) and — minutes

The sponsor proposed the dissolution specification as follows:

- For each unit tested, not less than — of the label claim of miglustat dissolves within 45 minutes.

Dissolution appears to be complete within — minutes of the dissolution methods. In that regarding, the following dissolution specification is recommended:

- Dissolution specification
  - Q= —at — minute.

6.5.2 Analytical

6.5.2.1 Is the analytical methods appropriately validated ?

The analytical method to measure miglustat in plasma was) assay. for Study OGT 918-001 and for other studies. The analytical methods were appropriately validated.

The method had a limit of quantitation to of plasma. Nominal calibration standard range was of plasma. Analysis of quality control (QC) was performed with miglustat concentrations of 0.11 and 10.47 µg/ml.

Inter-batch mean accuracy ranged from –9.1% to 8.0 % with precision ranging from 3.8% to 17.4 %. Intra-batch mean accuracy ranged from –18.2% to –9.1% with precision ranging from 23.2% to 38.6% for 0.11 µg/ml, and –12.4 with 4.9% for 10.47 µg/ml.

The method had a limit of quantitation of of plasma. Nominal calibration standard range was .

Inter-batch mean accuracy ranged between –5.2 to 3.4 % with precision ranging from 0.58% to 6.0%. Inter-batch accuracy for QC samples ranged from with precision ranging from . Intra-batch mean accuracy for quality control samples ranged from 5.6% to 11% with precision ranging from 1.3% to 6.6%.

Inter-laboratory cross-validation of miglustat methods were performed with two human plasma QC samples and 19 human plasma samples from Study OGT 918-001. A criterion for compatibility laboratory or method was that the percentage difference calculated was less than or equal to 30%. Percentage difference values for all samples ranged from –19% to 4.3% and results were within the acceptance criteria.

3 page(s) of revised draft labeling has been redacted from this portion of the review.

8 Appendix

8.1 Cross-study Population Pharmacokinetics of Zavesca in Subjects with Gaucher and Fabry Disease

6.1.1 SYNOPSIS

Objectives:

To describe the pharmacokinetics of Zavesca in Gaucher disease and to predict whether or not dosing adjustments may be necessary in certain subsets of the population.

Study Design:

Studies OGT 918-001 and –003 were Phase I/II, uncontrolled, open-label in Gaucher subjects and Study OGT 918-002 was a Phase I/II, uncontrolled, open-label study in Fabry subjects. Study OGT 918-004 was a Phase II, randomized, controlled, open-label, parallel study in Gaucher subjects.

Number of Subjects (planned and analyzed):

All subjects who had evaluable miglustat data were planned for inclusion in the analysis. The final NONMEM dataset for analysis contained data from 26 of 28 subjects in Study OGT 918-001 (2 subjects who did not have evaluable data were excluded), 16 of 16 subjects in Study OGT 918-002 (data only up to the 6-month visit were included), 18 of 18 subjects in Study 918-003, and 11 of 36 subjects in Study OGT 918-004 (only subjects who received Zavesca [alone or in combination with Cerezyme] and had evaluable data were included).

Methodology:

Nonlinear mixed effect models were used with the model building dataset to characterize the pharmacokinetics of miglustat in subjects with Gaucher disease (Studies OCT 918-001, -003, and -004) and Fabry disease (Study OGT 918-002). First, exploratory data analysis was undertaken to examine the basic structure of the concentration-time data. Second, population pharmacokinetic models, e.g., 1- or 2-compartment models with absorption were developed without covariates, and individual pharmacokinetic parameter estimates were obtained from the best model. Third, individual covariates were screened to determine if there was any relationship between individual pharmacokinetic parameter estimates and individual covariates. The following covariates were examined, age, gender, weight, body mass Index, race, serum or plasma creatinine, creatinine clearance (standardized for body surface area), alanine aminotransferase, aspartate aminotransferase, bilirubin, alkaline phosphatase, and concomitant medications (loperamide and Cerezyme: Y or N for administration during the study). Fourth, any significant covariates that were identified were entered into the population model as predictor variables Fifth, appropriate methods were used to evaluate the performance of the model. Lastly, once the final model was identified, individual pharmacokinetic parameter estimates were once again estimated and summarized by descriptive statistics.

Sensitivity analysis was used to evaluate the model performance and stability. In sensitivity analysis, the model inputs were randomly varied and their effect on the model parameters examined. Logistic regression was used to determine whether

there was a relationship between miglustat plasma concentrations and the efficacy variables or safety parameters of interest. The following efficacy variables were studied: spleen and liver organ volume responses, nnd hemoglobin and platelet responses- The safety parameters (adverse events) studied were: diarrhea and tremor.

Pharmacokinetic and Pharmacodynamic Results and Conclusions:

Miglustat plasma concentrations were best fit with a I-compartment model with oral administration. While there was some evidence to suggest that miglustat exhibits biexponential pharmacokinetics, the distribution phase was too small and poorly differentiated to allow adequate characterization in this analysis.

Apparent oral clearance (CL/F), apparent volume of distribution (V/F), and the oral absorption rate constant (Ka) were modeled as random effects, with inter-subject variability. Residual error (intra-subject variability) was modeled as a combination of additive and proportional error

Of a number of demographic and laboratory covariates studied, only adjusted creatinine clearance (adjusted CLcr; standardized for body surface area) and creatinine (Cr) were found to have an effect on CL/F and V/F, respectively.

The results of the analysis showed a pharmacokinetic difference between Gaucher and Fabry subjects, particularly for CL/F. This difference can be explained at least in part by differences in renal function between the populations, since miglustat is primarily excreted renally. Some subjects with Fabry disease had moderate to severe renal impairment as demonstrated by their adjusted CLcr values (≤ 50 ml/min/l.73m^2). Adjusted CLcr appeared to be a better predictor of CL/F under conditions of impaired renal function and creatinine appeared to be a better predictor of V/F when renal function tended to be normal.

The population estimate for CL/F (in units of l/hr) in Fabry subjects was 9.9 (l/hr) * adjusted CLcr (ml/min/l.73m^2)/125, and in Gaucher subjects was 12.4 l/hr. The population estimate for V/F was 119 l in Fabry subjects and l40 (l) * Cr (mg/dl)/l .2 in Gaucher subjects.

Bayesian posterior estimates of miglustat CL/F ranged from 57 to 305 ml/min across all subjects, with a median of 206 ml/mm. Estimates of V/F ranged from 37 to 187 l across all subjects, with a median of 90 l.

Individual CL/F estimates indicated that subjects with moderate to severe renal impairment have a 60% to 70% decrease in miglustat oral clearance, and would therefore require an adjustment in dose.

Over the range of values present in the population studied, no correlation was found between miglustat pharmacokinetics and laboratory markers of liver function (ALT. AST. alkaline phosphatase and bilirubin).

Of the adverse events (diarrhea and tremor) examined in this study, only diarrhea showed a concentration dependence with subjects with higher steady-state concentrations being more likely to experience a greater intensity of diarrhea than subjects with low concentrations.

Of the 6-month efficacy measurements evaluated in this study only spleen response showed a significant relationship with steady-state concentrations, with

subjects with higher concentrations being more likely to experience a favorable response (decrease in spleen volume).

6.1.2 DESCRIPTION ON METHODOLOGY

Pharmacokinetic Sampling:

Study OGT 918-001

Extensive Sampling:

Plasma samples (at some or all of the following times: predose, and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, and/or 24 hrs postdose) for pharmacokinetic profiling of miglustat were collected in 5 subjects on 100 mg TID after the first dose (Day 1) and after dosing at Month 1.

Sparse Sampling:

Additionally, all subjects (N=28) had plasma samples collected for miglustat measurement at predose and at 2.5 hours post-dose on Day 15 and/or Month 1, and on months 3, 6, and 12. In some subjects who underwent dose adjustments (including all cases of dose increases), additional plasma samples (predose and at 2.5 hours post-dose) were collected approximately one month following dose adjustment.

Study OGT 918-003

Extensive Sampling:

Plasma samples (at some or all of the following times: predose, and at 0.25, 0.5, 1, 2, 2.5, 3, 4, 6, and 8 hrs post-dose) for pharmacokinetic profiling of miglustat were collected in 6 subjects on 50 mg TID after the first dose (Day 1) and after dosing at Month 1.

Sparse Sampling:

Additionally, all subjects (N=18) had plasma samples collected for miglustat measurement at pre-dose and at 2.5 hours post-dose at months 1, 3, and 6.

Study OGT 918-004

Extensive Sampling:

Plasma samples (at some or all of the following times: predose, and at 1, 2, 2.5, 4, 6, and 8 hrs post-dose) for pharmacokinetic profiling of miglustat were collected at Month 1 in 6 subjects receiving Zavesca alone, and 5 subjects receiving Zavesca and Cerezyme combined. Miglustat data obtained from the 6 subjects receiving Zavesca alone and the 5 subjects receiving Zavesca and Cerezyme combined who had pharmacokinetic profiles collected at Month 1 have been included in this population analysis.

Study OGT 918-002

Extensive Sampling:

Over the 6-month period, plasma samples (pre-dose, and at 0.25, 0.5, 1, 2.5, 4, 6, 8, 12, and 24 hrs post-dose) for pharmacokinetic profiling of miglustat were collected in 6

subjects after the first dose (Day 1) and at Month 1, and limited plasma profiles were collected in these subjects at Month 3 and 6.

Sparse Sampling:

Limited plasma profiles (predose, and at 1, 1.5, 6, 12, and 24 hrs post-dose) were also collected in all other subjects (N=16) on Day 1, and Months 1, 3, and 6. In some subjects with dose adjustments (particularly in cases of dose increases) additional plasma samples (predose and at 2.5 hours post-dose) were collected approximately one month following dose adjustment.

Derived Variables

Body Surface Area (BSA; to be used for standardization of computed creatinine clearance values) using Gehan and George method:

$$\mathrm{BSA}\,(\mathrm{m}^2) = 0.024265 \times \mathrm{Weight}\,(\mathrm{kg})^{0.51456} \times \mathrm{Height}\,(\mathrm{cm})^{0.42246}$$

Body Mass Index (BMI) using Stevens et al.:

$$\mathrm{BMI} = \frac{\mathrm{Weight}\,(\mathrm{kg})}{\mathrm{Height}^2\,(\mathrm{m}^2)}$$

Creatinine Clearance (CLcr) from serum or plasma creatinine (Cr) using the following equation by Lott and Hayton:

$$\mathrm{CLcr} = \frac{[(140 - \mathrm{Age}) \times \mathrm{Weight}]}{\alpha \times \mathrm{Cr}}$$

, where α is 72 in males, and 85 in females.

Data Analysis Methods

The general modeling approach followed the guidelines set forth in Ette and Ludden, and Bruno et al.. Model selection was based on physiological and pharmacological rationale and the principle of parsimony — simpler models were chosen over more complex models when statistically justified.

First, exploratory data analysis was undertaken to examine the basic structure of the concentration-time data and to identify outliers, if any.

Second, population pharmacokinetic models were developed without covariates. Using conditional estimation methods, individual pharmacokinetic parameter estimates were obtained.

Third, individual covariates were screened to determine if there was any relationship between individual pharmacokinetic parameter estimates and individual covariates.

Fourth, any significant covariates identified previously were entered into the population model to identify the population model that best described the data.

Fifth, appropriate methods were used to evaluate the performance of the model.

Lastly, once the final model was identified, individual pharmacokinetic parameter estimates were again estimated and summarized by descriptive statistics.

Population Pharmacokinetic Model Development

Base Model Development

Miglustat concentration-time data were analyzed using NONMEM to develop a base structural population pharmacokinetic model: a 1-compartment model with oral absorption (with and without lag time) and a 2-compartment model with oral absorption (with and without lag time).

Random effects were assumed to have a log-normal distribution;

$$P_j = \theta \times \exp(\eta_j)$$

, where P was the parameter of interest, j was the jth subject, θ was the estimate of the population mean and η_j was the deviation from the population mean for the jth subject, under the assumption that $\eta \sim N(0, \omega_j^2)$. A diagonal covariance matrix was used for the multiple random effects.

Residual error was modeled as a combination of additive and proportional error:

$$Y_{ij} = C_{ij}\,(1+\varepsilon_{1ij}) + \varepsilon_{2ij}$$

, where i is the ith subject and j is the jth sample for that subject, Y_{ij} is the observed concentration, C_{ij} is the predicted concentration, ε_{1ij} is the random error of the proportional error term and ε_{2ij} is the random error of the additive error term.

The NONMEM objective function value (OFV) was used for selection of the model. If the difference between the OFVs for two nested models (reduced-full) was greater than the critical value based on a chi-square test with p-value 0.05, assuming both OFVs were obtained using the same estimation method, the full model was considered the superior model.

Once a base model was identified, individual subject pharmacokinetic parameters were calculated by the posterior conditional estimation technique (POSTHOC) of NONMEM. A scatter plot correlation matrix was made between pharmacokinetic parameters. Random effects covariance matrix was determined by Spearman's rank correlation coefficient.

Covariate Screening

For continuous covariate, dependency among covariates was examined and then pharmacokinetic parameters were regressed against the covariate. The F-test of the model was used as the criteria for covariate significance.

For categorical covariates, analysis of variance was used to test for differences in pharmacokinetic parameters between groups.

Covariates evaluated:

- Demographics: age, gender, weight, BMI, race

- Clinical laboratory parameters: serum or plasma creatinine, creatinine clearance, ALT, AST, bilirubin, alkaline phosphatase
- Concomitant medications: loperamide or Cerezyme

Covariate Submodels

Once significant covariate were identified, these covariates were then added to the base model incrementally and tested by NONMEM to determine if they were indeed statistically significant.

Covariate that were continuous in nature were entered into the model in a mean normalized manner:

$$P_j = \theta_0 + \theta_{1j} \times \left[\frac{X_{1j}}{M(X_{1j})} \right]$$

Centering of covariates has a number of advantages including:
(1) numerical instability is reduced in the parameter estimates when there are high correlations among the parameters,
(2) the extended least squares algorithm is least likely to terminate with rounding errors,
(3) more meaningful estimates are obtained in that the θ_0 represents the population mean parameter estimate at the mean of X_{1j}, while θ_1 represents the rate of change in the parameter per unit change in X_1.

If the scatter plot between the covariate and the PK parameter indicated a log-linear relationship, a multiplicative model was to be used:

$$P_j = [\theta_0 - M(X_{1j})] \times X_{ij}^{\theta 1j}$$

Categorical covariates were developed with dummy variable using a fractional change model:

$$P_j = \theta_0 \times (1 + \theta_{1j} \times X_{1j})$$

Once the model with covariates was developed, the significance of the covariates and other terms in the full model were evaluated.

Calculated Pharmacokinetic Parameters

Once the population pharmacokinetic covariate model was finalized, individual and population subject pharmacokinetic parameters were calculated using the POSTHOC technique (FOCE). Also pharmacokinetic parameters were summarized statistically by stratification as follows:
- study
- age (< 50 years, ≥ years)
- Adjusted creatinine clearance (≥ 80 ml/min/1.73 m^2, ≥ 50 but < 80 ml/min/1.73 m^2, ≥ 30 but < 50 ml/min/1.73 m^2 and < 30 min/1.73 m^2)

Pharmacodynamic Correlations

Logistic regression (significance level of 0.05) was used to assess if steady-state plasma concentrations were correlated to the efficacy and safety parameters of interest.

Efficacy Parameters

Responses at six months were regressed against steady-state plasma concentration at the end of study with

- Liver and spleen response
- Homoglobin response
- Platelet response

Safety parameters

Diarrhea and tremor were regresed against the maximum steady-state concentrations achieved during the study.

Method Performance and Stability

Parameter Stability

A nonparametric estimate of the standard error of the parameter estimates was estimated using the delete 10% jackknife.

Sensitivity to Model Inputs

- A sensitivity analysis was done varying the sampling times (except at pre-dose) by ± 10% of the observed sampling time assuming a uniform distribution.
- A sensitivity analysis was done varying the value of the covariates one at a time in the final model by ± 10% of the observed value assuming a uniform distribution.
- A sensitivity analysis was done varying the dosing interval by ± 10%, ± 20%, ± 30%, ± 40%, and ± 50% of the theoretical value (eg. 8/8/8 hours for TID dosing).

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