CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-348

MEDICAL REVIEW

Medical Officer's Review of Response to Not Approved Letter

NDA#: 21-348
Drug: Zavesca (miglustat; OGT 918)
Sponsor: Oxford Glycosciences, Ltd.
Reviewer: Anne Pariser, M.D.
Date of Submission: 07-February-2003
Review Date: 16-June-2003

Re: Response to Not Approved (NA) Letter for NDA

I. Introduction and Background

The sponsor has submitted a response to a Not Approved (NA) letter from the initial NDA submission for Zavesca (miglustat; OGT 918): NDA 21-348; 000-B2, dated 07-February-2003. Zavesca has previously been reviewed under: NDA 21-348; 000, the initial NDA submission for Zavesca in the treatment of type 1 Gaucher disease. Zavesca has also been reviewed under: IND — for types I — Gaucher disease (active date 24-Apr-2000), IND — for — disease (active date 02-Dec-1998), IND — for — and under NDA 21-348. Please refer to the following reviews for additional background information on OGT-918:

1) NDA 21-348: Medical Officer's Review of NDA 21-348 (Gaucher disease type 1), dated 02-May-2002
2) IND 60,197: N-012-YY Annual Report (period 24-May-2001 to 19-November-2002), review dated 06-March-2003
3) IND 60,197: types 1 — Gaucher disease (active date 24-Apr-2000)
4) IND — — disease (active date 02-Dec-1998)
5) IND — (active date 04-Mar-2002)
6) IND —(inactive 01-Jul-1998)
7) IND — (inactive 30-Jun-1998)

Deficiencies were noted in the initial NDA, including Clinical, Pre-Clinical, and Chemistry issues. Only the Clinical issues will be addressed here. The Pre-Clinical and Chemistry issues will be deferred to the Chemistry and Animal Pharmacotoxicology Reviewers.

It is also noted that prior to the submission of the NA response by the sponsor, a meeting was held between the sponsor and the Division to address the deficiencies noted in the NA letter [please refer to the Meeting Minutes from this meeting (meeting date 24-September-2002)]. Briefly, agreement was reached between the sponsor and the Division that management of the risk/benefit ratio for Zavesca could be achieved through appropriate labeling and restricted use and distribution of the drug. The Division recommended that the labeling be revised to identify a target population who could not take enzyme replacement therapy (ERT), such as patients intolerant of ERT or patient with poor vascular access. The indication would, therefore, be revised to address patients

with this unmet medical need, and a restricted distribution of the drug is warranted to ensure that only the appropriately targeted population receive Zavesca.

II. Review of Response to NA

The sponsor's response to the NA consists of answers to the Clinical deficiencies listed in the NA letter from the Division, a revision of the proposed label, and additional clinical data as follows [please refer to sponsor's submission for complete details]:

- Efficacy Update for Study 001
- Safety Update: 240-day safety update with integrated safety data collected from NDA Studies 001, 003, and 004 (including extensions for these studies), and additional safety data from ongoing Studies 005 and 014.
- Restricted Distribution Plan
- Ongoing and Future Studies with Zavesca

Some of the information included in the Safety Update had previously been submitted and reviewed in the Annual Safety Update and Updated Investigator's Brochure for Zavesca, both of which were submitted 09-January-2003 (review date 06-March-2003). [Please see Appendix 2 for the Medical Review of the Annual Safety Update.]

A. Subject Exposure to Zavesca

The initial NDA submission for Zavesca included subjects exposed to Zavesca in Study 001 and extension (up to 24 months of treatment), Study 003 and extension (up to 12 months), and Study 004 and extension (up to 12 months). The subject exposures summarized in the Extended Use phase of these studies in the current submission include subjects exposed to Zavesca for >24 months to up to 48 months (> 91 to >156 weeks). The numbers of patients exposed to Zavesca for >91 weeks is limited. Eighteen (18) subjects had any exposure to OGT-918 >91 weeks: 14 subjects in Study 001 (starting dose 100 mg TID), 3 subjects in Study 003 (50 mg TID), and 1 subject in Study 004 (100 mg TID). Only 14 subjects had exposure to Zavesca of >117 weeks, all of whom were in Study 001. A summary of the Subject Disposition in the current submission is summarized in the following table

Table 1: Summary of Subject Disposition in the 240-Day Safety Update

	Number of Subjects in Safety Population Exposed to Zavesca					
	Study 001	Study 003	Study 004			Overall
	Zavesca 100 mg	Zavesca 50 mg	Zavesca 100 mg	Combination	Cerezyme, then Zavesca 100 mg	
Weeks						
0-26, n =	28	18	12	12	10	80
>26-52, n =	23	16	10	9	9	67
>52-78, n =	20	12	9	9	7	57
>78-91, n =	15	11	7	6	-	39
>91-117, n =	14	3	1	-	-	18
>117-130, n =	14	-	-	-	-	14
>130-156, n =	14	-	-	-	-	14
>156, n =	7	-	-	-	-	7

B. Efficacy Update

An efficacy update was submitted from the final 3-year analysis of Study 001. Subjects in Study 001 who were continued in the Extended Use phase of the study (beyond Month 12 of the original study) were allowed to continue only if the investigator felt that the subject would benefit from extended therapy. Thus, any subject continuing in the study was likely to have responded to treatment, and would have had to have demonstrated tolerance to study medication. Thus, both the efficacy and safety results of the Extended Use phase of Study 001 are to be interpreted with caution, and may not apply to all subjects treated *de novo* with Zavesca.

1. Patient Disposition for Study 001

Patient disposition for Study 001 was as follows:
28 patients were included in original study, of whom 22 patients completed 12 months of treatment, and 6 patients discontinued (2 for GI events, 2 for personal reasons, 2 for pre-existing conditions). Of the 22 patients who completed the initial 12 months of Study 001, 4 chose not to continue beyond Month 12, and 18 enrolled in the initial 12-month extension (Study 001X). Fourteen (14) of these 18 patients completed 24 months of study treatment, and 4 patients discontinued [2 for peripheral neuropathy, 2 as a precaution (same center as peripheral neuropathy patients)]. Fourteen (14) patients continued in the Extended Use phase of Study 001 beyond Month 24, all of whom completed 36 months of treatment. Eleven (11) of the 14 patients discontinued study medication between Months 36 and 48 (1 dementia syndrome and 10 remaining patients discontinued at the Israeli center where dementia syndrome was diagnosed. Note: the additional 10 patients were discontinued as the IRB placed the study on hold while the case of dementia was being investigated. The patient with dementia was further evaluated by a neurologist and was later diagnosed with Alzheimer's disease, which was not felt to be related to study medication.). Three (3) patients were ongoing as of Month 48.

2. Efficacy Results

The efficacy results for Study 001 up to Month 36 for liver and spleen volumes, platelet counts, and hemoglobin concentrations are summarized for the safety population, and for patients with any evaluable efficacy result using the last observation carried forward (LOCF) method.

a) Liver Volume

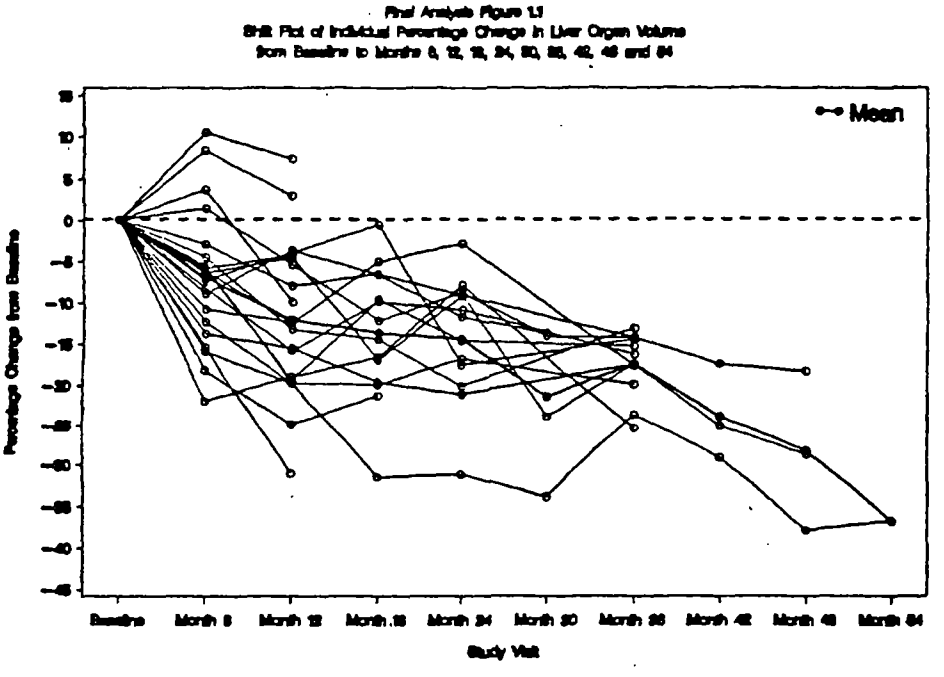
Efficacy results for changes from Baseline in liver volume show significant decreases in mean liver volume at all time points. The safety population showed progressive mean decreases in liver volume at Months 12 (n=21), 24 (n=12) and 36 (n=12) of −12%, -14% and −18%, respectively. However, on the LOCF analysis at Month 36, there was a mean decrease in liver volume of −15%, marginally lower than the −14% decrease seen at Month 24. The liver volume results are summarized in the following table

Table 2: Study 001 Liver Volume, Safety Population* and LOCF Analysis#

	n	Mean	Median	Minimum	Maximum	p-value	95% C.I.
Baseline	27	2.381 (l)	2.38 (l)			-	-
Month 12*	22	2.108	2.06			-	-
Change (l)	21	-0.281	-0.28			<.001	-0.38, -0.18
% Change	21	-12.11	-12.6			<.001	-16.37, -7.85
Month 24*	13	2.175	2.15			-	-
Change (l)	12	-0.359	-0.34			<.001	-0.48, -0.24
% Change	12	-14.46	-13.3			<.001	-19.27, -9.65
Month 36*	12	2.201	2.03			-	-
Change (l)	12	-0.438	-0.41			<.001	-0.53, -0.34
% Change	12	-17.51	-16.9			<.001	-19.96, -15.06
Month 36#	23	2.010	1.99			-	-
Change (l)	22	-0.343	-0.40			<.001	-0.44, -0.25
% Change	22	-14.51	-14.9			<.001	-18.38, -10.65

Liver volume results are also presented graphically by individual patient, and liver volume appears to be highly variable by individual patient. The individual liver volume percent changes from Baseline are depicted graphically in the following figure

Figure 1: Plot of Individual Percentage Change in Liver Volume



b) Spleen Volume

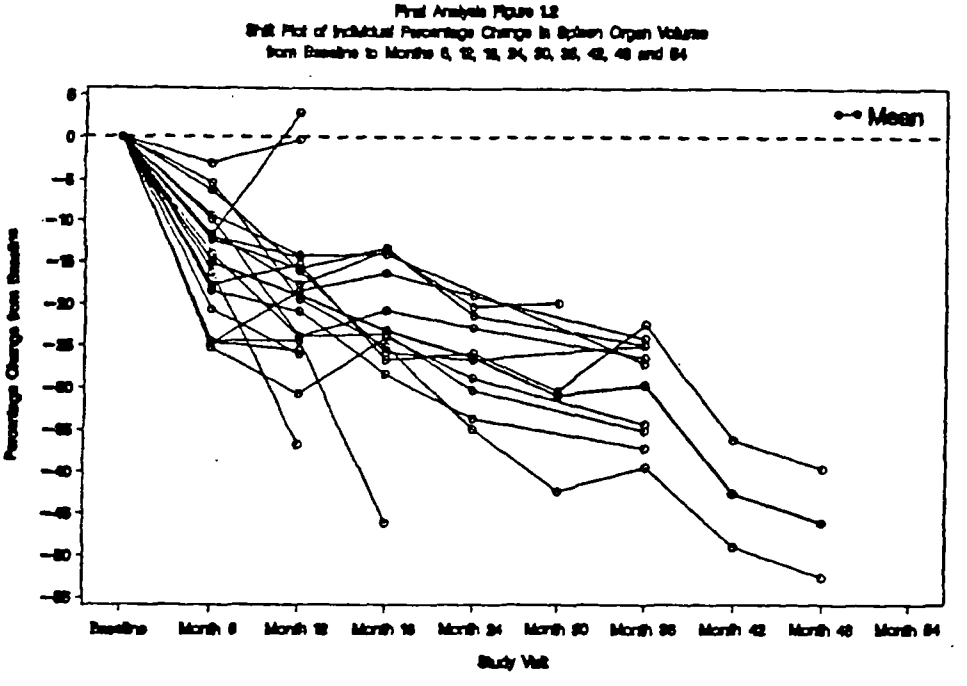
Efficacy results for changes from Baseline in spleen volume show significant decreases in mean spleen volume at all time points. The safety population showed progressive mean decreases in spleen volume at Months 12 (n=18), 24 (n=10) and 36 (n=10) of -19%, -26% and –30%, respectively. On the LOCF analysis at Month 36, there was a mean decrease in spleen volume of –25%, similar to the mean decrease of –26% seen at Month 24. The spleen volume results are summarized in the following table

Table 3: Study 001 Spleen Volume, Safety Population* and LOCF Analysis#

	n	Mean	Median	Minimum	Maximum	p-value	95% C.I.
Baseline	20	1.658	1.49			-	-
Month 12*	19	1.338	1.20			-	-
Change (l)	18	-0.320	-0.30			<.001	-0.42, -0.22
% Change	18	-18.98	-19.0			<.001	-23.71, -14.25
Month 24*	11	1.199	1.15			-	-
Change (l)	10	-0.416	-0.38			<.001	-0.53, -0.30
% Change	10	-26.40	-26.3			<.001	-30.36, -22.44
Month 36*	10	1.226	1.18			-	-
Change (l)	10	-0.525	-0.52			<.001	-0.69, -0.36
% Change	10	-29.64	-26.8			<.001	-34.08, -25.21
Month 36#	20	1.212	1.09			-	-
Change (l)	19	-0.419	-0.42			<.001	-0.55, -0.29
% Change	19	-25.31	-25.6			<.001	-31.24, -19.39

Spleen volume results are also presented graphically by individual patient. For the patients remaining in the Extended Use phase of the study after Month 24, most patients appear to continue to have progressive decreases in spleen volume. The individual spleen volume percent changes from Baseline are depicted graphically in the following figure

Figure 2: Plot of Individual Percentage Change in Spleen Volume



c) Hemoglobin

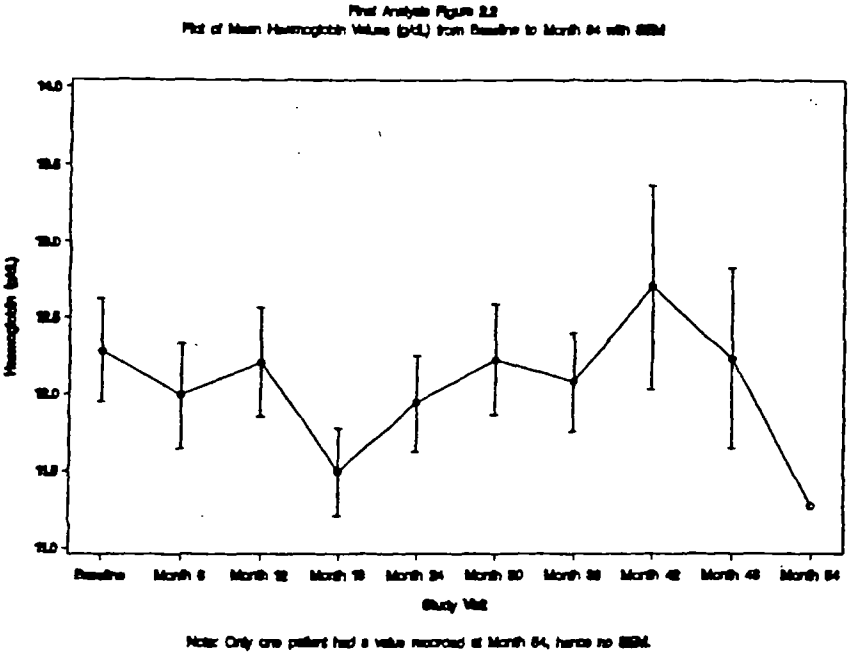
Efficacy results for changes from Baseline in hemoglobin concentration (Hgb) show significant increases in Hgb at Months 24 and 36. There were progressive mean increases in Hgb at Months 12 (n=22), 24 (n=13) and 36 (n=13) of +0.26, +0.91 and +0.95 g/dL, respectively. On the LOCF analysis at Month 36, there was a mean increase in Hgb of +0.74 g/dL. The clinical relevance of these mild increases in Hgb is unknown. The Hgb results are summarized in the following table

Table 4: Study 001 Hemoglobin, Safety Population* and LOCF Analysis#

	n	Mean	Median	Minimum	Maximum	p-value	95% C.I.
Baseline (g/dL)	28	12.28	12.30			-	-
Month 12*	22	12.21	12.20			-	-
Change (g/dL)	22	0.26	0.17			0.095	-0.05, 0.57
% Change	22	2.60	1.3			0.093	-0.47, 5.67
Month 24*	13	11.94	11.70			-	-
Change (g/dL)	13	0.91	1.10			.007	0.30, 1.53
% Change	13	9.05	10.1			.008	2.89, 15.21
Month 36*	13	12.08	12.30			-	-
Change (g/dL)	13	0.95	0.80			.006	0.34, 1.56
% Change	13	9.23	6.8			.008	2.92, 15.54
Month 36#	23	12.70	12.65			-	-
Change (g/dL)	23	0.74	0.65			.001	0.33, 1.14
% Change	23	7.02	5.7			.002	2.91, 11.13

Changes in mean Hgb from Baseline to Month 54 are also depicted graphically in the following figure

Figure 3: Plot of Mean Hemoglobin from Baseline to Month 54



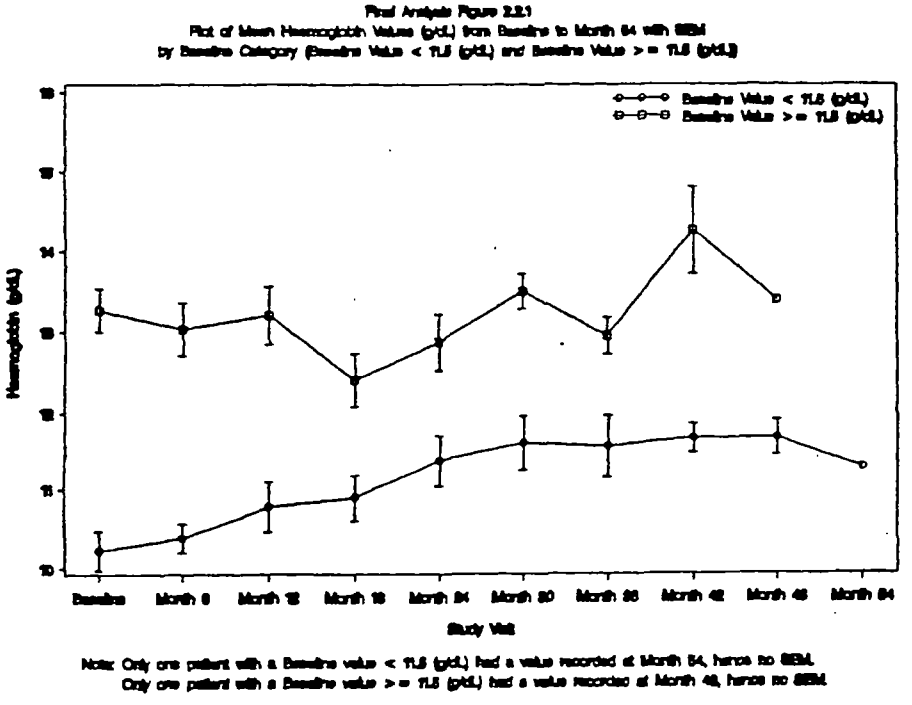
Mean changes in Hgb were also evaluated for patients with Baseline Hgb <11.5 or ≥11.5. Patients with Baseline Hgb levels <11.5 g/dL had a larger mean increase in Hgb at all time points than did patients with Baseline Hgb levels ≥11.5 g/dL. However, there appeared to be little change in Hgb from Month 24 to Month 36 in either group. For patients with Baseline Hgb <11.5 g/dL at Months 24 and 36, mean Hgb increases from Baseline were 1.29 and 1.30 g/dL, respectively. For patients with Baseline Hgb ≥11.5 g/dL at Months 24 and 36, mean Hgb increases from Baseline were 0.32 and 0.40 g/dL. The results are summarized in the following table

Table 5: Change from Baseline in Hgb by Baseline Hgb Level, Cohort Analysis

	Change from Baseline (g/dL)					
	Baseline Hgb <11.5 g/dL			Baseline Hgb ≥11.5 g/dL		
	n	Mean (g/dL)	p-value	n	Mean (g/dL)	p-value
Month 12	9	0.55	.130	13	0.06	.531
Month 24	8	1.29	.007	5	0.32	.440
Month 36	8	1.30	.013	5	0.40	.204

The mean Hgb results by Baseline Hgb level are also depicted graphically in the following figure

Figure 4: Plot of Mean Hemoglobin Value from Baseline to Month 54 by Baseline Hgb Category



d) Platelet Count

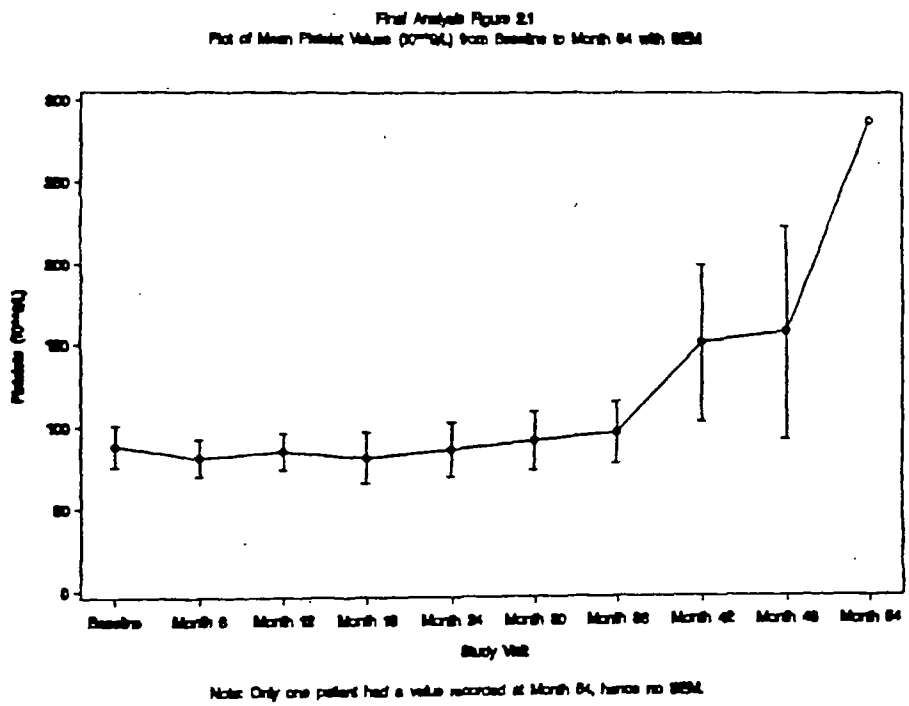
Efficacy results for changes from Baseline in platelet count (Plt) show significant increases in Plt at Months 24 and 36. There were progressive mean increases in Plt at Months 12 (n=22), 24 (n=13) and 36 (n=13) of +16.0, +26.1 and +34.3 $X10^9/l$, respectively. On the LOCF analysis at Month 36, there was a mean increase in Plt of +31.6 $X10^9/l$. The Plt results are summarized in the following table

Table 6: Study 001 Platelets, Safety Population* and LOCF Analysis#

	n	Mean	Median	Minimum	Maximum	p-value	95% C.I.
Baseline ($10^9/l$)	28	88.1	63.3			-	-
Month 12*	22	84.9	72.3			-	-
Change ($10^9/l$)	22	8.3	7.8			.014	1.9, 14.7
% Change	22	16.0	7.5			.060	-0.8, 32.8
Month 24*	13	85.9	66.0			-	-
Change ($10^9/l$)	13	13.6	13.5			<.001	7.7, 19.4
% Change	13	26.1	30.8			<.001	14.7, 37.5
Month 36*	13	96.0	71.0			-	-
Change ($10^9/l$)	13	22.2	18.0			<.001	12.3, 32.0
% Change	13	34.3	27.8			<.001	20.8, 47.9
Month 36#	23	97.2	77.0			-	-
Change ($10^9/l$)	23	19.7	18.0			<.001	12.1, 27.4
% Change	23	31.6	27.8			<.001	19.0, 44.2

Changes in mean Plt from Baseline to Month 54 are also depicted graphically in the following figure

Figure 5: Plot of Mean Platelets from Baseline to Month 54



e) Efficacy Update Conclusions

The sponsor has concluded from the efficacy update results that:

- Organ volumes, hematological changes and bone marrow fat fractions were consistent in showing improvement
- Improvements were progressive over time
- Improvements were sustained in the long term

This Reviewer is not in agreement with all of these conclusions. The number of patients continued in the Extended Use phase beyond Month 24 was small, with efficacy results in 14 or fewer patients at Month 36. Patients were continued in the Extended Use phase "only if the investigator felt that the subject would benefit from extended therapy". Thus, it is unlikely that non-responders (or patients who worsened) or suffered ill-effects of therapy would have been continued. Although spleen volume and platelet counts appeared to show some improvement in most patients who were continued on treatment, the response curves for liver volume and hemoglobin concentrations appeared to be rather flat and of questionable additional benefit after Month 24. Fat fraction results were included in this submission for 2 patients after 12 and 24 months of treatment, which had been previously reported in the initial NDA submission. No new fat fraction data were included, thus no conclusions can be reached on the effects of extended treatment on bone marrow fat fraction.

Given the limited efficacy results for treatment beyond Month 24 in a small, selected group of patients, the Extended Use phase efficacy results are, in the opinion of this Reviewer, difficult to interpret.

3. Safety Update

The safety update consisted of a 240-day safety update with integrated safety data collected from the NDA Studies 001, 003, and 004 (including extensions), and additional safety data from the ongoing Studies 005 and 014. The cut-off date for this analysis was March 20, 2002.

a) Adverse Events

The sponsor has summarized the most common Adverse Events (AEs) [experienced by $\geq$5% of subjects) for the original NDA safety dataset and for the original NDA dataset + AEs reported since the original NDA was submitted (240-day safety dataset). The additional subjects and time intervals included in the 240-day Safety Update do not substantively change the AE profile of long-term treatment with Zavesca described previously in the ISS, the Annual Report, and the updated Investigator's Brochure. Diarrhea (90-91%) and other Gastrointestinal (GI) complaints, and weight decrease (65-70%) were the most commonly reported AEs in both the original NDA safety dataset and in the 240-day safety dataset. The most commonly reported AEs are summarized in the following table

NOTE: Since the original NDA submission, coding of AEs in the dataset has been reviewed by the sponsor (WHO coding system), in the context of the neurological signs and symptoms reported in the studies. Any events of "numbness in hands and/or feet" or "needle-like pain in hands and/or feet" have been re-coded consistently to a preferred term of "paresthesia" and "cramps in leg and/or foot" have been re-coded consistently to a preferred term of "muscle cramps". The table below represents the revised coding. It is also noted that the number of subjects contributing to the dataset decreased considerably after Week 78 and again after Week 104.

Table 7: Most Common AEs (≥5% of Subjects) by WHO Body System & Preferred Term in NDA Safety Dataset and NDA + 240-Day Safety Dataset

	Original NDA Dataset	NDA + 240-Day Datasets
Number of Subjects, n =	80	80
Body System/Preferred Term	n (%)	n (%)
Gastrointestinal System		
Diarrhea	72 (90)	73 (91)
Flatulence	36 (45)	37 (46)
Abdominal pain	35 (44)	35 (44)
Nausea	12 (15)	15 (19)
Constipation	11 (14)	12 (15)
Vomiting	9 (11)	11 (14)
Metabolic & Nutritional Disorder		
Weight decrease	52 (65)	56 (70)
Weight increase	4 (5)	5 (6)
Central & Peripheral Nervous System		
Headache	29 (36)	29 (36)
Tremor	23 (29)	26 (33)
Dizziness	13 (16)	15 (19)
Cramps legs	8 (10)	0
Paresthesia	6 (8)	10 (13)
Neuropathy	2 (3)	4 (5)
Body as a Whole		
Influenza-like symptoms	24 (30)	24 (30)
Fatigue	9 (11)	14 (18)
Pain	7 (9)	9 (11)
Chest pain	6 (8)	7 (9)
Fever	6 (8)	6 (8)
Leg pain	6 (8)	7 (9)
Weakness generalized	6 (8)	7 (9)
Back pain	5 (6)	9 (11)
Pain trauma activated	4 (5)	4 (5)
Tiredness	2 (3)	5 (6)
Musculoskeletal Disorder		
Bone pain	6 (8)	12 (15)
Pain neck/shoulder	5 (6)	5 (6)
Cramps	4 (5)	4 (5)
Joint pain	3 (4)	7 (9)
Muscle cramp	2 (3)	12 (15)
Respiratory System Disorders		
Rhinitis	7 (9)	7 (9)
URI	7 (9)	9 (11)

Coughing	1 (1)	9 (11)
Platelet, Bleeding and Clotting Disorders		
Thrombocytopenia	7 (9)	8 (10)
Purpura	4 (5)	4 (5)
Nosebleed	3 (4)	4 (5)
Non-Classifiable Disorders		
Uncoded	6 (8)	9 (11)
Fall	5 (6)	5 (6)
Inflicted injury	4 (5)	7 (9)
Skin & Appendage Disorders		
Pruritis	3 (4)	6 (8)
Psychiatric Disorders		
Appetite absent	3 (4)	4 (5)
Vision Disorders		
Visual disturbance	5 (6)	5 (6)
Eye irritation	2 (3)	4 (5)
Urinary System Disorders		
Urinary Tract Infection	8 (10)	8 (10)

b) Adverse Events Over Time

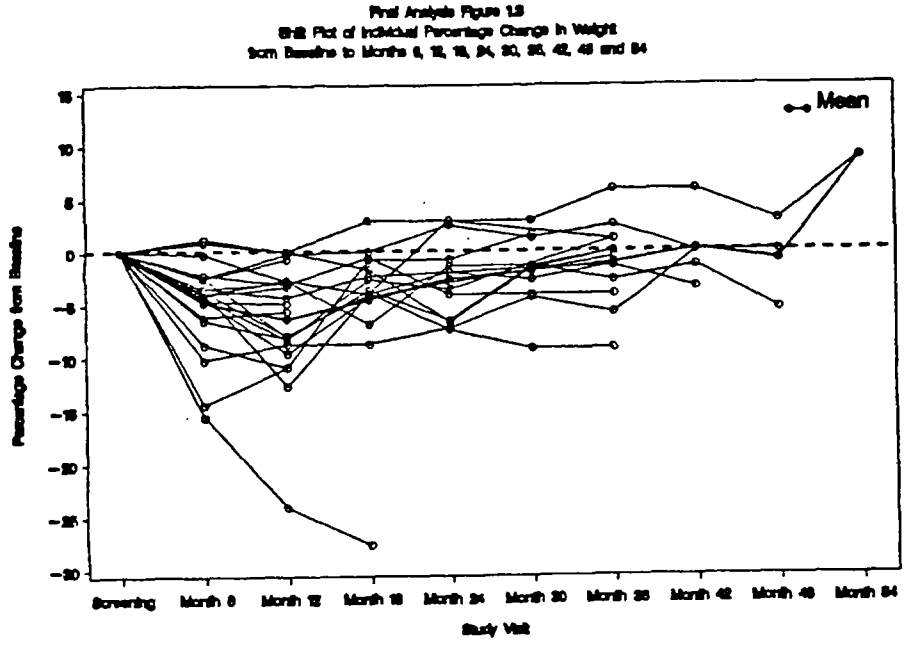
The most commonly reported AEs were also analyzed by time interval. [As all available safety data for the time intervals >117 weeks are from patients continuing in the Extended Use phase of Study 001 alone, only the safety findings for Study 001 will be presented below. The most common AEs for the Combined Safety Dataset overtime is included in Appendix 3.]. At the various time intervals during the first 104 weeks of the clinical studies, the most common AEs were diarrhea, flatulence, abdominal pain, weight decrease, headache, tremor, and influenza-like symptoms. The sponsor notes that the prevalence of diarrhea, flatulence, and abdominal pain decreased with increased duration of treatment. For example, the prevalence of diarrhea was 84% during 0 to 13 week interval, 59% during the >13 to 26 week time interval and ranged from 33% to 40% during the subsequent time intervals up to 104 weeks. However, as previously noted, patients were continued in the Extended Use phase of the study only at the Investigator's discretion, and there were a number of drop-outs due to AEs including diarrhea and other complaints. It is, therefore, unclear if the prevalence of diarrhea, flatulence, and abdominal pain actually decreased, or patients with these complaints were selected out as the Extended Use phase of the study progressed. In addition, Musculoskeletal & Connective Tissue system AEs were noted to increase over time, which is not unexpected given the population under study. The most common AEs over time for Study 001 are summarized in the following table

Table 8: Study 001 Most Common AEs Over Time

	Time Interval (Months)									Overall
	0-6	>6-12	>12-18	>18-24	>24-30	>30-36	>36-42	>42-48	>48-52	
N =	28	23	20	15	14	14	14	3	3	28
Body System/AE Term										
Blood & Lymphatic	6 (21)	3 (13)	1 (5)	0	1 (7)	1 (7)	1 (7)	0	0	8 (29)
Thrombocytopenia	4 (14)	2 (9)	0	0	0	0	0	0	0	5 (18)
General Disorders	8 (29)	5 (22)	5 (25)	3 (20)	4 (29)	4 (29)	4 (29)	1 (33)	1 (33)	11 (39)
Fatigue	1 (4)	3 (13)	3 (15)	3 (20)	3 (21)	3 (21)	3 (21)	1 (33)	1 (33)	5 (18)
GI Disorders	27 (98)	15 (65)	7 (35)	6 (40)	8 (57)	9 (64)	8 (57)	1 (33)	1 (33)	28 (100)
Diarrhea NOS	24 (86)	13 (57)	4 (20)	3 (20)	4 (29)	6 (43)	5 (36)	1 (33)	1 (33)	26 (93)
Flatulence	8 (29)	2 (9)	2 (10)	0	1 (7)	1 (7)	2 (14)	0	0	9 (32)
Abdominal pain NOS	5 (18)	2 (9)	0	0	0	0	0	0	0	6 (21)
Abdominal pain upper	1 (4)	1 (4)	0	0	0	1 (7)	2 (14)	0	0	4 (14)
Nausea	4 (14)	0	0	0	0	0	0	0	0	4 (14)
Dyspepsia	2 (7)	2 (9)	1 (7)	1 (7)	0	0	0	0	0	3 (11)
Vomiting NOS	2 (7)	0	0	0	1 (7)	0	0	0	0	3 (11)
Infections & Infestations	9 (32)	4 (17)	3 (15)	2 (13)	0	2 (14)	2 (14)	0	0	15 (54)
Nasopharyngitis	3 (11)	1 (4)	0	0	0	0	0	0	0	4 (14)
URI	3 (11)	0	0	0	0	1 (7)	1 (7)	0	0	4 (14)
Influenza	1 (4)	0	1 (5)	0	0	0	0	0	0	2 (7)
Injury, Poisoning, & Procedural	1 (4)	4 (17)	1 (5)	1 (7)	3 (21)	3 (21)	2 (14)	0	0	7 (25)
Injury	0	2 (9)	0	0	1 (7)	1 (7)	1 (7)	0	0	5 (18)
Investigations	7 (25)	10 (43)	11 (55)	7 (47)	3 (21)	3 (21)	4 (29)	0	0	15 (54)
Weight decreased	7 (25)	10 (43)	11 (55)	7 (47)	3 (21)	2 (14)	3 (21)	0	0	14 (50)
Metabolic & Endocrine	3 (11)	1 (4)	1 (5)	1 (7)	3 (21)	3 (21)	4 (29)	0	0	6 (21)
Appetite decreased NOS	3 (11)	1 (4)	1 (5)	0	0	0	1 (7)	0	0	3 (11)
Musculoskeletal & Connective Tissue	7 (25)	10 (43)	8 (40)	6 (40)	8 (57)	9 (64)	7 (50)	3 (100)	2 (67)	16 (57)
Bone pain	2 (7)	4 (17)	1 (5)	2 (13)	3 (21)	3 (21)	2 (14)	0	0	6 (21)
Muscle cramps	2 (7)	4 (17)	4 (20)	2 (13)	2 (14)	1 (7)	2 (14)	1 (33)	1 (33)	6 (21)
Back pain	2 (7)	1 (4)	1 (5)	1 (7)	1 (7)	2 (14)	1 (7)	1 (33)	0	3 (11)
Nervous System	12 (43)	9 (39)	10 (50)	6 (40)	7 (50)	7 (50)	9 (64)	0	0	17 (61)
Headache NOS	8 (29)	2 (9)	3 (15)	2 (13)	2 (14)	2 (14)	2 (14)	0	0	10 (36)
Tremor	2 (7)	5 (22)	4 (20)	2 (13)	3 (21)	3 (21)	3 (21)	0	0	6 (21)
Paresthesia	2 (7)	3 (13)	2 (10)	0	0	0	1 (7)	0	0	5 (18)
Respiratory	5 (18)	2 (9)	3 (15)	1 (7)	0	3 (21)	3 (21)	1 (33)	0	10 (36)
Cough	1 (4)	0	1 (5)	1 (7)	0	1 (7)	1 (7)	0	0	3 (11)
Epistaxis	2 (7)	0	0	0	0	1 (7)	0	0	0	3 (11)

Weight decrease over time was also presented graphically by individual patient. For those patients remaining on treatment, weight appears to have stabilized, or appears to have somewhat increased over time for most patients after Month 12. However, as previously stated, the results are to be interpreted with caution. The individual weight changes over time are depicted graphically in the following figure

Figure 6: Plot of Weight over time



c) Additional Safety Findings for Study 001

(1) Serious Adverse Events

There was 1 additional Serious Adverse Event (SAE) reported since the original NDA submission. Subject 409 experienced a post-procedural wound infection after undergoing hip replacement surgery (hip surgery previously reported in the original NDA submission). There were no deaths during the study, however, 1 subject (203) died approximately 6 months after being withdrawn due to a septic episode secondary to hepatocellular carcinoma considered unrelated to the study treatment (also previously reported).

There were no other notable safety findings for Study 001 in the submission.

- 9 subject EDX assessments are the Baseline measurements from Study 005

Ten of these subjects were receiving ERT at the time of EDX assessment.

Briefly, the EDX results from both treated and the 40 "control" subjects are summarized in the following table

Table 11: EDX Results from Treated and Control Subjects

	Control Subjects n (%)	Zavesca Treated Subjects n (%)
n =	40	68
EDX diagnosis		
Mononeuropathy/radiculopathy	14 (35)	4 (6)
Low sural SNAP only	4 (10)	9 (13)
Peripheral neuropathy	4 (10)	8 (12)
Total EDX Abnormals	22 (55)	21 (31)
Total EDX Normals	18 (45)	47 (59)

(4) Interim Data from Study 005

Interim data from Study 005, including neurological assessments at Baseline and following 12 months of treatment with Zavesca, have been collected on six subjects, and Baseline data are available in 9 subjects. The sponsor stated that Nerve Conduction Velocity (NCV) testing indicated abnormalities at Baseline primarily involving the ulnar sensory nerve, and that these findings have remained unchanged over the period of observations. Complaints of paresthesia (numbness in the fingertips) have been reported by one subject, and these complaints resolved spontaneously while being maintained on study drug.

(5) Follow-up Information on Tremor

Follow-up information was summarized on all subjects who withdrew from the clinical studies, and reports on formal assessments conducted by the NIH in 3 subjects were summarized. Follow-up showed that in all cases but 1, tremor or its exacerbation resolved. The 1 remaining subject was felt to have tremor secondary to bipolar disorder. The 3 subjects evaluated at NIH were felt to have an exaggerated physiological tremor similar to that seen with sympathomimetic agents, and that there was no evidence of any central component to the tremor or of a primary neurological cause.

4. Safety Conclusions

The sponsor has concluded from the safety update results that:

- New evidence that neurological symptoms and signs previously attributed to Zavesca are likely to be background feature of the underlying Gaucher disease
- New evidence that the tremor associated with Zavesca is benign and reversible
- Extended safety experience confirm that gastrointestinal disturbances with Zavesca improve with time, weight loss recovers with time, and there are no new safety issues in a cohort of 14 subjects treated for 3 years.

This Reviewer is not in agreement with all of these conclusions. Although certain neurologic features are seen with Gaucher disease, such as radicular symptoms secondary to bone disorders, and although there may be background neurologic complaints, such as leg cramps, elicited from a population of type I Gaucher disease patients on questionnaire, these findings do not address the concerns raised by the Division that treatment with Zavesca may worsen or cause neurologic AEs such as tremor or paresthesias. Zavesca may either contribute to or unmask these neurologic conditions in a vulnerable population and an association with treatment with Zavesca cannot be ruled out with the data presented. These assertions are further supported by safety data from the ongoing Study 005, where neurologic assessments were obtained at Baseline and at prespecified intervals over the course of the study. To date in Study 005 from data submitted with the Annual Safety Report, paresthesia and tremor have been reported by 3 subjects (approximately 30% of patients), which is consistent with results previously reported in Studies 001, 003, and 004.

The tremor associated with Zavesca appears to be an exaggerated physiologic tremor that resolved or improved in most patients off treatment or with a reduction in dose. It is still the recommendation of this Reviewer that the Zavesca labeling carry appropriate information on this tremor for both patients and the treating physician. In addition, the Informed Consent for future and ongoing studies should also carry information regarding the risk of experiencing tremor.

It is unclear from the information presented that diarrhea, other GI complaints, and weight loss improve over time. This may have been a result of patient drop-outs and selection bias, rather than from a true resolution of the AEs. It does appear, however, that weight loss and diarrhea at least stabilize or can be appropriately managed in most patients during Zavesca treatment.

In summary, the safety concerns previously raised with Zavesca in the original NDA review remain. Although these AEs, for the most part, appear to be manageable and monitorable, labeling for Zavesca must contain appropriate wording to adequately inform patients of the risks of treatment, particularly in light of the limited efficacy benefits.

D. Ongoing and Future Studies with Zavesca

There are currently ongoing or future planned studies with Zavesca. As follows:

- Study 005
-
-
-

1. Study 005

Study 005 is an ongoing Phase II monotherapy study of open-label Zavesca in adult subjects with type 1 Gaucher disease. Eleven (11) subjects have been enrolled, with a recruitment target of 12 to 14 subjects. The study is now extended for a further 12-month treatment period, which will give a total of 24 months safety and efficacy data. Zavesca is being administered as 100 mg TID. The efficacy analysis will be performed after all subjects have completed the initial 12 months of the study, and again at Month 24. Safety for the study was initially reported in the Annual Report (attached in Appendix 2), and after all subjects have completed 12 months and 24 months of study treatment. This study has been previously summarized, and interim safety results reported. No new or notable information was reported with this submission.

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

III. Conclusions

From a meeting between the sponsor and the Division 24-Sept-2002, it was agreed that Zavesca could be approved for use in adult type 1 Gaucher disease patients with mild to moderate disease manifestations and an unmet medical need. That is, the small number of patients who are unable to be treated with ERT due to problems such as allergy or poor venous access. No new efficacy or safety data were submitted for review with this submission that substantively change either the known efficacy or safety profiles previously determined in the original NDA submission. The NA response from the sponsor is mainly to address appropriate labeling of Zavesca for clinical use. Restricted distribution of the drug is also warranted.

IV. Recommendations

It is recommended that Zavesca receive approval, pending changes to the proposed label. Zavesca is to receive an indication for the treatment of adult patients with mild to moderate type 1 Gaucher disease who are unable to receive ERT. The recommended changes to the proposed label are extensive, and in the process of internal negotiations, and negotiations with the sponsor. Please consult the Action Package and labeling meeting minutes for all labeling recommendations, changes, and revisions.

V. Appendix 1: Medical Officer's Review of Annual Safety Update

IND #: 60,197; N-012-YY
Sponsor: Oxford GlycoSciences, Ltd.
Drug: OGT 918 (Zavesca/miglustat)
Reviewer: Anne Pariser, M.D.
Submission Date: 09-January-2003
Review Date: 06-March-2003

Re: Review of Annual Report [Period 24-May-2001 to 19-November-2002]

A. Introduction and Background

1. Introduction

The sponsor has submitted an Annual Report for OGT 918 (Zavesca/miglustat) IND 60,197; N-012-YY, dated 09-January-2003. This Annual Report summarizes the clinical experience with OGT 918 for the period 24-May-2001 to 19-November-2002. This Annual Report also includes updated manufacturing and pre-clinical information, which will be deferred to the Chemistry and Pharmacotoxicology Reviewers, and only the clinical information will be reviewed here.

OGT 918 has previously been reviewed under: IND 60,197 for Gaucher disease type I — (active date 24-Apr-2000), IND ——— disease (active date 02-Dec-1998), IND ——— and under NDA 21-348. Please refer to the following reviews for additional background information on OGT-918:

8) IND 60,197: Gaucher disease types 1 — active date 24-Apr-2000)
9) IND ——— disease (active date 02-Dec-1998)
10) IND ——— (active date 04-Mar-2002)
11) IND ——— (inactive 01-Jul-1998)
12) IND ——— (inactive 30-Jun-1998)
13) NDA 21-348: Medical Officer's Review of NDA 21-348 (Gaucher disease type 1), dated 02-May-2002

2. Background

OGT 918 is a synthetic analogue of D-glucose, and functions as a competitive and reversible inhibitor of the enzyme glucosylceramide synthase. Glucosylceramide synthase is the initial enzyme in a series of reactions responsible for the generation of glycosphingolipids. The product of the reaction, glycosylceramide, is the first intermediate in the synthesis of a family of glycosphingolipids

In glycosphingolipid storage disorders, glycosphingolipids accumulate due to deficient activity of specific catabolic enzymes. The aim of OGT 918 treatment is to reduce the rate of glycosphingolipid biosynthesis so that the amount of substrate is reduced to a level which allows the residual activity of the deficient enzyme to be more effective (substrate reduction therapy).

B. Review of Annual Report

1. Clinical Studies with OGT 918

There have been 6 completed clinical studies with OGT 918 in the treatment of Gaucher disease type 1. These studies were submitted to NDA 21-348 and were previously reviewed in detail. These studies will not be reviewed here. Please consult: Pariser A. MD, Medical Officer's Review of NDA 21-348, dated 02-May-2002, for complete review.

There are currently 2 ongoing studies with OGT 918 in the United States, and 1 recently completed study in Europe. The ongoing studies are long-term safety and efficacy studies in patients with Gaucher disease type 1 ——. The completed study is a single-dose, bioavailability and food effect study in healthy volunteers. These studies are briefly summarized in the following table

Table 12: Summary of Ongoing or Recently Completed Studies with OGT 918

Study Description	Results
Study 918-005: Open-label, uncontrolled, safety and efficacy study of OGT 918 100 mg TID in 14 adult patients with Gaucher disease Type 1, who are unable or unwilling to receive ERT. Period I treatment planned for 12 months, and an extension Period planned (details not provided).	At 1 clinical site nationally, 12 patients have entered, 6 patients have completed 12 months of OGT 918 treatment, and 5 patients have discontinued. Of the discontinued patients, 2 withdrew consent prior to receiving OGT 918, and 1 patient withdrew after completing 1 month of OGT 918. No efficacy results have been reported. Of the 9 subjects treated for > 1 month, 9/9 reported at least one AE. The most commonly reported AEs were diarrhea (8) subjects), flatulence (8), abdominal pain (7), weight decrease (4), fatigue (4), and appetite decreased (4). Paresthesia and tremor were reported by 3 subjects each. 1 subject experienced a decreased platelet count on Day 83 of treatment.
Study 918-006: Randomized, controlled, safety and efficacy study of OGT 918 in Gaucher disease type 3 patients, ages ≥12 years of age, who have been on stable ERT for at least 6 months. Efficacy assessments include changes in saccadic eye movement velocity and other markers of disease, particularly changes in the neurological and pulmonary assessments.	No patients have been entered into the study at this time.
Study 918-014: Randomized, open-label, single-dose, 3-way crossover, bioavailability and food effect (non-IND) study in 24 healthy male and female volunteers. This study was to assess the effect of food on the PK of OGT 918 given in a single dose.	24 patients were entered and completed the study at 1 clinical site in Europe. Consumption of a high-fat meal within 30 minutes of administration of OGT 918 significantly reduced peak exposure, but did not significantly affect the extent of systemic exposure of OGT 918. Cmax decreased by 36% with food, but AUC showed a nonsignificant 14% decrease with food (95% CI 80-125%). Under fasted conditions, the oral solution and a capsule formulation were bioequivalent.

2. Adverse Events

Please refer to NDA 21-348 for a detailed review of AEs during the Gaucher disease type 1 clinical trials. Preliminary safety data from Study 918-005 (A phase II monotherapy

study of open-label OGT 918 in adult patients with type 1 Gaucher disease) is summarized in the above table. Other notable safety information available since the last safety update in the 240 day safety update submitted to NDA 21-348, dated 03-May-2002, is summarized as follows:

- There have been no patient deaths during the OGT 918 clinical trials
- Patient Discontinuations for AEs: 2 patients withdrew from Study 918-005 for AEs. One patients withdrew for tingling in the fingers, and the other withdrew due to unacceptable gastrointestinal AEs.

3. Other

An updated Investigator's Brochure, dated 22-February-2002, was included with the Annual Report, which included safety and efficacy data from the Gaucher disease type 1 clinical trials reviewed under NDA 21-348.

C. Conclusion

Limited additional safety data from ongoing clinical studies with OGT 918 in the treatment of Gaucher disease type 1 from Study 918-005 was included in this Annual Report. Additional safety and efficacy information is expected from ongoing clinical trials in Gaucher disease type I and type III, and possibly from early phase Niemann-Pick disease type C and Fabry disease studies, but this information is not yet available. Thus at this time, no notable, serious, or significant safety data have been received that would warrant changes to the planned safety monitoring undertaken in ongoing and planned studies.

VI. Appendix 2: Combined Dataset: Most Common AEs Over Time

Table 13: Combined Dataset, Most Common (>5%) AEs Over Time

	Time Interval (Weeks)								
	0 to 13	>13 to 26	>26 to 39	>39 to 52	>52 to78	>78 to 104	>104 to 130	>130 to 156	>156
N =	80	74	67	63	57	39	14	14	7
Body System/AE Term									
Gastrointestinal System									
Diarrhea	67 (84)	44 (59)	27 (40)	22 (35)	21 (37)	13 (33)	4 (29)	6 (43)	2 (29)
Flatulence	29 (36)	18 (24)	7 (10)	10 (16)	10 (18)	6 (15)	2 (14)	2 914)	0
Abdominal pain	28 (35)	11 (15)	9 (13)	13 (21)	11 919)	6 915)	2 (14)	3 921)	2 (29)
Nausea	9 (11)	2 (3)	1 (1)	1 (2)	4 (7)	1 (3)	0	0	0
Constipation	7 (9)	3 (4)	2 (3)	4 (6)	3 (5)	4 (10)	0	0	0
Vomiting	6 (8)	1 (1)	1 (1)	1 (2)	2 (4)	0	1 (7)	0	0
Metabolic and Nutritional									
Weight decrease	26 (33)	41 (55)	47 (70)	45 (71)	40 (70)	23 (59)	3 (21)	2 (14)	2 (29)
Weight increase	3 (4)	3 (4)	2 (3)	1 (2)	1 (2)	0	0	1 (7)	1 (14)
Body as a Whole									
Influenza-like symptoms	9 (11)	10 (14)	10 (15)	7 (11)	7 (12)	3 (8)	0	0	0
Fatigue	5 (6)	6 (8)	6 (9)	7 (11)	6 (11)	2 (5)	2 (14)	2 (14)	0
Back pain	5 (6)	3 (4)	1 (1)	1 (2)	2 (4)	3 (8)	0	1 (7)	0
Pain	4 (5)	1 (1)	0	3 (5)	4 (7)	2 (5)	1 (7)	1 (7)	1 (14)
Chest pain	2 (3)	5 (7)	3 (4)	2 (3)	2 (4)	1 (3)	0	0	0
Leg pain	4 (5)	3 (4)	2 (3)	1 (2)	1 (2)	1 (3)	2 (14)	2 (14)	0
Weakness generalized	4 (5)	4 (5)	1 91)	2 (3)	2 (4)	1 (3)	0	0	0
Fever	3 (4)	3 (4)	0	0	0	0	0	0	0
Tiredness	0	0	0	3 (5)	3 (5)	2 (5)	1 (7)	1 (7)	1 (14)
Pain trauma activated	2 (3)	4 (5)	1 (1)	0	0	0	0	0	0
Central & Peripheral Nervous									
Headache	24 (30)	12 (16)	7 (10)	6 (10)	8 (14)	6 (15)	3 (21)	3 (21)	0
Tremor	16 (20)	18 (24)	10 (15)	8 (13)	6 (10)	5 (13)	2 (14)	2 (14)	2 (29)
Dizziness	9 (11)	4 (5)	0	0	4 (7)	2 (5)	1 (7)	1 (7)	0
Paresthesia	2 (3)	4 (5)	4 (6)	5 (8)	6 (10)	2 (5)	1 (7)	1 (7)	1 (14)
Neuropathy	0	0	0	1 (2)	4 (7)	2 (5)	0	0	0
Musculoskeletal									
Bone pain	4 (5)	5 (7)	3 (4)	2 (3)	4 (7)	2 (5)	2 (14)	3 (21)	0
Muscle cramp	4 (5)	5 (7)	5 (7)	6 (10)	6 (10)	4 (10)	3 (21)	2 (14)	1 (14)
Joint pain	0	1 (1)	3 (4)	2 (3)	3 (5)	3 (8)	0	0	0
Pain neck/shoulder	2 (3)	3 (4)	1 (1)	1 (2)	0	0	0	0	0

Cramps	2 (3)	1 (1)	1 (1)	2 (3)	1 (2)	0	0	0	0
Respiratory									
Coughing	1 (1)	1 (1)	1 (1)	1 (2)	4 (7)	3 (8)	0	1 (7)	0
URI	1 (1)	5 (7)	1 (1)	1 (2)	2 (4)	0	0	1 (7)	0
Rhinitis	1 (1)	4 (5)	2 (3)	0	1 (2)	0	0	0	0
Platelet, Bleeding, Coagulation									
Thrombocytopenia	6 (8)	5 (7)	5 (7)	4 (6)	2 (4)	2 (5)	0	0	0
Nosebleed	1 (1)	2 (3)	0	0	1 (2)	1 (3)	0	0	0
Purpura	0	0	2 (3)	3 (5)	2 (4)	2 95)	2 (14)	2 (14)	0
Non-Classifiable									
Uncoded	0	1 (1)	4 (6)	4 (6)	4 (7)	1 (3)	0	0	0
Inflicted injury	1 (1)	2 (3)	0	2 (3)	1 (2)	1 930	1 (7)	1 (7)	0
Fall	1 (1)	2 (3)	1 (1)	2 93)	1 92)	1 (3)	1 (7)	1 (7)	0
Skin and Appendages									
Pruritis	0	2 (3)	5 (7)	1 (2)	2 (4)	1 (3)	0	0	0
Psychiatric									
Appetite absent	2 (3)	3 (4)	3 (4)	3 (5)	1 (2)	0	0	0	0
Vision									
Visual disturbance	4 (5)	1 (1)	2 (3)	2 (3)	1 (2)	1 (3)	0	0	0
Eye irritation	3 (4)	3 (4)	2 (3)	2 (3)	3 (5)	2 (5)	0	0	0
Urinary System									
UTI	3 (4)	2 (3)	5 (7)	3 (5)	0	0	0	0	0

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/s/

Anne Pariser
6/16/03 02:30:34 PM
MEDICAL OFFICER

Mary Parks
6/17/03 10:01:07 AM
MEDICAL OFFICER
Concur with recommendation to AP pending changes to proposed labeling.

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #: 21-348	**Application Type:** NDA
Sponsor: Oxford Glycosciences (UK) Ltd	**Proprietary Name:** Zavesca
Investigator: Multiple (Not named)	**USAN Name:** OGT 918 (Miglustat)
Category: Inborn Error of Metabolism, Substrate Reduction Therapy	**Route of Administration:** Oral
Reviewer: Anne R. Pariser, M.D.	**Review Date:** 02-May-2002

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission Type	Comments
22-Aug-2001	22-Aug-2001	1S	

RELATED APPLICATIONS (If applicable)

Document Date	Application Type	Comments
	IND [redacted]	Closed
	IND [redacted]	Closed
	IND 60,197	Open
	IND [redacted]	Open
	IND [redacted]	Open

REVIEW SUMMARY:

The data from the clinical safety and efficacy studies submitted to NDA 21-348 were inadequate to assess the safety concerns seen with OGT 918. OGT 918 did not demonstrate efficacy in all populations of Gaucher disease type 1 patients studied in the clinical program, nor did it demonstrate efficacy in all the important clinical markers of Gaucher disease. It is therefore recommended that this NDA receive an approvable letter pending further safety and efficacy data.

For the efficacy data:

OGT 918 was evaluated in the uncontrolled studies 918-001 and 918-003 in treatment naïve patients (or in patients who had not received ERT for at least 3 months prior to study entry). In these patients, OGT 918 was found to produce beneficial effects on liver and spleen volumes after 6 months of treatment. Statistically significant, but clinically minor, improvements in hemoglobin and platelet counts were seen after 18 and 24 months of treatment. No beneficial effects on bone were seen up to 24 months of treatment with OGT 918; however, this is not unexpected as bone changes would be predicted to occur slowly, and bone effects were not studied in a consistent manner during the studies and across the treatment centers.

In patients who had been receiving ERT for a minimum of 2 years prior to study entry, there was no improvement or worsening in liver volume after switching to OGT 918 monotherapy, with continued ERT (with Cerezyme), or with Combination treatment. For mean spleen volume, switching to OGT 918 monotherapy at Month 6 resulted in non-significant increases in spleen volume at Month 12 in the Cerezyme and Combination groups, but the OGT 918 group had non-significant decreases in spleen volume over the 12 months of OGT 918 treatment. There were non-significant, small decreases in hemoglobin in all 3 treatment groups over the course of the

study. There were decreases in platelet counts seen in all 3 treatment groups after switching to OGT 918 monotherapy, which was particularly notable in the subgroup of patients with Baseline platelet values $\geq 150 \times 10^9$/L. In this subgroup, of the OGT 918 treatment group, the platelet count decrease was significant at Month 12. No beneficial effects on bone were seen in any treatment group over the course of the study; however the duration of follow-up was only 12 months. The biochemical markers of Gaucher disease, including chitotriosidase, hexosaminidase, acid phosphatase, and ACE were all also noted to increase over the course of the study. These results suggest that switching to OGT 918 monotherapy may have a detrimental effect in "well-controlled" patients with smaller liver and spleen volumes, and higher hemoglobin and platelet counts at baseline who had been receiving ERT. Finally, there was no evidence of an additional benefit seen with Combination treatment with OGT 918 and ERT compared to OGT 918 monotherapy.

For the safety data:

AEs in the Gastrointestinal system were the most commonly reported AEs in every study and in every patient population exposed to OGT 918. In the Combined Safety Dataset, diarrhea was the most commonly reported AE term, reported by 90% of patients. Weight loss was the next most commonly reported AE term, reported by 65% of patients. Adverse Events in the Neurologic system were also commonly reported in Gaucher disease patients. In the Combined Data Set, the incidence of tremor was 29% and paresthesia was 8%. If paresthesias and numbness are included in the definition, 15 patients (19%) reported these symptoms during the studies. Tremor appears to have a clear association with the use OGT 918 in Gaucher disease type 1 patients. Tremor was described as mild to moderate, and in all patients except one (for whom follow-up was not available) tremor resolved, usually within days of withdrawal of OGT 918. Of the patients who underwent neurologic assessment by electodiagnostic testing (EDX), 32% of patients in the Combined Safety Dataset had abnormal EDX results, either during or after study drug treatment; however, no patient had an EMG performed at baseline, and not all patients underwent EDX testing. On review of the individual patients reporting paresthesias, 5 patients appeared to have a definite sensorimotor peripheral neuropathy. The neuropathies tended to occur after 6-12 months of OGT 918 treatment, and in some cases, occurred or progressed several months after study drug had been stopped. The neuropathies did not appear to be reversible in any patient as of the final follow-up report. While many of these patients had other illnesses that could have contributed to the neuropathy, at least one patient had no other risk factor for neuropathy other than OGT 918 use. Therefore, despite the limitations in EDX testing and confounding concomitant medical issues, it is evident that there is a neuropathic signal associated with the use of OGT 918 in Gaucher disease type 1 patients. In addition, an SAE was received for memory loss in one patient (#411; Study 918-001) on 24-Apr-2002. A subsequent review of the safety database after this report was received revealed 6 patients who had reported "memory loss" or "amnesia" at any time during or after study drug treatment. Additional information has been requested from the sponsor; however, as the report was received close to the NDA due date, it is unlikely that this information will be available during this review cycle and a full review will be deferred to the next review cycle.

Other safety concerns noted with OGT 918 either in clinical or pre-clinical studies include bone marrow toxicity, lymphocyte toxicity and adverse effects on RBCs, and male reproductive

toxicity, most notably adverse effects on sperm and the male reproductive organs. The adverse effects on the male reproductive system, bone marrow and lymphocytes were seen in animals, while the effects on RBCs were seen in animals and in clinical studies with HIV-positive patients.

OUTSTANDING ISSUES:

1. The neurologic AEs were not felt to have been adequately assessed in this submission. The clinical program had a very small safety database (n=80), no standardized baseline neurological exam, no baseline EDX testing, and no standarized approach to determining the underlying cause of the neuropathy, such as laboratory testing, making interpretation of the results difficult. The follow-up of the paresthesias and numbness was also limited and of a relatively short duration, as the reversibility of neuropathy, if indeed it is reversible, would be expected to occur over months to years. It is recommended that additional neurologic safety assessments be performed prior to the consideration of the approval of OGT 918 in Gaucher disease type 1. Consultation to DNDP for specific recommendations on neurologic safety monitoring prior to future clinical studies being performed is recommended.

2. Memory loss was reported late in the review cycle, and further evaluations and review are pending at the time of this review. Baseline and ongoing neuropsychological testing will likely be recommended for future studies with OGT 918. Consultation to DNDP for specific recommendations is also recommended.

3. As there is a plausible pharmacotoxicity for the neurologic and neuropsychologic AEs seen with the use of OGT 918 in Gaucher disease type 1 due to the GSL depletion or ceramide toxicity, further pre-clinical or clinical evaluation of the neuropathic effects of OGT 918 is recommended. The neurologic AEs are of particular concern [redacted] OGT 918 has not been administered to pediatric patients to date, [redacted]

4. The Hgb and Plt responses were slow, with statistically significant, but clinically minor, improvements seen after 18 and 24 months of treatment with OGT 918. A better response would have been expected, considering the decrease in spleen volume, and considering the rapid and often dramatic improvements seen in the ERT studies. Adverse effects of OGT 918 on bone marrow, RBCs, and lymphocytes were noted in pre-clinical and clinical studies, and further exploration of the underlying mechanism of these adverse effects should be considered. Bone marrow assessment by serial evaluations of the validated QCSI test are recommended, in addition to other studies per discussions with the Animal Pharmacology Division and the sponsor.

5. The painful and debilitating skeletal manifestations of Gaucher disease are important factors to consider when assessing any treatment for Gaucher disease. In ERT studies, beneficial effects on bone were noted after 3-5 years of treatment. As OGT 918 is being proposed by the sponsor as a chronic treatment for Gaucher disease, it would be important to establish the effects of OGT 918 on the skeletal system in Gaucher disease patients. Thus, standard baseline and (serial) follow-up bone evaluations are recommended after 3-5 years of study

drug treatment, including (but not limited to) bone mineral density, fracture rates, incidence of bone crisis, and gross bone deformities/changes.

6. [redacted]

7. Male reproductive toxicities need to be further evaluated for reversibility, either in humans, animals, or both. A consultation to the Division of Reproductive and Urologic Drug Products (DRUDP) is pending. [redacted]

8. Labeling discussions are deferred pending resolution of outstanding safety and efficacy issues.

RECOMMENDED REGULATORY ACTION:	N drive location:
New clinical studies _____ **Clinical Hold** _____ **Study May Proceed**	
NDA, Efficacy/Label supplement: **XXApprovable** ___ **Not Approvable**	
SIGNATURES: **Medical Reviewer:** Anne Pariser, M.D.	**Date:** May 02, 2002
Medical Team Leader:	**Date:**

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Executive Summary

I. Recommendations on Approvability

The data from the clinical safety and efficacy studies submitted to NDA 21-348 were inadequate to assess the safety concerns seen with OGT 918. OGT 918 did not demonstrate efficacy in all populations of Gaucher disease type 1 patients studied in the clinical program, nor did it demonstrate efficacy in all the important clinical markers of Gaucher disease. It is therefore recommended that this NDA receive an approvable letter pending further safety and efficacy data.

For the efficacy data:

OGT 918 was evaluated in the uncontrolled studies 918-001 and 918-003 in treatment naïve patients (or in patients who had not received ERT for at least 3 months prior to study entry). In these patients, OGT 918 was found to produce beneficial effects on liver and spleen volumes after 6 months of treatment. Statistically significant, but clinically minor, improvements in hemoglobin and platelet counts were seen after 18 and 24 months of treatment. No beneficial effects on bone were seen up to 24 months of treatment with OGT 918; however, this is not unexpected as bone changes would be predicted to occur slowly, and bone effects were not studied in a consistent manner during the studies and across the treatment centers.

In patients who had been receiving ERT for a minimum of 2 years prior to study entry, there was no improvement or worsening in liver volume after switching to OGT 918 monotherapy, with continued ERT (with Cerezyme), or with Combination treatment. For mean spleen volume, switching to OGT 918 monotherapy at Month 6 resulted in non-significant increases in spleen volume at Month 12 in the Cerezyme and Combination groups, but the OGT 918 group had non-significant decreases in spleen volume over the 12 months of OGT 918 treatment. There were non-significant, small decreases in hemoglobin in all 3 treatment groups over the course of the study. There were decreases in platelet counts seen in all 3 treatment groups after switching to OGT 918 monotherapy, which was particularly notable in the subgroup of patients with Baseline platelet values $\geq 150 \times 10^9/L$. In this subgroup, of the OGT 918 treatment group, the platelet count decrease was significant at Month 12. No beneficial effects on bone were seen in any treatment group over the course of the study; however the duration of follow-up was only 12 months. The biochemical markers of Gaucher disease, including chitotriosidase, hexosaminidase, acid phosphatase, and ACE were all also noted to increase over the course of the study. These results suggest that switching to OGT 918 monotherapy may have a detrimental effect in "well-controlled" patients with smaller liver and spleen volumes, and higher hemoglobin and platelet counts at baseline who had been receiving ERT. Finally, there was no evidence of an additional benefit seen with Combination treatment with OGT 918 and ERT compared to OGT 918 monotherapy.

For the safety data: .

AEs in the Gastrointestinal system were the most commonly reported AEs in every study and in every patient population exposed to OGT 918. In the Combined Safety Dataset, diarrhea was the most commonly reported AE term, reported by 90% of patients. Weight loss was the next most commonly reported AE term, reported by 65% of patients. Adverse Events in the Neurologic system were also commonly reported in Gaucher disease patients. In the Combined Data Set, the incidence of tremor was 29% and paresthesia was 8%. If paresthesias and numbness are included in the definition, 15 patients (19%) reported these symptoms during the studies. Tremor appears to have a clear association with the use OGT 918 in Gaucher disease type 1 patients. Tremor was described as mild to moderate, and in all patients except one (for whom follow-up was not available) tremor resolved, usually within days of withdrawal of OGT 918. Of the patients who underwent neurologic assessment by electodiagnostic testing (EDX), 32% of patients in the Combined Safety Dataset had abnormal EDX results, either during or after study drug treatment; however, no patient had an EMG performed at baseline, and not all patients underwent EDX testing. On review of the individual patients reporting paresthesias, 5 patients appeared to have a definite sensorimotor peripheral neuropathy. The neuropathies tended to occur after 6-12 months of OGT 918 treatment, and in some cases, occurred or progressed several months after study drug had been stopped. The neuropathies did not appear to be reversible in any patient as of the final follow-up report. While many of these patients had other illnesses that could have contributed to the neuropathy, at least one patient had no other risk factor for neuropathy other than OGT 918 use. Therefore, despite the limitations in EDX testing and confounding concomitant medical issues, it is evident that there is a neuropathic signal associated with the use of OGT 918 in Gaucher disease type 1 patients. In addition, an SAE was received for memory loss in one patient (#411; Study 918-001) on 24-Apr-2002. A subsequent review of the safety database after this report was received revealed 6 patients who had reported "memory loss" or "amnesia" at any time during or after study drug treatment. Additional information has been requested from the sponsor; however, as the report was received close to the NDA due date, it is unlikely that this information will be available during this review cycle and a full review will be deferred to the next review cycle.

Other safety concerns noted with OGT 918 either in clinical or pre-clinical studies include bone marrow toxicity, lymphocyte toxicity and adverse effects on RBCs, and male reproductive toxicity, most notably adverse effects on sperm and the male reproductive organs. The adverse effects on the male reproductive system, bone marrow and lymphocytes were seen in animals, while the effects on RBCs were seen in animals and in clinical studies with HIV-positive patients.

Recommendations :

1. The neurologic AEs were not felt to have been adequately assessed in this submission. The clinical program had a very small safety database (n=80), no standardized baseline neurological exam, no baseline EDX testing, and no standarized approach to determining the underlying cause of the neuropathy, such as laboratory testing, making interpretation of the results difficult. The follow-up of the paresthesias and numbness was also limited and of a relatively short duration, as the reversibility of neuropathy, if indeed it is reversible, would be expected to occur over months to years. It is recommended that additional neurologic safety assessments be performed prior to the consideration of the approval of OGT 918 in Gaucher disease type 1. Before exposing a patient to OGT 918 in a clinical study, a thorough, well-documented neurological examination by a neurologist should be performed, including vibratory sense, pain and temperature, and epicritic sensation especially in the distal upper and lower extremities. If abnormalities are found on examination, the underlying cause should be discovered, which may require EMG/NCV, sural nerve j biopsy, B12 and other vitamin levels, rheumatoic serologies, serum electropheresis, ESR, blood chemistry, LFTs, thyroid function, evaluation for diabetes, Schilling test, and imaging (e.g., for nerve root compression due to vertebral collapse). In addition, documentation of baseline tremor, and any personal or family history should be performed at baseline. Tremor should be characterized by body part affected, approximate frequency of oscillations and amplitude, and whether or not tremor is rhythmic, at rest, in static posture or on attempted intentional movements, has diurunal fluctuations, and impacts on activities of daily living (ADLs). Consultation to the Division of Neuropharmacological Drug Products (DNDP) for specific recommendations on neurologic safety monitoring prior to future clinical studies being performed is recommended.

2. Memory loss was reported late in the review cycle, and further evaluations and review are pending at the time of this review. Baseline and ongoing neuropsychological testing will likely be recommended for future studies with OGT 918. Consultation to DNDP for specific recommendations is also recommended.

3. As there is a plausible pharmacotoxicity for the neurologic and neuropsychologic AEs seen with the use of OGT 918 in Gaucher disease type 1 due to the GSL depletion or ceramide toxicity, further pre-clinical or clinical evaluation of the neuropathic effects of OGT 918 is recommended.

4. The slow Hgb and Plt responses, with statistically significant, but clinically minor, improvements seen after 18 and 24 months of treatment with OGT 918 were somewhat surprising. A better response would have been expected, considering the

decrease in spleen volume [and improvements in bone marrow fat fraction on QCSI although only performed in 2 patients], and considering the rapid and often dramatic improvements seen in the ERT studies. Adverse effects of OGT 918 on bone marrow, RBCs, and lymphocytes were noted in pre-clinical and clinical studies, and further exploration of the underlying mechanism of these adverse effects should be considered. Bone marrow assessment by serial evaluations of the validated QCSI test are recommended, in addition to other studies per discussions with the Animal Pharmacology Division and the sponsor.

5. The painful and debilitating skeletal manifestations of Gaucher disease are important factors to consider when assessing any treatment for Gaucher disease. In ERT studies, beneficial effects on bone were noted after 3-5 years of treatment. As OGT 918 is being proposed by the sponsor as a chronic treatment for Gaucher disease, it would be important to establish the effects of OGT 918 on the skeletal system in Gaucher disease patients. Thus, standard baseline and (serial) follow-up bone evaluations are recommended after 3-5 years of study drug treatment, including (but not limited to) bone mineral density, fracture rates, incidence of bone crisis, and gross bone deformities/changes.

6.

7. Male reproductive toxicities need to be further evaluated for reversibility, either in humans, animals, or both. A consultation to the Division of Reproductive and Urologic Drug Products (DRUDP) is pending.

8. Labeling discussions are deferred pending resolution of outstanding safety and efficacy issues.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

This is the initial NDA for OGT 918. OGT 918 is being proposed as a treatment for Gaucher disease type 1. OGT 918 (miglustat), an N-alkylated imino sugar, is a synthetic analogue of D-glucose. OGT 918 functions as a competitive and reversible inhibitor of glucosylceramide synthase, which is the initial enzyme in a series of reactions responsible for the generation of glycosphingolipids (GSLs).

Glycosphingolipid storage disorders (of which Gaucher disease is the most common) are characterized by deficiencies in the activity of the specific catabolic enzymes that degrade GSLs. These enzyme deficiencies lead to the accumulation of enzyme substrate in the lysosome. Lysosomal storage is pathogenic as the cell's functions become increasingly compromised as the lysosome expands with un-degraded glycolipid, leading to the clinical manifestations of the diseases. Gaucher disease is a functional deficiency of glycocerebrosidase, which mediates the degradation of glucocerebroside (glucosylceramide) to ceramide and a glycan, and is the penultimate step in the degradation of GSLs. The clinical manifestations of Gaucher disease result from glucocerebroside accumulation in macrophages. These glucocerebroside-engorged macrophages (known as Gaucher cells) then cause enlargement and dysfunction of the liver, spleen and bone. Common clinical manifestations of Gaucher disease include: hepatomegaly, splenomegaly, anemia, thrombocytopenia, bone marrow infiltration, osteoporosis, and bone deformities, fractures, painful crises, and necrosis. Cachexia, wasting, and growth retardation can be seen in children. Unlike Gaucher disease types 2 and 3, Gaucher disease type 1 is not associated with central nervous system affects.

The rationale for the treatment of Gaucher disease type 1 patients with OGT 918 is to reduce the rate of glycosphingolipid biosynthesis so that the amount of substrate is reduced to a level which allows the residual activity of the deficient enzyme to be more effective (substrate reduction therapy). Specifically, the aim of substrate reduction therapy in Gaucher disease type 1 is to promote a balance between glycolipid synthesis and degradation, thereby reducing glucocerebrosidase storage and its associated pathology.

OGT 918 is being proposed at an initial dose of 100 mg TID for chronic administration. Dose range, depending on patient response and side-effects with treatment, is proposed at 100 mg daily to 200 mg TID. OGT 918 is also being proposed for use in combination with enzyme replacement therapy (ERT) with Cerezyme or Ceredase.

The OGT 918 clinical program seeks to demonstrate the efficacy of OGT 918 as an oral treatment for Gaucher disease type 1 by assessing its effects on liver volume, spleen volume, hemoglobin, platelets, biochemical markers of Gaucher disease, and other disease assessments. The clinical program also seeks to demonstrate the safety of OGT 918 for chronic administration, both as monotherapy and when combined with ERT. The sponsor's proposed indication for OGT 918 is for the oral treatment of adult (ages 18 to 70) Gaucher disease type 1 patients, in treatment naïve patients, patients switching from ERT, and as add-on therapy in patients currently receiving ERT.

The sponsor submitted 6 clinical studies in support of NDA 21-348 (not including PK studies). There were 2 uncontrolled studies + their extensions, and one active-comparator study + its extension. These studies are briefly summarized as follows:

1. Study 918-001 was a non-comparative, open-label study in 28 adult Gaucher disease type 1 patients who were either unable or unwilling to receive ERT. All patients

received OGT at a starting dose of 100 mg TID. Treatment was for 12 months, and 22 patients completed the study. The primary endpoints were changes from Baseline for individual patients in liver and spleen volume, hemoglobin, and platelet counts at Month 6 and Month 12. Secondary endpoints were changes from Baseline in biochemical markers of Gaucher disease at Month 6 and Month 12. Safety, tolerability, and PK assessments were also made. Other disease assessments were made per usual practice at the study centers.

2. Study 918-001X was a 12-month extension to 918-001. Eighteen (18) patients who completed Study 918-001 were entered into the extension study, and 14 patients completed a total of 24 months of study drug treatment. The primary endpoints were changes from Baseline for individual patients in liver and spleen volume, hemoglobin, platelet counts, and biochemical markers of Gaucher disease at Month 18 and Month 24. Secondary endpoints were changes from Baseline in other disease assessments at Months 18 and 24. Safety, tolerability, and PK assessments were also made.

3. Study 918-003 was a non-comparative, open-label study in 18 adult Gaucher disease type 1 patients who were either unable or unwilling to receive ERT. All patients received OGT 918 at a starting dose of 50 mg TID. Treatment was for 6 months, and 17 patients completed the study. This study was undertaken to allow comparison of safety and efficacy outcomes at the lower (50 mg TID) and higher (100 mg TID in the 918-001 study) doses of OGT 918. The primary endpoints were changes from Baseline for individual patients in liver and spleen volume, hemoglobin, platelet counts, and biochemical markers of Gaucher disease at Month 6. Secondary endpoints were changes from Baseline in other disease assessments at Month 6. Safety, tolerability, and PK assessments were also made.

4. Study 918-003X was a 6-month extension to 918-003. Sixteen (16) patients who completed Study 918-003 were entered into the extension study, and 13 patients completed a total of 12 months of study drug treatment. The primary endpoints were changes from Baseline for individual patients in liver and spleen volume, hemoglobin, platelet counts, and biochemical markers of Gaucher disease at Month 12. Secondary endpoints were changes from Baseline in other disease assessments at Months 12. Safety, tolerability, and PK assessments were also made.

5. Study 918-004 was an open-label, active-comparator, randomized study in 36 adult Gaucher disease type 1 patients who had received ERT for a minimum of 2 years. Patients were randomized to one of 3 treatment groups:
   - OGT 918 alone;
   - Cerezyme alone; or
   - OGT 918 + Cerezyme

   The starting dose of OGT 918 was 100 mg TID, and treatment was for 6 months. Twelve (12) patients were randomized to each treatment group, and 33 patients completed the study. The study was designed to investigate whether OGT 918 could safely be coadministered with ERT. The primary endpoints were change from

Baseline for individual patients in liver volume at Month 6, and the tolerability of Cerezyme and OGT 918 when given in combination. Secondary endpoints were changes from Baseline for individual patients in spleen volume, hemoglobin, platelet counts, biochemical markers of Gaucher disease, and weight at Month 6. Safety, tolerability, PK, and other disease assessments were also made.

6. Study 918-004X was a 6-month extension to 918-004. After completion of 918-004, patients were given the option to receive OGT 918 alone or in combination with Cerezyme for an unlimited period of time (minimum 6 months) regardless of their randomized treatment in the original study. Twenty-nine (29) patients entered the study and all 29 patients elected to receive OGT 918 alone. The starting dose was OGT 918 100 mg TID. Treatment was for 6 months, and 28 patients completed the extension study. The primary endpoint was safety. Secondary endpoints were changes from Baseline for individual patients in liver and spleen volume, hemoglobin, platelet counts, biochemical markers of Gaucher disease and other disease assessments.

B. Efficacy

All 6 clinical studies submitted to the NDA were reviewed individually in detail and provide the majority of the efficacy information on OGT 918 in Gaucher disease type 1. Due to the similar designs and patient populations included in the 918-001 and 918-003 studies (and their extensions), the efficacy results for these studies will be considered together. The 918-004 study (and its extension) will be considered separately. The results for these studies are summarized as follows.

Study 918-001 (and its extension 918-001X) and Study 918-003 (and its extension 918-003X), were non-comparative evaluations of OGT 918 at a dose of 100 mg TID (981-001) or 50 mg TID (981-003) in treatment naïve patients (or in patients who had not received ERT for at least 3 months). Study 918-004 (and its extension 918-004X) included patients who had been receiving ERT for at least 2 years at the time of study entry. The 981-001 and 918-003 study patients had larger spleen and liver volumes, and lower hemoglobin (Hgb) and platelet count (Plt) values at Baseline than did patients in the 918-004 study. This difference is important as the magnitude of response to treatment for Gaucher disease would depend on the patient's ability to respond. That is, patients with larger liver and spleen volumes and lower Hgb and Plt values would be expected to have a larger response to treatment than patients with smaller liver and spleen volumes and higher Hgb and Plt values at Baseline. Comparisons of Baseline liver, spleen, Hgb, and Plt values for Studies 918-001, 918-003, and 918-004 are summarized in the following table

Table 1: Baseline Characteristics, Comparison Across Studies

Study	918-001	918-003	918-004
Enrolled Patients, n =	28	18	36
Demographic Measure			
Liver Organ Volume (l), n =	27	18	35
Mean	2.38	2.47	1.74
Min, max			
Spleen Organ Volume (l), n =	20	11	24
Mean	1.66	1.97	0.71
Min, max			
Hemoglobin (g/dL)*, n =	28	18	36
Mean	12.28	11.65	12.71
Min, max			
Platelets ($X10^9/l$)**, n =	28	18	36
Mean	88.10	123.66	166.57
Min, max			

*LLN 11.5 g/dL
**LLN 150 X $10^9/l$

The 918-001 and 918-003 studies showed that:

Mean liver volumes were significantly decreased from Baseline at Month 6 and Month 12 in both studies, but the magnitude of the decrease was greater in the 100 mg TID treated patients. In the 918-001X extension, the mean decreases in liver volume seen from Baseline to Month 12 were maintained at Months 18 and 24, without a notable further decrease. The results are summarized in the following table

Table 2: Liver Volume Changes, Studies 918-001 and 918-003

	Liver Volume		
	Mean Decrease (L)	Mean % Decrease	p-value*
Study 918-001			
Month 6	-0.16	-7.0%	<.001
Month 12	-0.28	-12.1%	<.001
Month 18	-0.34	-13.7%	<.001
Month 24	-0.36	-14.5%	<.001
Study 918-003			
Month 6	-0.14	-5.9%	.007
Month 12	-0.17	-6.2%	.037

*for mean % decrease from Baseline

Mean spleen volumes were significantly decreased from Baseline at Month 6 and Month 12 in both studies, but the magnitude of the decrease was greater in the 100 mg TID treated patients. In the 918-001X extension, the mean spleen volume progressively decreased in Months 18 and 24. The results are summarized in the following table

Table 3: Spleen Volume Changes, Studies 918-001 and 918-003

	Spleen Volume		
	Mean Decrease (L)	Mean % Decrease	p-value*
Study 918-001			
Month 6	-0.24	-15.1%	<.001
Month 12	-0.32	-19.0%	<.001
Month 18	-0.38	-23.2%	<.001
Month 24	-0.42	-26.4%	<.001
Study 918-003			
Month 6	-0.09	-4.5%	.025
Month 12	-0.23	-10.1%	048

*for mean % decrease from Baseline

Mean Hgb levels were increased from Baseline at Month 6 in the 918-001 study, and decreased from Baseline at Month 6 in the 918-003 study. Both results were not significant. At Month 12, there were small, non-significant increases in Hgb in both studies. In the 918-001X extension, mean Hgb showed a progressive, significant increase at Months 18 and 24, although the clinical relevance of these relatively small increases in Hgb is uncertain. The results are summarized in the following table

Table 4: Hemoglobin Changes, Studies 918-001 and 918-003

	Hemoglobin		
	Mean Decrease (g/dL)	Mean % Change	p-value*
Study 918-001			
Month 6	0.03	0.5%	.596
Month 12	0.26	2.6%	.093
Month 18	0.39	3.9%	.032
Month 24	0.91	9.1%	.008
Study 918-003			
Month 6	-0.13	-1.3%	.378
Month 12	0.06	1.2%	.682

*for mean % decrease from Baseline

On subgroup analysis by Baseline Hgb, significant increases in Hgb were seen only in patients with Baseline Hgb <11.5 g/dL after 18 and 24 months of treatment with OGT 918. The results are summarized in the following table

Table 5: Hemoglobin Changes by Baseline Value (<11.5 vs ≥11.5 g/dL), Studies 918-001 and 918-003

	Hemoglobin <11.5 g/dL		Hemoglobin ≥11.5 g/dL	
Change from Baseline	Mean (g/dL)	p-value*	Mean (g/dL)	p-value*
Study 918-001				
Month 6	0.161	.312	-0.034	.831
Month 12	0.553	.130	0.105	.324
Month 18	0.666	.009	-0.033	.903
Month 24	1.282	.007	0.324	.440
Study 918-003				
Month 6	-0.214	.342	-0.039	.901
Month 12	0.863	.075	-0.300	.525

*for mean % decrease from Baseline

There were non-significant mean increases in Plt from Baseline at Month 6 and at Month 12, and the magnitude of the increase was similar for both doses of OGT 918. In the 918-001X extension, the mean Plt showed a progressive, statistically significant, but clinically minor, increase at Months 18 and 24. The results are summarized in the following table

Table 6: Platelet Count Changes, Studies 918-001 and 918-003

	Platelet Count		
	Mean Decrease ($X10^9$/L)	Mean % Change	p-value*
Study 918-001			
Month 6	3.60	4.2%	.146
Month 12	8.28	16.0%	.060
Month 18	11.16	18.5%	.016
Month 24	13.58	26.1%	<.001
Study 918-003			
Month 6	5.35	2.0%	.642
Month 12	14.00	14.7%	.070

*for mean % decrease from Baseline

There was only 1 patient in Study 981-001 with a Baseline Plt <150 $X10^9$/L, so a subgroup analysis by Baseline Plt could not be performed. For Study 918-003, there did not appear to be a relationship between Baseline Plt and Plt response. The results are summarized in the following table

Table 7: Platelet Count Changes by Baseline Platelet Counts (<150 $X10^9$/L vs ≥150 $X10^9$/L) Study 918-003

	Platelet Count <150 $X10^9$/L		Platelet Count ≥150 $X10^9$/L	
Change from Baseline	Mean ($X10^9$/L)	p-value*	Mean ($X10^9$/L)	p-value*
Month 6	(n=12)		(n=5)	
	-0.21	.969	18.7	.217
Month 12	(n=9)		(n=4)	
	16.39	.134	8.63	.614

*for mean % decrease from Baseline

Other markers of Gaucher disease, including the biochemical markers chitotriosidase, hexosaminidase, acid phosphatase, ACE, G_{M1}, and glucosylceramide were also measured in Studies 918-001 and 918-003.

For mean change in chitotriosidase, there were progressive, significant decreases in chitotriosidase at Month 6 and Month 12 in both studies, and continued progressive, significant decreases at Month 18 and Month 24 in the 918-001X extension. The magnitude of the decrease did not appear to depend on the dose of OGT 918 given. The results are summarized in the following table

Table 8: Chitotriosidase Changes, Studies 918-001 and 918-003

	Chitotriosidase	
	Mean % Decrease	**p-value***
Study 918-001		
Month 6	-6.4	.001
Month 12	-16.4	<.001
Month 18	-21.3	<.001
Month 24	-21.9	<.001
Study 918-003		
Month 6	-4.6	.039
Month 12	-15.3	.001

*for mean % decrease from Baseline

For mean change in hexosaminidase, there were progressive decreases at Month 6 and Month 12, with significant decreases at Month 12 only in both studies. The significant, progressive decreases continued at Month 18 and Month 24 in the 918-001X extension, and the magnitude of the decrease did not appear to depend on the dose of OGT 918 given. The results are summarized in the following table

Table 9: Hexosaminidase Changes, Studies 918-001 and 918-003

	Hexosaminidase	
	Mean % Decrease	**p-value***
Study 918-001		
Month 6	-3.4	.220
Month 12	-7.1	.019
Month 18	-8.4	.047
Month 24	-11.9	<.001
Study 918-003		
Month 6	-5.5	.117
Month 12	-13.1	.007

*for mean % decrease from Baseline

The mean changes in acid phosphatase were inconsistent over time, and the mean ACE decreased at all time points, but only reached significance at Month 18. G_{M1} was measured in only 7 patients in the 918-001 study, with a significant decrease at Month 12 only. Glycosylceramide was measured in the 918-001 study (n=8) and 918-001X extension (n=2) only. The results were variable and non-significant.

Other disease assessments were performed at the discretion of the Investigator and per usual practice at the study centers. Patients underwent assessments including skeletal assessments by DEXA and MRI scanning, bone marrow fat fraction by Quantitative Chemical Shift Imaging (QCSI), QoL assessment (Study 918-003 only; n=10), and pulmonary pressure assessment by echocardiography. The results showed essentially no