

change in skeletal assessments (bone density) up to 24 months of treatment with OGT 918, and no notable changes in pulmonary pressure. QCSI was performed in only 2 patients in the 918-001 study, with improvements to normal in both patients after 24 months of treatment. QoL results showed a significant increase in the improvement in energy scores only.

The 918-004 study (and 918-004X extension) showed that:

[Note: All treatment groups received OGT 918 from Month 6 to Month 12. Month 12 results are listed by original treatment group assignment. Therefore, at Month 12:

- 1) The OGT 918 group received OGT 918 for 12 Months
- 2) The Cerezyme group received Cerezyme alone for 6 months, then received OGT 918 alone for 6 months; and
- 3) The Combination group received OGT 918 + Cerezyme for 6 months, then received OGT 918 alone for 6 months]

Mean liver volumes showed non-significant, small decreases in the OGT 918 and Combination groups, and a non-significant, small increase in the Cerezyme group at Month 6. All 3 treatment group showed small, non-significant decreases from Baseline at Month 12. The decrease was numerically greater, albeit statistically insignificant, at Months 6 and 12 for the Combination group. The results are summarized in the following table

Table 10: Liver Volume Changes, Studies 918-004 and 918-004X

	Liver Volume		
	Mean Change (L)	Mean % Change	p-value*
Month 6			
OGT 918	-0.047	-2.9%	.277
Cerezyme	+0.035	+3.5%	.219
Combination	-0.087	-4.9%	.057
Month 12**			
OGT 918	-0.01	-0.8%	.749
Cerezyme	-0.05	-0.7%	.876
Combination	-0.08	-4.0%	.137

*for mean % decrease from Baseline

**All patients received OGT 918 monotherapy from Month 6 to Month 12

Mean spleen volumes showed non-significant decreases for all 3 treatment groups at Month 6. The result was numerically greater in the Combination group. At Month 12, the OGT 918 and Combination groups showed non-significant decreases, and the Cerezyme group showed a non-significant increase in spleen volume. Both the Cerezyme and Combination groups had increases in spleen volume at Month 12 after switching to OGT 918 monotherapy at Month 6. The results are summarized in the following table

Table 11: Spleen Volume Changes, Studies 918-004 and 918-004X

	Spleen Volume		
	Mean Change (L)	Mean % Change	p-value*
Month 6			
OGT 918	-0.027	-4.8%	.156
Cerezyme	-0.023	-2.1%	.249
Combination	-0.082	-8.5%	.253
Month 12**			
OGT 918	-0.05	-6.1%	.066
Cerezyme	+0.04	+1.5%	.724
Combination	-0.05	-4.8%	.533

*for mean % decrease from Baseline

**All patients received OGT 918 monotherapy from Month 6 to Month 12

Mean Hgb showed non-significant decreases for all 3 treatment groups at Months 6 and 12. The results are summarized in the following table

Table 12: Hemoglobin Changes, Studies 918-004 and 918-004X

	Hemoglobin		
	Mean Change (g/dL)	Mean % Change	p-value*
Month 6			
OGT 918	-0.31	-2.4%	.101
Cerezyme	-0.15	-1.2%	.198
Combination	-0.095	-0.5%	.815
Month 12**			
OGT 918	-0.13	-1.1%	.454
Cerezyme	-0.48	-3.1%	.207
Combination	-0.13	-0.8%	.682

*for mean % decrease from Baseline

**All patients received OGT 918 monotherapy from Month 6 to Month 12

Subgroup analysis by Baseline Hgb, was limited due to the small numbers of patients in any of the treatment groups with a Baseline Hgb <11.5 g/dL. Improvements in Hgb from Baseline were seen only in the Combination group patients with a Baseline Hgb <11.5 g/dL (n=4); however, no conclusions will be drawn from this given the small number of patients. The results are summarized in the following table

Table 13: Mean Change Hemoglobin by Baseline Value (<11.5 vs ≥11.5 g/dL), Studies 918-004 and 918-004X

Change from Baseline	Hemoglobin <11.5 g/dL			Hemoglobin ≥11.5 g/dL		
	n =	Mean (g/dL)	p-value*	n =	Mean (g/dL)	p-value*
Month 6						
OGT 918	1	-0.15	-	9	-0.33	.129
Cerezyme	0	-	-	10	-0.19	.201
Combination	4	0.09	.842	5	-0.48	.091
Month 12**						
OGT 918	1	-0.75	-	8	-0.50	.774
Cerezyme	0	-	-	10	-0.41	.200
Combination	4	0.21	.617	5	-0.41	.056

*for mean % decrease from Baseline

**All patients received OGT 918 monotherapy from Month 6 to Month 12

For mean Plt, the results were remarkable for a decrease in mean Plt when patients were switched to OGT 918 monotherapy. From Baseline to Month 6, the OGT 918 group showed a non-significant mean decrease in Plt that showed a further non-significant decrease at Month 12. The Cerezyme and Combination groups showed non-significant increases in mean Plt at Month 6, and both groups showed non-significant decreases in Plt at Month 12 after switching to OGT 918 monotherapy at Month 6. The results are summarized in the following table

Table 14: Platelet Count Changes, Studies 918-004 and 918-004X

	Platelet Count		
	Mean Change (X10 ⁹ /L)	Mean % Change	p-value*
Month 6			
OGT 918	-21.60	-9.6%	.073
Cerezyme	+15.29	+10.1%	.059
Combination	+2.73	+3.2	.577
Month 12**			
OGT 918	-27.39	-10.4%	.110
Cerezyme	-3.2	-3.2%	.391
Combination	-8.3	-8.3%	.241

*for mean % decrease from Baseline

**All patients received OGT 918 monotherapy from Month 6 to Month 12

On subgroup analysis, mean Plt results were most notable in the subgroup of patients with Baseline Plt ≥ 150 X10⁹/L. All 3 treatment group patients with Baseline Plt ≥ 150 X10⁹/L had decreases in their Plt after switching to OGT 918 monotherapy. A significant decrease in mean Plt seen only in the OGT 918 group patients with Baseline Plt ≥ 150 X10⁹/L at Month 12. The results are summarized in the following table

Table 15: Mean Change Platelet Count by Baseline Value (<150 X10⁹/L vs ≥ 150 X10⁹/L), Studies 918-004 and 918-004X

Change from Baseline	Plt <150 X10 ⁹ /L			Plt ≥ 150 X10 ⁹ /L		
	n =	Mean (10 ⁹ /L)	p-value*	n =	Mean (X10 ⁹ /L)	p-value*
Month 6						
OGT 918	5	-0.10	.979	5	-43.10	.093
Cerezyme	4	8.13	.490	6	24.75	.116
Combination	5	-5.20	.493	4	26.13	.222
Month 12**						
OGT 918	4	1.25	.880	5	-50.30	.032
Cerezyme	4	-3.75	.410	6	-3.75	.712
Combination	5	-11.10	.180	4	-13.63	.434

*for mean % decrease from Baseline

**All patients received OGT 918 monotherapy from Month 6 to Month 12

Other markers of Gaucher disease, including the biochemical markers chitotriosidase, hexosaminidase, acid phosphatase, and ACE were also measured.

Mean percent chitotriosidase showed an increase at Month 6 in the OGT 918 group, and decreases at Month 6 in the Cerezyme and Combination groups. The results were significant only for the OGT 918 group. At Month 12 on OGT 918 monotherapy, all 3 groups showed mean percent increases in chitotriosidase from Month 6. The results were

significant only for the OGT 918 group. The results are summarized in the following table

Table 16: Chitotriosidase Changes, Studies 918-004 and 918-004X

	Chitotriosidase	
	Mean % Decrease	p-value*
Month 6		
OGT 918	+33.0	.007
Cerezyme	-0.3	.960
Combination	-3.9	.270
Month 12**		
OGT 918	+84.5	.011
Cerezyme	+11.7	.242
Combination	+28.6	.038

*for mean % decrease from Baseline

**All patients received OGT 918 monotherapy from Month 6 to Month 12

Mean percent change in hexosaminidase showed progressive increases at Month 6 and Month 12 in all 3 treatment groups. The results were numerically greater in the OGT 918 group, and significant only in the OGT 918 group at Month 6 (p-value not calculated at Month 12). The results are summarized in the following table

Table 17: Hexosaminidase Changes, Studies 918-004 and 918-004X

	Hexosaminidase	
	Mean % Decrease	p-value*
Month 6		
OGT 918	+17.8	.010
Cerezyme	+5.0	.691
Combination	+5.5	.139
Month 12**		
OGT 918	+42.1	ND
Cerezyme	+13.0	ND
Combination	+31.1	ND

*for mean % decrease from Baseline

**All patients received OGT 918 monotherapy from Month 6 to Month 12

Mean percent change in acid phosphatase showed progressive increases at Month 6 and Month 12 in all 3 treatment groups. The results were numerically greater in the OGT 918 group, and significant only in the OGT 918 group at Month 6. Mean percent change in ACE showed a significant increase in the OGT 918 group at Month 6, and non-significant decreases in the Cerezyme and Combination groups. ACE was not analyzed at Month 12.

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 scanning, pulmonary pressure assessment by echocardiography, and QoL assessments up to Month 6. The results showed essentially no change in skeletal assessments (bone density) by DEXA scanning, and no notable changes in pulmonary pressure up to Month 12 of treatment in any of the treatment groups. QoL assessments showed marginally significant differences in improvement in Mental Health

scores, significantly greater improvement in convenience scores, and marginally significant improvement in overall satisfaction scores in the OGT 918 group at Month 6.

In summary:

- 1) OGT 918 produced significant decreases in liver volume in treatment naïve patients (or patients who had not received ERT for at least 3 months) that plateau'd after 12 months of treatment. The decreases in liver volume were then maintained from Month 12 to Month 24. The 100 mg TID dose of OGT 918 produced numerically greater decreases in liver volume than did the 50 mg TID dose. In patients who had received ERT for a minimum of 2 years prior to study entry and had smaller Baseline liver volumes, OGT 918 produced no further significant mean decreases in liver volume. There was also no notable increase in liver volume after switching to OGT 918 monotherapy over the 6-12 months of treatment with OGT 918 (depending on treatment group assignment), and no significant differences in mean change in liver volumes between the OGT 918 group and the Cerezyme and Combination groups.
- 2) OGT 918 produced progressive, significant decreases in spleen volume up to 24 months of treatment with OGT 918 in treatment naïve patients. The 100 mg TID dose of OGT 918 produced numerically greater decreases in spleen volume than did the 50 mg TID dose. In patients who had received ERT for a minimum of 2 years prior to study entry and had smaller Baseline spleen volumes, OGT 918 produced no further significant mean decreases in spleen volume. There were, however, non-significant mean increases in spleen volume from Month 6 to Month 12 in the Cerezyme and Combination groups after switching to OGT 918 monotherapy at Month 6.
- 3) There were increases in mean hemoglobin in treatment naïve patients that reached significance only after 18 and 24 months of treatment with OGT 918, and were seen only in patients treated with the 100 mg TID dose of OGT 918. At Month 24 (in the 918-001X extension), the mean actual hemoglobin increased 0.91 g/dL, which is statistically significant, although the clinical importance of this result is unknown. On subgroup analysis, only patients with a Baseline hemoglobin <11.5 g/dL showed a significant increase in hemoglobin, and only at Months 18 and 24. In patients who had received ERT for a minimum of 2 years prior to study entry and had higher Baseline hemoglobin values, there were non-significant, small decreases in hemoglobin in all 3 treatment groups at Month 6 and Month 12. Subgroup analysis could not be performed due to the small number of patients with hemoglobin <11.5 g/dL at Baseline in any treatment group.

The hemoglobin results in the treatment naïve patients are particularly notable when compared to the results seen in the initial studies with ERT. Patients in the ERT studies showed increases in hemoglobin, often with exponential increases, and often to normal levels, after 3-9 months of treatment with ERT. While the mechanism for the relatively poor hemoglobin response seen with OGT 918 is not completely understood, animal studies and studies in HIV positive patients with OGT

918 have suggested there may be a toxic effect of OGT 918 on the bone marrow, and particularly on red blood cells, that may have a counter productive effect on hemoglobin with chronic OGT 918 administration.

- 4) There were increases in mean platelet counts in treatment naïve patients that reached significance only after 18 and 24 months of treatment with OGT 918, and were seen only in patients treated with the 100 mg TID dose of OGT 918. Subgroup analysis by Baseline Platelet count could only be performed in the 918-003 study, with no notable differences between the subgroups at Month 6 and Month 12. In patients who had received ERT for a minimum of 2 years prior to study entry and had higher Baseline platelet values, the results were remarkable for a decrease in platelet counts when patients were switched to OGT 918 monotherapy. From Baseline to Month 6, the OGT 918 group showed a non-significant mean decrease in platelet count that showed a further non-significant decrease at Month 12. The Cerezyme and Combination groups showed non-significant increases in mean platelet count at Month 6, and both groups showed non-significant decreases in platelets at Month 12 after switching to OGT 918 monotherapy at Month 6. On subgroup analysis, these results were most notable in the subgroup of patients with Baseline platelet values $\geq 150 \times 10^9/L$. In this subgroup of patients, all 3 treatment groups had decreases in platelet counts after switching to OGT 918 monotherapy, with a significant decrease in mean platelet count seen in the OGT 918 group at Month 12.
- 5) The results for the biochemical markers of Gaucher disease measured in these studies are consistent with the proposed mechanism of action for OGT 918, that is, the decreased production of glycolipids. As with the clinical markers of Gaucher disease above (liver and spleen volumes, and hemoglobin and platelet counts), the biochemical markers more consistently decreased in treatment naïve patients, as opposed to the results seen in patients who had received ERT for a minimum of 2 years and presumably had lower burdens of glucocerebroside on entry into the study. In particular, in the patients who had received ERT for a minimum of 2 years, switching to OGT 918 monotherapy resulted in increases in all the biochemical markers in all 3 treatment groups.
- 6) Other disease assessments were not standardized across treatment centers in any of the studies. However, there was no evidence of progression to, or development of pulmonary hypertension in any patient during any of the studies. Skeletal assessments also did not show any meaningful differences in bone density up to 24 months of treatment with OGT 918; however, this is not unexpected as bone changes are expected to be produced slowly. In the follow-up to the initial ERT studies, improvements in skeletal assessments were noted after about 42 months of ERT, which suggests that further skeletal assessments should be evaluated after 3-5 years of treatment with OGT 918. Bone marrow assessments by QCSI were only performed in 2 patients, so no conclusions will be drawn. QoL assessments were performed at 1 center in Study 918-003 (n=10), and in Study 918-004 at Month 6 only. In Study 918-003, QoL results showed a significant increase in the improvement in energy scores only. In the 918-004 study, QoL assessments showed marginally significant

differences in improvement in Mental Health scores, significantly greater improvement in convenience scores, and marginally significant improvement in overall satisfaction scores in the OGT 918 group at Month 6.

Therefore, in treatment naïve patients, OGT 918 was found to produce beneficial effects on liver and spleen volumes. 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, and it is recommended that follow-up after 3-5 years of treatment be performed.

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, in 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. 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 Baseline liver and spleen volumes, and higher hemoglobin and platelet counts 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.

C. Safety

In the OGT 918 Gaucher disease type 1 clinical program, a total of 82 patients were enrolled: 80 patients were exposed to OGT 918, and 2 patients were exposed to Cerezyme alone without any OGT 918 exposure. Adverse Events were analyzed by pooling all the patients exposed to OGT 918 in the Combined Safety Dataset and by a detailed analysis of the individual studies. The results for all these safety analyses were similar. Additional safety information was also submitted from studies of OGT 918 in the treatment of HIV-positive patients and Fabry disease patients. In addition, a Consultation was requested by this Reviewer from the Division of Neuropharmacological Drug Products (DNBP) to assess the neurologic safety findings, including abnormal EDX test results, paresthesias, numbness, and tremors noted in the clinical studies. The results are summarized as follows.

All 80 patients reported at least one AE during the treatment period. The most common AEs (occurring in $\geq 5\%$ of patients) are listed in the following table

Table 18: Combined Data Set Incidence of Most Common AEs ($>5\%$ of Patients)

Exposed Patients, n =		80
Body System	WHO AE Term	n (%)
Musculoskeletal	Bone Pain	6 (8)
	Pain Neck/Shoulder	5 (6)
	Cramps	4 (5)
Neurological	Headache	29 (36)
	Tremor	23 (29)
	Dizziness	13 (16)
	Cramps Legs	8 (10)
	Paresthesia	6 (8)
Gastrointestinal	Diarrhea	72 (90)
	Flatulence	36 (45)
	Abdominal Pain	35 (44)
	Nausea	12 (15)
	Constipation	11 (14)
	Vomiting	9 (11)
Metabolic and Nutritional	Weight Decrease	52 (65)
	Weight Increase	4 (5)
Respiratory	Rhinitis	7 (9)
	Upper Respiratory Tract Infection	7 (9)
Platelet, Bleeding and Clotting	Thrombocytopenia	7 (9)
	Purpura	4 (5)
Body as a Whole	Influenza-like Symptoms	24 (30)
	Fatigue	9 (11)
	Pain	7 (9)
	Chest Pain	6 (8)
	Fever	6 (8)
	Leg Pain	6 (8)
	Weakness Generalized	6 (8)
	Back Pain	5 (6)
Pain Trauma Activated	4 (5)	

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. The incidence of diarrhea was noted to decrease over the course of the study, concurrent with an increase in the use of anti-diarrheal and other GI medications, most commonly loperamide. The incidence of weight loss was noted to increase over the course of the study. In the controlled study (918-004), diarrhea, other GI complaints, and weight loss were much less common in the Cerezyme group than in the OGT 918 and Combination groups. After cross-over to OGT 918 treatment, however, the Cerezyme group had a similar incidence of these complaints as the Cerezyme and Combination groups. Although complaints of diarrhea and weight loss were common, 6 patients (8%) and 1 patient (1%), respectively, in the Combined Safety Dataset listed these terms as a reason for discontinuing study participation.

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 usually began within the first month of OGT 918 use, and in many patients resolved between 1 to 3 months while treatment continued. Several patients had pre-existing tremor that seemed to be exacerbated by OGT 918. The severity of tremor was also affected by changes in dose. In all patients except one (for whom follow-up was not available) tremor resolved, usually within days of withdrawal of OGT 918. Three (3) patients listed tremor as a reason for discontinuing study participation.

EDX testing was added to the protocols after neurologic complaints were first noted in the initial Gaucher disease study (918-001), and 32% of patients in the Combined Safety Dataset who underwent EDX testing were noted to have abnormal EDX test results, either during or after study drug treatment. 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 patients 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. Finally, the proposed trade name Zavesca was noted to be unsuitable per DMETS consultation, due to its similarity to other commercially available look-alike and sound-alike drugs, leading to the potential for medication errors.

In summary:

1. OGT 918 use in Gaucher disease type 1 patients is associated with mild tremor in about 30% of patients. The tremor appears to be reversible after short-term exposure to the drug.
2. Despite the sponsor's conclusion that the neuropathic findings could be explained by concomitant medical conditions, it is the opinion of this Reviewer and of the DNDP Medical Consultant that treatment of Gaucher disease type 1 patients with OGT 918 is associated with a clear signal of neurotoxicity. OGT 918 may not necessarily have been the exclusive cause of neuropathy in all of the affected patients; however, OGT 918 may have contributed to the neuropathic findings in susceptible patients, and there is sufficient evidence of a neuropathic signal in these data to require further investigations. 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 standardized approach to determining the underlying cause of the neuropathy, such as laboratory testing. 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. In addition, animal studies were limited, with no further testing performed to delineate the mechanism of OGT 918-associated neurotoxicity. It is possible that the neurologic AEs seen with the use of OGT 918 in Gaucher disease type 1 patients are due to the mechanism of action of the drug, that is, due to the GSL depletion or ceramide toxicity associated with OGT 918 use. ζ

Similar concerns are also raised for the reports of memory loss seen in 6 patients exposed to OGT 918. Although further review and additional information is expected, given the lack of baseline information and the small safety database, further neuropsychologic investigations will likely be recommended.

3. Weight loss was a common finding associated with the use of OGT 918. This is of particular concern for its potential to adversely affect growth and development should there be plans to study this compound in pediatric patients, especially as delayed growth and sexual maturation are common findings in pediatric Gaucher disease type 1 patients.
4. Male reproductive toxicities, including effects on sperm and the male reproductive organs were noted in animals. These findings have not been evaluated for reversibility, either in humans or animals.

D. Dosing

OGT 918 is being proposed at a starting dose of 100 mg TID. The dose may be adjusted, from 100 mg qDay to 200 mg TID depending on side-effects and clinical response.

E. Special Populations

Fifty-seven (57%) of patients enrolled in the clinical program were female, and there were no significant differences or trends noted for safety or efficacy by gender. Gaucher disease type 1 has a much higher prevalence in the Ashkenazi Jewish population than in the general population, and not unexpectedly, 77% of patients enrolled in the clinical program were Ashkenazi Jews. Due to the small numbers of patients of other races enrolled in the clinical program, no subgroup analysis was performed by race. However, analysis by genotype of the glucocerebrosidase enzymatic defects, which not unexpectedly noted a high prevalence of the N370S defect (which is more common in the Ashkenazi Jewish population), did not find differences in safety or efficacy by enzyme genotype. OGT 918 was evaluated in Gaucher disease type 1 patients from 18 years to 69 years of age. A subgroup analysis by age >30 years vs age 18-30 years did not reveal any differences in safety or efficacy by age. An analysis by BMI demonstrated a significantly worse hemoglobin response in normal/underweight patients vs overweight/obese patients exposed to Combination therapy. There were no other differences in treatment response associated with by BMI.

OGT 918 was not evaluated in pediatric Gaucher disease type 1 patients <18 years of age, nor in geriatric patients >69 years of age.

Clinical trials submitted to the NDA have been performed in patients with compromised renal function (in Fabry disease patients), and adjustment of the dose for moderate to severe renal impairment (creatinine clearance 20-50) has been delineated. In addition, studies in patients with mild hepatic impairment have been performed, and no dosage adjustment is required. However, OGT 918 use in patients with moderate to severe hepatic impairment has not been evaluated.

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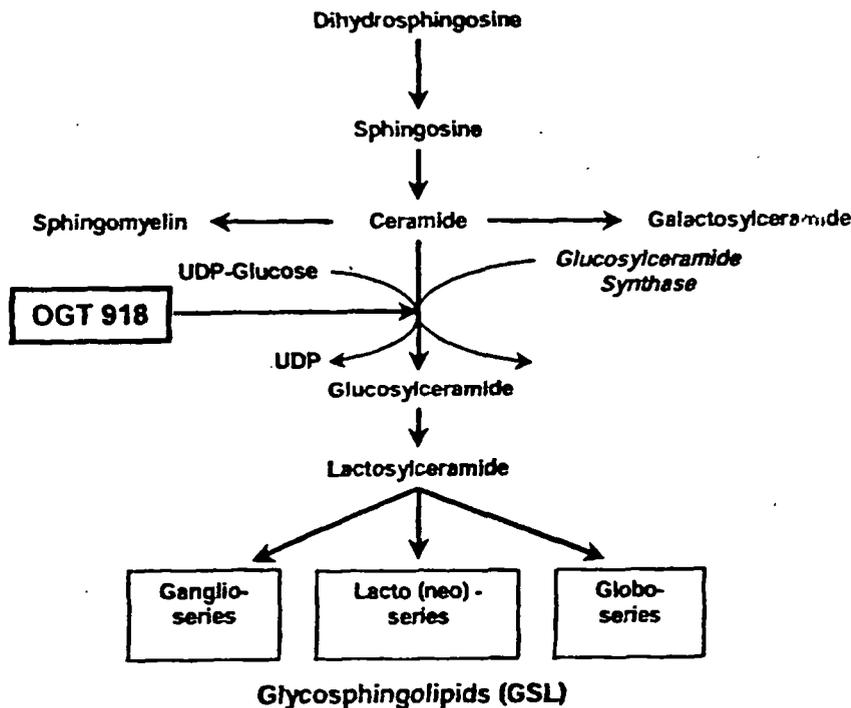
I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication, Dose, Regimens, Age Groups

OGT 918 has been submitted under NDA 21-348 under the proposed trade name of Zavesca (formerly Vevesca). OGT 918 is being proposed for use in patients with Gaucher disease type 1.

OGT 918 (miglustat), N-alkylated imino sugar, is a synthetic analogue of D-glucose. OGT 918 functions as a competitive and reversible inhibitor of glucosylceramide synthase (aka glucosyltransferase). Glucosylceramide synthase is the initial enzyme in a series of reactions responsible for the generation of glycosphingolipids. Glucosylceramide synthase catalyzes the transfer of glucose from an UDP-glucose donor to a ceramide acceptor. The product of the reaction, glucosylceramide, is the first intermediate in the synthesis of the glycosphingolipids. This biochemical pathway is summarized in the following figure: [Figure 1 electronically scanned and reproduced from: IND # — Oxford Glycosciences (UK) Ltd., Volume 1, Item 5 Investigators Brochure, page 36-37. Correspondence dated 01-Mar-2002]

Figure 1: Glucosylceramide Synthase Biochemical Pathway



OGT 918 is being proposed at a dose of 100 mg TID for chronic administration. OGT 918 has not been studied in pediatric patients, nor in patients over 65 years of age.

B. Background and Rationale

In order to present the rationale behind treatment with OGT 918 in Gaucher disease type 1, an overview of the lysosomal storage diseases and Gaucher disease will first be briefly discussed. [Information in this section from: Beutler et al, "The Metabolic & Molecular Bases of Inherited Disease"¹, and Grabowski et al, "Harrison's Principles of Internal Medicine"²]

1) Lysosomal Storage Diseases

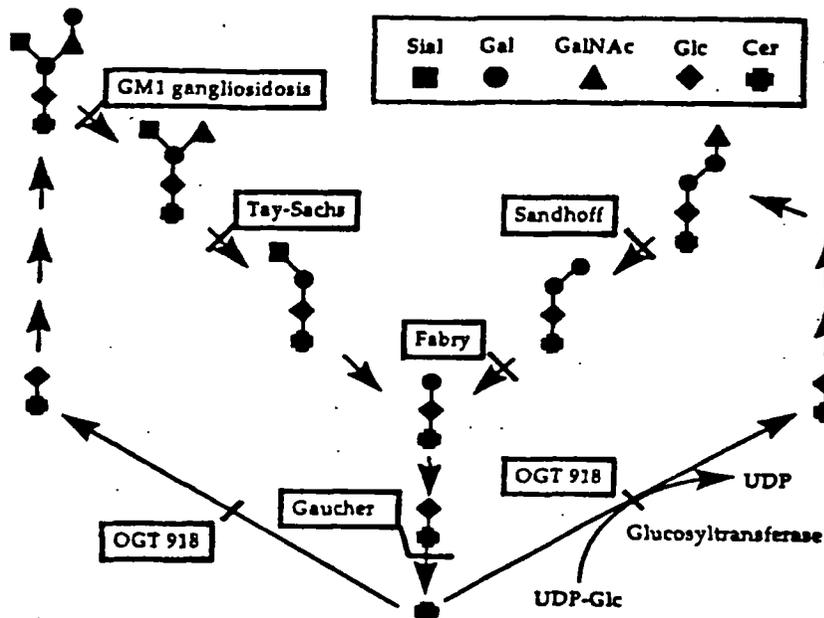
The lysosomal storage diseases are a group of biochemically related disorders in which the enzymes required for the catabolism of glycosphingolipids (GSLs) are defective. GSLs are ubiquitous components of eukaryotic cells and comprise a lipid component, ceramide, and a glycan that is covalently attached to the lipid. The degradation of the carbohydrate portion of the glycolipids is mediated by lysosomal enzymes called glycosidases. Glycosidases act in a sequential manner to remove one sugar at a time from an exposed terminal, and the action of each glycosidase is required to prepare the glycolipid for the next enzyme in the degradation pathway. A mutation in one of the glycosidases in the pathway can result in the accumulation of its glycolipid 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. Some examples of lysosomal storage diseases are Tay-Sachs, Fabry, and Gaucher diseases. The glycolipid biosynthetic and catabolic pathway is shown schematically in following figure [Figure 2 scanned and electronically reproduced from: IND # 60,197 N007 YY, Oxford Glycosciences Annual Report, page 8, dated 12-Sept-2001].

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¹ Beutler, Ernest and Grabowski, Gregory A. "Gaucher Disease." The Metabolic & Molecular Bases of Inherited Disease. 2001, Vol. III, 3635-3668.

² Grabowski, Gregory A. Lysosomal Storage Diseases. (2001). In *Harrison's Online*. [Online]. Harrison's Principles of Internal Medicine. (15th Edition, The McGraw-Hill Companies). <www.harrisonsonline.com> ["lysosomal storage diseases"] [01-Feb-2002].

Figure 2: Glycolipid Biosynthetic and Catabolic Pathway



2) Gaucher Disease

Gaucher disease, an autosomal recessive inherited disorder, is the most common of the lysosomal storage diseases. Gaucher disease occurs most often in Ashkenazi Jews with an incidence of around 1 in 800 births. In the overall population, an incidence of around 1 in 40,000 is estimated.

Gaucher disease is a functional deficiency of glycosphingolipidase (or beta-glycosidase). Glycosphingolipidase mediates the degradation of glycosphingolipid (glycosylceramide) to ceramide and a glycan, which is the penultimate step in the degradation of GSLs. The clinical manifestations of Gaucher disease result from glycosphingolipid accumulation in macrophages. These glycosphingolipid-engorged macrophages (known as Gaucher cells) then cause enlargement and dysfunction of the liver, spleen and bone. Splenomegaly, hepatomegaly, anemia and thrombocytopenia (from splenic enlargement and bone marrow replacement), osteoporosis, bone marrow infiltration, and bone deformities, fractures, painful crises and necrosis are common manifestations of the disease. Cachexia, wasting, and growth retardation can be seen in children. There are three variants of Gaucher disease, types 1, 2, and 3, the most common type being type 1 (non-neuropathic form). Involvement of the central nervous system occurs in the more severe forms (type 2 and type 3) but not in type 1. There is considerable variation in the clinical presentation of Gaucher disease type 1, with presentation ranging from severely affected individuals who often present as children, to asymptomatic individuals who may never come to medical attention or who are identified on screening after an affected family member has been diagnosed.

3) Rationale

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). The aim of treatment with OGT 918 in Gaucher disease type 1 is therefore, to promote a balance between glycolipid synthesis and degradation, thereby reducing glucocerebrosidase storage and its associated pathology.

C. State of Armamentarium for Indication

Therapy for Gaucher disease type 1 in the past consisted mainly of symptomatic and supportive care, including splenectomy, repair of fractured bones, supportive care for painful crises, and treatment of intercurrent infections. Bone marrow transplantation has also been tried with some success, but its obvious limitations, including availability of suitable donors and the risks of bone marrow transplantation, limited its use.

Since 1991, enzyme replacement therapy (ERT) [with alglucerase (Ceredase) or imiglucerase (Cerezyme)] has been shown to be successful in treating the signs and symptoms of Gaucher disease^{3,4}. The enzyme is administered on a regular intravenous dosing schedule (typically every 2 weeks) and results in a decrease in the size of the liver and spleen, and improvements in anemia and thrombocytopenia in most patients. In clinical trials, improvements in anemia were typically seen within 3 months, and improvements in platelet counts, and liver and spleen enlargement within 6 to 9 months. The clinical responses seen with Ceredase and Cerezyme are briefly summarized in the following table⁴ [n = 15; age range 12-69; 4 children, 11 adults]

Table 19: Ceredase and Cerezyme Changes in Disease Markers from Baseline

	Baseline	Change at 6 Months	Change at 9 Months
Liver Volume	(X normal volume)	(% decrease)	(% decrease)
Ceredase	1.83	-11.4	-16.4
Cerezyme	1.65	-13.4	-21.4
Spleen Volume	(X normal volume)	(% decrease)	(% decrease)
Ceredase	23.7	-32.1	-42.2
Cerezyme	19.3	-37.3	-47.1
Hemoglobin (g/L)	(g/L)	(g/L)	(g/L)
Ceredase	107.7	+16.0	+22.8
Cerezyme	107.1	+18.2	+25.4
Platelet Count (X10⁹/L)	(X10 ⁹ /L)	(X10 ⁹ /L)	(X10 ⁹ /L)
Ceredase	70.9	+33.5	+53.2
Cerezyme	72.1	+21.5	+43.5

*for mean % decrease from Baseline

³ Barton NW, Brady RO, Dambrosia JM, Di Bisceglie AM, Doppelt SH, Hill SC, Mankin HJ, Murray GJ, Parker RI, Argoff CE, Grewal RP, Yu KT, and Collaborators. Replacement therapy for inherited enzyme deficiency - macrophage-targeted glucocerebrosidase for Gaucher disease. N Engl J Med 1991;324:1464-1470.

⁴ Grabowski GA, Barton NW, Pastores G, Dambrosia JM, Banerjee TK, McKee MA, Parker C, Schiffmann R, Hill SC, Brady RO. Enzyme therapy in type 1 Gaucher disease: comparative efficacy of mannose-terminated glucocerebrosidase from natural and recombinant sources. Ann Intern Med 1995;122:33-39.

In longer term follow-up studies (approximately 42 months) with ERT, improvements in bone marrow replacement and bone disease were seen⁵. In children, improvements in growth have also been noted⁶. The side effects of ERT⁷ are most commonly hypersensitivity reactions, such as pruritus, flushing, and urticaria/angioedema, which are seen in about 4% of patients; however, anaphylactoid reactions occur in <1% of the total patient population. Adverse Events due to the route of administration are also seen in about 5% of patients. The cost of ERT has also been noted as a significant factor in the treatment of patients, with the cost of ERT treatment for a patient in the United States ranging from \$100,000 to \$400,000 per year.

Gene therapy is currently under investigation; however, this therapy is still in the early stages of development.

D. Other Relevant Clinical Experience with OGT 918

OGT 918 was initially developed by G.D. Searle under IND # — as a potential treatment for AIDS. Clinical studies in HIV positive patients were carried out with both OGT 918 and its p. — 1 (which is rapidly converted *in vivo* to OGT 918) [Studies of OGT 924 were conducted under IND # — 1. Trials of both compounds were subsequently terminated during the Phase II stage of development due to the difficulty in achieving the high plasma concentrations required to inhibit HIV replication. The tolerability profile of OGT 918 showed gastrointestinal disorders to be the primary toxicity. In clinical studies, doses of OGT 918 up to 1 gram TID were administered for up to 24 weeks with the major AEs noted being diarrhea (86% of patients), flatulence (51%), and nausea (40%) [Please see Safety section for a more complete listing of the Adverse Events].

OGT 918 is currently being investigated in an ongoing study in Gaucher disease type 1 under IND #60,197. This study plans to enroll 14 adult patients with Gaucher disease type 1, in 3 United States centers for 12 months (enrollment as of 21-Mar-2002, 9 patients at 1 center). OGT 918 also has an open IND — for the treatment of Fabry disease (initial study recently completed), and under IND — for OGT 918 in the treatment of Niemann-Pick type C disease (initial protocol submitted Feb-2002). Partial safety data from the initial Fabry disease trial is listed in the safety section. Please refer to these submissions and associated reviews for additional information.

⁵ Rosenthal DI, Doppelt, SH, Mankin HJ, Dambrosia JM, Xavier RJ, McKusick KA, Rosen BR, Baker J, Niklason LT, Hill SC, Miller SPF, Brady RO, Barton NW, and Collaborators. Enzyme replacement therapy for Gaucher disease: skeletal responses to macrophage-targeted glucocerebrosidase. *Pediatrics* 1995;96:629-637.

⁶ Kaplan P, Mazur A, Manor O, Charrow J, Esplin J, Gribble J, Wappner RS, Wisch JS, Weinreb NJ. Acceleration of retarded growth in children with Gaucher disease after treatment with alglucerase. *J Pediatr* 1996;129:149-153.

⁷ Cerezyme. (1999). In *PDR Electronic Library*. [Online]. Physicians' Desk Reference, 2002. <www.pdrel.com> ["Cerezyme"] [07-Feb-2002]

E. Important Milestones in Product Development

NDA 21-348 is covered under Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, and OGT 918 was designated an Orphan for Gaucher Disease on 29-May-1998. This NDA received Fast Track Designation on 15-Jun-2000. The initial NDA was submitted 28-Mar-2001, with the final piece of the submission received on 21-Aug-2001. Seven protocol amendments were received for the submitted protocols, with the significant changes, by protocol, noted as follows:

1) Protocol 918-001 and 918-001X

There were 3 amendments to the protocol(s):

- Amendment 1 (dated 17-Apr-1998) described PK sampling changes applicable to Centers 1 and 2 only
- Amendment 2 (dated 27-Jan-1999) described additional assessments and alteration of existing assessments to extend research on the mechanism of action of OGT 918 in Gaucher disease and to further elucidate its tolerability profile
- Amendment 3 (dated 08-May-2000) described the addition of EMG/NCV assessments to be carried out in next study visit in 918-001X after concerns over possible neurological effects of OGT 918 were noted

2) Protocol 918-003 and 918-003X

There were 2 amendments to the protocol(s):

- Amendment 1 (dated 14-Dec-1999) increased the recruitment of patients from 12 to 18, and changed the Quality of Life (QoL) questionnaire (eliminated the Investigator questionnaire and changed the patient questionnaire to validated the SF-36 from non-validated assessments)
- Amendment 2 (dated 20-Apr-2000) described option to enter extension study (918-003X), and to include additional tests to assess possible AEs including EMG/NCV at Month 6, quantitative skeletal assessment, and additional lab tests HbA1C, iron, IBC, and ferritin at Day 1 and Months 1, 3, 6.

3) Protocol 918-004 and 918-004X

There were 2 amendments to the protocol(s):

- Amendment 1 (dated 29-Feb-2000) added percentage change in liver organ volume as the primary efficacy endpoint, based on the results of the previous studies, and an EMG for all patients at Month 1 due to reports of tremor and peripheral neuropathy occurring in other OGT 918 studies. Alteration in the PK sampling to the first 6 patients at Month 1, alterations to the health survey content of the QoL questionnaires, and amendments to the statistical analysis section were made. Amendment 1 was written and finalized 2 days after the first patient commenced dosing with OGT 918 and no efficacy assessments had been carried out.
- Amendment 2 (dated 10-May-2000) allowed patients to receive OGT 918 monotherapy or OGT 918 with Cerezyme as combination therapy regardless of their previous dose regimen in the extended treatment period of the study (918-004X).

The IND Annual report with updated safety information was received on 10-Sept-2001 and is incorporated into the safety review of this NDA. A second update, the 120-day safety update for this NDA was received Jan-2002, and the IND annual report, which included an updated Investigator's Brochure, was received on 28-Feb-2002. These (predominantly safety) updates are incorporated into this review.

A Marketing Authorisation Application (MAA) for OGT 918 100 mg capsules for the oral treatment of type 1 Gaucher disease has also been submitted to the European Agency for the Evaluation of Medicinal Products (EMEA) on 29-Jun-2001.

F. Important Issues with Pharmacologically Related Agents

Two main classes of GSL biosynthesis inhibitors have been described to date, both of which inhibit ceramide-specific glucosyltransferase (glucosylceramide synthase or glucosyltransferase). The first class of inhibitors, the ceramide analogues of which the prototypic compound is PDMP⁸, has undergone pre-clinical evaluation. PDMP is a reversible inhibitor of ceramide-specific glucosyltransferase. The PDMP analogues are potent, relatively cytotoxic compounds, and treatment with PDMP analogues can result in the accumulation of free ceramide. Ceramide has been shown to trigger apoptosis, its concentration also plays a regulatory role as a second messenger, and it has been shown to have neurotoxic effects. Pre-clinical studies with OGT 918 did not demonstrate ceramide accumulation; however, it is not known if this has been evaluated in humans. It does not appear that the PDMP analogues have been evaluated in clinical trials.

The second class of glucosyltransferase inhibitors are the N-alkylated imino sugars, of which the prototype is OGT 918. OGT 918 is the glucose analogue in this class, and a galactose analogue (NB-DGJ) has also been synthesized and undergone pre-clinical evaluation⁸. Neither OGT 918 nor NB-DGJ inhibit the ceramide galactosyltransferase responsible for the synthesis of galactosylceramide, which are critical components of myelin. It does not appear that NB-DGJ has undergone clinical evaluation.

Other pre-clinical and clinical studies with OGT 918 have shown that OGT 918 may cause neurotoxicity due to its inhibition of GSL synthesis and the depletion of glycolipid in the nervous system⁹. GSLs are found in the membranes of all eukaryotic cells; however, their exact role in cell function is not known. Transgenic mice which completely lack higher gangliosides, have a relatively mild neurological phenotype in adult life; however, they do develop axonal degeneration and demyelination in the central and peripheral nervous systems. In man, antibodies to gangliosides are associated with peripheral neuropathy, and ganglioside may be involved in myelin-associated glycoprotein signaling between axons and myelin-forming glia.

⁸ Lachmann RH, Platt FM. Substrate reduction therapy for glycosphingolipid storage disorders. *Exp Opin Invest Drugs* 2001;10(3):455-466.

⁹ Platt FM, Butters TD. Substrate deprivation: a new therapeutic approach for the glycosphingolipid lysosomal storage diseases. *Expert Reviews in Molecular Medicine* 1-Feb-2000, <http://www-ermm.cbcu.cam.ac.uk>

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

Please refer to the Chemistry, Animal Pharmacology and Toxicology, Biopharmaceutics, Statistical, and Proposed Proprietary Name reviews for this NDA.

A. Animal Pharmacology

Briefly, per the sponsor's preclinical data:

OGT 918 is a competitive and reversible inhibitor of the enzymes alpha-glycosidase I and ceramide-specific glycosyltransferase. In intact cells, OGT 918 is more active as a glycosyltransferase inhibitor than an alpha-glucosidase I inhibitor due to differential intracellular access to the enzymes, and the inhibition of glycosyltransferase by OGT 918 may be achieved at much lower concentrations than those required for inhibition of alpha-glucosidase I. In mice, treatment with OGT 918 resulted in substantially reduced cell surface gangliosides in livers and spleens, indicating depletion of glycosphingolipids.

In animal ADME studies, OGT 918 was found to be rapidly absorbed. Linear pharmacokinetics were seen in single and multiple dosing studies. T_{max} in the monkey was approximately 1-2 hours. Distribution in mouse and rats showed extensive distribution to one or more tissues, but in the dog and monkey, the volume of distribution indicated that OGT 918 was not extensively distributed into many tissues. It is estimated, based on preclinical evidence, that OGT 918 crosses the blood-brain barrier with approximately 10% of plasma concentrations apparent in cerebrospinal fluid. Greater than 80% of OGT 918 was excreted unchanged in the urine, and OGT 918 was not found to be metabolized to any extent in mice, rats, dogs and monkeys. Adverse effects seen with OGT 918 in animals were most commonly gastrointestinal. One proposed mechanism for the effects on the GI tract is the activity of OGT 918 as an inhibitor of disaccharidases, which interferes with carbohydrate digestion. This may lead to an alteration in intestinal function, leading to osmotic diarrhea, cecal distention and increased calcium absorption and excretion.

In the review of the preclinical data, the Animal Pharmacology and Toxicology Reviewer has noted the following safety concerns [see Colerangle, John Ph.D., Animal Pharmacology and Toxicology Review of NDA #21-348 for more detail]:

1) Signals Suggestive of Neurotoxicity

Signals suggestive of neurotoxicity in animals were noted, and are summarized in the following table

Table 20: Preclinical Neurotoxicity Findings

Species	Dose (mg/kg/d)*	Duration	Clinical Signs or Histopathology	Multiple of Clinical (100 mg/d) Dose
Dog	85, 165, 495, 825	2 weeks	Ataxia, diminished/absent pupillary, palpebral or patellar reflexes at 495 or 825 mg/kg	495 = 160X 825 = 266X Based on mg/m ²
Dog	35, 70, 105, 140	4 weeks	Tremor at 105 mg/kg	105 = 34X
Monkey	750, 2000	1 year	Brain: vascular mineralization, mineralization and necrosis of white matter in males Spinal cord: vascular mineralization No clinical signs suggestive of neurotoxicity in males	750 = 4X 2000 = 6.5X (necrosis) Based on AUC

*Total dose divided into 3 equal doses/day

2) Diarrhea and Weight Loss Issues

The prodrug (OGT 924) did not cause diarrhea, but decreased body weight gain. The active metabolite (OGT 918) caused diarrhea and decreased body weight gain (>10%) in chronic monkey and rat studies. Diarrhea was frequent during the early dosing period, but subsided over time. Decreased food consumption appeared to explain the decreased body weight gain.

3) Male Reproductive Toxicity

Preclinical reproductive data show possible effects on male reproduction in the rat. In dose-ranging studies, there were effects on sperm morphology at all dose levels, namely, there were increases in the proportion of abnormal sperm, principally headless sperm, and sperm with achromosomal abnormalities. The abnormalities were not dose-dependent. Sperm motility was also affected. There were no treatment-related histological changes in the testes or the epididymis. Similarly, other male-reproductive phenomena were observed in long-term treatments. The sponsor claims that these findings are reversible. These findings for OGT 918 and the prodrug OGT 924 (SC 49483) are summarized in the following tables

Table 21: OGT 918 Preclinical Reproductive Toxicity

Male Reproductive Toxicity	Dose	Exposure (mg/M ²)	Human Exposure Multiple*
Rat (: 1, 3-month toxicity, male fertility)			
Motility, aberrant morphology (headless, reduced hook)	20 mg/kg/day	120	<1
Testes, epididymis, prostate weight Spermatogenesis/hypospermia Seminal vesicle/prostate atrophy Fertility index (40%)	200 mg/kg/day	600	<3X

*Assumes therapeutic dose 100 mg TID = 300 mg/day = 185 mg/M²

The effects on spermatogenesis/fertility appear to reverse following a 13-week recovery period. It is unknown if the histopathology is reversible since this was not examined.

Table 22: OGT 924 (Prodrug) Preclinical Reproductive Toxicity

Species	Sperm Assessment	Dose	Exposure (mg/M ²)	Human Exposure Multiple
Rat	Motility, concentration, aberrant morphology (headless, reduced hook)	300 mg/kg/day X 6 months	1800	<10X
Monkey	Concentration	750 mg/kg/day X 12 months	9000	<50X

In addition, cardiac, renal, lens (cataracts), bone marrow, lymphocyte, pancreatic, liver, and hematologic (RBC) toxicities were also noted. Bone marrow and RBC toxicities are especially noted, as these findings were also seen in studies in HIV-positive patients (see Other Relevant Clinical Experience with OGT 918 section above). In rats and monkeys, bone marrow effects, including bone marrow hypocellularity with fat replacement and necrosis were seen at 9-30X human equivalent dose (based on AUC). In the rat, dog, and monkey, hematologic effects, including decreases in RBC, hemoglobin and hematocrit, were seen at 4-10X human equivalent dose (based on AUC).

B. Human Pharmacokinetics and Pharmacodynamics

Please refer to the Biopharmaceutics review, by Chung, Sang, Ph.D, DMEDP, CDER.

Briefly, the sponsor's findings are:

In Gaucher disease patients, OGT 918 is rapidly absorbed following oral administration with a T_{max} of 2 to 2.5 hours. OGT 918 has a biexponential decline in concentration, with a small, shallow distribution phase followed by a longer elimination phase. In single-dosing, T_{1/2} is 6 to 7 hours. On multiple dosing, the degree of accumulation at steady state following TID dosing is approximately 2 to 2.5-fold compared to a single-dose. AUC at steady state with multiple-dosing is comparable to AUC following a single dose, indicating linear pharmacokinetics. In healthy volunteers, food significantly reduces peak exposure and time to peak concentration of OGT 918, but did not significantly affect the extent of systemic exposure.

OGT 918 is excreted by renal and hepatic elimination, and biliary excretion. There is no evidence of protein binding. An *in vitro* study in human liver microsomes has shown that OGT 918 does not undergo metabolism by cytochrome P450 enzymes. Following single and repeat oral doses of OGT 918 in Fabry patients, the extent of systemic exposure to OGT 918 is approximately 2-fold higher than that in patients with Gaucher disease, reflecting the renal impairment seen in Fabry disease patients.

C. Statistical Review

Please refer to the Statistical Review and Evaluation, by Pian, Lee-Ping Ph.D., Office of Biostatistics, dated 15-Apr-2002.

Briefly, the Statistical Reviewer performed a detailed analysis of the 6 clinical studies submitted to the NDA. In addition to the efficacy and safety findings reviewed in detail in the Efficacy and Safety sections of this review, the Statistical Reviewer also looked for

an association between clinical efficacy and the neurologic safety findings. The Reviewer's findings were notable only for a finding of a significantly better liver volume reduction in the Combination treatment group vs the Cerezyme group in the 918-004 study. There was no obvious association between neurologic AEs and efficacy in any treatment group.

D. Review of the Proposed Proprietary Name

Please refer to the Consultation performed by Fan, Jennifer Pharm.D., Office of Drug Safety, Division of Medication Errors and Technical Support, dated 01-Apr-2002.

The Office of Drug Safety, Division of Medication Errors and Technical Support (DMETS) performed a review of the proposed proprietary name Zavesca. Briefly, DMETS does not recommend the proprietary name Zavesca due to sound-alike and look-alike names that already exist in the U.S. marketplace leading to the potential for medication errors. However, it should be noted that the sponsor intends to distribute OGT 918.

Therefore, this Reviewer does not object to the proposed trade name under these circumstances.

III. Description of Clinical Data and Sources

A. Overall Data

There were 6 clinical studies submitted to the NDA from the Oxford Glycosciences Gaucher disease type 1 clinical program [not including PK studies]. Data were submitted to the NDA in a paper format, with SAS data sets submitted electronically. Relevant medical literature was referred to in the application, which was reviewed as appropriate. In addition, safety data from studies with OGT 918 in HIV positive patients, OGT 924 (prodrug) in HIV positive patients, and OGT 918 in Fabry disease were also submitted.

B. Tables Listing the Clinical Trials

There were 6 clinical studies of OGT 918 in the treatment of Gaucher disease type 1 submitted to the NDA. The Gaucher disease studies are briefly summarized in the following table:

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Table 23: OGT 918 Clinical Studies

Study	Description
918-001	Phase I/II non-comparative, open-label study in 28 adults with type 1 Gaucher disease who were either unable or unwilling to receive ERT. All patients received OGT at a starting dose of 100 mg TID, and could be increased to a maximum of 300 mg TID. Treatment was for 12 months. 22 patients completed the study.
918-001X	12-month extension to 918-001. 18 patients were entered after completion of 918-001. 14 patients completed a total of 24 months of study drug treatment.
918-003	Phase I/II non-comparative, open-label study in 18 adults with type 1 Gaucher disease who were either unable or unwilling to receive ERT. All patients received OGT 918 at a starting dose of 50 mg TID for a 6-month treatment period. This study was undertaken to allow comparison of safety and efficacy outcomes at the lower and higher doses of OGT 918. 17 patients completed the study.
918-003X	6-month extension to 918-003. 16 patients were entered after completion of 918-003. 13 patients completed a total of 12 months of study drug treatment.
918-004	Phase II open-label, active-comparator, randomized study in 36 adults with type 1 Gaucher disease who had received ERT for a minimum of 2 years. Patients were randomized to one of 3 treatment groups: <ul style="list-style-type: none">• OGT 918 alone;• Cerezyme alone;• OGT 918 + Cerezyme The starting dose of OGT 918 was 100 mg TID, and treatment was for 6 months. The study was designed to investigate whether OGT 918 could safely be coadministered with ERT. 33 patients completed the study.
918-004X	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. 29 patients entered the study and all 29 patients elected to receive OGT 918 alone. The starting dose was OGT 918 100 mg TID. 28 patients completed 6 months of the extension study.

C. Postmarketing Experience

OGT 918 is not an approved drug, and hence, there is no postmarketing experience with OGT 918.

D. Literature Review

Human experience with OGT 918 is contained in the review of the clinical trials conducted for this NDA. Other relevant published literature was reviewed as appropriate. Please refer to the Introduction and Background section of this review.

IV. Clinical Review Methods

A. How the Review was Conducted

All 6 clinical studies submitted to the NDA were reviewed individually in detail and provide the majority of safety and efficacy information on OGT 918 in Gaucher disease type 1 available for clinical review. In addition, the sponsor performed a pooled safety review of all 6 studies (the Combined Safety Data Set). The sponsor's efficacy and safety findings were confirmed or recalculated by this Reviewer using electronic data sets included with the submission.

B. Overview of Methods Used to Evaluate Data Quality and Integrity

No clinical site audits were completed during the NDA review. The majority of patients enrolled in the Gaucher disease type 1 clinical program were from 1 site in Israel, which was unable to be inspected during this time.

C. Were Trials Conducted in Accordance with Accepted Ethical Standards

The sponsor stated that "All OGS (Oxford Glycosciences) clinical studies performed in support of this application were conducted in accordance with Good Clinical Practice (GCP) for Trials of Medicinal Products and the ICH Guideline for GCP (CPMP/ICH/135/95), the ethical principles stated in the World Medical Association Declaration of Helsinki (revised editions Hong Kong, 1989 and South Africa, 1996), and the laws and regulations of the countries in which the research was conducted. The Fabry study, which was conducted in the USA, was also performed in compliance with applicable FDA GCP Regulations: 21 CFR Parts 50 (Protection of Human Subjects), 56 (Institutional Review Boards), 312 (Responsibilities of Sponsor and Investigators), and the Guidelines for the Monitoring of Clinical Investigations." The sponsor states further that "The HIV studies presented in item 8.6 were carried out by G.D. Searle as Sponsor. On review of the study protocols and study reports it would seem apparent that these studies were conducted in accordance with the appropriate regulations and guidance applicable at the time of the conduct of these studies." [Please refer to NDA 21-348, Oxford Glycosciences, Volume 2.1, Section 8.2.2, page 34, dated 03-Aug-2001.]

D. Evaluation of Financial Disclosure

A signed Form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) was submitted, which stated that the sponsor had not entered into any financial arrangement with any of the clinical investigators in the clinical studies. A signed Form 3455 (Disclosure: Financial Interests and Arrangements of Clinical Investigators) was also submitted for L _____ Financial disclosure included _____ payments for study participation in Studies 918-001 and 918-004 which "were considered necessary to support the Gaucher clinic at the Shaare Zedek Medical Center, as funding from _____ was either being withdrawn or was now considered inappropriate to accept". The sponsor further states that a financial and GCP audit was performed at the site, and that "OGS therefore considers that there is no bias of clinical study results as a result of these payments".

V. Integrated Review of Efficacy

A. Brief Statement of Conclusions

For the important clinical markers of Gaucher disease type 1, including liver and spleen volume, hemoglobin and platelet values, and bone disease:

In treatment naïve patients (or in patients who had not received ERT for at least 3 months), OGT 918 was found to produce beneficial effects on liver and spleen volumes. 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.

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, in 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. 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 Baseline liver and spleen volumes, and higher hemoglobin and platelet counts who had been receiving ERT. There was no evidence of an additional benefit seen with Combination treatment with OGT 918 and ERT compared to OGT 918 monotherapy.

B. General Approach to Review of the Efficacy of the Drug

As stated in Section V.A. (Clinical Review Methods, How the Review was Conducted), all 6 clinical studies submitted to the NDA were reviewed individually in detail and provide the majority of safety and efficacy information on OGT 918 in Gaucher disease type 1 available for clinical review. The sponsor's efficacy and safety findings were confirmed or recalculated by this Reviewer using electronic data sets included with the submission.

C. Detailed Review of Trials by Indication

The overall objectives of the clinical program for OGT 918 were to demonstrate: the efficacy of OGT 918 as an oral treatment for Gaucher disease type 1 by assessing organ volume and other markers of disease; and the safety and tolerability of OGT 918 in Gaucher disease type 1 patients. Studies 918-001, -001X, -003, -003X, -004, and -004X have been reviewed individually in detail, as follows.

1) Protocol 918-001

a) Study Design for Protocol 918-001

(1) Study Design

Protocol 918-001 "OGT 918-001: A phase I/II study of open-label OGT 918 in adult patients with Gaucher disease" was a non-comparative, multi-center, open-label study conducted at 4 international clinical sites. The study evaluated the efficacy and safety of OGT 918 at a dose of 100 mg TID for up to 12 months in 28 adult type I Gaucher disease patients who were unable or unwilling to be treated with Ceredase or Cerezyme.

(2) Study Objectives

The primary objective for the study was to evaluate OGT 918 as a treatment for Gaucher disease by assessing organ volume and other markers of the disease. Secondary objectives were to assess the tolerability and pharmacokinetic (PK) profile of OGT 918.

(3) Eligibility Criteria

(a) Inclusion Criteria

Patients were eligible for study participation if they:

- 1) Had type 1 Gaucher disease (confirmed by a glucocerebrosidase assay)
- 2) Were unable or unwilling to be treated with Ceredase or Cerezyme
- 3) Were 18 years of age or older at time of consent
- 4) Had a measurable organomegaly (liver or spleen)
- 5) Had an intact spleen and a hemoglobin concentration of <11.5 g/dL or a platelet count <100 X 10⁹/l or were splenectomized subjects who had hepatomegaly with liver weight >2.5% of their body weight

(b) Exclusion Criteria

Patients were ineligible for participation if they:

- 1) Were fertile subjects who did not agree to use adequate contraception throughout the study
- 2) Were pregnant or breast-feeding
- 3) Had received treatment with Ceredase or Cerezyme within 3 months of screening
- 4) Had a history of lactose intolerance
- 5) Were suffering from clinically significant diarrhea (more than 3 liquid stools per day for more than 7 days) without definable cause within 6 months of screening
- 6) Had a history of cataracts or a known increased risk of cataract formation
- 7) Were currently undergoing therapy with other investigational agents
- 8) Had an intercurrent medical condition that would render them unsuitable for study
- 9) Were known to have tested positive for HIV or Hepatitis B surface antigen
- 10) Were, in the opinion of the Investigator, thought to be unsuitable for the study

(4) Study Visits and Procedures

The study visits and procedures are summarized below and in the following table.

Table 24: 918-001 Study Visits and Procedures

Day	Screen	Treatment Period												Final	
		1	15	29	57	85	113	141	169	197	225	253	281		309
Month		1	2	3	4	5	6	7	8	9	10	11	12		
Procedure															
History	X														
Physical Examination	X		X	X			X			X			X	X	X
Vital Signs/Weight/ BSA/BMI	X		X	X			X			X			X	X	X
Height	X						X							X	
ECG	X		X				X							X	
Urine Pregnancy Test	X														
Urinalysis	X		X	X		X	X			X				X	
Biochemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK (Baseline/PK Profile)		X	X												
PK (Peak/Trough)			X	X	X			X							X
Chitotriosidase/ Hexosaminidase		X	X	X	X	X	X	X	X	X	X	X	X	X	X
G _{M1} /Oligosaccharides		X	X	X	X			X							X
Organ Volume	X							X							X
Glucosylceramide	X				X			X							X
Other Disease Assessments/ Body Composition	X														X
Proteome		X	X	X	X			X							X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
OGT 918 Dispensing		X	X	X	X	X	X	X	X	X	X	X	X	X	

(a) Screening Visit

All patients gave written informed consent before any study procedures or assessments were performed. At the Screening Visit, patients were assessed for their eligibility for the trial and underwent the following assessments:

- History
- Physical examination (including slit lamp exam)
- Vital signs
- Height
- Weight
- ECG
- Urine pregnancy test (females only)
- Urinalysis
- Biochemistry
- Hematology
- Organ Volume assessment (by MRI or CT scan)
- Other Disease Assessments (depending on patient's disease status and normal clinical practice at each center, may include skeletal response assessed by an MRI of the

femur, pelvis, lumbar spine or hips and DEXA of the femur and lumbar spine, and fat fraction by QCSI of the bone marrow in the lumbar spine)

- Concomitant Medications record

Eligible patients were entered into the study and assigned a 3 digit patient number.

(b) Day 1 Visit (within 14 days of Screening Visit)

At the Day 1 Visit, patients underwent the following assessments:

- Biochemistry
- Hematology
- PK baseline and profile (up to 6 patients had a PK profile on Day 1)
- Chitotriosidase/Hexosaminidase assessment
- Glucosylceramide analysis (HPLC analysis performed on an aliquot of plasma from the chitotriosidase/hexosaminidase sample)
- G_{M1} (ganglioside levels on white blood cells) assessment
- Proteome sample (research tool involving high throughput, multidimensional protein separation followed by mass spectrometry for identification of proteins which may be associated with Gaucher disease)
- Adverse Event (AE) assessment
- Concomitant Medications update

(c) Day 15 Visit

At the Day 15 Visit, patients underwent the following assessments:

- PK sample (trough)
- PK sample (peak)
- Concomitant medications update

(d) Day 29 (Month 1) Visit

At the Day 29 Visit, patients underwent the following assessments:

- Physical examination
- Vital signs
- Weight
- ECG
- Urinalysis
- Biochemistry
- Hematology
- PK sample (trough)
- PK sample (peak)
- Chitotriosidase/Hexosaminidase assessment
- G_{M1} assessment
- Proteome sample
- AE assessment
- Concomitant Medications update

(e) Day 52 (Month 2)

At the Day 52 Visit, patients underwent the following assessments:

- Biochemistry
- Hematology
- Chitotriosidase/Hexosaminidase assessment
- AE assessment
- Concomitant Medications update

(f) Day 85 (Month 3)

At the Day 85 Visit, patients underwent the following assessments:

- Physical examination
- Vital signs
- Weight
- Urinalysis
- Biochemistry
- Hematology
- PK sample (trough)
- PK sample (peak)
- Chitotriosidase/Hexosaminidase assessment
- G_{M1} assessment
- Glucosylceramide assessment
- Proteome sample
- AE assessment
- Concomitant Medications update

(g) Day 113 (Month 4)

At the Day 113 Visit, patients underwent the following assessments:

- Biochemistry
- Hematology
- Chitotriosidase/Hexosaminidase assessment
- AE assessment
- Concomitant Medications update

(h) Day 141 (Month 5)

At the Day 141 Visit, patients underwent the following assessments:

- Biochemistry
- Hematology
- Chitotriosidase/Hexosaminidase assessment
- AE assessment
- Concomitant Medications update

(i) Day 169 (Month 6)

At the Day 169 Visit, patients underwent the following assessments:

- Physical examination

- Vital signs
- Height
- Weight
- ECG
- Urinalysis
- Biochemistry
- Hematology
- PK sample (trough)
- PK sample (peak)
- Chitotriosidase/Hexosaminidase assessment
- G_{M1} assessment
- Organ volume assessment
- Glucosylceramide assessment
- Proteome sample
- AE assessment
- Concomitant Medications update

(j) Day 197 (Month 7)

At the Day 197 Visit, patients underwent the following assessments:

- Biochemistry
- Hematology
- Chitotriosidase/Hexosaminidase assessment
- AE assessment
- Concomitant Medications update

(k) Day 225 (Month 8)

At the Day 225 Visit, patients underwent the following assessments:

- Biochemistry
- Hematology
- Chitotriosidase/Hexosaminidase assessment
- AE assessment
- Concomitant Medications update

(l) Day 253 (Month 9)

At the Day 253 Visit, patients underwent the following assessments:

- Physical examination
- Vital signs
- Weight
- Biochemistry
- Hematology
- Chitotriosidase/Hexosaminidase assessment
- AE assessment
- Concomitant Medications update

(m) Day 281 (Month 10)

At the Day 281 Visit, patients underwent the following assessments:

- Biochemistry
- Hematology
- Chitotriosidase/Hexosaminidase assessment
- AE assessment
- Concomitant Medications update

(n) Day 309 (Month 11)

At the Day 309 Visit, patients underwent the following assessments:

- Biochemistry
- Hematology
- Chitotriosidase/Hexosaminidase assessment
- AE assessment
- Concomitant Medications update

(o) Day 337 (Month 12)

At the Day 337 Visit, patients underwent the following assessments:

- Physical examination (including slit lamp exam)
- Vital signs
- Height
- Weight
- ECG
- Urinalysis
- Biochemistry
- Hematology
- PK sample (trough)
- PK sample (peak)
- Chitotriosidase/Hexosaminidase assessment
- G_{M1} assessment
- Organ volume assessment
- Glucosylceramide assessment
- Other disease assessments
- Proteome sample
- AE assessment
- Concomitant Medications update

(p) Withdrawal/Follow Up Visit (up to 2 months after withdrawal from or completion of the study)

At the Withdrawal/Follow Up Visit, patients underwent the following assessments:

- Physical examination (including slit lamp exam)
- Biochemistry
- Hematology
- AE assessment

- Concomitant Medications update

(5) Study Medication Dispensing and Compliance

All patients received OGT 918 at a starting dose of 100 mg TID. The dose was adjusted to give the maximum well-tolerated dose within the required plasma concentration range of up to 2 microg/mL. The dose could be increased by increments of 100 mg TID and was not to exceed 500 mg. The dose could be reduced if a patient experienced any unacceptable toxicity thought to be related to OGT 918.

Protocol Amendment 2, dated 27-Jan-1999, amended the dosing guidelines to: Dose could be increased if the patient tolerated OGT 918 well (occasional Grade 1 GI problems or less) and had not shown a significant organ reduction (>10% corrected for body weight) after 6 months of treatment. The dose could be increased by increments of 100 mg TID and was not to exceed 300 mg TID until the target trough level of 2 microg/mL was reached, or until toxicities other than Grade 1 GI problems were noted.

On Day 15, patients were assessed for tolerability of OGT 918, and OGT 918 plasma levels were measured to ascertain that they were within the required range of up to 2 microg/ml. Patients were asked to return to the clinic 1 month after any change in dose to assess tolerability, and PK samples were taken to assess plasma concentration. PK sampling was also performed at 1, 3, 6, and 12 months of treatment.

All patients received OGT 918, which was supplied as 100 mg gelatin capsules for oral administration. As this was an open-label study, no blinding was necessary. Trial medication was supplied in bottles and dispensed as a one month's supply at a time. OGT 918 was taken three times a day at regular intervals, either two hours before or two hours after eating. Patients were advised to avoid high carbohydrate content food, and dietary recommendations were issued to all participants.

Compliance was assessed by a record of OGT 918 dose intake on diary cards and by a counting of returned capsules. Patients returned all empty bottles and unused study medication at their next study visit.

(6) Efficacy and Endpoint Measures

The study was designed to provide information on the safety and possible efficacy of OGT 918. No formal sample size calculation was performed and only within-group testing for differences of mean change from baseline was performed.

(a) Primary Efficacy Parameters

The primary efficacy parameters for the study were:

- Percentage change from baseline in liver organ volume
- Percentage change from baseline in spleen organ volume
- Actual change from baseline in hemoglobin
- Actual change from baseline in platelets

Organ volumes were determined at screening and at the 6 and 12 Month visits by MRI or CT scan (following the normal clinical practice of each center). Hemoglobin concentration (Hgb) and platelet counts (Plt) were recorded at Screening, Day 1 and monthly thereafter. For Hgb and Plt, baseline was defined as the average of the Screening and Day 1 values, Month 6 was the average of the 5- and 6-Month values, and Month 12 was the average of the 11- and 12-Month values. For each parameter, change from baseline was calculated at 6 and 12 months. The four parameters also comprised a composite endpoint for overall response; however, the composite endpoint was a non-validated endpoint and was not being considered by the sponsor for the ISE.

(b) Secondary Efficacy Parameters

The secondary efficacy parameters for the study were:

- Actual change from baseline in liver organ volume
- Percentage change from baseline in excess liver volume
- Actual change from baseline in spleen organ volume
- Percentage change from baseline in excess spleen volume
- Percentage change from baseline in chitotriosidase
- Percentage change from baseline in hexosaminidase
- Percentage change from baseline in acid phosphatase
- Percentage change from baseline in angiotensin converting enzyme (ACE)

For each secondary parameter, change from baseline was calculated at 6 and 12 months. For the biochemical markers, results were assessed as described for Hgb and plts above.

(c) Safety Assessments

Safety was assessed by the incidence and frequency of AEs, and changes in vital signs, physical examinations, ECGs, and clinical laboratory values.

(d) Study Population

The efficacy population was defined as all patients who received at least one dose of study medication and had baseline and 6 or 12-month data from liver or spleen organ volumes, hemoglobin, or platelets. The safety population was defined as all patients who received at least one dose of study medication.

b) Results

Twenty-nine (29) patients were screened at 4 study sites, and 28 patients entered the study. Of the 28 patients who entered the study, 23 patients comprised the efficacy population, and 22 patients completed 12 months of the study. All patients were screened, entered, and treated between 18-Mar-1998 and 11-Jan-2000.

(1) Baseline Characteristics and Demographics

Overall, 50% of patients were male, and 54% were Ashkenazi Jews. Patient ages ranged from 22 to 69 years of age, with a mean age of 44.0 years. The patients' baseline medical histories were notable for:

- 6 patients (21%) reported previous Ceredase/Cerezyme use
- Baseline body system abnormalities most frequently reported were in the musculoskeletal, dermatologic and "other" body systems [14 patients each (50%)], and in the GI system [13 patients (46%)].
- Gaucher disease evaluations at baseline were notable for: 24 patients (86%) noted at least one concurrent illness at screening. These concurrent illnesses were most frequently noted in the musculoskeletal system [18 patients (64%)], and in the circulatory system [9 patients (32%)]. Unspecified osteonecrosis in 10 patients (36%), and unspecified osteoporosis and joint pain in 8 patients each (29%) were the most frequently reported baseline illnesses.
- 11 patients (39%) had undergone surgery for Gaucher disease, and 7 patients (25%) were splenectomized.
- Physical examination abnormalities at baseline by organ system, were most frequently noted in the GI system (100% of patients), dermatologic system in 15 patients (54%) and the cardiovascular system in 12 patients (43%)
- Neurologic problems were noted in 4 patients (14%) at baseline (unspecified in 2 patients; Bell's palsy and Parkinson's disease in 1 patient each).
- Eight (8) patients reported taking at least one concomitant medication at screening, the most common being co-codamol and loperamide taken by 2 patients each.
- Baseline liver volumes were ranged from 1.1 to 2.7 X normal (mean 1.67) for all patients, and spleen volumes ranged from 5.1 to 24.8 X normal (mean 11.94) for all patients [based on expected liver volumes of 2.14% of patient's body weight, and expected spleen volume of 0.2% of patient's body weight].

The baseline characteristics and demographic data for all enrolled patients are summarized in the following table

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Table 25: 918-001 Baseline Characteristics and Demographics

	All
Enrolled Patients, n =	28
Demographic Measure	
Gender, n (%)	28
Male	14 (50)
Female	14 (50)
Age (years), n =	28
Mean	44.0
Min, max	22, 69
Race, n(%)	28
Ashkenazi Jew	15 (54)
Other	13 (46)
Mean BMI (kg/M²), n =	27
Mean	23.56
Min, max	
Liver Organ Volume (l), n =	27
Mean	2.38
Min, max	
Spleen Organ Volume (l), n =	20
Mean	1.66
Min, max	
Hemoglobin* (g/dL), n =	28
Mean	12.28
Min, max	
Platelets** (x10⁹/l), n =	28
Mean	88.10
Min, max	

*LLN 11.5 g/dL

**LLN 150 x10⁹/l

(2) Patient Disposition

(a) Screening and Enrollment

The number of screen failures was low as, given the nature of the disease and the familiarity of the patients to the study center, the study Investigators were aware of the patient's status prior to screening. There was only one screen failure patient who was not entered at site #4 (Jerusalem, Israel) secondary to cataracts noted at screening.

Patients were enrolled at 4 study centers internationally, with the majority (57%) of the enrollment occurring at Center #4 (Jerusalem; Dr. Zimran). Patient enrollment by study center is summarized as follows

Table 26: 918-001 Patient Enrollment by Study Center

Center Number	Center/Investigator	Patients Enrolled, n (%)
	All	28
1	Cambridge, England/Dr. Tim Cox	7 (25)
2	Amsterdam, The Netherlands/Dr. Carla Hollak	3 (11)
3	Prague, Czech Republic/Dr. Martin Hrebicek	2 (7)
4	Jerusalem, Israel/Dr. Ari Zimran	16 (57)

(b) Dropouts

Of the 28 patients entered in the study, 22 patients completed 12 months of the study. Six (6) patients (21%) withdrew prior to study completion. The most common reason for study discontinuation was at the request of the patient. Of the 6 patients who withdrew, 5 patients withdrew prior to the Month 6 visit and are therefore not included in the efficacy population. Study discontinuations are as follows

Table 27: 918-001 Patients Discontinued

	All
Enrolled Patients, n =	28
Number of Withdrawals, n (%)	6 (21)
Reason for Dropout*	
Adverse Event, n (%)	2 (7)
Serious Adverse Event, n (%)	1 (4)
Subject Request, n (%)	5 (18)
Investigator Request, n (%)	1 (4)

*Patient may have reported more than one reason for withdrawal

The withdrawals were also evaluated by study center. One (1) patient withdrew from the Cambridge site, 1 patient withdrew from the Amsterdam site, and 4 patients withdrew from the Jerusalem site, as follows

Table 28: 918-001 Patients Discontinued by Study Center

	All	Study Center			
		Cambridge	Amsterdam	Prague	Jerusalem
Enrolled Patients, n =	28	7	3	2	16
Number of Withdrawals, n (%)	6 (21)	1 (14)	1 (33)	0	4 (25)

There were no serious protocol violations; however, 1 patient (408) from the Jerusalem center did not meet inclusion/exclusion criteria. This patient had an intact spleen with a Hgb of 14.9 g/dL and plt of 132,000/L. However, as this patient had pulmonary hypertension, which was felt to artificially elevate his hematological parameters, and had measurable organomegaly (liver 1.8 X normal, and spleen 22.3 X normal), he was allowed to enter the study. This patient was included in all the analyses.

(3) Concomitant Medications

All 28 patients reported taking at least one concomitant medication at any time during the study. A large number of different medications were used during the study (over 100 different WHO preferred term medications were reported), the majority of which were used by only 1 patient. The most commonly reported medication used during the study was loperamide hydrochloride for diarrhea, which was taken by 16 patients (57%). The next most commonly used medication during the study was paracetamol, used by 9 patients (32%). The most commonly used concomitant medications (used by ≥ 3 patients, or $\geq 10\%$ of patients) are summarized in the following table

Table 29: 918-001 Most Common (≥ 3 Patients) Concomitant Medications

Randomized Patients, n =		28
Medication	n (%)	
Loperamide hydrochloride	16 (57)	
Paracetamol	9 (32)	
Cyanocobalamin	4 (14)	
Alendronate sodium	3 (11)	
Amoxicillin	3 (11)	
Captopril	3 (11)	
Co-codamol	3 (11)	
Propranolol	3 (11)	

(4) Patient Compliance

The sponsor defined non-compliance as missing more than 5 capsules of study medication per month. By this definition, overall patient compliance in all studies was >70%. Compliance was greater for patients taking study medication alternating once daily/twice daily (100%), than once daily (82%), twice daily (71%), and 3 times daily (82%). It appears that most patients, therefore, took the majority of their study medication as directed during the study.

(5) Efficacy Results

(a) Primary Efficacy Analysis

The sponsor's primary efficacy variables were percentage change from baseline in liver organ volume, percentage change from baseline in spleen organ volume, actual change from baseline in hemoglobin, and actual change from baseline in platelets.

(i) Liver Organ Volume

Twenty-two (22) of the 28 patients entered in the study had liver organ volume data available at Month 6, and 21 patients had data available at Month 12. Overall, there were statistically significant mean percent reductions from baseline in liver volume at Month 6 and Month 12 of -7.0% (p-value .001) and -12.1% (<.001) respectively. The minimum and maximum mean percent reductions at Month 6 were -22.0% and +10.4% respectively, and at Month 12 were -31.2% and +7.3%. The results are summarized in the following table

Table 30: 918-001 Liver Organ Volume Statistics

	Baseline	Month 6	Month 12
n	27	22	21
Mean	2.381 liters (L)	-7.0%	-12.1%
Median	2.38 (L)	-6.4%	-12.6%
Minimum			
Maximum			
p-value*		.001	<.001

*for mean % change from baseline at Months 6 and 12

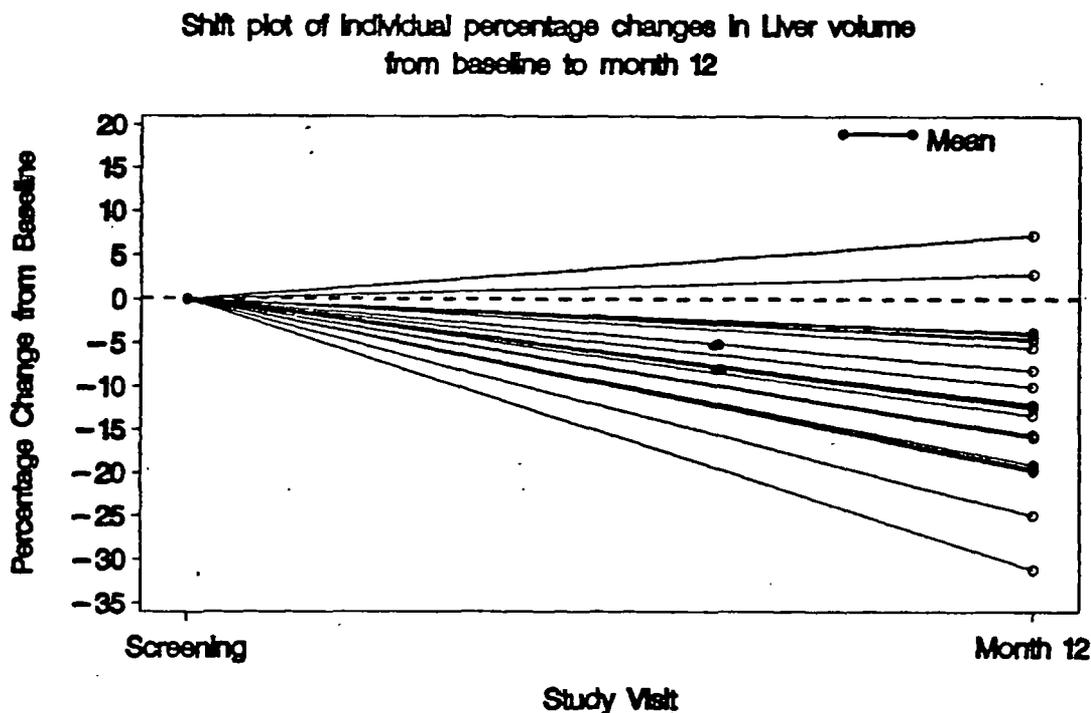
For individual patients, all patients but 2 had decreases in their liver volume. The sponsor also defined no response (NR) as a decrease of <10%, no change, or an increase in organ volume from baseline; moderate response (MR) as a decrease of 10% to <30% in organ volume; and a good response (GR) as a decrease of >30% in organ volume. By this definition, at Month 6, 15 of 22 patients (68%) had NR, 7 patients (32%) had MR, and no patient had GR. At Month 12, 8 patients (38%) had NR, 12 patients (57%) had MR, and 1 patient (5%) had GR.

Individual patient results at baseline, Month 6 and Month 12 are summarized in the following table and in the following figure [Figure electronically scanned and reproduced from: Oxford Glycosciences (UK) Ltd, NDA #21-348, Volume 2.3, page 52, dated 02-Aug-2001]

Table 31: 918-001 % Change from Baseline in Liver Volume, Individual Patient Data

Patient Number	Baseline (L)	Month 6 % Change from Baseline	Month 12 % Change from Baseline
101	1.92	-18.2	-25.0
103	1.73	-15.5	-31.2
104	1.70	-5.9	-4.4
105	2.21	-6.2	-12.6
106	2.20	3.6	-10.0
107	2.33	-5.6	-19.7
201	2.82	1.4	-5.5
202	2.59	-12.4	-19.8
301	2.51	-6.5	-4.7
302	2.53	10.4	7.3
402	1.49	-6.3	-
403	1.82	-4.6	-13.4
404	1.76	-7.3	-4.0
405	2.63	-16.0	-19.8
407	2.21	-10.8	-12.4
408	2.56	8.3	2.9
411	2.53	-3.0	-8.1
412	2.41	-13.8	-15.6
413	2.38	-8.4	-15.9
414	3.06	-22.0	-19.1
415	2.79	-6.0	-19.4
416	3.48	-9.0	-3.8

Figure 3: 918-001 % Change from Baseline in Liver Volume, Individual Patient Data



(ii) Spleen Organ Volume

Twenty (20) patients had spleen organ volume data available for analysis at baseline (7 of the 28 randomized patients had been splenectomized, and 1 patient with missing data had no baseline data available for comparison). Nineteen (19) of these patients had spleen organ volume data available at Month 6, and 18 patients had data available at Month 12. Overall, there were statistically significant mean percent reductions from baseline in spleen volume at Month 6 and Month 12 of -15.1% (p-value <.001) and -19.0% (<.001) respectively. The minimum and maximum mean percent reductions at Month 6 were -25.3% and -3.1%, and at Month 12, -36.8% and +2.9%. The results are summarized in the following table

Table 32: 918-001 Spleen Organ Volume Statistics

	Baseline	Month 6	Month 12
n	20	19	18
Mean	1.658 (L)	-15.1%	-19.0%
Median	1.49 (L)	-14.1%	-19.0%
Minimum			
Maximum			
p-value*		<.001	<.001

*for mean % change from baseline at Months 6 and 12

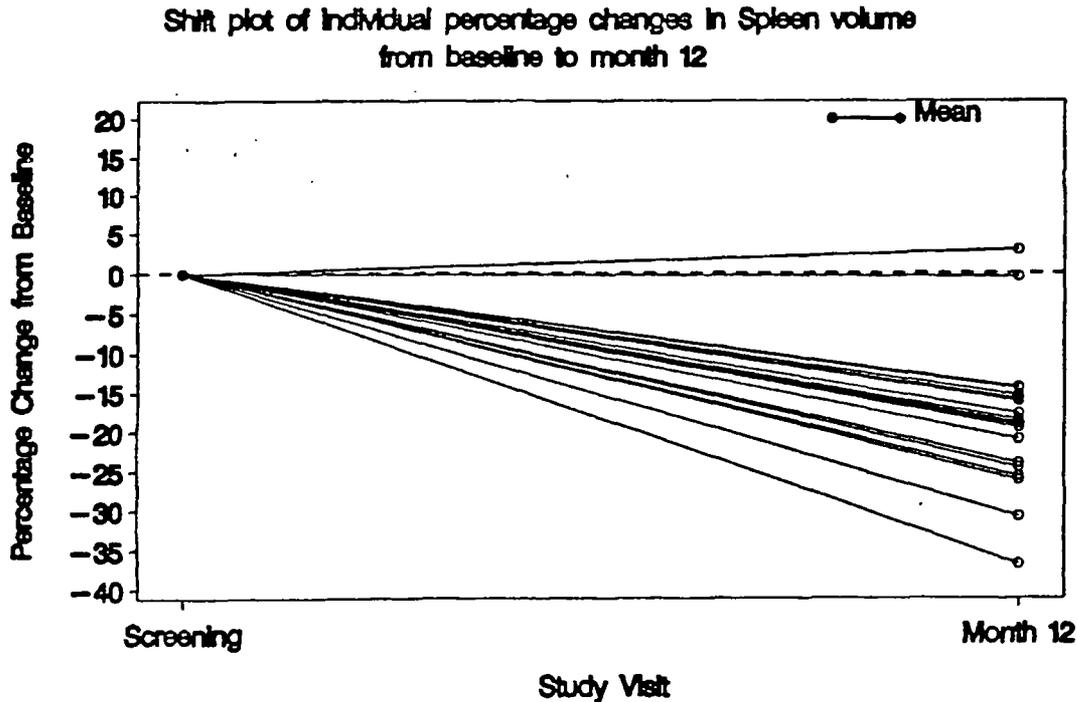
For individual patients, all patients but 1 had decreases in their spleen volume. By the sponsor's response definitions (see Liver Organ Volume section above), at Month 6, 5 of

19 patients (26%) had NR, 14 patients (74%) had MR, and no patient had GR. At Month 12, 2 of 18 patients (11%) had no response, 14 patients (78%) had MR, and 2 patients (11%) had GR. Individual patient results at baseline, Month 6 and Month 12 are summarized in the following table and in the following figure [Figure electronically scanned and reproduced from: Oxford Glycosciences (UK) Ltd, NDA #21-348, Volume 2.3, page 53, dated 02-Aug-2001]

Table 33: 918-001 % Change from Baseline in Spleen Volume, Individual Patient Data

Patient Number	Baseline (L)	Month 6 % Change from Baseline	Month 12 % Change from Baseline
101	1.43	-24.5	-24.5
103	1.00	-24.6	-25.6
104	0.68	-11.8	2.9
105	1.90	-16.2	-36.8
106	0.92	-20.7	-26.1
201	1.41	-5.4	-19.5
301	1.32	-17.7	-15.3
302	1.75	-3.1	-0.3
402	0.84	-18.1	-
403	1.53	-18.4	-20.9
404	0.91	-12.4	-15.8
405	2.21	-25.3	-30.8
407	1.75	-24.8	-18.5
408	2.96	-12.1	-14.5
411	3.36	-9.4	-14.3
412	1.01	-6.3	-16.1
413	2.19	-9.9	-23.9
415	1.81	-14.1	-24.0
416	1.44	-11.8	-17.7

Figure 4: 918-001 % Change from Baseline in Spleen Volume, Individual Patient Data



(iii) Hemoglobin

All 23 patients in the efficacy set had hemoglobin (Hgb) data at Month 6, and 22 patients had Hgb data at Month 12. Overall, there was a mean increase in Hgb from baseline to Month 6 of 0.03 g/dL (0.5%), and a mean increase at Month 12 of 0.26 g/dL (2.6%). These results were not statistically significant. The minimum and maximum mean changes from baseline at Month 6 were -0.81 g/dL and 1.0 g/dL, and at Month 12 were -0.65 g/dL and 2.40 g/dL. The results are summarized in the following table

Table 34: 918-001 Hemoglobin Statistics, Efficacy Set

	Baseline	Month 6		Month 12	
		Actual Change	% Change	Actual Change	% Change
n	23	23	23	22	22
Mean	11.96 (g/dL)	0.03 (g/dL)	0.5%	0.26 (g/dL)	2.6%
Median	12.00 (g/dL)	0 (g/dL)	0%	0.17 (g/dL)	1.3%
Minimum					
Maximum					
p-value*		0.769	0.596	0.095	0.093

*for mean change from baseline at Months 6 and 12

For individual patients, at Month 12, 16 of 22 patients (73%) had at least some increase from baseline in Hgb. The sponsor also defined no response (NR) as an increase of ≤ 0.5 g/dL, no change or a decrease in Hgb from baseline; a moderate response (MR) as an increase of >0.5 g/dL to 1.5 g/dL in Hgb; and a good response (GR) as an increase of >1.5 g/dL in Hgb. By this definition, at Month 6, 21 of 23 patients (91%) had NR, 2 patients (9%) had MR, and no patient had GR. At Month 12, 17 of 22 patients (77%) had NR, 3 patients (14%) had MR, and 2 patients (9%) had GR.

Individual patient results at baseline, Month 6 and Month 12 are summarized in the following table and in the following figure [Figure electronically scanned and reproduced from: Oxford Glycosciences (UK) Ltd, NDA #21-348, Volume 2.3, page 56, dated 02-Aug-2001]

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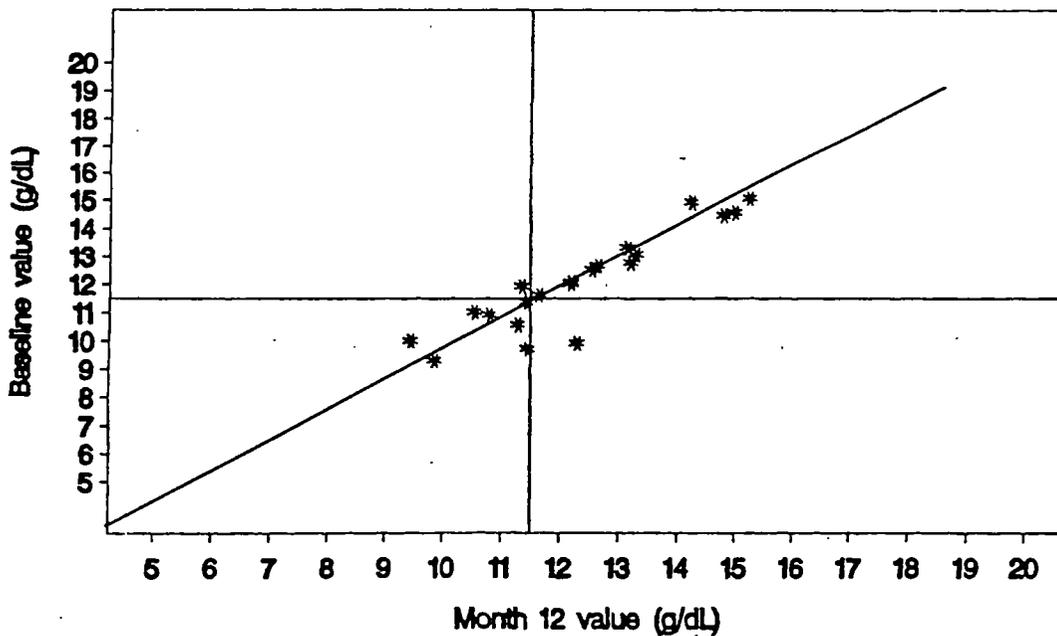
Table 35: 918-001 Change from Baseline in Hemoglobin, Individual Patient Data

Patient	Baseline*(g/dL)	Month 6		Month 12	
		Actual Change (g/dL)	% Change	Actual Change (g/dL)	% Change
101	11.90	0	0	-0.55	-4.6
103	12.65	0.35	2.8	0	0
104	12.50	-0.05	-4.0	0.05	0.4
105	14.45	0	0	0.35	2.4
106	15.05	0.30	2.0	0.20	1.3
107	12.05	-0.15	-1.2	0.15	1.2
201	13.05	-0.81	-6.2	0.24	1.9
202	10.55	0	0	0.72	6.9
301	11.35	0.10	0.9	0.10	0.9
302	14.55	0.05	0.3	0.45	3.1
402	12.40	0.30	2.4	-	-
403	11.60	-0.30	-2.6	0.05	0.4
404	9.30	0.45	4.8	0.55	5.9
405	12.00	0.85	7.1	0.20	1.7
407	9.30	0.50	5.4	0.55	5.9
408	14.90	-0.70	-4.7	-0.65	-4.4
409	10.00	-0.25	-2.5	-0.55	-5.5
411	9.90	0.30	3.0	2.40	24.2
412	10.90	-0.40	-3.7	-0.10	-0.9
413	9.70	1.00	10.3	1.75	18.0
414	12.75	-0.35	-2.7	0.45	3.5
415	13.30	0.15	1.1	-0.15	-1.1
416	11.00	-0.25	-2.3	-0.45	-4.1

*LLN 11.5 g/dL
Baseline <11.5 g/dL

Figure 5: 918-001 Scatter Plot of Hemoglobin Values, Baseline vs Month 12

Scatter plot of Haemoglobin values (g/dL) (Baseline v's Month 12)



Hemoglobin responses were further evaluated by baseline Hgb value. Nine (9) patients had a baseline hemoglobin < the lower limit of normal (LLN) (<11.5 g/dL), and 19 patients had baseline hemoglobin \geq 11.5 g/dL. Mean change from baseline for hemoglobin at Months 6 and 12 were greater for patients who had baseline hemoglobin <11.5 g/dL than for patients whose baseline was \geq 11.5 g/dL. At Month 6, patients with a baseline hemoglobin <11.5 g/dL had a mean increase of 0.16 g/dL, compared to a mean decrease of -0.06 g/dL in patients with a baseline hemoglobin \geq 11.5 g/dL. At Month 12, patients with a baseline hemoglobin <11.5 g/dL had a mean increase of 0.55 g/dL, compared to a mean increase of 0.06 g/dL in patients with a baseline hemoglobin \geq 11.5 g/dL. These results were not statistically significant. The results are summarized in the following tables

Table 36: 918-001 Hemoglobin Statistics, Patients with Hemoglobin <11.5 g/dL at Baseline

	Baseline	Month 6		Month 12	
		Actual Change	% Change	Actual Change	% Change
n	9	9	9	9	9
Mean	10.22	0.16	1.78	0.55	5.71
Median	10.00	0.10	0.9	0.55	5.9
Minimum					
Maximum					
p-value*		0.312	0.274	0.130	0.122

*for mean change from baseline at Months 6 and 12

Table 37: 918-001 Hemoglobin Statistics, Patient with Hemoglobin \geq 11.5 g/dL at Baseline

	Baseline	Month 6		Month 12	
		Actual Change	% Change	Actual Change	% Change
n	19	14	14	13	13
Mean	13.26	-0.06	-0.41	0.06	0.45
Median	13.05	0	0	0.15	1.2
Minimum					
Maximum					
p-value*		0.640	0.669	0.531	0.533

*for mean change from baseline at Months 6 and 12

(iv) Platelet Count

All 23 patients in the efficacy set had platelet count (Plt) data at Month 6, and 22 patients had Plt data at Month 12. Overall, there was a mean increase in Plt from baseline to Month 6 of $3.60 \times 10^9/l$, and a mean increase at Month 12 of $8.28 \times 10^9/l$. These results were statistically significant only for the mean actual change from Baseline at Month 12 ($P=0.014$). The minimum and maximum mean changes from baseline at Month 6 were $-19.50 \times 10^9/l$ and $35.50 \times 10^9/l$, and at Month 12 were $-13.50 \times 10^9/l$ and $56.50 \times 10^9/l$. The results are summarized in the following table

Table 38: 918-001 Platelet Count Statistics, Efficacy Set

	Baseline	Month 6		Month 12	
		Actual Change	% Change	Actual Change	% Change
n	23	23	23	22	22
Mean	77.42 (10 ⁹ /l)	3.60 (10 ⁹ /l)	4.2%	8.28 (10 ⁹ /l)	16.0%
Median	60.65 (10 ⁹ /l)	3.00 (10 ⁹ /l)	5.7%	7.75 (10 ⁹ /l)	7.5%
Minimum					
Maximum					
p-value*		0.146	0.146	0.014	0.060

*for mean change from baseline at Months 6 and 12

For individual patients, at Month 12, 16 of 22 patients had at least some increase from baseline in Plt. The sponsor also defined no response (NR) as an increase of $\leq 15 \times 10^9/l$, no change or a decrease in Plt from baseline; a moderate response (MR) as an increase of >15 to $30 \times 10^9/l$ in Plt; and a good response (GR) as an increase of $>30 \times 10^9/l$ in Plt. By this definition, at Month 6, 20 of 23 patients (87%) had NR, 2 patients (9%) had MR, and 1 patients (4%) had GR. At Month 12, 17 of 22 patients (77%) had NR, 4 patients (18%) had MR, and 1 patient (5%) had GR. Only 1 patient had a Plt $>150 \times 10^9/l$ ($>LLN$) at Baseline, so a subgroup analysis by Baseline Plt could not be performed.

Individual patient results at baseline, Month 6 and Month 12 are summarized in the following table and in the following figure [Figure electronically scanned and reproduced from: Oxford Glycosciences (UK) Ltd, NDA #21-348, Volume 2.3, page 58, dated 02-Aug-2001]

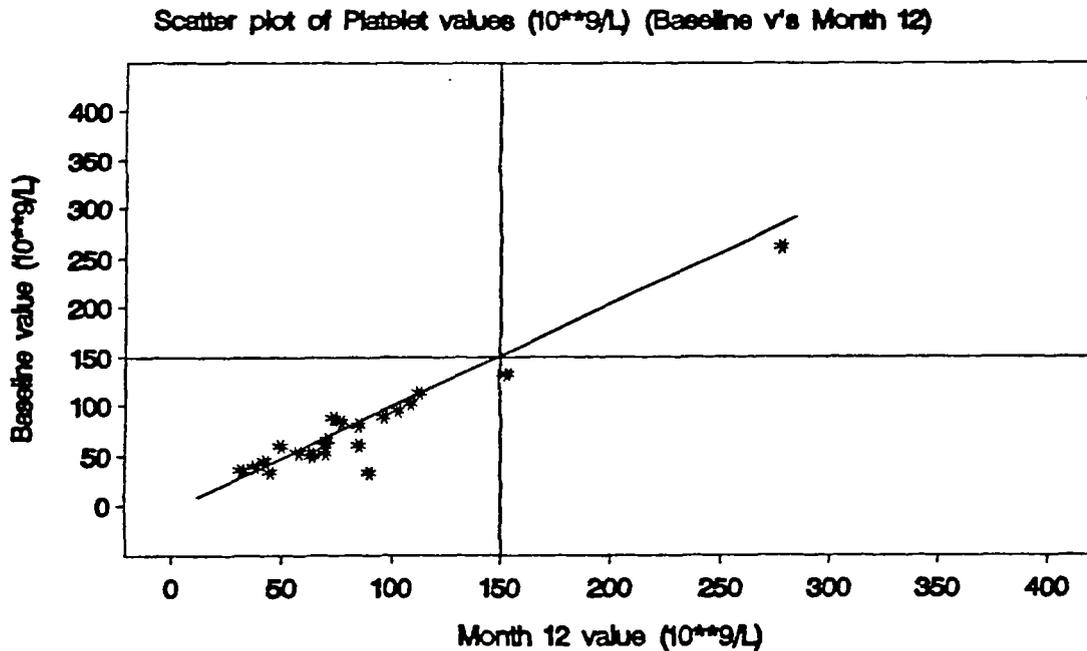
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Table 39: 918-001 Change from Baseline in Platelet Count, Individual Patient Data

Patient Number	Baseline* (10 ⁹ /l)	Month 6		Month 12	
		Actual Change (10 ⁹ /l)	% Change	Actual Change (10 ⁹ /l)	% Change
101	53.50	0	0	4.00	7.5
103	52.50	3.00	5.7	17.00	32.4
104	83.50	1.00	1.2	-6.50	-7.8
105	94.50	7.00	7.4	8.50	9.0
106	112.50	20.00	17.8	0.50	0.4
107	101.50	11.50	11.3	7.50	7.4
201	80.00	-6.00	-7.5	5.00	6.3
202	262.00	35.50	13.5	5.00	6.1
301	53.55	2.20	4.1	9.95	18.6
302	60.65	16.35	27.0	24.35	40.1
402	96.00	-7.50	-7.8	-	-
403	45.00	7.00	15.6	-2.00	-4.4
404	60.00	-5.00	-8.3	-10.00	-16.7
405	39.00	-7.00	-17.9	-0.50	-1.3
407	50.00	11.50	23.0	13.50	27.0
408	132.00	-19.50	-14.8	21.50	16.3
409	34.00	8.00	23.5	11.00	32.4
411	33.00	1.00	3.0	56.50	171.2
412	87.00	-8.50	-9.8	-13.50	-15.5
413	36.00	-6.50	-18.1	-3.50	-9.7
414	88.50	5.50	6.2	8.00	9.0
415	60.00	3.50	5.8	10.00	16.7
416	66.00	9.50	14.4	5.00	7.6

*LLN 150 x10⁹/l
>150 x10⁹/l

Figure 6: 918-001 Scatter Plot of Platelet Values, Baseline vs Month 12



(b) Secondary Efficacy Analysis

Secondary efficacy analyses were predominantly biochemical markers of Gaucher disease, and will be considered briefly below. The activities of a number of plasma enzymes, including acid phosphatase, hexosaminidase (a lysosomal enzyme), chitotriosidase, and angiotensin-converting enzyme (ACE), are usually increased in Gaucher disease. It has been proposed that chitotriosidase in particular might be useful in following the course of treatment. Chitotriosidase is a widespread non-specific clinical marker of Gaucher's disease activity, and a reduction in chitotriosidase levels is considered to be indicative of a reduction in the number of storage (Gaucher) cells¹⁰. Reductions in cell surface gangliosides (G_{M1}) are indicative of reduced glycolipid synthesis⁸.

(i) Chitotriosidase

There were statistically significant decreases in chitotriosidase from baseline at Months 6 and 12 of -6.4% and -16.4% respectively. The results are summarized in the following table

Table 40: 918-001 Chitotriosidase Statistics

	Baseline (nmol/ml.h)	Month 6	Month 12
n	27	21	20
Mean	15105.2	-6.4%	-16.4%
Median	16215.0	-8.1%	-14.4%
Minimum			
Maximum			
p-value*		.001	<.001

Control range: 7-124 nmol/ml.h

*for mean % change from baseline at Months 6 and 12

(ii) Hexosaminidase

There were decreases in hexosaminidase from baseline at Months 6 and 12 of -3.4% and -7.1% respectively. The results were significant at Month 12 only. The results are summarized in the following table

Table 41: 918-001 Hexosaminidase Statistics

	Baseline (nmol/ml.h)	Month 6	Month 12
n	27	22	21
Mean	2334.0	-3.4%	-7.1%
Median	2063.0	-2.9%	-9.8%
Minimum			
Maximum			
p-value*		.220	.019

Control range: 477-1845 nmol/ml.h

*for mean % change from baseline at Months 6 and 12

¹⁰ Lachmann RH, Platt FM. Substrate reduction therapy for glycosphingolipid storage disorders. *Exp Opin Invest Drugs* 2001;10(3):455-466.