d) Study 918-003X

(1) Adverse Events

All 16 patients (100%) reported at least one AE between entry into the original study (981-003) and extension study completion/termination. There were 80 different AE terms reported, with AEs in the Gastrointestinal system being the most commonly reported. Diarrhea and weight decrease were the most commonly reported AEs, reported by 15 patients each (94%). The next most commonly reported AEs were abdominal pain (63%), headache (56%), flatulence (50%), and influenza-like symptoms and tremor (44% each). These findings are similar to the pooled results reported in the Combined Data Set. The most common AEs (occurring in ≥10% of patients, or ≥2 patients) are listed in the following table [A complete list of all reported AEs is in the Appendix]

Table 156: 918-003X Incidence of Most Common AEs (≥10% of Patients)

Randomized Patients, n =		16
Body System	**WHO AE Term**	**n (%)**
Musculoskeletal	Cramps	4 (25)
	Bone Pain	2 (13)
	Joint Pain	2 (13)
	Pain Neck/Shoulder	2 (13)
Neurological	Headache	9 (56)
	Tremor	7 (44)
	Dizziness	4 (25)
	Cramps Legs	3 (19)
	Paresthesia	2 (13)
Vision	Visual Disturbance	4 (25)
	Eye Infection	2 (13)
	Eye Irritation	2 (13)
Gastrointestinal	Diarrhea	15 (94)
	Abdominal Pain	10 (63)
	Flatulence	8 (50)
	Nausea	4 (25)
	Vomiting	2 (13)
Metabolic and Nutritional	Weight Decrease	15 (94)
Respiratory	Nose Congestion	2 (13)
Platelet, Bleeding and Clotting	Nosebleed	2 (13)
Body as a Whole	Influenza-Like Symptoms	7 (44)
	Back Pain	3 (19)
	Pain	3 (19)
	Fatigue	2 (13)

(2) Adverse Events Over Time

The incidence of weight decrease was noted to increase over the course of the study, and the incidence of diarrhea was noted to decrease over the course of the study. Unlike Study 918-001, however, there was no notable change in the incidence of tremor or other GI complaints. The sponsor's summary of AEs by time interval of study drug treatment for GI disorders, tremor and weight loss are listed in the following table

Table 157: 918-003X Incidence of Selected Adverse Events Over the Course of the Study

		Time Interval (Weeks)		
	Overall	0 – 26	>26 – 39	>39
Patients, n =	16	16	16	13
WHO AE Term	n (%)	n (%)	n (%)	n (%)
GI System	15 (94)	15 (94)	12 (75)	9 (69)
Diarrhea	15 (94)	15 (94)	8 (50)	5 (38)
Tremor	7 (44)	7 (44)	4 (25)	3 (23)
Weight Decrease	15 (94)	12 (75)	15 (94)	12 (92)

(3) Adverse Events Resulting in Discontinuation

Two (2) patients discontinued study medication prior to study completion due to AEs.

Patient 110 withdrew due to unacceptable disease progression (increasing hepatomegaly), concurrent illness and unacceptable side effects (progressive weight loss). During the extended treatment phase, the patient also reported abdominal pain, decreased energy, reduced hematocrit and change in bowel habits. The patient was withdrawn at the Month 12 visit, and following withdrawal from the study, the patient was admitted to the hospital with rigors, pyrexia and possible sepsis. The patient underwent abdominal surgery and was subsequently diagnosed with large cell (B-cell) lymphoma of the spleen and stomach.

Patient 112 withdrew 240 days after screening at the Investigator's request due to flatulence, cramps and diarrhea. These symptoms were reported at the Day 8-15 visit.

(4) Serious Adverse Events

There were no SAEs during the study. There were no deaths.

(5) Other Significant Adverse Events

Please see Study 918-003 for neurologic AEs.

(6) Laboratory Assessments

Hemoglobin and platelet counts were included in the efficacy analysis and will not be considered here. There were no substantial changes in any laboratory parameter during the study. Trends noted from Baseline to Endpoint are as follows:

(a) White Blood Cell Count

There were mild increases in the WBC, which affected all cell lines, except eosinophils. Mean Baseline WBC was 5.7, and mean Endpoint was 6.1 (mean increase 12%). These changes were not clinically relevant.

(b) Alkaline Phosphatase, AST and ALT

Alkaline Phosphatase decreased from a mean of 82.3 U/l at Baseline to a mean of 69.9 U/l at Endpoint, a –15% decrease. ALT increased 27% (mean baseline 23.4 U/l, mean endpoint 28.2 U/l), and AST increased 3%.

There were no other notable changes in hematology or chemistry parameters, nor were there individual clinically significant abnormalities reported.

(7) Physical Findings

Physical Exams, slit lamp assessments, and ECGs were not performed during the extension phase of the study.

(a) Weight

Weight decreased for almost all patients from Baseline to Endpoint, with a mean decrease of –4 kg. Weight changes ranged from a +0.4 kg increase to a –9.0 kg decrease for all patients.

There were no other notable or clinically significant changes during the study.

e) Study 918-004

(1) Adverse Events

Thirty-five (35) of the 36 patients (97%) reported at least one AE during the study. There were 84 different AE terms reported, with AEs in the Gastrointestinal system being the most commonly reported overall. Diarrhea (reported in 69% of patients overall), abdominal pain and weight decrease (44% each) were the most commonly reported AE terms, all of which were more common in the groups exposed to OGT 918 than in the Cerezyme group. Complaints in the Neurologic system, including tremor (22% overall), headache (17%) and dizziness (14%) were reported exclusively in the groups exposed to OGT 918. The most common AEs (occurring in $\geq$5% of patients, or $\geq$2 patients), overall and by treatment group, are listed in the following table [A complete list of all reported AEs is in the Appendix]

Table 158: 918-004 Incidence of Most Common Adverse Events (>5% of Patients Overall)

		All	Treatment		
			OGT 918	Cerezyme	OGT 918 + Cerezyme
Randomized Patients, n =		36	12	12	12
Body System	WHO AE Term	n (%)	n (%)	n (%)	n (%)
Musculoskeletal	Bone Pain	4 (11)	0	2 (17)	2 (17)
	Fracture Rib	2 (6)	0	1 (8)	1 (8)
	Joint Pain	2 (6)	1 (8)	1 (8)	0
Neurological	Tremor	8 (22)	4 (33)	0	4 (33)
	Headache	6 (17)	3 (25)	0	3 (25)
	Dizziness	5 (14)	2 (17)	0	3 (25)
Vision	Visual Disturbance	2 (6)	1 (8)	0	1 (8)
Psychiatric	Appetite Decreased	2 (6)	1 (8)	0	1 (8)
Gastrointestinal	Diarrhea	25 (69)	12 (100)	3 (25)	10 (83)
	Abdominal Pain	16 (44)	8 (67)	1 (8)	7 (58)
	Flatulence	11 (31)	6 (50)	0	5 (42)
	Constipation	5 (14)	1 (8)	1 (8)	3 (25)
	Nausea	4 (11)	2 (17)	1 (8)	1 (8)
Metabolic and Nutritional	Weight Decrease	16 (44)	8 (67)	2 (17)	6 (50)
	Weight Increase	2 (6)	0	1 (8)	1 (8)
Cardiovascular	Hypotension	4 (11)	0	1 (8)	3 (25)
Heart Rate and Rhythm	Bradycardia	2 (6)	1 (8)	1 (8)	0
	Tachycardia	2 (6)	0	0	2 (17)
Respiratory	Rhinitis	2 (6)	1 (8)	1 (8)	0
	Throat Sore	2 (6)	0	0	2 (17)
Urinary	Urinary Tract Infection	2 (6)	1 (8)	0	1 (8)
Body as a Whole	Influenza-Like Symptoms	13 (36)	5 (42)	4 (33)	4 (33)
	Pain Trauma Activated	5 (14)	2 (17)	1 (8)	2 (17)
	Pain	4 (11)	1 (8)	1 (8)	2 (17)
	Fever	3 (8)	2 (17)	0	1 (8)
	Pain Legs	3 (8)	0	0	3 (25)
	Weakness Generalized	3 (8)	2 (17)	0	1 (8)
	Abdominal Distension	2 (6)	1 (8)	0	1 (8)
	Back Pain	2 (6)	1 (8)	0	1 (8)
	Chest Pain	2 (6)	2 (17)	0	0
	Fatigue	2 (6)	2 (17)	0	0
Unclassifiable	Fall	4 (11)	1 (8)	2 (17)	1 (8)
	Inflicted Injury	3 (8)	2 (17)	0	1 (8)

(2) Adverse Events Over Time

The incidence of diarrhea and other GI AEs were noted to decrease over the course of the study, and weight decreased, tremor, and psychiatric disorders were noted to increase over the course of the study. These findings were limited to the patients exposed to OGT 918, and psychiatric disorders were particularly notable in the Combination treatment group. The findings for GI AEs, weight loss and tremor are consistent with the results seen in the Combined Data Set; however, psychiatric disorders had not been noted to any appreciable extent in the previous studies. AE terms coding to psychiatric disorders include (# of patients reporting): insomnia (1), appetite decreased (2), appetite absent (1), memory loss (1), memory loss (1), jitteriness (1). Selected AEs by week of study drug treatment is listed in the following table

Table 159: 918-004 Incidence of Selected Adverse Events Over Course of Study

				Weeks		
		Treatment	Overall	0 – 4	>4 – 13	>13
Patients, n =		OGT 918	12	12	12	11
		Cerezyme	12	12	12	12
		Combination	12	12	12	11
Body System	WHO AE Term		n (%)	n (%)	n (%)	n (%)
Gastrointestinal	All	OGT 918	12 (100)	12 (100)	8 (67)	7 (64)
		Cerezyme	6 (50)	3 (25)	5 (42)	4 (33)
		Combination	11 (92)	11 (92)	8 (67)	7 (64)
	Diarrhea	OGT 918	12 (100)	12 (100)	8 (67)	7 (64)
		Cerezyme	3 (25)	1 (8)	3 (25)	0
		Combination	10 (83)	10 (83)	7 (58)	7 (64)
	Abdominal Pain	OGT 918	8 (67)	5 (42)	3 (25)	4 (36)
		Cerezyme	1 (8)	0	1 (8)	0
		Combination	7 (58)	6 (50)	3 (25)	2 (18)
	Flatulence	OGT 918	6 (50)	5 (42)	4 (36)	4 (36)
		Cerezyme	0	0	0	0
		Combination	5 (42)	4 (33)	3 (18)	2 (18)
Metabolic and Nutritional	Weight Decrease	OGT 918	8 (67)	2 (17)	6 (50)	8 (73)
		Cerezyme	2 (17)	0	0	2 (17)
		Combination	6 (50)	0	5 (42)	6 (55)
Nervous	Tremor	OGT 918	4 (33)	2 (17)	4 (33)	3 (36)
		Cerezyme	0	0	0	0
		Combination	4 (33)	2 (17)	3 (25)	3 (36)
Psychiatric Disorders	All	OGT 918	2 (17)	1 (8)	2 (17)	1 (9)
		Cerezyme	0	0	0	0
		Combination	5 (42)	1 (8)	5 (42)	4 (36)

(3) Adverse Events Resulting in Discontinuation

Three (3) patients discontinued study medication prior to study completion due to AEs: 2 patients in the OGT 918 alone group, and 1 patient in the Combination treatment group. One patient withdrew for tremor, one patient withdrew for diarrhea, and one patient withdrew for a constellation of symptoms including fatigue, weakness, mild general pain, mild loss of tactile sensitivity, and mild fever. These patients are as follows:

Patient 106 (OGT 918 alone) withdrew after 120 days at her request (wanted to have children), and at the Investigator's request due to worsening tremor. Tremor was first reported at the Day 57 visit with worsening on Day 85.

Patient 110 (OGT 918 alone) withdrew after 75 days at her request due to dissatisfaction with QoL on OGT 918, and due to side effects (Epstein Barr virus). Mild Epstein Barr was reported at the Day 85 visit, and the patient reported mild fatigue and weakness, mild general pain all over the body, mild loss of tactile sensitivity all over the body, and mild fever.

Patient 123 (Combination treatment) withdrew after 58 days due to diarrhea. Moderate diarrhea was first reported at the Day 15 visit, and treated with loperamide with resolution after 8 days.

(4) Serious Adverse Events

There was one SAE during the study. There were no deaths. The SAE is summarized as follows:

Patient 105 (Combination treatment) required hospitalization for elective respiratory tests due to shortness of breath. The patient had a past medical history significant for mild restrictive respiratory disease, mild bronchospasm and exertional dyspnea diagnosed in 1995. All tests were normal and the patient was diagnosed with subjective shortness of breath. The patient completed the study.

Table 160: 918-004 Serious Adverse Events

Patient	M/F	Age (yrs)	Serious Adverse Event	Body System	Onset (days)	Invest. Attrib.	Drug D/C?
105	M	52	Hospitalization - elective respiratory tests (shortness of breath)	uncodable	169	NR	No

(5) Neurologic Adverse Events

Studies 918-004 and 918-004X are being considered together as EDX testing may have occurred during either study. Sixteen (16) of 36 patients reported neurologic complaints of tremor, muscle cramping, or numbness or tingling of the extremities. Of these 16 patients, by randomization in the original study, 6 were randomized to the OGT 918 alone group, 4 to the Cerezyme alone group, and 6 to the Combination treatment group. EDX studies were performed in 29 of 36 patients, including 15 of the 16 patients with neurologic complaints. Ten (10) patients had abnormal EDX results including: In the OGT 918 alone group, 2 patients with neurologic complaints and 1 patient without neurologic complaints; In the Cerezyme alone group, 1 patient with neurologic complaints and 1 patient without neurologic complaints; and in the Combination treatment group, 4 patients with neurologic complaints and 1 patient without neurologic complaints. Patients who underwent EDX testing and their relevant medical histories are summarized in the following table [Results are also listed in the Appendix]

Table 161: 918-004 and 918-004X Patients Who Underwent Electrodiagnostic Testing

Patient	EDX Results	Findings
OGT 918 Alone Group		
102	Abnormal	No neurologic complaints. Pre-existing history of diabetes. EDX showed borderline low sural SNAP c/w mild peripheral neuropathy
103	Normal	Hand tremor reported.
106	Normal	Hand tremor reported.
110	Normal	Leg cramps and diminished tactile sensitivity over body
111	Normal	No neurologic complaints.
120	Abnormal	Pre-existing tremor. EDX showed low sural SNAP
121	Normal	No neurologic complaints.
126	Normal	No neurologic complaints.
130	Abnormal	Occasional hand tremor, congenital hand deformity.
133	Normal	Possible worsening of childhood tremor.
136	Normal	No neurologic complaints.
Cerezyme Alone Group		
101	Normal	No neurologic complaints.
107	Normal	No neurologic complaints.
112	Normal	No neurologic complaints.
113	Normal	Intermittent tremor after starting OGT 918 in extension phase.
116	Abnormal	Tremor before OGT 918. Pre-existing history of diabetes. EDX showed small bilateral sural SNAPs
117	Abnormal	No neurologic complaints. Patient developed multiple myeloma with melphelan treatment. EDX showed small sural SNAPs and chronic neurogenic changes on EMG c/w peripheral neuropathy
127	Normal	Hand tremor after starting OGT 918 during extension phase. Tremor resolved without dose reduction.
132	Normal	No neurologic complaints.
Combination Group		
104	Abnormal	Hand tremor, weakness in hands and legs. EDX showed absent sural SNAP on one side, which may have been due to technical difficulties.
105	Normal	Transient (I day) tremor, which resolved without dose change.
108	Normal	No neurologic complaints.
109	Abnormal	Leg cramps. Pre-existing history of epilepsy, treated with carbamazepine. EDX consistent with peripheral neuropathy
114	Normal	No neurologic complaints. History of B12 deficiency.
123	Abnormal	No neurologic complaints. EDX showed low sural SNAPs, and slight slowing of nerve conduction.
124	Normal	Occasional hand tremor, resolved within 1 month.
125	Abnormal	Tremor, shakiness, and eye twitch. EDX whoed low sural SNAPs
131	Normal	No neurologic complaints.
135	Abnormal	F patient. EDX at Month 2 showed borderline low sural SNAP. Reported pain in calves on Day 1 of study, numbness in right hand on Day 1, and transient numbness in one digit on Day 1. Continued study drug for 8 months without further recurrence.

(6) Other Significant Adverse Events

One patient (Patient #117; Cerezyme Group) developed multiple myeloma during the study. There were no other significant AEs.

(7) Laboratory Assessments

Hemoglobin and platelet counts were included in the efficacy analysis and will not be considered here. There were no substantial changes in any laboratory parameter during the study. WBC showed a small mean percent increase from Baseline in the OGT 918

and Cerezyme groups of +5.3% and +6.2%, respectively, and a small mean decrease from Bzseline in the Combination group of –0.4%. In the WBC differential populations of neutrophils and lymphocytes, only the Combination group had a small mean percent decrease from Baseline in the neutrophils of –1.0%. Trends noted from Baseline to Month 6 are as follows:

(a) Alkaline Phosphatase, AST and ALT

Alkaline phosphatase showed a mild increase of 4% in the OGT 918 group, and mild decreases in the Cerezyme group (-2%) and the Combination group (-8%). ALT increased in all treatment groups, with an increase in the OGT 918 group of 41%, in the Cerezyme group of 66%, and in the combination group of 65%. AST also increased in all treatment groups, with an increase in the OGT 918 group of 12%, in the Cerezyme group of 1%, and in the Combination group of 4%
There were no other notable laboratory results.

(8) Physical Findings

(a) Weight

There were mean decreases in weight for all treatment groups, with numerically greater mean decreases in the groups exposed to OGT 918. By treatment group, there was a mean decrease in the OGT 918 group of –4.6 kg, in the Cerezyme group of –1.0 kg, and in the Combination group of –2.6 kg. The results were significant in the OGT 918 and Combination groups (p=<.001 and p=.029, respectively). Weight changes are summarized in the following table

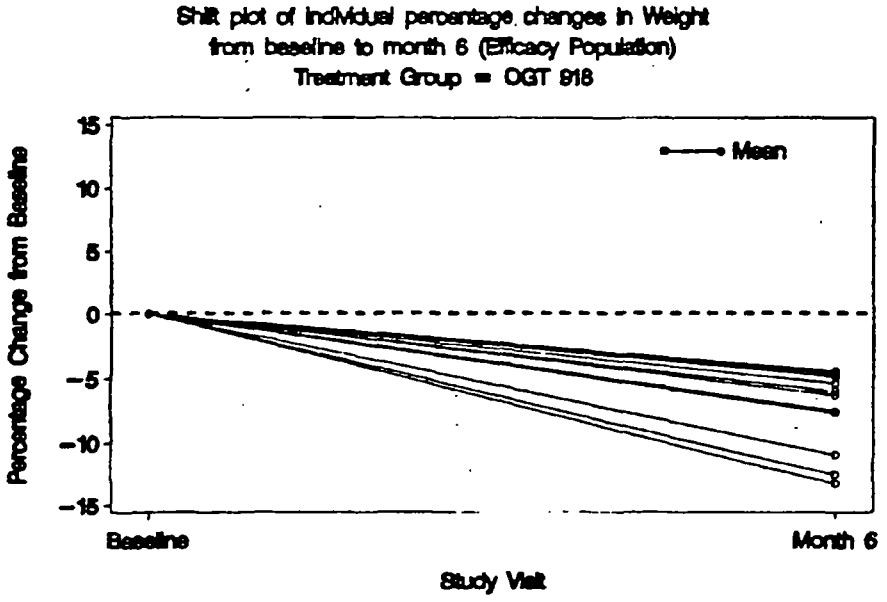
Table 162: 918-004 Weight Statistics

			Month 6		
Treatment	Statistic	Baseline (kg)	Month 6 (kg)	Change (kg)	% Change
OGT 918	n	10	10	10	10
	Mean	60.8	56.3	-4.6	-7.6
	Median	60.0	54.4	-3.7	-6.1
	Minimum				
	Maximum				
	p-value			<.001	<.001
Cerezyme	n	12	11	11	11
	Mean	70.2	69.2	-1.0	-1.2
	Median	70.1	70.0	-0.6	-0.9
	Minimum				
	Maximum				
	p-value			.097	0.148
Combination	n	11	11	11	11
	Mean	69.3	66.7	-2.6	-4.0
	Median	64.3	60.5	-3.0	-4.8
	Minimum				
	Maximum				
	p-value			.029	.016

Percentage change from Baseline to Month 6 in weight was plotted (by the sponsor) for individual patients, by treatment group. The results are as follows (see Figures):

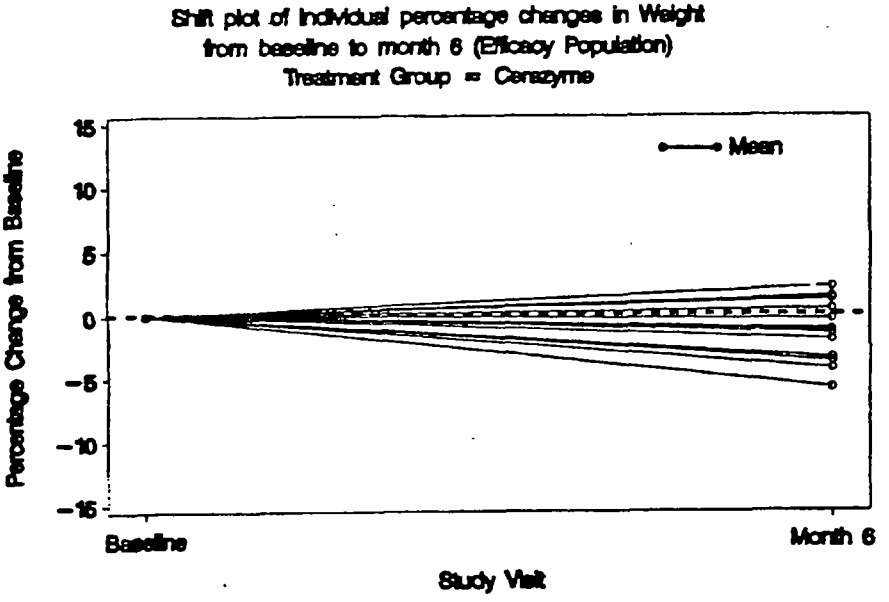
OGT 918 Group

Figure 45: 918-004 Percent Change from Baseline to Month 6 in Weight, OGT 918 Group



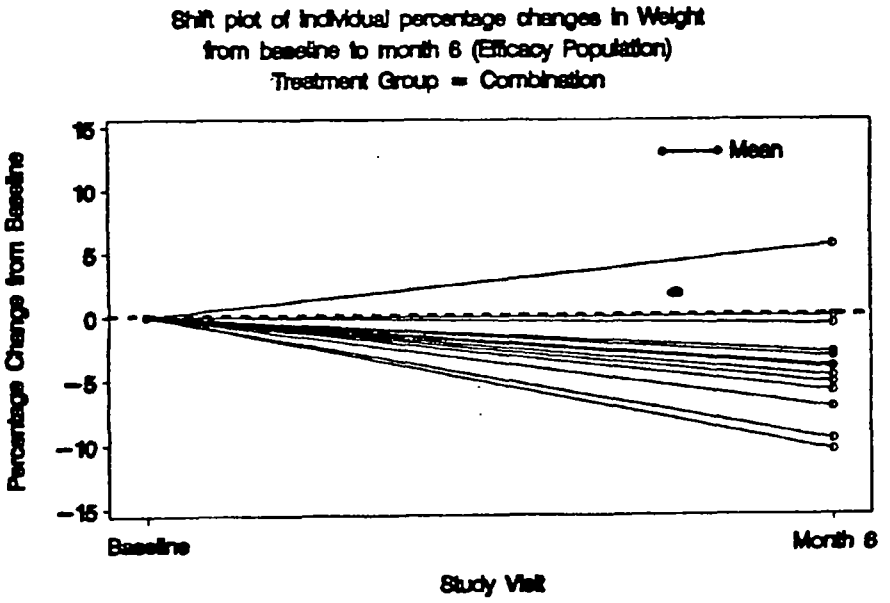
Cerezyme Group

Figure 46: 918-004 Percent Change from Baseline to Month 6 in Weight, Cerezyme Group



Combination Group

Figure 47: 918-004 Percent Change from Baseline to Month 6 in Weight, Combination Group



(b) Blood Pressure

Three (3) patients were reported as having a low diastolic blood pressure during the study: 2 patients in the Combination group (#125 and #135), and 1 patient in the Cerezyme group (#127). One patient was reported as having hypotension: Patient 134 in the Combination group. In addition, 2 patients were reported by the Investigator as having significantly decreased BP during the study. One patient (#110 in the OGT 918 group) was reported as having a low systolic BP at Month 3. This patient withdrew from the study and no further measurements were taken. The other patient (#111 in the OGT 918 gr4oup) was reported as having a low diastolic BP at Month 1, which improved through out the study.

(c) Cardiac

An increase in heart murmurs was noted in the Cerezyme group, with 7 patients reporting a Cardiovascular abnormality, of which 5 were heart murmurs. No other details were provided. There were no new Cardiovascular complaints in any of the other treatment groups.

(d) Other

There were no other notable or clinically significant changes in Physical Exam during the study (including slit lamp exam), nor were there any clinically significant changes in the ECGs.

f) Study 918-004X

(1) Adverse Events

All patients who continued in Study 918-004X received OGT 918 in the extension study. Adverse Events are reported from entry into the original study through extension study completion/termination, and patients are grouped by original randomization. All 29 patients (100%) reported at least one AE during the study. There were 89 different AE terms reported, with AEs in the Gastrointestinal system being the most commonly reported. Diarrhea was the most commonly reported AE term, reported by 90% of patients overall; however, unlike the original study (918-004), there were no substantial differences in incidence of diarrhea between the treatment groups. Weight decrease and AEs in the Neurologic system were also about as common in the Cerezyme alone group (by original randomization) as they were in the OGT 918 and Combination treatment group in the extension study. These findings make an association between treatment with OGT 918 and weight decrease, and GI and Neurologic system AEs likely. The most common AEs (occurring in $\geq$5% of patients, or $\geq$2 patients), by original treatment group randomization, are listed in the following table [A complete list of all reported AEs is in the Appendix]

Table 163: 918-004X Incidence of Most Common AEs (>5% of Patient Overall), by Original Treatment Group Randomization

		All	Treatment		
			OGT 918	Cerezyme	OGT 918 + Cerezyme
Randomized Patients, n =		29	10	10	9
Body System	WHO AE Term	n (%)	n (%)	n (%)	n (%)
	Uncoded	4 (14)	1 (10)	0	3 (33)
Skin and Appendage	Pruritus	3 (10)	1 (10)	1 (10)	1 (11)
Musculoskeletal	Bone Pain	3 (10)	0	2 (20)	1 (11)
	Pain Neck/Shoulder	3 (10)	1 (10)	1 (10)	1 (11)
	Joint Pain	2 (7)	1 (10)	1 (10)	0
Neurological	Tremor	9 (31)	3 (30)	3 (30)	3 (33)
	Headache	7 (24)	2 (20)	2 (20)	3 (33)
	Dizziness	5 (17)	1 (10)	1 (10)	3 (33)
Vision	Visual Disturbance	2 (7)	1 (10)	0	1 (11)
Psychiatric	Appetite Decreased	2 (7)	1 (10)	0	1 (11)
Gastrointestinal	Diarrhea	26 (90)	10 (100)	8 (80)	8 (89)
	Flatulence	17 (59)	9 (90)	2 (20)	6 (67)
	Abdominal Pain	16 (55)	8 (80)	1 (10)	7 (78)
	Constipation	8 (28)	2 (20)	2 (20)	4 (44)
	Nausea	3 (10)	1 (10)	1 (10)	1 (11)
	Vomiting	3 (10)	0	1 (10)	2 (22)
Metabolic and Nutritional	Weight Decrease	23 (79)	10 (100)	6 (60)	7 (78)
	Weight Increase	2 (7)	0	1 (20)	1 (11)
Cardiovascular	Hypotension	3 (10)	0	1 (10)	2 (22)
Heart Rate and Rhythm	Bradycardia	2 (7)	1 (10)	1 (10)	0
Respiratory	Throat Sore	3 (10)	0	0	3 (33)
	Pneumonia	2 (7)	1 (10)	1 (10)	0
	Rhinitis	2 (7)	1 (10)	1 (10)	0
	Upper Respiratory Tract Infection	2 (7)	1 (10)	0	1 (11)
Platelet, Bleeding and Clotting	Hematoma	2 (7)	0	1 (10)	1 (11)
Urinary	Urinary Tract Infection	6 (21)	2 (20)	1 (10)	3 (33)
Body as a Whole	Influenza-Like Symptoms	16 (55)	6 (60)	4 (40)	6 (67)
	Pain Trauma Activated	5 (17)	2 (20)	2 (20)	1 (11)
	Weakness Generalized	5 (17)	2 (20)	2 (20)	1 (11)
	Chest Pain	3 (10)	3 (30)	0	0
	Fatigue	3 (10)	2 (20)	0	1 (11)
	Fever	3 (10)	1 (10)	1 (10)	1 (11)
	Pain Legs	3 (10)	0	0	3 (33)
	Abdominal Distension	2 (7)	1 (10)	0	1 (11)
Unclassifiable	Fall	4 (14)	1 (10)	2 (20)	1 (11)
	Inflicted Injury	4 (14)	2 (20)	1 (10)	1 (11)

(2) Adverse Events Over Time

As in the previous studies with OGT 918, the OGT 918 was noted to have a decrease in diarrhea and other GI complaints over time, and increases in weight loss. There were no obvious increases in tremor or other Nervous system disorders after Week 26 however. In patients switching to OGT 918 monotherapy, diarrhea and GI complaints increased after 26 weeks, as did weight loss and Nervous system complaints. The incidence of selected AEs over the course of the study are summarized in the following table

Table 164: 918-004X Incidence of Selected Adverse Events Over Course of Study

				Weeks		
		Treatment	Overall	0-26	>26-39	>39
Patients, n =		OGT 918	10	10	10	9
		Cerezyme	10	10	10	10
		Combination	9	9	9	9
Body System	WHO AE Term		n (%)	n (%)	n (%)	n (%)
Gastrointestinal	All	OGT 918	10 (100)	10 (100)	4 (40)	3 (33)
		Cerezyme	9 (90)	7 (70)	6 (60)	5 (50)
		Combination	9 (100)	9 (100)	3 (33)	7 (78)
	Diarrhea	OGT 918	10 (100)	10 (100)	4 (40)	2 (22)
		Cerezyme	8 (80)	3 (30)	4 (40)	4 (40)
		Combination	8 (89)	8 (89)	3 (33)	6 (67)
Metabolic and Nutritional	Weight Decrease	OGT 918	10 (100)	8 (80)	9 (90)	7 (78)
		Cerezyme	6 (60)	1 (10)	4 (40)	6 (60)
		Combination	7 (78)	5 (56)	6 (67)	6 (67)
Nervous	All	OGT 918	6 (60)	6 (60)	1 (10)	3 (33)
		Cerezyme	4 (40)	2 (20)	3 (30)	3 (30)
		Combination	8 (89)	7 (78)	0	1 (11)
	Tremor	OGT 918	3 (30)	3 (30)	1 (10)	1 (11)
		Cerezyme	3 (30)	1 (10)	2 (20)	2 (20)
		Combination	3 (33)	3 (78)	0	0

(3) Withdrawals Due to Adverse Events

One patient discontinued study medication prior to study completion due to AEs. This patient, Patient 130 (OGT 918 group), withdrew at Month 12 due to diarrhea, abdominal complaints and tremor in hands. The tremor, diarrhea, and abdominal pain were initially reported at Month 2.

(4) Serious Adverse Events

One patient reported one SAE during the extension study. There were no deaths. This patient, Patient 108 (Combination treatment group), was hospitalized for an elective tonsillectomy.

Table 165: 918-004X Serious Adverse Events

Patient	M/F	Age (yrs)	Serious Adverse Event	Body System	Onset (days)	Invest. Attrib.	Drug D/C?
108	F	26	Tonsillectomy	Uncodable	Approx. 319	NR	No

(5) Other Significant Adverse Events

Please see Study 918-004 for a summary of the neurologic AEs. There were no other significant AEs during the study.

(6) Laboratory Assessments

There were no substantial changes in any laboratory parameter during the study. WBC showed a mean percent increase from Baseline in the OGT 918 group of +13.0%, and mean decreases from Bzseline in the Cerezyme and Combination groups of –4.3% and –11.9%, respectively. In the WBC differential populations of neutrophils and lymphocytes, the Cerezyme and Combination groups had mean percent decreases from Baseline in the neutrophils of –5.4% and –13.0%, respectively, and in the lymphocytes of

–6.0% and –9.8%, respectively. Other trends noted from Baseline to Endpoint are as follows:

(a) Alkaline Phosphatase, AST and ALT

There were differences between the groups in mean changes from baseline to Month 12 in alkaline phosphatase, ALT and AST. Alkaline phosphatase showed a mean increase in the OGT 918 group of 14%, and decreases in the Cerezyme group (-1%) and the Combination group (-3%). ALT showed mean increases in the OGT 918 group of 2% and in the Combination group of 109%, and a mean decrease in the Cerezyme group of –1%. AST showed mean increases in all treatment groups, with an increase in the OGT 918 group of 21%, in the Cerezyme group of 4%, and in the Combination group of 49%.

Two patients had abnormal results during extended treatment that were considered clinically signficant by the Investigator. Patient 113 (Cerezyme) had increased LFTs at Month 9 of ALT 105 U/l. AST 67 U/l. and gamma-GT of 197 U/l. At Month 12 the ALT and AST were normal (25 and 29 U/l respectively), but the gamma-GT remained elevated at 85 U/l (elevated at screening to 79 U/l). The other patient, Patient 114 (Combination) had an elevated ALT at Month 12 of 76 U/l. All previous values had been normal.

(7) Physical Findings

Vital signs, physical exams, and ECGs were not assessed during the extension phase of the study.

(a) Weight

Weight changes from Baseline for the treatment groups are summarized in the following table

Table 166: 918-004X Weight Statistics

		Baseline	Month 6			Month 12		
Treatment	Statistic	kg	kg	Change kg	% Change	kg	Change kg	% Change
OGT 918	n	10	10	10	10	9	9	9
	Mean	60.8	56.3	-4.6	-7.6	57.2	-3.5	-5.7
	Median	60.0	54.4	-3.7	-6.1	55.0	-4.0	-6.3
	Minimum							
	Maximum							
	p-value			<.001	<.001		.001	<.001
Cerezyme	n	10	10	10	10	10	10	10
	Mean	73.4	72.5	-1.0	-1.1	69.0	-4.4	-5.5
	Median	71.5	70.5	-0.6	-0.9	70.5	-16.0	-6.1
	Minimum							
	Maximum							
	p-value			.117	.163			.021
Combination	n	9	9	9	9	9	9	9
	Mean	68.8	66.3	-2.5	-4.1	65.7	-3.1	-5.0
	Median	64.3	60.5	-3.0	-5.3	62.0	-3.1	-5.3
	Minimum							
	Maximum							
	p-value			.076	.044		.029	.017

(b) Echocardiograms

Two patients had borderline pulmonary hypertension on entering the study (Patients 116 and 120) with a TI gradient of 30 mmHg each. Patient 116 was randomized to Cerezyme therapy. The TI gradients were 28 and 27 mmHg at Month 6 and Month 12, respectively. Patient 120 was randomized to OGT 918 with TI gradients of 26 and 23 mmHg at Months 6 and Month 12, respectively.

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3) Other Studies with OGT 918

a) Clinical Studies in HIV-1 Positive Patients

(1) Exposure

There were 4 studies in HIV positive patients with OGT 918 [2 Phase II studies and 2 Phase I studies]; and 8 studies with the pro-drug OGT 924 [1 Phase II study and 7 Phase I studies]. These studies are briefly summarized in the following table

Table 167: Studies in HIV Positive Patients With OGT 918 and OGT 924

Study	Dose	Description
OGT 918 Phase II Studies		
NS8-93-06-004	1000 mg TID	Double-blind, placebo-controlled, 3-phase, long-term (24-week), efficacy, tolerability, and PK study of OGT 918 + AZT. 118 patients enrolled, and 60 patients were exposed to OGT 918 (2 patients in extended-use phase)
NS8-94-06-009	500-1000 mg TID	Randomized, open-label, uncontrolled, long-term (12-week), efficacy, safety and PK study of OGT 918 + AZT. 67 patients enrolled, and 51 patients were exposed to OGT 918 (18 patients in extended-use phase)
Phase I		
NS8-93-06-001/PK	8-64 mg/kg/day	Open-label, ascending dose, single-dose and multi-dose (28-day) regimen, PK and tolerability study in 29 patients (10 patients in extended-use phase)
NS8-93-06-010/PK	1000 mg TID	Open-label, cross-over multi-dose (13-day), PK and tolerability study in 7 patients
OGT 924 Phase II		
NQ3-95-16-106	3-5 g TID	Randomized double-blind, placebo-controlled, long-term (24-week), efficacy and safety study of OGT 924 + AZT. 175 patients enrolled, and 113 were exposed to OGT 924
Phase I		
NQ3-94-06-101-01/PK	320 microCi/1.25 g	Single dose, open-label, radiolabeled study in 6 patients
NQ3-94-06-101-02/PK	1.25-5.0 g	Randomized, double-blind, comparator (placebo and OGT 918), single-dose, dose escalation, PK and tolerability study in 24 patients
NQ3-94-06-102/PK	3-5 g TID	Randomized, 3-phase [1) parallel group; 2) double-blind, placebo-controlled; 3) open-label], multi-dose (9-day), PK and tolerability study. 24 patients enrolled, and 20 patients were exposed to OGT 924
NQ3-94-06-103/PK	5 g TID	Randomized, open-label, parallel group, multi-dose (7-day), PK and tolerability study in 24 patients
NQ3-94-06-104/PK	3 g	Randomized, open-label, cross-over (to OGT 918), multi-dose (6-day), bioavailability, PK and tolerability study in 16 patients
NQ3-94-06-105/PK	5 g TID	Open-label, multi-dose (8-day), PK and tolerability study of OGT 924 + ddI in 12 patients
NQ3-94-06-107/ Bioavailability	3 g	Open-label, randomized, single-dose, cross-over, bioavailability study in 24 patients

In the OGT 918 Phase II studies (NS8-93-06-004 and NS8-94-06-009), 111 patients were exposed to OGT 918 for at least 3 months. There were also 36 patients enrolled in two Phase I PK studies, all of whom were exposed to OGT 918 for up to 28 days.

In the OGT 924 Phase II study (NQ3-95-16-106), 113 patients were exposed to OGT 924 for 24-weeks. There were also 100 patients enrolled in 7 Phase I single-dose and multi-dose, PK/bioavailability studies, who were exposed to OGT 924 for up to 9 days.

(2) Adverse Events

The OGT 918 Phase II studies were pooled by the sponsor, and AEs in the OGT 918 group were compared to placebo. As with the studies with OGT 918 in Gaucher disease patients, AEs in the Gastrointestinal system were the most commonly reported. Diarrhea, flatulence, and nausea were the most commonly reported AE terms (by 86%, 51%, and 40% of patients respectively) in the OGT 918 group, and were all more commonly reported in the OGT 918 group than in the placebo group (reported by 35%, 22%, and 28% respectively). The other AEs were relatively evenly reported across the 2 groups. It is notable that no complaints of tremor were reported, and paresthesia occurred in 8 patients (7%) exposed to OGT 918 and 2 patients (3%) given placebo. The most commonly reported AEs are listed in the following table

Table 168: Combined Phase II Studies in HIV-1 Positive Patients Incidence of AEs >5% of Patients

		OGT 918	Placebo
Exposed Patients, n =		111	74
Body System	WHO AE Term	n (%)	n (%)
Musculoskeletal	Myalgia	10 (9)	10 (14)
Neurological	Headache	43 (39)	22 (30)
	Paresthesia	8 (7)	2 (3)
	Dizziness	10 (9)	3 (4)
Gastrointestinal	Diarrhea	96 (86)	25 (34)
	Flatulence	57 (51)	16 (22)
	Abdominal Pain	31 (28)	15 (20)
	Nausea	44 (40)	21 (28)
	Anorexia	12 (11)	7 (9)
	Vomiting	19 (17)	10 (14)
	Oral Leucoplakia	15 (14)	8 (11)
Metabolic and Nutritional	Weight Decrease	7 (6)	2 (3)
Respiratory	Rhinitis	16 (14)	17 (23)
	Coughing	12 (11)	21 (28)
Body as a Whole	Fever	15 (14)	7 (9)
	Pain	7 (6)	4 (5)
	Fatigue	40 (36)	21 (28)
White Cell and RES	Granulocytopenia	9 (8)	4 (5)
	Lymphadenopathy	10 (9)	14 (19)
Skin and Appendage	Rash	9 (8)	7 (9)
Resistance Mechanism	Moniliasis	7 (6)	3 (4)
Hepatic	Abnormal Hepatic Function	0	2 (3)

In addition, the percentage of patients who discontinued study medication prior to study completion was higher in the OGT 918-exposed patients than in the placebo-exposed patients. Overall, 31% of patients discontinued study drug treatment prior to study completion: 36% in the OGT 918 group and 24% in the placebo group. The percentage of patients discontinuing for AEs was also higher in the OGT 918 group (14%) vs the placebo group (4%).

Table 169: 918-002 OGT 918 in the Treatment of Fabry Disease, All Adverse Events

Enrolled Patients, n =		All 16
Body System	**WHO AE Term**	**n (%)**
Gastrointestinal	All	16 (100)
	Diarrhea	15 (15)
	Flatulence	9 (56)
	Vomiting	5 (31)
	Nausea	4 (25)
	Abdominal Pain	2 (13)
Nervous System	All	14 (88)
	Tremor	13 (81)
	Dizziness	2 (13)
	Paresthesia	2 (13)
	Vertigo	2 (13)
Metabolic and Nutritional	All	13 (81)
	Weight Decrease	11 (69)
	Creatinine Increased	2 (13)
	Weight Increase	2 (13)
Body as a Whole	All	11 (69)
	Influenza-like symptoms	9 (56)
	Fatigue	4 (25)
	Edema	3 (19)
	Back Pain	2 (13)
	Chest Pain	2 (13)
	Fever	2 (13)
Psychiatric	All	6 (38)
	Depression	3 (19)
	Libido decreased	3 (19)
Skin and Appendage	All	4 (25)
	Itching	2 (13)
	Skin Dry	2 (13)
Musculoskeletal	All	3 (19)
	Arthralgia	3 (19)
Reproductive, male	All	3 (19)
	Sexual function abnormal	3 (19)
Non-classifiable	All	2 (13)
	Inflicted injury	2 (13)

As in other studies with OGT 918, diarrhea was noted to decrease overtime, and tremor and weight decrease were noted to increase over time. There were no clinically notable laboratory or vital sign results, with the exceptions of small decreases in weight and BMI.

D. Adequacy of Safety Testing

[Please also refer to the Summary of Critical Safety Findings and Limitations of Data section below]. Adverse Events were analyzed by individual studies, and pooled for all patients exposed to OGT 918 in the Combined Safety Dataset. The results for all these analyses were similar and, in general, the safety testing was adequate to assess common AEs frequently seen with the use of OGT 918. Specifically, all the studies of OGT 918 in Gaucher disease type 1 patients noted a high incidence of Gastrointestinal, Metabolic, and Nervous system AEs, in particular diarrhea and other GI complaints, weight loss, and tremor.

However, the clinical program was inadequate to assess the neurologic AEs associated with the use of OGT 918 in these patients. The studies included in this NDA 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, making interpretation of the results difficult and confusing. The follow-up of the paresthesias and numbness was also limited and of a relatively short duration. 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.

In addition, an SAE for memory loss was reported late in the NDA review cycle, and a review of the safety database revealed 6 patients who reported memory loss during or after the use of OGT 918. On preliminary review, at least 2 of these patients appear to have a persistent cognitive impairment. As with the parasthesias and numbness above, interpretation of the memory loss AEs is difficult due to lack of baseline evaluations and concurrent medical conditions, such as B12 deficiency. Further information has been requested from the sponsor, and further evaluation of memory loss is ongoing at the time of this review. 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

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OGT 918 has not been administered to pediatric patients to date, and the unknown effects of GSL depletion on the developing brain are concerning. The weight loss associated with the use of OGT 918 also has the potential to adversely effect growth and development in pediatric patients, especially as delayed growth and sexual maturation are common findings in pediatric Gaucher disease type 1 patients. careful review of a much larger adult safety database, careful monitoring of the central and peripheral nervous systems, and a detailed assessment of the effects on bone and nutrition should be undertaken.

Other safety concerns noted with OGT 918 either in clinical or pre-clinical studies that warrant further investigation 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. Male reproductive toxicities were noted in animals, and these findings have not been evaluated for reversibility, either in humans or animals [However, it should be noted that during the study, one male patient (Patient 402 in study 918-001) fathered a normal child approximately 15 months after study withdrawal.]

E. Summary of Critical Safety Findings and Limitations of Data

AEs in the Gastrointestinal system were the most commonly reported AEs in every study and in every patient population exposed to OGT 918. In the Combined Safety Dataset, diarrhea was the most commonly reported AE term, reported by 90% of patients. Weight loss was the next most commonly reported AE term, reported by 65% of patients. Diarrhea appears to be the result of the disaccharidase inhibitory activity of OGT 918, with a resultant osmotic diarrhea. It is unclear if weight loss results from the diarrhea and associated GI complaints, a decrease in food intake, or a combination of these or other factors. The incidence of diarrhea was noted to decrease over the course of the study, and was noted to result in 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 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.

The association of paresthesias, numbness, and abnormal EDX testing with the use of OGT 918 in Gaucher disease type 1 patients was less straight forward than that of tremor. As neurologic AEs had not been noted to any extent in previous studies with OGT 918 in HIV-positive patients, EDX testing was added to the protocols after these neurologic complaints were first noted in the initial Gaucher disease study (918-001). Thirty-two

percent (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; however, no patient had an EMG performed at baseline, and not all patients underwent EDX testing. Co-existing medical conditions, such as diabetes, vitamin B12 deficiency, and gammopathies were also noted in many patients with abnormal EDX studies, making the interpretation of the EDX results difficult. However, 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 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.

The mechanism by which OGT 918 produces neurotoxicity could be explained by 2 possible theories.

First of all, in pre-clinical studies with another class of ceramide-specific glucosyltransferase inhibitors, the ceramide analogues of which the prototypic compound is PDMP[13], treatment with PDMP analogues resulted in the accumulation of free ceramide. Ceramide has been shown to trigger apoptosis, and its concentration also plays a regulatory role as a second messenger. In Farber disease, another disorder of GSL degradation, affected patients cannot degrade ceramide. In one form of Farber disease, most of the affected patients have a peripheral neuropathy, that may be due, at least in part, to the neurotoxicity of ceramide[14]. OGT 918 has not been shown to cause ceramide accumulation in pre-clinical studies; however, it is not known if this has been evaluated in humans.

The second possible mechanism whereby OGT 918 may cause neurotoxicity may be due to its inhibition of GSL synthesis and the depletion of glycolipid in the nervous system.

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[13] Lachmann RH, Platt FM. Substrate reduction therapy for glycosphingolipid storage disorders. Exp Opin Invest Drugs 2001;10(3):455-466.
[14] Tremblay G. Consultative Review and Evaluation of Clinical Data, NDA 21-348, page 5.

Several pre-clinical and clinical observations support this theory[13, 15]. 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 ganglosides, 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.

Further evidence of neurotoxicity was seen in pre-clinical studies with OGT 918. In monkeys, OGT 918 at doses 4-6X the human equivalent dose resulted in mineralization and necrosis of white matter. There were no clinical signs of toxicity in the animals, however.

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.

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 standarized 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.

   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

[15] 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

expected, given the lack of baseline information and the small safety database, further neuropsychologic investigations will likely be recommended.

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. The neurologic AEs are of particular concern for _____ OGT 918 has not been administered to pediatric patients to date, _____

_____

3. Weight loss was a common finding associated with the use of OGT 918. This is of particular concern for its potential to adversely effect growth and development in _____ especially as delayed growth and sexual maturation are common findings in pediatric Gaucher disease type 1 patients.

3. Male reproductive toxicities, including affects on sperm and the male reproductive organs were noted in animals. These findings have not been evaluated for reversibility, either in humans or animals.

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VII. Dosing, Regimen, and Administration Issues

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.

VIII. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

Forty-seven (47) of the 82 patients (57%) enrolled in the clinical program were female. The sponsor performed a subgroup analysis by sex, and no statistically significant drug-gender interaction was found with respect to any of the 4 efficacy parameters (liver and spleen volume, and change in hemoglobin and platelet values). For safety, there were no significant differences and no trends in safety parameters noted by gender.

B. Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

OGT 918 was evaluated in Gaucher disease type 1 patients from 18 years to 69 years of age. A subgroup analysis was performed for patients ages 18-30 years vs >30 years, which did not show any significant drug-age group interactions for the efficacy parameters. Although Gaucher disease type 1 is a pan-ethnic disorder, it has a much higher prevalence in the Ashkenazi Jewish population. Thus, not unexpectedly, enrollment by race in the clinical program reflected the prevalence of the disease seen in the population, with 63 of the 82 patients (77%) enrolled being Ashkenazi Jews. Due to the small number of non-Ashkenazi Jews, particularly by treatment group in the 918-004 study, no meaningful comparisons by race could be made. However, the glucocerebrosidase enzyme defects were also analyzed by the sponsor, and, not unexpectedly, there was a high prevalence of the N370S genotype, the most common genotype especially in Askenazi Jews (accounting for 80-90% of Gaucher disease type 1 enzyme defects in Ashkenazi Jews). Forty-one (41) of 82 patients (50%) in the clinical studies had the N370S genotype. No significant drug-genotype interactions were found. A subgroup analysis by BMI , <25 kg/M^2 (underweight/normal) vs ≥ 25 kg/ M^2 (overweight/obese) was also performed. For the efficacy parameters, a significantly poorer hemoglobin response was seen in the normal/underweight subgroup compared to the overweight/obese subgroup with treatment with Combination therapy in the 918-004 study.

C. Evaluation of Pediatric Program

The clinical studies submitted to the NDA were all performed in patients ages >18 years, and no clinical data were submitted in pediatric patients. In addition, there does not appear to have been any clinical evaluation of OGT 918 in pediatric patients for any other indication to date, such as in HIV-positive patients. OGT 918 currently has an open IND for the use of OGT 918 in Niemann-Pick type C disease (NPC), which would be expected to enroll predominantly pediatric patients (ages >12years); however, enrollment has not yet begun in this clinical program. Given the drastically different clinical presentation, poor prognosis, and lack of alternate therapy for NPC patients, however; pediatric trials of OGT 918 in NPC can be justified at this time.

It is the recommendation of this Reviewer, and of the DNDP Medical Consultant and Team Leader, [redacted] in Gaucher disease type 1 not be allowed to proceed at this time. GSLs are present in high concentrations in the nervous system, and appear to play a role in cell-cell communication and signaling. [redacted]

[redacted] it is strongly encouraged that preclinical developmental studies, careful review of a much larger adult safety database, careful monitoring of both central and peripheral nervous system function, and a detailed evaluation of the effects of OGT 918 on bone and nutrition be undertaken.

D. Comments on Data Available or Needed in Other Populations

Clinical trials submitted to the NDA have been performed in patients with compromised renal function (in Fabry disease patients), and adjustment of dose for renal impairment has been delineated. In addition, studies in patients with mild hepatic impairment have also been performed, and no dosage adjustment is required. However, studies in patients with moderate to severe hepatic impairment have not been performed, and further data would need to be submitted prior to the recommended use of OGT 918 in patients with moderately to severly compromised hepatic function.

In addition, *in vitro* studies with human hepatocytes showed that OGT 918 was not metabolized to any extent by the cytochrome P450 system. However, no drug interaction assessments have been made, other than for the anti-diarrheal medications used in this study. Lack of available drug interaction data will limit labeling precautions, warnings, and recommendations for use of OGT 918 with other drugs.

IX. Conclusions and Recommendations

A. Conclusions

In conclusion, the data from the clinical safety and efficacy studies submitted to NDA 21-348 were inadequate to assess the safety concerns seen with OGT 918. OGT 918 did not demonstrate efficacy in all populations of Gaucher disease type 1 patients studied in the clinical program, nor did it demonstrate efficacy in in all the important clinical markers of Gaucher disease. The findings of the OGT 918 in Gaucher disease type 1 clinical program are summarized as follow.

For the efficacy data:

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

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

For the safety data:

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

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

B. Recommendations

It is recommended that this NDA receive an approvable letter pending further safety and efficacy evaluations, as follows:

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

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

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

4. The slow Hgb and Plt responses, with statistically significant, but clinically minor, improvements seen after 18 and 24 months of treatment with OGT 918 were somewhat surprising. A better response would have been expected, considering the decrease in spleen volume [and improvements in bone marrow fat fraction on QCSI although only performed in 2 patients], and considering the rapid and often dramatic improvements seen in the ERT studies. Adverse effects of OGT 918 on bone marrow, RBCs, and lymphocytes were noted in pre-clinical and clinical studies, and further exploration of the underlying mechanism of these adverse effects should be considered. Bone marrow assessment by serial evaluations of the validated QCSI test are recommended, in addition to other studies per discussions with the Animal Pharmacology Division and the sponsor.

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

6. [redacted]

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

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

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

XI. Appendix B

A. Adverse Events

1) Study 918-001

Table 170: 918-001 Incidence of All Adverse Events

Randomized Patients, n =		28
Body System	**WHO AE Term**	**n (%)**
Skin and Appendage	Eczema	1 (4)
	Furunculosis	1 (4)
	Skin Discoloration	1 (4)
	Skin Reaction	1 (4
Musculoskeletal	Myalgia	3 (11)
	Back Pain	2 (7)
	Skeletal Pain	2 (7)
	Arthralgia	1 (4)
	Arthropathy	1 (4)
Neurological	Headache	9 (32)
	Tremor	4 (14)
	Paresthesia	3 (11)
	Dizziness	2 (7)
	Burning Mucosal	1 (4)
	Cramps Legs	1 (4)
	Migraine	1 (4)
	Neuritis	1 (4)
	Vertigo	1 (4)
Vision	Vision Abnormal	1 (4)
Hearing and Vestibular	Vestibular Disorder	1 (4)
Special Senses	Taste Perversion	1 (4)
Psychiatric	Amnesia	1 (4)
	Depression	1 (4)
	Insomnia	1 (4)
Gastrointestinal	Diarrhea	25 (89)
	Flatulence	8 (29)
	Abdominal Pain	7 (25)
	Nausea	4 (14)
	Anorexia	3 (11)
	Dyspepsia	3 (11)
	Vomiting	2 (7)
	Constipation	1 (4)
	Hemorrhage Rectum	1 (4)
	Hemorrhoids	1 (4)
	Mouth Dry	1 (4)
	Tooth Ache	1 (4)
Metabolic and Nutritional	Weight Decrease	12 (43)
Cardiovascular	Hypertension Pulmonary	1 (4)
Heart Rate and Rhythm	Arrhythmia	1 (4)
Vascular	Flushing	1 (4)
Respiratory	Rhinitis	5 (18)
	Upper Respiratory Tract Infection	4 (14)
	Sinusitis	2 (7)

	Coughing	1 (4)
	Pleurisy	1 (4)
Red Cell	Anemia	1 (4)
White Cell and RES	Leucopenia	1 (4)
	Lymphadenopathy	1 (4)
Platelet, Bleeding and Clotting	Thrombocytopenia	5 (18)
	Purpura	4 (14)
	Epistaxis	2 (7)
	Ocular Hemorrhage	1 (4)
	Spleen Disorder	1 (4)
	Thrombosis	1 (4)
	Vaginal Hemorrhage	1 (4)
Urinary System	Urinary Tract Infection	1 (4)
Reproductive, Male	Testicular Pain	1 (4)
Reproductive, Female	Menstrual Disorder	1 (4)
Body as a Whole	Influenza-like Symptoms	3 (11)
	Chest Pain	2 (7)
	Fatigue	2 (7)
	Tiredness	2 (7)
	Eye Infection	1 (4)
	Fever	1 (4)
	Leg Pain	1 (4)
	Malaise	1 (4)
	Rigors	1 (4)
Resistance Mechanism	Infection Viral	1 (4)
Unclassifiable	Fall	2 (7)
	Bite	1 (4)

2) Study 918-001X

Table 171: 918-001X Incidence of All Adverse Events

Randomized Patients, n =		18
Body System	**WHO AE Term**	**n (%)**
Uncoded	"Hip Replacement"	1 (6)
Skin and Appendage	Eczema	1 (6)
	Nail Changes	1 (6)
	Skin Reaction	1 (6)
Musculoskeletal	Myalgia	3 (17)
	Back Pain	2 (11)
	Arthralgia	1 (6)
	Bone Pain	1 (6)
	Joint Effusion	1 (6)
	Muscle Cramp	1 (6)
	Skeletal Pain	1 (6)
Neurological	Headache	8 (44)
	Cramps Legs	3 (17)
	Dizziness	3 (17)
	Paresthesia	3 (17)
	Tremor	3 (17)
	Neuropathy	2 (11)
	Vertigo	2 (11)
	Burning Mucosal	1 (6)
	Dizziness Postural	1 (6)

	Migraine	1 (6)
	Neuritis	1 (6)
Vision	Eye Infection	1 (6)
Hearing and Vestibular	Tinnitus	1 (6)
	Vestibular Disorder	1 (6)
Special Senses	Taste Perversion	1 (6)
Psychiatric	Anorexia	3 (17)
	Memory Loss	2 (11)
	Amnesia	1 (6)
	Appetite Absent	1 (6)
	Depression	1 (6)
	Insomnia	1 (6)
Gastrointestinal	Diarrhea	16 (89)
	Flatulence	6 (33)
	Abdominal Pain	5 (28)
	Vomiting	3 (17)
	Nausea	2 (11)
	Constipation	1 (6)
	Dyspepsia	1 (6)
	Pain Right Upper Quadrant	1 (6)
	Rectal Bleeding	1 (6)
	Tooth Ache	1 (6)
Metabolic and Nutritional	Weight Decrease	11 (61)
	Hypertriglyceridemia	1 (6)
Vascular	Flushing	1 (6)
Respiratory	Rhinitis	3 (17)
	Upper Respiratory Tract Infection	3 (17)
	Sinusitis	2 (11)
	Chronic Obstructive Airways Disease	1 (6)
	Coughing	1 (6)
	Pharyngitis	1 (6)
	Pleurisy	1 (6)
	Pneumonia	1 (6)
Red Cell	Anemia	1 (6)
White Cell and RES	Leucopenia	1 (6)
	Lymphadenopathy	1 (6)
Platelets, Bleeding and Clotting	Purpura	4 (22)
	Thrombocytopenia	3 (17)
	Ecchymosis	1 (6)
	Epistaxis	1 (6)
Urinary	Urinary Tract Infection	1 (6)
Reproductive, Female	Vaginal Hemorrhage	1 (6)
Body as a Whole	Influenza-like Symptoms	4 (22)
	Fatigue	3 (17)
	Tiredness	2 (11)
	Fever	1 (6)
	Leg Pain	1 (6)
	Malaise	1 (6)
	Pain	1 (6)
	Pain Legs	1 (6)
	Rigors	1 (6)
Resistance Mechanism	Candidiasis	1 (6)
	Infection Viral	1 (6)
Unclassifiable	Fall	2 (11)
	Bite	1 (6)

3) Study 918-003

Table 172: 918-003 Incidence of All Adverse Events

Randomized Patients, n =		18
Body System	**WHO AE Term**	**n (%)**
Skin and Appendage	Blisters	1 (6)
	Sunburn	1 (6)
Musculoskeletal	Bone Pain	2 (11)
	Cramps	2 (11)
	Pain Neck/Shoulder	2 (11)
	Muscle Cramp	1 (6)
Neurological	Headache	9 (50)
	Tremor	7 (39)
	Dizziness	4 (22)
	Cramps Legs	2 (11)
	Migraine	1 (6)
	Muscle Spasticity	1 (6)
	Muscular Unrest	1 (6)
Vision	Visual Disturbance	3 (17)
	Eye Infection	2 (11)
	Eye Irritation	2 (11)
	Eye Pain	1 (6)
Special Senses	Taste Peculiar	1 (6)
Psychiatric	Appetite Absent	1 (6)
Gastrointestinal	Diarrhea	17 (94)
	Abdominal Pain	9 (50)
	Flatulence	9 (50)
	Nausea	4 (22)
	Vomiting	3 (17)
	Bloating	1 (6)
	Constipation	1 (6)
	Epigastric Pain Not Food Related	1 (6)
	Gastroenteritis	1 (6)
	Hemorrhoids	1 (6)
	Heartburn	1 (6)
	Mouth Dry	1 (6)
	Rectal Bleeding	1 (6)
	Tooth Caries	1 (6)
Metabolic and Nutritional	Weight Decrease	12 (67)
	Weight Increase	2 (11)
Cardiovascular	Ankle Edema	1 (6)
Heart Rate and Rhythm	Palpitation	1 (6)
Vascular	Eye Hemorrhage	1 (6)
Respiratory	Nose Congestion	2 (11)
	Bronchitis	1 (6)
	Chronic Obstructive Airways Disease	1 (6)
	Laryngitis	1 (6)
	Rhinitis	1 (6)
	Sneezing Excessive	1 (6)
	Throat Infection	1 (6)
	Upper Respiratory Tract Infection	1 (6)
Platelet, Bleeding and Clotting	Nosebleed	2 (11)
	Ecchymosis	1 (6)
	Petechiae	1 (6)

	Thrombocytopenia	1 (6)
Urinary	Cystitis	1 (6)
	Urinary Tract Infection	1 (6)
Reproductive, Female	Menorrhagia	1 (6)
	Menstrual Disorder	1 (6)
Body as a Whole	Influenza-Like Symptoms	6 (33)
	Back Pain	3 (17)
	Chest Pain	2 (11)
	Fatigue	2 (11)
	Back Ache	1 (6)
	Fever	1 (6)
	Hay Fever	1 (6)
	Lumbo-Sacral Pain	1 (6)
	Edema	1 (6)
	Pain	1 (6)
	Pain in Limb	1 (6)
	Syncope	1 (6)
Unclassifiable	Fall	1 (6)

4) Study 918-003X

Table 173: 918-003X Incidence of All Adverse Events

Randomized Patients, n =		16
Body System	**WHO AE Term**	**n (%)**
	Uncoded	1 (6)
Skin and Appendage	Blisters	1 (6)
	Hair Loss	1 (6)
	Itching	1 (6)
	Skin Disorder	1 (6)
	Sunburn	1 (6)
Musculoskeletal	Cramps	4 (25)
	Bone Pain	2 (13)
	Joint Pain	2 (13)
	Pain Neck/Shoulder	2 (13)
	Muscle Cramp	1 (6)
Neurological	Headache	9 (56)
	Tremor	7 (44)
	Dizziness	4 (25)
	Cramps Legs	3 (19)
	Paresthesia	2 (13)
	Migraine	1 (6)
	Muscle Spasticity	1 (6)
Vision	Visual Disturbance	4 (25)
	Eye Infection	2 (13)
	Eye Irritation	2 (13)
	Eye Pain	1 (6)
Special Senses	Taste Peculiar	1 (6)
Psychiatric	Appetite Absent	1 (6)
	Appetite Increased	1 (6)
	Depression	1 (6)
	Lethargy	1 (6)
Gastrointestinal	Diarrhea	15 (94)
	Abdominal Pain	10 (63)

	Flatulence	8 (50)
	Nausea	4 (25)
	Vomiting	2 (13)
	Bloating	1 (6)
	Constipation	1 (6)
	Epigastric Pain Not Food-Related	1 (6)
	Gastroenteritis	1 (6)
	Hemorrhoids	1 (6)
	Heartburn	1 (6)
	Mouth Dry	1 (6)
	Rectal Bleeding	1 (6)
	Tooth Caries	1 (6)
Metabolic and Nutritional	Weight Decrease	15 (94)
	Weight Increase	1 (6)
Endocrine	Hypothyroidism	1 (6)
Cardiovascular	Ankle Edema	1 (6)
Heart Rate and Rhythm	Palpitation	1 (6)
Vascular	Eye Hemorrhage	1 (6)
Respiratory	Nose Congestion	2 (13)
	Bronchitis	1 (6)
	Chronic Obstructive Airways Disease	1 (6)
	Laryngitis	1 (6)
	Rhinitis	1 (6)
	Sinus Headache	1 (6)
	Sneezing Excessive	1 (6)
	Throat Infection	1 (6)
	Upper Respiratory Tract Infection	1 (6)
Red Cell	Hemoglobin Decreased	1 (6)
Platelet, Bleeding and Clotting	Nosebleed	2 (13)
	Ecchymosis	1 (6)
	Gingival Bleeding	1 (6)
	Petechiae	1 (6)
	Thrombocytopenia	1 (6)
Urinary System	Cystitis	1 (6)
	Urinary Tract Infection	1 (6)
Reproductive, Female	Menorrhagia	1 (6)
	Menstrual Disorder	1 (6)
Body as a Whole	Influenza-Like Symptoms	7 (44)
	Back Pain	3 (19)
	Pain	3 (19)
	Fatigue	2 (13)
	Back Ache	1 (6)
	Chest Pain	1 (6)
	Fever	1 (6)
	Hay Fever	1 (6)
	Edema	1 (6)
	Pain in Limb	1 (6)
	Syncope	1 (6)
Application Site	Inflammation Localized	1 (6)
Resistance Mechanism	Otitis Media	1 (6)
Unclassifiable	Fall	1 (6)

5) Study 918-004

Table 174: 918-004 Incidence of All Adverse Events

			Treatment		
Randomized Patients, n =		All 36	OGT 918 12	Cerezyme 12	OGT 918 + Cerezyme 12
Body System	WHO AE Term	n (%)	n (%)	n (%)	n (%)
	Uncoded	1 (3)	0	0	1 (8)
Skin and Appendage	Pityriasis Rosea	1 (3)	0	0	1 (8)
	Rash	1 (3)	0	0	1 (8)
	Skin Dry	1 (3)	0	1 (8)	0
	Urticaria	1 (3)	1 (8)	0	0
Musculoskeletal	Bone Pain	4 (11)	0	2 (17)	2 (17)
	Fracture Rib	2 (6)	0	1 (8)	1 (8)
	Joint Pain	2 (6)	1 (8)	1 (8)	0
	Bone Disorder	1 (3)	0	1 (8)	0
	Pain Neck/Shoulder	1 (3)	0	0	1 (8)
Neurological	Tremor	8 (22)	4 (33)	0	4 (33)
	Headache	6 (17)	3 (25)	0	3 (25)
	Dizziness	5 (14)	2 (17)	0	3 (25)
	Cramps Legs	1 (3)	1 (8)	0	0
	Faintness	1 (3)	1 (8)	0	0
	Gait Unsteady	1 (3)	1 (8)	0	0
	Numbness Localized	1 (3)	0	0	1 (8)
	Paresthesia	1 (3)	0	1 (8)	0
	Sensory Disturbance	1 (3)	1 (8)	0	0
	Shaking	1 (3)	0	0	1 (8)
Vision	Visual Disturbance	2 (6)	1 (8)	0	1 (8)
	Eye Abnormality	1 (3)	0	0	1 (8)
	Eye Infection	1 (3)	0	1 (8)	0
	Eyelid Infection	1 (3)	1 (8)	0	0
Psychiatric	Appetite Decreased	2 (6)	1 (8)	0	1 (8)
	Affect Lack	1 (3)	0	0	1 (8)
	Appetite Absent	1 (3)	0	0	1 (8)
	Insomnia	1 (3)	0	0	1 (8)
	Jitteriness	1 (3)	0	0	1 (8)
	Memory Loss	1 (3)	1 (8)	0	0
Gastrointestinal	Diarrhea	25 (69)	12 (100)	3 (25)	10 (83)
	Abdominal Pain	16 (44)	8 (67)	1 (8)	7 (58)
	Flatulence	11 (31)	6 (50)	0	5 (42)
	Constipation	5 (14)	1 (8)	1 (8)	3 (25)
	Nausea	4 (11)	2 (17)	1 (8)	1 (8)
	Abdominal Distress	1 (3)	0	1 (8)	0
	Gastroenteritis	1 (3)	0	1 (8)	0
	Mouth Dry	1 (3)	1 (8)	0	0
	Mouth Ulceration	1 (3)	0	1 (8)	0
	Rectal Bleeding	1 (3)	0	1 (8)	0
	Tooth Disorder	1 (3)	0	1 (8)	0
Metabolic and Nutritional	Weight Decrease	16 (44)	8 (67)	2 (17)	6 (50)
	Weight Increase	2 (6)	0	1 (8)	1 (8)
	Diabetes Mellitus Aggravated	1 (3)	0	1 (8)	0
Endocrine	Estrogens Decreased	1 (3)	1 (8)	0	0

Cardiovascular	Hypotension	4 (11)	0	1 (8)	3 (25)
Heart Rate and Rhythm	Bradycardia	2 (6)	1 (8)	1 (8)	0
	Tachycardia	2 (6)	0	0	2 (17)
	Arrhythmia	1 (3)	0	1 (8)	0
	Sinus Bradycardia	1 (3)	0	1 (8)	0
Respiratory	Rhinitis	2 (6)	1 (8)	1 (8)	0
	Throat Sore	2 (6)	0	0	2 (17)
	Pneumonia	1 (3)	0	1 (8)	0
	Upper Respiratory Tract Infection	1 (3)	1 (8)	0	0
Platelet, Bleeding and Clotting	Ecchymosis	1 (3)	0	0	1 (8)
	Hematoma	1 (3)	0	0	1 (8)
	Thrombocytopenia	1 (3)	0	0	1 (8)
Urinary	Urinary Tract Infection	2 (6)	1 (8)	0	1 (8)
	Dysuria	1 (3)	0	0	1 (8)
	Kidney Stone	1 (3)	0	1 (8)	0
	Micturition Burning	1 (3)	0	0	1 (8)
Reproductive, Male	Genital Infection	1 (3)	0	0	1 (8)
Reproductive, Female	Menstrual Irregularity	1 (3)	0	0	1 (8)
Body as a Whole	Influenza-Like Symptoms	13 (36)	5 (42)	4 (33)	4 (33)
	Pain Trauma Activated	5 (14)	2 (17)	1 (8)	2 (17)
	Pain	4 (11)	1 (8)	1 (8)	2 (17)
	Fever	3 (8)	2 (17)	0	1 (8)
	Pain Legs	3 (8)	0	0	3 (25)
	Weakness Generalized	3 (8)	2 (17)	0	1 (8)
	Abdominal Distension	2 (6)	1 (8)	0	1 (8)
	Back Pain	2 (6)	1 (8)	0	1 (8)
	Chest Pain	2 (6)	2 (17)	0	0
	Fatigue	2 (6)	2 (17)	0	0
	Abdominal Distension Gaseous	1 (3)	1 (8)	0	0
	Chills	1 (3)	0	0	1 (8)
	Heaviness in Limbs	1 (3)	1 (8)	0	0
	Edema Legs	1 (3)	0	0	1 (8)
	Pain Groin	1 (3)	0	1 (8)	0
	Pre-Syncope	1 (3)	0	0	1 (8)
Resistance Mechanism	Infection	1 (3)	1 (8)	0	0
	Infection Fungal	1 (3)	0	0	1 (8)
	Infection Viral	1 (3)	1 (8)	0	0
Unclassifiable	Fall	4 (11)	1 (8)	2 (17)	1 (8)
	Inflicted Injury	3 (8)	2 (17)	0	1 (8)

6) Study 918-004X

Table 175: 918-004X Incidence of All Adverse Events

			Treatment		
Randomized Patients, n =		**All 29**	**OGT 918 10**	**Cerezyme 10**	**OGT 918 + Cerezyme 9**
Body System	**WHO AE Term**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
	Uncoded	4 (14)	1 (10)	0	3 (33)
Skin and Appendage	Pruritus	3 (10)	1 (10)	1 (10)	1 (11)
	Pityriasis Rosea	1 (3)	0	0	1 (11)
	Rash	1 (3)	0	0	1 (11)
	Skin Dry	1 (3)	0	1 (10)	0

	Urticaria	1 (3)	1 (10)	0	0
Musculoskeletal	Bone Pain	3 (10)	0	2 (20)	1 (11)
	Pain Neck/Shoulder	3 (10)	1 (10)	1 (10)	1 (11)
	Joint Pain	2 (7)	1 (10)	1 (10)	0
	Bone Disorder	1 (3)	0	1 (10)	0
	Fracture Rib	1 (3)	0	1 (10)	0
Neurological	Tremor	9 (31)	3 (30)	3 (30)	3 (33)
	Headache	7 (24)	2 (20)	2 (20)	3 (33)
	Dizziness	5 (17)	1 (10)	1 (10)	3 (33)
	Cramps Legs	1 (3)	0	0	1 (11)
	Faintness	1 (3)	1 (10)	0	0
	Numbness Localized	1 (3)	0	0	1 (11)
	Shaking	1 (3)	0	0	1 (11)
Vision	Visual Disturbance	2 (7)	1 (10)	0	1 (11)
	Blepharitis	1 (3)	0	0	1 (11)
	Eye Abnormality	1 (3)	0	0	1 (11)
	Eye Infection	1 (3)	0	1 (10)	0
Psychiatric	Appetite Decreased	2 (7)	1 (10)	0	1 (11)
	Appetite Absent	1 (3)	0	0	1 (11)
	Jitteriness	1 (3)	0	0	1 (11)
	Memory Loss	1 (3)	1 (10)	0	0
	Nervousness	1 (3)	1 (10)	0	0
Gastrointestinal	Diarrhea	26 (90)	10 (100)	8 (80)	8 (89)
	Flatulence	17 (59)	9 (90)	2 (20)	6 (67)
	Abdominal Pain	16 (55)	8 (80)	1 (10)	7 (78)
	Constipation	8 (28)	2 (20)	2 (20)	4 (44)
	Nausea	3 (10)	1 (10)	1 (10)	1 (11)
	Vomiting	3 (10)	0	1 (10)	2 (22)
	Abdominal Distress	1 (3)	0	1 (10)	0
	Gastroenteritis	1 (3)	0	1 (10)	0
	Mouth Dry	1 (3)	1 (10)	0	0
	Mouth Ulceration	1 (3)	0	1 (10)	0
	Rectal Bleeding	1 (3)	0	1 (10)	0
	Tooth Disorder	1 (3)	0	1 (10)	0
Liver and Biliary	Hepatic Enzymes Increased	1 (3)	0	1 (10)	0
Metabolic and Nutritional	Weight Decrease	23 (79)	10 (100)	6 (60)	7 (78)
	Weight Increase	2 (7)	0	1 (20)	1 (11)
	Diabetes Mellitus Aggravated	1 (3)	0	1 (10)	0
Endocrine	Estrogens Decreased	1 (3)	1 (10)	0	0
Cardiovascular	Hypotension	3 (10)	0	1 (10)	2 (22)
Heart Rate and Rhythm	Bradycardia	2 (7)	1 (10)	1 (10)	0
	Sinus Bradycardia	1 (3)	0	1 (10)	0
	Tachycardia	1 (3)	0	0	1 (11)
Respiratory	Throat Sore	3 (10)	0	0	3 (33)
	Pneumonia	2 (7)	1 (10)	1 (10)	0
	Rhinitis	2 (7)	1 (10)	1 (10)	0
	Upper Respiratory Tract Infection	2 (7)	1 (10)	0	1 (11)
	Chronic Obstructive Airways Disease	1 (3)	1 (10)	0	0
Platelet, Bleeding and Clotting	Hematoma	2 (7)	0	1 (10)	1 (11)
	Ecchymosis	1 (3)	0	0	1 (11)
	Epistaxis	1 (3)	0	1 (10)	0
	Nosebleed	1 (3)	0	0	1 (11)
	Thrombocytopenia	1 (3)	0	0	1 (11)
Urinary	Urinary Tract Infection	6 (21)	2 (20)	1 (10)	3 (33)
	Dysuria	1 (3)	0	0	1 (11)

	Hematuria	1 (3)	0	0	1 (11)
	Kidney Stone	1 (3)	0	1 (10)	0
	Micturition Burning	1 (3)	0	0	1 (11)
Reproductive, Male	Genital Infection	1 (3)	0	0	1 (11)
Body as a Whole	Influenza-Like Symptoms	16 (55)	6 (60)	4 (40)	6 (67)
	Pain Trauma Activated	5 (17)	2 (20)	2 (20)	1 (11)
	Weakness Generalized	5 (17)	2 (20)	2 (20)	1 (11)
	Chest Pain	3 (10)	3 (30)	0	0
	Fatigue	3 (10)	2 (20)	0	1 (11)
	Fever	3 (10)	1 (10)	1 (10)	1 (11)
	Pain Legs	3 (10)	0	0	3 (33)
	Abdominal Distension	2 (7)	1 (10)	0	1 (11)
	Abdominal Distension Gaseous	1 (3)	1 (10)	0	0
	Back Pain	1 (3)	1 (10)	0	0
	Chest Pressure Sensation of	1 (3)	0	0	1 (11)
	Chills	1 (3)	0	0	1 (11)
	Feeling Cold	1 (3)	0	0	1 (11)
	Leg Pain	1 (3)	0	1 (10)	0
	Edema	1 (3)	1 (10)	0	0
	Edema Legs	1 (3)	0	0	1 (11)
	Pain	1 (3)	0	0	1 (11)
	Pain Groin	1 (3)	0	1 (10)	0
	Pre-Syncope	1 (3)	0	0	1 (11)
Application Site	Inflammation Localized	1 (3)	0	1 (10)	0
Resistance Mechanism	Infection	1 (3)	1 (10)	0	0
	Infection Fungal	1 (3)	0	0	1 (11)
	Infection Localized	1 (3)	0	0	1 (11)
Unclassifiable	Fall	4 (14)	1 (10)	2 (20)	1 (11)
	Inflicted Injury	4 (14)	2 (20)	1 (10)	1 (11)

B. Electrodiagnostic Studies

1) Studies 918-001 and 918-001X

Table 176: 918-001 and 918-001X Patients Who Underwent Electrodiagnostic Testing

Patient	EDX Results	Findings
101	Abnormal	62 yo F with known IgA hypergammaglobulinemia (for 6 years at study entry), who experienced onset of tingling in hands, feet and lower legs with onset approximately 12 months after starting OGT 918. Progressed to numbness in feet, burning pain in lower legs, and paresthesias in the fingers of both hands. OGT 918 d/c'd at approx. Month 20. EDX testing at Month 20 and Month 25 c/w large fiber sensorimotor neuropathy, and a superimposed left ulnar neuropathy or C8/T1 radiculopathy. There was some improvement in symptoms in the hands after stopping OGT 918. Patient also had a >25% weight loss during the study; however, there was no documentation that she was malnourished or vitamin deficient as a result of her weight loss.
103	Abnormal	69 yo M who developed intermittent paresthesias in his hands and feet (1 week after starting OGT 918) with intermittent tremors (6 months after starting OGT 918). Both paresthesias and tremor resolved prior to stopping OGT 918 therapy. EDX perfomred at approx. Month 23 was incomplete, but c/w mild chronic peripheral neuropathy. The tremor returned after stopping OGT 918, and progressive paresthesias in his feet developed within 4-6 months of stopping OGT 918. A cranial MRI for headaches at approx. 2 ½ years after starting OGT 918 showed non-specific changes most likely related to chronic small vessel ischemia. A questionable history of alcoholism was raised; however, there is no documentation that vitamin levels were low or that nutrition was poor.
105	Abnormal	55 yo M who complained of hand tremor which worsened with increased dosing of OGT 918 (from 100 mg TID to 200 mg TID). Tremor stopped with a few days of stopping study drug (at approx. Month 14). About 3 weeks after stopping therapy, the patients complained of numbness in his feet, then in his hands. EDX testing 1 month later showed reduced sural sensory potentials and prolonged latencies. A possible mild cognitive impairment was noted at approx. Month 24, and a brain MRI was WNL. Follow-up EDX at Month 36 showed deterioration with new findings of early motor changes in the lower limbs.
106	Normal	Intermittent tremor began 10 months after starting OGT 918.
107	Normal	Paresthesias noted before start of OGT 918 and during the study, and leg cramps noted during the study. EDX incomplete (NCV only)
201	Abnormal	No neurologic complaints. Medical history significant for a history of B12 deficiency, vasculitis, and cryoglobulinemia. EDX showed low sural SNAP at Month 27
202	Normal	No neurologic complaints.
301	Normal	No neurologic complaints.
404	Abnormal	No neurologic complaints. Pre-existing B12 deficiency. EDX showed borderline low sural SNAPs c/w peripheral neuropathy at Month 12.
405	Normal	No neurologic complaints.
407	Abnormal	Muscle cramps. EDX showed low/absent sural SNAP at Month 24
411	Normal	No neurologic complaints.
412	Normal	No neurologic complaints.
414	Abnormal	No neurologic complaints. EDX showed low sural and medial SNAPs c/w peripheral neuropathy at Month 24.
416	Normal	Transient cramps at Month 8, and fine tremor began at Month 10.

2) Studies 918-003 and 918-003X

Table 177: 918-003 and 918-003X Patients Who Underwent Electrodiagnostic Testing

Patient	EDX Results	Findings
101	Normal	Tremor and paresthesias reported.
102	Normal*	Leg cramps reported. *EDX showed L5-S1 radiculopathy, but no generalized peripheral neuropathy at Month 9.
103	Normal**	Tremor and paresthesias reported. **EDX showed chronic C8-T1 radiculopathy bilaterally, but no generalized peripheral neuropathy at Month 9.
104	Normal	Tremor reported.
105	Normal	Tremor reported.
106	Normal	Leg cramps, paresthesias, and numbness reported.
107	Normal	No neurologic complaints reported.
110	Normal	Tremor and leg cramps reported.
111	Abnormal	F complained of paresthesias, including sensations of tingling, "needle-like pains in soles of feet", tingling in toes, that began about 5-6 months after starting OT 918. Diagnosed by a local neurologist with possible Charcot-Marie-Tooth; however, there was no family history, no gait disorder, and no peroneal motor involvement. EDX showed slightly prolonged latencies. Repeat EDX after 2 months off drug showed the same results.
112	Normal	Tremor reported.
201	Normal	No neurologic complaints reported.
203	Abnormal	No neurologic complaints reported. EDX showed mild denervation was noted on needle EMG examination in the first dorsal interosseous (hand muscle) and small sural SNAPs at Month 12. Patient had a history of low B12 levels.
`04	Normal	No neurologic complaints reported.
.05	Normal	No neurologic complaints reported.
207	Abnormal	No neurologic symptoms initially, and normal initial EDX testing. Later developed numbness and 2 subsequent EDX tests were c/w sensorimotor peripheral neuropathy.
208	Normal	Tremor reported.

3) Studies 918-004 and 918-004X

Table 178: 918-004 and 918-004X Patients Who Underwent Electrodiagnostic Testing

Patient	EDX Results	Findings
OGT 918 Alone Group		
102	Abnormal	No neurologic complaints. Pre-existing history of diabetes. EDX showed borderline low sural SNAP c/w mild peripheral neuropathy
103	Normal	Hand tremor reported.
106	Normal	Hand tremor reported.
110	Normal	Leg cramps and diminished tactile sensitivity over body
111	Normal	No neurologic complaints.
120	Abnormal	Pre-existing tremor. EDX showed low sural SNAP
121	Normal	No neurologic complaints.
126	Normal	No neurologic complaints.
130	Abnormal	Occasional hand tremor, congenital hand deformity.
133	Normal	Possible worsening of childhood tremor.
136	Normal	No neurologic complaints.
Cerezyme Alone Group		
101	Normal	No neurologic complaints.
107	Normal	No neurologic complaints.
112	Normal	No neurologic complaints.
113	Normal	Intermittent tremor after starting OGT 918 in extension phase.
116	Abnormal	Tremor before OGT 918. Pre-existing history of diabetes. EDX showed small bilateral sural SNAPs
117	Abnormal	No neurologic complaints. Patient developed multiple myeloma with melphelan treatment. EDX showed small sural SNAPs and chronic neurogenic changes on EMG c/w peripheral neuropathy
127	Normal	Hand tremor after starting OGT 918 during extension phase. Tremor resolved without dose reduction.
132	Normal	No neurologic complaints.
Combination Group		
104	Abnormal	Hand tremor, weakness in hands and legs. EDX showed absent sural SNAP on one side, which may have been due to technical difficulties.
105	Normal	Transient (1 day) tremor, which resolved without dose change.
108	Normal	No neurologic complaints.
109	Abnormal	Leg cramps. Pre-existing history of epilepsy, treated with carbamazepine. EDX consistent with peripheral neuropathy
114	Normal	No neurologic complaints. History of B12 deficiency.
123	Abnormal	No neurologic complaints. EDX showed low sural SNAPs, and slight slowing of nerve conduction.
124	Normal	Occasional hand tremor, resolved within 1 month.
125	Abnormal	Tremor, shakiness, and eye twitch. EDX whoed low sural SNAPs
131	Normal	No neurologic complaints.
135	Abnormal	F patient. EDX at Month 2 showed borderline low sural SNAP. Reported pain in calves on Day 1 of study, numbness in right hand on Day 1, and transient numbness in one digit on Day 1. Continued study drug for 8 months without further recurrence.

C. Other Laboratory Abnormalities

1) Study 918-001

Two patients had elevations in AST and ALT >2 X ULN from baseline.

Table 179: 918-001 AST and ALT values >2 X ULN During Treatment

Patient	Test	Date	Value
406	ALT	Screening	64
		Day 029	83
		Day 057	107
		Day 085	80
		Day 113	100
	AST	Screening	44
		Day 029	57
		Day 057	63
		Day 085	90
		Day 113	63
413	ALT	Screening	59
		Day 029	50
		Day 057	63
		Day 085	59
		Day 113	94
		Day 141	152
		Day 169	88
		Day 197	42
		Day 225	90
		Day 253	194
		Day 281	43
		Day 309	83
		Day 337	60
413	AST	Screening	27
		Day 029	29
		Day 057	41
		Day 085	45
		Day 113	40
		Day 141	82
		Day 169	45
		Day 197	24
		Day 225	81
		Day 253	139
		Day 281	26
		Day 309	44
		Day 337	32

ALT range 9-52 IU/L
AST range 14-36 IU/L

One patient had elevations in alkaline phosphatase >2X ULN, as follows

Table 180: 918-001 Alkaline Phosphatase >2 X ULN During Treatment

Patient	Test	Day	Result
107	Alk Phos	Screening	152
		Day 001	161
		Day 029	181
		Day 057	114
		Day 085	134
		Day 113	110
		Day 141	113
		Day 169	257
		Day 225	155
		Day 253	167
		Day 281	156
		Day 309	133
		Day 337	151

Alkaline phosphatase range 30-135 U/L

D. Other Disease Assessments

1) Study 918-001

Table 181: 918-001 Other Disease Assessments (Patients with follow-up exams only)

Patient	Assessment	Results (all follow-up occurred on Day 337)
101	DEXA (hip, spine, wrist)	no change
	MRI (hips)	no change
103	DEXA (hip, spine)	no change
	MRI (hips)	no change
104	DEXA (hip, spine)	no change
	MRI (hips)	no change
105	MRI (hips)	no change
106	DEXA (forearm, hip, L-spine)	no change
	MRI (hips)	no change
107	DEXA (hip, spine, wrist)	no change
	MRI (hips)	no change
201	MRI (L-spine, pelvis/femurs)	no change
	QSCI (L-spine)	from 0.22 to 0.26*
202	MRI (L-spine, pelvis/femurs)	no change
	QSCI (L-spine)	from 0.18 to 0.27*
403	Echo	T1 from 24 mmHg to 26 mmHg
404	Echo	T1 from 33 mmHg to 27 mmHg
405	Echo	T1 from 19 mmHg to 21 mmHg
407	Echo	T1 from 30 mmHg to 32 mmHg
408	Echo	T1 from 34 mmHg to 37 mmHg
409	DEXA (L-spine)	no change
	Echo	T1 from 31 mmHg to 29 mmHg
411	Echo	T1 from 23 mmHg to 27 mmHg
412	DEXA (femoral neck, L-spine)	L-spine: no change, femoral neck: change in z-score from 1.24 to –1.96
	Echo	T1 from 28 mmHg to 20 mmHg
414	Echo	T1 from 22 mmHg to 24 mmHg
415	Echo	T1 from 13 mmHg to 18 mmHg

*Per Rosenthal *et al*[16], normal range for healthy adults 23-35%. In Gaucher study with ERT mean QCSI prior to treatment 7.3% ±6.7%, and after 42-months of treatment 22.9% ±6.6%

[16] Rosenthal DI, Doppelt SH, Mankin HJ, Dambrosia JM, Xavier RJ, McKusicKA, 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(4):629-637.