Table 116: 918-004X Hexosaminidase Statistics

Treatment	Statistic	Baseline nmol/ml.h	Month 6 nmol/ml.h	Month 6 Change nmol/ml.h	Month 6 % Change	Month 12 nmol/ml.h	Month 12 Change nmol/ml.h	Month 12 % Change
OGT 918	n	10	10	10	10	8	8	8
	Mean	1295.4	1489.0	193.6	16.6	1706.3	492.8	42.1
	Median	1150.8	1508.5	151.5	13.4	1679.5	486.3	48.2
	Minimum							
	Maximum							
	p-value							
Cerezyme	n	10	10	10	10	10	10	10
	Mean	1411.6	1356.6	-55.0	-1.8	1588.8	177.2	13.0
	Median	1350.8	1448.0	-1.8	0.1	1472.5	132.0	9.8
	Minimum							
	Maximum							
	p-value							
Combination	n	9	9	9	9	9	9	9
	Mean	1151.4	1169.8	18.3	4.5	1457.8	306.3	31.1
	Median	1025.5	1119.0	78.0	6.6	1463.0	321.0	33.4
	Minimum							
	Maximum							
	p-value							

Acid Phosphatase

For the OGT 918, Cerezyme and Combination groups, there were mean increases in acid phosphatase from Baseline to Month 12 of 1392.8, 1183.2, and 956.6 nmol/ml.h, respectively. For the OGT 918 group, there was a mean increase in acid phosphatase of 880.0 nmol/ml.h from Month 6 to Month 12. For the Cerezyme and Combination groups, switching to OGT 918 monotherapy resulted in mean increases in acid phosphatase of 1006.9 and 923.2 nmol/ml.h, respectively.

ACE

ACE was not analyzed at Month 12.

(v) Other Disease Assessments

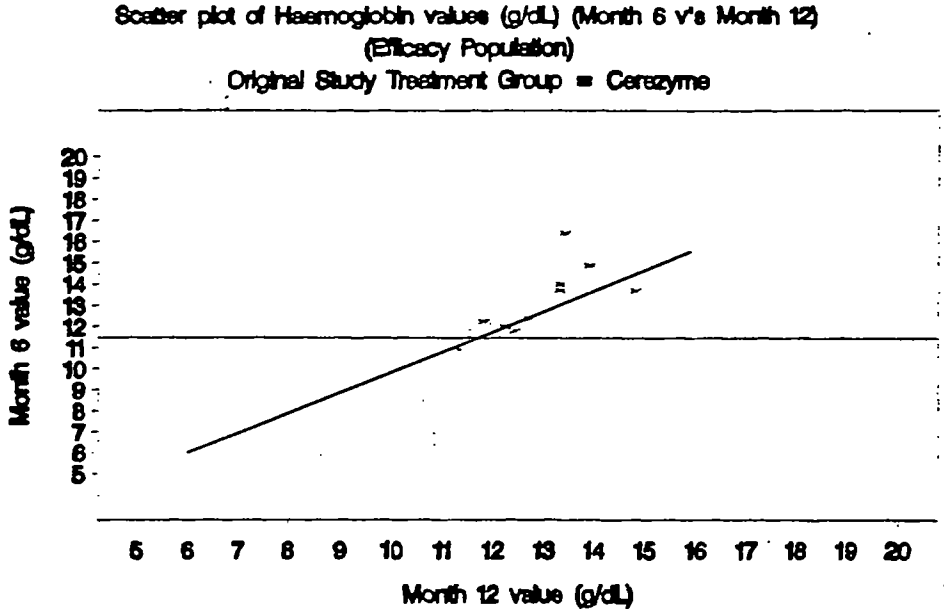
Other disease assessments were performed at the discretion of the Investigator as per usual practice at the study center. Twenty-seven (27) patients had at least one other disease assessment performed for which results were available at Baseline and Month 12. Twenty-four (24) patients underwent DEXA scanning, and 26 patients underwent echocardiography. There were no meaningful changes in skeletal assessments by DEXA, and no patient had a progression to, or development of, pulmonary hypertension by echocardiographic assessment of T1 at Month 12.

(vi) Subgroup Analysis

Please refer to the Hemoglobin and Platelet Count sections. No other subgroup analyses were performed.

Cerezyme Group :

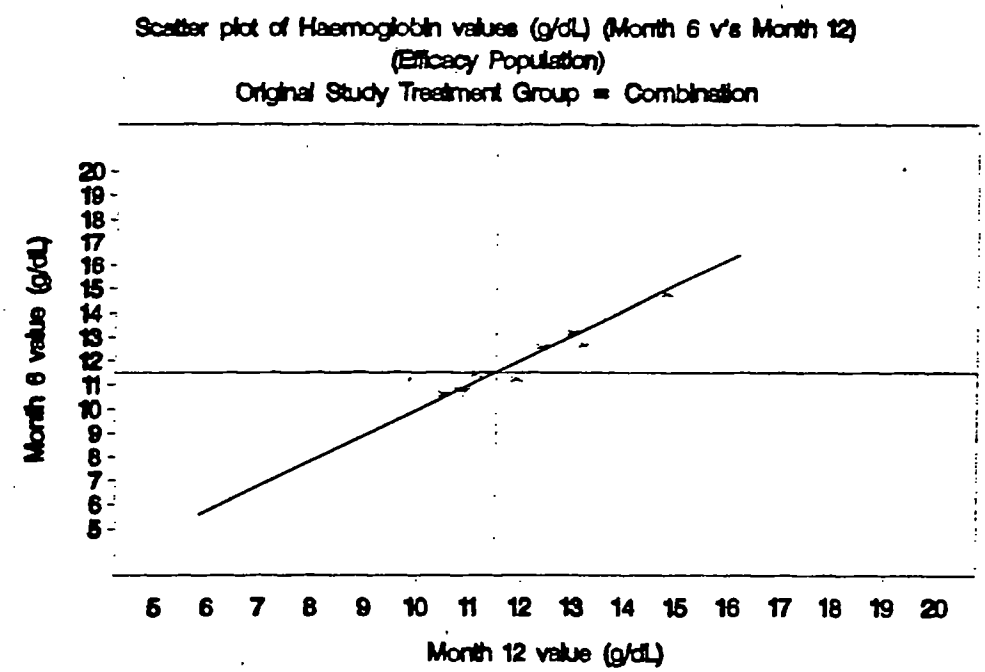
Figure 38: 918-004X Scatter Plot of Hemoglobin Values, Month 6 vs Month 12, Cerezyme Group



Note: All patients enrolling in the extension phase chose to receive OGT 918 alone.

Combination Group

Figure 39: 918-004X Scatter Plot of Hemoglobin Values, Month 6 vs Month 12, Combination Group



Note: All patients enrolling in the extension phase chose to receive OGT 918 alone.

Subgroup analysis by Baseline Hgb was limited due to the small number of patients with Hgb <11.5 g/dL at Baseline, and due to the small numbers of patients in each treatment group by Hgb subgroup. Only patients in the Combination treatment group with Baseline Hgb <11.5 g/dL (n=4) had a mean increase in Hgb at Month 12. However, due to the small number of patients, no conclusions will be drawn from this. The results are summarized in the following table

Table 112: 918-004X Mean Change Hemoglobin by Baseline Value (<11.5 vs ≥11.5 g/dL)

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

(iii) Platelet Count

Twenty-eight (28) patients had Plt data at Month 12. Overall, there were mean decreases in Plt from Baseline at Month 12 in all treatment groups. For the Cerezyme and Combination groups, switching to OGT 918 monotherapy from Month 6 to Month 12 resulted in significant mean decreases in Plt ($X10^9$/L) of –21.85 and –20.94 (for the Cerezyme and Combination groups, respectively). For the OGT 918 group, there was a smaller mean decrease in Plt of –4.06 $X10^9$/L from Month 6 to Month 12 with continued treatment with OGT 918. In the OGT 918 group, there were mean actual decreases in Plt ($X10^9$/L) from Baseline at Month 6 and Month 12 of –21.60 and –27.39, respectively. In the Cerezyme group, there were mean actual changes in Plt ($X10^9$/L) from Baseline at Month 6 and Month 12 of +18.10 and –3.75, respectively. In the Combination group, there were mean actual changes in Plt ($X10^9$/L) from Baseline at Month 6 and Month 12 of +8.72 and –12.22, respectively.

Fourteen (14) patients had notable decreases (<-10%) in Plt from Baseline to Month 12: 5 patients in the OGT 918 group, 3 patients in the Cerezyme group, and 6 patients in the Combination group. Conversely, 4 patients had notable increases (>10%) in Plt from Baseline to Month 12: 1 patient each in the OGT 918 and Combination groups, and 2 patients in the Cerezyme group.

The results are summarized in the following table

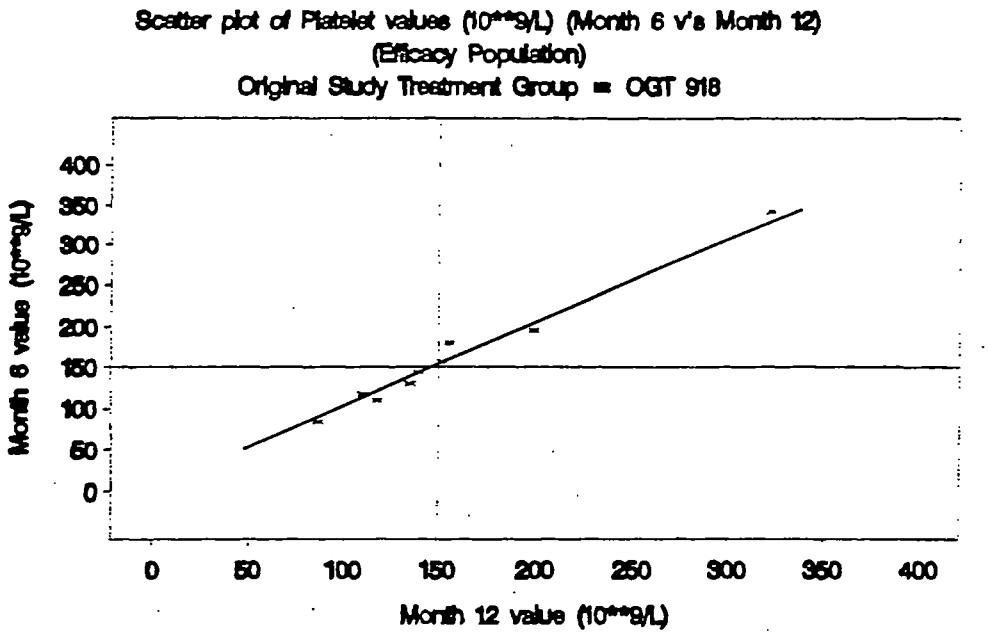
Table 113: 918-004X Platelet Count Statistics

Treatment	Statistic	Baseline (10^9/L)	Month 6 (10^9/L)	Month 6 Change (10^9/L)	Month 6 % Change	Month 12 (10^9/L)	Month 12 Change (10^9/L)	Month 12 % Change
OGT 918	n	10	10	10	10	9	9	9
	Mean	170.55	148.95	-21.60	-9.6	157.44	-27.39	-10.4
	Median	162.00	136.00	-6.50	-7.5	139.00	-17.50	-11.3
	Minimum							
	Maximum							
	p-value			.101	.073		.062	.110
Cerezyme	n	10	10	10	10	10	10	10
	Mean	170.05	188.15	18.10	12.0	166.30	-3.75	-3.2
	Median	174.75	186.50	11.75	6.5	155.50	-1.50	-0.8
	Minimum							
	Maximum							
	p-value			.071	.063		.529	.391
Combination	n	9	9	9	9	9	9	9
	Mean	136.33	145.06	8.72	3.7	124.11	-12.22	-8.3
	Median	145.50	151.00	5.50	3.8	130.00	-15.50	-14.8
	Minimum							
	Maximum							
	p-value			.389	.566		.126	.241

Comparisons of individual patient Plt values, by treatment group, Month 6 vs Month 12: are depicted in the following figures [Figures electronically scanned and reproduced from: Oxford Glycosciences (UK) Ltd, NDA #21-348, Volume 2.22, pages 65-66, dated 02-Aug-2001] [best reproductions]

OGT 918 Group

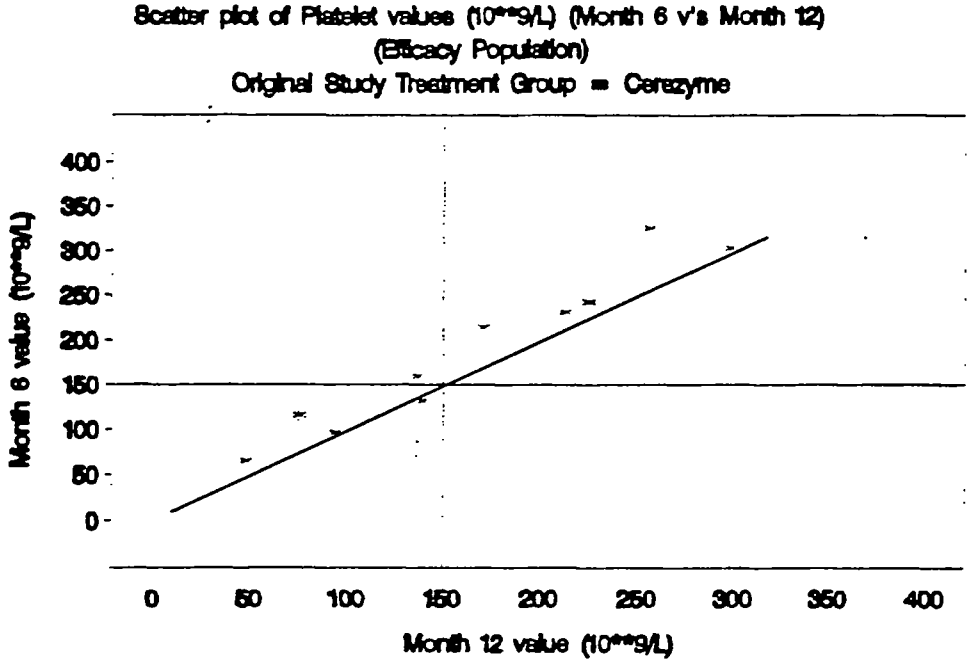
Figure 40: 918-004X Scatter Plot of Platelet Values, Month 6 vs Month 12, OGT 918 Group



Note: All patients enrolling in the extension phase chose to receive OGT 918 alone.
1 patient withdrew prior to month 12.

Cerezyme Group

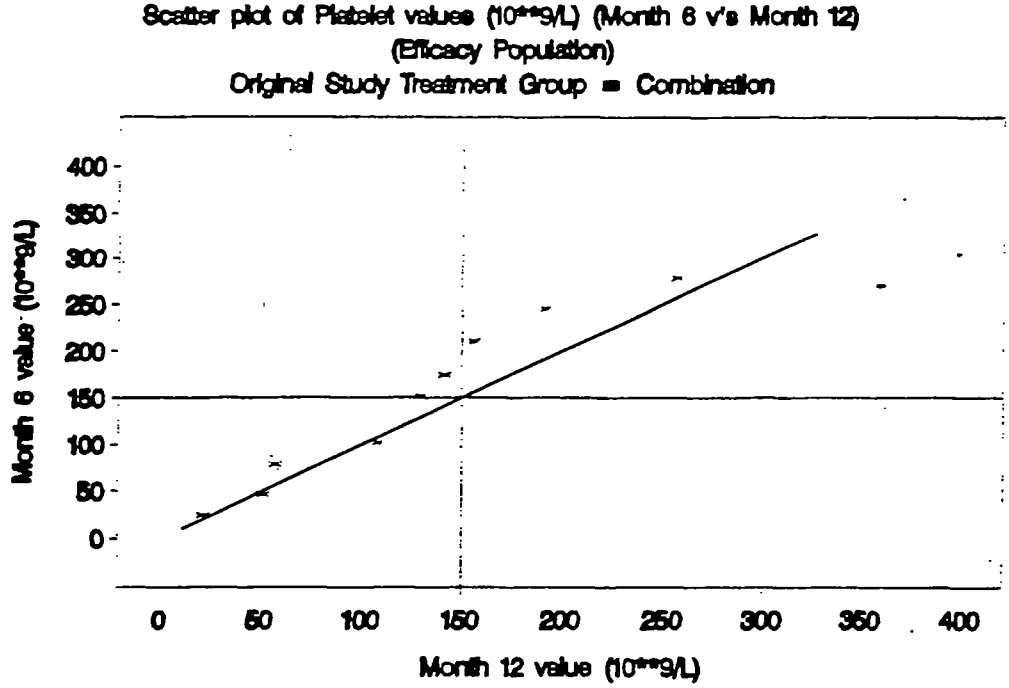
Figure 41: 918-004X Scatter Plot of Platelet Values, Month 6 vs Month 12, Cerezyme Group



Note: All patients enrolling in the extension phase chose to receive OGT 918 alone.

Combination Group

Figure 42: 918-004X Scatter Plot of Platelet Values, Month 6 vs Month 12, Combination Group



Note: All patients enrolling in the extension phase chose to receive OGT 918 alone.

On subgroup analysis, Plt results were most notable in the subgroup of patients with Plt $\geq$150 X10^9/L at Baseline. Patient with Plt $\geq$150 X10^9/L at Baseline in the OGT 918 group had a mean decrease in Plt of –43.10 X10^9/L at Month 6, and a significant decrease in Plt of –50.30 X10^9/L (p=.032) at Month 12. Patients with Plt $\geq$150 X10^9/L at Baseline in the Cerezyme and Combination groups had increases in Plt of +24.75 X10^9/L and +26.13 X10^9/L, respectively, at Month 6, and decreases of –3.75 X10^9/L and –13.63 X10^9/L, respectively, at Month 12, after switching to OGT 918 monotherapy at Month 6. The results are summarized in the following table

Table 114: 918-004X Mean Change Platelet Count by Baseline Value (<150 X10^9/L vs ≥150 X10^9/L)

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

(iv) Biochemical Markers

The biochemical markers of Gaucher disease measured in the study, chitotriosidase, hexosaminidase, acid phosphatase, and ACE, will be briefly summarized below.

Chitotriosidase

Overall, all 3 treatment groups showed increases in chitotriosidase at Month 12. These results were: for the OGT 918 group +84.5%, for the Cerezyme group +11.7%, and for the Combination group +28.6%. The results were significant for the OGT 918 and Combination groups only. For the Cerezyme and Combination treatment groups, switching to OGT 918 monotherapy resulted in significant mean increases in chitotriosidase from Month 6 to Month 12. In the OGT 918 group, continued treatment with OGT 918 also resulted in a significant increase in chitotriosidase from Month 6 to Month 12. The results are summarized in the following table

Table 115: 918-004X Chitotriosidase Statistics

Treatment	Statistic	Baseline nmol/ml.h	Month 6 nmol/ml.h	Month 6 Change nmol/ml.h	Month 6 % Change	Month 12 nmol/ml.h	Month 12 Change nmol/ml.h	Month 12 % Change
OGT 918	n	10	10	10	10	8	8	8
	Mean	5860.1	7626.0	1766.0	37.4	6901.3	2634.2	84.5
	Median	3375.8	4728.0	905.0	32.3	3910.0	2195.5	72.4
	Minimum							
	Maximum							
	p-value			.011	.003		.010	.011
Cerezyme	n	10	10	10	10	10	10	10
	Mean	6643.9	7467.6	823.8	-1.3	8624.5	1980.7	11.7
	Median	5254.0	5032.5	12.3	-1.2	5736.0	726.0	11.7
	Minimum							
	Maximum							
	p-value			.363	.863		.113	.242
Combination	n	9	9	9	9	9	9	9
	Mean	5083.8	5084.4	0.7	0.3	5640.8	557.0	28.6
	Median	5361.0	4842.0	-141.5	-3.2	5967.0	444.5	16.6
	Minimum							
	Maximum							
	p-value			.998	.949		.053	.038

Hexosaminidase

Overall, all 3 treatment groups showed increases in hexosaminidase at Month 12. These results were: for the OGT 918 group +42.1%, for the Cerezyme group +13.0%, and for the Combination group +31.1%. For the Cerezyme and Combination treatment groups, switching to OGT 918 monotherapy resulted in mean increases in chitotriosidase from Month 6 to Month 12. In the OGT 918 group, continued treatment with OGT 918 also resulted in an increase in chitotriosidase from Month 6 to Month 12. The results are summarized in the following table

(c) Conclusions on Efficacy Results for Protocol 918-004X

There were no significant mean decreases in liver or spleen volume seen in any treatment group from Baseline to Month 6. For liver volume, there were also no significant mean changes from Month 6 to Month 12 in any treatment group. For spleen volume, there were non-significant mean increases from Month 6 to Month 12 in the Cerezyme and Combination treatment groups, when patient in these groups switched to OGT 918 monotherapy. There were non-significant mean decreases in Hgb for all treatment groups from Baseline to Month 12, and no significant decrease in Hgb in any group from Month 6 to Month 12. There were too few patients with Baseline Hgb <11.5 g/dL to perform a subgroup analysis by Baseline Hgb. There were non-significant mean decreases in Plt from Baseline to Month 12 in all treatment groups. For the Cerezyme and Combination groups, switching to OGT 918 monotherapy from Month 6 to Month 12 resulted in a significant decrease in Plt, and for the OGT 918 group, continued treatment with OGT 918 also resulted in a significant decrease in Plt from Month 6 to Month 12. This Plt finding was especially evident in the subgroup of patients with Plt $\geq 150 \times 10^9/L$ at Baseline, in all 3 treatment groups after switching to OGT 918 monotherapy.

The biochemical markers of Gaucher disease measured at Month 12, chitotriosidase, hexosaminidase, and acid phosphatase, all showed increases from Baseline to Month 12. These results were significant only for chitotriosidase in the OGT 918 and Combination groups. DEXA scanning and echocardiography assessments showed essentially no change in any patient from Baseline at Month 12.

D. Efficacy Conclusions on Review of NDA 21-348

The efficacy results for OGT 918 in the treatment of Gaucher disease clinical program will be considered in the 2 different Gaucher disease type 1 patient populations studied in this NDA. Study 918-001 (and its extension 918-001X) and Study 918-003 (and its extension 918-003X), were non-comparative evaluations of OGT 918 at a dose of 100 mg TID (981-001) or 50 mg TID (981-003) in treatment naïve patients (or in patients who had not received ERT for at least 3 months). Study 918-004 (and its extension 918-004X) included patients who had been receiving ERT for at least 2 years at the time of study entry. The 981-001 and 918-003 study patients had larger spleen and liver volumes, and lower Hgb and Plt values at Baseline than did patients in the 918-004 study. This difference is important as the magnitude of response to treatment for Gaucher disease would depend on the patients ability to respond. That is, patients with larger liver and spleen volumes and lower Hgb and Plt values would be expected to have a larger response to treatment than patients with smaller liver and spleen volumes and higher Hgb and Plt values at Baseline. Comparisons of Baseline liver, spleen, Hgb, and Plt values for Studies 918-001, 918-003, and 918-004 are summarized in the following table

Table 117: Baseline Characteristics, Comparison Across Studies

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

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

Therefore, the responses seen in these studies will be considered separately, with the 918-001 and 918-003 studies (and their extensions) considered together, and the 918-004 (and its extension) considered alone.

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

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

Table 118: Liver Volume Changes, Studies 918-001 and 918-003

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

*for mean % decrease from Baseline

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

Table 119: Spleen Volume Changes, Studies 918-001 and 918-003

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

*for mean % decrease from Baseline

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

Table 120: Hemoglobin Changes, Studies 918-001 and 918-003

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

*for mean % decrease from Baseline

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

Table 121: Hemoglobin Changes by Baseline Value (<11.5 vs ≥11.5 g/dL), Studies 918-001 and 918-003

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

*for mean % decrease from Baseline

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

Table 122: Platelet Count Changes, Studies 918-001 and 918-003

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

*for mean % decrease from Baseline

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

Table 123: Platelet Count Changes by Baseline Platelet Counts (<150 $X10^9$/L vs ≥150 $X10^9$/L) Study 918-003

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

*for mean % decrease from Baseline

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

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

Table 124: Chitotriosidase Changes, Studies 918-001 and 918-003

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

*for mean % decrease from Baseline

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

Table 125: Hexosaminidase Changes, Studies 918-001 and 918-003

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

*for mean % decrease from Baseline

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

Other disease assessments were performed at the discretion of the Investigator and per usual practice at the study centers. Patients underwent assessments including skeletal assessments by DEXA and MRI scanning, bone marrow fat fraction by Quantitative Chemical Shift Imaging (QCSI), QoL assessment (Study 918-003 only; n=10), and pulmonary pressure assessment by echocardiography. The results showed essentially no 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 126: 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 127: 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 128: 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 129: 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 130: 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 $\geq$150 $X10^9$/L. All 3 treatment group patients with Baseline Plt $\geq$150 $X10^9$/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 $\geq$150 $X10^9$/L at Month 12. The results are summarized in the following table

Table 131: Mean Change Platelet Count by Baseline Value (<150 $X10^9$/L vs $\geq$150 $X10^9$/L), Studies 918-004 and 918-004X

Change from Baseline	Plt <150 $X10^9$/L			Plt $\geq$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 132: 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 133: 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.

VI. Integrated Review of Safety

The Integrated Summary of Safety (ISS) submitted safety information with a cut-off date of May-2001. Subsequent to that, the IND annual report with updated safety information was received on 10-Sept-2001, and the 120-day safety update for this NDA was received Jan-2002. These safety updates have been incorporated into this safety review.

A. Brief Statement of Conclusions

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, and was noted to result in an increase in the use of anti-diarrheal and other GI medications, most commonly loperamide. 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 patients (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. EDX testing was added to the protocols after these 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 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. Despite the sponsor's conclusion that the neuropathic findings could be explained by other 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.

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. Further information has been requested from the sponsor, and further evaluation of memory loss is ongoing at the time of this review.

B. Description of Patient Exposure

In the OGT 918 Gaucher disease 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. Of the patients exposed to OGT 918, 68 were exposed to OGT 918 alone, and 12 were exposed to OGT 918 in combination with Cerezyme. Doses and duration of exposure, by study, are summarized as follows:

Table 134: OGT 918 Exposure by Study

Study	Patients (n)	Mean duration of exposure (days)	Range (days)	Dose of OGT 918
918-001	28	297	2 – 463	100 mg BID to 200 mg TID (most 100 mg BID to 100 mg TID)
918-001X	18	671	408 – 800	100 mg qD to 200 mg TID (most 100 mg BID to 100 mg TID)
918-003	18	175	119 – 190	50 mg BID to 50 mg TID (50 mg BID in 2 patients only)
918-003X	16	322	192 – 367	50 mg BID to 50 mg TID (50 mg BID in 2 patients only)
918-004 All	36			
OGT 918 group	12	155	70 - 190	100 mg BID to 100 mg TID
Cerezyme group	12	175	168 – 191	N/A
Combination group	12	160 (OGT 918) 158 (Cerezyme)	54 – 180 (OGT 918) 22 – 297 (Cerezyme)	100 mg qD to 100 mg TID
918-004X	29			
OGT 918 group	10	332	236 - 357	100 mg BID to 100 mg TID
Cerezyme group	10	168 (OGT 918) 175 (Cerezyme)	148 – 189 (OGT 918) 168 – 191 (Cerezyme)	100 mg BID to 100 mg TID
Combination group	9	339 (OGT 918) 173 (Cerezyme)	317 – 357 (OGT 918) 140 – 279 (Cerezyme)	100 mg qD to 100 mg TID

C. Methods and Specific Findings of Safety Review

The sponsor performed a safety review with pooling of the safety data from the 6 studies: the Combined Safety Data Set. The Combined Safety Data Set included all patients from studies 918-001, 918-003 and 918-004 from 0-30 months of treatment, including data from both the primary and extended-use phases of all three studies. For 918-004, data from patients who received Cerezyme alone during the primary study period were not included; however, those patients who then participated in the extended-used phase of the study and were switched to OGT 918 have safety data from their extended treatment presented as 0-6 months of treatment included. There were only 2 patients from the 918-004 study in the Cerezyme alone group who were not exposed to OGT 918 at any time during the studies.

This Reviewer also performed safety evaluations for the 6 studies separately using paper and electronic data sets submitted with the NDA. These safety reviews will follow the

Combined Safety Data Set Review. Finally, safety results from studies with OGT 918 in HIV positive patients and Fabry Disease patients will be briefly summarized.

In addition, a Consultation was requested by this Reviewer from the Division of Neuropharmacological Drug Products (DNDP) to assess the neurologic safety findings, including abnormal EDX test results, paresthesias, and tremors, noted in the clinical studies. Findings of the DNDP Medical Reviewer have been referenced and included in the safety review.

1) Combined Safety Data Set

A total of 80 patients were exposed to OGT 918 at anytime in the Gaucher clinical program and are included in this Combined Safety Data Set.

a) Adverse Events

Adverse Events (AEs) included in the data set included those occurring in randomized patients who took at least one dose of study medication through study completion/discontinuation. Only treatment-emergent AEs are included, which were defined as events that started following initiation of study medication or a worsening of any pre-existing medical condition documented on Day 1 (Baseline). For patients who permanently discontinued study medication, treatment-emergent AEs were reported until the patient's study discontinuation visit. Recurrent or continuing AEs were counted only once. Adverse Event incidence rates were calculated using all randomized patients as the denominator. All AEs were coded using the World Health Organization (WHO) dictionary and are presented by body system and preferred term.

All 80 patients reported at least one AE during the treatment period. Adverse Events in the Gastrointestinal system were the most commonly reported. Diarrhea was the most commonly reported AE term, reported by 72 patients (90%). Weight decrease (65%), flatulence (45%), abdominal pain (44%), headache (36%), influenza-like symptoms (30%), and tremor (29%) were the next most commonly reported AEs. The most common AEs (occurring in $\geq$5% of patients, or $\geq$4 patients) are listed in the following table

Table 135: 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)

b) Adverse Events Over Time

There were notable trends in some AEs over time. Diarrhea (and some other GI AEs) and influenza-like symptoms decreased over time, and weight loss and tremor increased over time. This is particularly evident up until about Week 52. Thereafter, the trends are not as evident, possibly due to a smaller number of patients being exposed to OGT 918 after Week 52, and due to drop-outs of patients with these AEs. The incidences of diarrhea, weight loss, tremor and influenza-like symptoms over time are summarized in the following table [from NDA #21-348, Oxford Glycosciences (UK) Ltd, ISS, Volume 2.67, Table 8.8.5.8, page 147]

Table 136: Combined Data Set Incidence of Notable Adverse Events Over Time

		Weeks								
	Overall	0-4	>4-13	>13-26	>26-39	>39-52	>52-65	>65-78	>78-91	>91
Patients, n =	80	80	78	74	59	53	21	18	15	14
WHO AE Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Diarrhea	72 (90)	61 (76)	52 (67)	44 (59)	28 (47)	20 (38)	5 (24)	3 (17)	2 (13)	2 (14)
Influenza-like Symptoms	24 (30)	4 (5)	6 (8)	10 (14)	9 (15)	6 (11)	2 (10)	0	0	0
Weight Decrease	52 (65)	5 (6)	26 (33)	39 (53)	39 (66)	35 (66)	11 (52)	9 (50)	5 (33)	3 (21)
Tremor	23 (29)	5 (6)	14 (18)	17 (23)	7 (12)	8 (15)	3 (14)	3 (17)	1 (7)	1 (7)

c) Adverse Events Resulting in Discontinuation

Thirteen (13) of the 80 patients (16%) exposed to OGT 918 discontinued study medication prior to study completion due to AEs. Seven (7) patients withdrew during the original phase of the studies, and 6 patients withdrew during the extension phase of the studies. Discontinuations due to AEs in the Gastrointestinal system were the most common, with diarrhea being the most commonly reported AE term (6 patients). Flatulence (4 patients), tremor (3), and abdominal pain and neuropathy (2 each) were the next most commonly reported AE terms reported as the reason for study discontinuation. All reported AE terms that resulted in study discontinuation are summarized in the following table (patients could report more than 1 AE term as the reason for discontinuation)

Table 137: Combined Data Set Discontinuations Due to Adverse Events

		Overall
Randomized Patients, n =		80
Number of Withdrawals, n (%)		19 (24)
Discontinued for AE*, n (%)		13 (16)
Body System	WHO AE Term	n (%)
Gastrointestinal	Diarrhea	6 (8)
	Flatulence	4 (5)
	Abdominal Pain	2 (3)
	Constipation	1 (1)
Neurological	Tremor	3 (4)
	Neuropathy	2 (3)
Musculoskeletal	Joint Pain	1 (1)
Vision	Visual Disturbance	1 (1)
Special Senses	Taste Peculiar	1 (1)
Psychiatric	Appetite Absent	1 (1)
	Lethargy	1 (1)
	Depression	1 (1)
Metabolic and Nutritional	Weight Decrease	1 (1)
Red Cell	Hemoglobin Decreased	1 (1)
Platelet, Bleeding and Clotting	Thrombosis	1 (1)
Body as a Whole	Fatigue	1 (1)
Resistance Mechanism	Infection Viral	1 (1)
Unclassifiable	Uncoded (Furry coating on feces)	1 (1)

*Patients may have reported more than one AE term per discontinuation

d) Serious Adverse Events

There were 9 Serious Adverse Events (SAEs) that occurred in 8 patients. There were no deaths, but one patient in Study 918-001 died after being withdrawn from the study (Patient #203, died due to hepatocellular carcinoma and sepsis). SAEs in the neurologic system were the most commonly reported (3 patients). The SAEs are summarized as follows

Table 138: Combined Data Set Serious Adverse Events

Study	Patient	M/F	Age (yrs)	Serious Adverse Event	Body System	Onset (days)	Invest. Attrib.	Drug D/C?
918-001	107	F	28	Leg Pain	Body	156	NR	N
918-001	203	F	39	Thrombosis	Platelet, Bleeding and Clotting	-2	NR	Y
918-001	408	M	51	Arthropathy	Musculoskeletal	365	NR	N
918-001X	101	F	62	Neuritis	Neurologic	Approx. 630	Related	Y
918-001X	101	F	62	Neuropathy	Neurologic	Approx. 630	Related	Y
918-001X	105	M	54	Neuropathy	Neurologic	Approx. 480	Related	Y
918-001X	409	F	38	Uncoded (hip replacement)	Unclassified	Approx. 720	NR	N
918-004	105*	M	52	Hospitalization (elective respiratory tests)	Uncodable	169	NR	N
918-004X	108*	F	26	Tonsillectomy	Unclassified	Approx. 319	NR	N

*Both patients were randomized to the combination treatment group

e) Other Significant Adverse Events: Neurologic Adverse Events

(1) Paresthesia, Numbness, and Tremor

In the first study conducted with OGT 918 in patients with Gaucher disease (Study 918-001), a number of patients reported neurologic symptoms including paresthesias, tremor, cramps, and other symptoms suggestive of peripheral neuropathy. Due to concerns about these complaints, the protocols were amended to add EMG/NCV assessments either during or after treatment with study medication. No patient had EMG/NCV at baseline; however, the majority of patients underwent EMG/NCV evaluation at some point during or after study drug treatment. The electrodiagnostic (EDX) study methods were also not standardized between study centers. In addition, after the neurologic symptoms seen in the initial study were reported back to the study centers, the sponsor commented that the Investigators were noted to have a higher degree of vigilance for neurologic findings. This increased vigilance (for example, paper was placed on patients' out-stretched hands to detect tremor), may have increased the number of patients with reports of tremor and other neurologic complaints in subsequent studies, and may have been a source of bias in AE reporting.

The neurologic complaints for the Combined Data Set show that overall, 43% of study patients reported any neurologic complaint during study drug treatment. Tremor was more common in the 918-003 and 918-004 studies; however, as previously stated, this may have been at least partly due to greater vigilance by the study centers after neurologic complaints were noted in the initial study. The Cerezyme alone group had no reports of paresthesias, and 3 patients with tremor were reported to have developed

tremor (or worsening in a baseline tremor) after beginning OGT 918 in the extension phase of study 918-004. Patients with neurologic complaints by study and in the Combined Data Set are summarized in the following table

Table 139: Combined Data Set, Patients with Neurologic Complaints

Study	Dose OGT 918	Enrolled Patients, n =	Patients c/o Tremor, n (%)	Patients c/o Neuropathy, n (%)	Patients with Any Neuro Complaint, n (%)
918-001	100 mg TID	28	4 (14)	4 (14)	8 (29)
918-003	50 mg TID	18	8 (44)	2 (11)	11 (61)
918-004 All		36	12 (33)	2 (6)	16 (44)
OGT 918 Alone	100 mg TID	12	5 (42)	1 (8)	6 (50)
Cerezyme Alone		12	3 (25)	0	4 (33)
Combination	100 mg TID	12	4 (33)	1 (8)	6 (50)
Total		**82**	**24 (29)**	**8 (10)**	**35 (43)**

Tremor occurred in 29% of patients exposed to OGT 918 in the Combined Data Set: 4 patients in 918-001, 8 patients in 918-003, and 12 patients in 918-004. Tremor was decribed as a fine bilateral tremor of the hands, similar to physiological tremor with a frequency of about 8 Hz. In a few cases, the tremor was asymmetrical and in one case, tremor affected the neck. Tremor usually began during the first month of treatment and, in many cases, resolved between Month 1 and 3 while treatment continued (or the dose was decreased). Several patients had pre-existing tremor that appeared to be exacerbated by treatment with OGT 918. Follow-up is available on all patients except one, who withdrew with complaints of tremor, and in all these cases the tremor resolved. Tremor usually resolved within days of withdrawal of OGT 918.

The abnormal EDX testing results for the Combined Data Set show that overall, 32% of patients who underwent EDX testing had abnormal EDX results either during or after study drug treatment. Not all patients underwent EDX testing, no patient had baseline EDX testing performed, and for the Cerezyme Group, it is unclear for some patients when EDX testing occurred in relation to OGT 918 treatment. The EDX testing results by study and for the Combined Data Set are summarized in the following table

Table 140: Combined Data Set, Patients with EDX Testing and Abnormal Results

Study	Dose OGT 918	Enrolled Patients, n =	Patients with EDX Testing, n =	Patients with Abnormal EDX*, n (%)
918-001	100 mg TID	28	15	7 (46)
918-003	50 mg TID	18	16	3 (19)
918-004 All		36	29	10 (34)
OGT 918 Alone	100 mg TID	12	11	3 (27)
Cerezyme Alone		12	8	2 (25)
Combination	100 mg TID	12	10	5 (50)
Total		**82**	**60**	**19 (32)**

*% of patients tested

Six (6) patients (8%) in the Combined Safety Dataset reported paresthesias. If the AE is defined as paresthesias or numbness, 15 patients (19%) complained of these symtptoms during the studies. The individual patient results for the patients who underwent EDX testing are summarized in the Appendix and are included in the individual study safety

sections (to follow). On review of these cases by the DNDP Neurology Consultant, and by this Reviewer, 5 patients appeared to have definite sensorimotor peripheral neuropathy, including Patients 101, 103, and 105 (in the 918-001 Study), Patient 111 (918-003), and Patient 135 (918-004; Combination Group). The sensorimotor peripheral neuropathies were not noted to be reversible in any patient as of final follow-up submitted to the NDA, and in the case of Patients #103 and #111, may have worsened after study drug was discontinued. These 5 patients are summarized in the following table

Table 141: Combined Safety Dataset, Patients with Definite Sensorimotor Peripheral Neuropathy

Study	Patient	EDX Results	Findings
918-001	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.
918-001	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 performed 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.
918-001	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.
918-003	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.
918-004	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.

The sponsor also consulted a neuromuscular expert, _____, who performed an evaluation of the EDX reports generated from the assessments. However, it should be noted that there are discrepancies noted by the sponsor and by this Reviewer between the AE database and _____ reporting of associated symptoms (i.e., for some patients, neurologic symptoms were reported in the AE database that are not noted in the consultant report). In addition, _____ report for control subjects did not appear to account for the

cross-over of patients from Study 918-004 receiving Cerezyme alone, to Study 918-004X, where these patients received OGT 918. The Cerezyme alone group was considered by the consultant as a control group, which is not the case in Study 918-004X. [Please see NDA# 21-348, Oxford Glycosciences (UK) Ltd, ISS, Volume 2.67, pages 302-316, dated 12-Sept-2001 for Neurologic Findings].

——— findings, briefly, note that a number of patients with abnormal EDX testing had alternate explanations for the abnormal EDX test results, such as diabetes, vitamin B12 deficiency, and gammopathies. In addition, 8 control subjects with Gaucher disease who had never received OGT 918 also underwent EDX testing. Of these 8 patients, 5 patients had normal EDX testing, 2 had finding consistent with peripheral neuropathy and 1 had findings consistent with carpal tunnel. ——— summarized her findings as follows[12]:

"In summary, 25% of control patients with Gaucher disease who had EDX studies done had electrophyiologic evidence consistent with peripheral neuropathy. (These two patients had also been on Cerezyme therapy either currently or at some time in the past). This is in comparison to 29% of patients receiving OGT 918 alone who had EDX studies done, 25% receiving Cerezyme alone who had EDX studies done, and 50% of patients receiving OGT 918 in combination with Cerezyme who had EDX studies done..."

"If one excludes those patients with co-existent conditions that might cause a peripheral neuropathy, such as vitamin B12 deficiency or diabetes, the numbers then change. The control patients remain at 25%, those receiving OGT 918 alone are 21%, those receiving Cerezyme alone are 14%, and those receiving a combination of OGT 918 and Cerezyme who had EDX studies done are 44%, quite elevated in comparison to the control group, as well as the other groups..."

"Based on this information, OGT 918, used alone does not appear to carry a significant risk for developing peripheral neuropathy, above the control population, based on EDX studies. *However, there is a tendency for an increased incidence for abnormal EDX findings associated with peripheral neuropathy in patients starting at the lower dose, although the incidence in those starting at the higher dose is comparable to the control patients, although it should be noted that the two control patients with abnormal EDX studies had received Cerezyme therapy. The combination of OGT 918 and Cerezyme appears to carry an elevated risk for peripheral neuropathy based on EDX criteria."*

Despite the sponsor's (and the sponsor's Neurology consultant's) conclusion that the neuropathic findings could be explained by concomitant medical conditions, it was the opinion of the DNDP Neurology Consultant that treatment of Gaucher disease type 1 patients with OGT 918 was associated with a clear signal of neurotoxicity. Conclusions per the DNDP neurology consultant are summarized as follows [Neuropharmacologic Medical Review performed by Gerald Tremblay, M.D., Medical Reviewer, DNDP, at the

[12] ——— Evaluation of Peripheral Neuropathy and Tremor Associated with OGT 918 in Gaucher Disease (Final Report). Unpublished report (2001).

request of DMEDP; and secondary review by John Feeney, M.D., DNDP Neurology Team Leader. For more detail, please refer to: Tremblay, Gerald, M.D., NDA #21-348, Consultative Review and Evaluation of Clinical Data, dated 05-Apr-02.]

"OGT 918 is associated with mild tremor in a significant number of patients. The tremor appears to be reversible, at least after short-term exposure. It is not known if the tremor will continue to be reversible after longer exposures to the drug."

"Although risk factors may exist, it is not necessary that the study drug be the exclusive cause, but may contribute to the neuropathy in a susceptible person. There is sufficient evidence of a neuropathic signal in these data for the Agency to describe the signs and symptoms of it in labeling and to require further investigations. We disagree with the Sponsor's post-hoc approach of eliminating patients from consideration because they supposedly had alternative causes for their neuropathic signs and/or symptoms. OGT 918 may have *contributed* to neuropathy in any or all of the affected patients; it need not have been the *exclusive* cause. In practice, Gaucher patients will likely have the same risk factors as the patients in the clinical trials had, and an evaluation of safety has to consider the features of the population that is likely to take the drug."

In conclusion "Although there were no baseline electrodiagnostic test results and a safety database that was too small, we believe there is sufficient basis to conclude there is a signal of neurotoxicity in these data. Our back ground level of concern was raised by what we were told of the preclinical neuropathology. Next, the mechanism whereby OGT 918 lowers GSLs, and the fact that two of the drug's developers have expressed concerns that excessive depletion of some GSLs may adversely affect nerves further raised concerns." The secondary review by the Neuropharmacology Team Leader also stated [redacted]

[From: Feeney, John, NDA #21-348, Secondary Review, dated 08-Apr-2002]

(2) Memory Loss

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. These patients are described briefly in the following table

Table 142: Combined Safety Dataset, Patients who Complained of Memory Loss

Study	Patient	Description
918-001	411	66 yo M of high baseline intellect (retired chemical and electrical engineer, speaks 7 languages), who was on therapy for 3 years, having stopped therapy 7 months ago. The patient first complained of tinnitus, vertigo and memory loss 2 years ago. 9 months ago he again complained of memory loss, and an evaluation at memory clinic reported above average memory recall. His wife became aware of memory problems 6 months ago (trouble recalling words and tasks, having to make lists), and re-evaluation at memory clinic 22-Apr-02 reported "memory executive dysfunction with early language problems and mild idiomotor apraxia" thought to be early Alzheimers disease. A CT head scan was normal, and a SPECT scan and MRI are pending. Concurrent illness includes a low-normal B12 throughout the study, and a progressively rising methylmalonic acid (MMA) throughout the study.
918-001	415	30 yo M who continues to receive OGT 918 (for approximately 3 years), who complained of memory loss from Jan-99 to Jun-99. The patient is an actor, and he was under strain due to a move to Israel. The patient was able to memorize his lines in Hebrew despite Russian being his native language. This patient also had low B12 levels throughout the trial. Further details have been requested from the sponsor.
918-001	105	55 yo M who began OGT 918 Dec-98 and discontinued study drug Jan-2000 (after approximately 2 years of treatment). Mild cognitive deterioration was reported Nov-2000. A neuropsych evaluation showed a mild compromise of cognition in a pattern that is suggestive of a loss of executive efficiency. A cranial MRI was WNL. Further details have been requested from the sponsor.
918-004	120	45 yo M who withdrew from the study at Month 15 due to fatigue. The patient is physically disabled and was caring for his 2 terminally ill parents. Memory impairment involved forgetting the code to his father's computerized bed. Further details have been requested from the sponsor.
918-004	127	19 yo F student who noted memory loss after her father's death. The patient was evaluted at memory clinic and no evidence of neuropsychological deficit or memory problems were noted. Further details have been requested from the sponsor.
918-002 (Fabry disease)	201	Memory loss reported as an AE. No other information currently available and further details have been requested from the sponsor.

After the SAE report was received for Patient 411, the IRB/IEC at the study center placed the study on temporary hold pending additional information. Further information has been requested from the sponsor regarding the above patients, in addition to a request to query the HIV clinical program database for reports of memory loss. Additional information is expected; 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 [SAE not included in Combined Safety Dataset SAE table as patient was off study drug for 7 months at the time of the report, and had been receiving study drug beyond the 12 months of the 918-001X extension study].

f) Laboratory Abnormalities

There were no notable treatment emergent laboratory abnormalities during study drug treatment for any of the studies.

2) Individual Study Safety Assessment

a) Study 918-001

(1) Adverse Events

All 28 patients (100%) reported at least one AE during the study. There were 70 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 25 patients (89%). The next most commonly reported AEs were weight decrease (43%), headache (32%), flatulence (29%), abdominal pain (25%), rhinitis and thrombocytopenia (18% each), and nausea, purpura, upper respiratory tract infection, and tremor (14% each). These findings are similar to the pooled results reported in the Combined Data Set. The most common AEs (occurring in ≥5% of patients, or ≥2 patients) are listed in the following table [A complete list of all reported AEs is in the Appendix]

Table 143: 918-001 Incidence of Most Common Adverse Events (≥5% of Patients)

Randomized Patients, n =		28
Body System	**WHO AE Term**	**n (%)**
Musculoskeletal	Myalgia	3 (11)
	Back Pain	2 (7)
	Skeletal Pain	2 (7)
Neurological	Headache	9 (32)
	Tremor	4 (14)
	Paresthesia	3 (11)
	Dizziness	2 (7)
Gastrointestinal	Diarrhea	25 (89)
	Flatulence	8 (29)
	Abdominal Pain	7 (25)
	Nausea	4 (14)
	Anorexia	3 (11)
	Dyspepsia	3 (11)
	Vomiting	2 (7)
Metabolic and Nutritional	Weight Decrease	12 (43)
Respiratory	Rhinitis	5 (18)
	Upper Respiratory Tract Infection	4 (14)
	Sinusitis	2 (7)
Platelet, Bleeding and Clotting	Thrombocytopenia	5 (18)
	Purpura	4 (14)
	Epistaxis	2 (7)
Body as a Whole	Influenza-like Symptoms	3 (11)
	Chest Pain	2 (7)
	Fatigue	2 (7)
	Tiredness	2 (7)
Unclassifiable	Fall	2 (7)

(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 decrease and tremor were noted to increase over the course of the study. These findings are similar to the pooled results in the Combined Data Set. The

sponsor's summary of AEs with an incidence of ≥10%, by week of study drug treatment is listed in the following table (Note: there are minor differences in AE incidence calculations for some AEs compared to the Reviewer's results listed in previous table)

Table 144: 918-001 Incidence of Adverse Events in ≥10% of Patients Over Course of Study

	Overall	0-1 Month	1-3 Months	3-6 Months	6-9 Months	9-12 Months
Randomized Patients, n =	**28**	**28**	**26**	**24**	**23**	**22**
WHO AE Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Diarrhea	25 (89)	22 (79)	19 (73)	12 (50)	12 (52)	5 (23)
Weight Decrease	11 (39)	0	4 (15)	5 (25)	6 (26)	3 (14)
Headache	8 (29)	5 (18)	5 (19)	3 (13)	2 (9)	0
Flatulence	8 (29)	4 (14)	5 (19)	5 (21)	1 (4)	1 (5)
Abdominal Pain	7 (25)	4 (14)	3 (12)	2 (8)	3 (13)	3 (14)
Rhinitis	5 (18)	1 (4)	1 (4)	2 (8)	1 (4)	1 (5)
Tremor	4 (14)	0	1 (4)	1 (4)	2 (9)	4 (18)
Nausea	4 (14)	2 (7)	1 (4)	1 (4)	0	0
Purpura	4 (14)	0	0	0	2 (9)	3 (14)
Myalgia	3 (11)	0	0	1 (4)	1 (4)	1 (5)
Paresthesia	3 (11)	1 (4)	1 (4)	2 (8)	1 (4)	2 (9)
Anorexia	3 (11)	1 (4)	2 (8)	2 (8)	0	0
Dyspepsia	3 (11)	1 (4)	2 (8)	2 (8)	1 (4)	0
Upper Respiratory Tract Infection	3 (11)	0	0	3 (13)	0	0
Influenza-like Symptoms	3 (11)	2 (7)	1 (4)	2 (8)	1 (4)	1 (5)

(3) Adverse Events Resulting in Discontinuation

Three (3) of the 28 patients discontinued study medication prior to study completion due to AEs (1 was an SAE). Two patients (102 and 401) withdrew for diarrhea, and one patient (203) for thrombosis (see SAE below). The 2 patients with diarrhea first reported the diarrhea at the Day 15 visit

(4) Serious Adverse Events

Three (3) patients experienced 3 SAEs during the study. There were no deaths; however, Patient 203 died after being withdrawn from the study. This patient (203) was withdrawn due to a partial thrombosis of the portal vein. The 3 SAEs were all assessed by the Investigators as being not related to study medication. The SAEs are summarized below and in the following table

Patient 107 was hospitalized for leg pain, diagnosed as Gaucher bone crisis of the right tibia, and treated with analgesics. The event started approximately 8½ months after screening. Treatment was interrupted on Day 169 and resumed on Day 225. The patient completed the study.

Patient 203 was hospitalized for severe abdominal pain in the liver region and right lower quadrant of the abdomen, slight fever, nausea, anorexia, and constipation. Partial thrombosis of the portal vein was diagnosed 2 days after the screening visit, and 2 days prior to starting treatment with OGT 918. Withdrawal from the study occurred 5 days after enrollment. Follow-up information noted that the patient had hepatocellular

carcinoma complicated by portal thrombosis. The patient died 6 months later following a possible septic episode.

Patient 408 was hospitalized for a re-operation on the talus, approximately 1 year after the screening visit. There were no changes in study medication and the patient completed the study.

Table 145: 918-001 Serious Adverse Events

Patient	M/F	Age (yrs)	Serious Adverse Event	Body System	Onset (days)	Invest. Attrib.	Drug D/C?
107	F	28	Leg Pain	Body	156	NR	No
203	F	39	Thrombosis	Platelet, Bleeding and Clotting	-2	NR	Yes
408	M	51	Arthropathy	Musculoskeletal	365	NR	No

(5) Neurologic Adverse Events

Studies 918-001 and 918-001X are considered together as EDX testing could have occurred during either study. Eight (8) of the 28 patients (29%) enrolled in the studies reported neurologic complaints of tremor, muscle cramping, or numbness or tingling of the extremities. EDX studies were performed in 15 of the 28 patients in this study, including 7 of the 8 patients with neurologic complaints. Seven (7) patients had abnormal EDX results, including 3 of the 7 patients with neurologic complaints who underwent EDX testing, and 4 of 8 patients 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 146: 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 performed 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.

(6) Other Significant Adverse Events

Another patient (406) was withdrawn at the patient's request due to pre-existing pulmonary hypertension. On Day 85 of the study, the patient was noted to have a severe worsening of her pulmonary hypertension (TI gradient increased to 59 mmHg from 43 mmHg at screening), a
by the patients since 1995) was discontinued. Mild prolonged menstrual bleeding was subsequently reported, and the patient was withdrawn on approximately Day 97.

Patient 101 experienced a >20% weight loss during the study. The patient's weight went from 75.4 kg (obese range) at screening, to 57.2 kg (normal range) by Day 337.

Patient 402 withdrew approximately 7 months after study entry as he wanted to start planning a family. Approx. 15 months after study withdrawal, the patient reported his wife giving birth to a normal baby, with no problems observed during pregnancy and up to 8 months after birth.

(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. Trends noted from Baseline to Endpoint are as follows:

(a) White Blood Cell Count

There were mild decreases in the White Blood Cell Count (WBC), which affected all WBC cell lines except lymphocytes. These changes were mild, and are not considered clinically important, however. For individual patients, 8 patients had a WBC <3.0 at anytime during the study, all of whom had baseline WBC values <4. All WBC values ranged from 1.4 (baseline 2.0) to 15.6 (baseline 13.5) during the study. WBC parameters at Baseline and Endpoint are as follows

Table 147: 918-001 WBC Parameters

WBC Cell Line	Baseline	Endpoint	Actual Change	% Change
Patients, n =	28	26	26	26
WBC	6.01	5.38	-0.32	-5.3
Neutrophils	3.37	2.99	-0.35	-8.6
Lymphocytes	2.03	1.87	0.05	1.7
Monocytes	0.42	0.38	-0.01	-0.3
Eosinophils	0.14	0.10	-0.01	-6.1
Basophils	n = 23	n = 22	n = 21	n = 21
	0.05	0.03	-0.01	-35.4

(b) Alkaline Phosphatase, AST and ALT

Alkaline phosphatase decreased from a mean of 83.2 at baseline to 70.9 at endpoint (mean % change of –12.5%). One patient (107) had an elevation in alkaline phosphatase >2 X ULN, which was considered a reflection of a bone crisis. ALT increased 12.9% (mean baseline 38.5, mean endpoint 42.3), and AST increased 1%. There were 2 patients (406 and 413) who had elevations in AST and ALT >2 X ULN during study drug treatment. One of these elevations resolved (413), and one was ongoing at discontinuation (406; discontinued on Day 97 at patient's request due to worsening pulmonary hypertension). [Listings of these 3 patients' alkaline phosphatase, ALT, and AST results are in the Appendix.]

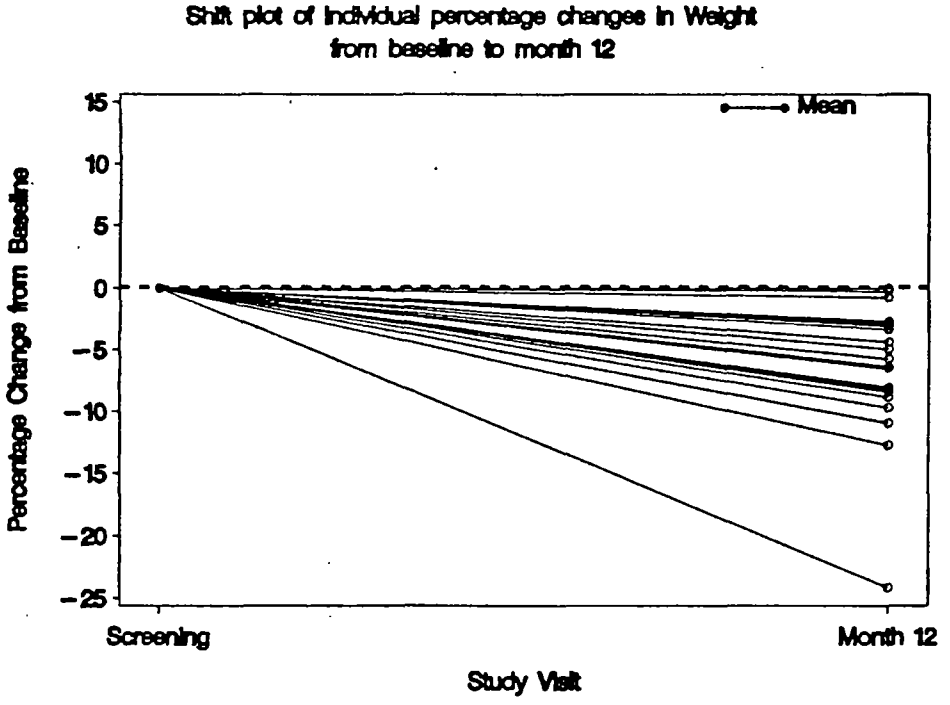
There were no other notable changes in hematology or chemistry parameters.

(8) Physical Findings

(a) Weight

Weight decreased for all patients from Baseline to Endpoint, with a mean decrease of 6%. By weight category (obese, overweight, normal, and underweight), one patient shifted from obese to normal; three patients from overweight to normal, and one patient from normal to underweight, during the study. One patient (101) experienced a >20% weight loss during the study. Percent weight change from baseline to Month 12 is shown graphically (in Figure 2) for the individual study patients, showing the progressive decrease in weight for all patients over the course of the study.

Figure 43: 918-001 Individual Percentage Weight Change from Baseline to Month 12



(b) Blood Pressure

Seven (7) patients had clinically significant changes in blood pressure during the study. Clinically significant was defined as:
An increase in SBP $\geq$180 mmHg, or $\geq$20 mmHg from baseline;
A decrease in SBP $\leq$90 mmHg, or $\geq$20 mmHg from baseline; or
A decrease in DBP $\leq$50 mmHg, or $\geq$15 mmHg from baseline.

The clinically significant BP changes during the study are as follows:
Patient 103: increased SBP at Months 1 and 9
Patient 107: decreased SBP at Month 1
Patient 402: decreased SBP at Month 3

Patient 413 decreased SBP at Month 1
Patient 404: decrease DBP at Month 6
Patient 409: decreased DBP at Month 12
Patient 411: decreased DBP at Month 1

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

b) Study 918-001X

(1) Adverse Events

All 18 patients (100%) reported at least one AE from entry into the original study (918-001) until extension study completion/termination. There were 75 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 16 patients (89%). The next most commonly reported AEs were weight decrease (61%), headache (44%), flatulence (33%), abdominal pain (28%), and purpura and upper respiratory tract infection (22% each). The most common AEs (occurring in ≥10% of patients, or ≥2 patients) cumulative from baseline (entry into the original study) through extension study completion/termination are listed in the following table [A complete list of all reported AEs is in the Appendix]

Table 148: 918-001X Incidence of Most Common AEs (>10% of Patients)

Randomized Patients, n =		18
Body System	**WHO AE Term**	**n (%)**
Musculoskeletal	Myalgia	3 (17)
	Back Pain	2 (11)
Neurological	Headache	8 (44)
	Cramps Legs	3 (17)
	Dizziness	3 (17)
	Paresthesia	3 (17)
	Tremor	3 (17)
	Neuropathy	2 (11)
	Vertigo	2 (11)
Psychiatric	Anorexia	3 (17)
	Memory Loss	2 (11)
Gastrointestinal	Diarrhea	16 (89)
	Flatulence	6 (33)
	Abdominal Pain	5 (28)
	Vomiting	3 (17)
	Nausea	2 (11)
Metabolic and Nutritional	Weight Decrease	11 (61)
Respiratory	Rhinitis	3 (17)
	Upper Respiratory Tract Infection	3 (17)
	Sinusitis	2 (11)
Platelets, Bleeding and Clotting	Purpura	4 (22)
	Thrombocytopenia	3 (17)
Body as a Whole	Influenza-like Symptoms	4 (22)
	Fatigue	3 (17)
	Tiredness	2 (11)
Unclassifiable	Fall	2 (11)

(2) Adverse Events Over Time

The incidence of diarrhea and other GI AEs were noted to decrease over the course of the study. Unlike the Study 918-001, tremor and weight decrease are not shown to increase after Week 52 of the study; however, this is at least in part accounted for by patients with

these complaints dropping out of the study. The incidence of selected AEs over time are summarized in the following table

Table 149: 918-001X Incidence of Selected AEs Over Course of Study

		Time Interval (Weeks)				
	Overall	0-52	>52-65	>65-78	>78-91	>91
Randomized Patients, n =	18	18	18	17	15	14
WHO AE Term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
GI System Disorders	18 (100)	18 (100)	6 (33)	5 (29)	5 (33)	7 (50)
Diarrhea	16 (89)	16 (89)	3 (17)	3 (18)	2 (13)	2 (14)
Nervous System Disorders	13 (72)	10 (56)	9 (50)	9 (53)	7 (47)	5 (36)
Headache	8 (44)	5 (28)	3 (17)	3 (18)	3 (20)	2 (14)
Paresthesia	3 (17)	2 (11)	3 (17)	2 (12)	1 (7)	1 (7)
Tremor	3 (17)	3 (17)	3 (17)	3 (18)	1 (7)	1 (7)
Metabolic/Nutritional Disorders	12 (67)	9 (50)	9 (50)	9 (53)	5 (33)	4 (29)
Weight Decrease	11 (61)	9 (50)	9 (50)	9 (53)	5 (33)	3 (21)

(3) Withdrawals due to AEs

Two (2) patients (101 and 105) discontinued study medication prior to study completion due to AEs. Both AEs were neuropathy, and both were SAEs (see SAE section below).

(4) Serious Adverse Events

Four (4) patients experienced 5 SAEs during the study. One of the SAEs, leg pain in Patient 107, was previously reported in Study 918-001 and will not be recounted here. Three (3) of the remaining 4 SAEs were in the neurologic system, including neuropathy and neuritis. There were no deaths. The SAEs are summarized below and in the following table

Patient 101 experienced severe neuropathy (NCI toxicity grade 3) and severe neuritis (NCI toxicity grade 3) reported at the Month 21 visit. The patient found it difficult to walk due to the painful paresthesia and numbness in her upper and lower limbs. The patient initially reported mild paresthesia at approximately Month 12, and moderate peripheral neuropathy at approximately Month 16. EMG and NCV testing were performed, and the EMG assessment was consistent with chronic sensorimotor peripheral neuropathy, possibly superimposed with left ulnar neuropathy or C8/T1 radiculopathy. She was diagnosed with generalized sensory motor peripheral neuropathy of the axonal type and was withdrawn from the study at Month 21. This patient also reported a significant weight loss (>20%) during the original 12 months of the study.

Patient 105 reported mild tremor in his hands from approximately Month 1 to Month 12. Mild peripheral neuropathy was reported from Month 12 to Month 14, and moderate neuropathy was reported on Month 14. The neuropathy consisted of numbness in both hands and feet, and was reported to be of sufficient severity as to be considered disabling. EMG and NCV were performed and the EMG was consistent with peripheral neuropathy. The patient received his last dose of study medication in Month 12, and was discontinued from the study Month 14. This patient also reported significant alcohol intake.

Patient 409 had a past history of drainage of an infected hip joint in 1989, a total right hip replacement in 1993, and avascular necrosis (not otherwise defined). The patient underwent a total replacement of the right hip reported at the Month 24 visit (onset reported as Month 23) due to moderate increased bone pain in the right hip from approximately Month 21.

Table 150: 918-001X Serious Adverse Events

Patient	M/F	Age (yrs)	Serious Adverse Event	Body System	Onset (days)	Invest. Attrib.	Drug D/C?
101	F	62	Neuritis	Neurologic	Approx. 630	Related	Y
101	F	62	Neuropathy	Neurologic	Approx. 630	Related	Y
105	M	54	Neuropathy	Neurologic	Approx. 480	Related	Y
409	F	38	Uncoded (hip replacement)	Unclassified	Approx. 720	NR	N

(5) Other Significant Adverse Events

Please see the neurologic findings section in Study 918-001.

(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

Unlike Study 918-001, overall, there were no decreases in the WBC at Endpoint (Month 24); however, there were *mild* increases in all WBC cell lines at endpoint. The magnitude of these changes was not considered clinically important. WBC parameters are as follows

Table 151: 918-001X WBC Parameters

WBC Cell Line	Baseline	Endpoint	Actual Change	% Change
Patients, n =	18	18	18	18
WBC	5.22	5.59	0.37	12.0
Neutrophils	3.17	3.26	0.09	7.7
Lymphocytes	1.57	1.85	0.28	23.6
Monocytes	0.35	0.35	-0.01	14.9
Eosinophils	0.094	0.110	0.016	5.5
Basophils	n = 15 0.04	n = 15 0.05	n = 15 0.01	n = 15 11.1

(b) Alkaline Phosphatase, AST and ALT

Overall, alkaline phosphatase decreased from a mean of 77.1 at baseline to 72.4 at Endpoint (mean % change of –5.0%). Mean ALT mildly decreased 1.9% (mean baseline 37.4, mean endpoint 35.2), and mean AST decreased 5.2%.

There were no other notable changes in hematology or chemistry parameters.

(7) Physical Findings

(a) Weight

Weight changes for all patients ranged from +2.0 kg to –18.1 kg from Baseline to Endpoint, with a mean weight decrease of –3.01 kg.

Physical examinations, slit lamp, and ECG assessments were not performed during the extended treatment period.

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c) Study 918-003

(1) Adverse Events

Seventeen (17) of the 18 patients (94%) reported at least one AE during the study. There were 67 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 17 patients (94%). The next most commonly reported AEs were weight decrease (67%), abdominal pain, flatulence, and headache (50% each), and tremor (39%). 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 152: 918-003 Incidence of Most Common AEs (≥10% of Patients)

Randomized Patients, n =		18
Body System	**WHO AE Term**	**n (%)**
Musculoskeletal	Bone Pain	2 (11)
	Cramps	2 (11)
	Pain Neck/Shoulder	2 (11)
Neurological	Headache	9 (50)
	Tremor	7 (39)
	Dizziness	4 (22)
	Cramps Legs	2 (11)
Vision	Visual Disturbance	3 (17)
	Eye Infection	2 (11)
	Eye Irritation	2 (11)
Gastrointestinal	Diarrhea	17 (94)
	Abdominal Pain	9 (50)
	Flatulence	9 (50)
	Nausea	4 (22)
	Vomiting	3 (17)
Metabolic and Nutritional	Weight Decrease	12 (67)
	Weight Increase	2 (11)
Respiratory	Nose Congestion	2 (11)
Platelet, Bleeding and Clotting	Nosebleed	2 (11)
Body as a Whole	Influenza-Like Symptoms	6 (33)
	Back Pain	3 (17)
	Chest Pain	2 (11)
	Fatigue	2 (11)

(2) Adverse Events Over Time

As with Study 918-001, the incidence of tremor and weight loss were noted to increase over the course of the study. However, unlike Study 918-001, there were no substantial decreases in GI AEs over the course of the study, which may reflect the shorter time interval for the 918-003 study (6 months, vs 12 months for the 918-001 study). 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 153: 918-003 Incidence of Selected Adverse Events Over the Course of the Study

		Time Interval (Weeks)		
	Overall	0 – 4	>4 – 13	>13
Patients, n =	18	18	18	18
WHO AE Term	n (%)	n (%)	n (%)	n (%)
GI System	17 (94)	17 (94)	15 (83)	14 (78)
Diarrhea	17 (94)	14 (78)	14 (78)	13 (72)
Abdominal Pain	9 (50)	6 (33)	6 (33)	4 (22)
Flatulence	9 (50)	8 (44)	7 (39)	5 (28)
Nausea	4 (22)	3 (17)	1 (6)	2 (11)
Vomiting	3 (17)	2 (11)	2 (11)	1 (6)
Tremor	7 (39)	0	4 (22)	7 (39)
Weight Decrease	12 (67)	1 (6)	7 (39)	12 (67)

(3) Adverse Events Results in Discontinuation

One patient discontinued study medication prior to study completion due to an AE and at the patient's request. This patient (202) withdrew at Day 126 due to diarrhea and gas. The patient first reported diarrhea at the Day 15 study visit, with onset of symptoms at Day 4. The patient also reported mild gas and mild abdominal pain at Month 3, and received his last dose of study medication at Month 4.

(4) Serious Adverse Events

There were no serious adverse events during the study, and there were no deaths.

(5) Neurologic Adverse Events

Studies 918-003 and 918-003X are being considered together as EDX testing could have been performed during either study. Eleven (11) of 18 patients (61%) reported neurologic complaints of tremor, muscle cramps or symptoms of peripheral neuropathy. EDX studies were performed in 16 of 18 patients, including 10 of the 11 patients with neurologic complaints. Three (3) patients had abnormal EDX results, including 1 patient of the 10 with neurologic complaints who underwent EDX testing, and 1 of the 7 patients 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 154: 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.
204	Normal	No neurologic complaints reported.
205	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.

(6) Other Significant Events

Patient 206 experienced moderate menorrhagia and low hemoglobin (6.1 g/dL) noted at the Month 1 visit, with onset of menorrhagia noted at Day 29. Menorrhagia was found to be secondary to a miscarriage. The patient had a negative pregnancy test at screening, but was not using any birth control. The patient completed the study.

Patient 208 was noted by the Investigator to have worsening thrombocytopenia at the Day 169 visit. The patient's platelet count at screening was 34,000, and dropped to 24,000 at Month 6. The patient completed the study. The patient's platelet counts at each study visit are as follows

Table 155: 918-003 Platelet Counts for Patient 208

Visit	Platelet Count (X1,000)
Screening	34
Month 1	37
Month 2	26
Month 3	38
Month 4	31
Month 5	30
Month 6	24
Endpoint	24

(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. There were no decreases in WBC, neutrophils, or lymphocytes noted, with an overall mean percent increase in WBC of +2.8% from Baseline. Trends noted from Baseline to Endpoint are as follows:

(a) Alkaline Phosphatase, ALT and AST

Alkaline phosphatase decreased from a mean of 83.5 U/l at Baseline to 72.9 U/l at Endpoint (mean % change of –12.2). ALT increased 10.5% and AST decreased –2.8%. Acid phosphatase increased 10.2% to 43.9% (at Centers 2 and 1 respectively), and ACE increased 1.8% and 13.0% (at Centers 2 and 1 respectively).

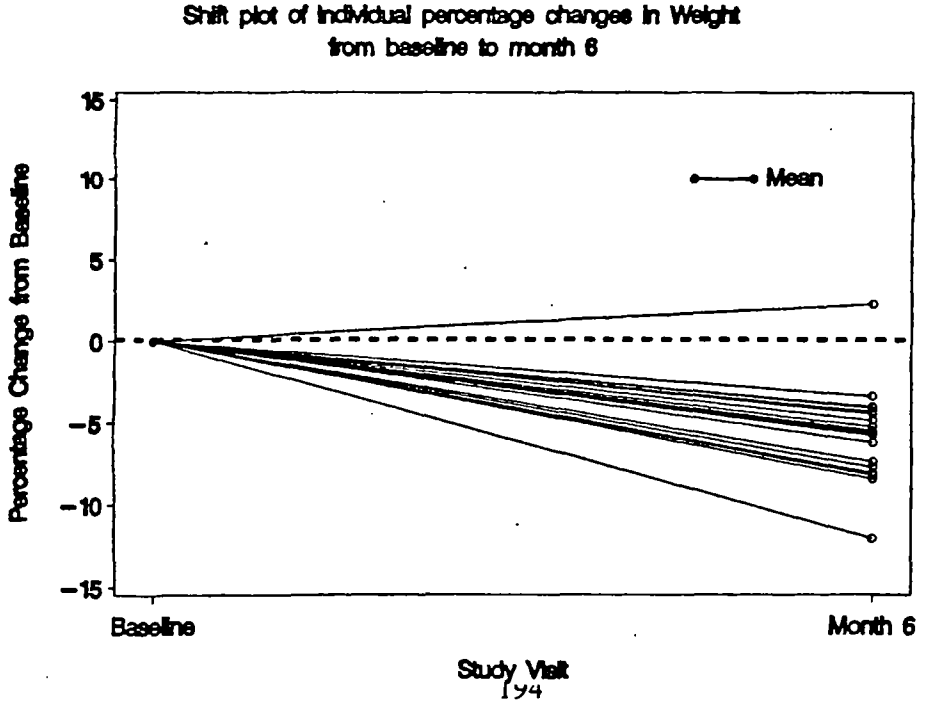
There were no other notable changes in hematology or chemistry parameters.

(8) Physical Findings

(a) Weight

Weight decreased for all patients but 1 from Baseline to Endpoint, with a mean decrease of –3.46 kg (6%). By weight category (obese, overweight, normal, and underweight), one patient shifter from obese to overweight, 3 patients from overweight to normal, and 2 patients from normal to underweight, during the study. Percent weight change from baseline to Month 6 is also shown graphically (in Figure 3) for the individual study patients, showing the progressive decrease in weight in almost all the patients over the course of the study [Figure electronically scanned and reproduced from: Oxford Glycosciences (UK) Ltd, NDA #21-348, Volume 2.10, page 289, dated 02-Aug-2001].

Figure 44: 918-003 Individual Percentage Weight Change from Baseline to Month 6



(b) Blood Pressure

One patient had clinically significant changes in blood pressure during the study.
Clinically significant was defined as:
An increase in SBP ≥180 mmHg, or ≥20 mmHg from baseline;
A decrease in SBP ≤90 mmHg, or ≥20 mmHg from baseline; or
A decrease in DBP ≤50 mmHg, or ≥15 mmHg from baseline.

The clinically significant BP changes during the study was:
Patient 208: decreased SBP at Month 1

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