(iii) Acid Phosphatase

There were significant mean decreases in acid phosphatase from Baseline at Month 6 of –9.2% (p-value .014), and at Month 12 of –9.9% (.047). The results are summarized in the following table

Table 42: 918-001 Acid Phosphatase Statistics

	Baseline (nmol/ml.h)	Month 6	Month 12
n	27	21	20
Mean	2699.3	-9.2	-9.9
Median	1836.0	-12.9	-9.4
Minimum			
Maximum			
p-value*		.014	.047

Control range: 94-342 nmol/ml.h
*for mean % change from baseline at Months 6 and 12

(iv) Angiotensin Converting Enzyme

There were mean changes in ACE from baseline at Months 6 and 12 of +0.5% and –4.4% respectively. The results were not significant. The results are summarized in the following table

Table 43: 918-001 Angiotensin Converting Enzyme Statistics

	Baseline (nmol/ml.min)	Month 6	Month 12
n	26	20	19
Mean	119.3	0.5	-4.4
Median	95.0	0.4	-8.0
Minimum			
Maximum			
p-value*		.852	.061

Control range: 20-43 nmol/ml.min
*for mean % change from baseline at Months 6 and 12

(v) G_{M1} Analysis

G_{M1} analysis (cell surface expression in leukocytes) was performed for only 7 patients at baseline. There was no significant change from baseline in G_{M1} analysis at Month 6 (+0.5%; p= 0.072), but there was a statistically significant mean percentage decrease from Baseline at Month 12 of -38.5% (p= 0.006). This finding is consistent with the anticipated effect of OGT 918 on lowering the rate of glycolipid biosynthesis.

(vi) Glucosylceramide

Glucosylceramide assessments were performed in a subgroup of 8 patients. At Month 6, there was a mean percentage decrease of –1.7% (p=.920), and at Month 12 there was a mean percentage increase of +0.9% (p=.970).

(vii) Other Disease Assessments

Other disease assessments were performed at the discretion of the Investigator and per usual practice at the study centers. Eighteen patients had at least one other disease assessment for whom results are available at Screening and at Month 12. Patients underwent skeletal assessments including DEXA and MRI scanning, bone marrow assessment by QSCI, and echocardiography [a complete listing of tests performed is in the Appendix]. A discussion of the other disease assessments is in the Study 918-001X review.

(c) Subgroup Analysis

Subgroup analyses were performed by:

- Baseline Hgb <11.5 g/dL vs ≥11.5 g/dL (see Hemoglobin above)
- Chitotriosidase, acid phosphatase, hexosaminidase, and ACE by "non-expressors" vs "expressors" of these markers. The results of these subgroup analyses did not differ from the analyses of the groups as a whole.

(d) Conclusions on Efficacy Results for Protocol 918-001

There were statistically significant mean decreases in liver and spleen volumes from Baseline to Month 6 and Month 12. *Mean liver volume decreased* –7.0% at Month 6 and –12.1% at Month 12, and mean spleen volume decreased –15.1% at Month 6 and –19.0%. There were no significant mean increases in Hgb at Month 6 or Month12; however, there were greater mean actual increases in Hgb at Month 12 than Month 6. Mean Hgb increased 0.03 g/dL (0.5%) at Month 6, and increased 0.26 g/dL (2.6%) at Month 12. On subgroup analysis, patients with a Baseline Hgb <11.5 g/dL (<LLN) had greater mean increases in Hgb than patients with Baseline Hgb ≥11.5 g/dL, although these results were not statistically significant. Patients with Baseline Hgb <11.5 g/dL had a mean increase of 0.16 g/dL (1.78%) at Month 6 and an increase of 0.55 g/dL (5.71%) at Month 12, vs a decrease of -.06 g/dL (-0.41%) at Month 6 and an increase of 0.06 g/dL (0.45%) at Month 12 for patients with Baseline Hgb ≥11.5 g/dL. There was no significant mean increase in Plt at Month 6; however, there was a significant mean actual increase n Plt at Month 12 of 8.28 X $X10^9$/l. Only 1 patient had Plt >150 $X10^9$/l at Baseline, so a subgroup analysis by Baseline Plt could not be performed. Secondary efficacy analyses of biochemical markers of Gaucher disease, including chitotriosidase, hexosaminidase, acid phosphatase, ACE, and G_{M1}, showed decreases from Baseline at Month 6 and Month 12.

Overall, these efficacy findings are consistent with decreases in organ volumes in Gaucher disease type 1 patients treated with OGT 918. There was no significant increase in Hgb, and statistically significant but clinically minor increases in Plt were seen after 12 months of treatment.

2) Study 918-001X

a) Study Design for Protocol 918-001X

(1) Study Design

Protocol 918-001X "A phase I/II study of open-label OGT 918 in adult patients with Gaucher disease" was a non-comparative, multi-center, open-label extension study to Protocol 918-001. Protocol 918-001X evaluated the efficacy and safety of OGT 918 at a dose of 100 mg TID for an additional 12 months after successful completion of Protocol 918-001. Eighteen (18) adult patients with type I Gaucher disease who were unable or unwilling to receive Ceredase or Cerezyme were enrolled at 4 international clinical sites.

(2) Study Objectives

The primary objective for the study was to evaluate OGT 918 as a treatment for Gaucher disease by assessing organ volume and other markers of the disease after an additional 12 month treatment period. The secondary objective was to assess the tolerability of OGT 918 during an additional 12 months of treatment.

(3) Eligibility

Patients were eligible for the extension phase if they had completed the Month 12 visit in the original study (Protocol 918-001) and the Investigator felt they would benefit from extended use treatment. Ongoing enrollment in the extended use phase was confirmed quarterly based on improvements in organ volume parameters, hematological parameters or general symptoms.

(4) Study Visits and Procedures

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

Table 44: 918-001X Study Visits and Procedures

	Extended Use Treatment Period			
Month	**15**	**18**	**21**	**24**
Procedure				
History				
Physical Examination				
Vital Signs				
Weight/BSA/BMI	X	X	X	X
Height				
ECG				
Urine Pregnancy Test				
Urinalysis				
Biochemistry	X	X	X	X
Hematology	X	X	X	X
Chitotriosidase/Hexosaminidase	X	X	X	X
Organ Volume		X		X
Glucosylceramide		X		X
Other Disease Assessments				X
EMG and NCV			X	
Adverse Events	X	X	X	X
Concomitant Medications	X	X	X	X
OGT 918 Dispensing	X	X	X	X

As Protocol 918-001X was an extension to the original 12-month treatment period (Protocol 918-001), it continued with the same study design. Patients signed a second informed consent specific to the extended treatment period of the study prior to continuing in the extended treatment phase. Safety and efficacy assessments were made every 3 months, beginning at Month 15 after completion of Month 12 in the original treatment period. In addition, a protocol amendment for the addition of EMG/NCV assessments in Protocol 918-001X was submitted in May-2000 after concerns over possible neurologic effects of OGT 918 were noted.

(a) Month 15 Visit

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

- Weight
- Biochemistry
- Hematology
- Chitotriosidase/Hexosaminidase assessment
- EMG/NCV assessment performed once for each patient between the Month 15 and Month 24 Visits
- AE assessment
- Concomitant Medications update

(b) Month 18 Visit

At the Month 18 Visit, patients underwent the following assessments:

- Weight
- Biochemistry
- Hematology
- Chitotriosidase/Hexosaminidase assessment

- Glycosylceramide assessment
- Organ volume assessment
- AE assessment
- Concomitant Medications update

(c) Month 21 Visit

At the Month 21 Visit, patients underwent the following assessments:

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

(d) Month 24 Visit

At the Month 24 Visit, patients underwent the following assessments:

- Weight
- Biochemistry
- Hematology
- Chitotriosidase/Hexosaminidase assessment
- Glycosylceramide assessment
- Organ volume assessment
- Other disease assessments (depending on patient's disease status and the normal clinical practice at each center)
- AE assessment
- Concomitant Medications update

(5) Study Medication Dispensing and Compliance

All patients received OGT 918 at the same dose and schedule as were being taken when they completed the original 12-month treatment period. As in the original 12-month treatment period (Protocol 918-001), the patient's dose could be increased by 100 mg TID per month up to a maximum of 300 mg TID, until the target trough level of 2 microg/mL was reached, or until toxicities (other than Grade I GI problems) were noted, if the patient tolerated OGT 918 well, and had not shown a significant organ volume reduction (ie. >10% corrected for body weight) after 6 months of treatment. The dose could be decreased at the investigator's discretion or where significant toxicities were noted other than Grade 1 GI problems. Additional PK samples were taken 1 month after increasing the OGT dose or after other significant changes in the dosing regimen.

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

As this was an open-label study, no blinding was necessary, and all patients received OGT 918. OGT 918 was supplied as 50 mg or 100 mg gelatin capsules for oral

administration. Patients were dispensed a 3-month supply of OGT 918 at each study visit. OGT 918 was taken 3 times a day at regular intervals, either 2 hours before or 2 hours after eating. Patients were advised to avoid high carbohydrate content food.

(6) Efficacy and Endpoint Measures

The study was designed to provide an additional 12 months of information on the safety and possible efficacy of OGT 918.

(a) Primary Efficacy Parameters

The primary efficacy parameters for the study were:

- Liver and spleen organ volume response (actual and percent change from baseline)
- Biochemical and hematological response including change from baseline in absolute and percentage: hemoglobin, platelets, chitotriosidase, hexosaminidase, acid phosphatase, ACE, and glucosylceramide
- Overall response
- Subgroup analyses

Liver and spleen organ volume responses and overall response were assessed at 18 and 24 months. Biochemical and hematological parameters were summarized at 15, 18, 21 and 24 months. Baseline was the mean of the Screening and Day 1 values. From Month 15 onwards, only single values were obtained for each visit. An overall patient response was determined at 6, 12, 18, and 24 months from a combination of the individual response parameters. For the subgroup analyses for chitotriosidase, hexosaminidase, acid phosphatase, and ACE, the percentage change from baseline to Months 6, 12, 15, 18, 21 and 24 were summarized excluding non-expressers and for those patients with baseline values within and above the specified control ranges separately. Disease activity assessments were the same as for Study 918-001 and were performed every 6 months. Hgb, plts, chitotriosidase and other biochemical markers were collected every 3 months during the extension study.

(b) Secondary Efficacy Parameters

The secondary efficacy parameters for the study were:

- Other disease assessments, including bone density, fat fraction, pulmonary hypertension, and organ volume by ultrasound were measured at Month 24.
- Further exploratory analyses including correlation between percentage change in organ volumes and percentage change in weight from baseline at Months 18 and 24.

(c) Safety Assessments

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

(d) Study Population

The efficacy population and the safety population were the same for the extension study, and were defined as all patients who received at least one dose of study medication.

b) Results

A total of 28 patients were entered into Protocol 918-001, and 22 of those patients completed the study. Thus, 22 patients were eligible to enter Protocol 918-001X. Eighteen (18) of the 22 patients who completed the original study chose to enter the extended treatment phase. Fourteen (14) of the 18 patients completed the study and 4 withdrew prior to the extension study completion. Patients were screened, entered, and treated (beginning with entry into the original study) from 18-Mar-1998 and 23-Nov-2000.

(1) Baseline Characteristics and Demographics

Of the patients who continued in the extension study, 39% of patients were male and 56% were Ashkenazi Jews. Patient ages ranged from 22 to 62 years of age, with a mean age of 43.2 years. Baseline characteristics were also compared to the baseline characteristics of the original study population. Patients continuing in the extension study were somewhat more likely to be female (61% in the extension study vs 50% in the original study), and had slightly larger liver organ volumes, and lower baseline hemoglobin concentrations and platelet counts. Baseline spleen organ volumes were the similar for both groups. The original and extension study populations were otherwise similar at baseline. The baseline characteristics for the extension and original study populations are summarized in the following table.

Table 45: 918-001 and 918-001X Baseline Characteristics and Demographics

	Extension Study Population	Original Study Population
Enrolled Patients, n =	18	28
Demographic Measure		
Gender, n (%)	18	28
Male	7 (39)	14 (50)
Female	11 (61)	14 (50)
Age (years), n =	18	28
Mean	43.2	44.0
Min, max	22-62	22, 69
Race, n(%)	18	28
Ashkenazi Jew	10 (56)	15 (54)
Other	8 (44)	13 (46)
Mean BMI (kg/M^2), n =	17	27
Mean	23.82	23.56
Min, max		
Liver Organ Volume (l), n =	17	27
Mean	2.50	2.38
Min, max		
Spleen Organ Volume (l), n =	14	20
Mean	1.66	1.66
Min, max		
Hemoglobin (g/dL), n =	18	28
Mean	11.56	12.28
Min, max		
Platelets ($x10^9/l$), n =	18	28
Mean	75.34	88.10
Min, max		

(2) Patient Disposition

(a) Screening and Randomization

Twenty-two (22) patients were eligible for entry into the extension study, and 18 patients were enrolled. Four (4) patients did not enter the extension study (screen failures): 2 patients at site #1 (Cambridge, England) due to patient's decision, 1 patient at site #3 (Prague, Czech Republic) due to non-compliance, and 1 patient at site #4 (Jerusalem, Israel) due to non-response to OGT 918.

Compared to the patients entered in the original study, similar percentages of patients continued in the extension as were originally entered at each study center, with the majority (61%) of the patients continuing at Center #4 (Jerusalem; Dr. Zimran). Patients continued in the extension study and patients entered in the original study are summarized by study center as follows

Table 46: 918-001 and 918-001X Patient Continuation by Study Center

Center Number	Center/Investigator	Extension Study Continued, n (%)	Original Study Enrolled, n (%)
	All	**18**	**28**
1	Cambridge, England/Dr. Tim Cox	4 (22)	7 (25)
2	Amsterdam, The Netherlands/Dr. Carla Hollak	2 (11)	3 (11)
3	Prague, Czech Republic/Dr. Martin Hrebicek	1 (6)	2 (7)
4	Jerusalem, Israel/Dr. Ari Zimran	11 (61)	16 (57)

(b) Dropouts

Of the 18 patients entered in the study, 14 patients completed the 24 months of the study (12 months of the original study + 12 months of the extension). Four (4) patients (22%) withdrew prior to extension study completion: 2 patients for AEs (both were SAEs) and 2 patients at the Investigator's request. The reasons for study discontinuation in the original and extension studies are as follows

Table 47: 918-001 and 918-001X Patients Discontinued

	Extension Study Patients, n (%)	Original Study Patients, n (%)
Enrolled Patients, n =	18	28
Number of Withdrawals, n (%)	4 (22)	6 (1)
Reason for Dropout*		
Adverse Event, n (%)	2 (11)	2 (7)
Serious Adverse Event, n (%)	2 (11)	1 (4)
Subject Request, n (%)	0	5 (18)
Investigator Request, n (%)	2 (11)	1 (4)

*Patient may have reported more than one reason for withdrawal

All 4 of the patients who withdrew from the extension study were withdrawn from Center #1 (Cambridge). Two of these patients were withdrawn due to SAEs, and the remaining 2 patients at the Cambridge center were withdrawn at the request of the Investigator as precautionary measures. No other patient was discontinued. The 11 patients who were entered into the extension study at Center #4 (Jerusalem) had their doses of study

medication reduced upon entry into the extension phase in an attempt to optimize the patients' hematological response, and not due to any drug-related toxicity.

(3) Concomitant Medications

All 18 patients reported taking at least one concomitant medication at any time during the course of the 24-month treatment period. A large number of different medications were used during the study, the majority of which were used by a small number of patients. The most commonly reported medication used during the study was loperamide hydrochloride for diarrhea, which was taken by 8 patients (44%). It is notable that the number of patients taking GI medications (most commonly loperamide) declined progressively during the study, with 8 patients (44%) taking GI medications between Weeks 0-52, 4 patients (22%) between Weeks 52 and 78, 2 patients between Weeks 78 and 91, and 1 patient (7%) after Week 91. The most commonly (≥3 patients) used concomitant medications used by the patients from the start of the original study through extension study completion or termination are summarized in the following table

Table 48: 918-001 *and* 918-001X Most Common (≥3 Patients) Concomitant Medications

	Extension Study	Original Study
Randomized Patients, n =	18	28
Medication	n (%)	n (%)
Loperamide hydrochloride	8 (44)	16 (57)
Paracetamol	6 (33)	9 (32)
Cyanocobalamin	4 (22)	4 (14)
Amoxicillin	4 (22)	3 (11)
Alendronate sodium	2 (11)	3 (11)
Augmentin	2 (11)	2 (7)
Calcium +Vitamin D	2 (11)	2 (7)
Ibuprofen	2 (11)	2 (7)
Metamizole	2 (11)	2 (7)
Microgynon (oral contraceptive)	2 (11)	2 (7)
Multivitamins	2 (11)	2 (7)
Zinc	2 (11)	2 (7)
Captopril	1 (6)	3 (11)
Co-codamol	1 (6)	3 (11)
Propranolol	1 (6)	3 (11)

(4) Patient Compliance

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

(5) Efficacy Results

(a) Primary Efficacy Analysis

The sponsor's primary efficacy variables were percentage and actual change from baseline in organ volume responses (liver and spleen), percentage and actual change from baseline in Hgb, Plt, chitotriosidase, hexosaminidase, acid phosphatase, ACE and glucosylceramide, and overall response.

(i) Liver Organ Volume Response

Twelve (12) patients had liver volume data at Month 24. There were statistically significant mean percent reductions in liver organ volume from Baseline at Months 6, 12, 18 and 24, with reductions of –8.5%, -13.5%, -13.7%, and –14.5% respectively. Mean actual decreases (not shown in table) were –0.213 L, -0.326 L, -0.343 L, and –0.359 L for Months 6, 12, 18 and 24 respectively, which were also statistically significant. These results show a progressive decrease in liver volume to Month 12, with the decreases then being maintained from Month 12 to Month 24. The results for mean percent reductions in liver organ volume are summarized in the following table

Table 49: 918-001X Liver Organ Volume Statistics from Baseline to Month 24, Efficacy Set

	Baseline	Month 6	Month 12	Month 18	Month 24
n	17	17	17	14	12
Mean	2.45 (L)	-8.5%	-13.5%	-13.7%	-14.5%
Median	2.41 (L)	-7.3%	-13.4%	-13.4%	-13.3%
Minimum					
Maximum					
p-value*		<.001	<.001	<.001	<.001

*for mean % change from baseline at Months 6, 12, 18, and 24

For individual patients, all patients who continued in the extension study had decreases in their liver volume over the course of the study. By the sponsor's response definition (see Study 918-001, Efficacy Results: Liver Organ Volume section), for the 12 patients who had change from Baseline to Month 24 results, 4 patients (33%) had NR, 7 patients (58%) had MR, and 1 patient (8%) had GR.

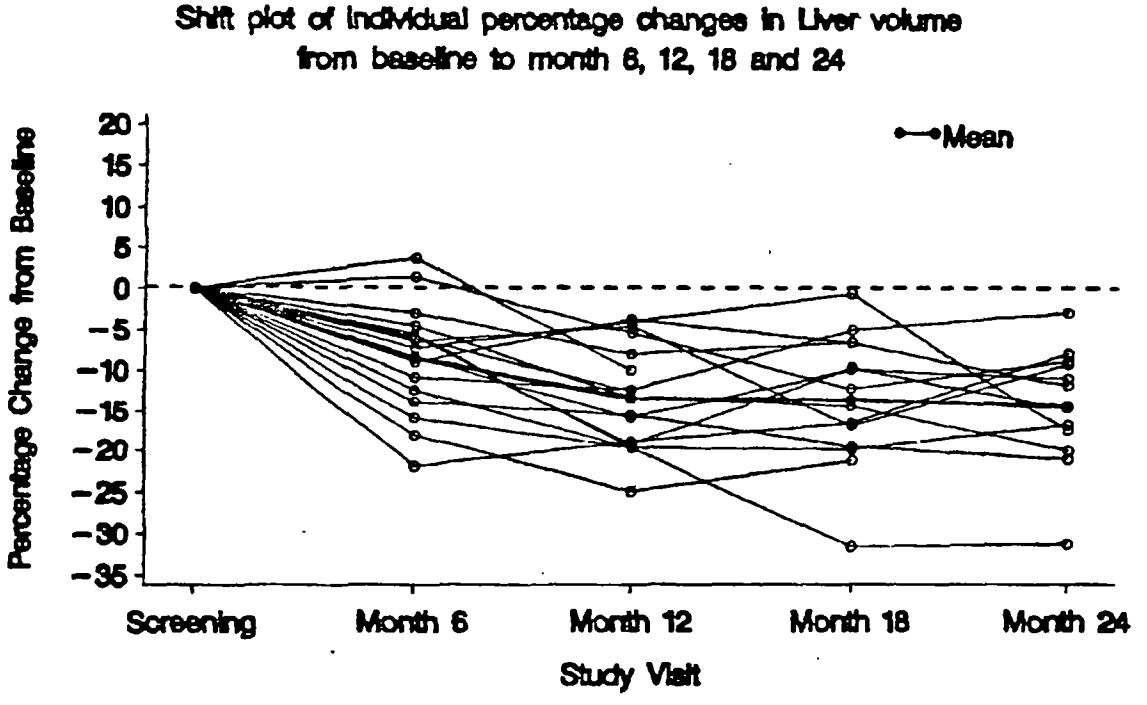
Individual patient results at baseline, Month 6, 12, 18 and 24 are summarized in the following table and in the following figure [Figure electronically scanned and reproduced from: Oxford Glycosciences (UK) Ltd, NDA #21-348, Volume 2.7, page 49, dated 02-Aug-2001]

Table 50: 918-001X % Change from Baseline in Liver Volume, Individual Patient Data

Patient Number	Baseline (L)	Month 6 % Change from Baseline	Month 12 % Change from Baseline	Month 18 % Change from Baseline	Month 24 % Change from Baseline
101	1.92	-18.2	-25.0	-21.4	-
201	2.82	1.4	-5.5	-12.2	-8.9
202	2.59	-12.4	-19.8	-31.6	-31.3
301	2.51	-6.5	-4.7	-17.0	-9.2
403	1.82	-4.6	-13.4	-14.5	-20.2
404	1.76	-7.3	-4.0	-0.6	-17.6
405	2.63	-16.0	-19.8	-20.0	-16.9
407	2.21	-10.8	-12.4	-5.1	-2.9
409	*				
411	2.53	-3.0	-8.1	-6.6	-
412	2.41	-13.8	-15.6	-19.7	-21.2
413	2.38	-8.4	-15.9	-9.9	-10.9
414	3.06	-22.0	-19.1	-16.7	-7.9
415	2.79	-6.0	-19.4	-9.6	-14.7
416	3.48	-9.0	-3.8	-6.7	-11.8

*Patient 409 had no baseline data, and % changes could not be calculated

Figure 7: 918-001X % Change from Baseline in Liver Volume, Individual Patient Data



(ii) Spleen Organ Volume Response

Ten (10) patients had spleen volume data available at Month 24. Overall, there were statistically significant mean percent reductions in spleen organ volume from Baseline at Months 6, 12, 18 and 24, with reductions of –15.5%, -21.7%, -23.2%, and –26.4% respectively. Mean actual decreases (not shown in table) were –0.255 L, -0.364 L, -0.381 L, and –0.416 L for Months 6, 12, 18 and 24 respectively, which were also statistically significant. These results shown a steeper, more progressive decrease in spleen volume at Month 12, and a continued decline in organ volume size that was more gradual from Month 12 to Month 24. The results for percent reductions in spleen organ volume are summarized in the following table

Table 51: 918-001X Spleen Organ Volume Statistics from Baseline to Month 24, Efficacy Set

	Baseline	Month 6	Month 12	Month 18	Month 24
n	14	14	14	12	10
Mean	1.66 (L)	-15.5%	-21.7%	-23.2%	-26.4%
Median	1.49 (L)	-15.2%	-20.2%	-23.9%	-26.3%
Minimum					
Maximum					
p-value*		<.001	<.001	<.001	<.001

*for mean % change from baseline at Months 6, 12, 18, 24

For individual patients, all patients who continued in the extension study had decreases in their spleen volume over the course of the study. By the sponsor's response definition (see Study 918-001, Efficacy Results: Liver Organ Volume section), for the 10 patients who had change from Baseline to Month 24 results, no patient had NR, 7 patients (70%) had MR, and 3 patients (30%) had GR.

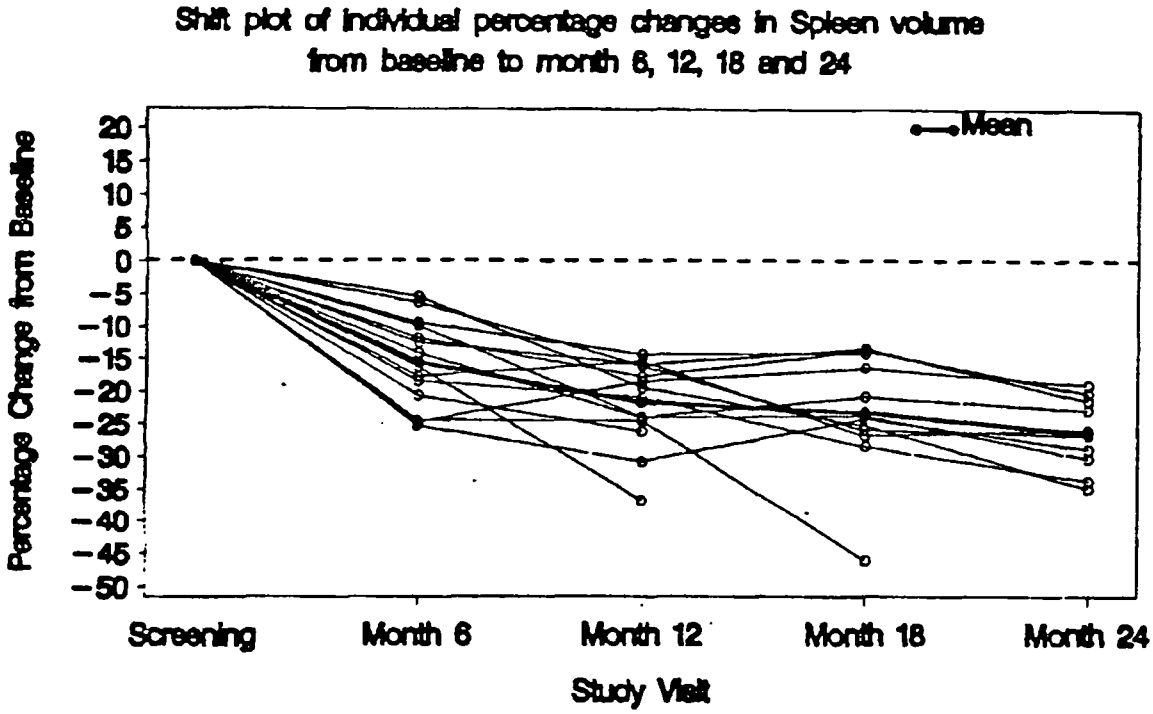
Individual patient results at baseline, Month 6, 12, 18 and 24 are summarized in the following table and in the following figure [Figure electronically scanned and reproduced from: Oxford Glycosciences (UK) Ltd, NDA #21-348, Volume 2.7, page 52, dated 02-Aug-2001]

Table 52: 918-001X % Change from Baseline in Spleen Volume, Individual Patient Data

Patient Number	Baseline (L)	Month 6 % Change from Baseline	Month 12 % Change from Baseline	Month 18 % Change from Baseline	Month 24 % Change from Baseline
101	1.43	-24.5	-24.5	-46.2	-
201	1.41	-5.4	-19.5	-25.1	-34.9
301	1.32	-17.7	-15.3	-26.7	-25.9
403	1.53	-18.4	-20.9	-28.4	-33.7
404	0.91	-12.4	-15.8	-13.4	-21.4
405	2.21	-25.3	-30.8	-24.0	-28.8
407	1.75	-24.8	-18.5	-16.3	-19.0
409*					
411	3.36	-9.4	-14.3	-14.1	-
412	1.01	-6.3	-16.1	-25.8	-26.7
413	2.19	-9.9	-23.9	-23.7	-30.3
415	1.81	-14.1	-24.0	-20.8	-22.9
416	1.44	-11.8	-17.7	-13.7	-20.3

*Patient 409 had no baseline data, and % changes could not be calculated

Figure 8: 918-001X % Change from Baseline in Spleen Volume, Individual Patient Data



(iii) Hemoglobin

Thirteen (13) patients had Hgb data at Endpoint (Month 24). Overall, there was a mean increase in Hgb from baseline at Months 6, 12, 18 and 24; however this increase reached statistical significance only at Months 18 and 24. There was a progressive mean actual increase in Hgb at Months 6, 12, 18, and 24 of 0.06 g/dL, 0.33 g/dL, 0.39 g/dL, and 0.91 g/dL, respectively. Mean percent increases in Hgb at Months 6, 12, 18, and 24 were

0.8%, 3.2%, 3.9%, and 9.1% respectively. The results are summarized in the following table

Table 53: 918-001X Hemoglobin Statistics, Efficacy Set

	Baseline	Month 6		Month 12		Month 18		Month 24	
		Actual Change	% Change	Actual Change	% Change	Actual Change	% Change	Actual Change	% Change
n	18	18	18	18	18	15	15	13	13
Mean	11.56 (g/dL)	0.06 (g/dL)	0.8%	0.33 (g/dL)	3.2%	0.39 (g/dL)	3.9%	0.91 (g/dL)	9.1%
Median	11.48 (g/dL)	0 (g/dL)	0%	0.20 (g/dL)	1.5%	0.50 (g/dL)	5.1%	1.10 (g/dL)	10.1%
Minimum									
Maximum									
p-value*		0.559	0.455	0.077	0.083	0.045	0.032	0.007	0.008

*for mean change from baseline at Months 6, 12, 18, and 24

For individual patients, 11 patients (85%) had any increase in Hgb at Month 24. By the sponsor's response definition (see Study 918-001, Efficacy Results: Hemoglobin section), for the 13 patients who had available Hgb data at Month 24, 5 patients (38%) had NR, 6 patients (46%) had MR, and 2 patients (15%) had GR.

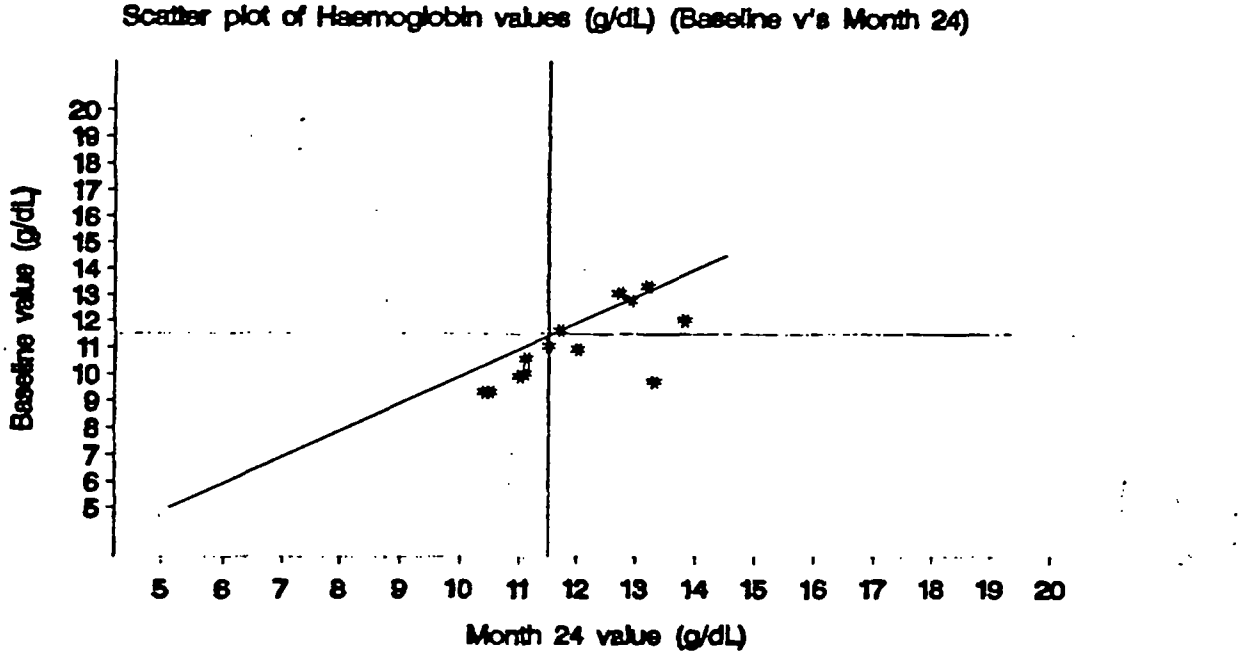
Individual patient results at baseline, Month 6, 12, 18 and 24 are summarized in the following table and in the following figure [Figure electronically scanned and reproduced from: Oxford Glycosciences (UK) Ltd, NDA #21-348, Volume 2.7, page 60, dated 02-Aug-2001]

Table 54: 918-001X Change from Baseline in Hemoglobin, Individual Patient Data

Patient Number	Baseline (g/dL)	Month 6		Month 12		Month 18		Month 24	
		Actual Change (g/dL)	% Change	Actual Change (g/dL)	% Change	Actual Change (g/dL)	% Change	Actual Change (g/dL)	% Change
101	11.90	0	0	-0.55	-4.6	0.2	1.7	-	-
105	14.45	0	0	0.35	2.4	-	-	-	-
106	15.05	0.30	2.0	0.20	1.3	-	-	-	-
107	12.05	-0.15	-1.2	0.15	1.2	-	-	-	-
201	13.05	-0.81	-6.2	0.24	1.9	0.85	6.5	-0.33	-2.5
202	10.55	0	0	0.72	6.9	1.05	9.9	0.56	5.3
301	11.35	0.10	0.9	0.10	0.9	0.65	5.7	-	-
403	11.60	-0.30	-2.6	0.05	0.4	0	0	0.10	0.9
404	9.30	0.45	4.8	0.55	5.9	0.60	6.5	1.20	12.9
405	12.00	0.85	7.1	0.20	1.7	0	0	1.80	15.0
407	9.30	0.50	5.4	0.55	5.9	0.80	8.6	1.10	11.8
409	10.00	-0.25	-2.5	-0.55	-5.5	-0.20	-2.0	1.10	11.0
411	9.90	0.30	3.0	2.40	24.2	0.50	5.1	1.10	11.1
412	10.90	-0.40	-3.7	-0.10	-0.9	0.80	7.3	1.10	10.1
413	9.70	1.00	10.3	1.75	18.0	1.80	18.6	3.60	37.1
414	12.75	-0.35	-2.7	0.45	3.5	-0.15	-1.2	0.15	1.2
415	13.30	0.15	1.1	-0.15	-1.1	-1.10	-8.3	-0.10	-0.8
416	11.00	-0.25	-2.3	-0.45	-4.1	0	0	0.50	4.5

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

Figure 9: 918-001X Scatter Plot of Hemoglobin Values, Baseline vs Month 24



A subgroup analysis was also performed by Baseline Hgb value. Patients with Baseline Hgb <11.5 g/dL had larger mean increases in Hgb than patients with Baseline Hgb ≥11.5 g/dL at Months 6, 12, 18, and 24. At Months 18 and 24; patients with baseline Hgb <11.5 g/dL had mean increases of 0.666 g/dL and 1.282 g/dL, respectively, which were statistically significant at Months 18 and 24. Patients with Hgb ≥11.5 g/dL had mean changes at Months 18 and 24 of –0.033 g/dL and +0.324 g/dL, respectively, which were not significant. The results are summarized in the following table

Table 55: 918-001X 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	
	Mean (g/dL)	p-value	Mean (g/dL)	p-value
Month 6	n = 9 0.161	0.312	n = 9 -0.034	0.831
Month 12	n = 9 0.553	0.130	n = 9 0.105	0.324
Month 18	n = 9 0.666	0.009	n = 6 -0.033	0.903
Month 24	n = 8 1.282	0.007	n = 5 0.324	0.440

(iv) Platelet Count

Thirteen (13) patients had Plt data at Endpoint (Month 24). Overall, there was a mean increase in Plt from baseline at Months 6, 12, 18 and 24; however this increase reached statistical significance only at Months 18 and 24. There was a progressive mean actual increase at Months 6, 12, 18, and 24 of 4.96 $X10^9$/l, 7.00 $X10^9$/l, 11.16 $X10^9$/l, and 13.58 $X10^9$/l, respectively. Mean percent increases in Plt at Months 6, 12, 18, and 24 were

4.7%, 15.1%, 18.5%, and 26.1%, respectively. The results are summarized in the following table .

Table 56: 918-001X Platelet Count Statistics. Efficacy Set

	Baseline (10^9/l)	Month 6		Month 12		Month 18		Month 24	
		Actual Change	% Change	Actual Change	% Change	Actual Change	% Change	Actual Change	% Change
n	18	18	18	18	18	15	15	13	13
Mean	75.34	4.96	4.7%	7.00	15.1%	11.16	18.5%	13.58	26.1%
Median	60.00	4.50	6.0%	6.25	7.4%	7.50	12.0%	13.50	30.8%
Minimum									
Maximum									
p-value*		.070	.140	.058	.138	.009	.016	<.001	<.001

*for mean % change from baseline at Months 6, 12, 18, and 24

For individual patients, 11 patients (85%) had any increase in Plt at Month 24. By the sponsor's response definition (see Study 918-001, Efficacy Results: Platelet Count section), for the 13 patients who had available Plt data at Month 24, 7 patients (54%) had NR, 6 patients (46%) had MR, and no patient had GR.

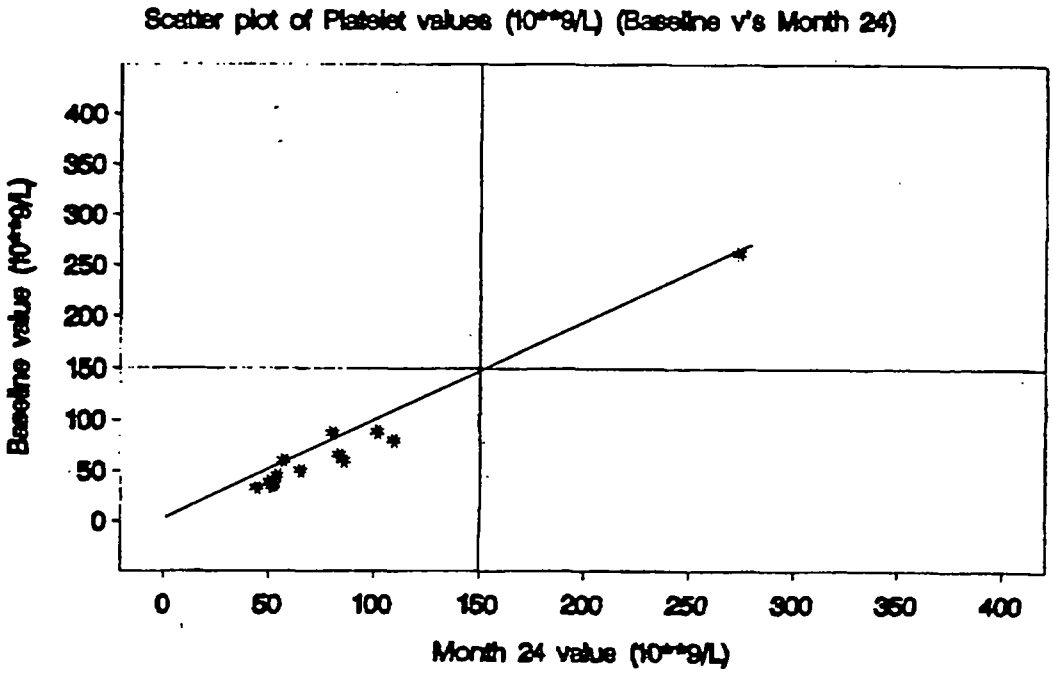
Individual patient results at baseline, Month 6, 12, 18 and 24 are summarized in the following table and in the following figure [Figure electronically scanned and reproduced from: Oxford Glycosciences (UK) Ltd, NDA #21-348, Volume 2.7, page 64, dated 02-Aug-2001]

Table 57: 918-001X Change from Baseline in Platelet Counts. Individual Patient Data

Patient Number	Baseline (10^9/l)	Month 6		Month 12		Month 18		Month 24	
		Actual Change (10^9/l)	% Change	Actual Change (10^9/l)	% Change	Actual Change (10^9/l)	% Change	Actual Change (10^9/l)	% Change
101	53.50	0	0	4.00	7.5	7.50	14.0	-	-
105	94.50	7.00	7.4	8.50	9.0	-	-	-	-
106	112.50	20.00	17.8	0.50	0.4	-	-	-	-
107	101.50	11.50	11.3	7.50	7.4	-	-	-	-
201	80.00	-6.00	-7.5	5.00	6.3	43.00	53.8	30.00	37.5
202	262.00	35.50	13.5	16.00	6.1	19.00	7.3	12.00	4.6
301	53.55	2.20	4.1	9.95	18.6	33.45	62.5	-	-
403	45.00	7.00	15.6	-2.00	-4.4	-4.00	-8.9	10.00	22.2
404	60.00	-5.00	-8.3	-10.00	-16.7	-5.00	-8.3	-2.00	-3.3
405	39.00	-7.00	-17.9	-0.50	-1.3	11.00	28.2	12.00	30.8
407	50.00	11.50	23.0	13.50	27.0	6.00	12.0	16.00	32.0
409	34.00	8.00	23.5	11.00	32.4	23.00	67.6	18.00	52.9
411	33.00	1.00	3.0	56.50	171.2	7.00	21.2	12.00	35.4
412	27.00	-8.50	-9.8	-13.50	-15.5	9.00	10.3	-6.00	-6.9
413	36.00	-6.50	-18.1	-3.50	-9.7	-8.00	-22.2	17.00	47.2
414	88.50	5.50	6.2	8.00	9.0	2.50	2.8	13.50	15.3
415	60.00	3.50	5.8	10.00	16.7	20.00	33.3	26.00	43.3
416	66.00	9.50	14.4	5.00	7.6	3.00	4.5	18.00	27.3

LLN <150 X(10^9/l)
Baseline >150 X(10^9/l)

Figure 10: 918-001X Scatter Plot of Platelet Values, Baseline vs Month 24



(v) Biochemical Markers

The biochemical markers of Gaucher disease response measured in this study will be summarized briefly below.

Chitotriosidase

There were statistically significant, progressive mean decreases in chitotriosidase from Baseline at Months 6, 12, 18, and 24 of –8.5%, -15.0%, -21.3% and –21.9%. The results are summarized in the following table

Table 58: 918-001X Chitotriosidase Statistics

	Baseline (nmol/ml.h)	Month 6	Month 12	Month 18	Month 24
n	17	17	17	14	14
Mean	16876.5	-8.5%	-15.0%	-21.3%	-21.9%
Median	17137.0	-7.6%	-15.3%	-18.6%	-24.9%
Minimum					
Maximum					
p-value*		<.001	<.001	<.001	<.001

*for mean % change from baseline at Months 6, 12, 18, and 24
Control range: 7-124 nmol/ml.h

Hexosaminidase

There were progressive mean decreases in hexosaminidase from Baseline at Months 6, 12, 18, and 24 of –5.1%, -6.0%, -8.4% and –11.9%. The results were statistically significant only at Months 18 and 24. The results are summarized in the following table

Table 59: 918-001X Hexosaminidase Statistics

	Baseline (nmol/ml.h)	Month 6	Month 12	Month 18	Month 24
n	17	17	17	14	14
Mean	2187.1	-5.1%	-6.0%	-8.4%	-11.9%
Median	1998.0	-6.1%	-6.2%	-10.1%	-7.1%
Minimum					
Maximum					
p-value*		.0176	.063	.047	<.001

*for mean % change from baseline at Months 6, 12, 18, and 24
Control range: 477-1845 nmol/ml.h

Acid Phosphatase

The results for acid phosphatase were inconsistent through time with no clear trend discernible. At Months 6 and 12 there were mean decreases, and at Months 18 and 24, there were mean increases. In addition, no subgroup analysis was performed (to examine patients classified as "expressors") as no patients could be excluded as "nonexpressors".

Angiotension Converting Enzyme

There were mean decreases in ACE for Months 6, 12, 18, and 24 of –2.0, -3.2, -14.2, and –8.9 nmol/ml.min (control range: ACE 20-43 nmol/ml.h). Only the Month 18 result was significant. No subgroup analysis was performed (to examine patients classified as "expressors") as no patients could be excluded as "nonexpressors".

Glucosylceramide

Only 2 patients at Month 18 and no patient at Month 24 had a glucosylceramide assessment. At Month 18, these 2 patients had percent changes in glucosylceramide of +1.2% and –30.7% (mean 14.8%; p=.525).

(b) Secondary Efficacy Analysis

(i) Other Disease Assessments

Thirteen (13) patients had at least one other disease assessment for whom results were available at Screening and Month 24. Other disease assessment could have included skeletal assessments by DEXA or MRI, bone marrow assessment by QCSI (fat fraction), or echocardiography [A complete listing of test performed is in the Appendix]. Skeletal assessments showed essentially no changes in bone density from Baseline to Month 24. Two (2) patients underwent bone marrow assessment by QCSI (validated measure of fat fraction in the bone marrow). Per previous reports[11], an increased fat fraction is indicative of decreasing bone marrow involvement with Gaucher cells. QCSI results for these 2 patients are summarized in the following table

[11] Rosenthal DI, Doppelt SH, Mankin HJ, Dambrosia JM, Xavier RJ, McKusicKA, Rosen BR, Baker J, Niklason LT, Hill SC, Miller SPF, Brady RO, Barton NW,and Collaborators. Enzyme replacement therapy for Gaucher disease: skeletal responses to macrophage-targeted glucocerebrosidase. Pediatrics 1995;96(4):629-637.

Table 60: 918-001X Other Disease Assessments, QCSI Results

Patient	Assessment	Results (all follow-up occurred at Month 24)
201	QSCI (L-spine)	from 0.23 (Baseline) to 0.25 (Month 12) to 0.30-0.31 (Month 24)*
202	QSCI (L-spine)	from 0.16 (Baseline) to 0.2 (Month 12) to 0.25-0.26 (Month 24)*

*Per Rosenthal et al[9], normal range for healthy adults 23-35%. In Gaucher study with ERT mean QCSI prior to treatment 7.3% ±6.7%, and after 42-months of treatment 22.9% ±6.6%

There were no notable changes in echocardiography for any patient, which was consistent with no progression to, or development of, pulmonary hypertension.

(c) Subgroup Analysis

Subgroup analysis by Baseline Hgb level is in the Hemoglobin section above. No other subgroup analyses were performed.

(d) Conclusions on Efficacy Results for Protocol 918-001X

There were statistically significant mean decreases in liver and spleen volumes from Baseline to Months 6, 12, 18, and 24. Mean liver volumes showed mean percent decreases from Baseline to Month 6, 12, 18, and 24 of –8.5%, -13.5%, -13.7%, and –14.5%, respectively, which show a progressive decreases from Baseline to Month 12, and with the decreases then being maintained from Month 12 to Month 24. Mean spleen volume decreased progressively from Baseline to Months 6, 12, 18, and 24, with decreases of -15.5%, -21.7%, -23.2%, and –26.4%, respectively. Mean Hgb increased progressively from Baseline to Months 6, 12, 18, and 24, with increases of 0.06 g/dL, 0.33 g/dL, 0.39 g/dL, and 0.91 g/dL, respectively. These increases reached statistical significance at Months 18 and 24. On subgroup analysis, significant increases in Hgb were only seen in patients with Hgb <11.5 g/dL (<LLN) at Baseline. Patients with Baseline Hgb <11.5 g/dL had mean increases from Baseline to Month 24 of 1.282 g/dL, whereas patients with baseline Hgb ≥11.5 g/dL had mean increases of 0.324 g/dL from Baseline to Month 24. Mean platelet counts also progressively increased from Baseline to Months 6, 12, 18, and 24, with increases ($X10^9$/L) of 4.96, 7.00, 11.16, and 13.58, respectively. These results were statistically significant for Months 18 and 24 only. Only one patient had a platelet count >150 $X10^9$ at baseline, and thus, a subgroup analysis could not be performed.

Biochemical markers for Gaucher disease were notable for progressive, significant decreases in chitotriosidase (decrease of –21.9% from Baseline at Month 24). Hexosaminidase also progressively decreased from Baseline (decrease of –11.9% at Month 24); however, the results were significant only at Month 18. ACE also decreased from Baseline at Month 6, 12, 18, and 24, and these results were also only significant at Month 18. Acid phosphatase results were inconsistent, and glucosylceramide was measured in only 2 patients at Month 18 and no patients at Month 24.

Other disease assessments were performed at the discretion of the Investigator, and 13 patients had at least one assessment available at Screening and Month 24. The results showed essentially no change in skeletal assessments (bone density) and echocardiography (for pulmonary hypertension). Two (2) patients underwent QCSI for

bone marrow fat fraction, with improvement to a normal range in both patients by Month 24.

3) Protocol 918-003

a) Study Design for Protocol 918-003

(1) Study Design

Protocol 918-003 "A phase I/II study of open label OGT 918 (50 mg TID) in adult patients with type I Gaucher disease" was a non-comparative, multi-center, open-label study conducted at 2 international clinical sites. The study evaluated the efficacy and safety of OGT 918 at a dose of 50 mg TID for up to 6 months in 18 adult type I Gaucher disease patients who were unable or unwilling to be treated with Ceredase or Cerezyme.

(2) Study Objective

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

Additionally, as this study involved identical inclusion/exclusion criteria to the OGT-918-001 study, Study OGT-918-003 was designed to allow cross-study comparisons between the two dosing regimens.

(3) Eligibility Criteria

(a) Inclusion Criteria

Patients were eligible for study participation if they:
1) Had type 1 Gaucher disease (confirmed by a glucocerebrosidase assay)
2) Were unable or unwilling to be treated with Ceredase or Cerezyme
3) Were 18 years of age or older at time of consent
4) Had a measurable organomegaly (liver or spleen)
5) Had an intact spleen with a hemoglobin concentration of <11.5 g/dL or a platelet count <100 X 10^9/l or were splenectomized subjects who had hepatomegaly with liver weight >2.5% of their body weight

(b) Exclusion Criteria

Patients were ineligible for participation if they:
1) Were fertile subjects who did not agree to use adequate contraception throughout the study and for 3 months after cessation of OGT 918 treatment
2) Were pregnant or breast-feeding
3) Had received treatment with Ceredase or Cerezyme within 3 months of screening
4) Had a history of lactose intolerance
5) Were suffering from clinically significant diarrhea (more than 3 liquid stools per day for more than 7 days) without definable cause within 6 months of screening

6) Had a history of cataracts or known increased risk of cataract formation
7) Were currently undergoing therapy with other investigational agents
8) Had an intercurrent medical condition that would render them unsuitable for study
9) Were known to have tested positive for HIV or Hepatitis B surface antigen
10) Were, in the opinion of the Investigator, thought to be unsuitable for the study

(4) Study Visits and Procedures

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

Table 61: 918-003 Study Visits and Procedures

	Screen	Treatment Period								Final
Day		1	8 to 15	29	57	85	113	141	169	
Month				1	2	3	4	5	6	
Procedure										
History	X									
Physical Examination	X			X		X			X	X*
Vital Signs	X			X		X			X	X
Height	X								X	X*
Weight (BSA/BMI)	X	X		X	X	X	X	X	X	X
ECG	X			X					X	X*
EMG									X	X*
Pregnancy test	X									
Urinalysis	X	X		X		X			X	
Biochemistry	X	X		X	X	X	X	X	X	X
Hematology	X	X		X	X	X	X	X	X	X
PK (Baseline/PK profile)		X		X						
PK (Trough)				X		X			X	
PK (Peak)				X		X			X	
Organ Volume	X								X	X*
Other Disease Assessments	X	X		X		X			X	X*
Chitotriosidase/Hexosaminidase	X	X		X	X	X	X	X	X	X*
Proteome		X							X	X*
Questionnaire		X				X			X	
Adverse Events		X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
OGT 918 Dispensing		X		X	X	X	X	X		

*If not performed at 6 Month Visit

A protocol amendment for the addition of EMG/NCV assessments at Month 6 in Protocol 918-003 was submitted in Apr-2000.

(a) Screening Visit

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

- History
- Physical examination (including slit lamp exam)
- Vital signs
- Height
- Weight
- ECG

- Pregnancy test (females only)
- Urinalysis
- Biochemistry
- Hematology
- Organ Volume assessment (by MRI or CT scan)
- Other Disease Assessments (depending on patient's disease status and normal clinical practice at each center, may include skeletal response assessed by an MRI of the femur, pelvis, lumbar spine or hips, DEXA of the femur and lumbar spine, fat fraction by QCSI of the bone marrow in the lumbar spine, and a quantitative skeletal assessment)
- Chitotriosidase/Hexosaminidase assessment
- Concomitant Medications record

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

(b) Day 1 Visit (within 4 weeks of Screening Visit)

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

- Weight
- Urinalysis
- Biochemistry
- Hematology
- PK baseline and profile (The first 6 patients had a PK profile performed on Day 1 and Month 1)
- Other Disease Assessments
- Chitotriosidase/Hexosaminidase assessment
- Proteome assessment
- Questionnaire [SF-36 Quality of Life Assessment (QoL) at Center #1 only]
- AE assessment
- Concomitant Medications update

(c) Day 8 to 15 Visit (either in-clinic or by telephone)

At the Day 8 to 15 Visit, patients underwent the following assessments:

- AE assessment
- Concomitant Medications update

(d) Day 29 (Month 1) Visit

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

- Physical Examination
- Vital signs
- Weight
- ECG
- Urinalysis
- Biochemistry
- Hematology

- PK baseline and profile (first 6 patients only)
- PK sample (trough)
- PK sample (peak)
- Other Disease Assessments
- Chitotriosidase/Hexosaminidase assessment
- AE assessment
- Concomitant Medications update

(e) Day 57 (Month 2) Visit

At the Day 57 Visit, patients underwent the following assessments:

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

(f) Day 85 (Month 3) Visit

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

- Physical Examination
- Vital signs
- Weight
- Urinalysis
- Biochemistry
- Hematology
- PK sample (trough)
- PK sample (peak)
- Other Disease Assessments
- Chitotriosidase/Hexosaminidase assessment
- Questionnaire
- AE assessment
- Concomitant Medications update

(g) Day 113 (Month 4) Visit

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

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

(h) Day 141 (Month 5) Visit

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

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

(i) Day 169 (Month 6) Visit

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

- Physical Examination (including slit lamp exam)
- Vital signs
- Height
- Weight
- ECG
- EMG
- Urinalysis
- Biochemistry
- Hematology
- PK sample (trough)
- PK sample (peak)
- Organ volume assessment
- Other Disease Assessments
- Chitotriosidase/Hexosaminidase assessment
- Proteome sample
- Questionnaire
- AE assessment
- Concomitant Medications update

(j) Withdrawal/Early Termination Visit (within 4 weeks of completion of or withdrawal from the study)

At the Withdrawl/Early Termination Visit, patients underwent the following assessments:

- Physical Examination (including slit lamp exam)*
- Vital signs
- Height*
- Weight
- ECG*
- EMG*
- Biochemistry
- Hematology
- Organ volume assessment*
- Other Disease assessments*
- Chitotriosidase/Hexosaminidase assessment*
- Proteome sample*
- AE assessment

- Concomitant Medications update

*Performed only if not performed at Month 6 Visit

(5) Study Medication Dispensing and Compliance

All patients received OGT 918 at a starting dose of 50 mg TID. The dose could be adjusted to 50 mg BID if a patient experienced any unacceptable toxicity that was thought to be related to the study medication or if the patient's trough plasma concentration exceeded 2 mcg/ml.

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

All patients received OGT 918, which was supplied as 50 mg gelatin capsules for oral administration. As this was an open-label study, no blinding was necessary. Trial medication was supplied in bottles and dispensed as a one month's supply at a time. OGT 918 was to be taken 3 times a day (or twice a day if the dose had been reduced) at regular intervals, either 2 hours before or two hours after eating. Patients were advised to avoid high carbohydrate content food, and dietary recommendations were issued to all participants.

(6) Efficacy and Endpoint Measures

(a) Primary Efficacy Parameters

The primary efficacy parameters for the study were change from Baseline in:

1) Liver volume
2) Spleen volume
3) Hemoglobin concentration
4) Platelet counts
5) Chitotriosidase response
6) Hexosaminidase response
7) Overall response

(b) Secondary Efficacy Parameters

1) Other disease assessments
2) Further exploratory analyses

(c) Safety Assessments

Safety was assessed by the incidence and frequency of AEs, and changes in vital signs, physical examinations, ECG, EMG/NCV assessments, and clinical laboratory values.

(d) Study Population

The efficacy population (ITT population) and the safety population were identical in this study, and were defined by the sponsor as all patients who received at least one dose of study medication.

b) Results

Twenty-one (21) patients were screened at 2 study sites, and 18 patients entered the study. Of the 18 patients who entered the study, 17 patients completed the study. All patients were screened, entered, and treated between 07-Dec-1999 and 18-July-2000.

(1) Baseline Characteristics and Demographics

Overall, 72% of patients were female, and 83% were Ashkenazi Jews. Patient ages ranged from 22 to 61years of age, with a mean age of 42.4 years. The patients' baseline medical histories were notable for:

- 2 patients (11%) reported previous Ceredase/Cerezyme use.
- Baseline body system abnormalities most frequently reported were in the musculoskeletal body system [4 patients (22%)], and the ears, nose and throat, genitourinary, and "other" body systems [3 patients each (17%)].
- 14 patients (78%) noted at least one concurrent illness at screening. The most frequently noted concurrent illnesses were vitamin B12 deficiency anemia and low lymphocyte count [3 patients each (17%)].
- 9 patients (50%) had undergone surgery for Gaucher disease.
- Physical examination abnormalities at baseline by organ system were most frequently noted in the GI system (100% of patients), dermatologic system in 11 patients (61%), eye abnormalities in 8 patients (44%), and cardiovascular and musculoskeletal systems in 6 patients each (33%).
- Neurologic problems were not noted in any patient at baseline by medical history.
- 10 patients reported taking at least one concomitant medication at screening, the most common being vitamin C taken by 2 patients.
- Baseline liver volumes were 1.1 to 3.4 X normal for all patients, and spleen volumes were 2.8 to 29.6 X normal for all patients.

In addition, Study 918-003 was intended to have a similar design and patient population as Study 918-001 for purposes of comparison. Comparison of the baseline characteristics and demographic data between the two studies show that the Study 918-003 patients were more likely to be female and more likely to be Ashkenazi Jews than Study 918-001 patients. Otherwise, baseline characteristics and demographics were similar between the two studies. The baseline characteristics and demographic data for all enrolled patients are summarized in the following table

Table 62: 918-003 Baseline Characteristics and Demographics

	All
Enrolled Patients, n =	18
Demographic Measure	
Gender, n (%)	18
Male	5 (28)
Female	13 (72)
Age (years), n =	18
Mean	42.4
Min, max	22, 61
Race, n(%)	18
Ashkenazi Jew	15 (83)
Other	3 (17)
Mean BMI (kg/M^2), n =	18
Mean	23.11
Min, max	
Liver Organ Volume (l), n =	18
Mean	2.47
Min, max	
Spleen Organ Volume (l), n =	11
Mean	1.97
Min, max	
Hemoglobin (g/dL), n =	18
Mean	11.65
Min, max	
Platelets ($x10^9/l$), n =	18
Mean	123.66
Min, max	

(2) Patient Disposition

(a) Screening and Randomization

There were 3 screen failure patients, all of whom were at site #1 (Johannesburg). As with the 918-001 study, the number of screen failures was low due to the familiarity of the patients to the study Investigators prior to study entry. Of the 3 screen failures, one patient had cataracts noted at screening, and 2 did not meet the study criteria for anemia or thrombocytopenia.

Patients were enrolled at 2 study centers internationally, with 10 patients (56%) enrolled at Center #1 (Johannesburg, South Africa), and 8 patients (44%) enrolled at Center #2 (Jerusalem, Israel). Patient enrollment by study center is summarized as follows

Table 63: 918-003 Patient Enrollment by Study Center

Center Number	Center/Investigator	Patients Enrolled, n (%)
	All	**18**
1	Johannesburg, South Africa/Dr. Rene Heitner	10 (56)
2	Jerusalem. Israel/Dr. Ari Zimran	8 (44)

(b) Dropouts

Of the 18 patients entered in the study, 17 patients completed the study. One patient withdrew due to unacceptable side effects (diarrhea) and the patient requested withdrawal. This patient withdrew after >13 weeks of treatment and was from the Israel center. There were no protocol violators, but one patient failed to meet inclusion/exclusion criteria. Patient 110 in Johannesburg center did not meet inclusion criteria for anemia and thrombocytopenia, but given the extent of the patient's organomegaly, this patient was included in the study. Subsequent investigation of this patient determined that the patient suffered from B-cell lymphoma.

The reasons for study discontinuation are as follows

Table 64: 918-003 Patients Discontinued

	All
Enrolled Patients, n =	18
Number of Withdrawals, n (%)	1 (6)
Reason for Dropout*	
Adverse Event, n (%)	1 (6)
Subject Request, n (%)	1 (6)
Investigator Request, n (%)	0

*Patient may have reported more than one reason for withdrawal

(3) Concomitant Medication

Seventeen (17) of 18 patients (94%) reported taking at least one concomitant medication at any time during the study. A large number of different medications were used during the study (>100 different medications reported), the majority of which were used by one patient. The most commonly reported medications used during the study were acetaminophen + codeine, used by 7 patients (39%) and loperamide hydrochloride for diarrhea, used by 4 patients (22%). The most commonly reported category of medications used were the antidiarrheal medications, which were used by 10 patients (56%) at any time during the study (including loperamide, hyoscine butylbromide, carbosylane, Inteflora and metoclopramide hydrochloride). The most commonly ($\geq$2 patients or $\geq$10% of patients) used concomitant medications are summarized in the following table

Table 65: 918-003 Most Common (≥2 Patients) Concomitant Medications

Randomized Patients, n =	18
Medication	**n (%)**
Acetaminophen + codeine phosphate	7 (39)
Paracetamol	5 (28)
Loperamide	4 (22)
Vitamin B12	3 (17)
Vitamin C	3 (17)
Augmentin	2 (11)
Scopolamine	2 (11)
Carbosylane (antidiarrheal)	2 (11)
Chlorpheniramine maleate	2 (11)
Codeine Phosphate	2 (11)
Ethinylestradiol	2 (11)
Folic Acid	2 (11)
Inteflora (antidiarrheal)	2 (11)
Levonorgestrel	2 (11)
Amoxicillin	2 (11)
Myprodol (analgesic)	2 (11)
Ibuprofen	2 (11)
Ophthalmologicals	2 (11)
Optalgin (analgesics)	2 (11)
Phenylephrine hydrochloride	2 (11)
Pseudoephedrine hydrochloride	2 (11)
Cyclizine	2 (11)

(4) Patient Compliance

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

(5) Efficacy Results

(a) Primary Efficacy Analysis

The sponsor's primary efficacy variables were absolute and percentage changes from Baseline in liver and spleen organ volume at Month 6; absolute and percentage change from Baseline in hemoglobin concentration, platelet counts, chitotriosidase, and hexosaminidase from screening to Month 6; and overall response at Month 6 (from a combination of the individual response parameters).

(i) Liver Organ Volume

Seventeen (17) of 18 patients entered into the study had liver organ volume data available at Month 6. Overall, there were statistically significant mean percentage reductions from Baseline to Month 6 in liver volume of –5.9% (p =.007), and significant mean reductions in absolute liver volume from Baseline to Month 6 of –0.142 L (p =.014). The minimum

and maximum mean percent reductions at Month 6 were [redacted] The results are summarized in the following table

Table 66: 918-003 Liver Organ Volume Statistics, Efficacy Set

	Baseline	Month 6		
	Organ Volume (L)	Organ Volume (L)	Change (L)	% Change
n	17	17	17	17
Mean	2.45	2.3	-0.14	-5.9
Median	2.40	2.23	-0.10	-6.7
Minimum	[redacted]			
Maximum				
p-value			0.014	.007

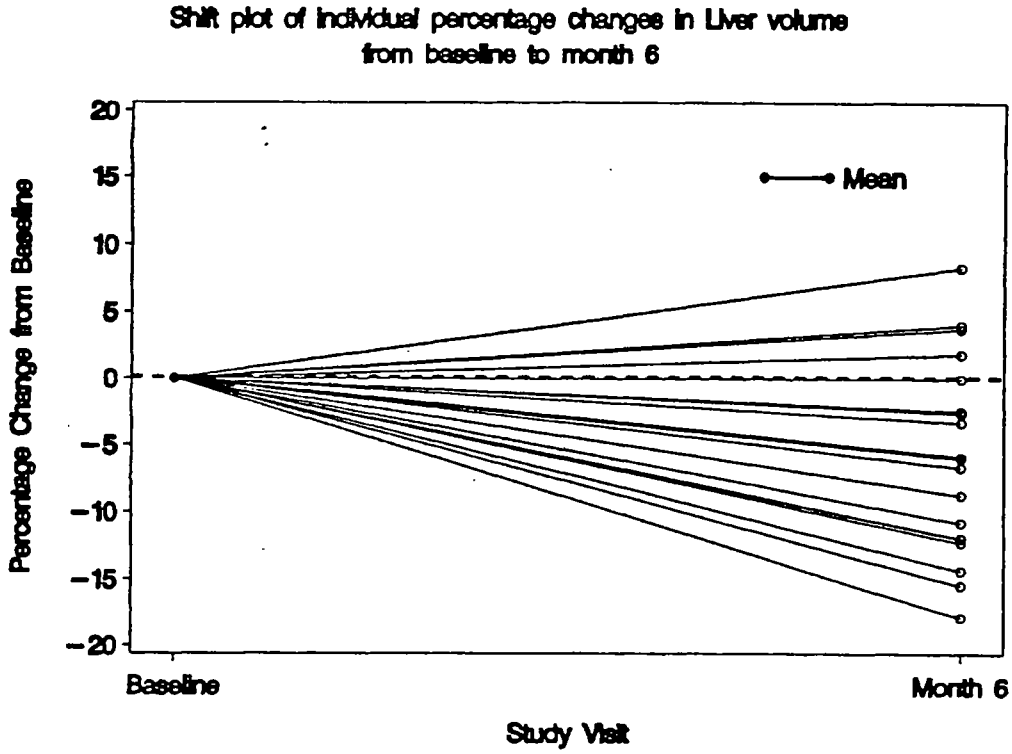
For individual patients, 12 of 17 patients had at least some decrease in their liver volume by Month 6. The sponsor also defined no response (NR) as a decrease of <10%, no change, or an increase in organ volume from Baseline; moderate response (MR) as a decrease of 10% to <30% in organ volume; and a good response (GR) as a decrease of >30% in organ volume. By this definition, at Month 6, 10 of 17 patients (59%) had NR, 7 patients (41%) had MR, and no patient had GR.

Individual patient results at Baseline and Month 6 are summarized in the following table and in the following figure [Figure electronically scanned and reproduced from: Oxford Glycosciences (UK) Ltd, NDA #21-348, Volume 2.10, page 46, dated 02-Aug-2001]

Table 67: 918-003 % Change from Baseline in Liver Organ Volume, Individual Patient Data

Patient Number	Baseline Organ Volume (L)	Month 6 Organ Volume (L)	Change from Baseline (L)	% Change from Baseline
101	1.52	1.47	-0.05	-3.3
102	2.50	2.20	-0.30	-11.9
103	2.50	2.23	-0.27	-10.8
104	1.71	1.50	-0.21	-12.3
105	2.40	2.60	0.20	8.3
106	2.30	2.30	0.00	0.0
107	1.67	1.43	-0.24	-14.4
110	2.50	2.20	-0.30	-12.0
111	1.50	1.40	-0.10	-6.7
112	4.10	4.00	-0.10	-2.4
201	3.56	2.92	-0.64	-17.9
202	3.06	-	-	-
203	2.26	2.34	0.08	3.8
204	1.78	1.63	-0.16	-8.8
205	3.43	3.34	-0.09	-2.6
206	3.35	3.49	0.14	4.1
207	1.79	1.82	0.03	1.9
208	2.70	2.29	-0.42	-15.5

Figure 11: 918-003 % Change from Baseline in Liver Organ Volume, Individual Patient Data



(ii) Spleen Organ Volume

Eleven (11) patients had spleen organ volume data available at Baseline and Month 6, and 7 patients had been splenectomized prior to study start. Overall, there were statistically significant mean percent and absolute spleen volume reductions from Baseline at Month 6 of –4.5% (p =.025) and –0.094 L (p =.027) respectively. The minimum and maximum mean percent reductions at Month 6 were
The results are summarized in the following table

Table 68: 918-003 Spleen Organ Volume Statistics, Efficacy Set

	Baseline	Month 6		
	Organ Volume (L)	Organ Volume (L)	Change (L)	% Change
n	11	11	11	11
Mean	1.98	1.88	-0.09	-4.5
Median	1.34	1.30	-0.06	-4.8
Minimum				
Maximum				
p-value			0.027	0.025

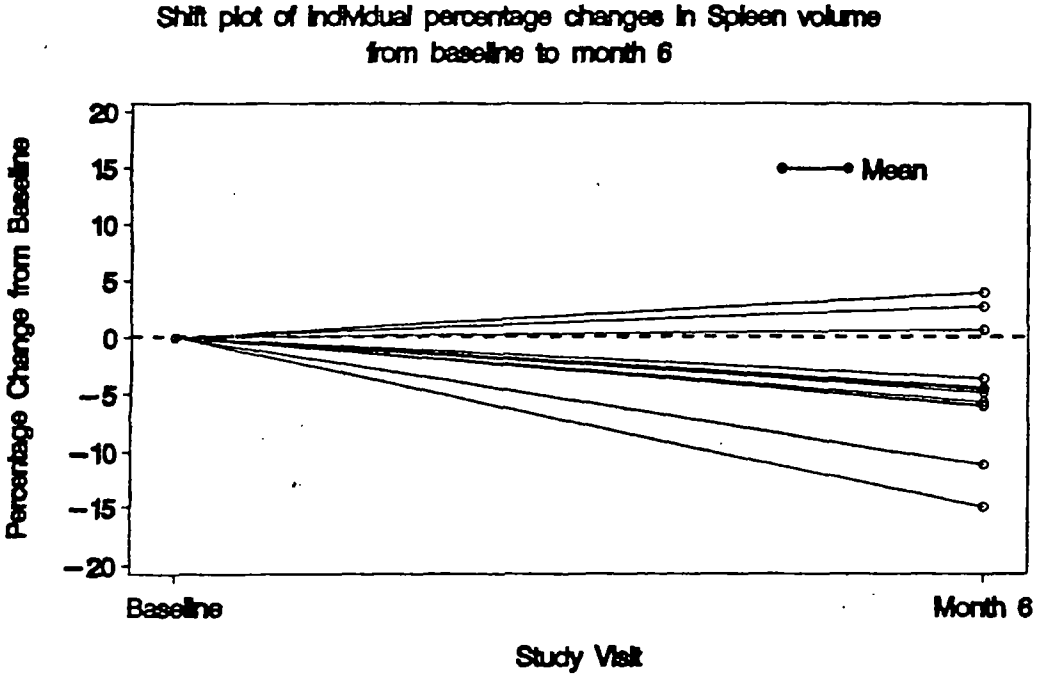
For individual patients, 8 of 11 patients had at least some decrease in their spleen volume at Month 6. By the sponsor's response definition (see Liver Organ Volume section above), at Month 6, 9 patients (82%) had NR, 2 patients had MR (18%), and no patient had GR.

Individual patient data are summarized as follows and in the following figure [Figure electronically scanned and reproduced from: Oxford Glycosciences (UK) Ltd, NDA #21-348, Volume 2.10, page 48, dated 02-Aug-2001]

Table 69: 918-003 % Change from Baseline in Spleen Organ Volume, Individual Patient Data

Patient Number	Baseline Organ Volume (L)	Month 6 Organ Volume (L)	Month 6 Change from Baseline (L)	Month 6 % Change from Baseline
101	1.00	0.94	-0.06	-6.0
107	0.36	0.37	0.01	2.8
110	1.25	1.30	0.05	4.0
111	0.89	0.85	-0.04	-4.5
201	3.39	3.01	-0.38	-11.2
203	2.72	2.63	-0.10	-3.6
204	0.95	0.81	-0.14	-15.0
205	3.91	3.94	0.03	0.7
206	2.93	2.76	-0.16	-5.6
207	1.34	1.28	-0.06	-4.8
208	2.98	2.81	-0.18	-5.9

Figure 12: 918-003 % Change from Baseline in Spleen Organ Volume, Individual Patient Data



(iii) Hemoglobin

Seventeen (17) of 18 patients had Hgb data at Month 6. Overall, there was a mean decrease in Hgb from Baseline to Month 6 of –0.132 g/dL (-1.3%), which was not statistically significant (p =.378). The minimum and maximum mean changes from

Baseline at Month 6 were –1.15 g/dL and +1.75 g/dL (-9.9% and 12.8% respectively). The results are summarized in the following table

Table 70: 918-003 Hemoglobin Statistics, Efficacy Set

	Baseline	Month 6		
	(g/dL)	g/dL	Change (g/dL)	% Change
n	17	17	17	17
Mean	11.60	11.47	-0.13	-1.3
Median	11.60	11.55	-0.40	-3.9
Minimum				
Maximum				
p-value			0.467	0.378

For individual patients at Month 6, 6 of 17 patients (35%) had at least some increase from Baseline in Hgb. The sponsor also defined no response (NR) as an increase of ≤0.5 g/dL, no change or a decrease in Hgb from Baseline; a moderate response (MR) as an increase of >0.5 g/dL to 1.5 g/dL in Hgb; and a good response (GR) as an increase of >1.5 g/dL in Hgb. By this definition, at Month 6, 15 of 17 patients (88%) had NR, 1 patient (6%) had MR, and 1 patient (6%) had GR.

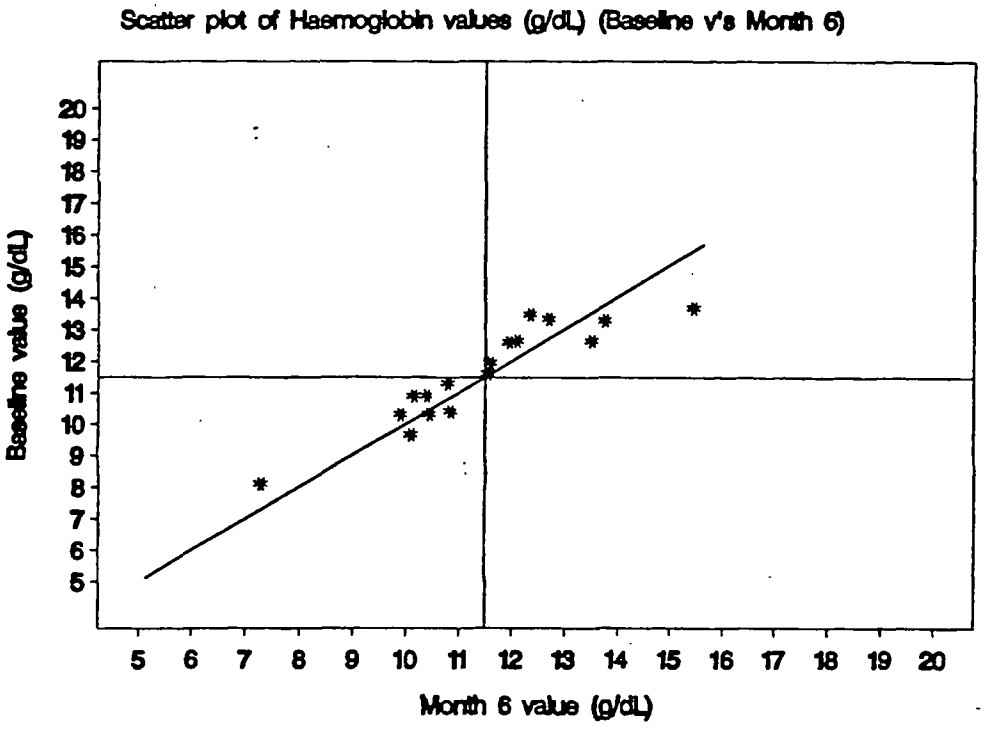
Individual patient data are summarized in the following table and in the following figure [Figure electronically scanned and reproduced from: Oxford Glycosciences (UK) Ltd, NDA #21-348, Volume 2.10, page 50, dated 02-Aug-2001]

Table 71: 918-003 Change from Baseline in Hemoglobin, Individual Patient Data

Patient Number	Baseline* (g/dL)	Month 6		
		g/dL	Change from Baseline (g/dL)	% Change from Baseline
101	13.30	13.75	0.45	3.4
102	13.70	15.45	1.75	12.8
103	11.60	11.55	-0.05	-0.4
104	13.35	12.70	-0.65	-4.9
105	10.30	9.90	-0.40	-3.9
106	11.95	11.60	-0.35	-2.9
107	12.65	13.50	0.85	6.7
110	13.50	12.35	-1.15	-8.5
111	12.65	12.10	-0.55	-4.3
112	10.90	10.15	-0.75	-6.9
201	9.65	10.10	0.45	4.7
202	12.70	-	-	-
203	11.30	10.80	-0.50	-4.4
204	10.40	10.85	0.45	4.3
205	12.60	11.95	-0.65	-5.2
206	8.10	7.30	-0.80	-9.9
207	10.90	10.40	-0.50	-4.6
208	10.30	10.45	0.15	1.5

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

Figure 13: 918-003 Scatter Plot of Hemoglobin Values, Baseline vs Month 6



Hemoglobin responses were further evaluated by Baseline Hgb value. Eight (8) patients had a Baseline Hgb <LLN (<11.5 g/dL), and 10 patients had Baseline Hgb ≥11.5 g/dL. There were numerically greater decreases in Hgb for patients with Baseline Hgb <11.5 g/dL than for patients with Baseline Hgb ≥11.5 g/dL, of –0.237 vs –0.04 g/dL, respectively. These results were not significant for either group, however. The results are summarized as in the following table

Table 72: 918-001 Hemoglobin Statistics by Baseline Hemoglobin Value

	Baseline Hgb <11.5 g/dL			Baseline Hgb ≥11.5 g/dL		
	Baseline	Actual Change	% Change	Baseline	Actual Change	% Change
n	8	8	8	10	9	9
Mean	10.23	-0.237 g/dL	-2.4	12.80	-0.04 g/dL	-0.4
Median	10.35	-0.45 g/dL	-4.2	12.68	-0.35 g/dL	-2.9
Minimum						
Maximum						
p-value*		0.231	0.231		0.901	0.872

(iv) Platelets

Seventeen (17) of 18 patients had Plt data at Month 6. Overall, there was a mean increase in Plt from Baseline to Month 6 of 5.35 X 10^9/L (2.0%) which was not statistically significant (p =.345). The minimum and maximum mean changes from Baseline at Month 6 were –40.00 X10^9/L and 55.00 X10^9/L (-28.2% and 32.5%, respectively). The results are summarized in the following table

Table 73: 918-003 Platelet Count Statistics, Efficacy Set

	Baseline	Month 6		
	(10^9/L)	10^9/L	Change (10^9/L)	% Change
n	17	17	17	17
Mean	116.47	121.82	5.35	2.0
Median	85.00	76.00	1.50	4.8
Minimum				
Maximum				
p-value			0.345	0.642

For individual patients, at Month 6, 11 of 17 patients (65%) had at least some increase from Baseline in Plt. The sponsor also defined no response (NR) as an increase of ≤15 $X10^9$/l, no change or a decrease in Plt from Baseline; a moderate response (MR) as an increase of >15 to 30 $X10^9$/l in Plt; and a good response (GR) as an increase of >30 $X10^9$/l in Plt. By this definition, at Month 6, 12 of 17 patients (71%) had NR, 2 patients (12%) had MR, and 3 patients (18%) had GR.

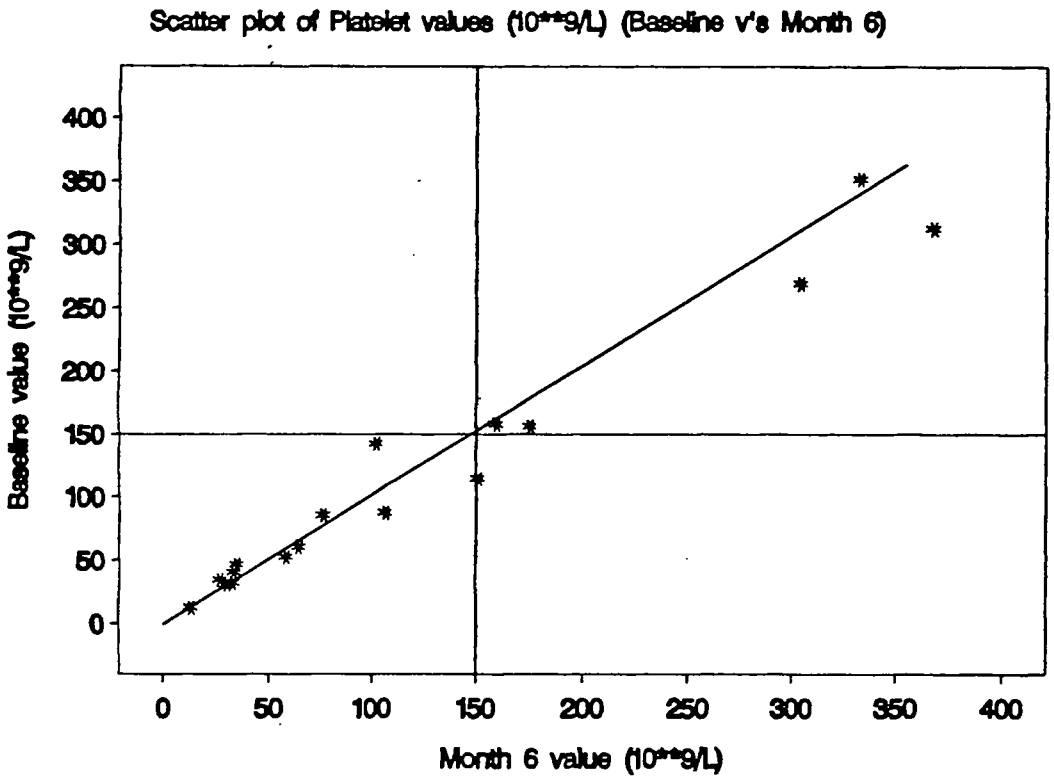
Individual patient data are summarized in the following table and in the following figure [Figure electronically scanned and reproduced from: Oxford Glycosciences (UK) Ltd, NDA #21-348, Volume 2.10, page 52, dated 02-Aug-2001]

Table 74: 918-003 Change from Baseline in Platelet Count, Individual Patient Data

Patient Number	Baseline* (10^9/L)	Month 6		
		10^9/L	Change from Baseline (10^9/L)	% Change from Baseline
101	52.00	58.50	6.50	12.5
102	351.50	333.00	-18.50	-5.3
103	157.50	159.50	2.00	1.3
104	269.00	304.50	35.50	13.2
105	142.00	102.00	-40.00	-28.2
106	312.50	367.50	55.00	17.6
107	87.00	106.50	19.50	22.4
110	114.00	151.00	37.00	32.5
111	85.00	76.00	-9.00	-10.6
112	156.00	175.50	19.50	12.5
201	31.50	33.00	1.50	4.8
202	246.00	-	-	-
203	30.00	30.50	0.50	1.7
204	60.00	64.50	4.50	7.5
205	12.00	13.50	1.50	12.5
206	40.00	33.50	-6.50	-16.3
207	46.00	35.00	-11.00	-23.9
208	34.00	27.00	-7.00	-20.6

LLN <150 $X10^9$/L
Baseline <150 $X10^9$/L

Figure 14: 918-003 Scatter Plot of Platelet Values, Baseline vs Month 6



Plt responses were further evaluated by Baseline Plt. Twelve (12) patients had a Baseline Plt <LLN (<150 $X10^9$/L), and 6 patients had baseline Plt ≥150 $X10^9$/L. Patients with a Baseline Plt <150 $X10^9$/L had a mean decrease in Plt of –0.21 $X10^9$/L at Month 6, whereas patients with a Baseline Plt ≥150 $X10^9$/L had a mean *increase* in Plt of +18.7 $X10^9$/L at Month 6. These results were not significant for either group. The results are summarized as in the following table

Table 75: 918-003 Platelet Count Statistics by Baseline Platelet Counts

	Baseline Plt <150 $X10^9$/L			Baseline Plt ≥150 $X10^9$/L		
	Baseline	Actual Change	% Change	Baseline	Actual Change	% Change
n	12	12	12	6	5	5
Mean	61.1 $X10^9$/L	-0.21 $X10^9$/L	-0.48	248.8 $X10^9$/L	18.7 $X10^9$/L	7.58
Median	49.0 $X10^9$/L	1.00 $X10^9$/L	3.2	257.5 $X10^9$/L	19.5 $X10^9$/L	12.5
Minimum						
Maximum						
p-value*		0.969	0.934		0.217	0.138

(v) Biochemical Markers

The results for the biochemical markers of Gaucher disease measured in this study, chitotriosidase and hexosaminidase, will be briefly summarized below.

Chitotriosidase

There was a mean decrease in chitotriosidase from Baseline at Month 6 of –383.1 nmol/ml.h, which was not significant. However, the mean percentage decrease was 4.6%, which was significant (p =.039). The results are summarized in the following table

Table 76: 918-003 Chitotriosidase Statistics

	Baseline	Month 6		
	(nmol/ml.h)	nmol/ml.h	Change (nmol/ml.h)	% Change
n	18	17	17	17
Mean	14177.9	13517.2	-383.1	-4.6
Median	12039.0	10054.0	-248.5	-4.1
Minimum				
Maximum				
p-value			0.176	0.039

Hexosaminidase

There was a mean decrease in hexosaminidase from Baseline at Month 6 of –160.3 nmol/ml.h (–5.5%), which was not significant. The results are summarized in the following table

Table 77: 918-003 Hexosaminidase Statistics

	Baseline	Month 6		
	(nmol/ml.h)	nmol/ml.h	Change (nmol/ml.h)	% Change
n	18	17	17	17
Mean	1980.4	1822.8	-160.3	-5.5
Median	1737.3	1602.0	-96.5	-7.7
Minimum				
Maximum				
p-value			0.072	0.117

(b) Secondary Efficacy Analysis

Secondary efficacy analyses included pharmacokinetic (PK) profiles, other disease assessments (such as bone density, fat fraction, pulmonary hypertension, and organ volume) at screening and Month 6; QoL questionnaire. Exploratory analyses for correlations between percentage changes in organ volume (liver, spleen and combined), percentage changes in platelet counts, hemoglobin, and percentage change in weight from Baseline to Month 6 were investigated.

(i) Other Disease Assessments

Other disease assessments were performed at the discretion of the Investigator and per usual practice at the study centers. Three (3) patients had at least one other disease assessment performed for whom results are available at screening and at Month 6. These 3 patients all underwent echocardiograms to assess their T1 gradient, none of whom showed any deterioration [A complete listing of tests performed in the Appendix].

(ii) Quality of Life (QoL) Questionnaire

The QoL questionnaire was the validated SF-36 Health Survey, which assessed QoL in eight dimensions: physical function, enhanced role limitations due to physical problems, bodily pain, general health perceptions, vitality, social function, enhanced role limitations due to emotional problems, and mental health. The QoL questionnaire was administered only at Center 1 (due to lack of non-English translation) and administered only to patients and not Investigators. Ten (10) patients at Center 1 (Johannesburg, South Africa) completed a QoL questionnaire at Day 1, Month 3, and Month 6. On Day 1, these patients reported poorer levels of physical functioning, less energy, and poorer perceptions of their general health relative to the US general population. By Month 6, these patients reported improvements in these areas of 9.4%, 16.5%, and 8.4% respectively (improvements of 5% are considered clinically meaningful); however, results were significant only for improvements in energy levels ($p = .004$). There were no significant results at Month 3.

(c) Subgroup Analyses

Subgroup analyses were performed by:

- Baseline Hgb <11.5 g/dL vs ≥11.5 g/dL (see Hemoglobin Section above)
- Baseline Plt <150 $X10^9$/L vs ≥150 $X10^9$/L (see Platelet Count section above)
- Chitotriosidase and hexosaminidase by "non-expressors". The results of these subgroup analyses did not differ from the analyses of the groups as a whole.

(d) Conclusions on Efficacy Results for Protocol 918-003

There were statistically significant mean decreases in liver and spleen volumes from Baseline to Month 6. Mean liver volume decreased –5.9% at Month 6, and mean spleen volume decreased –4.5%. There were no significant changes in mean Hgb and Plt. Subgroup analyses by Baseline Hgb and Plt showed a non-significant decrease in Hgb in both patients with Baseline Hgb <11.5 g/dL and Baseline Hgb ≥11.5 g/dL. For Plt, patients with baseline Plt <150 $X10^9$/L had a non-significant decrease in Plt, whereas patients with Baseline Plt ≥150 $X10^9$/L had a non-significant increase in Plt. Analyses of the biochemical markers chitotriosidase and hexosaminidase showed decreases from Baseline at Month 6, that were only significant for percent decrease from Baseline in Chitotriosidase. For the secondary parameters, the QoL questionnaire was only administered to patients at Center 1, and showed a significant change from Baseline only in energy levels at Month 6. Other disease assessments available at screening and at Month 6 include 3 patients with echocardiograms showing no deterioration in T1.

These efficacy findings are consistent with beneficial effects of OGT 918 on organ volume; however, no significant benefit on the hematologic parameters Hgb and Plt were seen during the 6-month treatment period.

4) Protocol 918-003X

a) Study Design for Protocol 918-003X

(1) Study Design

Protocol 918-003X "A phase I/II of open label OGT 918 (50 mg TID) in adult patients with type I Gaucher disease (extended treatment period)" was a non-comparative, multi-center, open-label extension study to Protocol 918-003. Protocol 918-003X evaluated the efficacy and safety of OGT 918 at a dose of 50 mg TID for an additional 6 months after successful completion of Protocol 918-003. Sixteen (16) adult patients with type I Gaucher disease who were unable or unwilling to be treated with Ceredase or Cerezyme were enrolled at 2 international sites.

(2) Study Objectives

The primary objective of the study was to evaluate OGT 918 as a treatment for Gaucher disease by assessing organ volume and other markers of the disease after an additional 6 month treatment period. The secondary objective was to assess the tolerability of OGT 918 during an additional 6 months of treatment.

(3) Eligibility Criteria

Patients were eligible for the extension phase if they had completed the Month 6 visit in the original study (Protocol 918-003) and the Investigator felt they would benefit from extended use treatment. Patients were given the option to continue in the extension study at the Month 6 visit in the original study.

(4) Study Visits and Procedures

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

Table 78: 918-003 and 918-003X Study Visits and Procedures

	Screen	6-Month Treatment Phase 918-003								Extended Use Treatment Phase 918-003X	
Day		1	8 to 15	29	57	85	113	141	169		
Month				1	2	3	4	5	6	9	12
Procedure											
Weight (BMI/BSA)	X	X		X	X	X	X	X	X	X	X
History	X										
Physical Examination/ Vital Signs	X			X		X			X		
ECG	X			X					X		
EMG and NCV									X		
Biochemistry & Hematology	X	X		X	X	X	X	X	X	X	X
Organ Volume	X								X		X
Other Disease Assessments	X	X		X		X			X		X
Chitotriosidase & Hexosaminidase	X	X		X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X
OGT 918 Dispensing		X		X	X	X	X	X	X	X	X

As Protocol 918-003X was an extension to the original 6-month treatment period (Protocol 918-003), it continued with the same study design. Patients signed a second informed consent specific to the extended treatment period of the study prior to continuing in the extended treatment phase. Safety and efficacy assessments were made every 3 months, beginning at Month 9 after completion of Month 6 in the original treatment period.

(a) Month 9 Visit

At the Month 9 Visit, patients underwent the following assessments:

- Weight
- Biochemistry and Hematology
- Chitotriosidase and Hexosaminidase assessment
- AE assessment
- Concomitant Medications update

(b) Month 12 Visit

At the Month 12 Visit, patients underwent the following assessments:

- Weight
- Biochemistry and Hematology
- Organ Volume Assessment
- Other Disease Assessments
- Chitotriosidase and Hexosaminidase assessment
- AE assessment
- Concomitant Medications update

(5) Study Medication Dispensing and Compliance

All patients received OGT 918 at the same dose and schedule as were being taken when they completed the original 6-month treatment period. As in the original 6-month treatment period (Protocol 918-003), the patient's dose could be decreased to 50 mg BID if a patient experienced any unacceptable toxicity that was thought to be related to the study medication.

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

As this was an open-label study, no blinding was necessary, and all patients received OGT 918. OGT 918 was supplied as 50 mg gelatin capsules for oral administration. Patients were given a 3-month supply of OGT 918 at a time. OGT 918 was to be taken 3 times a day (or twice a day if the dose had been reduced) at regular intervals, either 2 hours before or two hours after eating. Patients were advised to avoid high carbohydrate content food, and dietary recommendations were issued to all participants.

(6) Efficacy and Endpoint Measures

This study was designed to provide an additional 6 months of information on the safety and possible efficacy of OGT 918.

(a) Primary Efficacy Parameters

The primary efficacy parameters for the extension study were change from baseline in:

- Liver volume
- Spleen volume
- Hemoglobin concentration
- Platelet counts
- Chitotriosidase response
- Hexosaminidase response
- Overall response

(b) Secondary Efficacy Parameters

- Other disease assessments
- Further exploratory analyses

(c) Safety Assessments

Safety was assessed by the incidence and frequency of AEs, and changes in vital signs, physical examinations, ECG, EMG/NCV assessments, and clinical laboratory values.

(d) Study Population

The efficacy population (ITT population) and the safety population were identical in this study, and were defined by the sponsor as all patients who received at least one dose of study medication.

b) Results

A total of 18 patients were entered into Protocol 918-003, and 17 of those patients completed the original study. Thus, 17 patients were eligible to enter Protocol 918-003X. Sixteen (16) of the 17 patients who completed the original study chose to enter the extended treatment phase. Twelve (12) of the 16 patients completed the study and 4 withdrew prior to extension study completion. Patients were screened, entered, and treated (beginning with entry into the original study) from 07-Dec-1999 and 28-Dec-2001

(1) Baseline Characteristics and Demographics

Of the patients who continued in the extension study, 25% of patients were male and 81% were Ashkenazi Jews. Patient ages ranged from 22 to 61 years of age, with a mean age of 43.9 years. Baseline characteristics were also compared to the baseline characteristics of the original study population. The mean platelet count was somewhat lower in the extension group compared to the original group due to the withdrawal of Patient 202 who had a baseline platelet count of 246k. The two populations were otherwise quite similar

at baseline. The baseline characteristics for the extension and original study populations are summarized in the following table

Table 79: 918-003 and 918-003X Baseline Characteristics and Demographics

	Extension Study Population	Original Study Population
Enrolled Patients, n =	16	18
Demographic Measure		
Gender, n (%)	16	18
Male	4 (25)	5 (28)
Female	12 (75)	13 (72)
Age (years), n =	16	18
Mean	43.9	42.4
Min, max	22, 61	22, 61
Race, n (%)	16	18
Ashkenazi Jew	13 (81)	15 (83)
Other	3 (19)	3 (17)
Mean BMI (kg/M^2), n =	16	18
Mean	23.43	23.11
Min, max		
Liver Organ Volume (l), n =	16	18
Mean	2.45	2.47
Min, max		
Spleen Organ Volume (l), n =	11	11
Mean	1.98	1.97
Min, max		
Hemoglobin (g/dL), n =	16	18
Mean	11.68	11.65
Min, max		
Platelets ($x10^9/l$), n =	16	18
Mean	114.88	123.66
Min, max		

(2) Patient Disposition

(a) Screening and Randomization

Seventeen patients were eligible for entry into the extension study, and 16 patients were enrolled. The one screen failure was from site #1 (Johannesburg). This patient had bipolar disease, was receiving anti-psychotic drugs, and was considered to be unsuitable for continuation in the trial by the Investigator.

Compared to the patients entered in the original study, the same percentages of patients continued in the extension as were entered originally at each study center, as follows

Table 80: 918-003 and 918-003X Patient Continuation by Study Center

Center Number	Center/Investigator	Extension Study Continued, n (%)	Original Study Enrolled, n (%)
	All	**16**	**18**
1	Johannesburg, South Africa/Dr. Rene Heitner	9 (56)	10 (56)
2	Jerusalem, Israel/Dr. Ari Zimran	7 (44)	8 (44)

(b) Dropouts

Of the 16 patients entered in the extension study, 12 patients completed the 12 months of the study (6 months of the original study + 6 months of the extension). Four (4) patients (19%) withdrew prior to extension study completion: 3 patients at the Investigator's request: 1 of which (Patient 110) was due to unacceptable disease progression (increasing hepatosplenomegaly) at the Month 12 Visit, and 1 patient due to an AE (flatulence, cramps and diarrhea). Patient 110 was later found to have chronic intra-abdominal sepsis and large cell lymphoma of B cell origin. Three (3) withdrawals occurred at >26 weeks-39 weeks of study drug treatment, and 1 patient at the Month 12 visit. The reasons for study discontinuation in the original and extension studies are as follows

Table 81: 918-003 and 918-003X Patients Discontinued

	Extension Study Patients, n (%)	Original Study Patients, n (%)
Enrolled Patients, n =	16	18
Number of Withdrawals, n (%)	4 (25)	1 (6)
Reason for Dropout*		
Adverse Event, n (%)	2 (13)	1 (6)
Subject Request, n (%)	0	1 (6)
Investigator Request, n (%)	3 (19)	0

*Patient may have reported more than one reason for withdrawal

There was one protocol violator during the extension, Patient 206, who failed to comply with contraception throughout the study. This patient remained in the study, however, due to a lack of alternative treatment for this patient and her organomegaly. One patient (Patient 110) failed to meet inclusion/exclusion criteria [see Study 918-003 Section III A. 3) f) (2)].

(3) Concomitant Medication

Fifteen (15) of 16 patients in the study reported the use of at least one concomitant medication from entry into the original study (918-003) until extension study completion/termination. The analgesic paracetamol was the most commonly used medication reported during the extension study [10 patients (63%)], followed by loperamide and ibuprofen (31% each) and ascorbic acid (25%). GI medications were commonly reported, with 10 patients (63%) taking GI medications including loperamide, saccharomyces boulardii, hyoscine butylbromide, carosylane, and metoclopramide. The most commonly ($\geq$2 patients or $\geq$10% of patients) used concomitant medications, used by the patients from the start of the original study through extension study completion or termination, are summarized in the following table

Table 82: 918-003 and 918-003X Most Common (>2 Patients) Concomitant Medications

	Extension Study	Original Study
Randomized Patients, n =	16	18
Medication	n (%)	n (%)
Acetaminophen + codeine phosphate	0	7 (39)
Paracetamol	10 (63)	5 (28)
Loperamide	5 (31)	4 (22)
Ibuprofen	5 (31)	2 (11)
Vitamin C	4 (25)	3 (17)
Acetylsalicylic Acid	3 (19)	0
Actifed	3 (19)	1 (6)
Augmentin	3 (19)	2 (11)
Phenylephrine hydrochloride	3 (19)	2 (11)
Saccharomyces Boulardii	3 (19)	0
Vitamin B12	3 (19)	3 (17)
Amoxicillin	2 (13)	2 (11)
Beclomethasome	2 (13)	0
Chlorpheniramine maleate	2 (13)	2 (11)
Codeine Phosphate	2 (13)	2 (11)
Cyclizine	2 (13)	2 (11)
Ferrous Sulfate	2 (13)	1 (6)
Folic Acid	2 (13)	2 (11)
Hyoscine butylbromide	2 (13)	2 (11)
Levothyroxine	2 (13)	0
Magnesium	2 (13)	1 (6)
Mersyndol (cough and cold preparation)	2 (13)	0
Metamizole	2 (13)	0
Myprodol (analgesic)	2 (13)	2 (11)
Ophthalmologicals	2 (13)	2 (11)
Carbosylane (antidiarrheal)	1 (6)	2 (11)
Ethinylestradiol	1 (6)	2 (11)
Levonorgestrel	1 (6)	2 (11)
Pseudoephedrine hydrochloride	1 (6)	2 (11)
Inteflora (antidiarrheal)	0	2 (11)
Optalgin (analgesics)	0	2 (11)
Scopolamine	0	2 (11)

(4) Patient Compliance

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

(5) Efficacy Results

(a) Primary Efficacy Analysis

The sponsor's primary efficacy variables were absolute and percentage changes from Baseline in liver and spleen organ volume at Endpoint (Month 12); absolute and percentage change from Baseline in hemoglobin concentration, platelet counts,

chitotriosidase, and hexosaminidase from screening to Endpoint; and overall response at Endpoint (from a combination of the individual response parameters).

(i) Liver Organ Volume Response

Thirteen (13) of 16 patients entered in the extension study had liver organ volume data available at Month 12. Overall, there were statistically significant mean percentage reductions from Baseline to Month 12 in liver volume of –6.2% (p =.037), and significant mean reductions in absolute liver volume from Baseline to Month 12 of –0.17 L (p=.033). The minimum and maximum mean percent reductions at Month 12 were +7.2% and –20.7%. The results show essentially no mean change in liver volume from Month 6 (end of original study treatment phase, Study 918-001) to Month 12. The results are summarized in the following table

Table 83: 918-003X Liver Organ Volume Statistics

	Baseline	Month 6			Month 12		
	Organ Volume (L)	Organ Volume (L)	Change (L)	% Change	Organ Volume (L)	Change (L)	% Change
n	16	16	16	16	13	13	13
Mean	2.45	2.29	-0.16	-6.8	2.19	-0.17	-6.2
Median	2.40	2.22	-0.13	-7.7	2.23	-0.12	-4.1
Minimum							
Maximum							
p-value			.005	.002		.033	.037

For individual patients, 9 of 13 patients (69%) had at least some decrease in their liver volume at Month 12. By the sponsor's response definition (see Study 918-003, Efficacy Results: Liver Organ Volume section), at Month 12, 9 of 13 patients (69%) had NR, 4 patients (31%) had MR, and no patient had GR.

Individual patient results at Baseline, Month 6, and 12 are summarized in the following table and in the following figure [Figure electronically scanned and reproduced from: Oxford Glycosciences (UK) Ltd, NDA #21-348, Volume 2.13, page 46, dated 02-Aug-2001]

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Table 84: 918-003X Change from Baseline in Liver Volume, Individual Patient Data

Patient Number	Baseline	Month 6			Month 12		
	Organ Volume (L)	Organ Volume (L)	Change (L)	% Change	Organ Volume (L)	Change (L)	% Change
101	1.52	1.47	-0.05	-3.3	1.57	0.05	3.3
102	2.50	2.20	-0.30	-11.9	1.98	-0.52	-20.7
103	2.50	2.23	-0.27	-10.8	2.42	-0.08	-3.2
104	1.71	1.50	-0.21	-12.3	1.59	-0.12	-7.0
106	2.30	2.30	0.00	0.0	2.40	0.10	4.3
107	1.67	1.43	-0.24	-14.4	1.79	0.12	7.2
110	2.50	2.20	-0.30	-12.0	2.50	0.00	0.0
111	1.50	1.40	-0.10	-6.7	1.19	-0.31	-20.7
112	4.10	4.00	-0.10	-2.4	-	-	-
201	3.56	2.92	-0.64	-17.9	2.88	-0.68	-19.0
203	2.26	2.34	0.08	3.8	2.23	-0.02	-1.0
204	1.78	1.63	-0.16	-8.8	-	-	-
205	3.43	3.34	-0.09	-2.6	2.97	-0.46	-13.3
206	3.35	3.49	0.14	4.1	3.22	-0.14	-4.1
207	1.79	1.82	0.03	1.9	1.67	-0.12	-6.7
208	2.70	2.29	-0.42	-15.5	-	-	-

Figure 15: 918-003X % Change from Baseline in Liver Volume, Individual Patient Data