### (ii) Spleen Organ Volume

Nine (9) patients had spleen volume data available at Month 12. Overall, there were statistically significant mean actual and percent reductions in spleen organ volume from Baseline at Month 12 of –0.23 L (p =.049) and –10.1% (p =.048) respectively. These results show a progressive mean percent decrease in spleen volume from Baseline at Month 6 and Month 12 of –4.5% and –10.1%, respectively. In addition, one patient (Patient 110) had a substantial increase in hepatosplenomegaly, and was later found to have B-cell lymphoma. Subsequent analysis after exclusion of Patient 110 indicated stronger improvement at Month 12 (decrease of -13.9%, p<.001) [see individual patients below]. The results for mean changes from Baseline at Months 6 and 12 are summarized in the following table

**Table 85: 918-003X Spleen Organ Volume Statistics, Efficacy Set**

| | Baseline | Month 6 | | | Month 12 | | |
|---|---|---|---|---|---|---|---|
| | Organ Volume (L) | Organ Volume (L) | Change (L) | % Change | Organ Volume (L) | Change (L) | % Change |
| n | 11 | 11 | 11 | 11 | 9 | 9 | 9 |
| Mean | 1.98 | 1.88 | -0.094 | -4.5 | 1.75 | -0.23 | -10.1 |
| Median | 1.34 | 1.30 | -0.06 | -4.8 | 1.50 | -0.20 | -11.1 |
| Minimum | | | | | | | |
| Maximum | | | | | | | |
| p-value | | | .027 | .025 | | .049 | .048 |

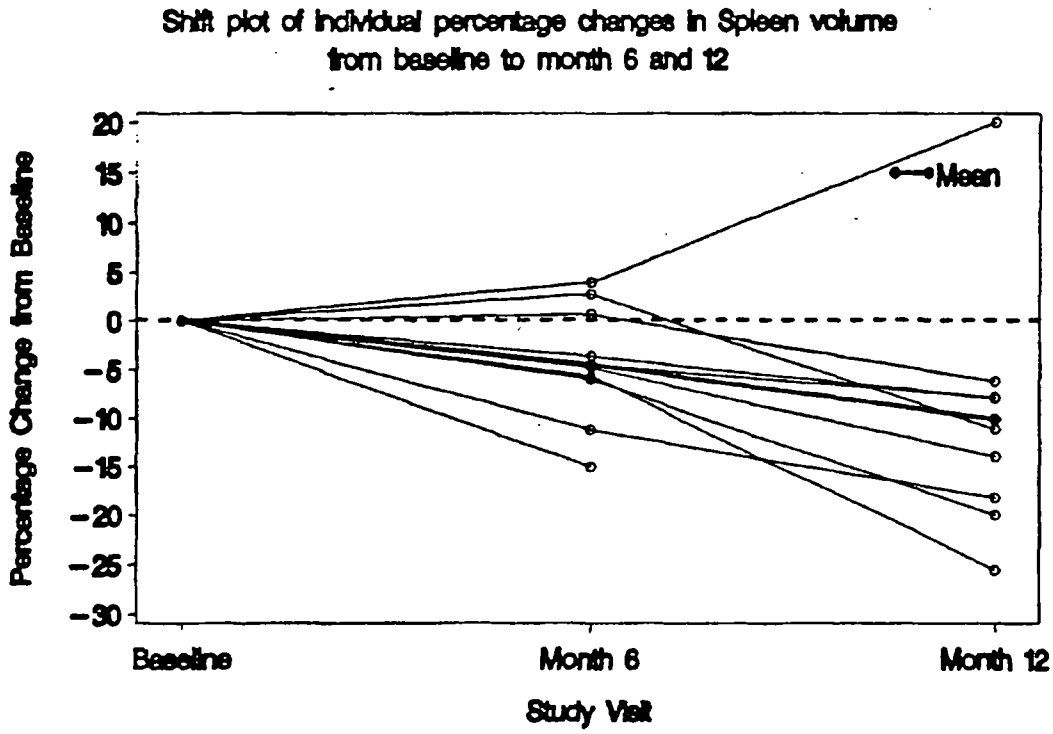
For individual patients, 8 of 9 patients (89%) had at least some decrease in their spleen volume at Month 12. By the sponsor's response definition (see Study 918-003, Efficacy Results: Liver Organ Volume section), at Month 12, 4 of 9 patients (44%) had NR, 5 patients (56%) had MR, and no patient had 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 48, dated 02-Aug-2001]

**Table 86: 918-003X Change from Baseline in Spleen Volume, Individual Patient Data**

| | Baseline | Month 6 | | | Month 12 | | |
|---|---|---|---|---|---|---|---|
| Patient Number | Organ Volume (L) | Organ Volume (L) | Change (L) | % Change | Organ Volume (L) | Change (L) | % Change |
| 101 | 1.00 | 0.94 | -0.06 | -6.0 | 0.80 | -0.20 | -20.0 |
| 107 | 0.36 | 0.37 | 0.01 | 2.8 | 0.32 | -0.04 | -11.1 |
| 110 | 1.25 | 1.30 | 0.05 | 4.0 | 1.50 | 0.25 | 20.0 |
| 111 | 0.89 | 0.85 | -0.04 | -4.5 | 0.82 | -0.07 | -7.9 |
| 201 | 3.39 | 3.01 | -0.38 | -11.2 | 2.77 | -0.62 | -18.2 |
| 203 | 2.72 | 2.63 | -0.10 | -3.6 | 2.51 | -0.22 | -8.0 |
| 204 | 0.95 | 0.81 | -0.14 | -15.0 | - | - | - |
| 205 | 3.91 | 3.94 | 0.03 | 0.7 | 3.67 | -0.24 | -6.2 |
| 206 | 2.93 | 2.76 | -0.16 | -5.6 | 2.18 | -0.75 | -25.6 |
| 207 | 1.34 | 1.28 | 0.06 | -4.8 | 1.15 | -0.19 | -13.9 |
| 208 | 2.98 | 2.81 | -0.18 | -5.9 | - | - | - |

Figure 16: 918-003X % Change from Baseline in Spleen Volume, Individual Patient Data




### (iii) Hemoglobin

Thirteen (13) patients had Hgb data at Endpoint (Month 12). Overall, there was a mean increase in Hgb from Baseline at Month 12 of 0.06 g/dL (1.2%); however, this was not statistically significant. These results are summarized in the following table

Table 87: 918-003X Hemoglobin Statistics, Efficacy Set

| | Baseline | Month 6 | | | Month 12 | | |
|---|---|---|---|---|---|---|---|
| | (g/dL) | g/dL | Change (g/dL) | % Change | g/dL | Change (g/dL) | % Change |
| n | 16 | 16 | 16 | 16 | 13 | 13 | 13 |
| Mean | 11.68 | 11.56 | -0.12 | -1.2 | 12.00 | 0.06 | 1.2 |
| Median | 11.78 | 11.58 | -0.42 | -3.6 | 12.30 | 0.10 | 0.9 |
| Minimum | | | | | | | |
| Maximum | | | | | | | |
| p-value | | | 0.548 | 0.462 | | 0.876 | 0.682 |

For individual patients, 6 patients (46%) had any increase in Hgb at Month 12. By the sponsor's response definition (see Study 918-003, Efficacy Results: Hemoglobin section), for the 13 patients who had available Hgb data at Month 12, 9 patients had NR (69%), 2 patients had MR (15%), and 2 patients had GR (15%).

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:

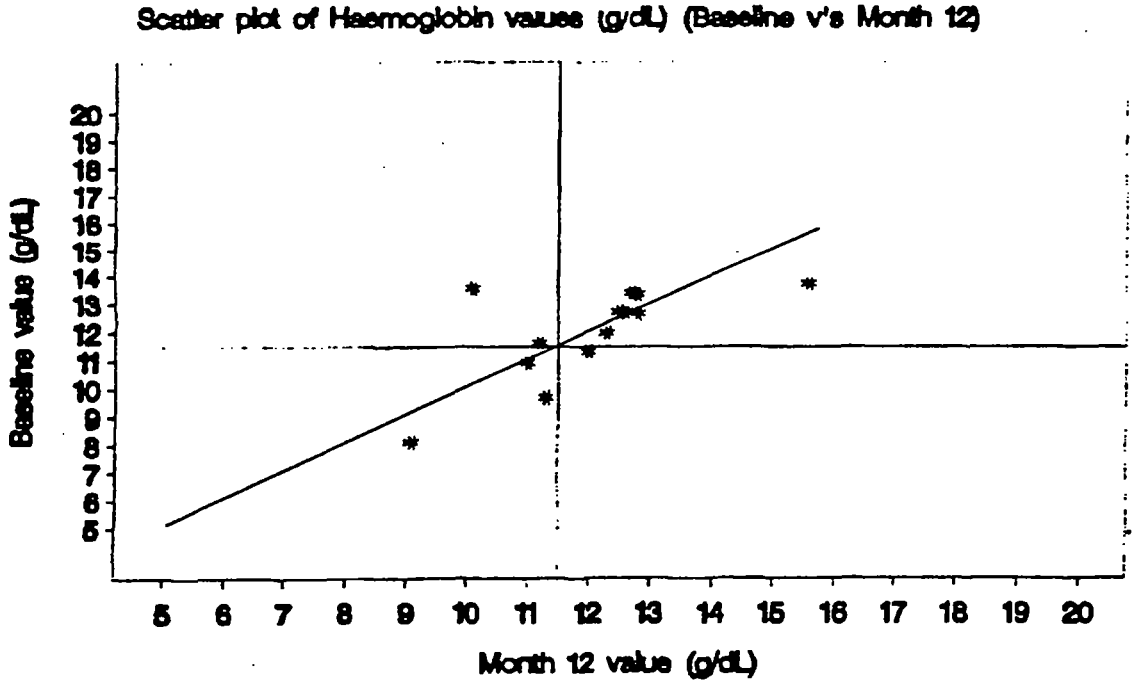
Oxford Glycosciences (UK) Ltd, NDA #21-348, Volume 2.13, page 50, dated 02-Aug-2001]

**Table 88: 918-003X Change from Baseline in Hemoglobin, Individual Patient Data**

| Patient Number | Baseline* (g/dL) | Month 6 g/dL | Month 6 Change (g/dL) | Month 6 % Change | Month 12 g/dL | Month 12 Change (g/dL) | Month 12 % Change |
|---|---|---|---|---|---|---|---|
| 101 | 13.30 | 13.75 | 0.45 | 3.4 | 12.80 | -0.50 | -3.8 |
| 102 | 13.70 | 15.45 | 1.75 | 12.8 | 15.60 | 1.90 | 13.9 |
| 103 | 11.60 | 11.55 | -0.05 | -0.4 | 11.20 | -0.40 | -3.4 |
| 104 | 13.35 | 12.70 | -0.65 | -4.9 | 12.70 | -0.65 | -4.9 |
| 106 | 11.95 | 11.60 | -0.35 | -2.9 | 12.30 | 0.35 | 2.9 |
| 107 | 12.65 | 13.50 | 0.85 | 6.7 | 12.50 | -0.15 | -1.2 |
| 110 | 13.50 | 12.35 | -1.15 | -8.5 | 10.10 | -3.40 | -25.2 |
| 111 | 12.65 | 12.10 | -0.55 | -4.3 | 12.60 | -0.05 | -0.4 |
| 112 | 10.90 | 10.15 | -0.75 | -6.9 | - | - | - |
| 201 | 9.65 | 10.10 | 0.45 | 4.7 | 11.30 | 1.65 | 17.1 |
| 203 | 11.30 | 10.80 | -0.50 | -4.4 | 12.00 | 0.70 | 6.2 |
| 204 | 10.40 | 10.85 | 0.45 | 4.3 | - | - | - |
| 205 | 12.60 | 11.95 | -0.65 | -5.2 | 12.80 | 0.20 | 1.6 |
| 206 | 8.10 | 7.30 | -0.80 | -9.9 | 9.10 | 1.00 | 12.3 |
| 207 | 10.90 | 10.40 | -0.50 | -4.6 | 11.00 | 0.10 | 0.9 |
| 208 | 10.30 | 10.45 | 0.15 | 1.5 | - | - | - |

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

**Figure 17: 918-003X Scatter Plot of Hemoglobin Values, Baseline vs Month 12**



A subgroup analysis was also performed by Baseline Hgb. Patients with Baseline Hgb <11.5 g/dL had a numerically greater increase in their Hgb compared to patients with Baseline Hgb ≥11.5 g/dL. Patients with a Baseline Hgb <11.5 g/dL had a small but statistically significant increase in Hgb from Baseline to Month 12 of 0.863 g/dL, whereas patients with a Baseline Hgb ≥11.5 g/dL had a non-significant decrease in Hgb from Baseline to Month 12 of –0.30 g/dL. The results are summarized in the following table

**Table 89: 918-003X 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 = 7<br>-0.214 | p=.0342 | n = 9<br>-0.039 | p=0.901 |
| Month 12 | n =4<br>0.863 | p=0.075 | n = 9<br>-0.300 | p=0.525 |

### (iv) Platelets

Thirteen (13) patients had Plt data at Endpoint (Month 12). Overall, there was a mean increase in Plt from Baseline at Month 12 of 14.00 $X10^9$/L (14.7%); however, this was not statistically significant. There was also a progressive mean percent increase in Plt from Baseline at Month 6 and Month 12 of 3.9% and 14.7%, respectively. These results are summarized in the following table

**Table 90: 918-003X Platelet Statistics, Efficacy Set**

| | Baseline | Month 6 | | | Month 12 | | |
|---|---|---|---|---|---|---|---|
| | ($10^9$/L) | $10^9$/L | Change ($10^9$/L) | % Change | $10^9$/L | Change ($10^9$/L) | % Change |
| n | 16 | 16 | 16 | 16 | 13 | 13 | 13 |
| Mean | 114.88 | 123.06 | 8.19 | 3.9 | 136.15 | 14.00 | 14.7 |
| Median | 72.50 | 70.25 | 1.75 | 6.1 | 86.00 | 4.00 | 8.7 |
| Minimum | | | | | | | |
| Maximum | | | | | | | |
| p-value | | | .124 | .344 | | .105 | .070 |

For individual patients, 10 patients (77%) had any increase in Plt at Month 12. By the sponsor's response definition (see Study 918-003, Efficacy Results: Platelet Count section), for the 13 patients who had available Plt data at Month 12, 9 patients had NR (69%), no patient had MR, and 4 patients had GR (31%).

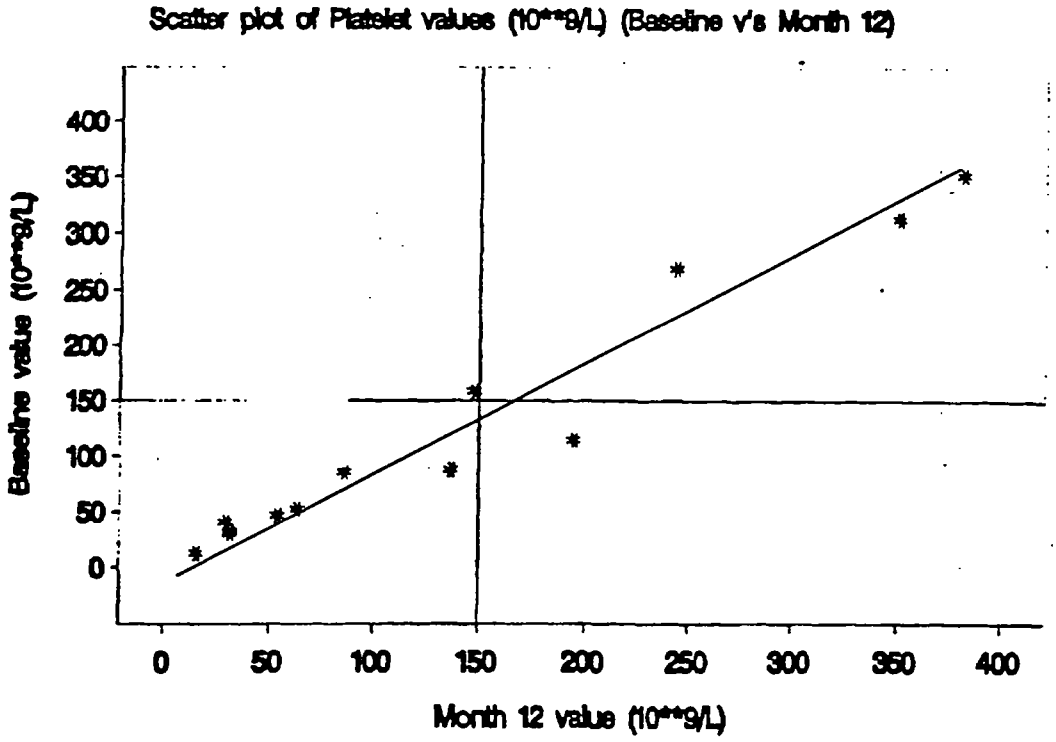
Individual patient results at Baseline, Month 6, and Month 12 are summarized in the following table and in the following figure [Figure electronically scanned and reproduced from: Oxford Glycosciences (UK) Ltd, NDA #21-348, Volume 2.13, page 53, dated 02-Aug-2001]

**Table 91: 918-003X Change from Baseline in Platelet Counts, Individual Patient Data**

| Patient Number | Baseline* | Month 6 | | | Month 12 | | |
|---|---|---|---|---|---|---|---|
| | ($10^9$/L) | $10^9$/L | Change ($10^9$/L) | % Change | $10^9$/L | Change ($10^9$/L) | % Change |
| 101 | 52.0 | 58.5 | 6.5 | 12.5 | 63.0 | 11.0 | 21.2 |
| 102 | 351.5 | 333.0 | -18.5 | -5.3 | 382.0 | 30.5 | 8.7 |
| 103 | 157.5 | 159.5 | 2.0 | 1.3 | 148.0 | -9.5 | -6.0 |
| 104 | 269.0 | 304.5 | 35.5 | 13.2 | 244.0 | -25.0 | -9.3 |
| 106 | 312.5 | 367.5 | 55.0 | 17.6 | 351.0 | 38.5 | 12.3 |
| 107 | 87.0 | 106.5 | 19.5 | 22.4 | 137.0 | 50.0 | 57.5 |
| 110 | 114.0 | 151.0 | 37.0 | 32.5 | 195.0 | 81.0 | 71.1 |
| 111 | 85.0 | 76.0 | -9.0 | -10.6 | 86.0 | 1.0 | 1.2 |
| 112 | 156.0 | 175.5 | 19.5 | 12.5 | - | - | - |
| 201 | 31.5 | 33.0 | 1.5 | 4.8 | 32.0 | 0.5 | 1.6 |
| 203 | 30.0 | 30.5 | 0.5 | 1.7 | 32.0 | 2.0 | 6.7 |
| 204 | 60.0 | 64.5 | 4.5 | 7.5 | - | - | - |
| 205 | 12.0 | 13.5 | 1.5 | 12.5 | 16.0 | 4.0 | 33.3 |
| 206 | 40.0 | 33.5 | -6.5 | -16.3 | 30.0 | -10.0 | -25.0 |
| 207 | 46.0 | 35.0 | -11.0 | -23.9 | 54.0 | 8.0 | 17.4 |
| 208 | 34.0 | 27.0 | -7.0 | -20.6 | - | - | - |

*LLN 150 X $10^9$/L
Baseline <150 X $10^9$/L

**Figure 18: 918-003X Scatter Plot of Platelet Values, Baseline vs Month 12**



Plt responses were further evaluated by Baseline Plt value. Nine (9) patients had a Baseline Plt <150 $X10^9$/L and 4 patients had a Baseline Plt ≥150 $X10^9$/L. Patients with Baseline Plt <150 $X10^9$/L had a numerically greater mean increase in Plt from Baseline to Month 12; however, neither subgroup had a statistically significant increase in Plt. It should be noted that the number of patients with Baseline Plt ≥150 $X10^9$/L was small. Mean change from Baseline to Month 6 and to Month 12 by Baseline Plt are summarized in the following table

**Table 92: 918-003X Mean Change in Platelet Count by Baseline Value (<150 $X10^9$/L vs ≥150 $X10^9$/L)**

| Change from Baseline | Platelet Count <150 $X10^9$/L | | Platelet Count ≥150 $X10^9$/L | |
|---|---|---|---|---|
| | Mean ($X10^9$/L) | p-value | Mean ($X10^9$/L) | p-value |
| Month 6 | n = 11<br>3.41 | p=.441 | n = 5<br>18.70 | p=.217 |
| Month 12 | n =9<br>16.39 | p=.134 | n = 4<br>8.63 | p=.614 |

### (v) Biochemical Markers of Gaucher Disease

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

### Chitotriosidase

There was a significant mean decrease in chitotriosidase from Baseline at Month 12 of -1984.0 nmol/ml.h (-15.3%). This result was also a numerically greater decrease from the Month 6 result. The results are summarized in the following table

**Table 93: 918-003X Chitotriosidase Statistics**

| | Baseline (nmol/ml.h) | Month 6 | | Month 12 | |
|---|---|---|---|---|---|
| | | Change (nmol/ml.h) | % Change | Change (nmol/ml.h) | % Change |
| n | 16 | 16 | 16 | 13 | 13 |
| Mean | 14292.6 | -512.4 | -8.2 | -1984.0 | -15.3 |
| Median | 9967.0 | -441.8 | -5.5 | -1118.0 | -12.4 |
| Minimum | | | | | |
| Maximum | | | | | |
| p-value | | 0.090 | 0.023 | .007 | .001 |

### Hexosaminidase

There was a significant mean decrease in hexosaminidase from Baseline at Month 12 of -308.9 nmol/ml.h (-13.1%). This result was also a numerically greater decrease from the Month 6 result. The results are summarized in the following table

Table 94: 918-003X Hexosaminidase Statistics

| | Baseline (nmol/ml.h) | Month 6 | | Month 12 | |
|---|---|---|---|---|---|
| | | Change (nmol/ml.h) | % Change | Change (nmol/ml.h) | % Change |
| n | 16 | 16 | 16 | 13 | 13 |
| Mean | 2024.1 | -164.2 | -6.1 | -308.9 | -13.1 |
| Median | 1743.3 | -62.0 | -4.0 | -140.5 | -12.1 |
| Minimum | | | | | |
| Maximum | | | | | |
| p-value | | .051 | .062 | .013 | .007 |

### (b) Secondary Efficacy Analysis

Secondary efficacy analyses included PK profiles, other disease assessments (such as bone density, fat fraction, pulmonary hypertension, and organ volume) at screening and Month 6; and QoL questionnaire. Exploratory analysis 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. Four (4) patients had at least one other disease assessment performed at Screening for whom follow-up results were available at Month 12. Four (4) patients underwent DEXA scans, which showed small decreases in z-scores from Baseline to Month 12 in all 4 patients. Two (2) patients underwent echocardiography, which showed no increase in T1 for either patient at Month 12.

### (c) Subgroup Analyses

Subgroup analyses were performed by:

- Baseline Hgb <11.5 g/dL vs. Hgb ≥11.5 g/dL (see Hemoglobin section above)
- Baseline Plt <150 $X10^9$/L vs. Plt ≥150 $X10^9$/L (Platelet Count section above)

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

There were statistically significant mean decreases in liver and spleen volumes from Baseline to Month 12. The mean percentage decrease in liver volume was similar to the mean percentage decrease seen at Month 6, with decreases at Month 6 of –6.8% and at Month 12 of –6.2%. The mean percentage decrease in spleen volume at Month 12 was greater than at Month 6 suggesting a progressive decrease in spleen volume over the 12 months of the study. Mean spleen volume decreased from Baseline at Month 6 by –4.5%, and at Month 12 by –10.1%. One patient (#110), was found to have a marked increase in spleen volume at Month 12, and was subsequently diagnosed with B-cell lymphoma of the stomach and spleen. There were no significant mean increases in Hgb or Plt at Month 6 or Month 12. Mean actual change from Baseline at Month 6 was –0.12 g/dL, and at Month 12 was +0.06 g/dL. On subgroup analysis, however, there was a significant increase in mean Hgb at Month 12 only for patients with Baseline Hgb of <11.5 g/dL. Patients with Baseline Hgb <11.5 g/dL had a mean actual increase of 0.863 g/dL at Month 12, whereas patients with Baseline Hgb ≥11.5 g/dL had a mean actual decrease of –0.30 g/dL. Mean Plt results showed a non-significant, progressive mean increase ($X10^9$/L) from Baseline at Month 6 of 8.19, and at Month 12 of 14.7.

The biochemical markers of Gaucher disease, chitotriosidase and hexosaminidase, showed progressive decreases from Baseline at Month 6 and Month 12, which were significant only at Month 12 for both markers (at Month 12 chitotriosidase –15.3%, hexosaminidase –13.1%). Four (4) patients had other disease assessments performed at screening and Month 12. DEXA scans in these 4 patients showed small decreases in z-scores. Two (2) patients underwent echocardiography, neither of whom showed an increase in T1.

## 5) Protocol 918-004

### a) Study Design for Protocol 918-004

#### (1) Study Design

Protocol 918-004 "A phase II, randomisation study of open-label OGT 918 and Cerezyme given as monotherapy or combination therapy in adult patients with type I Gaucher disease" was a comparative, open-label study conducted at a single international site. The study evaluated the efficacy and safety of OGT 918 100 mg TID monotherapy, OGT 918 100 mg TID in combination with Cerezyme, and Cerezyme alone for up to 6 months in 36 adult type I Gaucher disease patients. Patients must have been receiving ERT for a minimum of 2 years prior to entry.

#### (2) Study Objectives

The primary objective was to assess the tolerability of OGT 918 and Cerezyme in combination compared to either agent alone. The secondary objectives were to assess the PK profiles of OGT 918 and Cerezyme when given in combination, and to compare organ volume measurements and other markers of Gaucher disease between monotherapy and combination therapy.

#### (3) Eligibility Criteria

##### (a) Inclusion Criteria

Patients were eligible if they:

- Had type I Gaucher disease (confirmed by a glucocerebrosidase assay)
- Had been receiving continuous Ceredase or Cerezyme therapy for a minimum of 2 years prior to screening and had received their current dose for a minimum of 6 months
- Were 18 years of age or older at the time of consent

##### (b) Exclusion Criteria

Patients were ineligible if they:

- Were fertile patients who did not agree to use adequate contraception throughout the study and for 3 months after cessation of OGT 918 treatment
- Were pregnant or breast-feeding
- Had a history of significant lactose intolerance
- 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 or who had a history of significant gastrointestinal disorders
- Had a history of cataracts or a known increased risk of cataract formation
- Were currently undergoing therapy with other investigational agents
- Had an intercurrent medical condition that would render them unsuitable for study
- Were known to have tested positive for HIV or hepatitis B surface antigen
- 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 95: 918-004 Study Visits and Procedures

| | Screen | Treatment Period | | | | | | | | Withdrawal/FU |
|---|---|---|---|---|---|---|---|---|---|---|
| **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 | | | | | | | | | |
| Weight | X | X | | X | X | X | X | X | X | X |
| ECG | X | | | X | | | | | X | X* |
| EMG | | | | X | | | | | | |
| Pregnancy Test | X | | | | | | | | | |
| Urinalysis | 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 profiles | | | | X | | | | | | |
| Organ Volume | X | | | | | | | | X | X* |
| Other Disease Assessments | X | X | | X | | X | | | X | X* |
| Plasma Storage | X | X | | X | X | X | X | X | X | X* |
| Proteome | | X | | | | | | | X | X* |
| QoL Questionnaires | | X | | | | 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 | | |

*No need to perform if performed at Month 6 Visit, or if patient continued in the extension study

A protocol amendment for the addition of an EMG assessment for all patients at Month 1 was submitted in Feb-2000 after reports of tremor and peripheral neuropathy were noted in the other OGT 918 studies.

#### (a) Screening Visit

All patients gave written informed consent before any study procedures or assessments were performed. The Screening Visit took place up to 4 weeks prior to the Day 1 Visit. 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 [temperature, blood pressure (BP), respiratory rate (RR), and heart rate]
- Height
- Weight
- ECG
- Urine pregnancy test (females only)
- Urinalysis
- Biochemistry
- Hematology

- Organ Volume assessment (by MRI or CT scan)
- Other Disease Assessments (depending on patient's disease status and normal clinical practice at the center, may include skeletal response assessed by an MRI of the femur, pelvis, lumbar spine or hips and DEXA of the femur and lumbar spine, and fat fraction by QCSI of the bone marrow in the lumbar spine)
- Plasma sample for storage (used to measure levels of chitotriosidase and hexosaminidase as markers of disease activity)
- Concomitant Medications record

**(b) Day 1 Visit**

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

- Weight
- Biochemistry
- Hematology
- Other Disease Assessments
- Plasma sample for storage
- Proteome (research tool involving high throughput, multidimensional protein separation followed by mass spectrometry for identification proteins that may be associated with Gaucher disease)
- Quality of Life (QoL) questionnaires (SF-36 Health Questionnaire (8) plus a health distress survey, a symptom survey and a treatment evaluation survey)
- Adverse Event (AE) assessment
- Concomitant Medications update

**(c) Day 8 to 15 Visit**

At the Day 8 to 15 Visit (which could be performed by telephone contact or clinic 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
- EMG (standard EMG and NCV)
- Urinalysis
- Biochemistry
- Hematology
- PK profiles (in 18 patients - the first 6 patients in each treatment group)
- Other Disease Assessments
- Plasma sample for storage
- AE assessment

- Concomitant Medications update

**(e) Day 57 (Month 2) Visit**

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

- Weight
- Biochemistry
- Hematology
- Plasma sample for storage
- 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
- Other Disease Assessments
- Plasma sample for storage
- QoL questionnaires
- AE assessment
- Concomitant Medications update

**(g) Day 113 (Month 4) Visit**

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

- Weight
- Biochemistry
- Hematology
- Plasma sample for storage
- AE assessment
- Concomitant Medications update

**(h) Day 141 (Month 5) Visit**

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

- Weight
- Biochemistry
- Hematology
- Plasma sample for storage
- 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
- Weight
- ECG
- Urinalysis
- Biochemistry
- Hematology
- Organ Volume assessment
- Other Disease assessments
- Plasma sample for storage
- Proteome sample
- QoL questionnaires
- AE assessment
- Concomitant Medications update

**(j) Follow-Up/Withdrawal Visit**

The Follow-up/Withdrawal Visit was to occur 4 weeks after completion or withdrawal from the study. Patients underwent the following assessments:

- Physical examination (including slit lamp exam)*
- Vital signs
- Weight
- ECG*
- Urinalysis
- Biochemistry
- Hematology
- Organ Volume assessment*
- Other Disease assessments*
- Plasma sample for storage*
- Proteome sample*
- QoL questionnaires*
- AE assessment
- Concomitant Medications update

* No need to perform if performed at the Month 6/Day 169 Visit or if patient continued in the extended treatment period (Protocol 918-004X)

**(5) Study Medication Dispensing and Compliance**

Patients randomized to one of the OGT 918 arms of the study received OGT 918 at a starting dose of 100 mg TID. The dose of OGT 918 could be reduced to 100 mg BID if the patient experienced any side effects associated with OGT 918. Patients randomized

to one of the Cerezyme arms of the study continued to receive their current dose of Cerezyme for the 6-month study period.

OGT 918 was supplied as 50 mg or 100 mg gelatin capsules for oral administration. As this was an open-label study, blinding was not performed. The administration of dummy infusions of Cerezyme was considered impractical and unethical, and due to the high incidence of diarrhea observed in previous clinical trials of OGT 918, any attempt at blinding of oral medication was thought likely to have been ineffective. OGT 918 was dispensed as a 1 month supply at a time. OGT 918 was taken three times a day at regular intervals, either two hours before or two hours after eating. Patients were advised to avoid high carbohydrate content food, and dietary recommendations were issued to all participants.

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

**(6) Efficacy and Endpoint Measures**

The study was designed to compare the tolerability and pharmacokinetics of OGT 918 and Cerezyme both individually and as a combination therapy. Amendment 1 (29-Feb-2000) introduced percentage change in liver organ volume as the primary efficacy endpoint.

**(a) Primary Efficacy Parameter**

The primary efficacy parameter for the study was the percentage change from Baseline to Month 6 in liver volume. The other primary analysis of the study was to assess the tolerability of Cerezyme and OGT 918 when given in combination.

**(b) Secondary Efficacy Parameters**

The secondary efficacy parameters for the study were:

- Absolute change from Baseline in liver volume
- Absolute and percentage change from Baseline in spleen volume
- Absolute and percentage change from Baseline in hemoglobin, platelets, chitotriosidase, hexosaminidase, acid phosphatase, ACE, AST and ALT
- Response in liver and spleen volumes and response in platelet and hemoglobin values
- Absolute and percentage change in weight

The other secondary analysis included PK profiles in the first 6 patients in each treatment group (18 patients) performed at Month 1.

Organ volumes for both primary and secondary efficacy parameters were determined at Screening and at the 6 Month visits by MRI or CT scan (following the normal clinical practice of the study center).

**(c) Safety Assessments**

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

**(d) Study Population**

The efficacy population was defined as all patients who received at least one dose of study medication, and had a screening value and at least one Month 6 value for either liver or spleen volume, hemoglobin, or platelets. The safety population was defined as all patients who received at least one dose of study medication.

**b) Results**

Thirty-seven (37) patients were screened at one study site, and 36 patients entered the study. Of the 36 patients who entered the study, 33 patients comprised the efficacy population, and 33 patients completed the study. All patients were screened, entered, and treated between 22-Dec-1999 and 10-Sept-2000

**(1) Baseline Characteristics and Demographics**

Overall, 44% of patients were male, and 92% were Ashkenzai Jews. Patient ages ranged from 17 to 69 years of age, with a mean age of 37.2 years. There were imbalances between the treatment groups for gender (with 42%, 50%, and 83% of patients being male in the OGT 918 alone, Cerezyme alone, and combination treatment groups respectively). The treatment groups were otherwise relatively well-balanced by baseline characteristics. The patients' baseline medical histories were notable for:

- Baseline body system abnormalities most frequently reported were in the musculoskeletal body system [21 patients (58%)], genitourinary [17 patients (47%)], and "other" body systems [16 patients (44%)].
- 33 patients (92%) noted at least one concurrent illness at screening. The most frequently noted concurrent illnesses were headache [7 patients (19%)] and disorders of lipoprotein metabolism and other lipidemias [6 patients each (17%)].
- 23 patients (64%) had undergone surgery for Gaucher disease, and 11 patients (31%) were splenectomized.
- Physical examination abnormalities at baseline by organ system were most frequently noted in the GI system [33 patients (94%)], dermatologic system in 31 patients (86%), eye abnormalities in 26 patients (72%), and cardiovascular and musculoskeletal systems in 6 patients each (33%).
- 7 patients overall reported Neurologic problems at baseline by Medical History (including migraines, extrapyramidal and movement disorders, sleep disorders, epilepsy, and other degenerative disease of nervous system NEC).
- 26 patients (72%) reported taking at least one concomitant medication at screening. The most frequently reported medications overall, at screening, were heparin sodium taken by 11 patients (31%) [used to flush the catheters for Cerezyme administration], and cyanocobalamin used by 6 patients (17%).
- Baseline liver volumes ranged from 0.9 to 7.5 X normal for all patients, and spleen volumes ranged from 1.3 to 11.8 X normal for all patients.

The baseline characteristics and demographic data for all enrolled patients, overall and by treatment group, are summarized in the following table

**Table 96: 918-004 Baseline Characteristics and Demographics**

| | All | OGT 918 | Cerezyme | OGT 918 + Cerezyme |
|---|---|---|---|---|
| **Enrolled Patients, n =** | 36 | 12 | 12 | 12 |
| **Demographic Measure** | | | | |
| **Gender, n (%)** | 36 | 12 | 12 | 12 |
| Male | 16 (44) | 5 (42) | 6 (50) | 10 (83) |
| Female | 20 (56) | 7 (58) | 6 (50) | 2 (17) |
| **Age (years), n =** | 36 | 12 | 12 | 12 |
| Mean | 37.2 | 34.6 | 40.4 | 37.2 |
| Min, max | 17-69 | 18-49 | 19-69 | 17-55 |
| **Race, n(%)** | 36 | 12 | 12 | 12 |
| Ashkenazi Jew | 33 (92) | 11 (92) | 12 (100) | 10 (83) |
| Other | 3 (8) | 1 (8) | 0 | 2 (17) |
| **Mean BMI ($kg/M^2$), n =** | 36 | 12 | 12 | 12 |
| Mean | 23.92 | 22.83 | 24.47 | 24.47 |
| Min, max | | | | |
| **Liver Organ Volume (l), n =** | 35 | 12 | 12 | 11 |
| Mean | 1.74 | 1.53 | 1.81 | 1.91 |
| Min, max | | | | |
| **Spleen Organ Volume (l), n =** | 24 | 8 | 9 | 7 |
| Mean | 0.71 | 0.63 | 0.74 | 0.76 |
| Min, max | | | | |
| **Hemoglobin (g/dL)*, n =** | 36 | 12 | 12 | 12 |
| Mean | 12.71 | 12.49 | 13.18 | 12.46 |
| Min, max | | | | |
| **Platelets ($X10^9/l$)**, n =** | 36 | 12 | 12 | 12 |
| Mean | 166.57 | 173.04 | 165.75 | 160.92 |
| Min, max | | | | |

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

In addition, it should be noted that patients entered into Study 918-004 represented a different patient population than those entered in the 918-001 and 918-003 studies. Patients entered into the 918-004 study had been receiving ERT for a minimum of 2 years. Their mean liver and spleen volumes were smaller and their mean Hgb and Plt values were higher at Baseline than those of patients in Studies 918-001 and 918-003. These findings are important, as the magnitude of response to treatment would depend on the patient's ability to respond. That is, patients with larger liver and spleen volumes, and lower Hgb and Plt values (implying more Gaucher cell disposition) would be expected to have a better response to treatment than patients with smaller liver and spleen volumes and higher Hgb and Plt values at Baseline. Patient Disposition [Please refer to Efficacy Conclusions on Review of NDA 21-348 section VI.D. for table summarizing comparisons of baseline differences across the studies].

### (a) Screening and Randomization

The number of screen failures was low as, given the nature of the disease and the familiarity of the patients to the study center, the study Investigator was aware of the patient's status prior to screening. There was one screen failure patient, who was not entered secondary to not meeting age eligibility requirements (patient was under 18 years of age).

### (b) Dropouts

Of the 36 patients entered in the study, 33 patients competed 6 months of the study. Three (3) patients (8%) withdrew prior to study completion. The most common reasons for study discontinuation were due to an AE and at the request of the patient. The reasons for study discontinuation by treatment group are summarized in the following table

**Table 97: 918-004 Patients Discontinued**

| | | Treatment | | |
|---|---|---|---|---|
| | **All** | **OGT 918** | **Cerezyme** | **OGT 918 + Cerezyme** |
| **Enrolled Patients, n =** | 36 | 12 | 12 | 12 |
| Number of Withdrawals, n (%) | 3 (8) | 2 (17) | 0 | 1 (8) |
| **Reason for Dropout*** | | | | |
| Adverse Event, n (%) | 3 (8) | 2 (17) | 0 | 1 (8) |
| Subject Request, n (%) | 3 (8) | 2 (17) | 0 | 1 (8) |
| Investigator Request, n (%) | 1 (3) | 1 (8) | 0 | 0 |

*Patient may have reported more than one reason for withdrawal

Of the 3 patients who withdrew, all 3 withdrew prior to the Month 6 Visit [2 patients withdrew between Weeks 4 and 13, and 1 patient withdrew after Week 13]. Two (2) of these patients were in the OGT 918 alone treatment group, and 1 was in the combination treatment group. No patient withdrew from the Cerezyme alone group. This is not unexpected, however, as patients must have been on Cerezyme for at least 2 years, and therefore tolerant of Cerezyme therapy prior to study entry.

There were no serious protocol violations; however, 1 patient (#135) was 17 years of age at the time of screening. No study procedures were performed and consent was not taken from this patient until the patient was 18 years of age.

### (2) Concomitant Medication

All 36 patients reported taking at least one concomitant medication at any time during the study. A large number of different medications were used during the study (over 100 different WHO preferred term medications were reported), the majority of which were used by a small number of patients (use reported by $\leq$2 patients). The most commonly reported medications used during the study were paracetamol, used by 16 patients overall (44%), and loperamide hydrocholoride, used by 13 patients (36%) overall. The Cerezyme-alone group took less loperamide [1 patient (8%)] during the study than the OGT 918-alone and the combination groups [6 patients each (50%)]. Loperamide was

taken specifically to control diarrhea. GI medications of any kind (including loperamide) were also used more commonly in the OGT 918 groups than in the Cerezyme group. The most commonly used concomitant medications (≥3 patients or ≥8% of patients) are summarized in the following table

**Table 98: 918-004 Most Common (≥3 Patients) Concomitant Medications**

| Treatment | All | OGT 918 | Cerezyme | OGT 918 + Cerezyme |
|---|---|---|---|---|
| Randomized Patients, n = | 36 | 12 | 12 | 12 |
| Medication | n (%) | n (%) | n (%) | n (%) |
| Paracetamol | 16 (44) | 5 (42) | 2 (17) | 9 (75) |
| Loperamide | 13 (36) | 6 (50) | 1 (8) | 6 (50) |
| Heparin | 11 (31) | 3 (25) | 4 (33) | 4 (33) |
| Cyanocobalamin | 7 (19) | 3 (25) | 2 (17) | 2 (17) |
| Metamizole | 7 (19) | 3 (25) | 2 (17) | 2 (17) |
| Diclofenac | 5 (14) | 1 (8) | 2 (17) | 2 (17) |
| Herbal Preparation | 4 (11) | 1 (8) | 1 (8) | 2 (17) |
| Ibuprofen | 4 (11) | 1 (8) | 1 (8) | 2 (17) |
| Calcium | 3 (8) | 2 (17) | 1 (8) | 0 |
| Estradiol | 3 (8) | 0 | 3 (25) | 0 |
| Femodene | 3 (8) | 1 (8) | 1 (8) | 1 (8) |
| Multivitamins | 3 (8) | 2 (17) | 0 | 1 (8) |
| Naproxen | 3 (8) | 1 (8) | 2 (17) | 0 |

### (3) Patient Compliance

The sponsor defined non-compliance as missing more than 5 capsules of study medication per month. By this definition, overall patients 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.

### (4) Efficacy Results

### (a) Primary Efficacy Analysis

The sponsor's primary efficacy variable was percentage change from Baseline to Month 6 in liver volume.

### (i) Liver Volume

Thirty-two (32) of the 36 patients entered in the study had liver volume data available at Month 6. Overall, there was a non-significant mean percent reduction in liver volume from Baseline to Month 6 in the OGT 918 alone group of –2.9% (p-value .277), a non-significant increase in the Cerezyme alone group of 3.5% (p-value .219), and a non-significant decrease in the Combination group of –4.9% (p-value .057). When the groups were compared, there was a significant difference of –8.4% between the Combination group and the Cerezyme group with respect to percentage change in liver volume (ANCOVA p=.047), but no significant difference between the OGT 918 group and the

Cerezyme group, and between the Combination group and OGT 918 group. The results are summarized in the following table

Table 99: 918-004 Liver Volume Statistics

| | | | Month 6 | | |
|---|---|---|---|---|---|
| Treatment | Statistic | Baseline (L) | Month 6 (L) | Change (L) | % Change |
| OGT 918 | n | 10 | 10 | 10 | 10 |
| | Mean | 1.58 | 1.54 | -.047 | -2.9 |
| | Median | 1.58 | 1.5 | -.05 | -3.1 |
| | Minimum | | | | |
| | Maximum | | | | |
| | p-value | | | .253 | .277 |
| Cerezyme | n | 12 | 11 | 11 | 11 |
| | Mean | 1.81 | 1.85 | .035 | 3.5 |
| | Median | 1.74 | 1.80 | .03 | 2.0 |
| | Minimum | | | | |
| | Maximum | | | | |
| | p-value | | | .470 | .219 |
| Combination | n | 10 | 9 | 9 | 9 |
| | Mean | 1.97 | 1.92 | -.087 | -4.9 |
| | Median | 1.97 | 1.94 | -.05 | -2.7 |
| | Minimum | | | | |
| | Maximum | | | | |
| | p-value | | | .068 | .057 |

Individual patient results at Baseline and Month 6, by treatment group, are depicted graphically in the following figures [Figures electronically scanned and reproduced from: Oxford Glycosciences (UK) Ltd, NDA #21-348, Volume 2.16, pages 54-55, dated 02-Aug-2001].

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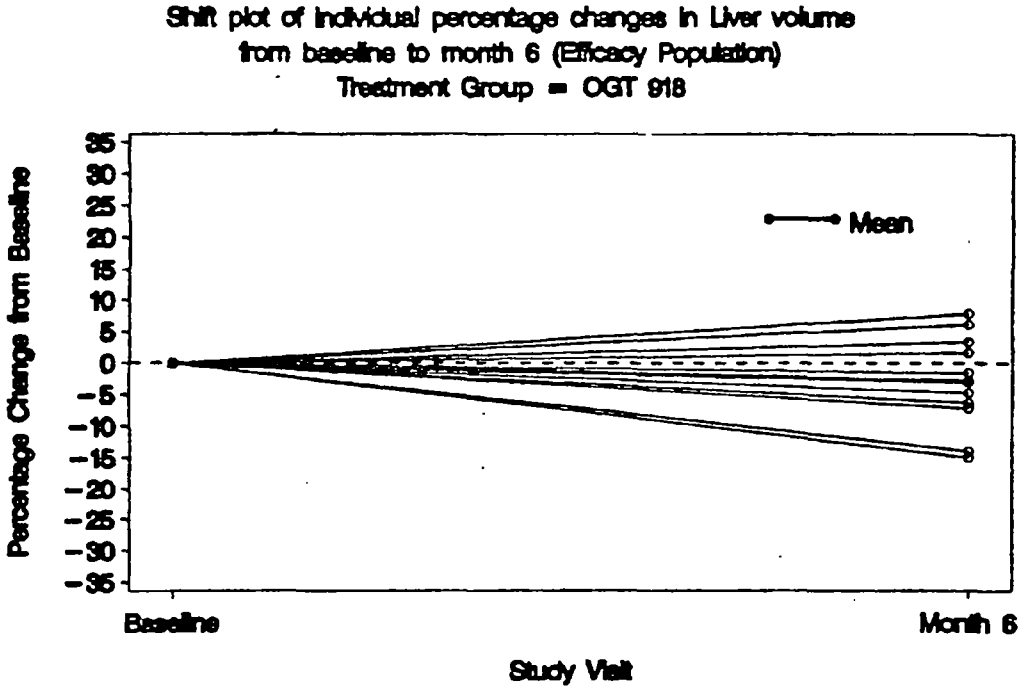
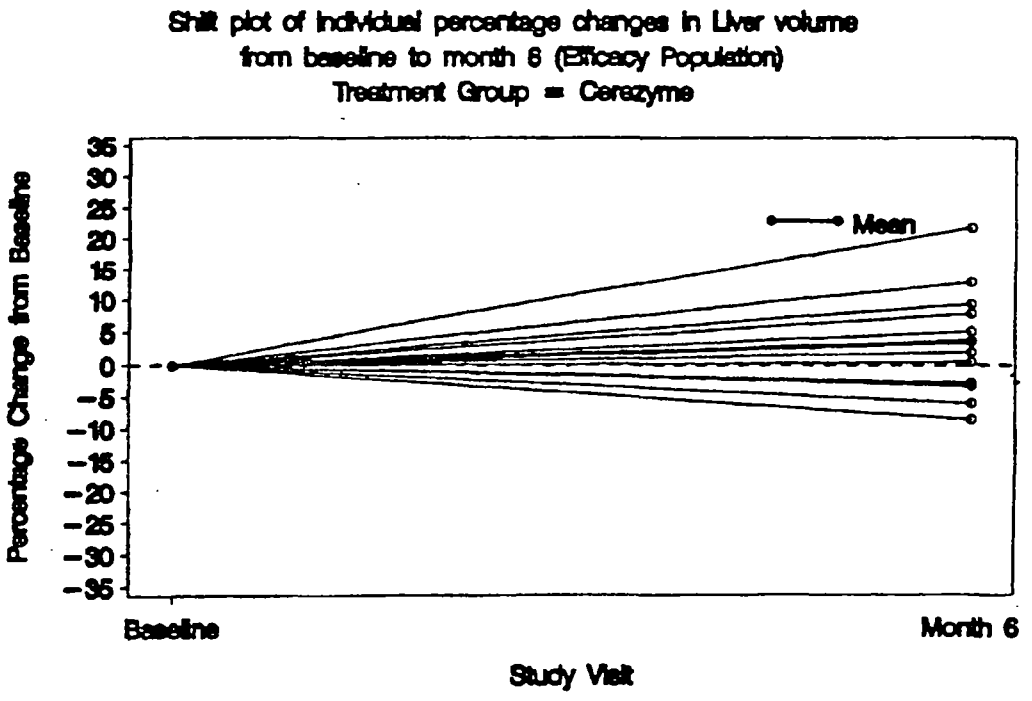
## OGT 918 Group

**Figure 19: 918-004 % Change from Baseline in Liver Volume, OGT 918 Alone Group**



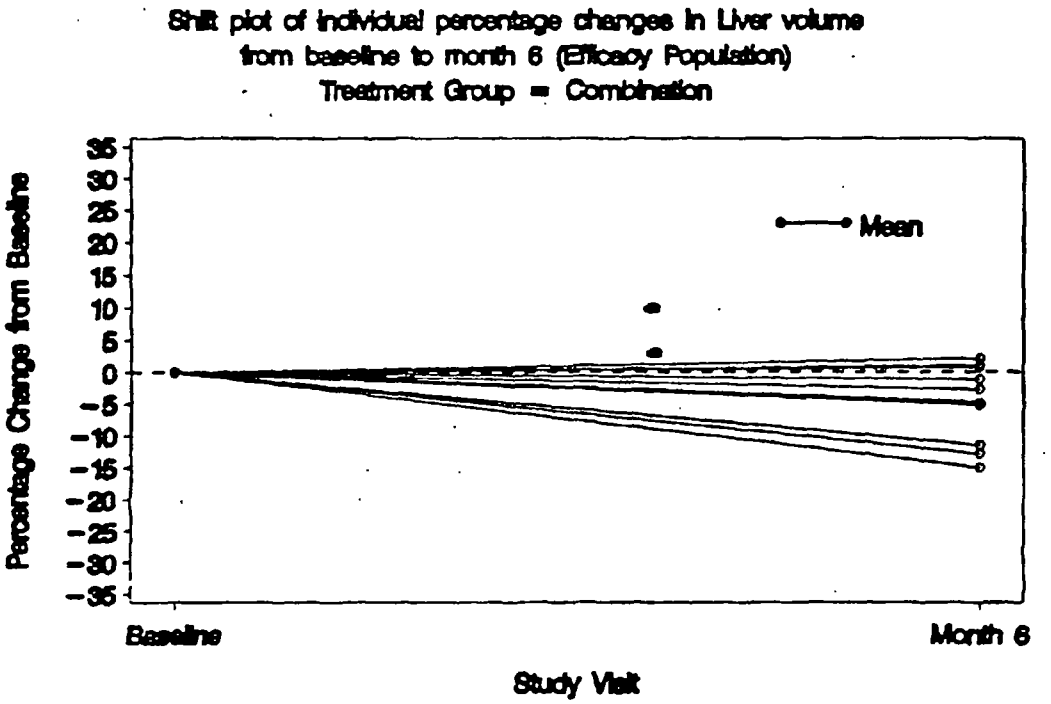

## Cerezyme Group

**Figure 20: 918-004 % Change from Baseline in Liver Volume, Cerezyme Alone Group**



Combination Group

Figure 21: 918-004 % Change from Baseline in Liver Volume, Combination Group




(b) Secondary Efficacy Analysis

(i) Spleen Volume

Twenty-three (23) of the 36 patients had spleen volume data available at Month 6. Overall, there were non-significant mean percent reductions in spleen volume from Baseline to Month 6 in the OGT 918 group of -4.8% (p=.156), the Cerezyme group of -2.1% (p=.249), and the Combination group of -8.5% (p=.253). None of the pairwise comparisons between the 3 treatment groups were statistically significant. The results are summarized in the following table

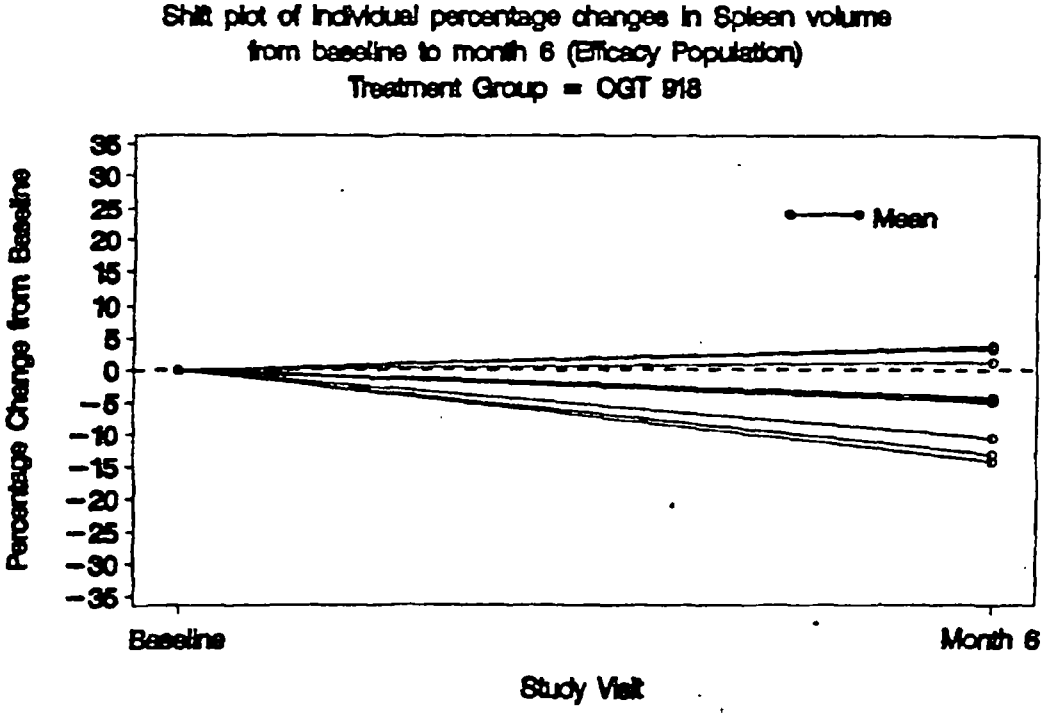
Table 100: 918-004 Spleen Volume Statistics

| Treatment | Statistic | Baseline (L) | Month 6 (L) | Month 6 Change (L) | Month 6 % Change |
|---|---|---|---|---|---|
| OGT 918 | n | 7 | 7 | 7 | 7 |
| | Mean | .69 | .66 | -.027 | -4.8 |
| | Median | .65 | .56 | -.01 | -4.2 |
| | Minimum | | | | |
| | Maximum | | | | |
| | p-value | | | .310 | .156 |
| Cerezyme | n | 9 | 8 | 8 | 8 |
| | Mean | .74 | .59 | -.023 | -2.1 |
| | Median | .62 | .53 | -.01 | -2.1 |
| | Minimum | | | | |
| | Maximum | | | | |
| | p-value | | | .283 | .249 |
| Combination | n | 7 | 7 | 7 | 7 |
| | Mean | .76 | .67 | -.082 | -8.5 |
| | Median | .95 | .66 | -.06 | -12.3 |
| | Minimum | | | | |
| | Maximum | | | | |
| | p-value | | | .139 | .253 |

Individual patient results at Baseline and Month 6, by treatment group, are depicted graphically in the following figures [Figures electronically scanned and reproduced from: Oxford Glycosciences (UK) Ltd, NDA #21-348, Volume 2.16, pages 57-58, dated 02-Aug-2001].

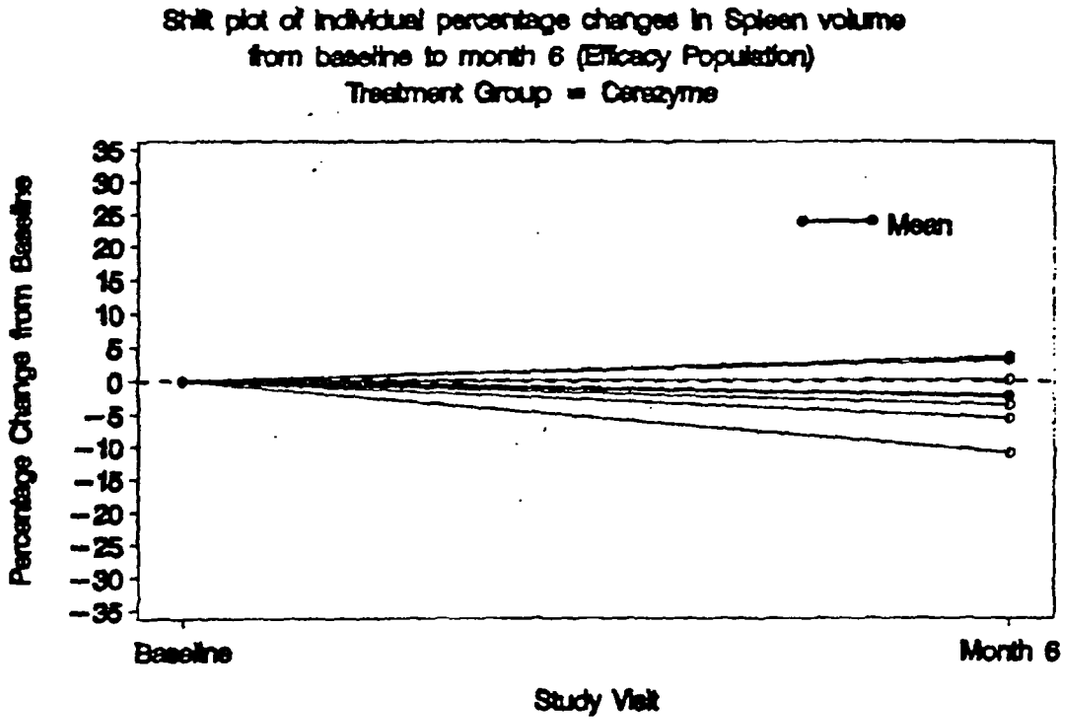
## OGT 918 Group

Figure 22: 918-004 % Change from Baseline in Spleen Volume, OGT 918 Group



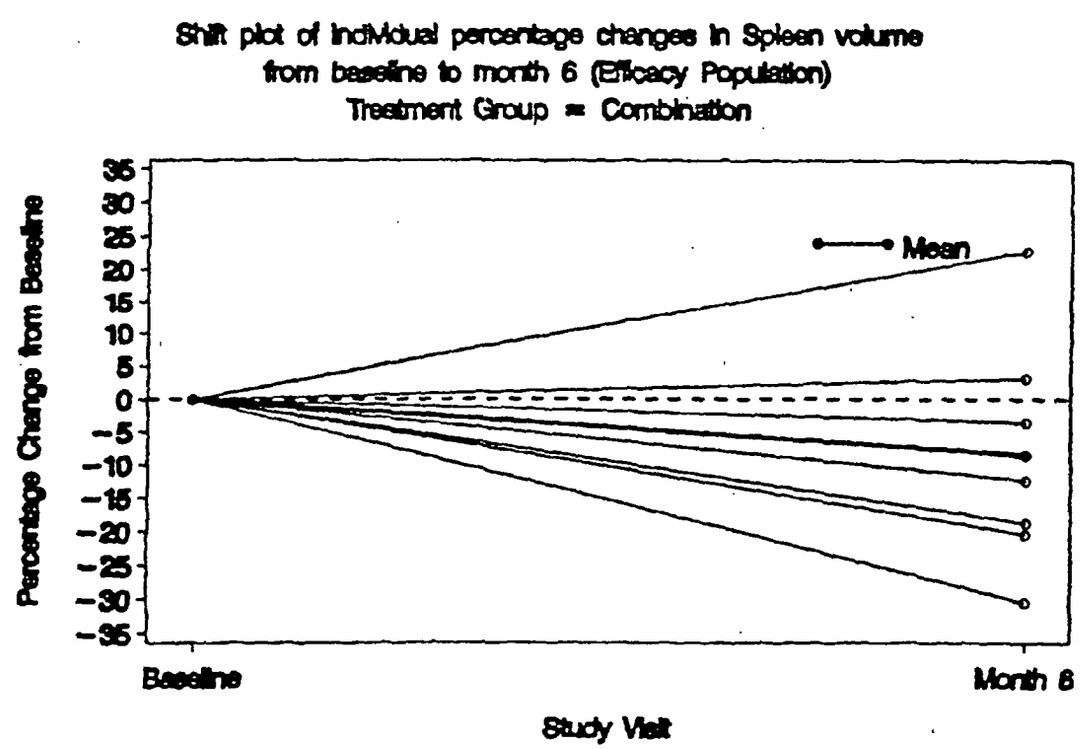
## Cerezyme Group

**Figure 23: 918-004 % Change from Baseline in Spleen Volume, Cerezyme Group**




## Combination Group

**Figure 24: 918-004 % Change from Baseline in Spleen Volume, Combination Group**



### (ii) Hemoglobin

Thirty-three (33) of the 36 patients had Hgb data at Month 6. Overall there were non-significant mean reductions in Hgb from Baseline to Month 6 in the OGT 918 group of –0.31 g/dL (p=.109), the Cerezyme group of –0.15 g/dL (p=.212), and the Combination group of –0.095 g/dL (p=.670). None of the pairwise comparisons between the 3 treatment groups were significant. The results are summarized in the following table

**Table 101: 918-004 Hemoglobin Statistics**

| | | | Month 6 | | |
|---|---|---|---|---|---|
| Treatment | Statistic | Baseline (g/dL) | Month 6 (g/dL) | Change (g/dL) | % Change |
| OGT 918 | n | 10 | 10 | 10 | 10 |
| | Mean | 12.44 | 12.13 | -0.31 | -2.4 |
| | Median | 12.30 | 12.18 | -0.23 | -1.9 |
| | Minimum | | | | |
| | Maximum | | | | |
| | p-value | | | .109 | .101 |
| Cerezyme | n | 12 | 12 | 12 | 12 |
| | Mean | 13.18 | 13.03 | -0.15 | -1.2 |
| | Median | 12.88 | 12.68 | -0.03 | -0.2 |
| | Minimum | | | | |
| | Maximum | | | | |
| | p-value | | | .212 | .198 |
| Combination | n | 11 | 11 | 11 | 11 |
| | Mean | 12.38 | 12.29 | -0.095 | -0.5 |
| | Median | 11.65 | 12.55 | -0.10 | -0.7 |
| | Minimum | | | | |
| | Maximum | | | | |
| | p-value | | | 0.670 | .815 |

Individual patient results at Baseline and Month 6, by treatment group, are depicted graphically in the following figures [Figures electronically scanned and reproduced from: Oxford Glycosciences (UK) Ltd, NDA #21-348, Volume 2.16, pages 64-65, dated 02-Aug-2001].

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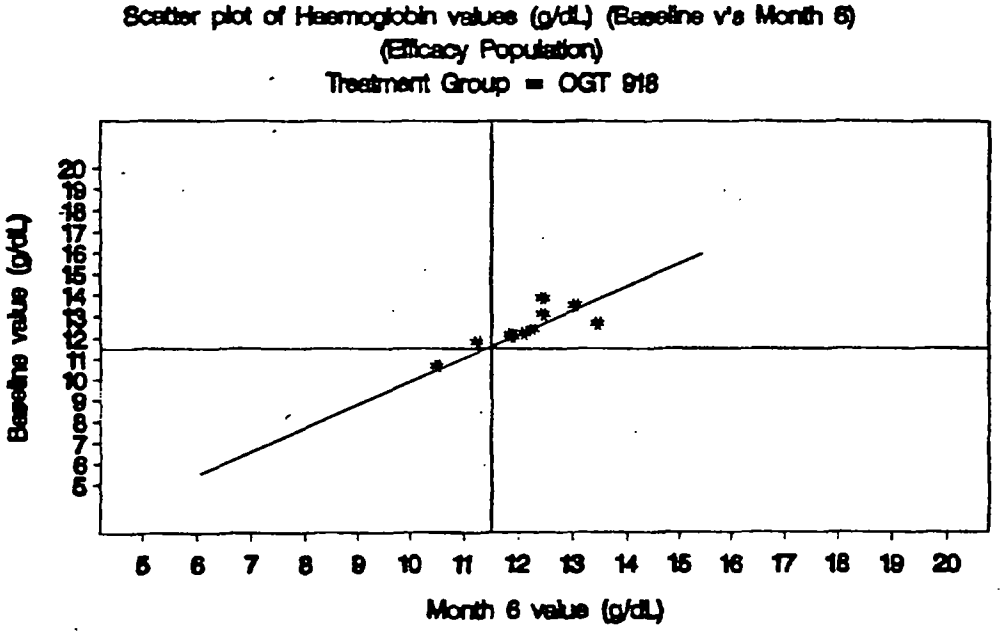
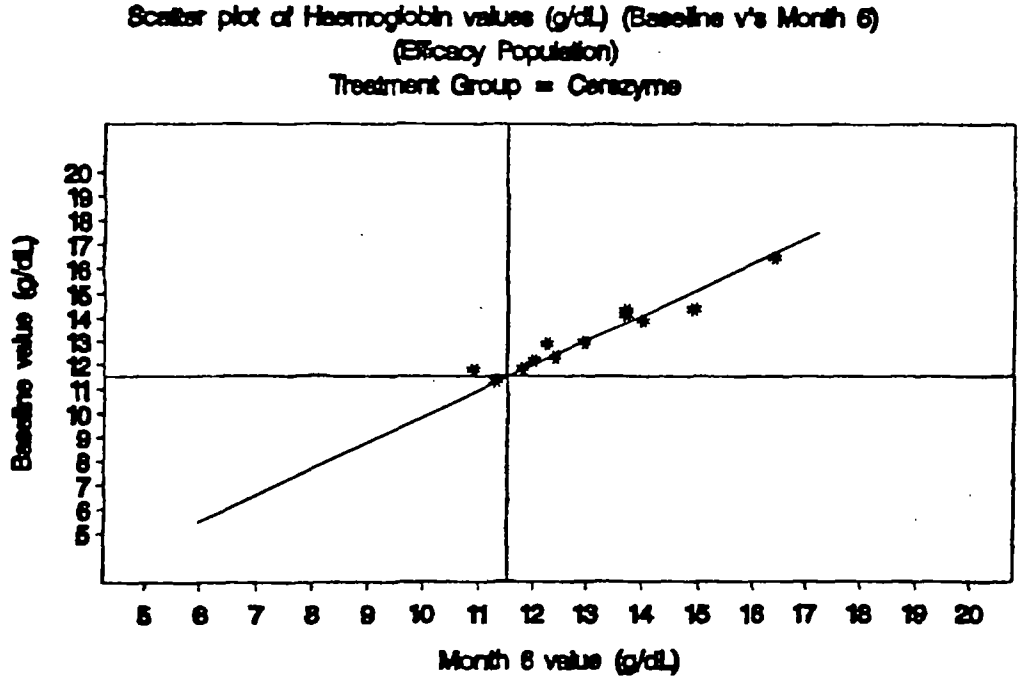
## OGT 918 Group

Figure 25: 918-004 Scatter Plot of Hemoglobin Values, Baseline vs Month 6, OGT 918 Group



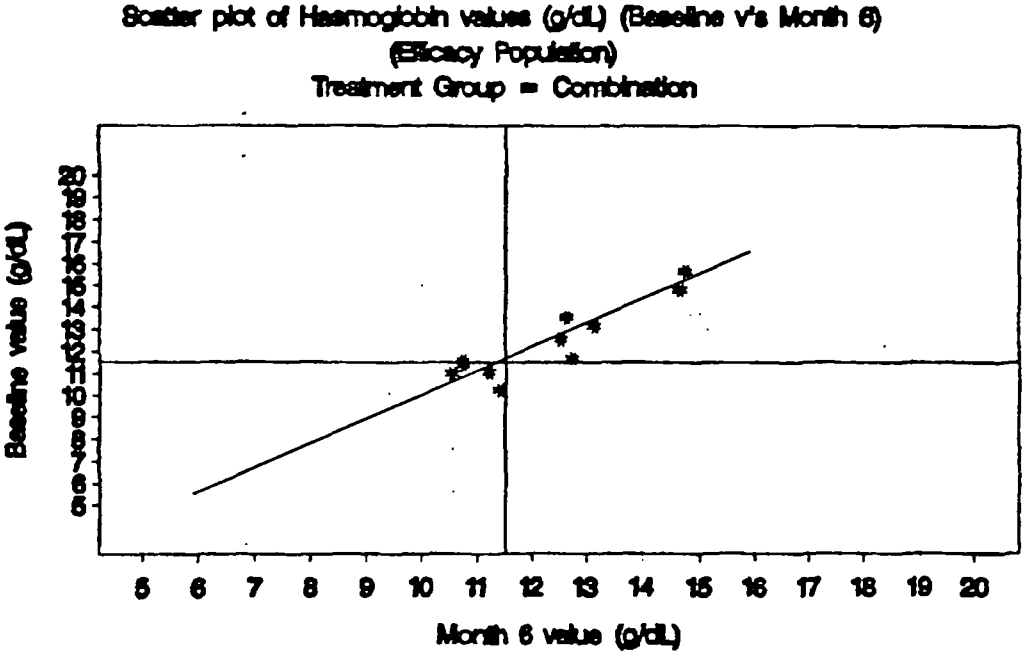

## Cerezyme Group

Figure 26: 918-004 Scatter Plot of Hemoglobin Values, Baseline vs Month 6, Cerezyme Group



## Combination Group

**Figure 27: 918-004 Scatter Plot of Hemoglobin Values, Baseline vs Month 6, Combination Group**




Hemoglobin responses were further evaluated by Baseline Hgb value. Six (6) patients had Baseline Hgb of <11.5 g/dL: 1 patient each in the OGT 918 and Cerezyme groups, and 4 patients in the Combination group. Mean changes from Baseline for these patients were –0.15 g/dL, 0.0 g/dL, and 0.09 g/dL for the OGT 918, Cerezyme, and Combination groups, respectively.

Twenty-seven (27) patients had Baseline Hgb of ≥11.5 g/dL: 9 patients in the OGT 918 group, 11 patients in the Cerezyme group, and 7 patients in the Combination group. Mean changes from Baseline for these patients were –0.328 g/dL, -0.164 g/dL, and –0.20 g/dL for the OGT 918, Cerezyme, and Combination groups, respectively.

The changes in Hgb were not notably different by subgroup, and as the number of patients with Baseline Hgb <11.5 g/dL was small, no conclusions will be drawn from this.

### (iii) Platelet Count

Thirty-three (33) of the 36 patients had Plt data at Month 6. For the Cerezyme and Combination groups, there were non-significant mean increases in Plt from Baseline to Month 6 of 15.29 $X10^9$/L (p=.068) and 2.73 $X10^9$/L (p=.798), respectively. The OGT 918 group had a non-significant mean decrease in Plt of –21.60 $X10^9$/L (p=.101) . For the pairwise comparisons, there was a significant difference of –34.42 between the OGT 918 and the Cerezyme group with respect to actual change in Plt (ANCOVA p=.028). There were no significant differences between the Combination group and the Cerezyme

group, and between the Combination group and the OGT 918 group. The results are summarized in the following table

**Table 102: 918-004 Platelet Statistics**

| | | | Month 6 | | |
|---|---|---|---|---|---|
| **Treatment** | **Statistic** | **Baseline ($X10^9$/L)** | **Month 6 ($X10^9$/L)** | **Change ($X10^9$/L)** | **% Change** |
| **OGT 918** | **n** | 10 | 10 | 10 | 10 |
| | **Mean** | 170.55 | 148.95 | -21.60 | -9.6 |
| | **Median** | 162.00 | 136.00 | -6.50 | -7.5 |
| | **Minimum** | | | | |
| | **Maximum** | | | | |
| | **p-value** | | | .101 | .073 |
| **Cerezyme** | **n** | 12 | 12 | 12 | 12 |
| | **Mean** | 165.75 | 181.04 | 15.29 | 10.1 |
| | **Median** | 164.00 | 165.50 | 2.25 | 1.9 |
| | **Minimum** | | | | |
| | **Maximum** | | | | |
| | **p-value** | | | .068 | .059 |
| **Combination** | **n** | 11 | 11 | 11 | 11 |
| | **Mean** | 152.14 | 154.86 | 2.73 | 3.2 |
| | **Median** | 145.50 | 151.00 | 5.50 | 3.8 |
| | **Minimum** | | | | |
| | **Maximum** | | | | |
| | **p-value** | | | .798 | .577 |

Individual patient results at Baseline and Month 6, by treatment group, are depicted graphically in the following figures [Figures electronically scanned and reproduced from: Oxford Glycosciences (UK) Ltd, NDA #21-348, Volume 2.16, pages 67-68, dated 02-Aug-2001].

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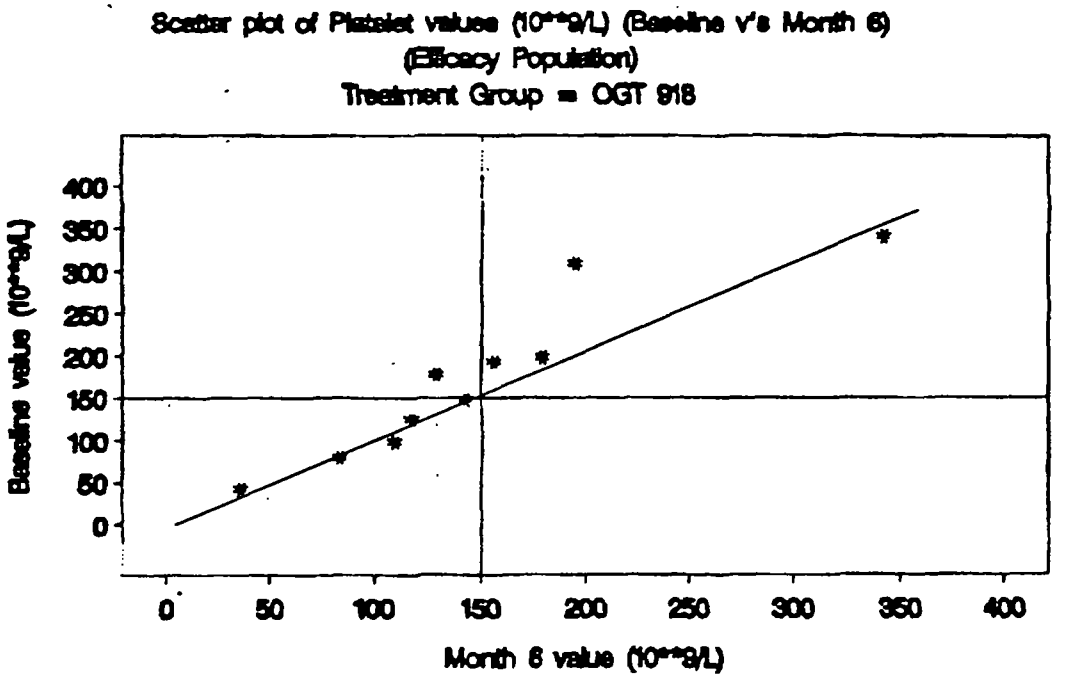
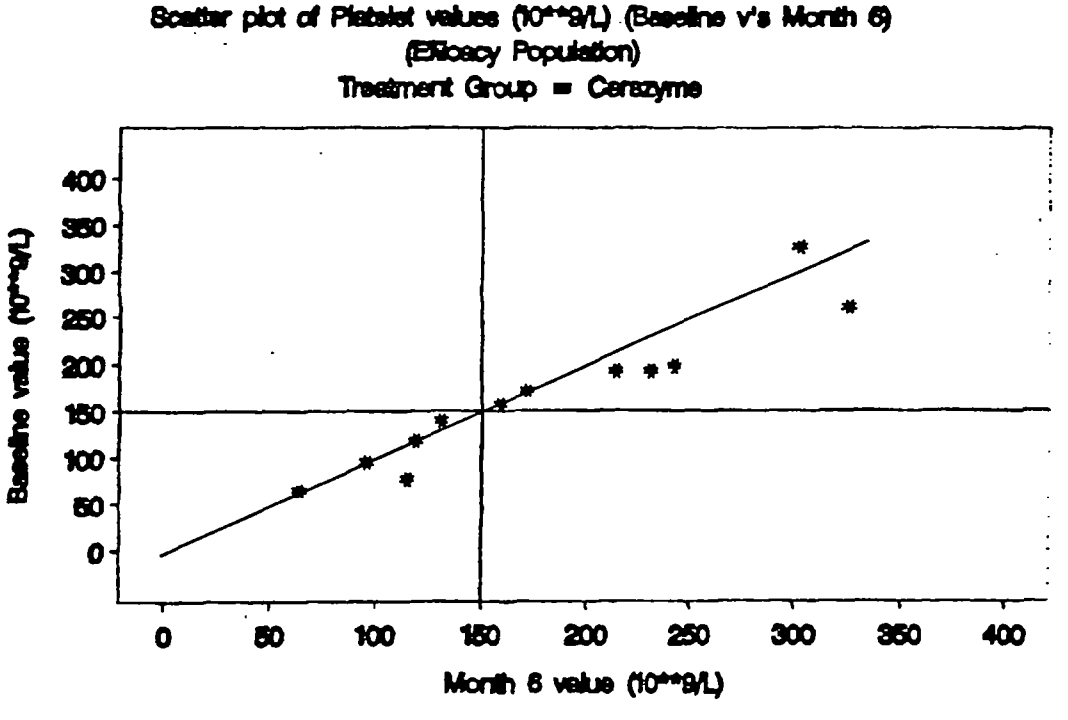
## OGT 918 Group

Figure 28: 918-004 Scatter Plot of Platelet Values, Baseline vs Month 6, OGT 918 Group



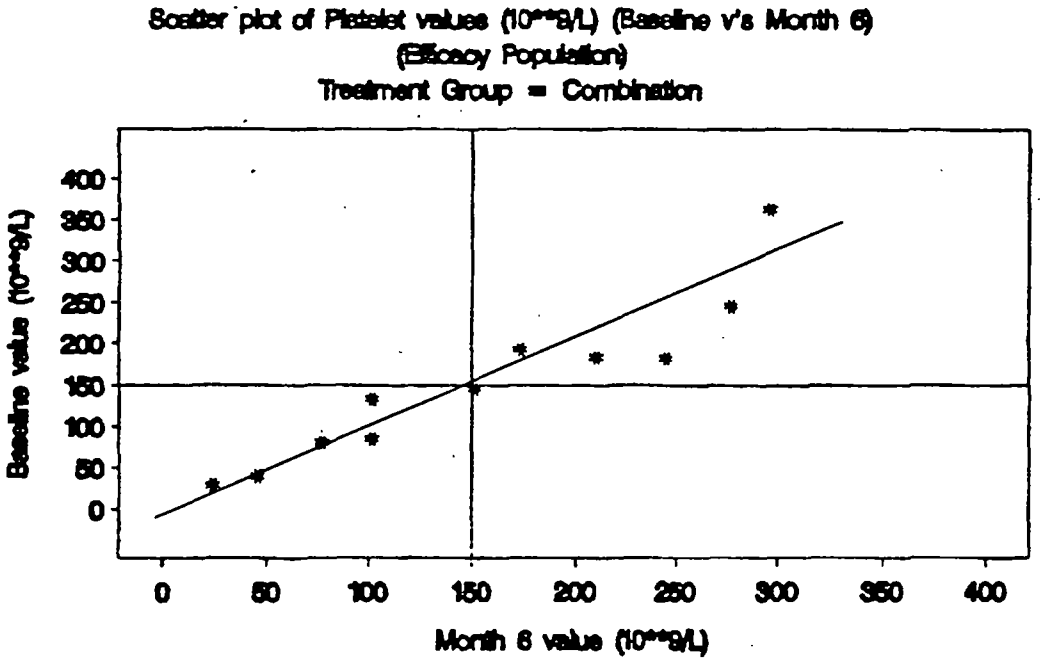

## Cerezyme Group

Figure 29: 918-004 Scatter Plot of Platelet Values, Baseline vs Month 6, Cerezyme Group



## Combination Group

**Figure 30: 918-004 Scatter Plot of Platelet Values, Baseline vs Month 6, Combination Group**




Platelet responses were further evaluated by Baseline Plt value. Sixteen (16) patients had Baseline Plt of <150 $X10^9$/L: 5 patients each in the OGT 918 and Cerezyme groups, and 6 patients in the Combination group. Mean changes from Baseline for these patients were ($X10^9$/L) –0.10, 6.90, and –1.42 for the OGT 918, Cerezyme, and Combination groups, respectively.

Seventeen (17) patients had Baseline Plt of ≥150 $X10^9$/L: 5 patients in the OGT 918 group, 7 patients in the Cerezyme group, and 5 patients in the Combination group. Mean changes from Baseline for these patients were ($X10^9$/L) –43.10, 21.29, and 7.70 for the OGT 918, Cerezyme, and Combination groups, respectively.

As the number of patients in each subgroup, by treatment group, was small, no conclusions will be drawn from these results.

### (iv) Biochemical Markers

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

#### Chitotriosidase

The OGT 918 and Cerezyme groups showed mean increases, and the Combination group showed a mean decrease in chitotriosidase from Baseline to Month 6. These results were significant only for the OGT 918 group. On pairwise comparisons, there were significant differences between the OGT 918 and Combination groups, and between the OGT 918

and Cerezyme groups. There was no significant difference between the Cerezyme and Combination groups. The results are summarized in the following table

Table 103: 918-004 Chitotriosidase Statistics

| | | | Month 6 | | |
|---|---|---|---|---|---|
| Treatment | Statistic | Baseline (nmol/ml.h) | Month 6 (nmol/ml.h) | Change (nmol/ml.h) | % Change |
| OGT 918 | n | 10 | 10 | 10 | 10 |
| | Mean | 5391.7 | 7012.1 | 1620.4 | 33.0 |
| | Median | 3343.0 | 4517.8 | 1281.0 | 34.6 |
| | Minimum | | | | |
| | Maximum | | | | |
| | p-value | | | .011 | .007 |
| Cerezyme | n | 12 | 12 | 12 | 12 |
| | Mean | 6098.6 | 6746.7 | 648.0 | -0.3 |
| | Median | 5216.5 | 5225.8 | -76.0 | -3.0 |
| | Minimum | | | | |
| | Maximum | | | | |
| | p-value | | | .349 | .960 |
| Combination | n | 11 | 11 | 11 | 11 |
| | Mean | 4467.3 | 4328.4 | -139.0 | -3.9 |
| | Median | 2315.5 | 2232.0 | -54.0 | -3.9 |
| | Minimum | | | | |
| | Maximum | | | | |
| | p-value | | | .409 | .270 |

### Hexosaminidase

The OGT 918 and Combination groups showed mean increases, and the Cerezyme group showed a mean decrease in hexosaminidase from Baseline to Month 6. These results were significant only for the OGT 918 group. On pairwise comparisons, there were significant differences between the OGT 918 and Combination groups, and between the OGT 918 and Cerezyme groups. There was no significant difference between the Cerezyme and Combination groups. The results are summarized in the following table

Table 104: 918-004 Hexosaminidase Statistics

| Treatment | Statistic | Baseline (nmol/ml.h) | Month 6 (nmol/ml.h) | Month 6 Change (nmol/ml.h) | % Change |
|---|---|---|---|---|---|
| OGT 918 | n | 10 | 10 | 10 | 10 |
| | Mean | 1214.4 | 1424.7 | 210.3 | 17.8 |
| | Median | 1125.3 | 1307.3 | 172.5 | 15.3 |
| | Minimum | | | | |
| | Maximum | | | | |
| | p-value | | | .016 | .010 |
| Cerezyme | n | 12 | 12 | 12 | 12 |
| | Mean | 1276.4 | 1273.6 | -2.8 | 178 |
| | Median | 1154.3 | 1285.0 | 53.8 | 5.0 |
| | Minimum | | | | |
| | Maximum | | | | |
| | p-value | | | .966 | .691 |
| Combination | n | 11 | 11 | 11 | 11 |
| | Mean | 1092.8 | 1130.4 | 37.6 | 5.5 |
| | Median | 1011.0 | 1075.5 | 23.0 | 1.8 |
| | Minimum | | | | |
| | Maximum | | | | |
| | p-value | | | .331 | .139 |

### Angiotensin Converting Enzyme (ACE)

There were mean reductions in ACE in the Cerezyme and Combination groups, of –5.5 and –1.9 nmol/ml.h, respectively. There was a mean increase of 18.4 nmol/ml.h in the OGT 918 group. Only the increase for the OGT 918 group was statistically significant. On pairwise comparisons, there were significant differences between the Combination and OGT 918 groups, and between the OGT 918 and Cerezyme groups. There was no significant difference between the Combination and the Cerezyme groups.

### Acid Phosphatase

There were mean increases in acid phosphatase in the OGT 918, Cerezyme, and Combination groups of 478.8, 187.7, and 12.8 nmol/mL.h, respectively. Only the increase for the OGT 918 group was statistically significant. On pairwise comparisons, there were significant differences between the Combination and OGT 918 groups, and between the OGT 918 and Cerezyme groups. There was no significant difference between the Combination and the Cerezyme groups.

### (v) Other Disease Assessments

Other disease assessments were performed at the discretion of the Investigator and per usual practice at the study center. Thirty-one (31) patients had at least one other disease assessment for which results were available at Baseline and at Month 6. Thirty (30) patients underwent DEXA scanning, and 22 patients underwent echocardiography. There were no meaningful changes in skeletal assessments by DEXA, and no patient had a progression to, or the development of, pulmonary hypertension by echocardiographic assessment of T1 at Month 6.

**(vi) QoL Questionnaire**

QoL questionnaires were performed at Day 1, Month 3, and Month 6. The questionnaire included 4 health surveys that assessed general areas of QoL, Gaucher-related distress, symptom bother, and treatment-related issues. From Baseline to Month 6, there were no significant differences across treatment groups in general QoL areas, Gaucher-related distress, or symptoms. There was a marginally significant difference in SF-36 Mental Health scores such that patients in the OGT 918 group reported improvements of about 9%, whereas patients in the Cerezyme and Combination groups reported decreases of about 8% each. For treatment related issues, there was a significantly greater improvement in convenience and marginally non-significant (p=.053) improvement in overall satisfaction at Month 6 in the OGT 918 group.

**(vii) Subgroup Analysis**

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

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

There were no significant mean decreases in liver or spleen volumes seen in any treatment group from Baseline to Month 6. On pairwise comparisons, however, there was a significant difference seen between the Cerezyme and Combination treatment groups, with the Combination group having a decrease in liver volume and the Cerezyme group having an increase in liver volume at Month 6. There were also no significant mean increases in Hgb or Plt values seen in any treatment group from Baseline to Month 6. On pairwise comparisons, there was a significant difference between the OGT 918 group and the Cerezyme group, with the OGT 918 having a decrease in Plt and the Cerezyme group having an increase in Plt at Month 6.

The biochemical markers of Gaucher disease measured in this study, chitotriosidase, hexosaminidase, and ACE showed significant increases in the OGT 918 group for all 3 markers, and non-significant results in the Cerezyme and Combination groups. On pairwise comparisons, there were also significant differences between the OGT 918 and Cerezyme groups, and between the OGT 918 and Combination groups, with greater increases seen in the OGT 918 group for all 3 markers. For acid phosphatase, all 3 treatment groups had mean increases, which were only significant for the OGT 918 group. On pairwise comparison, there were also significant differences between the OGT 918 and Cerezyme groups, and between the OGT 918 and Combination groups, with greater increases seen in the OGT 918 group. DEXA scanning and echocardiography showed essentially no change in any patient from Baseline at Month 12. The QoL questionnaire results showed marginally significant improvements in Mental Health, improvement in convenience, and improvement in overall satisfaction scores in the OGT 918, but not in the Cerezyme or Combination treatment groups.

## 6) Protocol 918-004X

### a) Study Design for Protocol 918-004X

#### (1) Study Design

Protocol 918-004X "A phase II, randomisation study of open-label OGT 918 and Cerezyme given as monotherapy or combination therapy in adult patients with type I Gaucher disease (extended treatment period)" was an open-label extension study to Protocol 918-004. Protocol 918-004X evaluated the efficacy and safety of OGT 918 100 mg TID monotherapy, or OGT 918 100 mg TID in combination with Cerezyme for an additional 6 months after successful completion of Protocol 918-004. Twenty-nine (29) adult patients with type I Gaucher disease were treated in the extension study and were given the option to receive OGT 918 alone or in combination with Cerezyme for an unlimited period (for a minimum of a further 6 months) regardless of their randomized treatment in the original study (918-004). These patients must have been receiving ERT for a minimum of 2 years to prior to entry in the original study 918-004. The cut-off date for data submitted to the NDA was the Month 12 visit.

#### (2) Study Objectives

The primary objective of the extended use phase was to assess the tolerability of OGT 918 for those continuing with OGT 918 and those opting to switch from Cerezyme or combination therapy to OGT 918. The secondary objective was to evaluate OGT 918 as a treatment for Gaucher disease by assessing organ volume and other markers of disease.

#### (3) Eligibility Criteria

Patients were eligible for the extended treatment phase study (918-004X) if they had completed the Month 6 visit in the original study 918-004 and the Investigator considered they would benefit from extended treatment. Patients were given the option to continue in the extension study at the Month 6 visit of the original study.

#### (4) Study Visits and Procedures

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

Table 105: 918-004 and 918-004X Study Visits and Procedures

| | Screen | 6-Month Treatment Phase 918-004 | | | | | | | | Extended Use Treatment Phase 918-004X | | Final |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | | 1 | 8 to 15 | 29 | 57 | 85 | 113 | 141 | 169 | 253 | 337 | |
| Month | | | | 1 | 2 | 3 | 4 | 5 | 6 | 9 | 12 | |
| **Procedure** | | | | | | | | | | | | |
| History | X | | | | | | | | | | | |
| Physical Examination | X | | | X | | X | | | X | | | |
| Vital Signs | X | | | X | | X | | | X | | | |
| Height | X | | | | | | | | | | | |
| Weight (BMI/BSA) | X | X | | X | X | X | X | X | X | X | X | X |
| ECG | X | | | X | | | | | X | | | |
| EMG/NCV | | | | X | | | | | | | | |
| Biochemistry | X | X | | X | X | X | X | X | X | X | X | X |
| Hematology | X | X | | X | X | X | X | X | X | X | X | X |
| Organ Volume | X | | | | | | | | X | | X | X |
| Other Disease Assessments | X | X | | X | | X | | | X | | X | |
| Adverse Events | | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant Medications | X | X | X | X | X | X | X | X | X | X | X | X |
| OGT 918 Dispensing | | X | | X | X | X | X | X | X | X | X | |

Protocol 918-004X is an extension to the original 6-month treatment period (Protocol 918-004) and continues 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
- Hematology
- AE assessment
- Concomitant medication update

### (b) Month 12 Visit

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

- Weight
- Biochemistry
- Hematology
- Organ Volume assessment
- Other disease assessments
- AE assessment
- Concomitant medication update

**(5) Study Medication Dispensing and Compliance**

Patients were given the option to choose either OGT 918 monotherapy or OGT 918 and Cerezyme as combination therapy. **In practice, all patients chose to receive OGT 918 monotherapy** and thus, there was no control treatment.

The initial dose of OGT 918 in the original 6-month treatment period was 100 mg TID and could be reduced to 100 mg BID in patients who experienced any side effects associated with OGT 918. Patients already taking OGT 918 in the original study were continued on their same dose of OGT 918 in the extension study.

OGT 918 was supplied as 50 mg or 100 mg gelatin capsules for oral administration. As this was an open-label study, no blinding was necessary. Trial medication was dispensed as a 3-month supply of OGT 918 at each extension 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.

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

**(6) Efficacy and Endpoint Measures**

**(a) Primary Efficacy Parameters**

All efficacy analyses were secondary. The primary endpoint was safety.

**(b) Secondary Efficacy Parameters**

The secondary efficacy parameters were change from Baseline to Endpoint in:

- Liver and spleen volume
- Organ volume
- Biochemical and hematological response parameters (hemoglobin, platelets, chitotriosidase, hexosaminidase, acid phosphatase and ACE)
- Biochemical and hematological response (hemoglobin and platelets)
- Subgroup analyses
- Other disease assessments; and
- 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 was defined as all patients who received at least one dose of study medication, and had a screening value and at least one post Month 6 value for either liver or spleen volume, hemoglobin or platelets. The safety population consisted of

all patients who had completed the original 6-month treatment period of the study, who opted to continue or switch to OGT 918 alone or as a combined therapy with Cerezyme and received at least one dose of study medication in the extended treatment period.

**b) Results**

A total of 36 patients entered into Protocol 918-004, and 33 of those patients completed the study. Thus, 33 patients were eligible to enter Protocol 918-004X. Twenty-nine (29) of the 33 patients who completed the original study chose to enter the extended treatment phase. Twenty-eight (28) of the 29 patients completed Month 12 of the extension study. Patients were screened, entered, and treated (beginning with entry into the original study) from 22-Dec-1999 to 20-Feb-2001.

**(1) Baseline Characteristics and Demographics**

Of the patients who continued in the extension study, 48% of patients were male and 90% were Ashkenazi Jews. Patient ages ranged from 17 to 69 years of age, with a mean age of 36.3 years. Baseline characteristics were compared to the baseline characteristics of the original study population, and overall, the two populations were similar. By treatment group, however, patients in the combination treatment group who continued in the extension study were more likely to be female and had somewhat lower baseline platelet counts. By original treatment group assignment, the baseline characteristics are summarized as follows

Table 106: 918-004X Baseline Characteristics and Demographics

| | All | OGT 918 | Cerezyme | OGT 918 + Cerezyme |
|---|---|---|---|---|
| **Enrolled Patients, n =** | 29 | 10 | 10 | 9 |
| **Demographic Measure** | | | | |
| **Gender, n (%)** | 29 | 10 | 10 | 9 |
| Male | 14 (48) | 5 (50) | 6 (60) | 3 (33) |
| Female | 15 (52) | 5 (50) | 4 (40) | 6 (67) |
| **Age (years), n =** | 29 | 10 | 10 | 9 |
| Mean | 36.3 | 34.9 | 41.3 | 32.3 |
| Min, max | 17, 69 | 18, 49 | 19, 69 | 17, 52 |
| **Race, n (%)** | 29 | 10 | 10 | 9 |
| Ashkenazi Jew | 26 (90) | 9 (90) | 10 (100) | 7 (78) |
| Other | 3 (10) | 1 (10) | 0 | 2 (22) |
| **Mean BMI ($kg/M^2$), n =** | 29 | 10 | 10 | 9 |
| Mean | 24.10 | 22.59 | 25.25 | 24.48 |
| Min, max | | | | |
| **Liver Organ Volume (l), n =** | 28 | 10 | 10 | 8 |
| Mean | 1.84 | 1.58 | 1.94 | 2.04 |
| Min, max | | | | |
| **Spleen Organ Volume (l), n =** | 20 | 7 | 7 | 6 |
| Mean | 0.78 | 0.69 | 0.83 | 0.84 |
| Min, max | | | | |
| **Hemoglobin (g/dL), n =** | 29 | 10 | 10 | 9 |
| Mean | 12.69 | 12.44 | 13.39 | 12.20 |
| Min, max | | | | |
| **Platelets ($x10^9/l$), n =** | 29 | 10 | 10 | 9 |
| Min, max | 159.76 | 170.55 | 170.05 | 136.33 |
| Min, max | | | | |

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## (2) Patient Disposition

### (a) Screening and Randomization

Thirty-three (33) patients were eligible for entry into the extension study, and 20 patients were enrolled. Four (4) patients did not enter the extension study (screen failures): 2 patients in the original OGT 918 alone treatment group, and 2 patients in the Cerezyme alone treatment group. The patients chose not to continue in the extension study due to:

Patient 104 (OGT 918 alone group): chose to stay on Cerezyme as concerned about tremor and GI side-effects, and due to the Investigator's decision due to poor compliance.
Patient 134 (OGT 918 alone group): due to decreased weight and reduced energy (AEs).
Patient 115 (Cerezyme alone group): chose to stay on Cerezyme as did not want to undergo EMG assessment and wanted to see study results before switching therapy
Patient 137 (Cerezyme alone group): chose to stay on Cerezyme as was deterred by reports of GI problems.

### (b) Dropouts

Of the 29 patients who entered the extension study, 1 patient withdrew prior to study completion, at the Month 12 visit. This patient was in the original OGT 918 alone group,

and withdrew due to AEs. The other 28 patients completed Month 12 of the study. The reasons for study discontinuation in the original and extension studies are summarized as follows

Table 107: 918-004 and 918-004X Dropouts

| | 918-004X Extension Study | | | | 918-004 Original Study | | | |
|---|---|---|---|---|---|---|---|---|
| | All | OGT 918 | Cerezyme | OGT 918 + Cerezyme | All | OGT 918 | Cerezyme | OGT 918 + Cerezyme |
| **Enrolled Patients, n =** | 29 | 10 | 10 | 9 | 36 | 12 | 12 | 12 |
| **Withdrawals, n (%)** | 1 (3) | 1 (10) | 0 | 0 | 3 (8) | 2 (17) | 0 | 1 (8) |
| **Reason for Dropout*** | | | | | | | | |
| Adverse Event, n (%) | 1 (3) | 1 (10) | 0 | 0 | 3 (8) | 2 (17) | 0 | 1 (8) |
| Subject Request, n (%) | 0 | 0 | 0 | 0 | 3 (8) | 2 (17) | 0 | 1 (8) |
| Investigator Request, n (%) | 0 | 0 | 0 | 0 | 1 (3) | 1 (8) | 0 | 0 |

*Patient may have reported more than one reason for withdrawal

### (3) Concomitant Medication

All 29 patients reported taking at least one concomitant medication at any time during the course of the 12-month treatment period. Concomitant medication use was listed by original treatment group assignment, and was cumulative from the start of Study 918-004. It was not indicated which treatment the patient was receiving at the time of concomitant medication use. Paracetamol, used by 44% of patients overall, and loperamide (36% overall) continued to be the most commonly used medications in the extension study. However, loperamide use was similar in the 3 treatment groups (by original randomization) in the extension study, while all patients were receiving treatment with OGT 918. The most common ($\geq$3 patients or $\geq$10% of patients) concomitants medications used, comparing the results from the end of Month 6 (end of 918-004) and at the end of Month 12 (including 918-004X results, in which all patients were receiving OGT 918) are listed in the following table

Table 108: 918-004 and 918-004X Most Common (>3 Patients) Concomitant Medications

| | Extension Study 918-004X | | | | Original Study 918-004 | | | |
|---|---|---|---|---|---|---|---|---|
| Treatment | All | OGT 918 | Cerezyme | OGT 918 + Cerezyme | All | OGT 918 | Cerezyme | OGT 918 + Cerezyme |
| Patients, n = | 29 | 10 | 10 | 9 | 36 | 12 | 12 | 12 |
| Medication | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Paracetamol | 15 (52) | 4 (40) | 3 (30) | 8 (89) | 16 (44) | 5 (42) | 2 (17) | 9 (75) |
| Loperamide | 11 (38) | 5 (50) | 2 (20) | 4 (44) | 13 (36) | 6 (50) | 1 (8) | 6 (50) |
| Metamizole | 8 (28) | 3 (30) | 3 (30) | 2 (22) | 7 (19) | 3 (25) | 2 (17) | 2 (17) |
| Heparin | 7 (24) | 1 (10) | 4 (40) | 2 (22) | 11 (31) | 3 (25) | 4 (33) | 4 (33) |
| Coldex | 5 (17) | 1 (10) | 2 (20) | 2 (22) | 2 (6) | 1 (8) | 1 (8) | 0 |
| Cyanocobalamin | 5 (17) | 2 (20) | 1 (10) | 2 (22) | 7 (19) | 3 (25) | 2 (17) | 2 (17) |
| Diclofenac | 5 (17) | 1 (10) | 2 (20) | 2 (22) | 5 (14) | 1 (8) | 2 (17) | 2 (17) |
| Ibuprofen | 5 (17) | 1 (10) | 2 (20) | 2 (22) | 4 (11) | 1 (8) | 1 (8) | 2 (17) |
| Acetylcysteine | 4 (14) | 2 (20) | 1 (10) | 1 (11) | 2 (6) | 1 (8) | 1 (8) | 0 |
| Amoxicillin | 4 (14) | 2 (20) | 1 (10) | 1 (11) | 2 (6) | 0 | 1 (8) | 1 (8) |
| Naproxen | 4 (14) | 1 (10) | 3 (30) | 0 | 3 (8) | 1 (8) | 2 (17) | 0 |
| Alendronate | 3 (10) | 2 (20) | 0 | 1 (11) | 2 (6) | 0 | 0 | 2 (17) |
| Analgesics | 3 (10) | 2 (20) | 0 | 1 (11) | 2 (6) | 1 (8) | 0 | 1 (8) |
| Clavulin | 3 (10) | 1 (10) | 0 | 2 (22) | 1 (3) | 1 (8) | 0 | 0 |
| Femodene | 3 (10) | 1 (10) | 1 (10) | 1 (11) | 3 (8) | 1 (8) | 1 (8) | 1 (8) |
| Herbal preparation | 3 (10) | 1 (10) | 1 (10) | 1 (11) | 4 (11) | 1 (8) | 1 (8) | 2 (17) |
| Laxatives | 3 (10) | 1 (10) | 0 | 2 (22) | 2 (6) | 0 | 0 | 2 (17) |
| Multivitamins | 3 (10) | 2 (20) | 0 | 1 (11) | 3 (8) | 2 (17) | 0 | 1 (8) |
| Phenazopyridine | 3 (10) | 2 (20) | 0 | 1 (11) | 1 (3) | 1 (8) | 0 | 0 |

### (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%. 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 primary analysis was safety. Please refer to the safety section.

### (b) Secondary Efficacy Analysis

The secondary objective of the extended treatment period was to assess organ volume measurements and other markers of Gaucher disease for the efficacy population.

### (i) Liver Organ Volume Response

Twenty-six (26) patients had liver volume data available at Month 12. There were no significant mean decreases in liver volume from Baseline at Month 12 in any treatment group, and there were no significant changes in liver volume in any treatment group from Month 6 to Month 12. There was a mean percent decrease in liver volume from Baseline to Month 6 and Month 12 in the OGT 918 group of –2.9% and –0.8%, respectively. In the Cerezyme group, mean percent changes from Baseline to Months 6 and 12 were

+3.2% (on Cerezyme) and –0.7% (after cross-over to OGT 918), respectively. In the Combination treatment group, mean percent changes from Baseline to Months 6 and 12 were –5.6% (on Combination treatment) and –4.0% (after cross-over to OGT 918), respectively.

Two (2) patients had notable (>10%) increases in liver volume from Baseline to Month 12:

Patient 122 (Cerezyme): had a +26% increase in liver volume from Baseline to Month 12, compared to a +0.6% increase from Baseline to Month 6.
Patient 107 (Cerezyme): had a +15.3% increase from Baseline to Month12, and a 21.8% increase from Baseline to Month 6.

However, 5 patients also had notable (<-10%) decreases in liver volume from Baseline to Month 12: 1 patient in the OGT 918 group, and 2 patients each in the Cerezyme and Combination treatment groups.

The results are summarized in the following table

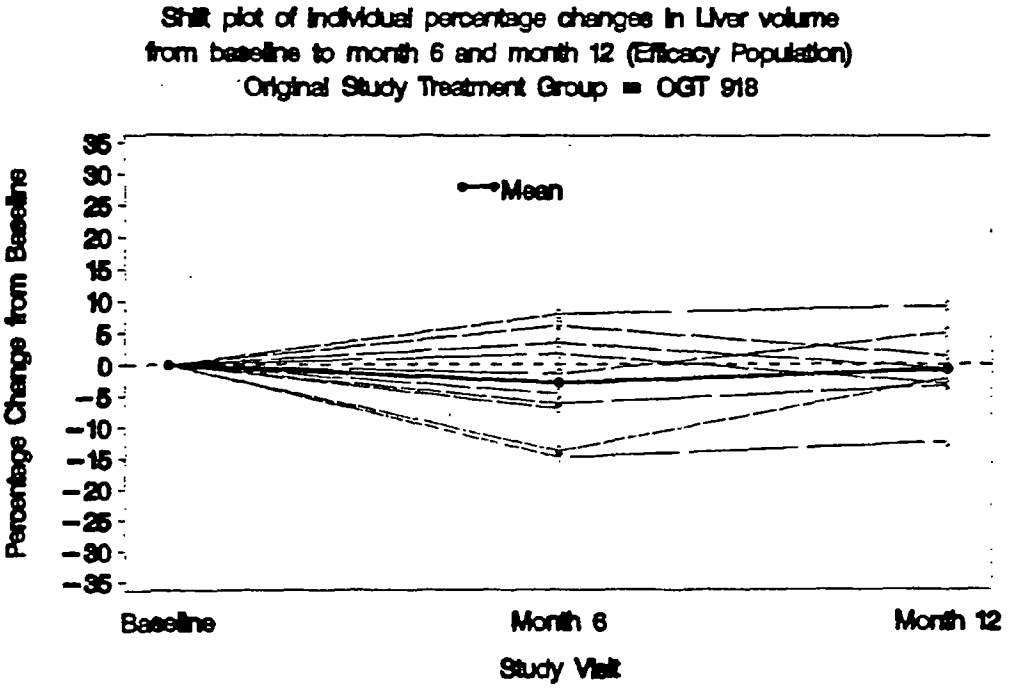
**Table 109: 918-004X Liver Organ Volume Statistics**

| | | Baseline | Month 6 | | | Month 12 | | |
|---|---|---|---|---|---|---|---|---|
| Treatment | Statistic | Organ Volume (L) | Organ Volume (L) | Change (L) | % Change | Organ Volume (L) | Change (L) | % Change |
| OGT 918 | n | 10 | 10 | 10 | 10 | 8 | 8 | 8 |
| | Mean | 1.58 | 1.54 | -0.05 | -2.9 | 1.58 | -0.01 | -0.8 |
| | Median | 1.58 | 1.55 | -0.05 | -3.1 | 1.54 | -0.02 | -1.4 |
| | Minimum | | | | | | | |
| | Maximum | | | | | | | |
| | p-value | | | .253 | .277 | | .732 | .749 |
| Cerezyme | n | 10 | 9 | 9 | 9 | 10 | 10 | 10 |
| | Mean | 1.94 | 1.99 | 0.03 | 3.2 | 1.89 | -0.05 | -0.7 |
| | Median | 1.83 | 1.91 | 0.03 | 2.0 | 1.94 | -0.04 | -2.5 |
| | Minimum | | | | | | | |
| | Maximum | | | | | | | |
| | p-value | | | .582 | .327 | | .581 | .876 |
| Combination | n | 8 | 8 | 8 | 8 | 8 | 8 | 8 |
| | Mean | 2.04 | 1.94 | -0.10 | -5.6 | 1.96 | -0.08 | -4.0 |
| | Median | 2.05 | 1.97 | -0.08 | -3.9 | 1.95 | -0.06 | -2.7 |
| | Minimum | | | | | | | |
| | Maximum | | | | | | | |
| | p-value | | | .058 | .047 | | .123 | .137 |

Individual patient results at Baseline, Month 6, and Month 12, by treatment group, are depicted graphically in the following figures [Figures electronically scanned and reproduced from: Oxford Glycosciences (UK) Ltd, NDA #21-348, Volume 2.22, pages 51-52, dated 02-Aug-2001]

## OGT 918 Group

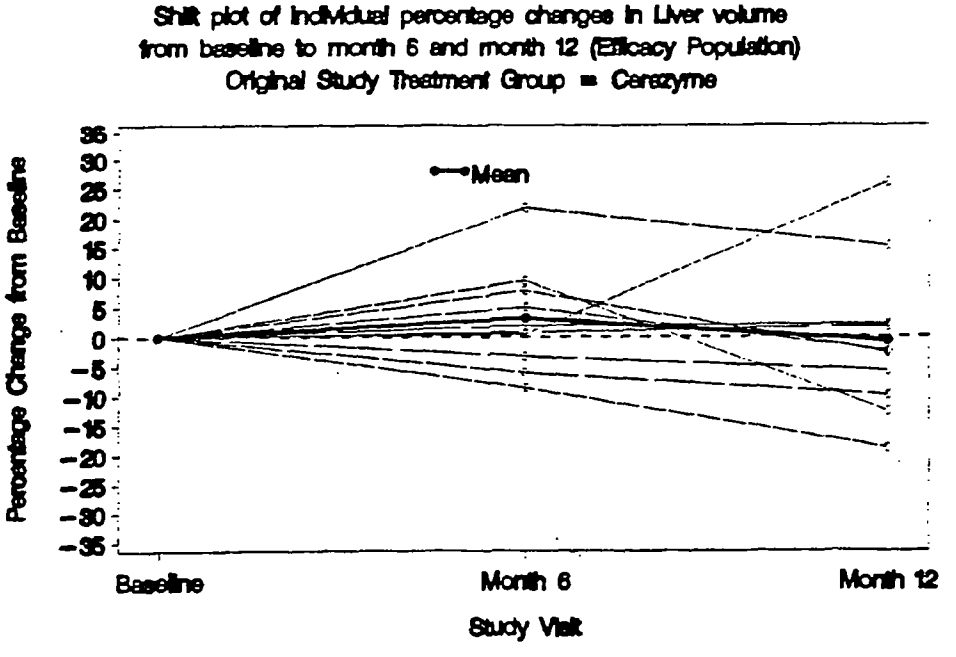
Figure 31: 918-004X % Change from Baseline in Liver Volume, OGT 918 Group




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

## Cerezyme Group

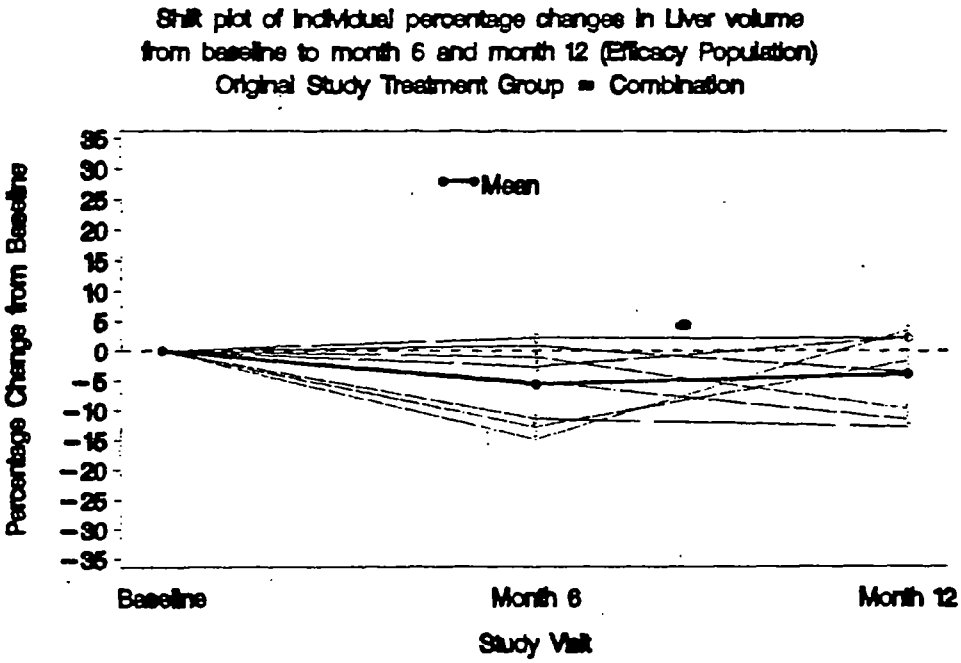
Figure 32: 918-004X % Change from Baseline in Liver Volume, Cerezyme Group




Note: All patients enrolling in the extension phase chose to receive OGT 918 alone.
1 patient had a missing value at month 6.

## Combination Group

**Figure 33: 918-004X % Change from Baseline in Liver Volume, Combination Group**




Note: All patients enrolling in the extension phase chose to receive OGT 918 alone.
Patient 119 had no data recorded at baseline, month 6 and month 12.

### (ii) Spleen Volume

Nineteen (19) patients had spleen volume data available at Month 12, and 10 patients had undergone splenectomy prior to study start (4 patients in the OGT 918 group, and 3 patients each in the Cerezyme and Combination groups). There were no significant mean decreases in spleen volume from Baseline at Month 12 in any treatment group. There were no significant changes in spleen volume from Month 6 to Month 12 in any treatment group; however, for the Cerezyme and Combination groups, switching to OGT 918 monotherapy resulted in mean percent increases in spleen volume. There was a mean percent decrease in spleen volume from Baseline to Month 6 and Month 12 in the OGT 918 group of –4.8% and –6.1%, respectively. In the Cerezyme group, mean percent changes from Baseline to Months 6 and 12 were –4.0% (on Cerezyme) and +1.5% (after cross-over to OGT 918), respectively. In the Combination treatment group, mean percent changes from Baseline to Months 6 and 12 were –13.7% (on Combination treatment) and –4.8% (after cross-over to OGT 918), respectively.

Three (3) patients had notable (>10%) increases in spleen volume from Baseline to Month 12:

Patient 127 (Cerezyme): had a +13.8% increase in spleen volume from Baseline to Month 12, compared to a –2.1% increase from Baseline to Month 6.

Patient 131 (Combination): had a +14.8% increase from Baseline to Month 12, and a +3.3% increase from Baseline to Month 6.
Patient 135 (Combination): had a +16.8% increase from Baseline to Month 12, and a –18.7% decrease from Baseline to Month 6.

However, 6 patients also had notable (<-10%) decreases in spleen volume from Baseline to Month 12: 1 patient in the OGT 918 group, 2 patients in the Cerezyme group, and 3 patients in the Combination treatment group.

The results are summarized in the following table

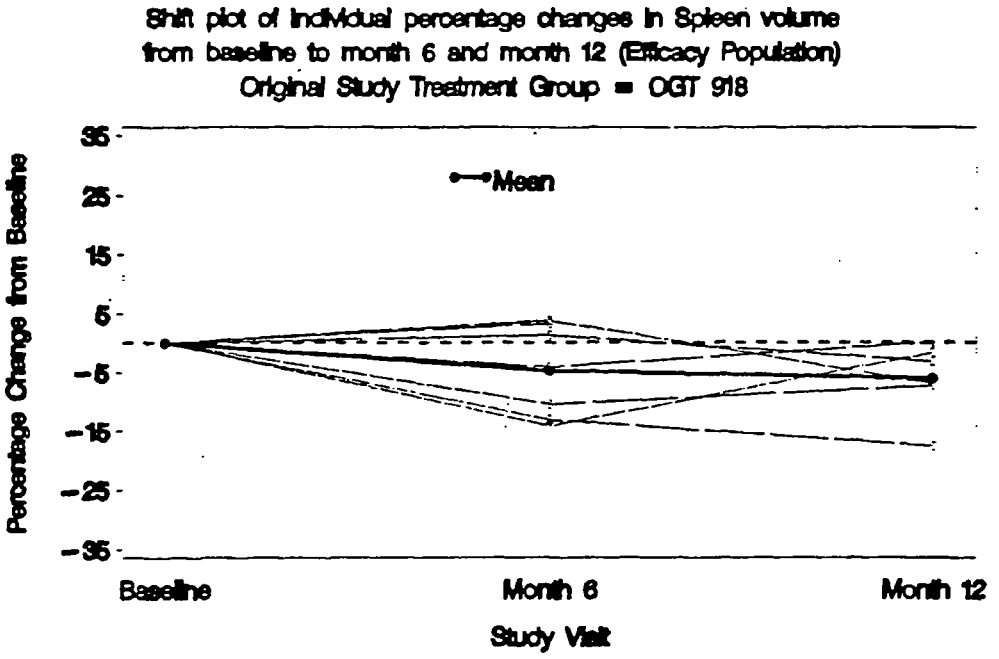
**Table 110: 918-004X Spleen Organ Volume Statistics**

| | | Baseline | Month 6 | | | Month 12 | | |
|---|---|---|---|---|---|---|---|---|
| Treatment | Statistic | Organ Volume (L) | Organ Volume (L) | Change (L) | % Change | Organ Volume (L) | Change (L) | % Change |
| OGT 918 | N | 7 | 7 | 7 | 7 | 6 | 6 | 6 |
| | Mean | 0.69 | 0.66 | -0.03 | -4.8 | 0.52 | -0.05 | -6.1 |
| | Median | 0.65 | 0.56 | -0.01 | -4.2 | 0.51 | -0.02 | -5.0 |
| | Minimum | | | | | | | |
| | Maximum | | | | | | | |
| | p-value | | | .310 | .156 | | .138 | .066 |
| Cerezyme | n | 7 | 6 | 6 | 6 | 7 | 7 | 7 |
| | Mean | 0.83 | 0.64 | -0.04 | -4.0 | 0.87 | 0.04 | 1.5 |
| | Median | 0.63 | 0.53 | -0.01 | -2.8 | 0.62 | 0.04 | 3.6 |
| | Minimum | | | | | | | |
| | Maximum | | | | | | | |
| | p-value | | | .201 | .055 | | .245 | .724 |
| Combination | n | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| | Mean | 0.84 | 0.73 | -0.11 | -13.7 | 0.79 | -0.05 | -4.8 |
| | Median | 0.97 | 0.75 | -0.07 | -15.5 | 0.83 | -0.07 | -7.1 |
| | Minimum | | | | | | | |
| | Maximum | | | | | | | |
| | p-value | | | .088 | .040 | | .472 | .533 |

Individual patient results at Baseline, Month 6, and Month 12, by treatment group, are depicted graphically in the following figures [Figures electronically scanned and reproduced from: Oxford Glycosciences (UK) Ltd, NDA #21-348, Volume 2.22, pages 55-56, dated 02-Aug-2001]

## OGT 918 Group

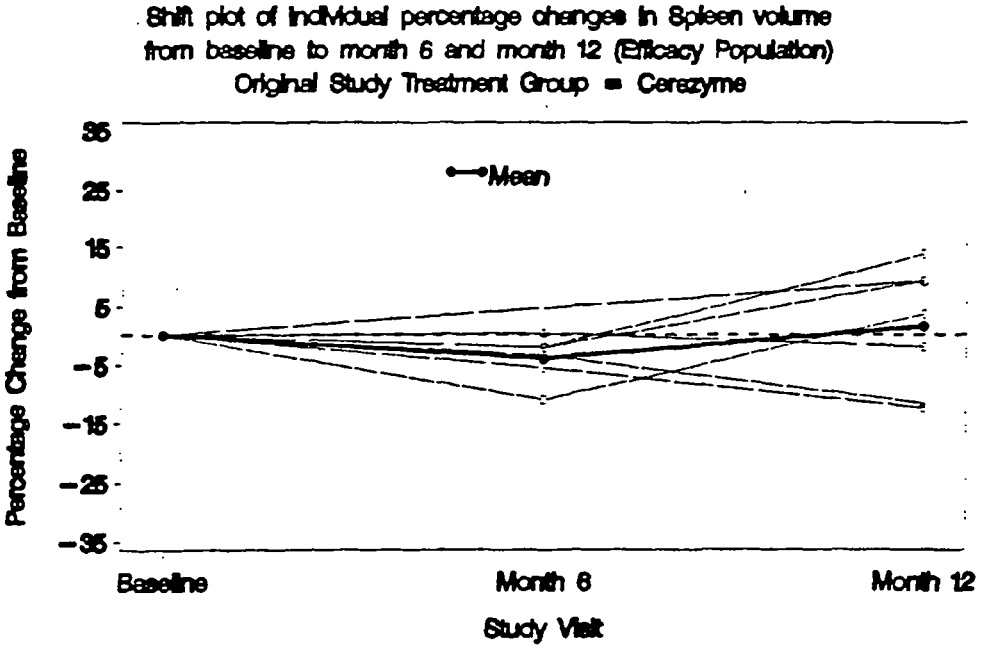
Figure 34: 918-004X % Change from Baseline in Spleen Volume, OGT 918 Group




Note: All patients enrolling in the extension phase chose to receive OGT 918 alone.
1 patient withdrew prior to month 12. 3 patients had missing values at screening.

## Cerezyme Group

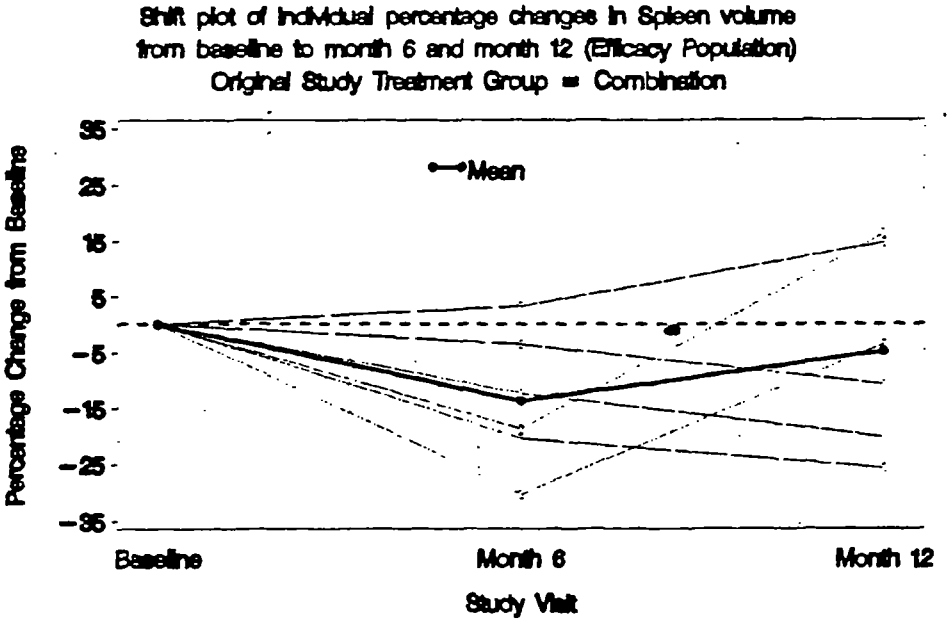
Figure 35: 918-004X % Change from Baseline in Spleen Volume, Cerezyme Group




Note: All patients enrolling in the extension phase chose to receive OGT 918 alone.
1 patient had a missing value. 3 patients had missing values at screening.

## Combination Group

Figure 36: 918-004X % Change from Baseline in Spleen Volume, Combination Group




Note: All patients enrolling in the extension phase chose to receive OGT 918 alone.
3 patients had missing values at screening.

### Hemoglobin

Twenty-eight (28) patients had Hgb data at Month 12. Overall, there were non-significant, small mean decreases in Hgb from Baseline at Month 12 in all treatment groups. There were also no significant changes in Hgb from Month 6 to Month 12 in any treatment group. In the OGT 918 group, there were mean actual decreases in Hgb from Baseline at Month 6 and Month 12 of –0.31 g/dL and –0.13 g/dL, respectively. In the Cerezyme group, there were mean actual decreases in Hgb from Baseline at Month 6 and Month 12 of –0.19 g/dL and –0.48 g/dL, respectively. In the Combination group, there were mean actual decreases in Hgb from Baseline at Month 6 and Month 12 of –0.23 g/dL and –0.80 g/dL, respectively.

One patient in the Cerezyme group (Patient 177) had a notable decrease (<-10%) in Hgb of –18.5% from Baseline to Month 12, compared to a –0.3% decrease from Baseline to Month 6. No patient in any treatment group had an increase in Hgb >10% from Baseline to Month 12.

The results are summarized in the following table

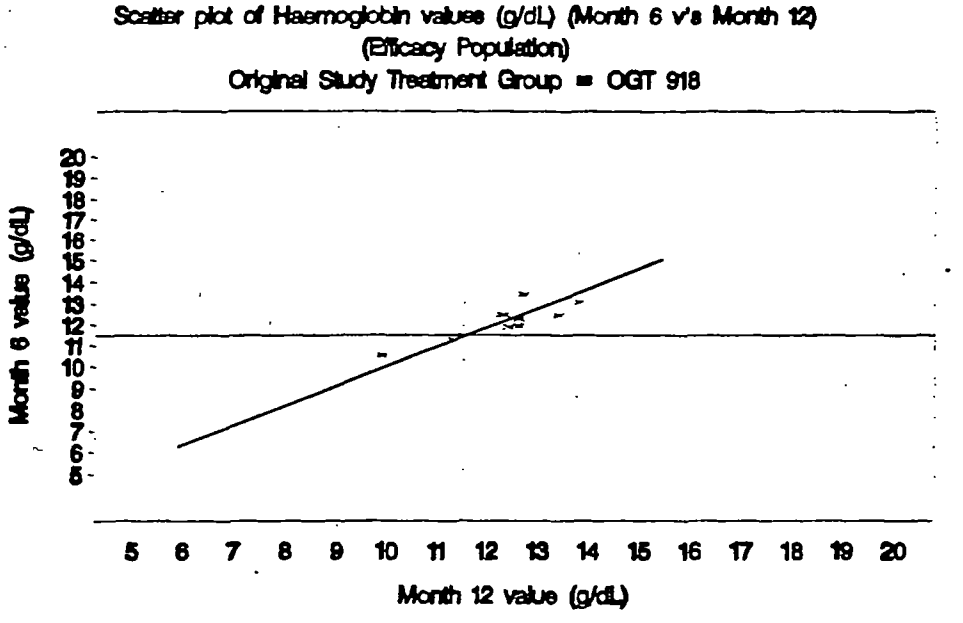
Table 111: 918-004X Hemoglobin Statistics

| | | Baseline | Month 6 | | | Month 12 | | |
|---|---|---|---|---|---|---|---|---|
| Treatment | Statistic | g/dL | g/dL | Change (g/dL) | % Change | g/dL | Change g/dL | % Change |
| OGT 918 | n | 10 | 10 | 10 | 10 | 9 | 9 | 9 |
| | Mean | 12.44 | 12.13 | -0.31 | -2.4 | 12.33 | -0.13 | -1.1 |
| | Median | 12.30 | 12.18 | -0.23 | -1.9 | 12.60 | 0.05 | 0.4 |
| | Minimum | | | | | | | |
| | Maximum | | | | | | | |
| | p-value | | | .109 | .101 | | .466 | .454 |
| Cerezyme | n | 10 | 10 | 10 | 10 | 10 | 10 | 10 |
| | Mean | 13.39 | 13.21 | -0.19 | -1.5 | 12.91 | -0.48 | -3.1 |
| | Median | 13.35 | 13.05 | -0.10 | -0.8 | 13.00 | -0.45 | -3.5 |
| | Minimum | | | | | | | |
| | Maximum | | | | | | | |
| | p-value | | | .201 | .188 | | .200 | .207 |
| Combination | n | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| | Mean | 12.20 | 11.97 | -0.23 | -1.5 | 12.07 | -0.13 | -0.8 |
| | Median | 11.55 | 11.40 | -0.40 | -3.7 | 11.90 | -0.30 | -2.2 |
| | Minimum | | | | | | | |
| | Maximum | | | | | | | |
| | p-value | | | .339 | .461 | | .538 | .682 |

Comparisons of individual patient Hgb 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 61-62, dated 02-Aug-2001] [best reproductions]

## OGT 918 Group

Figure 37: 918-004X Scatter Plot of Hemoglobin 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.