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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-348

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

CLINICAL STUDIES

NDA:	21-348
Name of drug:	Zavesca™ (miglustat) 100 mg Capsule
Applicant:	Oxford GlycoSciences (UK) Ltd.
Indication:	Treatment of Type 1 Gaucher Disease
Documents reviewed:	Vols. 1.142, 64-142 \\CDSESUB1\N21348\N_000\2001-08-16
Project manager:	Samuel Wu (HFD-510)
Clinical reviewer:	Anne Pariser, M.D. (HFD-510)
Dates:	Received August 16, 2001; user fee (10 months) June 21, 2002
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Keywords:	NDA review, orphan drug

1 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 CONCLUSION

Two noncomparative (Phase I/II) and one comparative (Phase II) open label studies were designed to assess treatment of Zavesca on organ volume and other markers of type 1 Gaucher disease. Although sample size was not calculated and no formal statistical analysis was intended for the studies, the studies nevertheless provide some information concerning the drug's efficacy in the intended population. This review summarizes the efficacy data and selected safety data, specifically tremor and/or paraesthesia using descriptive statistics and graphic displays without formal statistical inference. Appropriate variables and analyses were selected based on discussions with the reviewing medical officer, Dr. Pariser.

1.2 OVERVIEW OF CLINICAL PROGRAM AND STUDIES REVIEWED

Zavesca (Miglustat) is intended for treatment of type 1 Gaucher disease which is a hereditary enzyme deficiency disease. The majority of patients in the 3 clinical studies conducted for type 1 Gaucher disease were from a single study center in Jerusalem. Table 1 is a summary of the study designs. The length of each study extension was the same as the study length.

Table 1 Summary of type 1 Gaucher studies

Study	Design	n	OGT 918 dose	Center	Duration
OGT918-001, (001X)	open label, noncomparative	28	100mg (up to 300 mg) TID	Cambridge, UK, Amsterdam, Prague and Jerusalem	12 months
OGT918-003, (003X)	open label, noncomparative	18	50 mg TID	Johannesbury, Jerusalem	6 months
OGT918-004, (004X)	open label, comparative	36	100 mg TID ERT 100mg TID+ERT	Jerusalem	6 months

The first study (OGT 918-001) was conducted to evaluate the therapeutic potential of OGT 918 at an oral dose of 100 mg TID for 12 months in 28 adult patients who were either unable or unwilling to receive enzyme replacement therapy (ERT). Design of the second study (OGT 918-003) was similar, however, 18 patients received a lower dose of OGT 918 (50mg TID) for a 6-month treatment period. The third study (OGT 918-004) was designed to investigate the safety of OGT 918 coadministered with ERT in patients who had received regular I.V. infusion of ERT for at least 2 years. Tweleve patients each were randomized either to continue ERT monotherapy, to OGT 918 100 TID monotherapy, or to combination therapy of OGT 918 and ERT.

2 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 INTRODUCTION AND BACKGROUND

Zavesca (OGT 918) is designated as an Orphan for Gaucher Disease. Type 1 Gaucher disease is an inherited enzyme deficiency found predominantly in Ashkenazi Jews. The clinical signs and symptoms of type 1 Gaucher disease include enlargement of the liver, spleen and the bone marrow. Studies 001 and 003 were phase I/II open label, noncomparative studies using a TID dose of OGT 918 100mg and 50 mg, respectively, for 12 months and 6 months, respectively. Study 004 was an open label, randomized, comparative study with Cerezyme monotherapy as the control group. Cerezyme, an enzyme replacement therapy, is the only currently approved therapy for Gaucher disease. The study objective was to examine the added benefits of combination therapy compared with monotherapy and to determine whether response could be maintained after switching from Cerezyme to OGT 918 therapy. No formal sample size calculation was conducted. The study enrolled 36 type 1 Gaucher patients from a single center in Israel.

Zavesca has also been studied for the treatment of Farby disease, an inherited deficiency of the α-galactosidase. High doses (up to 1 g TID) of Zavesca was studied for HIV-1.

2.2 DATA ANALYZED AND SOURCES

The studies and their extensions and the integrated summary of safety (ISS) and integrated summary of efficacy (ISE) are organized in the following folders (Table 2) in the Electronic Document Room (EDR).

Table 2 Contents of electronic dataset

Study	Description	folder name
918-001	Gaucher Disease (100 mg TID)	crt\datasets\918-001
918-001X	Extension phase of S1[a]	crt\datasets\918-001x
918-002	Farby Disease	crt\datasets\918-002
918-003	Type 1 Gaucher Disease (50 mg TID)	crt\datasets\918-003
918-003X	Extension phase of S3[b]	crt\datasets\918-003x
918-004	Randomized, Type 1 Gaucher Disease	crt\datasets\918-004
918-004X	Extension phase of S4[c]	crt\datasets\918-004x
ISS001	S1 (0-30 months)	crt\datasets\iss001
ISSCDS1	Combined dataset (0-30 months), S1, 1X[d], S3, 3X, S4, 4X	crt\datasets\isscds1
ISSCDS2	Combined dataset (0-6 months), S1, S3, S4	crt\datasets\isscds2
ISE	Combined dataset, S1 and S3	crt\datasets\ise

[a] S1=918-001, [b] S2=918-003, [c] S4=918-004, X[d] = extension phase

Using study 004 as an example, names and locations of datasets are displayed in Table 3.

Table 3 *Names and descriptions of Study 918-004 datasets*

Dataset	Description of dataset	Location of dataset
patinfaf	Patient Information	crt\datasets\918-004\patinfaf.xpt
aeaf	Adverse Events	crt\datasets\918-004\aeaf.xpt
conmedaf	Concomitant Medications	crt\datasets\918-004\conmedaf.xpt
pefficaf	Primary Efficacy	crt\datasets\918-004\pefficaf.xpt
sefficaf	Secondary Efficacy	crt\datasets\918-004\sefficaf.xpt
labaf	Laboratory Data	crt\datasets\918-004\labaf.xpt
vitalaf	Vital Signs	crt\datasets\918-004\vitalaf.xpt
ecgaf	ECG's	crt\datasets\918-004\ecgaf.xpt

2.3 STATISTICAL EVALUATION OF EVIDENCE ON EFFICACY / SAFETY

2.3.1 SPONSOR'S RESULTS AND CONCLUSIONS

The primary efficacy variables for studies 001 and 003 were percentage change from baseline in liver organ volume, percentage change from baseline in spleen organ volume, actual change from baseline in hemoglobin, and actual change from baseline in platelets. The primary efficacy variable for study 004 was percentage change from baseline in liver organ volume. The mean percent change of liver volume from baseline to endpoint is displayed in Table 4 for the 3 studies.

Table 4 Descriptive statistics of % change of liver volume

Study	n	Mean (SD)	95% CI	Median	Min	Max
OGT918-001						
Month 6	22	-7.0 (8.0)	(-10.5, -3.4)	-6.4		
Endpoint or Month 12	22	-11.8 (9.2)	(-15.9, -7.8)	-12.5		
OGT918-001X	17	-14.3 (7.0)	(-18.0, -10.7)	-12.6		
OGT918-003	17	-5.9 (7.8)	(-9.9, -1.9)	-6.7		
OGT918-003X	16	-6.7 (8.9)	(-11.5, -2.0)	-5.4		
OGT918-004						
Zavesca	12	-2.4 (7.2)	(-7.0, 2.2)	-0.7		
ERT	12	+3.3 (8.7)	(-2.2, 8.8)	+1.3		
Zavesca+ERT	11	-4.0 (6.2)	(-8.2, 0.2)	-1.1		
OGT918-004X	28	-2.0 (9.2)	(-5.6, 1.5)	-2.5		

The sponsor's conclusion from the 2 noncomparative studies was Zavesca improved key clinical features of Gaucher disease. Hematological variables showed an upward trend after one year of Zavesca therapy. The sponsor concluded from the comparative study that patients could be switched to Zavesca from ERT without clinical deterioration. Reductions in mean liver and spleen volumes suggest a small improvement on switching to Zavesca, while reduction in mean platelets count and chitotriosidase activity suggest some degree of deterioration. The sponsor't conservative interpretation was that no consistent change in disease status was apparent, and no rapid deterioration occurs.

The sponsor's results on liver volume and spleen volume for studies 001, 003 and 004 are displayed in Tables in the Appendix.

From Studies 001 and 003 the sponsor concluded that Zavesca 100 mg treatment group showed greater mean percentage improvement at 6 months in liver and spleen organ volume than patients who received Zavesca 50 mg, particularly for spleen organ volume. Changes in mean hemoglobin and platelets counts in both groups were small and not significant.

From Study 004 the sponsor concluded that Zavesca 100 mg and Zavesca 100 mg/Cerezyme treatment groups both showed improvements in liver organ volume at 6 months with mean percentage decreases of 2.9% and 4.9%, respectively. The Cerezyme treatment group however had a mean percentage increase in liver organ volume of 3.6%. There was a nominally statistically significant difference of 8.4% between the Zavesca 100 mg/Cerezyme and Cerezyme treatment groups with respect to percentage

change from baseline in liver organ volume (ANCOVA, p=0.047), in favor of Zavesca 100 mg/Cerezyme. However, the differences between the Zavesca 100 mg and Cerezyme treatment groups (4.5%) and between the Zavesca 100 mg/Cerezyme and Zavesca treatment groups (3.9%) were not statistically significant (ANCOVA, p=0.297 and p=0.428, respectively).

2.3.2 STATISTICAL METHODOLOGIES

The sponsor intended to perform exploratory statistical analysis on the efficacy measures using baseline versus endpoint evaluations. The sponsor cautioned that in the absence of a comparator, any significant findings might have occurred because of factors other than a drug effect (e.g., natural changes in the state of disease over time, effects of participating in a clinical study).

The sponsor stated that "Although not planned in the statistical analysis plan, within-subject comparisons were undertaken in the percentage and absolute changes from baseline for liver and spleen volumes at Months 6 and 12. In each case, a two-sided paired t-test was used and the corresponding 95% confidence interval for the change from baseline was produced to show precision."

2.3.3 DETAILED REVIEW OF INDIVIDUAL STUDIES

Study 001, 001X

Of the 28 patient enrolled in the study, 22 (79%) completed the study and 6 (21%) withdrew. The reasons for withdrawal were unacceptable side effects (2, Diarrhea), serious adverse event (1), and patient request (3).

The numbers of patients enrolled in the 4 centers: Jerusalem (Israel), Cambridge (UK), Amsterdam (The Netherlands), and Prague (Czech Republic) were 16 (57%), 7 (25%), 3 (11%) and 2 (7%), respectively.

Of the 28 patients, half were male and half were female. More than half (15) of the patients were Ashkenazi Jews. The mean age was 44 years (range 22, 69). Mean weight was 67.9 kg.

Of the 18 patients who continued into the extension period (OGT918-001X), 14 completed the 12-month extension. All 4 withdrawn patients were from center UK. Two (101, 105) patients withdrew for reason of serious adverse events (peripheral neuropathy) and the investigator withdrew the 2 remaining patients (106, 107) as a precautionary measure.

Organ volume was assessed for liver and spleen. Splenectomized patients were assessed for liver volume only. The absolute and percent change from screening to month 6 and 12 were summarized using descriptive statistics.

The sample size (N) in sponsor's table varies from baseline to Month 12. This reviewer examined endpoint statistics in patients who had a baseline value and at least one post baseline value for the study variable (Table 5).

Table 5 Descriptive statistics of liver volume – Study 001

	Baseline	Endpoint	Change	% Change
N	22	22	22	22
Mean (SD)	2.348 (0.482)	2.075 (0.506)	-0.273 (0.215)	-12% (9.2%)
95% CI	(2.134, 2.562)	(1.851, 2.300)	(-0.368, -0.178)	(-16%, -8%)

Table 6 Descriptive statistics of spleen volume – Study 001

	Baseline	Endpoint	Change	% Change
N	19	19	19	19
Mean (SD)	1.601 (0.712)	1.324 (0.599)	-0.320 (0.198)	-19% (9.5)
95% CI	(1.258, 1.944)	(1.026, 1.622)	(-0.418, -0.222)	(-23.711, -14.253)

Figure 1 Median percent change from baseline in liver volume and spleen volume

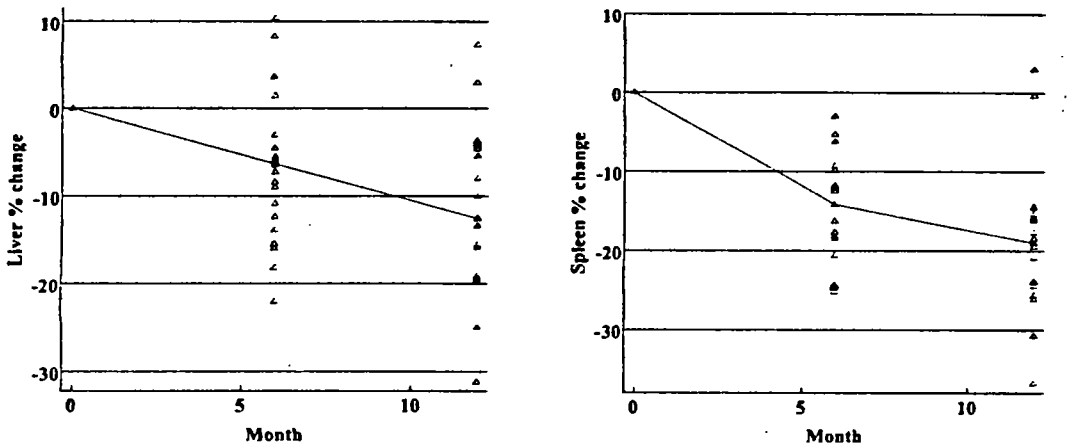


Table 7 Descriptive statistics of liver volume – Study 001X

	Baseline	Endpoint	Change	% Change
N	12	12	12	12
Mean (SD)	2.538 (0.485)	2.175 (0.475)	-0.359 (0.186)	-14.% (7.6%)
95% CI	(2.230, 2.845)	(1.888, 2.462)	(-0.368, -0.178)	(-19%, -10%)

Table 8 Descriptive statistics of spleen volume –Study 001X

	Baseline	Endpoint	Change	% Change
N	10	10	10	10
Mean (SD)	1.558 (0.439)	1.143 (0.318)	-0.416 (0.157)	-26% (5.5)
95% CI	(1.245, 1.872)	(0.915, 1.370)	(-0.528, -0.303)	(-30.4, -22.4)

Percent changes of liver volume and spleen volume are presented in Figure 2 for each patient. Patients #101, #103, #105, and #416 experienced drug related neurological adverse events at days 321, 9, 32, and 282, respectively. Patients #101 and #103 experienced paraesthesia, patient #105 experienced tremor of hands and patient #416, fine tremor.

Figure 2. % changes of liver volume and spleen volume by patient – Study 1

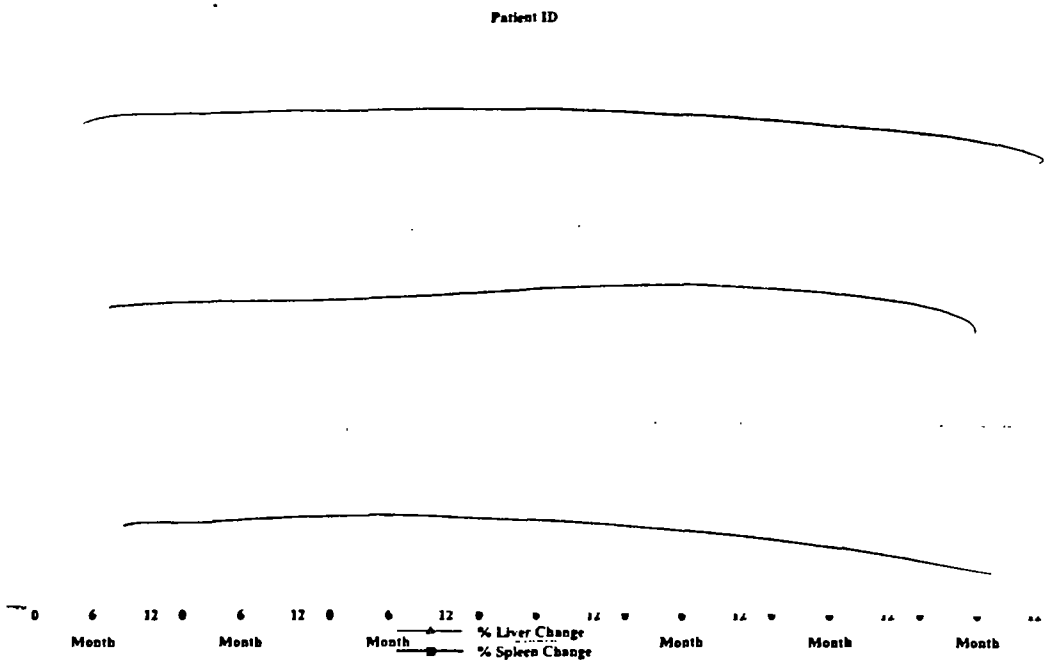
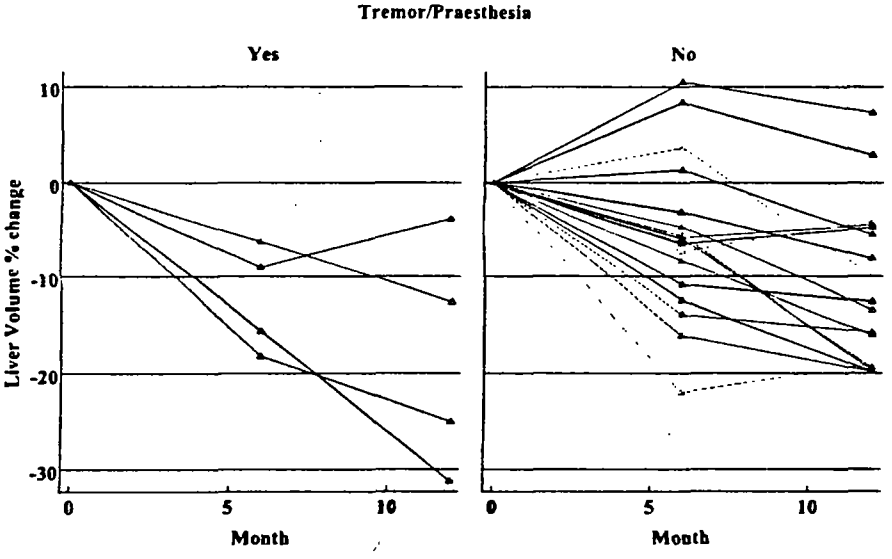


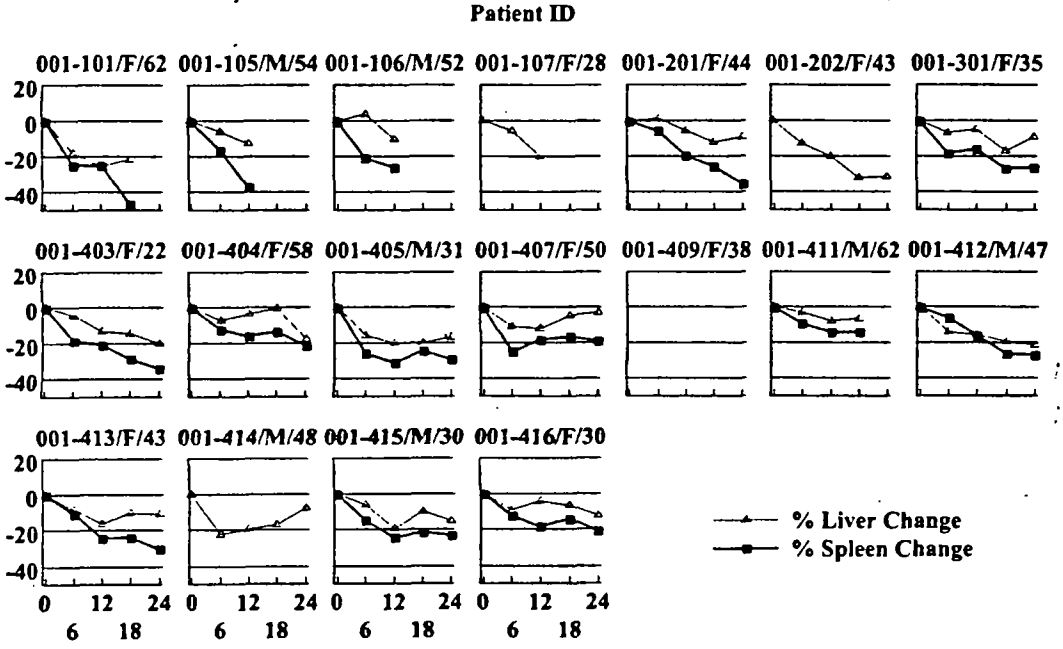
Figure 3 displays percent change of liver volume by patient with or without the AE of tremor/paraesthesia.

Figure 3 Liver volume percent change with or without tremor/paraesthesia - Study 001



The median percent liver volume changes from baseline were –12% and –19% at month 6 and month 12 , respectively for the 4 patient with tremor/paraesthesia and –6% and –12%, respectively, for patients without the AE.

In the extension, patient 105 experienced tremor at day 32 and 366 (Figure 4).



Hemoglobin and Platelets

The descriptive statistics for hemoglobin and platelets are in Tables 9 and 10. Figure 4 is a display of median percent change of hemoglobin and platelets over time

Table 9 Hemoglobin (g/dl) statistics (n=23) – Study 001

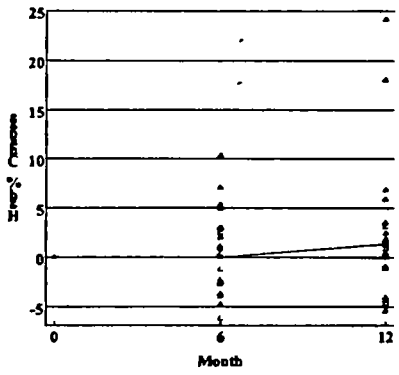
	Baseline	Endpoint	Change	% Change
Mean (SD)	12.0 (1.8)	12.2 (1.6)	0.26 (0.69)	2.6 (6.8)
95% CI	(11.2, 12.7)	(11.5, 12.9)	(-0.0, 0.6)	(-0.3, 5.5)
Median	12	12.2	0.2	1.3

Table 10 Platelets (10^9/l) statistics (n=23) – Study 001

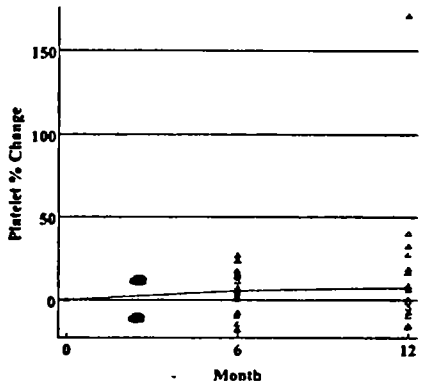
	Baseline	Endpoint	Change	% Change
Mean (SD)	77.4 (48.3)	85.0 (50.4)	7.6 (14.5)	15.0 (37.3)
95% CI	(56.5, 98.3)	(63.2, 106.8)	(1.3, 13.9)	(-1.2, 31.1)
Median	60.7	72.5	7.5	7.5

Figure 4 Median percent change of hemoglobin and platelets

Hemoglobin



Platelets



The enrolled and completers percent change of liver, spleen, hemoglobin, and platelets are displayed in Tables 11 and 12.

Table 11. % change from baseline of liver, spleen, hemoglobin and platelets -Study 001

	Enrolled			Completers		
	n	Mean (SD)	Median	n	Mean(SD)	Median
Liver	22	-11.8 (9.2) (-15.9, -7.8)	-12.5	21	-12.1 (9.4) (-16.4, -7.8)	-12.6
Spleen	19	-18.9 (9.2) (-23.4, -14.5)	-18.5	18	-19 (9.5) (-23.7, -14.3)	-19
Hemoglobin	23	2.6 (6.8) (-0.3, 5.5)	1.3	22	2.6 (6.9) (-0.5, 5.7)	1.3
Platelets	23	15 (37) (-1.2, 31.1)	7.5	22	16 (38) (-0.8, 32.8)	7.5

Table 12. % change from baseline of liver, spleen, hemoglobin and platelets -Study 001X

	Enrolled			Completers		
	n	Mean (SD)	Median	n	Mean(SD)	Median
Liver	17	-14.3 (7.0) (-18, -10.7)	-12.6	12	-14.5 (7.6) (-19.3, -9.6)	-13.3
Spleen	14	-27.7 (8.3) (-32.5, -22.8)	-26.4	10	-26.4 (5.5) (-30.4, -22.4)	-26.3
Hemoglobin	18	7.7 (8.9) (3.3, 12.2)	5.5	13	9.0 (10.2) (2.9, 15.2)	10.1
Platelets	18	26.2 (19.5) (16.5, 35.9)	31.4	13	26.1 (18.9) (14.6, 37.5)	30.8

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Study 003

This was a phase I/II open label, noncomparative, 6-month study of 50 mg TID OGT 918 in patients who were unable or unwilling to be treated with Ceredase or Cerezyme.

A total of 18 patients were enrolled in the study. One patient (#202) experienced unacceptable side effects (diarrhoea and gas) and was withdrawn after 13 weeks. The majority of patients were female (72%) and the majority were Ashkenazi Jews (83%). The mean age was 42.4 years. Mean weight was 62.14 kg.

The descriptive statistics of liver, spleen, hemoglobin, and platelets are displayed in Tables 13-17.

Table 13 Liver organ volume (l) (n=17) – Study 003

	Baseline	Endpoint	Change	% Change
Mean (SD)	2.4 (0.8)	2.3 (0.8)	-0.1 (0.2)	-5.9 (7.8)
95% CI	(2.0, 2.8)	(1.9, 2.7)	(-0.3, -0.03)	(-9.9, -1.9)
Median	2.4	2.2	-0.1	-6.7

Table 14 Spleen organ volume (l) (n=11) – Study 003

	Baseline	Endpoint	Change	% Change
Mean (SD)	2.0 (1.2)	1.9 (1.2)	-0.1 (0.1)	-4.5 (5.6)
95% CI	(1.2, 2.8)	(1.1, 2.7)	(-0.2, -0.01)	(-8.2, -0.7)
Median	1.3	1.3	-0.1	-4.8

Table 15 Hemoglobin (g/dl) statistics (n=17) – Study 003

	Baseline	Endpoint	Change	% Change
Mean (SD)	11.6 (1.6)	11.5 (1.8)	-0.1 (0.7)	-1.3 (6.0)
95% CI	(10.8, 12.4)	(10.5, 12.4)	(-0.5, 0.2)	(-4.4, 1.8)
Median	11.6	11.6	-0.4	-3.9

Table 16 Platelets (10^9/l) statistics (n=17) – Study 003

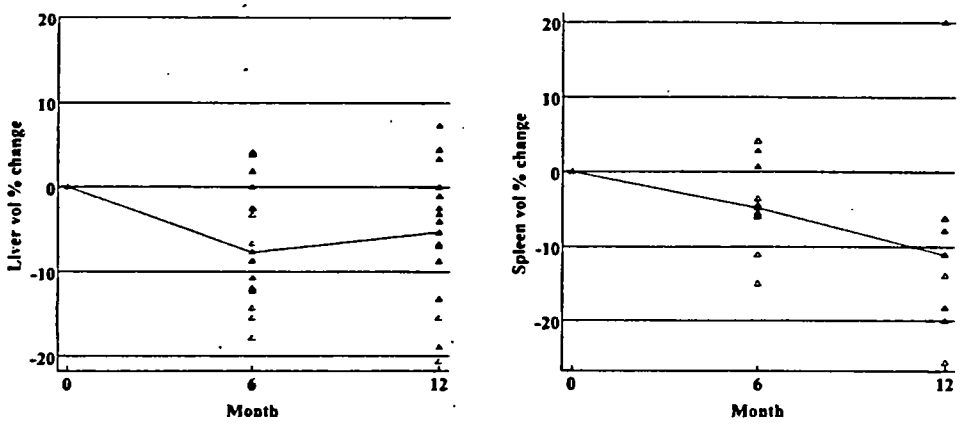
	Baseline	Endpoint	Change	% Change
Mean (SD)	116.5 (104.1)	121.8 (113.4)	5.4 (22.7)	2.0 (17.2)
95% CI	(63.0, 170.0)	(63.5, 180.1)	(-6.3, 17.0)	(-6.9, 10.8)
Median	85	76	1.5	4.8

Table 17 % change from baseline in liver, spleen, hemoglobin and platelets-Study 003X

	n	Mean (SD)	95% CI	Median	n	Mean (SD)	95% CI	Median
Liver	16	-6.7 (8.9)	(-11.5, -2.0)	-5.4	13	-6.2 (9.6)	(-12, -0.5)	-4.1
Spleen	11	-10.2 (11.8)	(-18.1, -2.2)	-11.1	9	-10.1 (13)	(20.1, -0.1)	-11.1
Hemoglobin	16	1.5 (10.1)	(-3.8, 6.9)	1.3	13	1.2 (10.6)	(-5.2, 7.7)	0.9
Platelets	16	11.7 (25.6)	(-1.9, 25.3)	8.1	13	14.7 (26.5)	(-1.4, 30.7)	8.7

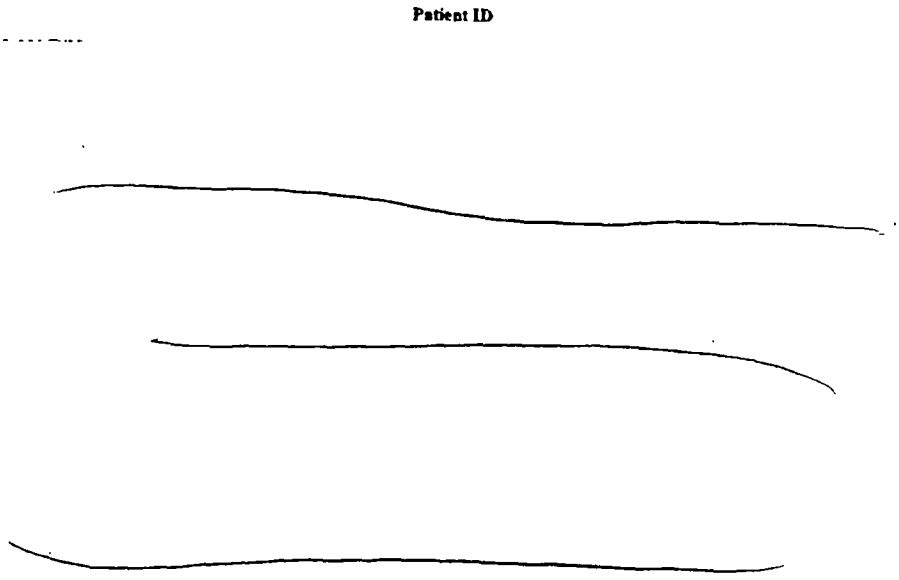
The median percent changes of liver volume (n=16) and spleen volume (n=11) over time are displayed in Figure 6. The medians were –7.7%, -5.4% at Month 6 and Month 12, respectively, for liver and –5% and –11%, respectively, for spleen (Fig 6).

Figure 6 Median % change of liver and spleen – Study 003X



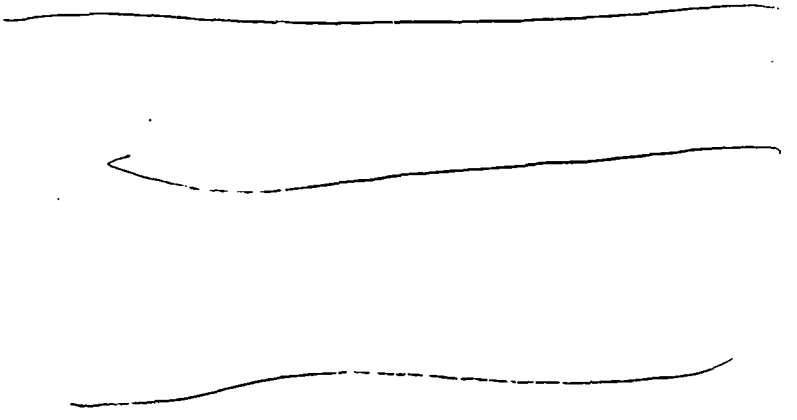
Percent change of liver and spleen volume by patient over time is displayed in Figure 7. Patients 101, 104, 105, 110, 111, 112, and 208 experienced tremor during the study starting on days 149, 149, 57, 76, 85, 149, and 57, respectively. Patient 208 had a second episode that started on day 139.

Figure 7. % change of liver and spleen volume – Study 003



During the extension, patient 103 experienced tremor/paraesthesia starting on days 179 and 271. For patient 111 paraesthesia began on days 117 and 304 (Figure 8).

Figure 8. % change of liver volume and spleen volume over time – Study 003X



The percentages of liver volume change over time are plotted for patients with and without tremor/paraesthesia in Figure 9.

Figure 9. % change of liver volume with or without tremor/paraesthesia – S003X

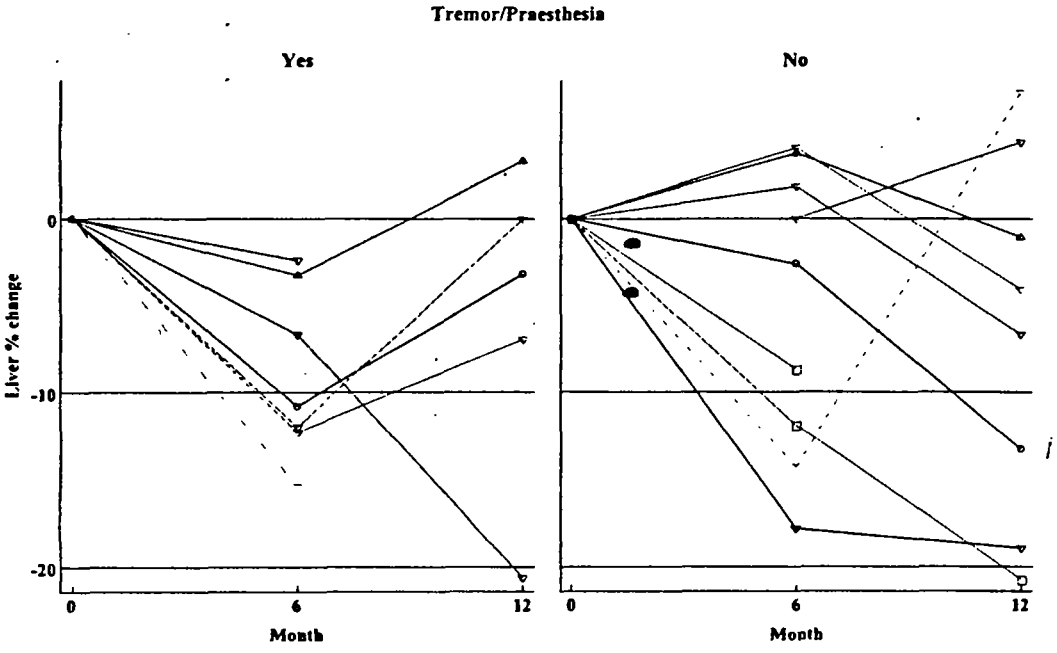


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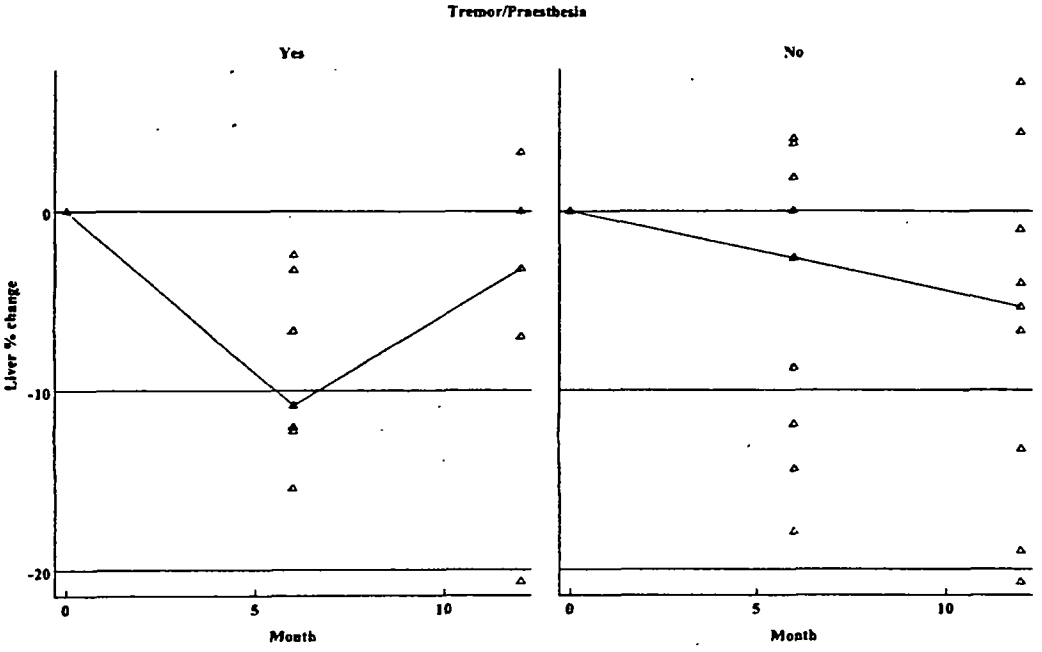
Figure 10 Median % change of liver volume with or without tremor/paraesthesia



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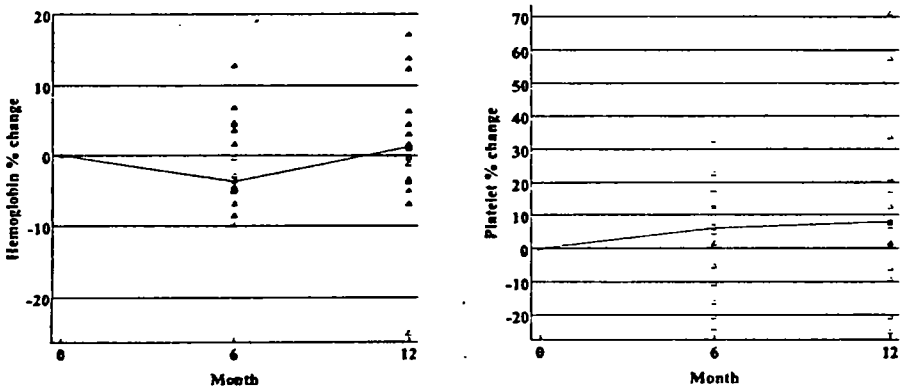
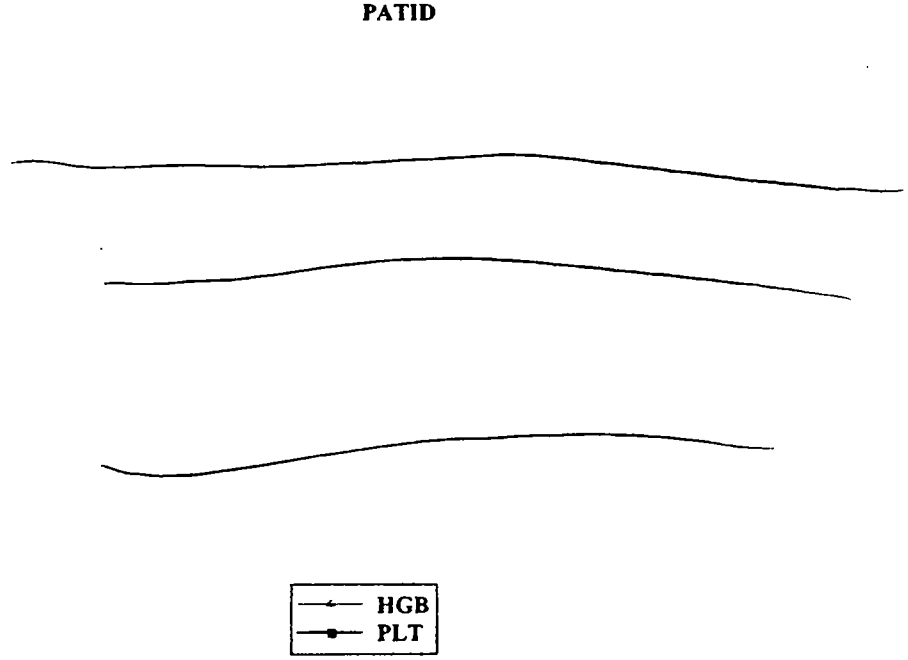
The median percent changes in hemoglobin and platelets are displayed in Figure 11. Medians were –3.5% and +1.2%, at Month 6 and Month 12, respectively for hemoglobin and 6% and 8% at Month 6 and Month 12, respectively for platelets.

Figure 11 Median % change of hemoglobin and platelets (n=16) – Study 3X (LOCF)



The individual patient hemoglobin and platelets value by time are displayed in Figures 12 for Study 003/003X.

Figure 12 Individual hemoglobin (g/dl) and platelets count (10^9/l) – Study 003, 003X



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Study 004

This was a Phase 2 study of open-label OGT 918 and Cerezyme, given alone or in combination in up to 36 adult patients with type 1 Gaucher disease who have received Enzyme Replacement Therapy (ERT) for a minimum of 2 years.

The primary objective of the study was to assess the tolerability of OGT 918 and Cerezyme given in combination compared with Cerezyme and OGT 918 alone. The justification for Patient Sample Size indicated that "This is the first study to compare tolerability and pharmacokinetics between OGT 918 alone, Cerezyme alone and OGT918/Cerezyme combination therapy. No formal sample size has been performed for this study. It is therefore designed to obtain as much information on the tolerability and pharmacokinetics of these dosing regimens as quickly and efficiently as possible." Since efficacy was not the primary objective, a formal statistical analysis was not intended: "Although no formal statistical analyses are intended, exploratory analyses may be undertaken as defined in the statistical analysis plan."

The primary analysis in the Statistical Plan was tolerability analysis. The secondary analyses were pharmacokinetics profiles and efficacy assessments.

In Protocol Amendment #1 (2/29/00), the primary efficacy endpoint was the percentage change in liver volume from baseline to 6 months. The treatment groups were to be compared using an ANCOVA model with terms for screening liver volume, and the minimization factors: gender, age; splenectomy; AVN; and length of time on ERT. Age and length of time on ERT would be fitted as continuous covariates. The pairwise differences between combination therapy and Cerezyme alone and between combination therapy and OGT 918 alone would be estimated together with the corresponding 95% confidence intervals.

In the Analysis Plan dated December 1, 2000, a step-down procedure was proposed for the multiple pairwise comparisons. The first comparison was to be between combination therapy and Cerezyme alone at the 5% level of significance. If this was statistically significant then OGT 918 alone was to be compared to Cerezyme alone at the 5% level. The comparison between combination therapy and OGT 918 alone was considered secondary. A complete cohort of 36 patients received one of 3 treatment groups using a minimization procedure. The minimization algorithm used a random component to allocate patients to the preferred group and the other 2 groups with odds of 7:1:1. Therefore, treatment assignment was not entirely deterministic. The factors used to balance across the 3 treatment groups in the minimization procedure were sex (M/F), age (18-30 years; >30-45 years; >45 years), splenectomy (Y/N), avascular necrosis (AVN) (Y/N), and length of time on ERT (>0-5 years; >5-7.5 years; >7.5 years). Patients in the OGT 918 group received 100 mg TID of OGT. Patients in the Cerezyme group continued to receive Cerezyme at their current dose. Patients in the combination group continued their current dose of Cerezyme and in addition received 100 mg TID of OGT 918.

The primary efficacy variable was percent change in liver volume from baseline to month 6. The sponsor's analysis of covariance (ANCOVA) model included treatment, gender, splenectomy, AVN as fixed factors and baseline liver volume, age and length of time on ERT as continuous covariates.

To control for multiplicity, the sponsor proposed pairwise treatment comparisons using a step-down procedure. The primary comparison was between the combination group and the Cerezyme group alone at the 5% level of significance. If the comparison was statistically significant then the OGT 918 group was to be compared to the Cerezyme group at the 5% level. The sponsor however, presented 3 treatment contrasts that were not adjusted for multiplicity. This reviewer performed analysis using the step-down procedure and the sponsor's model. The first pairwise comparison was between the combination group and the Cerezyme group. The least squared mean was –7.4% (-16.8%, 2.0%, CI). The p-value was 0.11 which was greater than 0.05, therefore, the comparison between the OGT 918 and Cerezyme was not performed.

The sponsor's model included many fixed factors and covariates, an inefficient model for a small sample size. This reviewer performed pairwise comparisons using t-tests comparing the combination to Cerezyme and OGT 918 to Cerezyme. The results are displayed in Table 18.

Table 18 T-test results of mean % change from baseline in liver volume – Study 004

OGT 918 n=10 mean	Cerezyme n=11 mean	Combination n=9 mean	Combination vs. Cerezyme mean difference (C.I.)	OGT 918 vs. Cerezyme mean difference (C.I.)
-2.89%	3.56%	-4.88%	-8.45 (-16.03, 0.87)	-6.45 (-14.22, 1.32)
			p=0.031	p=0.099

The results was statistically significant between the combination and Cerezyme. The difference between OGT 918 and Cerezyme showed a statistical trend.

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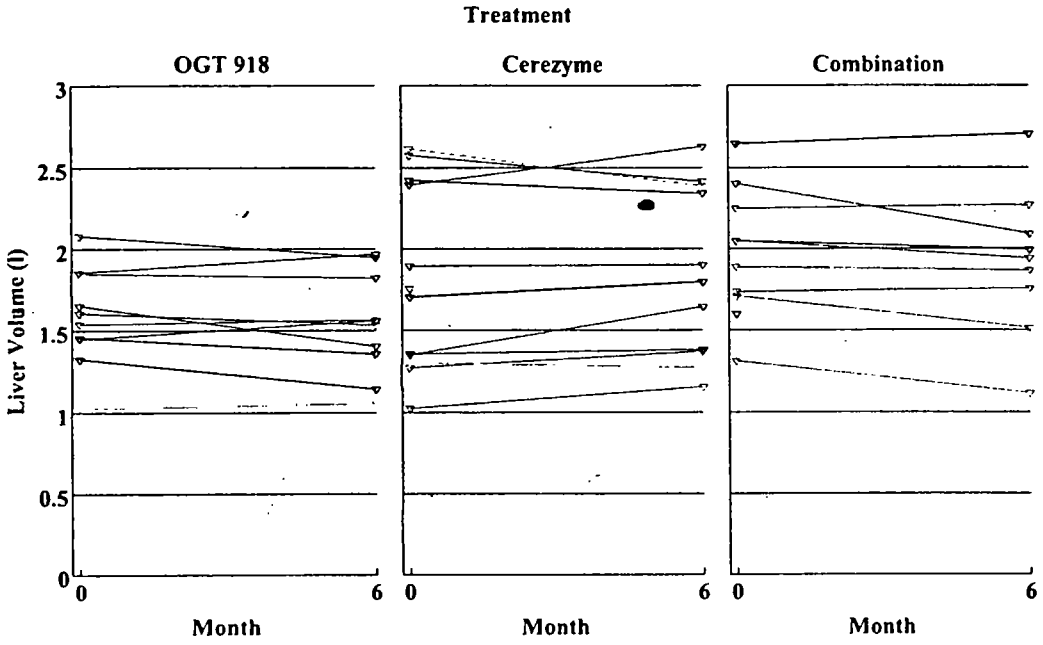
Figure 13 displays liver volume at baseline and at month 6 for each patient and treatment group.

Figure 13 Liver volume (l) by patient and treatment group – Study 004



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Figures 14 through 17 display percent change in liver organ volume, hemoglobin, and platelets by treatment group and patient.

Figure 14 Percent change in liver volume by treatment group – S004

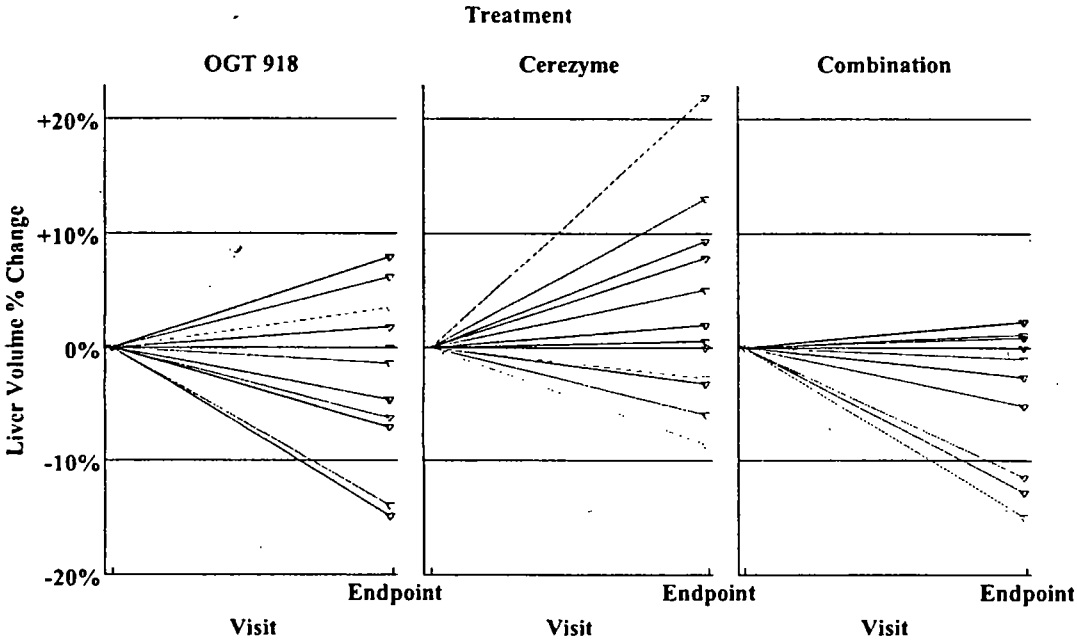

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Figure 15 Spleen volume % change by treatment and patient – Study 004

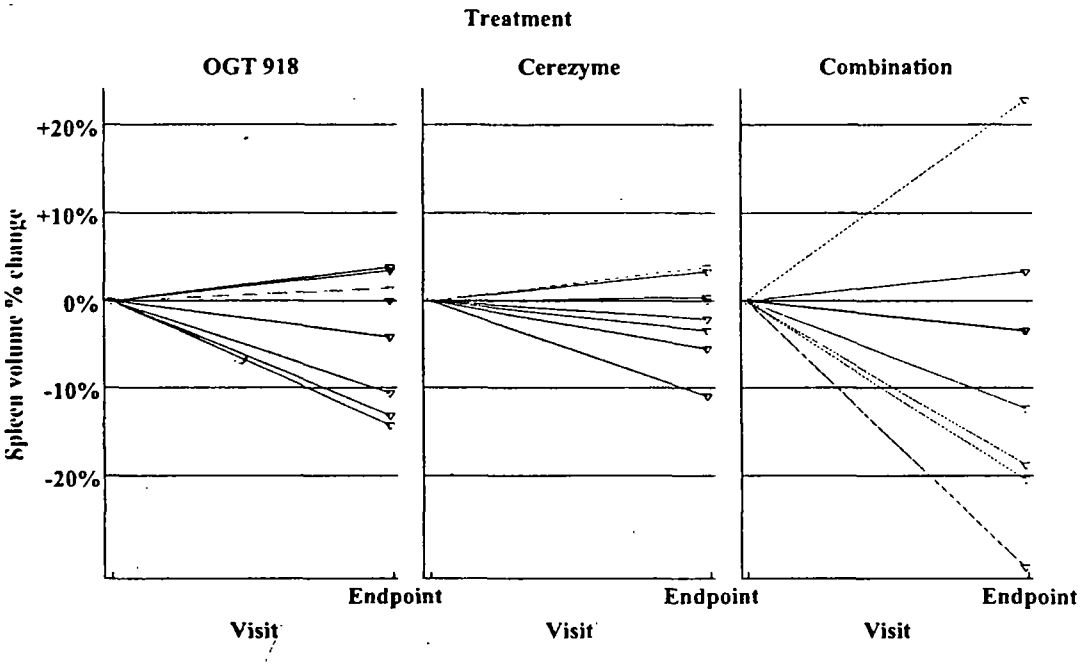


Figure 16 Hemoglobin (g/dl) change from baseline by treatment group and patient – Study 004

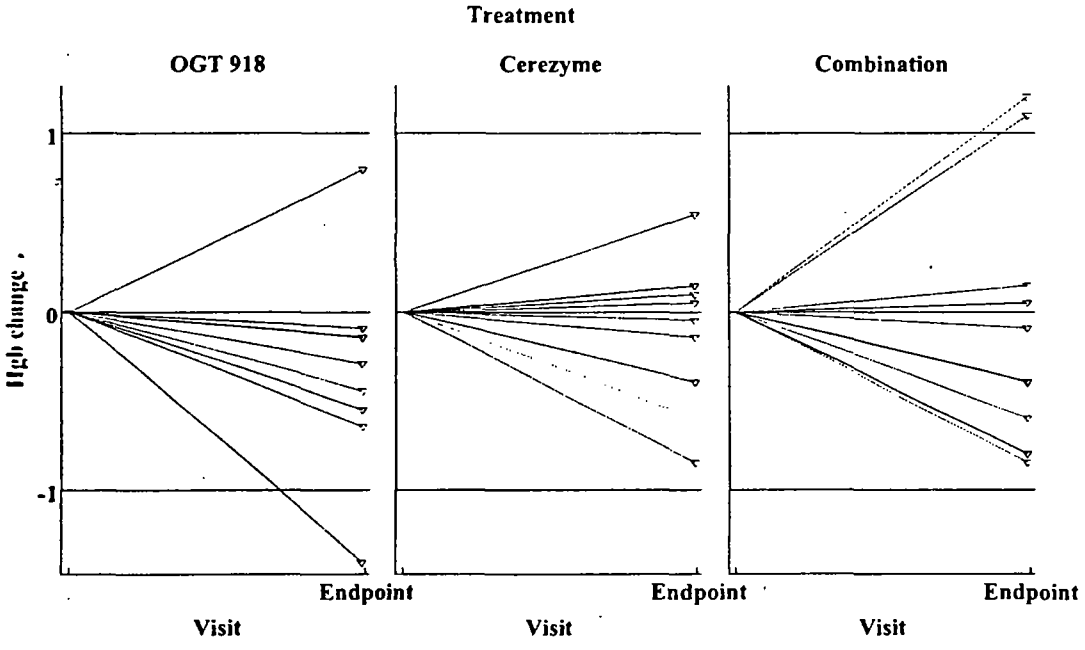
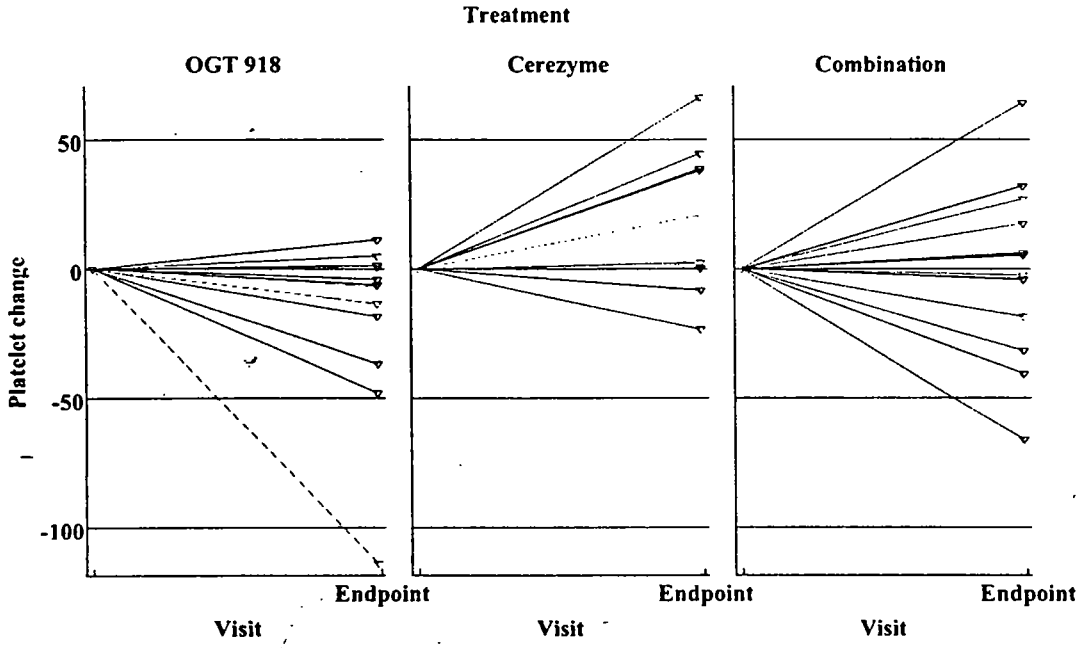


Figure 17 Platelets change (10^9/l) from baseline by treatment and patient – Study 004



The median percent liver change of patients with or without tremor and/or paraesthesia by treatment groups is displayed in Figure 18 and Table 19.

Figure 18 Median % change of liver volume of patients with or without neurological event by treatment group.

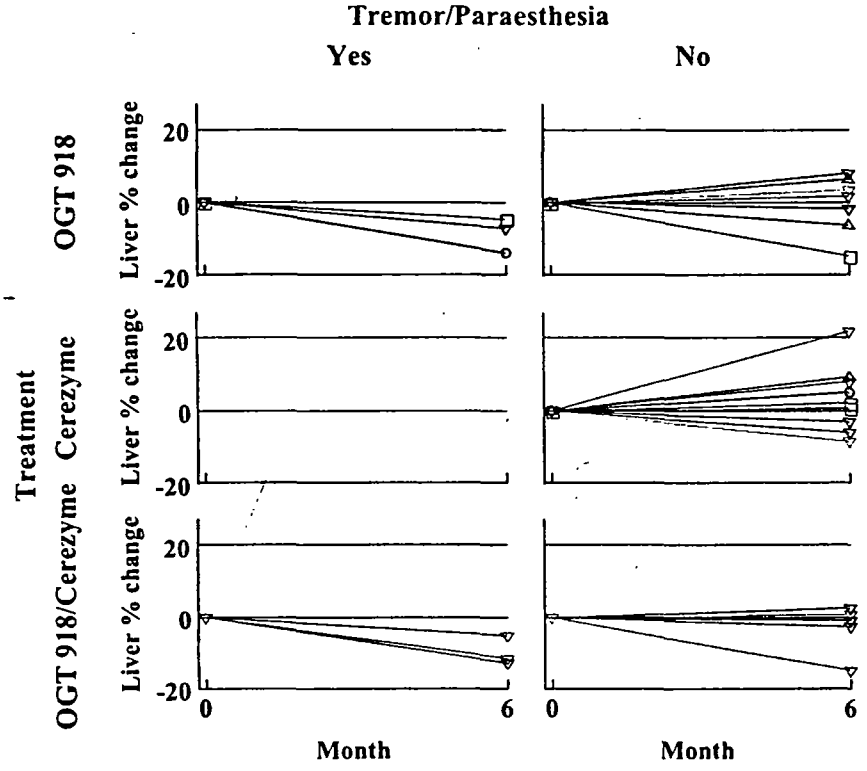
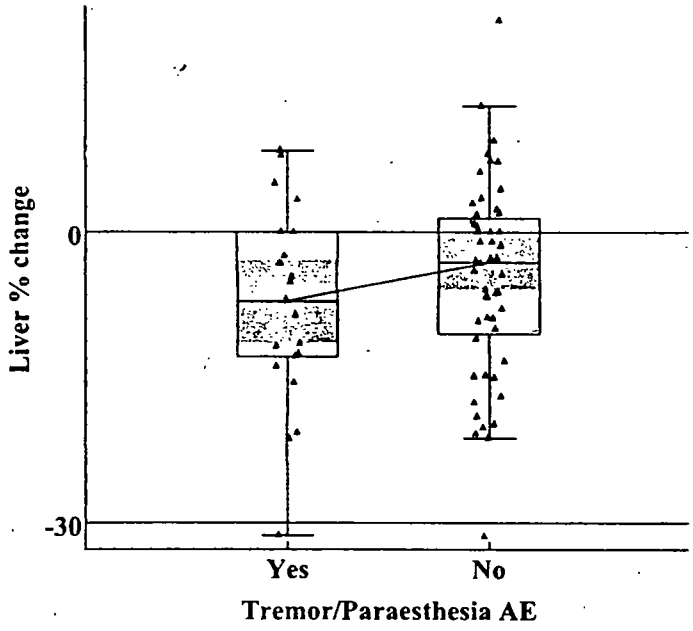


Table 19 Median % change of liver volume

Tremor/Paraesthesia	OGT 918		Cerezyme		Combination	
	n	Median	n	Median	n	Median
Yes	3	-7.1%	0	-	3	-11.4%
No	7	1.7%	9	2%	5	-1.1%

Liver volume median-percent changes from baseline to endpoint by patient with or without tremor/paraesthesia from studies 1, 1X, 3, 3X, 4 and 4X are displayed in Figure 19. The median percent change of liver volume for the 22 patients with tremor/paraesthesia was –7.1% and for the 52 patients without the AE was–3.1%.

Figure 19 Median % change from baseline to endpoint of liver volume



2.4 CONCLUSIONS AND RECOMMENDATIONS

The primary objective for the comparative study was to assess the tolerability of OGT 918 and Cerezyme given in combination compared with Cerezyme and OGT 918 alone. The efficacy analysis of liver volume was exploratory since no clinically meaningful difference was hypothesized and no sample size was determined. The sample size was too small to show consistent significant results that the liver percent change from baseline was different between the combination and Cerezyme. However, using pairwise t-test, the Combination was significantly better than Cerezyme in reducing liver volume..

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/s/

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