2. SYNOPSIS

NAME OF COMPANY **Genzyme Corporation** **500 Kendall Street** **Cambridge, MA 02142** NAME OF FINISHED PRODUCT NA NAME OF ACTIVE INGREDIENT **deferitrin**	SUMMARY TABLE Referring to Part of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

TITLE OF STUDY:

Safety and efficacy of rising doses of deferitrin in beta-thalassemia patients

INVESTIGATOR AND STUDY CENTER(S):

Three study centres in Italy participated in this clinical trial.

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PUBLICATION (REFERENCE):

Not applicable.

STUDIED PERIOD:

Approximately 50 months, from 01 March 2005 (first patient enrolled) to 31 May 2007 (last patient completed).

PHASE OF DEVELOPMENT:

Phase 2

OBJECTIVES:

The primary objective was:

- To determine the safety of deferitrin when administered in patients with iron overload secondary to beta-thalassemia.

The secondary objectives were:

- To examine the efficacy of deferitrin on liver iron concentration in patients with iron overload secondary to beta-thalassemia.
- To examine the pharmacokinetics (PK) of deferitrin when administered in patients with iron overload secondary to beta-thalassemia.

METHODOLOGY:

This was an open-label, dose escalation study of deferitrin in patients with iron overload secondary to beta-thalassemia. A total of 150 patients were planned to be screened to assess suitability for participation in the study.

At screening, eligible patients, who had signed an informed consent, had their medical history taken, concomitant medications and therapies recorded, received a physical examination (including vital signs), electrocardiogram (ECG), Superconducting Quantum Interference Device (SQUID) assessment, and a laboratory safety assessment. For patients in Cohort 4, magnetic resonance imaging (MRI) T2* and FerriScan (R_2 MRI method) assessments of cardiac and liver iron concentration, respectively, were also performed at the screening visit. Following screening, subjects who met the requirements of the study's inclusion and exclusion criteria were enrolled into the study.

There were 4 patient Cohorts with 15-20 patients to be treated in Cohorts 1, 2 and 3 and up to 30 patients to be treated in Cohort 4. Patients in Cohort 1 received approximately 5 mg/kg/day of deferitrin for the treatment duration, with Cohorts 2 and 3 receiving approximately 10 mg/kg/day and 15 mg/kg/day,

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respectively. Patients in Cohort 4 received 25 mg/kg/day in 2 doses of 12.5 mg/kg separated by approximately 12 hours. Treatment duration was 12 weeks for Cohorts 1, 2 and 3, while treatment duration was 48 weeks for Cohort 4. Once a minimum of 10 patients had completed 6 weeks of treatment the laboratory values and adverse event (AE) data were reviewed by the Principal Investigators, and discussed with the Medical Monitor focusing on any clinically significant abnormalities. If there were no clinically significant safety concerns, the next Cohort of patients was then allowed to commence dosing.

Study Procedures Cohorts 1, 2 and 3

For patients entering the study in Cohorts 1, 2 and 3, all other iron chelators were stopped at least 5 days prior to commencing deferitrin therapy. At screening, initiation of treatment, then every week, and at the follow-up visit, renal function was monitored by assessment of serum electrolytes, urea and creatinine as well as urinalysis, urine chemistries, and urinary beta 2-microglobulin. Additionally patient's serum chemistry, liver function and complete blood count was assessed at screening, initiation of treatment, then every two weeks, and at the follow-up visit. ECGs were repeated at Week 6, and the end of the study. Trough pharmacokinetic measurements of deferitrin were assessed via collection of blood samples pre-dose during Weeks 1, 6 and 12 from all patients. In addition, where possible, in a sub-set of five patients per Cohort, blood samples were collected for pharmacokinetic measurements immediately pre-dose and then 1, 2, 4 and 8 hours after study drug administration on Day 0 and Week 12.

Study Procedures for Cohort 4

For patients entering the study in Cohort 4, all other iron chelators were stopped at least 5 days prior to commencing deferitrin therapy. For visits up to Week 12, all safety laboratories, ECGs and pharmacokinetic measurements were performed as in Cohorts 1, 2 and 3. Additional visits occurred every 2 weeks until Week 24 and every 4 weeks thereafter until Week 48. At each of these additional visits, renal function was monitored by assessment of serum electrolytes, urea, and creatinine as well as urinalysis, urine chemistries, and urinary beta 2-microglobulin. Serum chemistry, liver function and complete blood count were assessed at every study visit. Serum pregnancy tests were repeated at Weeks 12, 24, 36, 48 and 52 on all women of child bearing potential. ECGs were also collected at Weeks 12, 24, 36, 48 and 52. Trough pharmacokinetic measurements of deferitrin were assessed via collection of blood samples pre-dose during Weeks 24, 36 and 48 from all patients. In addition, where possible, in a sub-set of five patients, blood samples were collected for pharmacokinetic measurements immediately pre-dose and then 1, 2, 4, and 8 hours after study drug administration and pre-dose for the 12 hour assessment on Weeks 24 and 48. FerriScan and SQUID assessments were repeated at Weeks 12, 24, 36 and 48. MRI T2* was repeated at Weeks 24 and 48.

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As the primary objective of this study was to assess the safety of deferitrin, a Data Safety Monitoring Board (DSMB) was established. The DSMB provided ongoing, expert, independent review of safety data to assure that the risks to the study patients were minimised during the conduct of the study.
The DSMB reviewed safety data at the end of 12 weeks therapy for all Cohorts and in addition for Cohort 4, after 24 and 48 weeks therapy. They also reviewed the Liver Function Tests data from Cohorts 2 - 4 when 10 patients had completed 6 weeks of treatment. They met urgently if (1) laboratory abnormalities or AEs were found consistent with renal damage (e.g., serum creatinine increase to 1.5x the upper limit of normal) or thrombocytopenia (platelets < 50,000/mm^3) or (2) any serious unexpected AEs had occurred. Following its review, all DSMB recommendations and decisions were communicated to the Sponsor in writing for appropriate follow-up.

Previous Data and Possible Side Effects

Prior to the beginning of the current study, iron balance studies indicated that deferitrin induced iron excretion and the likely efficacious dose was 15 mg/kg/day or above. At the time deferitrin had only been administered for 10 days at 11 mg/kg/day, therefore the initial dose for Cohort 1 was chosen to be 5 mg/kg/day. Preliminary analysis of the data from Cohorts 1, 2 and 3 indicated that doses of 10 and 15 mg/kg/day approached an efficacious dose. However, iron excretion was similar at these doses; therefore in light of the 3-4 hour half life of deferitrin, Cohort 4 examined a dose of 25 mg/kg/day in two divided doses (i.e., approximately 12.5 mg twice a day).
Possible side effects reported from the previous and ongoing studies in people include, but are not limited to: headaches, dizziness, palpitations, nausea, vomiting, abdominal pain, arthralgia, back pain, cannula site reaction, constipation, diarrhoea, oedema, weakness, decreased haemoglobin, hyperglycaemia, increases in liver enzymes and upper respiratory infection. Studies in animals showed that at high doses, animals (rats and dogs) given deferitrin experienced kidney damage. Studies in monkeys did not show these effects. Studies in humans to date have not shown any kidney damage. However, this clinical trial included many measurements of kidney function to ensure that any risks were minimised. In this study, patients received one of four doses of deferitrin. Patients were allowed to have received a prior dose of deferitrin (either in this study or another) as long as the last dose was > 12 months prior to entry into Cohort 4. Safety information from each cohort of patients was reviewed by the Sponsor's Medical Monitor and Investigators prior to the treatment of the next cohort of patients.

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NUMBER OF PATIENTS (PLANNED AND ANALYSED):

A total of up to 90 patients were planned to participate; 15-20 patients in Cohorts 1, 2, and 3, and up to 30 patients in Cohort 4.

A total of 58 patients were treated; 14 patients in Cohort 1, 15 patients in Cohort 2, 18 patients in Cohort 3, and 11 patients in Cohort 4. The 11 patients in Cohort 4 were withdrawn from treatment by the Sponsor due to unexpected related adverse events in 3 patients and they were entered into the follow-up period of 4 weeks. All patients completed the follow-up visits.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

INCLUSION:

Subjects who met all of the following inclusion criteria were eligible to participate in this study:

1. Patients who provided voluntary signed and dated written informed consent to participate in this study prior to performing any protocol-related procedures.
2. Beta-thalassemia patients, 18 years of age or older, undergoing chronic blood transfusion therapy and iron chelation therapy.
3. a. Cohorts 1, 2 and 3: Evidence of systemic iron overload at screening as assessed by a) serum ferritin between 800 and 3000 ng/mL and b) liver iron concentration as determined by SQUID between 2 and 10 mg/g dry weight
   b. Cohort 4: Evidence of systemic iron overload at screening as assessed by a) serum ferritin ≥ 350 ng/mL and b) liver iron concentration as determined by SQUID > 5 mg/g dry weight.
4. Cohort 4 only: Patients had either (1) a cardiac MRI showing T2* > 20 msec; or (2) for patients with a cardiac MRI T2* between 12 - 20 msec a cardiac echocardiogram had to be performed, and patients had a normal left ventricular ejection fraction.
5. Willing and able to discontinue other chelation therapy use for the period of study.
6. Female patients of childbearing potential had to use a medically acceptable form of birth control during the study and for 1 month afterward. Acceptable birth control measures were: abstinence, oral contraceptives, hormonal contraceptive implants, barrier contraceptives (condom, diaphragm with spermicide), intrauterine device, and/or vasectomised partner. Male patients had also to use barrier contraceptives during the study and for 1 month afterward.
7. Had a level of understanding and willingness to cooperate with all study procedures as described in the consent form and as scheduled by the study site.
8. a. Cohorts 1, 2 and 3: Weight ≥ 40 kg.
   b. Cohort 4: Weight ≥ 35 kg.

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EXCLUSION:

Subjects who met any of the following exclusion criteria were not eligible for participation in this study:

1. History of any condition which, in the opinion of the Investigator, would jeopardise the safety of the patient or impact the validity of the study results.
2. Calculated glomerular filtration rate (GFR) less than 60 mL/min. GFR was calculated using the Cockcroft-Gault formula.
3. Platelet count less than 100,000/mm^3 (100 x 10^9/L).
4. Alanine transaminase (ALT) greater than 3 times the upper limit of normal.
5. Clinically significant history of renal disease or transient renal failure including a history of clinically significant proteinuria.
6. Clinically significant cardiac ventricular arrhythmia in the last two years.
7. History of a generalised seizure disorder.
8. HIV sero-positive patients.
9. History of serious immunologic hypersensitivity to any medication, such as anaphylaxis or angioedema.
10. Participation in an investigational drug study within 30 days preceding screening or during the study.
11. Women who were pregnant, breast-feeding or had a positive serum pregnancy test at screening.
12. Current alcohol or drug abuse.
13. a. Cohort 1, 2 and 3: Prior administration of deferitrin in another clinical trial was not an exclusion, but patients were not to receive deferitrin at more than one dosing level in this trial.
    b. Cohort 4: Patients who had taken deferitrin within the past 12 months.
14. Patients with any form of magnetic contamination that cannot be removed e.g., surgical staples, cardiac pacemakers, or dental braces.

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION; BATCH NUMBER:

In Cohorts 1, 2 and 3 deferitrin was administered orally once a day for 12 weeks, at doses of 5, 10 and 15 mg/kg/day, respectively. In Cohort 4 deferitrin was administered orally twice a day for 48 weeks. The total daily dose was 25 mg/kg/day, administered in two divided doses approximately 12 hours apart (i.e., approximately 12.5 mg/kg twice daily).

Deferitrin was supplied as capsules. For Cohorts 1, 2 and 3 there were two capsule strengths: 50 mg and

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250 mg. The 5 mg/kg/day group only received the 50 mg capsules; the 10 and 15 mg/kg/day dose groups usually received a combination of 50 mg and 250 mg capsules. In Cohort 4, 100 mg and/or 250 mg capsules were available for use, however only 250 mg capsules were used.
The following batch (lot) numbers were used in this clinical trial: [redacted]

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION; BATCH NUMBER:

Not applicable.

DURATION OF TREATMENT:

Total study duration was approximately 16 weeks for Cohorts 1, 2 and 3 including 12 weeks of treatment. Total study duration was intended to be approximately 56 weeks for Cohort 4 including 48 weeks of treatment. Due to early study termination, no patient in Cohort 4 received deferitrin for more than 8 weeks before being entered into the full follow-up period.

CRITERIA FOR EVALUATION:

SAFETY:

Safety was evaluated on the basis of AEs (reported and/or observed), changes in safety laboratory assessments, and concomitant medications usage. As the primary objective of this study was to assess the safety of deferitrin, all safety data were frequently reviewed by the study staff and the Medical Monitor. In addition a DSMB was established, which provided ongoing, expert, independent review of safety data to ensure that any risks to the study patients were minimised during the conduct of the study.

EFFICACY:

Efficacy in Cohorts 1, 2 and 3 was assessed by comparing the liver iron concentration as determined by SQUID measurements at Baseline and End of Treatment. Efficacy in Cohort 4 was also assessed with SQUID and FerriScan measurements at Baseline, Week 12, Week 24 and Week 48. The change in serum ferritin was also examined for all Cohorts.

STATISTICAL METHODS:

SAFETY:

Adverse events were summarised overall, by system organ class, and by Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Listings are provided for AEs leading to discontinuation from the study. Results from laboratory parameters including serum electrolytes, renal measures, other chemistries, liver function tests, coagulation parameters, urinalysis, urine chemistries, and urinary beta-2 microglobulin

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were summarised by dose group and time point. Changes from Baseline to the end of study were also summarised by dose group.
The number and percentage of patients receiving concomitant medication and new concomitant medications were summarised for each dose by therapeutic class. Concomitant medications were coded to anatomic therapeutic class and preferred term using the WHODRUG dictionary.

EFFICACY:
Efficacy was evaluated on the basis of the change from Baseline (Day 0) to End of Treatment in liver iron concentration as assessed by SQUID (all Cohorts) and FerriScan (patients in Cohort 4 only) by treatment group. The change in serum ferritin from Baseline to End of Treatment was also assessed for each dose group. Efficacy parameters were assessed taking into consideration the effect of iron intake via blood transfusion.

PHARMACOKINETICS:
Plasma pharmacokinetic measurements of deferitrin and its metabolites were determined by model independent (non-compartmental) analyses. The following parameters were determined: Css(24), AUC(0-t), AUC(0-inf), Kel, T½el, Cmax, and Tmax.

SUMMARY CONCLUSIONS

A total of 84 patients were screened, 61 patients were enrolled, and 58 patients (24 males, 34 females) were treated with deferitrin in the study (Cohort 1, 14 patients; Cohort 2, 15 patients; Cohort 3, 18 patients; and Cohort 4, 11 patients). All 47 patients treated in Cohorts 1,2 and 3 completed the study. The study was stopped prematurely and all ongoing patients in Cohort 4 were withdrawn from treatment due to unexpected related renal AEs in 3 patients. One patient in Cohort 1 withdrew consent before treatment was initiated. Two patients scheduled for Cohort 4, were unable to be entered into washout and treatment due to the early study termination.

SAFETY

A total of 52 of the 58 treated patients (89.7%), divided in similar proportions over the 4 cohorts experienced a total of 197 treatment-emergent AEs. The most frequently involved System Organ Classes (SOC) were Infections and Infestations, Gastrointestinal Disorders, Nervous System Disorders, and Musculoskeletal and Connective Tissue Disorders. The most frequently reported AEs by Preferred Term were headache, abdominal pain, rhinitis, back pain, pharyngitis, and abdominal pain upper. No differences were observed with regard to the types of AEs (i.e., Preferred Terms) that were experienced during

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treatment between the different Cohorts, except that in Cohort 4 more events were reported for the SOC of Renal and Urinary Disorders.

The majority of the AEs were considered by the Investigators to be mild or moderate in intensity. In Cohorts 1, 2, and 3, 8 AEs in 8 patients were considered by the Investigators to be related (possible, probable, definite) to deferitrin treatment, while in Cohort 4 14 AEs in 6 patients were considers related. One patient without a history of congestive heart failure or arrhythmia experienced a cardiac failure of severe intensity, 2 days after study completion and 21 days after last study medication. The patient was hospitalised and died 11 days later. The event was considered by the investigator as not related to study treatment.

Three patients experienced a total of 7 serious adverse events (SAEs), of which 2 were considered as probably related to deferitrin treatment. Two of these 7 SAEs occurred in Cohort 1, 3 SAEs occurred in Cohort 2, and 2 SAEs occurred in Cohort 4. Three SAEs in 2 patients (cardiac failure, acute renal failure, and interstitial nephritis) were reported to be of severe intensity. As mentioned above, one patient died following the SAE of cardiac failure, while the other patients recovered from the SAEs. In Cohort 4, three patients were suspended from treatment due to renal adverse events and a further patient was suspended due to an AE of worsening haemolytic anaemia. Treatment with 12.5mg/kg deferitrin twice daily was consequently discontinued due to the unacceptable renal toxicity.

EFFICACY

The results of the study showed that the PK for deferitrin dosed once daily was linear and dose proportional. The serum half-life was 1.3-1.8 hrs, clearance was 226-340 mL/min, and mean residence time was 2.8-3.4 hrs for once daily dosing. PK data from Cohort 4 was very limited and data presented in this report is based on data from Cohorts 1-3 using once daily dosing.

Mean iron excretion in mg/kg/day (SD) for Cohort 1 was 0.23 (0.22), Cohort 2 was 0.46 (0.14) and Cohort 3 was 0.33 (0.12). The reasons for the lack of dose proportionality in iron excretion are unknown. Deferitrin dosed once daily was associated with a mean iron excretion of 0.34 mg/kg/day. Efficacy could not be assessed in Cohort 4 due to early termination of the study.

CONCLUSION

[redacted]