2 SYNOPSIS

NAME OF COMPANY Genzyme Corporation **NAME OF FINISHED PRODUCT** Mipomersen **NAME OF ACTIVE INGREDIENT** ISIS 301012 ($C_{230}H_{305}N_{67}O_{122}P_{19}S_{19}Na_{19}$)	**SUMMARY TABLE** Referring to Part of the Dossier: Volume: Page: Reference:	**FOR NATIONAL AUTHORITY USE ONLY:**

Title of Study: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Varying Loading and Maintenance Dosing Regimens of ISIS 301012 Administered to Hypercholesterolemic Subjects

Investigator: [redacted]

Study Centers: 1 study center in Germany

Publication (reference): None

Study Period: 24 months

Initiation Date: 23 August 2005

Completion Date: 29 August 2007

Phase of Development: 2

Study Objectives:

The objectives of this study included the following:

- To examine the safety and tolerability of varying load and maintenance dose/regimens of mipomersen in hypercholesterolemic subjects
- To determine the optimal load and maintenance dose/regimen for mipomersen activity in hypercholesterolemic subjects
- To characterize the pharmacokinetics and pharmacodynamics of mipomersen during and following 3 months of treatment in hypercholesterolemic subjects

Methodology:

This was a randomized, double-blind, placebo-controlled, Phase 2 study of mipomersen in otherwise healthy subjects 18 to 65 years of age with hypercholesterolemia. Participation in the study lasted approximately 11 months and consisted of a 21-day screening period, a 2-week subcutaneous (SC) loading dose treatment period (or no load), an 11-week SC maintenance dose treatment period, and a 6-month post-treatment follow-up period. Baseline was defined as the day the subject received the first dose of study drug.

Approximately 60 subjects were to be dosed to achieve 50 evaluable subjects. Subjects were assigned to 1 of 3 parallel dose cohorts (A to C) or 1 of 2 subsequent dose escalation cohorts (D or E). At least 8 subjects per dose cohort were randomized to receive mipomersen and 2 subjects were randomized to receive placebo.

The study cohorts were as follows:

- Cohort A (slow load [200 mg × 4 doses] with every other week [QOW] 200 mg maintenance): mipomersen 200 mg/placebo 4 loading doses within the first 11 days followed by mipomersen 200 mg/placebo QOW for 11 weeks (6 total maintenance doses)

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- Cohort B (slow load [200 mg × 4 doses] with QOW 100 mg maintenance): mipomersen 200 mg/placebo 4 loading doses within the first 11 days followed by mipomersen 100 mg/placebo QOW for 11 weeks (6 total maintenance doses)
- Cohort C (no load; once weekly [QW] 200 mg maintenance): mipomersen 200 mg/placebo QW for 13 weeks (13 total maintenance doses)
- Cohort D (no load; QW 300 mg maintenance): mipomersen 300 mg/placebo QW for 13 weeks (13 total maintenance doses)
- Cohort E (no load; QW 400 mg maintenance): mipomersen 400 mg/placebo QW for 13 weeks (13 total maintenance doses)

Screening Period

The screening period took place within a maximum of 21 days before the first dose of study drug was administered. Subjects were seen twice during this period with at least 1 week between visit dates. Fasting lipid panels were collected at each visit.

At the first screening visit, blood and urine samples were collected for clinical laboratory tests, including a standard safety profile comprised of a chemistry panel, hematology (complete blood count with differential), urinalysis, coagulation (activated partial thromboplastin time [aPTT] and prothrombin time [PT]), thyroid hormones (thyroid-stimulating hormone and T4), full fasting lipid panel, hepatitis B surface antigen, antibodies to hepatitis C virus, pregnancy test (female subjects only), and a urine drug screen and alcohol screen. Subjects were also counseled by a staff nutritionist or dietician to maintain a consistent diet and exercise regimen throughout the course of the study. Subjects were asked to report all significant deviations to their diet or physical activity to the study staff at each visit throughout the study.

Subjects returned to the study center at least 1 week after their first screening visit to discuss their diet and physical activity levels with the study center staff. Blood samples were also taken at this visit for a fasting lipid panel.

Adverse events (AEs) and concomitant medications were recorded beginning from the day that informed consent was signed until the subject had completed the end of the post-treatment follow-up period, or 6 months after the last dose of study drug, whichever occurred later.

Treatment Period

For Cohorts A and B, the treatment period included a 2-week SC loading dose treatment period (total of 4 loading doses) followed by an 11-week SC maintenance dose treatment period (total of 6 maintenance doses). For Cohorts C, D, and E, the treatment period included a 13-week SC maintenance dose treatment period (total of 13 maintenance doses). Subjects in Cohorts C, D, and E did not receive loading doses.

Subjects who satisfied all eligibility criteria were randomized into the treatment period on Day 1.

Subjects reported to the study center on the morning of Day 1 after a minimum 12-hour fast. Prior to study drug administration, inclusion criteria were reviewed and vital signs were taken. Blood and urine samples were collected for clinical laboratory evaluations, including urinalysis, chemistry, hematology, coagulation, complement, vitamins A and E, a full lipid panel, and anti-mipomersen antibodies.

Randomization to study drug took place on Day 1, just prior to the first dose. All doses of study drug were administered by SC injection. Loading doses were given on Days 1, 4, 8, and 11 for Cohorts A and B.

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Blood was drawn for coagulation and complement. Subjects reported AEs, concomitant medications, and diet and physical activity levels to the study center staff.

Following administration of the first dose of study drug on Day 1, all subjects were admitted for an overnight stay at the study center for observation and safety assessments. A subject could have been discharged from the study center following the 24-hour post-dose assessments.

At each study visit, vital signs and a urinalysis were performed, and blood samples were collected for clinical laboratory evaluations, including chemistry, hematology, full lipid panel, coagulation, complement, and pharmacokinetic sampling. Subjects reported AEs, concomitant medications, and diet and physical activity levels to the study center staff.

All subjects were admitted to the study center for an overnight stay after the last dose of study drug was administered for serial pharmacokinetic sampling.

Post-Treatment Follow-up Period

Following the last dose of study drug, subjects entered the 6-month post-treatment follow-up period. At each visit during the post-treatment follow-up period, vital signs were measured, a urinalysis was performed, a blood sample was collected for a full lipid panel, and subjects reported AEs, and concomitant medications, and diet and physical activity levels to the study center staff. Blood was collected for clinical laboratory evaluations, including chemistry, hematology, and pharmacokinetic sampling. An electrocardiogram (ECG) and a complete physical examination were performed at selected visits. Thyroid hormones, vitamins A and E, and anti-mipomersen antibodies were evaluated at selected visits.

Duration of Treatment: 13 weeks

Number of Subjects:

Planned: 60

Dosed: 50 (10 placebo and 40 mipomersen)

Completed treatment period: 38 (8 placebo and 30 mipomersen)

Discontinued treatment period: 12 (2 placebo and 10 mipomersen)

Completed post-treatment follow-up period: 47 (9 placebo and 38 mipomersen)

Discontinued post-treatment follow-up period: 3 (1 placebo and 2 mipomersen)

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Diagnosis and Main Criteria for Inclusion:

The study population included male and female subjects 18 to 65 years of age with hypercholesterolemia, defined as stable low-density lipoprotein cholesterol (LDL-C) ≥130 mg/dL (3.36 mmol/L) (from at least 1 of the screening measurements) and triglycerides (TG) ≤400 mg/dL (4.55 mmol/L) after at least a 12-hour fast. Other key inclusion criteria included a body mass index ≥25 kg/m^2 and ≤32 kg/m^2 and stable body weight (± 5%) ≥3 months prior to randomization. Subjects were not to have been on weight-altering or diet-modification regimens for 3 months prior to randomization and were to refrain from such regimens throughout the course of the study, including the post-treatment follow-up period. Subjects were not to be on any lipid-lowering drugs within 30 days or 5 half-lives (of the lipid-lowering drug), whichever was longer, prior to entering the screening period.

Investigational Product and Comparator Information:

Test product: 100 mg/vial mipomersen lyophized drug product

Comparator: 0.9% sterile saline provided by the study center

Criteria for Evaluation:

Efficacy:

The efficacy variables included LDL-C, apolipoprotein (apo) B, high-density lipoprotein cholesterol (HDL-C) (by direct measurement), TG, total cholesterol (TC), non-high-density lipoprotein cholesterol (non-HDL-C), very-low-density lipoprotein cholesterol (VLDL-C), apo A1, lipoprotein(a) (Lp[a]), and ratios of LDL-C/HDL-C, TC/HDL-C, and apo B/apo A1. All lipid parameters were measured using the direct method. A 2-step precipitation method was used in addition to the direct method to measure HDL-C.

Pharmacokinetics:

The pharmacokinetic variables included plasma concentration of mipomersen.

Safety:

The safety variables included AEs, serious adverse events (SAEs), laboratory parameters, physical examination data, vital signs, and 12-lead ECGs.

The immunogenicity variables included anti-mipomersen antibodies.

Statistical Methods:

Efficacy:

The primary efficacy analysis was performed on the Intent-to-Treat population, which included all randomized subjects. Placebo subjects from the 5 cohorts were pooled for all efficacy analyses. The primary efficacy variable was the percent reduction in LDL-C from baseline to Week 15 with last post-baseline value carried forward. Summary statistics for the percent change in LDL-C from baseline to Week 15 are provided for each cohort. Comparisons between the mipomersen treatment groups and the placebo group were performed using the exact Wilcoxon rank sum test. Analyses of the secondary efficacy variables were performed in the same manner.

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Pharmacokinetics:

Plasma mipomersen concentrations (from both serial and trough sampling) were summarized by cohort, dose, study day, and time point, when applicable, using descriptive statistics. Plasma pharmacokinetic parameters for mipomersen (for the last SC dose administered) were calculated using non-compartmental methods. Calculated plasma pharmacokinetic parameters were summarized by cohort and dose using descriptive statistics. Nominal time was used when summarizing plasma-concentration time profiles by descriptive statistics. Plasma concentrations below the lower limit of quantitation were treated as missing in the calculation of descriptive statistics.

The relationship between the inhibitory activity of serum apo B (normalized by baseline) and plasma trough concentrations of mipomersen on Day 99 (Cohorts A to D) or Day 78 (Cohort E) was explored using an inhibitory sigmoidal maximal effect (E_{max}) model.

Safety:

All safety analyses were performed on the Safety population, which included all randomized subjects who received at least 1 dose of study drug. Summaries of extent of exposure, including number of injections, duration of treatment, total amount of study drug received, average daily dose received, and percent compliance are provided for each treatment group. The incidence of treatment-emergent adverse events (TEAEs) is summarized for each treatment group. Treatment-emergent AEs were defined as AEs that had a start date on or after the first dose date of double-blind study drug. Summaries were also provided for vital signs over time as well as a tabulation of the number and percentage of subjects in each treatment group with elevations in alanine transaminase (ALT) and aspartate transaminase (AST).

Immunogenicity results were counted for both the screening and specificity assays and percentages were calculated. The percentage of subjects deemed antibody positive (positive for both screening and specificity assays) was determined.

Sample Size:

The primary analysis included the pairwise comparisons between each mipomersen treatment group and the pooled placebo group in reduction in LDL-C from baseline to Week 15 using the exact Wilcoxon rank sum test. It was assumed that the standard deviation of the LDL-C percent change was 12% and that there were 5 pairwise comparisons in the analysis. The 5 pairwise comparisons included the comparisons between each of the 5 mipomersen treatment groups versus the pooled placebo group. With at least 6 subjects per group, there was at least 80% power to detect a 33% difference in LDL-C percent reduction between the mipomersen treatment groups (33% in the treatment group and 0% in the placebo group), with a statistical significance level of 0.01.

Summary of Results:

Efficacy:

In total, 50 subjects received study drug: 10 subjects received placebo, 8 subjects received mipomersen 100 mg QOW, 8 subjects received 200 mg QOW, 8 subjects received 200 mg QW, 8 subjects received 300 mg QW, and 8 subjects received 400 mg QW.

The median percent change in LDL-C from baseline to Week 15 for the placebo group and the mipomersen 100 mg QOW, 200 mg QOW, 200 mg QW, 300 mg QW, and 400 mg QW groups was 0.9%, -12.4%, -17.6%, -42.1%, -61.6%, and -66.5%, respectively. The pairwise treatment comparisons between mipomersen 200 mg QOW and placebo ($p=0.0266$), 200 mg QW and placebo ($p<0.0001$), 300 mg QW and placebo ($p<0.0001$), and

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400 mg QW and placebo (p<0.0001) for median percent change in LDL-C were statistically significant. The pairwise treatment comparison between mipomersen 100 mg QOW and placebo (p=0.3154) was not statistically significant. Prolonged, clinically meaningful, and statistically significant median percent reductions in LDL-C to Day 175 in the mipomersen 200 mg QW group and to Day 205 in the mipomersen 300 mg QW and 400 mg QW groups were observed. The active treatment period ended at Day 85 for Cohorts A to D and at Day 64 for Cohort E.

Treatment with mipomersen resulted in a median percent reduction in apo B from baseline to Week 15 in the mipomersen 100 mg QOW group (-22.1%), 200 mg QOW group (-21.2%), 200 mg QW group (-46.6%), 300 mg QW group (-60.8%), and 400 mg QW group (-67.7%). The pairwise treatment comparisons between mipomersen 200 mg QOW and placebo (p=0.0002), 200 mg QW and placebo (p<0.0001), 300 mg QW and placebo (p<0.0001), and 400 mg QW and placebo (p<0.0001) for median percent change in apo B were statistically significant. The pairwise treatment comparison between mipomersen 100 mg QOW and placebo (p=0.0676) was not statistically significant.

Treatment with mipomersen (all dose levels) resulted in median percent reductions in TC, non-HDL-C, TG, VLDL-C, lipoprotein(a) (Lp[a]), apo B/apo A1 ratio, TC/HDL-C ratio, and LDL-C/HDL-C ratio from baseline to Week 15 with last observation carried forward.

No consistent trends in median percent change in HDL-C (using either the direct or the precipitation methods) or apo A1 relative to placebo were observed.

Pharmacokinetics:

The median time to maximum plasma concentrations (C_{max}) following the final SC injection of mipomersen occurred between 3 hours or 4 hours post-dose over the dose range of 100 mg to 300 mg. After reaching C_{max}, plasma concentrations of mipomersen declined bi-exponentially with time. Maximum plasma concentrations were dose dependent with mean values ranging from 1.16 µg/mL to 4.32 µg/mL over the dose range of 100 mg to 300 mg. Plasma drug concentrations decreased ≥10 fold from C_{max} by 24 hours. Both plasma peak (C_{max}) and total (AUC) plasma exposure measures were approximately dose proportional over the evaluated SC dose range. In general, peak (C_{max}) and total (AUC) plasma exposure measures tended to decrease with increasing total or ideal body weight, but this trend was not observed for plasma trough concentrations (C_{trough}). The effect of gender on plasma pharmacokinetic parameters was not assessed in this study, given the limited number of females (3) treated with mipomersen. Characterization of the terminal elimination phase following the last SC dose of study drug resulted in a mean terminal elimination half-life of 45.7 days to 48.5 days over the studied dose range.

Mean plasma trough concentrations (C_{trough}; 168 hours or 7 days from the previous dose of study drug) monitored during the treatment period were generally dose dependent (increased with increasing dose). In cohorts with a loading regimen (Cohorts A and B), mean plasma concentrations achieved during the loading period were either maintained (Cohort A) or decreased slightly (Cohort B) during the maintenance period, as would be predicted by the terminal elimination half-life and the particular maintenance dose regimen evaluated (mipomersen 200 mg QOW and 100 mg QOW for Cohorts A and B, respectively). In cohorts with no loading regimen (Cohorts C, D, and E), mean C_{trough} gradually increased with time (up to Day 92), consistent with the long terminal elimination half-life, once weekly maintenance dosing, and expected increase in mipomersen exposure (accumulation) in tissues.

Using an inhibitory sigmoidal E_{max} model, an exploration of the relationship between inhibition of serum apo B (percent baseline values) and C_{trough} of mipomersen on Day 99 (Cohorts A to D) or Day 78 (Cohort E) provided a

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50% of maximum drug-induced effect estimate of 10 ng/mL ± 1.9 ng/mL.

Safety:

Duration of exposure to study drug was similar across all treatment groups (mean: 78.0 days to 85.0 days; median: 85.0 days) except in the mipomersen 400 mg QW group; this treatment group was discontinued early. The mipomersen 400 mg QW group was discontinued by the Sponsor because of an administrative decision that maximal efficacy (apo B reduction) had been achieved. Mean duration of exposure to study drug was 63.9 days (median: 64.0 days) for the mipomersen 400 mg QW group.

Mipomersen treatment was generally safe and well tolerated. All 40 subjects in the mipomersen treatment groups and 9 (90.0%) subjects in the placebo group had a TEAE during the study. The incidence of TEAEs related to injection site reactions was higher in all mipomersen treatment groups compared with placebo, with the highest incidence in the 300 mg QW group. The most frequently reported TEAEs related to study drug for subjects in the mipomersen treatment groups were Injection site erythema (39 [97.5%] subjects), Injection site pruritis (20 [50.0%] subjects), Headache (21 [52.5%] subjects), and Injection site swelling (19 [47.5%] subjects). Five (62.5%) subjects in the mipomersen 400 mg QW group had an AE of Hepatic enzyme increased. Other than injection site reactions and Hepatic enzyme elevations, there were no meaningful differences in the incidence of TEAEs between the mipomersen treatment groups and the placebo group. The incidence of severe TEAEs was low overall.

No subjects died during the study. One (12.5%) subject in the mipomersen 200 mg QOW group had an SAE (Encephalitis not other specified [NOS]), which led to discontinuation from the study. The Investigator considered the SAE of Encephalitis NOS as not related to study drug; the subject was considered recovered at the end of the study. Four subjects in the mipomersen 400 mg QW group discontinued from the study due to a TEAE (Hepatic enzyme increased). No subjects in the other mipomersen treatment groups discontinued from the study due to a TEAE.

Elevations in ALT ≥3 × upper limit of normal (ULN) occurred in 9 (18.0%) subjects: 1 (12.5%) subject in the mipomersen 100 mg QOW group, 1 (12.5%) subject in the 200 mg QW group, 2 (25.0%) subjects in the 300 mg QW group, and 5 (62.5%) subjects in the 400 mg QW group. Elevations in AST ≥3 × ULN occurred in 4 (8.0%) subjects: 1 (12.5%) subject in the mipomersen 200 mg QW group and 3 (37.5%) subjects in the 400 mg QW group. No subjects in the placebo group had an elevation in ALT or AST ≥3 × ULN. No clinically relevant differences between the mipomersen treatment groups and the placebo group with respect to changes from baseline in other safety laboratory parameters were observed.

In total, 98 blood samples (20 samples from placebo-treated subjects and 78 samples from mipomersen-treated subjects) were collected and evaluated from all 50 subjects (10 placebo-treated subjects and 40 mipomersen-treated subjects) and analyzed for anti-mipomersen antibodies. Fifty of these samples were collected on Day 1 (10 samples from placebo-treated subjects and 40 samples from mipomersen-treated subjects) and 48 samples were collected on Day 99 (10 samples from placebo-treated subjects and 38 samples from mipomersen-treated subjects). Eleven of the samples collected on Day 99 exhibited a potentially positive signal in the initial screening. Two of the 11 samples from Day 99 were specific to mipomersen and thus deemed antibody positive. These samples lost signal upon titer dilutions and had a titer of 1.

No clinically meaningful safety findings or dose-related trends in vital signs or ECG parameters were noted.

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Conclusions:

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