Long-term safety and efficacy of mipomersen in patients with familial hypercholesterolemia not controlled by maximally tolerated lipid lowering therapy

Objective

- To evaluate mipomersen’s long-term safety and efficacy in a Phase 3 Extension Study

Mipomersen is an investigational product and not currently marketed.
DISCLOSURE INFORMATION:
Consultant for Mipomersen

UNLABELED/UNAPPROVED USE:
Mipomersen is an investigational drug

This study (CS6) was sponsored by Genzyme Corporation,
a Sanofi Company

clinicaltrials.gov  NCT00694109
Mipomersen Crosses the Hepatocyte and Nuclear Membrane to Target the mRNA for Apo B

Mipomersen (Apo B) antisense strand

Hepatocyte cell membrane

mRNA-antisense duplex

RNase H recognizes duplex

RNA is cleaved
Mipomersen
2nd Generation ASO that targets Apo B-100

- Apo B-100 is a key structural and functional component of all atherogenic lipoproteins produced by the liver
- Blocking Apo B-100 synthesis blocks production of VLDL and LDL
- Mipomersen is a 2nd generation antisense oligonucleotide (ASO) designed to inhibit Apo B protein synthesis

Phase 3: Study Design
Across Four Phase 3 Studies

- Randomized, double-blind, placebo-controlled, multi-center
- All patients on stable maximally tolerated LLT
- Weekly subcutaneous injections of mipomersen 200 mg or placebo for 26 weeks (option to self-administer)
- Primary efficacy endpoint: % change in LDL-C from baseline to week 28, or 2 weeks after the last dose
**Phase 3: Efficacy**

Primary End Point Achieved in All Four Phase 3 Trials

<table>
<thead>
<tr>
<th>LDL-C Phase 3 Study</th>
<th>Mipomersen Baseline (mg/dL)</th>
<th>Mipomersen Change (mg/dL)</th>
<th>Placebo % Change</th>
<th>Mipomersen % Change *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homozygous FH</td>
<td>439</td>
<td>-113</td>
<td>-3</td>
<td>-25</td>
</tr>
<tr>
<td>Severe HC</td>
<td>276</td>
<td>-101</td>
<td>+13</td>
<td>-36</td>
</tr>
<tr>
<td>Heterozygous FH</td>
<td>153</td>
<td>-49</td>
<td>+5</td>
<td>-28</td>
</tr>
<tr>
<td>High Risk</td>
<td>123</td>
<td>-47</td>
<td>-5</td>
<td>-37</td>
</tr>
</tbody>
</table>

**Average Reduction >100 mg/dL**

- 50% of Patients Achieved <70 mg/dL

- 45% of Patients Achieved <100 mg/dL

*Values presented are the mean.

* All p-values <0.001
Phase 3 Extension Study

Study Design

- Multi-center, phase 3 open-label extension study at 33 sites in 7 countries
- 200 mg mipomersen weekly SC injection for up to 4 years
- Assessments include safety parameters, liver MRI, lipid parameters
- Index study data is included for patients who initiated OLE <6-mo from last dose of mipomersen in the index study

<table>
<thead>
<tr>
<th>Condition</th>
<th>Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>HoFH</td>
<td>n = 38*</td>
</tr>
<tr>
<td></td>
<td>(86%)</td>
</tr>
<tr>
<td>Severe HeFH</td>
<td>n = 9*</td>
</tr>
<tr>
<td></td>
<td>(100%)</td>
</tr>
<tr>
<td>HeFH</td>
<td>n = 94*</td>
</tr>
<tr>
<td></td>
<td>(82%)</td>
</tr>
<tr>
<td>N</td>
<td>141</td>
</tr>
</tbody>
</table>

* n, represents number of patients enrolled from the index study. Value in parenthesis is the percent of eligible patients enrolled.
† Eight of 26 sites that participated in the index study were open for the extension study.
Phase 3 Extension Study
Patient Disposition (Interim Data Analysis – Nov 2011)

- In total, 141 patients have received mipomersen treatment
  - 1 yr efficacy results are available for 111 patients
  - 2 yr efficacy results are available for 53 patients
- 63 of 141 patients remain in treatment or completed treatment
  - 40 patients have consented to an additional 2 year extension period for a total of 4 years of treatment
- 78 of 141 patients have discontinued treatment
  - 62 due to Treatment-Emergent AEs
  - 16 for other reasons (non-AE)
# Phase 3 Extension Study

## Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Severe HeFH * (n = 20)</th>
<th>HeFH (n = 83)</th>
<th>HoFH (n = 38)</th>
<th>All (N=141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD) years</td>
<td>56 (12)</td>
<td>56 (10)</td>
<td>32 (12)</td>
<td>49 (15)</td>
</tr>
<tr>
<td>Male Gender, n (%)</td>
<td>8 (40)</td>
<td>59 (71)</td>
<td>17 (45)</td>
<td>84 (60)</td>
</tr>
<tr>
<td>BMI, mean (SD) kg/m²</td>
<td>29 (5)</td>
<td>29 (4)</td>
<td>27 (5)</td>
<td>28 (5)</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>5 (25)</td>
<td>32 (39)</td>
<td>6 (16)</td>
<td>43 (30)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lipid-lowering Therapy, n (%)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin</td>
<td>20 (100)</td>
<td>78 (94)</td>
<td>37 (97)</td>
<td>135 (96)</td>
</tr>
<tr>
<td>Maximal dose of statin</td>
<td>10 (50)</td>
<td>57 (69)</td>
<td>34 (89)</td>
<td>101 (72)</td>
</tr>
<tr>
<td>Ezetemibe</td>
<td>12 (60)</td>
<td>66 (80)</td>
<td>29 (76)</td>
<td>107 (76)</td>
</tr>
<tr>
<td>Bile Acid Sequestrants</td>
<td>5 (25)</td>
<td>14 (17)</td>
<td>2 (5)</td>
<td>21 (15)</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>2 (10)</td>
<td>25 (30)</td>
<td>6 (16)</td>
<td>33 (23)</td>
</tr>
<tr>
<td>Fish oil or Omega-3</td>
<td>7 (35)</td>
<td>27 (33)</td>
<td>4 (11)</td>
<td>38 (27)</td>
</tr>
</tbody>
</table>

* Table represents patients by FH phenotype. Severe HeFH includes patients from the HeFH index study who had baseline LDL-C ≥ 200 mg/dL.
Phase 3 Extension Study
Sustained Reduction in LDL-C, Apo B & Lp(a) with Long-term Treatment on top of Max Tolerated Lipid Lowering Therapy
# Phase 3 Extension Study

Sustained Reduction of Atherogenic Lipoprotein on top of Max Tolerated Lipid Lowering Therapy

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Baseline Mean (95% CI)</th>
<th>Wk 26 Mean (95% CI)</th>
<th>Wk 52 Mean (95% CI)</th>
<th>Wk 76 Mean (95% CI)</th>
<th>Wk 104 Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>233 (147)</td>
<td>-28‡ (-32, -25)</td>
<td>-27‡ (-31, -23)</td>
<td>-27‡ (-33, -22)</td>
<td>-28‡ (-35, -22)</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>256 (151)</td>
<td>-27‡ (-30, -24)</td>
<td>-25‡ (-29, -21)</td>
<td>-25‡ (-30, -20)</td>
<td>-27‡ (-33, -21)</td>
</tr>
<tr>
<td>Apo B</td>
<td>175 (81)</td>
<td>-29‡ (-32, -26)</td>
<td>-28‡ (-32, -24)</td>
<td>-30‡ (-35, -26)</td>
<td>-31‡ (-37, -26)</td>
</tr>
<tr>
<td>Lp(a)</td>
<td>61 (55)</td>
<td>-21‡ (-25, -17)</td>
<td>-16‡ (-23, -10)</td>
<td>-17‡ (-24, -10)</td>
<td>-14‡ (-22, -5)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>46 (14)</td>
<td>+6† (3, 10)</td>
<td>+6* (2, 10)</td>
<td>+3 (-1, 8)</td>
<td>+10† (3, 17)</td>
</tr>
</tbody>
</table>

Baseline values are the mean (SD) in mg/dL. P-values were determined by the Wilcoxon Rank Sign test.
* p-value <0.05, † p-value <0.01, ‡ p-value <0.001.
Phase 3 Extension Study
Safety Summary

- No new safety findings
  - Similar profile to that observed in all four 6-month Phase 3 studies

- Most patients experienced injection site reactions
  - Incidence was infrequent by injection
    • 1 in 10 injections; or 5 per year on average
    • Generally self-limiting and mild to moderate in severity

- Some patients experienced flu-like symptoms
  - Most common symptom was fatigue
  - Incidence was very infrequent by injection
    • 1 in 50 injections; or 1 per year on average

- Similar liver safety to that observed in 6-month Phase 3
  - no Hy's law
## Phase 3 Extension Study

Discontinuation Rate due to Adverse Events

Frequency of patients with TEAEs that led to treatment discontinuation

<table>
<thead>
<tr>
<th>Treatment Period</th>
<th># Patients</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-12 months</td>
<td>33</td>
<td>23%</td>
</tr>
</tbody>
</table>
  (n = 141)           |            |         |
| 12-24 months        | 22         | 23%     |
  (n = 96)            |            |         |
| 24-36 months        | 6          | 12%     |
  (n = 49)            |            |         |
| >36 months          | 1          | 17%     |
  (n = 6)             |            |         |
Phase 3 Extension Study
6-Month Incidence of ISRs, FLS and ALT Events

ISR denotes injection site reaction and includes the related preferred MedDRA terms, e.g. erythema, pain, haematoma, discoloration, pruritis and swelling.

FLS denotes flu-like symptoms and includes the following preferred MedDRA terms: chills, fatigue, influenza-like illness, malaise, pyrexia, arthralgia and myalgia.
Phase 3 Extension Study
Patients completing 2 yrs of treatment: 6-Month Incidence of ISR, FLS and ALT Events

<table>
<thead>
<tr>
<th>Time Period</th>
<th>AE Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 26 wk</td>
<td>ISR: 90%</td>
</tr>
<tr>
<td></td>
<td>(N=52)</td>
</tr>
<tr>
<td>26-52 wk</td>
<td>ISR: 80%</td>
</tr>
<tr>
<td></td>
<td>(N=52)</td>
</tr>
<tr>
<td>52-76 wk</td>
<td>ISR: 50%</td>
</tr>
<tr>
<td></td>
<td>(N=52)</td>
</tr>
<tr>
<td>76-104 wk</td>
<td>ISR: 40%</td>
</tr>
<tr>
<td></td>
<td>(N=52)</td>
</tr>
<tr>
<td>104-130 wk</td>
<td>ISR: 30%</td>
</tr>
<tr>
<td></td>
<td>(N=49)</td>
</tr>
</tbody>
</table>

ISR denotes injection site reaction and includes the related preferred MedDRA terms, e.g. erythema, pain, haematoma, discolouration, pruritis and swelling.
FLS denotes flu-like symptoms and includes the following preferred MedDRA terms: chills, fatigue, influenza-like illness, malaise, pyrexia, arthralgia and myalgia.
Phase 3 Extension Study
Increase in Median ALT Level Stabilizes with Extended Dosing

Median ALT (IQR), U/L

ULN
3xULN
ULN

Time Point (Weeks)

N = 141 140 139 135 134 130 121 118 113 111 84 70 80 66 75 65 63 54 40 36 30 32 16 10 5 2
Phase 3 Extension Study
Time to First Occurrence of ALT ≥3x ULN on two consecutive occasions at least 7 days apart

- Initial occurrence of persistent ALT elevations observed predominantly in the 1st year
- At one year approximately 90% of patients remained free from this event over the course of treatment
Phase 3 Extension Study
Increase in Median % Liver Fat Returns Towards Baseline with Extended Dosing and in Post-Treatment F/U

Values shown represent the median change from baseline in percent liver fat.
Phase 3 Extension Study

Summary

- Sustained lipid-lowering activity with extended treatment
  - In addition to maximally tolerated lipid lowering therapy
  - All atherogenic lipids measured remained reduced with extended treatment including LDL-C, Apo B, Lp(a), non-HDL-C and TGs
  - No loss of LDL-C response over 2 years of treatment

- Safety and tolerability profile remains consistent with Phase 3 index studies

- Increase in median ALT levels stabilized with extended dosing
  - A large majority of patients remained free of persistent ALT levels \( \geq 3xULN \) over the course of treatment; otherwise such increases occurred mostly within the 1st year of treatment

- Preclinical observations of liver adaptation to reduced lipid transport apparent in long-term clinical experience
  - Increase in median % liver fat decreased with continued dosing
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