ATP Citrate Lyase Inhibition–A New Mechanism for LDL-C Reduction

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Crucial role of ACL as a precursor supplier for both fatty acid and cholesterol synthesis

ACC, acetyl-CoA carboxylase; ACL, ATP citrate lyase; ATP, adenosine triphosphate; CoA, coenzyme A; HMG, hydroxymethylglutaryl; TCA, tricarboxylic acid

ATP-Citrate Lyase

Historical Perspective

- **1960s**: (-)-hydroxycitrate identified as an ACL inhibitor by Watson and Lowenstein

- **1970s**: Roche characterized (-)-hydroxycitrate and analogues for inhibition of cholesterol and fatty acid synthesis

- **1980s-1990s**: Multiple large pharmaceutical companies initiated ACL inhibitor discovery programs

- **1990-2000s**: Programs halted due to the inability to synthesize inhibitors that were bioavailable and cell permeable

Inhibition of ATP-Citrate Lyase by (-)-hydroxycitric acid increases LDL receptor binding in HepG2 Cell

Adapted from Berkhout et. al. BiochemJ:272 181-186 (1990)
STRATEGIES FOR ATP-CITRATE LYASE INHIBITION
CITRYL-COA MIMETICS AND IMPROVED CELL PERMEABILITY

Cell-Penetrant γ-Lactone Prodrug

Intracellular Conversion

Active ACL Inhibitor

Lipid Synthesis

Adapted from Biochem. J. (1998) 334, 113±119
ETC-1002

- Mechanism of action
- Efficacy on lipids
  - Monotherapy
  - Statin-intolerant patients ± ezetimibe
  - Added to background statin therapy
ETC-1002
Pharmacologic Properties

- Oral, once-daily small molecule
- Half-life: 15-24 hours
- Target organ: Liver
  - Minimal metabolism in preclinical and clinical studies
  - Primary biliary and minimal kidney excretion
- No competitive liver uptake with statins (e.g. OATP1B1)
- MOA: Inhibits ATP-citrate lyase (ACL) and activates AMP-activated protein kinase (AMPK)
ATP-CITRATE LYASE INHIBITION BY ETC-1002
BUILDING ON THE PRODRUG CONCEPT

Coenzyme Activation by Acyl-CoA Synthetase (ACS)

Inactive Prodrug
ETC-1002

Active ACL Inhibitor
ETC-1002-CoA

ETC-1002 is converted to an active ACL inhibitor (ETC-1002-CoA) by endogenous liver ACS activity
MECHANISM OF ACTION

ETC-1002 REDUCES LDL-C VIA INHIBITION OF ATP-CITRATE LYASE (ACL)

ETC-1002 is converted to ETC-1002-CoA in the liver which directly inhibits ACL, reduces cholesterol synthesis, and up-regulates LDL receptor activity.
ETC-1002 INHIBITS LIPID SYNTHESIS AND UP-REGULATES LDL RECEPTOR ACTIVITY

**McARDLE CELLS**

ETC-1002 inhibits cholesterol and cholesteryl ester synthesis, and increases LDL receptor protein expression and activity in McArdle cells.

Data on file, Esperion Therapeutics.
ETC-1002 IS RAPIDLY CONVERTED TO ETC-1002-COA

*Primary Rat Hepatocytes*

ETC-1002 is rapidly converted to ETC-1002-CoA in rat liver cells

Source: Pinkosky (2013)
ETC-1002-COA inhibits recombinant human ATP-citrate lyase and is competitive for coenzyme A.

Data on file, Esperion Therapeutics.
ETC-1002 REDUCES LIPID SYNTHESIS IN VIVO

Rat Liver

Cholesterol Synthesis
ETC-1002 Dose Response

A single dose of ETC-1002 inhibits sterol synthesis and reduces metabolic intermediates of cholesterol synthesis in rats. n = 5, * p < 0.05

Source: Pinkosky (2013)
ETC-1002 MECHANISM SUMMARY

LDL-C LOWERING VIA TISSUE-SPECIFIC ACL INHIBITION

- ETC-1002 inhibits cholesterol synthesis by inhibiting ACL – an enzyme upstream of HMG-CoA reductase
- ETC-1002 upregulates LDL receptors and lowers LDL-C similar to statin drugs
- ETC-1002 is CoA activated by endogenous ACS activity
- ETC-1002 is an inactive prodrug while its CoA activated form (ETC-1002-CoA) is a direct inhibitor of recombinant human ACL
# ETC-1002: PHASE 2 CLINICAL STUDIES

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Short Title</th>
<th>LDL-C Lowering* (pbo corrected)</th>
<th>Dose Range (mg)</th>
<th>Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>003</td>
<td>Phase 2a in Patients with Hypercholesterolemia (N=177/133)</td>
<td>Up to 27% (25%)</td>
<td>40, 80, 120</td>
<td>12 Wks</td>
</tr>
<tr>
<td>005</td>
<td>Phase 2a in Patients with Hypercholesterolemia and Type 2 Diabetes (N=60/30)</td>
<td>43% (39%)</td>
<td>80, 120</td>
<td>4 Wks</td>
</tr>
<tr>
<td>006</td>
<td>Phase 2a in Patients with Hypercholesterolemia and a History of Statin Intolerance (N=56/37)</td>
<td>32% (29%)</td>
<td>60, 120, 180, 240</td>
<td>8 Wks</td>
</tr>
<tr>
<td>007</td>
<td>Phase 2a in Patients with Hypercholesterolemia Added-on to Atorvastatin 10 mg (N=58/42)</td>
<td>22% (22%)</td>
<td>60, 120, 180, 240</td>
<td>8 Wks</td>
</tr>
<tr>
<td>008</td>
<td>Phase 2b in Patients with Hypercholesterolemia with or without Statin Intolerance vs. Ezetimibe (N=349/249)</td>
<td>Up to 30% (1002) Up to 48% (1002 + ezetimibe)</td>
<td>120, 180, 120 + ezetimibe, 180 + ezetimibe</td>
<td>12 Wks</td>
</tr>
<tr>
<td>009</td>
<td>Phase 2b in Patients with Hypercholesterolemia while on Stable Statin Therapy (N=134/88)</td>
<td></td>
<td>120, 180</td>
<td>12 Wks</td>
</tr>
<tr>
<td>014</td>
<td>Phase 2a in Patients with Hypercholesterolemia and Hypertension (N=143/72)</td>
<td></td>
<td>180</td>
<td>6 Wks</td>
</tr>
</tbody>
</table>

*Average LDL-C % Change from Baseline
Efficacy and safety of ETC-1002-003 in patients with hypercholesterolemia

- Multicenter, randomized, double-blind, placebo-controlled, parallel-group trial
- 177 patients with LDL-C 130–220 mg/dL, stratified by baseline TG (<150 mg/dL or 150–<400 mg/dL)
- Randomized to 40, 80, or 120 mg of ETC-1002 or placebo once daily for 12 weeks
- Endpoints: changes in LDL-C (primary endpoint), other lipids, and cardiometabolic risk factors; safety

ETC-1002-003: Percent Change from Baseline in LDL-C

Stratified by Baseline Triglycerides

Stratified by Baseline Triglycerides

<table>
<thead>
<tr>
<th>% Change from Baseline</th>
<th>Normal TG</th>
<th>Elevated TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120 mg</td>
<td></td>
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</tr>
</tbody>
</table>

Timecourse of Change (All Subjects)

- Wk 0: Initial Baseline
- Wk 2: Two Weeks of Treatment
- Wk 4: Four Weeks of Treatment
- Wk 8: Eight Weeks of Treatment
- Wk 12: Twelve Weeks of Treatment

Use of ETC-1002-006 to treat hypercholesterolemia in patients with statin intolerance

Least squares mean percent change from baseline to week 8 in calculated LDL-C (primary endpoint). *P < .0001 based on analysis of covariance model with effect of treatment and baseline value as a covariate.

### ETC-1002-008 PHASE 2B STUDY

**Overview and Objectives – “Statin Intolerant Study”**

<table>
<thead>
<tr>
<th>Elevated LDL-C Patients With or Without (1:1) Statin Intolerance</th>
<th>ETC-1002 120 mg (n = 99)</th>
<th>ETC-1002 180 mg (n = 100)</th>
<th>Ezetimibe 10 mg (n = 99)</th>
<th>ETC-1002 120 mg + Ezetimibe 10 mg (n = 26)</th>
<th>ETC-1002 180 mg + Ezetimibe 10 mg (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening, Washout &amp; 5-Week Placebo Run-in</td>
<td>12 Week Treatment</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

- Characterize the effects of ETC-1002 vs. ezetimibe in patients with (n = 177) or without (n = 171) statin intolerance (total n = 348)
  - Assess the LDL-C lowering of ETC-1002 monotherapy vs. ezetimibe (primary endpoint)
  - Assess ETC-1002 dose response
  - Assess additional lipid and cardiometabolic biomarkers (non-HDL-C, HDL-C, ApoB, ApoA-I, TC, TG, hsCRP and LDL-, HDL- and VLDL- particle number)
  - Assess the LDL-C lowering of ETC-1002 + ezetimibe combination vs. ezetimibe
  - Characterize the safety, tolerability, and rates of muscle-related adverse events of ETC-1002, ezetimibe and the combination

Thompson PD. Presented at ACC, San Diego, 14 Mar 2015 (moderated poster #116M-03).
DEFINITION OF STATIN INTOLERANCE (SI)

- Statin intolerance (for relevant patients only) defined as patient-reported inability to tolerate at least 2 statins due to skeletal muscle-related symptoms (other than those due to strain or trauma), such as pain, aches, weakness, or cramping, that began or increased during statin therapy and resolved when statin therapy was discontinued.

- Inability to tolerate at least 2 statins must meet the following criteria:
  - Inability to tolerate one statin at the lowest daily approved dose, defined as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, or pitavastatin 2 mg (current treatment with less than the lowest daily approved dose of a statin [i.e., skipping days/intermittent therapy provided that the average daily dose is less than the lowest daily approved dose] will be considered equivalent to not tolerating one statin at the lowest daily approved dose) AND
  - Inability to tolerate another statin at any dose

- Patients NOT meeting this definition will be considered statin tolerant (ST)

Thompson PD. Presented at ACC, San Diego, 14 Mar 2015 (moderated poster #116M-03).
LDL-C REDUCTION OCCURRED WITHIN FIRST 2 WEEKS OF DOSING AND WAS SUSTAINED OVER THE TREATMENT PERIOD

LDL-C % Change Over Time

Thompson PD. Presented at ACC, San Diego, 14 Mar 2015 (moderated poster #116M-03).
ETC-1002 LOWERED LDL-C SIMILARLY IN BOTH STATIN INTOLERANT AND TOLERANT PATIENTS

Thompson PD. Presented at ACC, San Diego, 14 Mar 2015 (moderated poster #116M-03).
LOWERING OF ATHEROGENIC LIPIDS AND LIPOPROTEINS WAS CONSISTENT WITH LDL-C LOWERING (1002-008)

Lipid/Lipoprotein % Change

- LDL-C
- Total Cholesterol
- ApoB
- non-HDL-C
- LDL Particle Number

ETC-1002 120mg
- ETC-1002 180mg
- ezetimibe 10mg
- ETC-1002 120mg + ezetimibe 10mg
- ETC-1002 180mg + ezetimibe 10mg

*p ≤ 0.05 vs. ezetimibe
**p ≤ 0.01 vs. ezetimibe
***p < 0.0001 vs. ezetimibe

Thompson PD. Presented at ACC, San Diego, 14 Mar 2015 (moderated poster #116M-03).
ETC-1002 ALSO LOWERED HSCRP MORE THAN EZETIMIBE

Thompson PD. Presented at ACC, San Diego, 14 Mar 2015 (moderated poster #116M-03).
INCONSISTENT CHANGES WERE NOTED IN HDL PARAMETERS

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>n</th>
<th>Baseline Mean (SD)</th>
<th>Week 12 Mean (SD)</th>
<th>% Change from Baseline</th>
<th>LS Mean (SE)</th>
<th>p-value vs. ezetimibe</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL-C (mg/dL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETC-1002 120mg</td>
<td>97</td>
<td>54 (16)</td>
<td>50 (15)</td>
<td>-5.84% (1.4)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>ETC-1002 180mg</td>
<td>99</td>
<td>52 (13)</td>
<td>50 (16)</td>
<td>-4.80% (1.4)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Ezetimibe 10mg</td>
<td>98</td>
<td>49 (12)</td>
<td>51 (13)</td>
<td>5.00% (1.4)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>ETC-1002 120mg + eze 10mg</td>
<td>24</td>
<td>52 (15)</td>
<td>50 (15)</td>
<td>-3.08% (2.8)</td>
<td>0.0111</td>
<td></td>
</tr>
<tr>
<td>ETC-1002 180mg + eze 10mg</td>
<td>22</td>
<td>50 (16)</td>
<td>49 (20)</td>
<td>-3.72% (3.0)</td>
<td>0.0082</td>
<td></td>
</tr>
</tbody>
</table>

INCONSISTENT CHANGES WERE NOTED IN HDL PARAMETERS

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INCONSISTENT CHANGES WERE NOTED IN HDL PARAMETERS

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<thead>
<tr>
<th>Treatment Group</th>
<th>n</th>
<th>Baseline Mean (SD)</th>
<th>Week 12 Mean (SD)</th>
<th>% Change from Baseline</th>
<th>p-value vs. ezetimibe</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LS Mean (SE)</td>
<td></td>
</tr>
<tr>
<td><strong>ApoA-I (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETC-1002 120mg</td>
<td>92</td>
<td>161 (28)</td>
<td>159 (25)</td>
<td>-0.19% (1.1)</td>
<td>0.1811</td>
</tr>
<tr>
<td>ETC-1002 180mg</td>
<td>86</td>
<td>160 (28)</td>
<td>159 (30)</td>
<td>0.13% (1.2)</td>
<td>0.2610</td>
</tr>
<tr>
<td>Ezetimibe 10mg</td>
<td>94</td>
<td>152 (25)</td>
<td>154 (23)</td>
<td>1.97% (1.1)</td>
<td>-</td>
</tr>
<tr>
<td>ETC-1002 120mg + eze 10mg</td>
<td>20</td>
<td>164 (30)</td>
<td>156 (27)</td>
<td>-2.77% (2.4)</td>
<td>0.0804</td>
</tr>
<tr>
<td>ETC-1002 180mg + eze 10mg</td>
<td>21</td>
<td>154 (20)</td>
<td>149 (25)</td>
<td>-4.09% (2.4)</td>
<td>0.0221</td>
</tr>
<tr>
<td><strong>HDL Particle Number (μmol/L)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETC-1002 120mg</td>
<td>92</td>
<td>34 (7)</td>
<td>35 (6)</td>
<td>5.00% (1.3)</td>
<td>0.3769</td>
</tr>
<tr>
<td>ETC-1002 180mg</td>
<td>83</td>
<td>33 (6)</td>
<td>35 (7)</td>
<td>6.19% (1.4)</td>
<td>0.8061</td>
</tr>
<tr>
<td>Ezetimibe 10mg</td>
<td>93</td>
<td>32 (5)</td>
<td>34 (6)</td>
<td>6.66% (1.3)</td>
<td>-</td>
</tr>
<tr>
<td>ETC-1002 120mg + eze 10mg</td>
<td>19</td>
<td>35 (7)</td>
<td>37 (7)</td>
<td>7.34% (2.9)</td>
<td>0.8333</td>
</tr>
<tr>
<td>ETC-1002 180mg + eze 10mg</td>
<td>20</td>
<td>33 (5)</td>
<td>35 (5)</td>
<td>5.10% (2.8)</td>
<td>0.6169</td>
</tr>
</tbody>
</table>

Thompson PD. Presented at ACC, San Diego, 14 Mar 2015 (moderated poster #116M-03).
ETC-1002’S EFFECT ON TRIGLYCERIDES APPEARS TO BE NEUTRAL

### Triglyceride % Change

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>n</th>
<th>Baseline Median</th>
<th>Week 12 Median</th>
<th>% Change from Baseline Median (IQR)</th>
<th>p-value vs. ezetimibe</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Triglycerides (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ETC-1002 120mg</td>
<td>97</td>
<td>136</td>
<td>143</td>
<td>0% (42)</td>
<td>0.1110</td>
</tr>
<tr>
<td>ETC-1002 180mg</td>
<td>99</td>
<td>161</td>
<td>160</td>
<td>-3% (46)</td>
<td>0.5428</td>
</tr>
<tr>
<td>Ezetimibe 10mg</td>
<td>98</td>
<td>163</td>
<td>146</td>
<td>-7% (35)</td>
<td>-</td>
</tr>
<tr>
<td>ETC-1002 120mg + eze 10mg</td>
<td>24</td>
<td>154</td>
<td>131</td>
<td>-19% (25)</td>
<td>0.2235</td>
</tr>
<tr>
<td>ETC-1002 180mg + eze 10mg</td>
<td>22</td>
<td>158</td>
<td>130</td>
<td>-12% (37)</td>
<td>0.3546</td>
</tr>
</tbody>
</table>

Thompson PD. Presented at ACC, San Diego, 14 Mar 2015 (moderated poster #116M-03).
MUSCLE-RELATED AES WERE SIMILAR BETWEEN THE GROUPS IN STATIN INTOLERANT PATIENTS

<table>
<thead>
<tr>
<th>Muscle-Related Treatment Emergent Adverse Events (AEs)</th>
<th>Number (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ETC-1002 120mg N=51</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Musculoskeletal chest pain</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal stiffness</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Sensation of heaviness</td>
<td>0</td>
</tr>
</tbody>
</table>

Overview of Muscle-Related AEs in Statin Intolerant Patients

- Any Muscle-related AE: 7 (14%) 6 (12%) 9 (18%) 2 (17%) 2 (17%)
- Leading to Discontinuation: 1 (2%) 2 (4%) 4 (8%) 0 0

Muscle-Related AE(s) in Statin Intolerant Patients by MedDRA Preferred Term

Pre-specified analysis of all Musculoskeletal and Connective Tissue Disorders AE terms except arthralgia, back pain, bone pain, bunion, bursitis, groin pain, intervertebral degeneration, intervertebral disc protrusion, joint stiffness, joint swelling, neck pain, osteoarthritis, plantar fasciitis, rotator cuff syndrome, and synovial cyst.

Thompson PD. Presented at ACC, San Diego, 14 Mar 2015 (moderated poster #116M-03).
### LABORATORY

<table>
<thead>
<tr>
<th>Lab Abnormality (Repeated and Verified)</th>
<th>Number (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ETC-1002 120mg N=99</td>
</tr>
<tr>
<td>ALT or AST &gt; 3 x ULN</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>CK &gt; 5 x ULN</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lab Parameter</th>
<th>Mean (SD) at Baseline and Week 12</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Uric Acid</td>
<td>Baseline Week 12</td>
<td>5.8 (1.3) 6.8 (1.5) 6.0 (1.3) 7.0 (1.6) 5.8 (1.4) 5.7 (1.6) 6.3 (1.3) 6.9 (1.5) 5.9 (1.4) 7.0 (1.5)</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>Baseline Week 12*</td>
<td>11.5 (3.3) 13.5 (3.9) 11.3 (2.9) 13.6 (3.7) 12.0 (4.1) 11.5 (3.5) 11.4 (2.7) 12.9 (3.3) 11.1 (3.1) 13.5 (4.6)</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>Baseline Week 12</td>
<td>14.4 (1.2) 13.9 (1.3) 14.3 (1.2) 13.9 (1.1) 14.2 (1.2) 14.1 (1.1) 14.3 (1.6) 13.9 (1.3) 14.4 (1.5) 13.9 (1.4)</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>Baseline Week 12</td>
<td>77 (20) 62 (14) 82 (22) 65 (16) 79 (22) 80 (21) 83 (20) 70 (19) 74 (19) 60 (16)</td>
</tr>
</tbody>
</table>

Normal range for uric acid (3-7\(^F\)/4-8.5\(^M\) mg/dL); homocysteine (6-15 \(\mu\)mol/L); hemoglobin (12-16\(^F\)/13.6-18\(^M\) g/dL); and alkaline phosphatase (37-116 U/L)

Thompson PD. Presented at ACC, San Diego, 14 Mar 2015 (moderated poster #116M-03).
ETC-1002-008 STUDY

SUMMARY

• This was the largest ETC-1002 clinical study completed to date (n=348)
• In patients receiving ETC-1002 monotherapy:
  – LDL-C lowering of up to 30% with ETC-1002 – significantly more LDL-C lowering than ezetimibe
  – hsCRP lowering of up 40% with ETC-1002 – significantly more hsCRP lowering than ezetimibe
  – ETC-1002 appeared to be safe and well tolerated
• In patients receiving ETC-1002 and ezetimibe:
  – LDL-C lowering of up to 48%
  – The combination appeared to be safe and well tolerated
• In patients treated with ETC-1002, including those with statin intolerance, there was no increases in muscle-related adverse events as compared to ezetimibe

Thompson PD. Presented at ACC, San Diego, 14 Mar 2015 (moderated poster #116M-03).
"ETC-1002 Incrementally Lowers Low Density Lipoprotein-Cholesterol in Patients with Hypercholesterolemia Receiving Stable Statin Therapy"

to be presented at AHA Scientific Sessions, 9 November 2015.
Summary

• In phase 2 studies, ETC-1002 has been shown to reduce LDL-C as monotherapy, combined with ezetimibe, and added to statin therapy.

• Although rodent studies had suggested potential effects of inhibition of ATP citrate lyase on both fatty acid synthesis and cholesterol synthesis, the clinical profile in humans shows major effect on cholesterol synthesis.

• Phase 3 program will be needed to gain more information on both efficacy and safety in a larger patient population with longer exposure.