IMPproved REDuction of OUTcomes: Vytarin EFFicacy INTernational TRIal

On-Treatment Analysis

A Multicenter, Double-Blind, Randomized Study to Establish the Clinical Benefit and Safety of Vytarin (Ezetimibe/Simvastatin Tablet) vs Simvastatin Monotherapy in High-Risk Subjects Presenting With Acute Coronary Syndrome
Ezetimibe Background

- Inhibits Niemann-Pick C1-like 1 (NPC1L1) protein
  - Located primarily on the epithelial brush border
  - Resulting in reduced cholesterol absorption
- LDL-C lowering additive to that with a statin
  - ~20% further reduction in LDL-C
- Two recent human genetic studies found polymorphisms in NPC1L1 associated with lower LDL-C and reduced risk of CV events

*MI Genetics Consortium Investigators NEJM 2014; online Nov 12; Ference BA et al AHA 2014
Patients stabilized post ACS ≤ 10 days:
LDL-C 50-125*mg/dL (or 50-100**mg/dL if prior lipid-lowering Rx)

N=18,144

Standard Medical & Interventional Therapy

Simvastatin
40 mg

Ezetimibe / Simvastatin
10 / 40 mg

Follow-up Visit Day 30, every 4 months

Duration: Minimum 2 ½-year follow-up (Final 5314 events)

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

Cannon CP AHJ 2008;156:826-32; Califf RM NEJM 2009;361:712-7; Blazing MA AHJ 2014;168:205-12
Milestones

- **FPI**
  - 26-Oct-2005

- **LPI**
  - 08-Jul-2010
  - Minimum trial Duration ~ 4 yrs.

- **50% Interim Analysis**
  - Mar-2010

- **DSMB Review (88%)**
  - Mar-2013

- **75% Interim Analysis**
  - Mar-2012

- **Database Lock:**
  - Oct-2014
  - **Results Presentation:**
    - Nov-2014
Milestones and Events

**2005**
- FPI 26-Oct-2005

**2006**

**2007**
- ENHANCE Study Results (Jan-2008)

**2008**
- SEAS Study Results (Jul-2008)

**2009**
- ARBITER-6 (Nov-2009)
- 50% Interim Analysis Mar-2010

**2010**
- LPI 08-Jul-2010
- DSMB Review (88%) Mar-2013
- 75% Interim Analysis Mar-2012
- FDA Simva Label Change 80mg dose (Jun-2011)

**2011**
- Database Lock Oct-2014

**2012**
- 5250 Events

**2013**

**2014**

**2015**
Primary Endpoint — ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

HR 0.936 CI (0.887, 0.988)
p=0.016

6.4% Treatment effect
Primary Endpoint — ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke

HR 0.936 CI (0.887, 0.988)  
p=0.016

Simva — 34.7%  
2742 events

EZ/Simva — 32.7%  
2572 events

NNT= 50

6.4% Treatment effect

Reaffirms the LDL-C hypothesis

7-year event rates
On Treatment Analysis

Statistical Methodology

➢ Prespecified exploratory analysis
  – Concern about off-treatment events possibly diluting treatment effects and eroding study power

➢ Excluded participants documented to have not taken drug

➢ Data censored at minimum of:
  – 30 days after last dose
  or
  – Last complete endpoint ascertainment of clinical events
Participant Disposition for 1° Endpoint — OT Population

*1° event on drug (4011) or non-CV death on drug or full assessment on drug during closeout

**EPs = endpoints

Completed on drug*

ITT: 18,144
(5314 1° EPs*)

n = 10,573

S
5281
EZ/S
5292

4.4 yrs.

OT: 17,706

n = 7133

S
3574
EZ/S
3559

2 yrs.

Followed off drug
(1303 1° ITT EPs* occurred > 30d off drug)

438 — Drug never taken

Mean years of F/U on drug for primary endpoint

= 60,298 total patient-years of F/U OT

80,286 patient years follow up for primary endpoint in ITT
## Baseline Characteristics

### On-Treatment Population

<table>
<thead>
<tr>
<th></th>
<th>Completed on drug n = 10,573</th>
<th>Did not complete on drug n = 7133</th>
<th>On treatment N = 17,706</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>62.8</td>
<td>63.8</td>
<td>63.2</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>21.6%</td>
<td>28.2%</td>
<td>24.2%</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>26.9%</td>
<td>27.4%</td>
<td>27.1%</td>
</tr>
<tr>
<td><strong>Previous MI</strong></td>
<td>21.6%</td>
<td>19.9%</td>
<td>20.9%</td>
</tr>
<tr>
<td><strong>UA/NSTEMI / STEMI</strong></td>
<td>24% / 48% / 29%</td>
<td>24% / 47% / 29%</td>
<td>24% / 47% / 29%</td>
</tr>
<tr>
<td><strong>Days post ACS to rand</strong></td>
<td>5.0</td>
<td>5.0</td>
<td>5.0</td>
</tr>
<tr>
<td><strong>Cath / PCI for ACS event</strong></td>
<td>88% / 72%</td>
<td>88% / 68%</td>
<td>88% / 70.2%</td>
</tr>
<tr>
<td><strong>Prior lipid Rx</strong></td>
<td>37.5%</td>
<td>32.4%</td>
<td>35.5%</td>
</tr>
<tr>
<td><strong>Median LDL-C (mg/dL) at QE</strong></td>
<td>94-E/S; 95-S</td>
<td>96-E/S; 94-S</td>
<td>95-E/S; 95-S</td>
</tr>
</tbody>
</table>
Mean LDL-C at 1 Year
OT & ITT

LDLC values at 1 year

- Simva OT LDLC 69.5 mg/dL
- EZ/Simva OT LDLC 52.5 mg/dL
- Simva ITT LDLC 69.9 mg/dL
- EZ/Simva ITT LDLC 53.2 mg/dL

OT ΔLDLC 17.0 mg/dL
ITT ΔLDLC 16.7 mg/dL

LDL-C (mg/dL)

Rand

Time since randomization

QE

4 mo

1 yr

2 yrs

3 yrs

4 yrs

5 yrs

6 yrs

7 yrs

8 yrs

Simva

EZ/Simva
Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

HR 0.924 CI (0.868, 0.983)  
p=0.012

Simva — KM 32.4%  
2079 events

EZ/Simva — KM 29.8%  
1932 events

7.6% Treatment effect
Primary Endpoint:

On Treatment:

Simva — KM 32.4%  
2079 events

EZ/Simva — KM 29.8%  
1932 events

HR 0.924 CI (0.868, 0.983)  
p = 0.012

19% greater treatment effect than ITT

NNT = 38

Primary Endpoint: CV death, MI, hospital admission for UA, coronary revascularization (≥ 30 days after randomization), or stroke

7 year event rates
<table>
<thead>
<tr>
<th>Endpoint Type</th>
<th>ITT</th>
<th>Simva*</th>
<th>EZ/Simva*</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>ITT</td>
<td>34.7</td>
<td>32.7</td>
<td>0.936</td>
</tr>
<tr>
<td>Secondary #1</td>
<td>ITT</td>
<td>40.3</td>
<td>38.7</td>
<td>0.948</td>
</tr>
<tr>
<td>Secondary #2</td>
<td>ITT</td>
<td>18.9</td>
<td>17.5</td>
<td>0.912</td>
</tr>
<tr>
<td>Secondary #3</td>
<td>ITT</td>
<td>36.2</td>
<td>34.5</td>
<td>0.945</td>
</tr>
</tbody>
</table>

*7-year event rates

1 = All-cause death, major coronary event, or stroke post randomization
2 = CHD death, non-fatal MI, or urgent CABG or PCI (>30 days) after randomization
3 = CV death, non-fatal MI, documented UA requiring rehospitalization, all revascularization (>30 days) after randomization, or non fatal stroke
### Primary and 3 Prespecified Secondary Endpoints ITT & OT

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>ITT</th>
<th>On Treatment</th>
<th>OT</th>
<th>Simva*</th>
<th>EZ/Simva*</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>ITT</td>
<td>34.7</td>
<td>32.7</td>
<td>0.936</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>32.4</td>
<td>29.8</td>
<td>0.924</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td>ITT</td>
<td>40.3</td>
<td>38.7</td>
<td>0.948</td>
<td></td>
<td></td>
</tr>
<tr>
<td>#1</td>
<td>OT</td>
<td>33.9</td>
<td>31.4</td>
<td>0.924</td>
<td></td>
<td></td>
</tr>
<tr>
<td>生产线</td>
<td>ITT</td>
<td>18.9</td>
<td>17.5</td>
<td>0.912</td>
<td></td>
<td></td>
</tr>
<tr>
<td>#2</td>
<td>OT</td>
<td>16.3</td>
<td>14.4</td>
<td>0.885</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td>ITT</td>
<td>36.2</td>
<td>34.5</td>
<td>0.945</td>
<td></td>
<td></td>
</tr>
<tr>
<td>#3</td>
<td>OT</td>
<td>34.0</td>
<td>31.6</td>
<td>0.929</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*7-year event rates

1 = All-cause death, major coronary event, or stroke post randomization

2 = CHD death, non-fatal MI, or urgent CABG or PCI (>30 days) after randomization

3 = CV death, non-fatal MI, documented UA requiring rehospitalization, all revascularization (>30 days) after randomization, or non fatal stroke
Effect of censoring duration on OT +30 d., +6 mo. and +12 mo.

Increasing censoring cut off from +30 d to +6mo or +12mo
Increases the number of events in OT
Results in progressive increase in treatment effect

30 d. - 7.6%
6 mo. - 7.8%
12 mo. - 8.1%

<table>
<thead>
<tr>
<th>Censor time</th>
<th>Simvastatin (n = 8855)</th>
<th>Simvastatin/EZ (n = 8851)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Off drug</td>
<td>Events</td>
<td>KM</td>
<td>Events</td>
<td>KM</td>
<td>HR (CI)</td>
</tr>
<tr>
<td>+30 d.</td>
<td>2072</td>
<td>32.4%</td>
<td>1932</td>
<td>29.8%</td>
<td>0.924 (0.868-0.983)</td>
</tr>
<tr>
<td>+6 mo.</td>
<td>2256</td>
<td>33.7%</td>
<td>2093</td>
<td>30.9%</td>
<td>0.922 (0.868-0.978)</td>
</tr>
<tr>
<td>+12 mo.</td>
<td>2331</td>
<td>33.8%</td>
<td>2156</td>
<td>30.9%</td>
<td>0.919 (0.866-0.974)</td>
</tr>
</tbody>
</table>
CTT Conclusion:
“…each 1.0 mmol/L reduction reducing the annual rate of (these) major vascular events by just over a fifth”
CTTHR per 1 mM LDL-C
Reduction for 26 Statin Trials

CTT Conclusion:
“…each 1.0 mmol/L reduction reducing the annual rate of (these) major vascular events by just over a fifth”
HR per 1mM LDLC reduction
IMPROVE-IT ITT vs OT

Major vascular events (MCE+ CR+ stroke)

- Simva*: 37.4
- EZ/Simva*: 35.3
- HR: 0.866

- Simva*: 35.4
- EZ/Simva*: 32.7
- HR: 0.860

Major coronary events (nfMI+CHD)

- Simva*: 18.4
- EZ/Simva*: 17.0
- HR: 0.794

- Simva*: 15.8
- EZ/Simva*: 13.8
- HR: 0.723

Non-fatal MI

- Simva*: 14.4
- EZ/Simva*: 12.8
- HR: 0.726

- Simva*: 13.5
- EZ/Simva*: 11.6
- HR: 0.714

CHD death (coronary death)

- Simva*: 5.8
- EZ/Simva*: 5.7
- HR: 0.901

- Simva*: 3.1
- EZ/Simva*: 3.1
- HR: 0.894

Coronary revasc.

- Simva*: 27.7
- EZ/Simva*: 26.1
- HR: 0.897

- Simva*: 27.4
- EZ/Simva*: 25.3
- HR: 0.913

Any stroke

- Simva*: 4.8
- EZ/Simva*: 4.2
- HR: 0.700

- Simva*: 4.5
- EZ/Simva*: 3.7
- HR: 0.594

Ischemic stroke

- Simva*: 4.1
- EZ/Simva*: 3.4
- HR: 0.586

- Simva*: 3.9
- EZ/Simva*: 3.2
- HR: 0.582

CTT Collaboration. Lancet 2010
**Safety — OT Population**

**Muscle and Gallbladder**

No statistically significant differences in muscle- or gallbladder-related events

<table>
<thead>
<tr>
<th>Event</th>
<th>Simva (n=8855)</th>
<th>EZ/Simva (n=8851)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT and/or AST &gt;3xULN, consecutive</td>
<td>2.2%</td>
<td>2.3%</td>
<td>0.540</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>1.2%</td>
<td>1.0%</td>
<td>0.279</td>
</tr>
<tr>
<td>Gallbladder-related AEs</td>
<td>2.8%</td>
<td>2.4%</td>
<td>0.068</td>
</tr>
<tr>
<td>Rhabdomyolysis*</td>
<td>0.2%</td>
<td>0.1%</td>
<td>0.273</td>
</tr>
<tr>
<td>Myopathy*</td>
<td>0.1%</td>
<td>0.1%</td>
<td>0.393</td>
</tr>
<tr>
<td>Rhabdo, myopathy, myalgia with CK elevation*</td>
<td>0.6%</td>
<td>0.5%</td>
<td>0.428</td>
</tr>
</tbody>
</table>

* Adjudicated events

Total patient years follow up for primary endpoint = 60,298
Summary and Conclusions

The on-treatment analyses of IMPROVE-IT further support the ITT findings that ezetimibe added to a statin results in a reduction of major vascular events.

Comparison with CTT data suggest the treatment effect per 1mM reduction of LDL-C associated with adding ezetimibe to a statin is consistent with that achieved per 1mM of LDLC reduction with statins.