The Efficacy of New Fixed-Dose Combination of Olmesartan and Rosuvastatin in Patients with Coronary Atherosclerotic Vascular Disease

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Hee Chul (Stephan) Chang, PhD
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   • The need for a Combination in the treatment of Hypertension and Dyslipidemia
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4. Summary
Prevalence of Vascular Disease Risk Factors
among adults aged > 20 years *

Dyslipidemia (35.6%)
Hypertension (27.6%)
Diabetes Mellitus (8.7%)

Overlap of hypertension and dyslipidemia

* NHANES III = The Third National Health and Nutrition Examination Survey.
Estimated based on application of age- and sex-specific prevalence estimated for each Condition from the NHANES III data to the Kaiser-Permanente membership to stimulate full ascertainment, Selby JV et al. Am J Manag Care. 2004;10:163-170
The Multiple Risk Factor Intervention Trial (MRFIT)

Prognosis improvement $\rightarrow$ Mortality reduction of complex CV disease patients

Neaton at al., *Arch Intern Med.* 1992;152(1):56-64
## Recommendations of Treatment Guidelines

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCEP ATP III (2002, 2004 updated)</td>
<td>In persons with both elevated cholesterol and high blood pressure, CHD risk is synergistically increased. Conversely, reducing blood pressure, like cholesterol lowering, decreases risk for cardiovascular disease. In persons with concomitant hypertension and hypercholesterolemia, both conditions should be treated aggressively, especially in persons with known CHD.</td>
</tr>
<tr>
<td>ESH-ESC (2007,2009 reappraisal)</td>
<td>All hypertensive patients with established cardiovascular disease or with type 2 diabetes should be considered for statin therapy aiming at serum total and LDL cholesterol levels of, respectively, &lt;4.5mmol/l (175mg/dl) and &lt;2.5mmol/l (100mg/dl), and lower, if possible. Hypertensive patients without overt cardiovascular disease but with high cardiovascular risk (&gt;20% risk of events in 10 years) should also be considered for statin treatment even if their baseline total and LDL serum cholesterol levels are not elevated.</td>
</tr>
<tr>
<td>NICE guideline (2008)</td>
<td>Before offering lipid modification therapy for primary prevention, all other modifiable CVD risk factors should be considered and their management optimized if possible. Baseline blood tests and clinical assessment should be performed, and comorbidities and secondary causes of dyslipidemia should be treated. Assessment should include: smoking status, alcohol consumption, blood pressure (see 'Hypertension', NICE clinical guideline 34), body mass index or other measure of obesity (see 'Obesity', NICE clinical guideline 43), fasting total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides (if fasting levels are not already available) fasting blood glucose, renal function</td>
</tr>
</tbody>
</table>
Benefits of Combination Therapy

Treatment with beta-blocker, ACEI/ARB, statin, or combinations

Factors Considered in Molecule Selection

• Compliance – Once daily
• Efficacy in lowering
  • blood pressure
  • lipids
• Proven by large-scale clinical evidence
• Most recently developed molecule
• Drug-drug interaction – Metabolizing enzyme
Best in Class

Reduction in the values of blood pressure (BP) over 24 h of each angiotensin II AT1 receptor antagonist and placebo


LS mean percent change from baseline in LDL-C(%)

Rosuvastatin
- 10mg (n=156)
- 20mg (n=160)

Atorvastatin
- 10mg (n=158)
- 40mg (n=156)

Simvastatin
- 10mg (n=165)
- 40mg (n=162)

Pravastatin
- 10mg (n=160)
- 40mg (n=161)

Clinically Proven Outcome Improvement

**OLIVUS-Ex exTension Trial**
- Cumulative event-free from MACCE

- **MACCE**

<table>
<thead>
<tr>
<th></th>
<th>Olmesartan (n=126)</th>
<th>Control (n=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>60</td>
<td>80</td>
</tr>
<tr>
<td>200 days</td>
<td>85</td>
<td>65</td>
</tr>
<tr>
<td>400 days</td>
<td>70</td>
<td>50</td>
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<td>600 days</td>
<td>60</td>
<td>40</td>
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<tr>
<td>800 days</td>
<td>50</td>
<td>30</td>
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<tr>
<td>1000 days</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>1200 days</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>1400 days</td>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>

*Cumulative event-free from MACCE*

P = 0.04 (log-rank test)

**OLIVUS-Ex extension trial**
(impact of Olmesartan on progression of coronary atherosclerosis: evaluation by intravascular ultrasound)


**JUPITER Study**
- Cumulative incidence of the primary endpoint

- **MACCE**

<table>
<thead>
<tr>
<th></th>
<th>Olmesartan (n=126)</th>
<th>Control (n=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>60</td>
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</tr>
<tr>
<td>400 days</td>
<td>70</td>
<td>50</td>
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<tr>
<td>600 days</td>
<td>60</td>
<td>40</td>
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<tr>
<td>800 days</td>
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<td>30</td>
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<tr>
<td>1000 days</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>1200 days</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>1400 days</td>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>

*Cumulative incidence of the primary endpoint*

Risk Reduction 44%
Hazard Ratio 0.56
(95% CI 0.46-0.69)
P < 0.00001

20mg Rosuvastatin

**No. at Risk**
- Rosuvastatin: 8901 8631 8412 6540 3893 1958 1353 983 538 157
- Placebo: 8901 8621 8353 6508 3872 1963 1333 955 531 174

**JUPITER**
(Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin) study

Discovery and Development of ARBs and Statins

- EXP-7711
  - lipophilic compound with oral activity
- Losartan (1986)
- Candesartan (1990)
- Telmisartan (1991)
- Olmesartan (1995)
- Valsartan (1990)
- Irbesartan (1990)
- Irbesartan (1990)

- Mevastatin (1976)
- Lovastatin (1978)
- Pravastatin (1989)
- Simvastatin (1988)
- Fluvastatin (1994*)
- Atorvastatin (1985)
- Rosuvastatin (2003*)

* FDA approval
Drug-Metabolizing Enzyme

### Antihypertensive drugs

<table>
<thead>
<tr>
<th>Classification</th>
<th>Drug</th>
<th>Main metabolic enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCB</td>
<td>Amlodipine</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>ARB</td>
<td>Irbesartan</td>
<td>CYP2C9</td>
</tr>
<tr>
<td>ARB</td>
<td>Candesartan</td>
<td>CYP2C9 (minor liver metabolism)</td>
</tr>
<tr>
<td>ARB</td>
<td>Losartan</td>
<td>CYP2C9 CYP3A4</td>
</tr>
<tr>
<td>ARB</td>
<td>Temisartan</td>
<td>Conjugation</td>
</tr>
<tr>
<td>ARB</td>
<td>Valsartan</td>
<td>CYP2C9</td>
</tr>
<tr>
<td>ARB</td>
<td>Fimarsartan</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>B blocker</td>
<td>Carvedilol</td>
<td>CYP2C9 CYP2D6</td>
</tr>
<tr>
<td>ARB</td>
<td>Olmesartan</td>
<td>None</td>
</tr>
</tbody>
</table>

### Antihyperlipidemic agents

<table>
<thead>
<tr>
<th>Classification</th>
<th>Drug</th>
<th>Main metabolic enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin</td>
<td>Atorvastatin</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Statin</td>
<td>Pitavastatin</td>
<td>CYP2C9</td>
</tr>
<tr>
<td>Statin</td>
<td>Simvastatin</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Statin</td>
<td>Lovastatin</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Statin</td>
<td>Pravastatin</td>
<td>-</td>
</tr>
<tr>
<td>Statin</td>
<td>Fluvastatin</td>
<td>CYP2C9</td>
</tr>
<tr>
<td>Statin</td>
<td>Cerivastatin</td>
<td>CYP3A4</td>
</tr>
<tr>
<td>Statin</td>
<td>Rosuvastatin</td>
<td>CYP2C9 (minor liver metabolism)</td>
</tr>
</tbody>
</table>
Factors in Selecting a Specific Molecule

Co-Prescription Rate Between Anti-Hypertensive and Lipid Regulator

Olmesartan Rx.

Rosuvastatin Rx.

Global Market

- Anti-hypertensive drugs: US $ 40B
- Anti-dyslipidemia drugs: US $ 30B

2016: Top 50 Selling Products in the World

(Research and Markets, 2010)

(EvaluatePharma®, 2010)
### Global Market

Rankings of the top 50 pharmaceutical products, as compiled by GlobalData

<table>
<thead>
<tr>
<th>#</th>
<th>Product</th>
<th>2014 ($m)</th>
<th>2013 ($m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Humira</td>
<td>13021</td>
<td>11105</td>
</tr>
<tr>
<td>2</td>
<td>Sovaldi/Harvoni</td>
<td>12410</td>
<td>139</td>
</tr>
<tr>
<td>3</td>
<td>Remicade</td>
<td>10151</td>
<td>9900</td>
</tr>
<tr>
<td>4</td>
<td>Enbrel</td>
<td>9120</td>
<td>8894</td>
</tr>
<tr>
<td>5</td>
<td>Lantus</td>
<td>8152</td>
<td>7343</td>
</tr>
<tr>
<td>6</td>
<td>MabThera/Rituxan</td>
<td>7356</td>
<td>7410</td>
</tr>
<tr>
<td>7</td>
<td>Avastin</td>
<td>6841</td>
<td>6667</td>
</tr>
<tr>
<td>8</td>
<td>Seretide/Advair</td>
<td>6700</td>
<td>8356</td>
</tr>
<tr>
<td>9</td>
<td>Herceptin</td>
<td>6690</td>
<td>6481</td>
</tr>
<tr>
<td>10</td>
<td>Crestor</td>
<td>6617</td>
<td>6960</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>Olmetec</td>
<td>3187</td>
<td>3761</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Rationale Guiding Drug Combination

• Use of a fixed-dose combination is highly recommended because of the therapeutic benefit to patients driven by high adherence to treatment.

• Treatment guidelines recommend fixed-dose combination for its:
  – Better adherence to a therapeutic regimen
  – Patient compliance
  – Economic benefit

• Olmesartan and Rosuvastatin are the latest developed molecules in their drug classes and have proven efficacy and safety.

• Both drugs are reported to be the best in class for achieving therapeutic goals and improving clinical outcomes.
Technique Applied in Formulation Design

Technological point: Dissolution-rate-adjusted bi-layer tablet

1. Minimize the physicochemical interaction
2. Optimize the dissolution profile suitable for absorption of each drug

Bi-layer tablet

Independent dissolution of each layer

Control and optimize the dissolution profile in GI tract

Development History

I. Single pill

II. Double layer

III. Double layer with controlled dissolution rate
In a single pill, drug interaction occurs.

1. Development

- Rosuvastatin Single tablet
- Olmesartan Single tablet
- Two molecules Mixed single tablet

2. Evaluation

- Olmesartan Equivalent
- Rosuvastatin Non-equivalent
- Rosuvastatin dissolution ↓
- Rosuvastatin absorption ↓
Drug interaction was avoided and difference in absorption was observed.

1. Development

Two molecules
Mixed single tablet

Two molecules
Bi-layer tablet

Physicochemical interaction

2. Evaluation

**Olmesartan Non-equivalent**

**Rosuvastatin Equivalent**
Dissolution rate was controlled to overcome the difference in transporter affinity.

1. Development

2. Evaluation
OLOSTAR

- OLOSTAR is a FDC consisted of Olmesartan and Rosuvastatin
- Olmesartan + Rosuvastatin
  4 different strengths 40/20, 20/20, 20/10, 20/5
Contents

1. Introduction: Development Background
2. Results of Phase I Clinical Trials
3. Results of Phase III Clinical Trial
4. Summary
## Clinical Trials in Korea (Phase 1) – Healthy Adult

<table>
<thead>
<tr>
<th></th>
<th>Phase1 (DDI)</th>
<th>Phase1 (BE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title</strong></td>
<td>Pharmacokinetic Interaction between Rosuvastatin and Olmesartan</td>
<td>Pharmacokinetic Comparison of Co-administration of Rosuvastatin and Olmesartan with OLOSTAR</td>
</tr>
<tr>
<td><strong>Result</strong></td>
<td>Rosuvastatin and Olmesartan did not significantly influence each other’s pharmacokinetics when co-administered.</td>
<td>The pharmacokinetics of the newly developed OLOSTAR were bioequivalent to those of co-administration. The two formulations were well tolerated with no serious adverse events observed.</td>
</tr>
<tr>
<td><strong>Objectives</strong></td>
<td>To investigate the pharmacokinetic profile of co-administration of Rosuvastatin 20 mg tablet and Olmesartan 40 mg tablet and the associated drug-drug interaction</td>
<td>To evaluate the bioequivalence between OLOSTAR and co-administration</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Randomized, open-label, 3-period, crossover, and multiple-dose (7days)</td>
<td>Randomized, open-label, 2-period, crossover, and single-dose</td>
</tr>
<tr>
<td><strong>Number of Subjects</strong></td>
<td>34</td>
<td>54</td>
</tr>
</tbody>
</table>
Results of DDI Study (Phase I)

<table>
<thead>
<tr>
<th></th>
<th>Geometric Mean</th>
<th>Ratio (R+O / (R or O))</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;tau&lt;/sub&gt; (ng*hr/mL)</td>
<td>238.33</td>
<td>215.55</td>
<td>90.44</td>
</tr>
<tr>
<td>C&lt;sub&gt;ss,max&lt;/sub&gt; (ng/mL)</td>
<td>24.31</td>
<td>21.65</td>
<td>89.08</td>
</tr>
<tr>
<td>Olmesartan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;tau&lt;/sub&gt; (ng*hr/mL)</td>
<td>8,198.69</td>
<td>8,118.93</td>
<td>99.03</td>
</tr>
<tr>
<td>C&lt;sub&gt;ss,max&lt;/sub&gt; (ng/mL)</td>
<td>1,238.84</td>
<td>1,204.06</td>
<td>97.19</td>
</tr>
</tbody>
</table>

There is no drug-drug interaction (Acceptance criteria: 80~125)
Results of BE Study (Phase I)

<table>
<thead>
<tr>
<th>Drug</th>
<th>AUC_{last} (ng·h/mL)</th>
<th>C_{max} (ng/mL)</th>
<th>Ratio</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin</td>
<td>173.98</td>
<td>20.88</td>
<td>91.31</td>
<td>85.60 - 97.40</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>6718.94</td>
<td>1086.97</td>
<td>101.61</td>
<td>97.69 - 105.69</td>
</tr>
</tbody>
</table>

Absorption rate of drugs are acceptable (Acceptance criteria: 80~125)
Contents

1. Introduction: Development Background
2. Results of Phase I Clinical Trials
3. Results of Phase III Clinical Trial
4. Summary
Clinical Trial in Korea (Phase 3)

Phase 3 – Hypertension and Dyslipidemia Patients

- Title of Study:
  Clinical trial to evaluate the efficacy and safety of OLOSTAR in patients with hypertension and dyslipidemia

- Result:
  OLOSTAR was significantly more effective than olmesartan alone in lowering subjects’ LDL-C levels, and significantly more effective than rosuvastatin alone in lowering subjects’ DBP. OLOSTAR was well tolerated with no serious adverse events observed.

- Primary objectives:
  1. To confirm the superiority of OLOSTAR in the percentage change of LDL-C compared with olmesartan 40mg
  2. To confirm the superiority of OLOSTAR in the change of DBP compared with Rosuvastatin 20mg

- Design: A multi-center, randomized, double-blind, double-dummy, placebo-controlled, factorial design, 4-arms

- Institution: 25 sites

- Number of Subjects: 162

- Treatment period: 8 weeks
EFFICACY

LIPID PARAMETER
Changes in LDL-C

Ref.: Data on File. Daewoong. DW_DWJ1276003

*p < 0.0001 (comparing with week 0)
% Change from Baseline in LDL-C

Week 4

- **OLOSTAR**: -52.1%
- **Ormesartan 40mg**: -1.2%
- **Rosuvastatin 20mg**: -7.8%
- **Placebo**: -47.8%

Δ = 3.4%
P = 0.4034

Week 8

- **OLOSTAR**: -52.3%
- **Ormesartan 40mg**: -0.6%
- **Rosuvastatin 20mg**: -3.2%
- **Placebo**: -46.9%

Δ = 5.4%
P = 0.1864

* p < 0.0001 (comparing with OLOSTAR)

Ref. > Data on File. Daewoong. DW_DWJ1276003
Changes in TC

Ref.: Data on File. Daewoong. DW_DWJ1276003

* p<0.0001 (comparing with week 0)
% Change from Baseline in TC

Week 4

- OLOSTAR
- Olmesartan 40mg
- Rosuvastatin 20mg
- Placebo

Change from baseline (%)

-36.1%
-33.9%

\[ \Delta = 2.2\% \]
\[ P = 0.4038 \]

Week 8

- OLOSTAR
- Olmesartan 40mg
- Rosuvastatin 20mg
- Placebo

Change from baseline (%)

-37.1%
-32.8%

\[ \Delta = 4.3\% \]
\[ P = 0.1483 \]

Ref.: Data on File. Daewoong. DW_DWJ1276003

* p<0.0001 (comparing with OLOSTAR)
Changes in TG

Ref: Data on File. Daewoong. DW_DWJ1275003
*p<0.0001 (comparing with week 0)
% Change from Baseline in TG

Week 4
- OLOSTAR: -15.5%
- Olmesartan 40mg: -13.7%
- Rosuvastatin 20mg: -8.7%
- Placebo: -8.1%

$\Delta = 6.8\%$
P=0.4323

Week 8
- OLOSTAR: -17.8%
- Olmesartan 40mg: -13.7%
- Rosuvastatin 20mg: 0.9%
- Placebo: -8.1%

$\Delta = 5.6\%$
P=0.5700

§ p<0.05 (comparing with OLOSTAR)

Ref.: Data on File. Daewoong, DW_DWJ1276003
% of Subjects Who Achieved the Treatment Goal in LDL-C at Week 8

- Goal of Treatment by NCEP ATP III

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>10yr risk assessment</th>
<th>Goal of Tx In LDL-C (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>&lt;160</td>
</tr>
<tr>
<td>≥2</td>
<td>&lt;10%</td>
<td>&lt;130</td>
</tr>
<tr>
<td>≥2</td>
<td>10~20%</td>
<td></td>
</tr>
<tr>
<td>CHD or CHD equivalents</td>
<td>&gt;20%</td>
<td>&lt;100</td>
</tr>
</tbody>
</table>

Δ= 3.4%  
P=0.4813

Ref.> Data on File. Daewcong. DW_DWJ1276003  
* p<0.0001 (comparing with OLOSTAR)
EFFICACY

BLOOD PRESSURE
Changes in DBP

Ref.> Data on File. Daewoong. DW_DWJ1276003
*p<0.0001 (comparing with week 0)
Change from Baseline in DBP

**Week 4**

- **OLOSTAR**
  - Olmesartan 40mg
  - Rosuvastatin 20mg
- **Placebo**

- Change from baseline (mmHg):
  - **Δ = 0.7mmHg**
  - **P = 0.6695**
  - *p < 0.0001, § p < 0.05 (comparing with OLOSTAR)

**Week 8**

- **OLOSTAR**
  - Olmesartan 40mg
  - Rosuvastatin 20mg
- **Placebo**

- Change from baseline (mmHg):
  - **Δ = 2.3mmHg**
  - **P = 0.2096**

Ref.: Data on File, Daewoong. DW_DWJ1276003
Changes in SBP

- **OLOSTAR**
  - Week 0: 150.6
  - Week 4: 135.6
  - Week 8: 132.6

- **Olmesartan 40mg**
  - Week 0: 150.6
  - Week 4: 133.9
  - Week 8: 133.4

- **Rosuvastatin 20mg**
  - Week 0: 148.9
  - Week 4: 150.2
  - Week 8: 153.4

- **Placebo**
  - Week 0: 152.2
  - Week 4: 151.5
  - Week 8: 154.2

Ref: Data on File. Daewcong, DW_DWJ1276003

*p < 0.0001 (comparing with week 0)
Change from Baseline in SBP

Week 4

- OLOSTAR
- Omesartan 40mg
- Rosuvastatin 20mg
- Placebo

$\Delta = 1.7\text{mmHg}$
$P=0.5996$

Week 8

- OLOSTAR
- Omesartan 40mg
- Rosuvastatin 20mg
- Placebo

$\Delta = 0.8\text{mmHg}$
$P=0.8147$

Ref. > Data on File. Daewoong, DW_DWJ1276003

* $p < 0.0001$ (comparing with OLOSTAR)
% of Subjects Who Achieved the Treatment Goal Defined by JNC7 in BP at Week 8

- Goal of Treatment by JNC 7:
  - < 140/90 mmHg
  - (in case of DM, CKD: < 130/80 mmHg)

- Δ = 15.7%
- P = 0.1360

- OLOSTAR: 57.4%
- Olmesartan 40mg: 41.7%
- Rosuvastatin 20mg: 11.1%*
- Placebo: 20.7%§

* p < 0.0001, § p < 0.05 (comparing with OLOSTAR)

Ref.: Data on File. Daewoong. DW_DWJ1276003
% of Subjects Who Achieved the Treatment Goal Defined by JNC8 in BP at Week 8

- Goal of Treatment by JNC 8
  1) age < 60 years: < 140/90 mmHg
  2) age ≥ 60 years: < 150/90 mmHg
  3) in case of DM, CKD: < 140/90 mmHg

<table>
<thead>
<tr>
<th>Group</th>
<th>% of Subjects Achieving Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLOSTAR</td>
<td>73.8%</td>
</tr>
<tr>
<td>Olmesartan 40mg</td>
<td>61.1%</td>
</tr>
<tr>
<td>Rosuvastatin 20mg</td>
<td>19.4%*</td>
</tr>
<tr>
<td>Placebo</td>
<td>34.5%§</td>
</tr>
</tbody>
</table>

Δ= 12.7%, P=0.1935

Ref.> Data on File. Daewoong

* p<0.0001, § p<0.05 (comparing with OLOSTAR)
Summary of Safety

*Safety results show that all treatments were generally well tolerated.*

<table>
<thead>
<tr>
<th></th>
<th>OLOSTAR (N=71)</th>
<th>OMT 40 (N=38)</th>
<th>RSV 20 (N=38)</th>
<th>Placebo (N=38)</th>
<th>Total (N=181)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of AE</td>
<td>24.9%</td>
<td>18.4%</td>
<td>23.7%</td>
<td>23.5%</td>
<td>22.7%</td>
</tr>
<tr>
<td>P-value*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.9202</td>
</tr>
<tr>
<td>No. of ADR</td>
<td>2.8%</td>
<td>0</td>
<td>5.3%</td>
<td>2.9%</td>
<td>2.8%</td>
</tr>
<tr>
<td>P-value**</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.5990</td>
</tr>
<tr>
<td>No. of SAE</td>
<td>0</td>
<td>2.6%</td>
<td>2.6%</td>
<td>0</td>
<td>1.1%</td>
</tr>
<tr>
<td>No. of Serious ADR</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

AE : Treatment-Emergent Adverse Events
ADR : Treatment-Emergent Adverse Drug Reactions
SAE : Serious Adverse Events
ADR : Adverse Drug Reactions

* Difference among treatment groups (chi-square test)
** Difference among treatment groups (Fishers exact test)
### Adverse Drug Reaction

<table>
<thead>
<tr>
<th>System Organ Class Preferred Term</th>
<th>OLOSTAR (N=71)</th>
<th>OMT 40 (N=38)</th>
<th>RSV 20 (N=38)</th>
<th>Placebo (N=38)</th>
<th>Total (N=181)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of subjects</strong></td>
<td>2 (2.82%) [4]</td>
<td>0</td>
<td>2 (5.26%) [2]</td>
<td>1 (2.94%)</td>
<td>5 (2.76%)</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>2 (2.82%) [4]</td>
<td>0</td>
<td>1 (2.94%)</td>
<td>3 (1.66%)</td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase increased</td>
<td>2 (2.82%) [1]</td>
<td>0</td>
<td>0</td>
<td>1 (0.55%)</td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>1 (1.41%) [1]</td>
<td>0</td>
<td>0</td>
<td>1 (0.55%)</td>
<td></td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>1 (1.41%) [1]</td>
<td>0</td>
<td>0</td>
<td>1 (0.55%)</td>
<td></td>
</tr>
<tr>
<td>Blood triglycerides increased</td>
<td>0</td>
<td>0</td>
<td>1 (2.94%)</td>
<td>1 (0.55%)</td>
<td></td>
</tr>
<tr>
<td>Creatinine renal clearance decreased</td>
<td>1 (1.41%) [1]</td>
<td>0</td>
<td>0</td>
<td>1 (0.55%)</td>
<td></td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td>0</td>
<td>2 (5.26%) [2]</td>
<td>0</td>
<td>2 (1.10%)</td>
<td>2 (1.10%) [2]</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>2 (5.26%) [2]</td>
<td>0</td>
<td>2 (1.10%)</td>
<td>2 (1.10%) [2]</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td>0</td>
<td>1 (2.63%) [1]</td>
<td>0</td>
<td>1 (0.55%)</td>
<td>1 (0.55%) [1]</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0</td>
<td>1 (2.63%) [1]</td>
<td>0</td>
<td>1 (0.55%)</td>
<td>1 (0.55%) [1]</td>
</tr>
</tbody>
</table>

AE : Treatment-Emergent Adverse Events
Note : Denominator of percentage is the number of subjects in the column. AEs are displayed as number of subjects (percentage of subjects) [number of events].
Contents

1. Introduction: Development Background
2. Results of Phase I Clinical Trials
3. Results of Phase III Clinical Trial
4. Summary
Summary

- Market data reveal ARBs and statins are *widely co-prescribed* because hypertensive patients commonly also have dyslipidemia.

- Both components of OLOSTAR, olmesartan and rosuvastatin, are *the most recently developed molecules* in their respective classes. Numerous studies have proven the efficacy and outcome improvement of each component.

- Use of a fixed-dose (or single pill) combination is preferred because simplifying treatment improves *treatment compliance*. Good adherence to drug therapy is associated with positive health outcomes.

- An optimized bi-layer formulation facilitated a dissolution profile suitable for absorption of each drug and *proved bioequivalence* between the fixed-dose combination versus co-administration of each drug.

- Our Phase 3 study demonstrates that the *efficacy* of reducing cholesterol levels and blood pressure by a fixed-dose combination of olmesartan and rosuvastatin was not inferior to blood pressure reduction by olmesartan and cholesterol level reduction by rosuvastatin in patients being simultaneously treated for both diseases in a free-dose regimen.
Acknowledgments

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  - Kang Sul Hee
  - Park Bo Gyeom
  - Jung Hwa Park
  - Kwon Jo Lim
  - Won Ho Kang
  - Min Jee Lee
  - Kwang Hyun Kim
Questions

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