EVALUATION OF DRUG-DRUG INTERACTION POTENTIAL BETWEEN SACUBITRIL/VALSARTAN (LCZ696) AND STATINS USING A PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODEL

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Introduction

• LCZ696 (sacubitril/valsartan) has been shown to offer superior clinical benefits (reduced mortality & hospitalizations) to Heart Failure patients compared to the standard of care (enalapril).

• Sacubitril was shown to be an OATP1B1 and OATP1B3 inhibitor *in vitro*
  — Static predictions estimated a change in exposure in excess of 125% for sensitive OATP1B1 substrates
  — Co-administration with atorvastatin showed ~2-fold increase in atorvastatin Cmax; exposure (AUC) to atorvastatin (or its metabolites) was not significantly increased (<34%)
  — In a separate investigation, no change in simvastatin pharmacokinetics was observed when co-administered with LCZ696

• A physiological-based pharmacokinetic modeling approach was developed to explore atorvastatin and simvastatin interactions with LCZ696

• Additional modeling was done to evaluate the statin-specific DDI risk due to OATP inhibition by LCZ696
LCZ696 (sacubitril/valsartan) Disposition

Hydrolysis and transport across polarized cell monolayers

Sacubitril (AHU377)

Valsartan

Sacubitril (LBQ657)

BCRP

MRP2

Basolateral to Apical Transport

Wild-type

+ LY335979

Sacubitril

(77.8%)

LBQ657

(22.2%)

P-gp/BCRP

knockout

Sacubitril

(78.2%)

LBQ657

(21.8%)

P-gp/MRP2

knockout

Sacubitril

(100%)

LBQ657

(BLQ)

Hanna et al., (2017) Xenobiotica, In press
Sacubitril OATP inhibition

Equipotent OATP1B1/OATP1B3 inhibition

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>plasma unbound fraction</th>
<th>$I_{\text{inlet,max}}$ unbound, µM</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>0.030</td>
<td>0.642</td>
</tr>
</tbody>
</table>

Static Predictions $\Delta$AUC
OATP1B1 inhibition ~1.29
OATP1B3 inhibition ~1.15

Effect of LCZ696 on the pharmacokinetics of atorvastatin and its metabolites

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Geometric Mean Ratio (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$C_{\text{max}}$</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>1.74 (1.49 – 2.02)</td>
</tr>
<tr>
<td>$p$-hydroxy</td>
<td>1.68 (1.49 – 1.91)</td>
</tr>
<tr>
<td>o-Hydroxy</td>
<td>2.08 (1.75 – 2.49)</td>
</tr>
</tbody>
</table>

Ayalasomayajula 2016, Eur J Drug Metab Pharmacokinet, In press
Effect of OATP1B1 polymorphism (reduced activity) on statin exposure

Simvastatin lactone  
*(inactive)*

Simvastatin acid  
*(active)*

Simvastatin acid is the most susceptible statin to DDIs as a result of OATP1B1 inhibition

Niemi et al 2011 Pharm rev. 63:157
Effect of LCZ696 on SVA Pharmacokinetics

- **Simvastatin acid (ng/mL)**
  - SVA, Control
  - SVA, 2 h post LCZ696

- **Time, h**
  - 0
  - 2
  - 4
  - 8
  - 12

- **Fold change, (90% CI)**
  - $C_{\text{max}}$ 1.16 (1.00-1.35)
  - $AUC_{\text{last}}$ 1.01 (0.88-1.17)

Ayalasomayajula et al., 2016, J Clin Pharm Ther., 41, 424–431
Sacubitril PK prediction

*Combined bottom-up and top-down approach Simcyp (Version 15 release 1)*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption (First order absorption model)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Papp, cm/s</td>
<td>$3.87 \times 10^{-6}$</td>
<td>Caco-2 permeability</td>
</tr>
<tr>
<td>Tlag (h)</td>
<td>0.14</td>
<td>Optimized to fit clinical PK</td>
</tr>
<tr>
<td>$ka$ (h$^{-1}$)</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>$Q_{\text{gut}}$ (L/h)</td>
<td>7.48</td>
<td>Simcyp predicted</td>
</tr>
<tr>
<td>Distribution (minimal PBPK)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vss</td>
<td>0.253</td>
<td></td>
</tr>
<tr>
<td>Elimination (in vivo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$CL_{\text{iv}}$ (l/h)</td>
<td>27</td>
<td>User defined</td>
</tr>
<tr>
<td>Cl renal</td>
<td>0</td>
<td>minimal unchanged sacubitril in urine</td>
</tr>
<tr>
<td>Interaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OATP1B1 IC$_{50}$</td>
<td>1.91 µM</td>
<td>Hanna et al, 2017</td>
</tr>
</tbody>
</table>

Healthy volunteer population (10 trials, 10 subjects per trial)
Observed data from 3 clinical trials shown as data points
Qualification of simvastatin and simvastatin acid-linked PBPK model

Paraoxonases, Carboxylesterases

Simvastatin lactone (inactive)

Simvastatin acid (SVA) (active)

<table>
<thead>
<tr>
<th>Simvastatin/LCZ696</th>
<th>SVA: AUC Ratio</th>
<th>SVA: Cmax Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Predicted</td>
<td>Observed</td>
</tr>
<tr>
<td>SV dosed 2 h after LCZ696</td>
<td>1.06</td>
<td>1.01</td>
</tr>
<tr>
<td>SV dosed 1 h after LCZ696</td>
<td>1.08</td>
<td>0.90</td>
</tr>
<tr>
<td>Co-administration</td>
<td>1.10</td>
<td>0.89</td>
</tr>
</tbody>
</table>
Why was there no DDI observed?

Sacubitril: short Tmax, rapidly cleared via hydrolysis

Rapidly absorbed statin (Tmax: <1.5 h)
- Cmax increase max 2-fold
- AUC increase < 1.5-fold

Slowly absorbed statin (Tmax: >1.5 h)
- No meaningful effect on PK with sacubitril

Static DDI predictions: do not take into consideration Tmax, Ft, Papp,passive

Hepatic OATP uptake clearance/statin PK parameter sensitivity analysis

- Sacubitril has the potential to act as a short-lived perpetrator of OATP-mediated DDIs
- Maximal increases of approximately 1.2 fold in the exposure of statins that exhibit a delayed Tmax are anticipated (e.g. simvastatin/lovastatin acid, rosuvastatin)
- Maximum change in exposure ~1.6-fold is anticipated with statins that exhibit Tmax values that coincide with that of sacubitril (e.g. atorvastatin, pitavastatin, pravastatin)

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