Background and Purpose

➢ HepQuant SHUNT test quantifies liver function and physiology [1]

➢ Child-Pugh (CP) classification is the standard classification method for the assessment of liver disease severity and dysfunction in hepatic impairment trials during drug development [2]

➢ Child-Pugh classification has limitations with respect to stratifying patients with liver function for quantification of the liver’s metabolic capacity and thus is a crude predictor of drug pharmacokinetics [3, 4]

➢ Ampreloxetine is a novel norepinephrine reuptake inhibitor being developed for treatment of symptomatic neurogenic orthostatic hypotension and is primarily eliminated by the liver

➢ The aim of this study was to compare the performance of HepQuant with Child-Pugh (CP) classification in predicting the pharmacokinetics of ampreloxetine in subjects with varying degrees of hepatic impairment

Clinical Study Design

This was a multicenter, non-randomized, open label, parallel-group, single-dose study (NCT02000197) conducted in adult subjects with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, C) and in matching healthy subjects. The study was conducted in two sequential parts with subjects with mild (n = 6) and moderate (n = 7) hepatic impairment enrolled first with corresponding healthy matching controls (n = 6). An additional cohort of subjects with severe (n = 6) hepatic impairment were subsequently enrolled with corresponding healthy matching controls (n = 3 additional). A single ampreloxetine dose of 10 mg was administered to all subjects.

HepQuant SHUNT Test

HepQuant SHUNT test was administered on the day prior to ampreloxetine dosing to establish baseline hepatic function. HepQuant Disease Severity Index (DSI), score of 0-50 and SHUNT% (portal-systemic shunting, 0-100%) were measured from 5 serum samples obtained within 90 min of administration of [24-13C]choline intravenously and [2,2,3,3-2H4]-choline orally. Cholate serum concentrations were assessed by LC-MS/MS. Cholate clearances, DSI, and SHUNT% were calculated from the serum concentrations of 13C2-cholate and 2H4-cholate.

Ampreloxetine Pharmacokinetics

PK blood samples were collected at the following times: predose, 0.5, 1, 2, 4, 6, 8, 10, 12, 14, 24, 36, 48, 72, 120, 144, 240, 288, and 336 hr. ampreloxetine plasma concentrations were determined by LC-MS/MS. Ampreloxetine PK parameters (Cmax, AUC0-inf, t1/2) were calculated using noncompartmental methods.

Multivariate Regression

The software package, MedCalc 20.115, was used for the uni- and multi-variable regression analyses.

Methods

Table 1: Baseline Hepatic Function

<table>
<thead>
<tr>
<th>Child-Pugh Classification</th>
<th>DSI</th>
<th>SHUNT%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Controls [A, B, C]</td>
<td>17.7 ± 3.0</td>
<td>25.2 ± 5.9</td>
</tr>
<tr>
<td>Child-Pugh A</td>
<td>18.5 ± 3.1</td>
<td>27.1 ± 5.3</td>
</tr>
<tr>
<td>Child-Pugh B</td>
<td>26.0 ± 6.1</td>
<td>40.4 ± 17.8</td>
</tr>
<tr>
<td>Child-Pugh C</td>
<td>34.3 ± 10.7</td>
<td>61.1 ± 22.1</td>
</tr>
</tbody>
</table>

Multivariate Regression

<table>
<thead>
<tr>
<th>HepQuant Variable</th>
<th>p-values (DSI Model)</th>
<th>p-values (SHUNT% Model)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>0.32</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Results

➢ Ampreloxetine plasma exposure (AUC0-inf) is increased in subjects with moderate (1.7-fold; Child-Pugh B) and severe (2.5-fold; Child-Pugh C) hepatic impairment

➢ Ampreloxetine exposure (AUC0-inf) correlates with Child-Pugh score and more strongly with the HepQuant parameters DSI and SHUNT% relative to Child-Pugh score

➢ Similar performance for the simple, practical HepQuant STAT test

➢ Variability is observed in ampreloxetine exposure (AUC0-inf) in subjects with moderate (CP B) and severe hepatic impairment (CP C). The variability can be explained for individual subjects by their DSI and SHUNT%.

➢ Multivariable regression models demonstrate DSI and SHUNT% as superior predictors of ampreloxetine exposure (AUC0-inf) relative to Child-Pugh score

➢ HepQuant DSI and SHUNT% (as opposed to CP class) may be more useful predictors of drug exposure and thus serve to better optimize dose recommendations for novel therapeutics in patients with liver disease.

References

1. Burton et al., The within-individual reproducibility of the disease severity index from the HepQuant STAT test of liver function and physiology.


3. El-Khatib et al., Review article: time to revisit Child-Pugh score as the basis for predicting drug clearance in hepatic impairment. American Journal of Therapeutics and Pharmacotherapeutics (2021) 51: 309-401


5. Jitendra Kanodia, Hugh Giovinazzo, Wayne Yates, and David L. Bourdet are current or former employees of Theravance Biopharma. Steve M. Helmke is a HepQuant employee (CSO) and equity holder and has intellectual property in HepQuant technology; Gregory T. Eason is a HepQuant employee (CEO) and equity holder and has intellectual property in HepQuant technology.

Contact Information

Dbourdet@theravance.com;  WYates@theravance.com;  s.helmke@hepquant.com;  g.everson@hepquant.com

HepQuant SHUNT IS SUPERIOR TO CHILD-PUGH IN DEFINING HEPATIC IMPAIRMENT FOR PHARMACOKINETIC STUDIES: EXPERIENCE WITH AMPRELOXETINE (AN ENCORE PRESENTATION)

Jitendra Kanodia*, Hugh Giovinazzo†, Wayne Yates†, David L. Bourdet†, Steve M. Helmke‡, and Gregory T. Eason‡

1. Theravance Biopharma US, Inc., South San Francisco, CA USA.

2. HepQuant, LLC, Denver, CO USA

* Former employee of Theravance Biopharma

Results Table 3: Multivariable Regression Analyses for Predictors SHUNT%, DSI, and Ampreloxetine AUC0-inf

<table>
<thead>
<tr>
<th>HepQuant Variable</th>
<th>p-values (DSI Model)</th>
<th>p-values (SHUNT% Model)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child-Pugh Score</td>
<td>0.0143 (DSI)</td>
<td>0.0024 (SHUNT%)</td>
</tr>
<tr>
<td>Age</td>
<td>0.36</td>
<td>0.73</td>
</tr>
<tr>
<td>Gender</td>
<td>0.30</td>
<td>0.16</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>0.59</td>
<td>0.49</td>
</tr>
<tr>
<td>BMI</td>
<td>0.32</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Coefficient of Determination, r2

HepQuant Variable | 0.8518 (DSI) | 0.8851 (SHUNT%)

Ampreloxetine exposure (AUC0-inf) is increased in subjects with moderate (1.7-fold; Child-Pugh B) and severe (2.5-fold; Child-Pugh C) hepatic impairment

Ampreloxetine exposure (AUC0-inf) correlates with Child-Pugh score and more strongly with the HepQuant parameters DSI and SHUNT% relative to Child-Pugh score

Similar performance for the simple, practical HepQuant STAT test

Variability is observed in ampreloxetine exposure (AUC0-inf) in subjects with moderate (CP B) and severe hepatic impairment (CP C). The variability can be explained for individual subjects by their DSI and SHUNT%.

Multivariable regression models demonstrate DSI and SHUNT% as superior predictors of ampreloxetine exposure (AUC0-inf) relative to Child-Pugh score

HepQuant DSI and SHUNT% (as opposed to CP class) may be more useful predictors of drug exposure and thus serve to better optimize dose recommendations for novel therapeutics in patients with liver disease.

Disclosures

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HepQuant COMPARE SHUNT test quantifies liver function and physiology[1]. Child-Pugh (CP) classification is the standard classification method for the assessment of liver disease severity and dysfunction in hepatic impairment trials during drug development[2]. Child-Pugh classification has limitations with respect to stratifying patients with liver function for quantification of the liver’s metabolic capacity and thus is a crude predictor of drug pharmacokinetics[3, 4]. Ampreloxetine is a novel norepinephrine reuptake inhibitor being developed for treatment of symptomatic neurogenic orthostatic hypotension and is primarily eliminated by the liver. The aim of this study was to compare the performance of HepQuant with Child-Pugh (CP) classification in predicting the pharmacokinetics of ampreloxetine in subjects with varying degrees of hepatic impairment. This was a multicenter, non-randomized, open label, parallel-group, single-dose study (NCT02000197) conducted in adult subjects with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, C) and in matching healthy subjects. The study was conducted in two sequential parts with subjects with mild (n = 6) and moderate (n = 7) hepatic impairment enrolled first with corresponding healthy matching controls (n = 6). An additional cohort of subjects with severe (n = 6) hepatic impairment were subsequently enrolled with corresponding healthy matching controls (n = 3 additional). A single ampreloxetine dose of 10 mg was administered to all subjects.

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