Population Pharmacokinetic Analysis of Telaprevir in Adult Patients with Chronic Genotype 1 Hepatitis C Virus Infection

Pooled Analysis of Phase 2 and Phase 3 Telaprevir Trials

Joshua Henshaw¹, Marc Gastonguay², Tim Bergsma², Holly Kimko³, Maria Rosario¹, Rolf van Heeswijk³, and Varun Garg¹

¹Vertex Pharmaceuticals Incorporated, Cambridge, MA, USA;
²Metrum Research Group, Tariffville, CT, USA;
³Janssen Research & Development LLC, Raritan, NJ (HK) and Beerse, Belgium (RvH)
Disclosures

M. Gastonguay, T. Bergsma are paid contract research providers for Vertex Pharmaceuticals Incorporated

H. Kimko, R. van Heeswijk are employees of Janssen Pharmaceuticals and may own stock and stock options in that company

V. Garg is an employee of Vertex Pharmaceuticals and may own stock or stock options

J. Henshaw and M. Rosario are former employees of Vertex Pharmaceuticals and may own stock or stock options
Background

- Telaprevir (TVR) in combination with peginterferon (Peg-IFN) and ribavirin (RBV) is approved for treatment of genotype 1 chronic HCV infection in adults with compensated liver disease\(^1\)

- Objective: To develop a population pharmacokinetic (PK) model of TVR in combination with Peg-IFN and RBV:
  - Obtain estimates of typical PK parameters
  - Assess inter- and intra-subject variability
  - Evaluate the influence of covariates

\(^1\)INCIVEK™ [US Prescribing Information] Cambridge, MA, USA: Vertex Pharmaceuticals Incorporated; 2012
Methods

- Four Phase 2 and three Phase 3 studies of adults with chronic genotype 1 HCV infection*
- 14,413 observations from 1836 subjects
- Studies varied in design, population and schedules of PK assessments
  - All patients received TVR 750 mg q8h† and concomitant Peg-IFN with or without RBV
  - Main demographics pooled across studies: (a) mean age, 48 years (b) mean weight, 80 kg (c) racial distribution, 88% White
- One-compartment population PK model with first-order absorption and linear elimination was used
- A full model estimation approach evaluated covariate effects on TVR PK in the context of exposure-response relationships
  - Oral clearance (CL/F): age, weight, race, concomitant RBV
  - Volume of distribution (V/F): weight

† Particular studies included an initial starting tvr dose of 1125 or 1250 mg
# Population PK Analysis of Telaprevir

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (Standard Error)</th>
<th>% RSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of Distribution V/F</td>
<td>252 L (13.5)</td>
<td>5.36</td>
</tr>
<tr>
<td>Clearance CL/F</td>
<td>32.4 L/hr (0.336)</td>
<td>1.04</td>
</tr>
<tr>
<td>Absorption Rate Constant</td>
<td>0.230 hr^{-1} (0.0125)</td>
<td>5.43</td>
</tr>
</tbody>
</table>

% relative standard error (%RSE) = |Standard Error/Estimate|*100
Population PK Analysis of Telaprevir: Graphical Diagnostics

![Graphical diagnostics for population PK analysis of Telaprevir.](image)
Covariate Clinical Relevance: Full Model Estimation Approach

No potential for clinical impact

Potential for clinical impact
- Evaluated against PK/PD relationships

No potential for clinical impact
Summary

- One-compartment population PK model with first-order absorption described the PK of telaprevir
  - CL/F and V/F of telaprevir estimated to be 32.4 L/hr and 252 L
  - Inter-individual variability estimated to be 27.2% for CL/F and 72.2% for V/F

- Patient age, race, and concomitant RBV administration did not have a clinically relevant impact on average steady-state exposure of telaprevir

- Patient weight was an influential covariate on the clearance of telaprevir.
  - Exposure-response results suggest that the magnitude of the effect of weight did not have a clinically relevant impact on the safety or efficacy of telaprevir.
  - Interindividual variability in telaprevir clearance explained by weight was minimal compared to overall interindividual variability in clearance estimated for the population.
Exposure-response Relationships in Telaprevir Combination Therapy in Treatment-naïve Genotype 1 Chronic HCV Patients

Joshua Henshaw¹, Stuart C Gordon², Andrew J Muir³, Varun Garg¹

¹Vertex Pharmaceuticals Incorporated, Cambridge, MA, USA
²Henry Ford Health Systems, Detroit, MI, USA
³Duke Clinical Research Institute, Durham, NC, USA
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J Henshaw is a former employee and may own stock or stock options of Vertex Pharmaceuticals Incorporated at the time this research was performed.

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BACKGROUND

- ADVANCE and ILLUMINATE were Phase 3 trials that evaluated the safety and efficacy of TVR combination therapy in treatment-naïve genotype 1 chronic HCV infected patients\(^4,5\)
  - Overall SVR rates in ADVANCE: 79% (T12PR) and 46% (PR)\(^1-3\)
  - Overall SVR rates in ILLUMINATE: 74% (T12PR)\(^1-3\)
- In patients who received TVR-based therapy compared with PR, respectively, anemia (all grades) occurred in 36% and 17%, rash (all grades) in 56% and 34%, and anorectal discomfort in 11% and 3%\(^1\)
- In this analysis, we evaluated the relationships between efficacy and safety parameters and exposure to TVR, Peg-IFN alfa-2a (40 KDa), and RBV

Methods

- Treatment-naïve patients (N=472) from ADVANCE/ILLUMINATE with pharmacokinetic (PK) data available were included in logistic regression and receiver operating characteristic (ROC) analyses that investigated associations between drug exposures and efficacy/safety parameters.
  - Logistic regression - incidence of safety events dichotomized using a cutoff grade of ≥2 for anemia (defined by 2004 DAIDS toxicity grading) and anorectal discomfort, and a cutoff grade of ≥3 for rash.
- If a patient had >1 AE event, the highest severity event was used.
- For TVR, sparse PK samples were collected at Weeks 1, 2, 4, 8, and 12. Pop PK derivedCss was used as measure of TVR exposure.
- For RBV and Peg-IFN, observed Week 4 concentrations were used as representative exposure measures.
Correlation between TVR Exposure and Virologic Endpoints during the TVR Phase

<table>
<thead>
<tr>
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<th>ROC Analysis (AUC)</th>
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<tbody>
<tr>
<td></td>
<td>eRVR</td>
</tr>
<tr>
<td>TVR</td>
<td>0.53</td>
</tr>
<tr>
<td>Peg-IFN</td>
<td>0.55</td>
</tr>
<tr>
<td>RBV</td>
<td>0.53</td>
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</tbody>
</table>

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Correlation between Drug Exposure and Anemia During the TVR phase

Median drug exposure plots: white line = median, end of shaded box=interquartile range (IQR), whiskers=1.5+IQR, single line=outlier. Logistic regression curves: open circles=individual patient data (value=1 indicates patient met PD endpoint, value=0 indicates patient did not meet PD endpoint), solid line= probability predicted by logistic regression model, dashed line=95%CI.

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Correlation between Drug Exposure and Anemia During the TVR phase

**Median Drug Exposure**

- TVR
- TVR Plasma Conc. (ng/ml)

- Peg-IFN
- Peg-IFN Serum Conc. (pg/ml)

**Logistic Regression**

- Probability (Anemia)

Median drug exposure plots: white line = median, end of shaded box = interquartile range (IQR), whiskers = 1.5+IQR, single line = outlier. Logistic regression curves: open circles = individual patient data (value=1 indicates patient met PD endpoint, value=0 indicates patient did not meet PD endpoint), solid line = probability predicted by logistic regression model, dashed line = 95% CI.

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Correlation between Drug Exposure and Anemia During the TVR phase

Median Drug Exposure

Logistic Regression

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Correlation of Rash and Anorectal Discomfort with Drug Exposure During TVR Phase

**Rash**

Median Drug Exposure

**Anorectal Discomfort**

Median Drug Exposure

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Median drug exposure plots: white line = median, end of shaded box=interquartile range (IQR), whiskers=1.5+IQR, single line=outlier. Logistic regression curves: open circles=individual patient data (value=1 indicates patient met PD endpoint, value=0 indicates patient did not meet PD endpoint), solid line= probability predicted by logistic regression model, dashed line=95%CI. Gordon et al. *Digestive Disease Week* San Diego, CA; 2012
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Correlation of Rash and Anorectal Discomfort with Drug Exposure During TVR Phase

**Rash**

- **Median Drug Exposure**
  - TVR
    - Median: 2926 mg/mL, 2962 mg/mL, 2662 mg/mL, 3042 mg/mL
  - Peg-IFN
    - Median: 15400 pg/mL, 16600 pg/mL, 15650 pg/mL, 16950 pg/mL
  - RBV
    - Median: 2590 pg/mL, 2850 pg/mL, 2805 pg/mL, 2675 pg/mL

**Anorectal Discomfort**

- **Median Drug Exposure**
  - TVR
    - Median: 2937 mg/mL, 2933 mg/mL, 2744 mg/mL, 2606 mg/mL
  - Peg-IFN
    - Median: 15400 pg/mL, 16100 pg/mL, 16900 pg/mL, 13800 pg/mL
  - RBV
    - Median: 2680 pg/mL, 2870 pg/mL, 2570 pg/mL, 2570 pg/mL

Median drug exposure plots: white line = median, end of shaded box = interquartile range (IQR), whiskers = 1.5×IQR, single line = outlier. Logistic regression curves: open circles = individual patient data (value = 1 indicates patient met PD endpoint, value = 0 indicates patient did not meet PD endpoint), solid line = probability predicted by logistic regression model, dashed line = 95% CI.

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Conclusions

- These data support the current recommended doses for telaprevir, peginterferon, and ribavirin\(^1\)\(^-\)\(^3\)

- Within the observed concentration ranges, telaprevir, peginterferon, and ribavirin exposures had non-significant associations with eRVR and SVR

- Treatment-emergent anemia correlated with telaprevir, peginterferon, and ribavirin exposures, with the strongest association with ribavirin

- The absence of correlations between drug exposure and rash or anorectal discomfort occurrence or severity suggests that dose adjustment is unlikely to significantly impact these parameters

\(^1\)INCIVEK\(^\text{TM}\) [US Prescribing Information] 2012. Vertex Pharmaceuticals Incorporated: Cambridge, MA;
\(^2\)INCIVO\(^\text{®}\) [Summary of product characteristics] 2012. Janssen Pharmaceuticals: Beerse, Belgium;
\(^3\)INCIVEK\(^\text{TM}\) [Canadian Product Monograph] 2011. Vertex Pharmaceuticals Incorporated: Laval, Quebec
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