Population Pharmacokinetic Analysis of Yimitasvir in Chinese Healthy Volunteers and Patients with Chronic Hepatitis C Virus Infection

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Abstract

Aims Yimitasvir is a novel, oral hepatitis C virus (HCV) non-structural protein 5A inhibitor for the treatment of chronic HCV genotype 1 infection. The objective of this analysis was to develop a population pharmacokinetic model of yimitasvir in Chinese healthy volunteers and HCV infection patients. Methods The model was performed using data from 219 subjects across 6 studies. Nonlinear mixed effects models were developed using Phoenix NLME software. The covariates were evaluated using a stepwise forward inclusion ($P < 0.01$) and then a backward exclusion procedure ($P < 0.001$). Results A two-compartment model with sequential zero-first order absorption and first-order elimination reasonably described yimitasvir pharmacokinetics (PK). The apparent oral clearance and central volume of distribution were 13.8 l h-1 and 188 l, respectively. The bioavailability (F) of yimitasvir decreased 12.9% for each 100 mg dose increase. Food was found to affect absorption rate (Ka) and F. High-fat meal decreased Ka and F by 90.9% and 38.5%, respectively. Gender and alanine aminotransferase were identified as significant covariates on apparent oral clearance. Female subjects had lower clearance than male subjects. Zero-order absorption duration was longer in healthy volunteers (2.17 h) than that in patients (1.43 h). Conclusions The population pharmacokinetic model described yimitasvir PK profile well. Food decreased Ka and F significantly, so it was recommended to take yimitasvir at least 2 h before or after a meal. Other significant covariates were not clinically important.

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Keywords population pharmacokinetic, yimitasvir, hepatitis C virus, non-structural protein 5A inhibitor, Phoenix NLME

Aims

Yimitasvir is a novel, oral hepatitis C virus (HCV) non-structural protein 5A inhibitor for the treatment of chronic HCV genotype 1 infection. The objective of this analysis was to develop a population pharmacokinetic model of yimitasvir in Chinese healthy volunteers and HCV infection patients.

Methods

The model was performed using data from 219 subjects across 6 studies. Nonlinear mixed effects models were developed using Phoenix NLME software. The covariates were evaluated using a stepwise forward inclusion ($P < 0.01$) and then a backward exclusion procedure ($P < 0.001$).

Results

A two-compartment model with sequential zero-first order absorption and first-order elimination reasonably described yimitasvir pharmacokinetics (PK). The apparent oral clearance and central volume of distribution were 13.8 l h^{-1} and 188 l, respectively. The bioavailability (F) of yimitasvir decreased 12.9% for each 100 mg dose increase. Food was found to affect absorption rate (Ka) and F. High-fat meal decreased Ka and F by 90.9% and 38.5%, respectively. Gender and alanine aminotransferase were identified as significant covariates on apparent oral clearance. Female subjects had lower clearance than male subjects. Zero-order absorption duration was longer in healthy volunteers (2.17 h) than that in patients (1.43 h).

Conclusions

The population pharmacokinetic model described yimitasvir PK profile well. Food decreased Ka and F significantly, so it was recommended to take yimitasvir at least 2 h before or after a meal. Other significant covariates were not clinically important.

Introduction

Chronic infection with hepatitis C virus (HCV) is a public health concern in the world, which can lead to liver cirrhosis, and/or hepatocellular carcinoma (primary liver cancer) [1]. In 2002, National Institutes of Health Consensus Development Conference Statement reported more than 184 million persons had HCV infection [2]. An epidemiology in 2015 estimated that 1.0% of the world population corresponding to approximate 71 million people were active cases [3]. Every year three to four million people are newly infected and approximately 350,000 deaths occur [4]. HCV demonstrates great genetic diversity with 7 genotypes and at least 67 subtypes [1]. Overall, genotype 1 dominates with 44% of infections, followed by genotype 3 (25%) and 4 (15%) [3]. In China, it is estimated that at least 25 million individuals infected with HCV [5] and genotype 1b is the most common type (56.8%), followed by genotype 2 (24.1%) and 3 (9.1%) [6].

Yimitasvir is a novel, oral HCV non-structural protein 5A (NS5A) inhibitor for the treatment of chronic HCV genotype 1 infection in combination with sofosbuvir. The chemical structure of yimitasvir is shown in Figure 1. The pharmacokinetic profile of yimitasvir has been evaluated in healthy volunteers and patients with chronic HCV infection [7, 8]. Following fasted single oral dose of yimitasvir in healthy volunteers, yimitasvir was absorbed with a peak concentration (C_{max}) 3.5-4.0 h post-dose. Area under the concentration-time curve (AUC) and C_{max} increased in a dose-proportional manner from 30 to 100 mg but a less than proportional manner from 100 to 600 mg (single ascending dose [SAD] study) [7]. Similarly, less than dose-proportional manner was found in multiple ascending dose (MAD) study in the range of 100-400 mg once daily for 7 consecutive days. However, the result from phase 1b study in patient population showed that yimitasvir exhibited near dose-proportional increase in exposure from 30 to 200 mg administered during the night (4 h after dinner) [8]. Yimitasvir was approximately 79.2-86.6% bound to human plasma proteins and the binding

was independent of drug concentration over the range of 100-2000 ng ml^{-1}. No metabolism of yimitasvir was detected in vitro during incubations with hepatic microsomes from mice, rats, dogs, monkeys and humans. Less than 0.04% of yimitasvir was recovered in urine as the parent drug through 7 days post-dose and fecal excretion of parent drug was the major route of elimination [7]. The terminal half-life ($t_{1/2}$) of yimitasvir was 13.4-19.7 h, supporting once daily dosing schedule. Steady state was achieved by day 5 following the once daily dosing regimen. The accumulation ratio was 1.32-1.34, consistent with half-life. A high-fat meal reduced absorption rate with T_{max} occurring at 5-12 h post-dose and resulted in approximate 50% and 63% decrease in yimitasvir AUC and C_{max}, respectively [7]. Yimitasvir is a substrate and inhibitor of the drug transporter P-glycoprotein (P-gp). Yimitasvir is a weak inhibitor of cytochrome P450 (CYP) 2C8, but does not inhibit CYPs 1A2, 2B6, 2C9, 2C19, 2D6 and 3A4. Yimitasvir may be a weak inducer of CYP3A4.

In phase 2 study, yimitasvir 100 or 200 mg was administered once daily for 12 weeks in combination with 400 mg sofosbuvir in patients with chronic HCV infection. Similar to other HCV NS5A inhibitors such as velpatasvir [9] and ledipasvir [10], yimitasvir PK profile was not affected by co-medication of sofosbuvir. The primary endpoint of phase 2 study was sustained virologic response (HCV RNA less than lower limit of quantification [LLOQ]) 12 (SVR12) weeks after the completion of treatment. SVR12 rates were achieved 100% in both 100 mg yimitasvir/400 mg sofobuvir and 200 mg yimitasvir/400 mg sofobuvir groups. The adverse reaction rates were comparable between 100 mg (35.9%) and 200 mg (36.9%) groups. The most common adverse reactions were neutropenia (3.9%), leukopenia (3.1%), hypercholesterolemia (3.1%) and fatigue (3.1%). All of these adverse reactions were grade 1 or 2 in severity. In summary, no dose-response relationship for efficacy and safety was observed in phase 2 study.

The aim of our study was to develop a population PK model to characterize yimitasvir PK in Chinese population and to identify the significant covariates affecting yimitasvir PK. This model will be further updated with much more patient PK data from phase 3 study and be used for predicting individual subject exposure for efficacy and safety exposure-response analysis of yimitasvir.

Methods

Patients

The current population PK analysis of yimitasvir was performed using rich and sparse PK samples collected from 6 clinical pharmacology trials (4 phase 1 [7], 1 phase 1b [8] and 1 phase 2 studies) in Chinese healthy volunteers and HCV-infected patients. Rich sampling entailed serial blood sampling at defined time points, and sparse sampling (single sample) only in phase 2 study entailed blood collection at every study visits. Patients with genotype 1 HCV infection were eligible, while patients with prior use of direct-acting antiviral agents (DAA) for HCV infection treatment were excluded in phase 1b and phase 2 studies. Detailed study design and sampling schedule are shown in Table 1.

All studies were conducted in accordance with the Declaration of Helsinki. Study protocols were approved by local ethics committees. Written informed consent was obtained from all subjects prior to study.

Bioanalytical Methods and Data Handling

A fully validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method determining yimitasvir concentration in phase 1 and phase 1b studies had been reported elsewhere [7, 8].

Plasma concentration of yimitasvir in phase 2 study was analyzed using a validated LC-MS/MS method equipped with a Shimadzu LC-30AD liquid chromatography-SCIEX API6500 mass spectrometer. Chromatographic retention and separation were achieved on a XBridge Peptide BEH C18, 50 × 2.1 mm, 3.5 μm column. Gradient elution was used with 2 mM ammonium acetate in water with 0.1% formic acid as mobile phase A and acetonitrile:methanol (30:70, v:v) as mobile phase B at a flow rate of 0.5 ml min^{-1}. The column temperature was maintained at 45 °C. Quantitation was accomplished in positive mode with precursor-to-production pairs of m/z 428.5-315.3 for yimitasvir and m/z 432.5-319.5 for the internal standard d8-DAG (isotope-labelled yimitasvir), respectively.

The calibration curve was linear in the range of 5.00-5000 ng ml^{-1} for both methods, and the lower limit of quantitation (LLOQ) was 5.00 ng ml^{-1}. Accuracy and precision were within the acceptable criteria of +-15% for quality control (QC) samples and of +-20% for LLOQs. Both methods were fully validated in accordance with National Medical Products Administration (NMPA) of China, U.S. Food and Drug Administration (U.S. FDA) and European Medicines Agency (EMA) guidelines. These two bioanalytical methods were not cross-validated.

Pharmacokinetic data with an absolute value of conditional weighted residual (CWRES) |CWRES| > 6 in the structural models were regarded as outliers. Outliers were omitted because these observations had a potential to negatively influence the convergence and/or poor estimation precision of parameters. If outliers were removed in the process of model development, the final model was re-run with or without the outliers to assess the potential influence on parameter estimates. If the frequency of LLOQ data was less than 10%, PK samples below LLOQ were excluded from model development. Otherwise, Beal's M3 method was used for handling the LLOQ data [11]. For covariates with missing values in less than 10% of subjects, continuous covariates were imputed as the population median, while a new category of 'missing' is generated for categorical covariates. No formal covariate screen procedure would be conducted if the covariates missed in more than 10% of the subjects.

Model Development

Population pharmacokinetic analysis of yimitasvir was performed by Phoenix NLME software (Version 8.1, Certara) using the first-order conditional estimation-extended least squares (FOCE-ELS) method.

The structural model was first tested by fitting a one-compartment or two-compartment model to the log-transformed PK data. Different absorption models including first-order absorption with or without a lag time, sequential zero-first order absorption, transit absorption and saturable Michaelis-Menten absorption model, were also tested. The optimal structural model was selected based on the Akaike Information Criteria (AIC), minimization success, visual inspection of goodness-of-fit plots and individual fit.

Inter-subject variability was estimated by exponential model for PK parameters as follows (Eq. 1):

$$\vartheta_i = \vartheta_{TV} \times e^{\eta_i} \quad (1)$$

where ϑ_i is the parameter estimation for the i th individual, ϑ_{TV} is the typical value of the parameter estimation in the population, η_i is a random variable which assumed to be normally distributed with a mean of 0 and a variance of ω^2. Proportional error model and proportional plus additive error model were tested as residual error models.

Following the development of structural model, the dose effect on bioavailability was evaluated first due to the less than dose-proportional profile of yimitasvir. Sigmoidal maximum effect (Emax) (Eq.2) and linear models (Eq.3) were tested to quantify the relationship between bioavailability and dose:

$$F = \vartheta_F - F_{max} \times (Dose - 100)/(F_{50} + (Dose - 100)) \quad (2)$$

where ϑ_F is the bioavailability in individuals who received 100 mg yimitasvir, which was fixed to 1. $F_{max}$is the maximal reduction in bioavailability and F_{50} is the dose associated with a half-maximal reduction in bioavailability.

$$F = \vartheta_F - Alpha \times (Dose - 100)/100 \quad (3)$$

where Alpha is a slope term determining the relative change in bioavailability for each 100 mg increase in yimitasvir dose.

Subsequently, different covariates were tested using a stepwise forward inclusion (a decrease in objective function value [OFV] of > 6.63, $P < 0.01$) and a stricter backward exclusion procedure (an increase in OFV of > 10.83,$P < 0.001$). The covariates included age, gender, body weight (BW), body mass index (BMI), baseline haemoglobin (HGB), baseline aspartate aminotransferase (AST), baseline alanine aminotransferase (ALT), baseline albumin (ALB), baseline total bilirubin (TBIL), baseline creatinine clearance (CLcr) calculated by

Cockcroft-Gault formula[12], co-medication of sofosbuvir, disease status (healthy volunteers vs patients) and food effect.

The effect of continuous covariates was modeled using a power function after normalization by the population median (Eq. 4):

$\vartheta_{\mathrm{i}} = \vartheta_{\mathrm{TV}} \times (cov_{\ \mathrm{i}}/cov_{\ \mathrm{median}})^{\vartheta\xi}$ (4)

The effect of categorical covariates was modeled using exponential format as follows (Eq. 5):

$\vartheta_{\mathrm{i}} = \vartheta_{\mathrm{TV}} \times e^{\vartheta\xi\ \varsigma o = \varkappa}$(5)

where $cov_{\ \mathrm{i}}$ and $cov_{\ \mathrm{median}}$represent covariate values for the i th individual and the population median, respectively. k is a categorical variable, and ϑ_{x} is a coefficient used to describe the strength of the covariate effect.

When two covariates were highly correlated ($r^2 > 0.7$) such as ALT versus AST, only the most significant one was reserved in the model if both covariates were considered to be significant for the same PK parameter during univariate screen process.

Model Evaluation and Simulation

. The predictive performance of the final model was assessed by prediction-corrected visual predictive check (pcVPC) method using 1000 trial replicates stratified by study. The observed data were plotted against the median, the 5th and 95th percentiles of predicted concentrations. The model was considered to be precise if the observed data were evenly distributed around the median prediction and within the 90% predicted intervals. In addition, a bootstrap procedure (n = 1000) sampling with replacement from the original data was used to further test the robustness of the final model.

Individual empirical Bayes estimates PK parameters from the final model were used to predict the steady state exposure of yimitasvir. The simulated dosing regimen was yimitasvir 100 mg once daily for 12 consecutive weeks. The sensitive plot was plotted to present the effect of a significant covariate on yimitasvir exposure [steady state area under curve (AUC_{ss}), steady state minimum concentration ($C_{trough,ss}$) and steady state maximum concentration ($C_{max,ss}$)]. The steady state exposure was calculated using PK parameters with incorporation of the isolated effect from the covariate and with other unaffected PK parameters fixed to the typical value. The overall exposure variability of the population was compared with the variability from those significant covariates.

Results

A total of 3540 pharmacokinetic records (99.1%) from 219 subjects (72 healthy volunteers and 147 HCV infection patients) were included for model development. 31 (0.9%) samples below LLOQ were excluded from analysis. All CWRES ranged between -6 and 6. No PK data points were identified as outliers in the structural model and were excluded in the process of model development. Baseline demographics and subject characteristics were summarized in Table 2.

A two-compartment model with sequential zero-first order absorption and first-order elimination was investigated to describe the pharmacokinetics of yimitasvir. The structural model was first established using intensive PK data from single ascending dose and multiple ascending dose (CTR20140854, CTR20150048 and CTR20170932) in healthy volunteers. A two-compartment model with first-order elimination was superior to a one-compartment model to describe yimitasvir PK profile. For the tested absorption model including first-order absorption with or without a lag time, sequential zero-first order absorption, transit absorption and saturable Michaelis-Menten absorption, transit absorption model had the smallest AIC value and fitted the data best from the goodness-of-fit plots. Sequential zero-first order absorption model also performed well. When the full PK data were used, transit absorption model converged difficultly and slowly. Finally, we chose sequential zero-first order absorption model. Residual variability was modeled by proportional error model.

After the base structural model was established, the dose effect on PK parameters was tested first. The linear model was simple and adequate to describe the effect of dose on bioavailability. With incorporation of linear model, the objective function value (OFV) decreased by 82 units. Model fitting was improved significantly especially for high concentration data points. The typical value of Alpha was fixed to 0.129 according to the model result using data from SAD and MAD studies, which indicated that the bioavailability of yimitasvir decreased 12.9% for each 100 mg dose increase.

Subsequently, a stepwise forward inclusion and a backward exclusion procedure were performed to screen different covariates. During univariate screen procedure, covariates of ALT and AST, which were highly correlated ($r^2 = 0.93$), were statistically significant on the same PK parameter of apparent clearance. ALT was considered to be more significant (decrease in OFV 18.291) than AST (decrease in OFV 12.675). As a result, the effect of ALT on clearance was reserved for further covariate screening. Following the stepwise forward inclusion process, food status was identified to be a significant covariate on first-order absorption rate (Ka) and bioavailability (F), gender and ALT were significant covariates on apparent clearance and disease status on duration of zero-order absorption (Td). None of these significant covariates was removed during the process of backward elimination. The final model parameter estimiates and their associated precisions (percent confidence of variation, CV%), including the effect of significant covariates ($P < .001$), were provided in Table 3. The typical values (for a healthy male volunteer with ALT value of 31.6 IU l^{-1}taking yimitasvir under fasted state) for apparent oral clearance (CL/F) and central volume of distribution (V/F) were 13.8 l h^{-1} and 188 l, respectively. Inter-individual variability for CL/F and V/F and the covariance of them were 48.5%, 73.6% and 56.5%, respectively. The shrinkage values for CL/F and V/F were 3.25% and 8.69%, respectively, which indicated that individual empirical Bayes estimates PK parameters could be used to predict yimitasvir exposures [13]. High-fat meal decreased Ka and F by 90.9% and 38.5%, respectively. Male subjects had a 22.2% higher yimitasvir CL/F than females. Baseline ALT was another significant covariate on apparent clearance. Duration of Zero-order absorption duration was longer in healthy volunteers (2.17 h) than that in patients (1.43 h). All the parameters were estimated with good precisions.

Goodness-of-fit plots for the final pharmacokinetic model are shown in Figure 2. The population and individual predictions agreed with the yimitasvir observations well, but there was a trend of under-prediction at high concentration data points (Figure 2A and 2B). Most of these data were from 200 mg group of phase 2 study. One possible assumption for the bias was the lack of precise dosing history in phase 2 trial although the last dosing time before each PK sampling was recorded. Most CWRES ranged from $y = \pm 4$ and were evenly distributed at $y = 0$ (Figure 2C and 2D) with no obvious bias over the population predictions and time indicating the proper choice of proportional model for the residual variability.

Figure 3 shows the pcVPC plot stratified by study. The observed data were evenly distributed around the median prediction and were mostly within the 90% percentiles of the predicted concentrations, which indicated that the model could adequately describe PK profile of yimitasvir. In the bootstrap for the final model, all the 1000 replications ran successfully. The population parameter estimates were close to the median values from bootstrapping analysis and fell within 95% confidence intervals (Table 3), suggesting that the final model was robust and accurate.

The influence of significant covariates on predicted steady state exposure (AUC_{ss}, $C_{trough,ss}$ and $C_{max,ss}$) was presented in Figure 4. The result revealed that food status had a great impact on yimtasvir $AUC_{ss}$and $C_{max,ss}$, but not $C_{trough,ss}$. AUC_{ss} and $C_{max,ss}$ decreased by 38.5% and 58.9% after a high-fat meal, respectively. These results were consistent with the result of the yimitasvir food effect study. The $C_{trough,ss}$ of females was 54% higher than that of males, while AUC_{ss} and $C_{max,ss}$ of females were less than 30% higher than that of males. The magnitude of ALT on the steady-state exposure of yimitasvir was mild (˜30%) for healthy volunteers with extreme ALT values (5th and 95th percentiles) relative to the typical healthy volunteers. There was no difference in exposures between patients and healthy volunteers.

Discussion

This population PK analysis was established using rich and sparse PK samples collected from 6 clinical

trials including 72 healthy volunteers and 147 HCV infection patients. A two-compartment model with a sequential zero-first order absorption and first-order elimination could described the PK profiles of yimitasvir well. After a stepwise forward inclusion and backward exclusion covariate screen procedure, statistically significant covariates in the final model were food status on Ka and F, gender and ALT on CL/F, and disease status on Td.

Results from phase 1 SAD study in healthy volunteers suggested that the exposure (AUC and C_{max}) of yimitasvir increased less than proportionally in the range of 30-600 mg. Similar exposures were found between 400 mg and 600 mg groups indicating a limited absorption. Less than dose proportionality was also observed in phase 2 study in patients after oral administrations of 100 or 200 mg yimitasvir in combination with 400 mg sofosbuvir. Sofosbuvir did not affect the pharmacokinetic properties of yimitasvir, which had been proven by other drugs targeting HCV NS5A protein like velpatasvir [9] and ledipasvir [10]. However, the exposure of yimitasvir was dose-proportional in phase 1b trial in patients with chronic HCV genotype 1 infection after single and multiple oral dosing from 30 to 200 mg. The mechanism behind the difference in the PK linearity of yimitasvir between phase 1b and the other trials is unclear. One significant difference in clinical trial design was that subjects in phase 1b trial administered yimitasvir in the evening after dinner for more than 4 h, while subjects in other trials took the drug in the morning under fasted state. The inefficiency of gastric emptying resulted in decrease of absorption rate with a median time to peak concentration (T_{max}) of 4-12 h and a 40% AUC decrease when compared to phase 1 SAD trial. The decrease in exposure may contribute to the linearity of yimitasvir in phase 1b trial.

Food status was a significant covariate affecting the absorption rate (Ka) and bioavailability (F). In this population PK analysis, food was classified into three categories. Subjects who took the drug under fasted and fed (high-fat meal) condition were classified as food = 0 (as reference) and food = 2, respectively, while subjects in phase 1b trial who administered yimitasvir in the evening after dinner more than 4 h were classified as food = 1. Administration with a high-fat meal or in the evening after dinner more than 4 h resulted in a 28.9% and a 38.5% decrease in AUC_{ss}, a 10.0% and 3.52% decrease in $C_{trough,ss}$, and a 46.1% and 58.9% decrease in $C_{max,ss}$, respectively (Figure 4). The results from the population PK analysis were consistent with the results from previous studies. The decrease in steady state exposures might be due to the solubility of yimitasvir. Yimitasvir exhibited a pH-dependent solubility profile. In the fasted condition, yimitasvir solubility increased due to a low gastric pH in the stomach. However, a high-fat meal resulted in higher gastric pH for drug dissolution reduction [14]. Whether the decreased exposure after a high-fat meal would be clinically significant was not clear. It was recommended that yimitasvir was administered at least 2 h before or after a meal.

Gender was found to be a significant covariate for yimitasvir CL/F. Female subjects had lower apparent clearance than male subjects. The steady state exposures (AUC_{ss}, $C_{trough,ss}$, $C_{max,ss}$) in female subjects were 15.1-54.0% higher than male subjects. Baseline ALT was another significant covariate on Cl/F. The apparent clearance decreased with the increase of baseline ALT.

There was no difference in PK parameters between patients and healthy volunteers, except for parameter Td, which was a little longer in healthy volunteers than that in patients. The difference in Td between the two kinds of population did not result in exposure differences.

In phase 2 clinical trial, yimitasvir 100 or 200 mg was administered once daily for consecutive 12 weeks in combination with 400 mg sofosbuvir in HCV infection patients. The primary endpoint of SVR12 rates were achieved 100% in both 100 mg yimitasvir/400 mg sofobuvir and 200 mg yimitasvir/400 mg sofobuvir groups. The adverse reaction rates were comparable between 100 mg (35.9%) and 200 mg (36.9%) groups. The most common adverse reactions were neutropenia (3.9%), leukopenia (3.1%), hypercholesterolemia (3.1%) and fatigue (3.1%). All of these adverse reactions were grade 1 or 2 in severity. No dose-response relationship for efficacy and safety was identified in phase 2 clinical trial. Considering the high response rate and favorable safety profiles of yimitasvir in phase 2 clinical study, the significant covariates of gender and baseline ALT on clearance was not clinically relevant.

Except for gender, other baseline demographics such as age and BW had no effect on yimitasvir PK properties. It seems that there is no need to adjust dosage based on these factors. But due to the small sample size of phase 2 study, this conclusion should be further validated in a larger patient population.

This is the first time to establish a population PK model of a new HCV NS5A inhibitor, yimitasvir, in Chinese healthy volunteers and patients with chronic HCV genotype 1 Infection. It is very helpful for us to know statistically significant covariates affecting the pharmacokinetic property of yimitasvir. This work can be used as a basis for subsequent population PK model development including more patient data from phase 3 trial.

The population pharmacokinetic model was demonstrated to be appropriate and effective to describe the pharmacokinetics of yimitasvir in Chinese population. Food status, disease status (healthy volunteers vs patients), gender and baseline ALT were identified as statistically significant covariates to affect yimitasvir pharmacokinetics. High-fat meal decreased absorption rate and bioavailability, so it is recommended to take yimitasvir at least 2 h before or after a meal. Considering the favorable safety profile of yimitasvir and 100% SVR12 rate in phase 2 study, the impact of gender and ALT on yimitasvir exposure was not considered clinically relevant. This conclusion should be further validated in a larger patient population from phase 3 clinical trial.

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Declaration of Conflicting Interests

Ying-jun Zhang, Hong-ming Xie, Lin Luo and Dan Wu are employees of Sunshine Lake Pharma Co., Ltd..

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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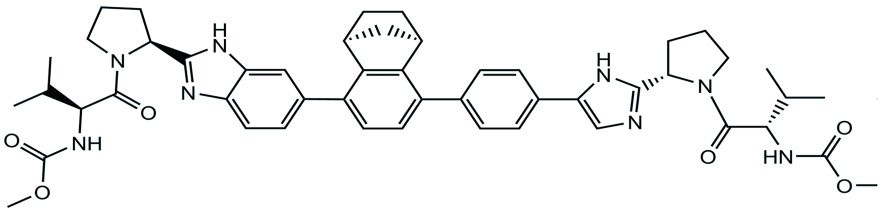
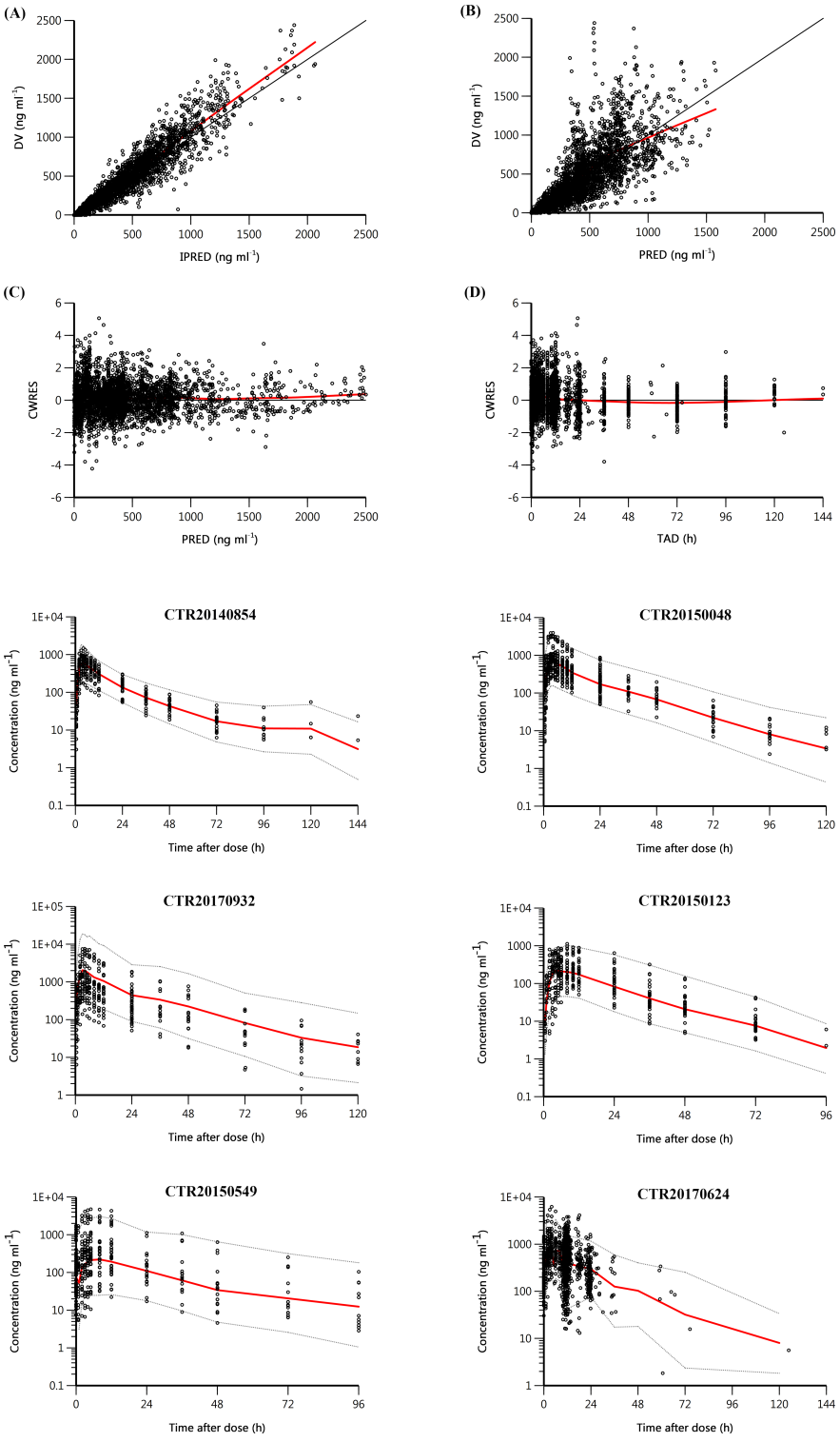
Figure 1. The chemical structure of yimitasvir.

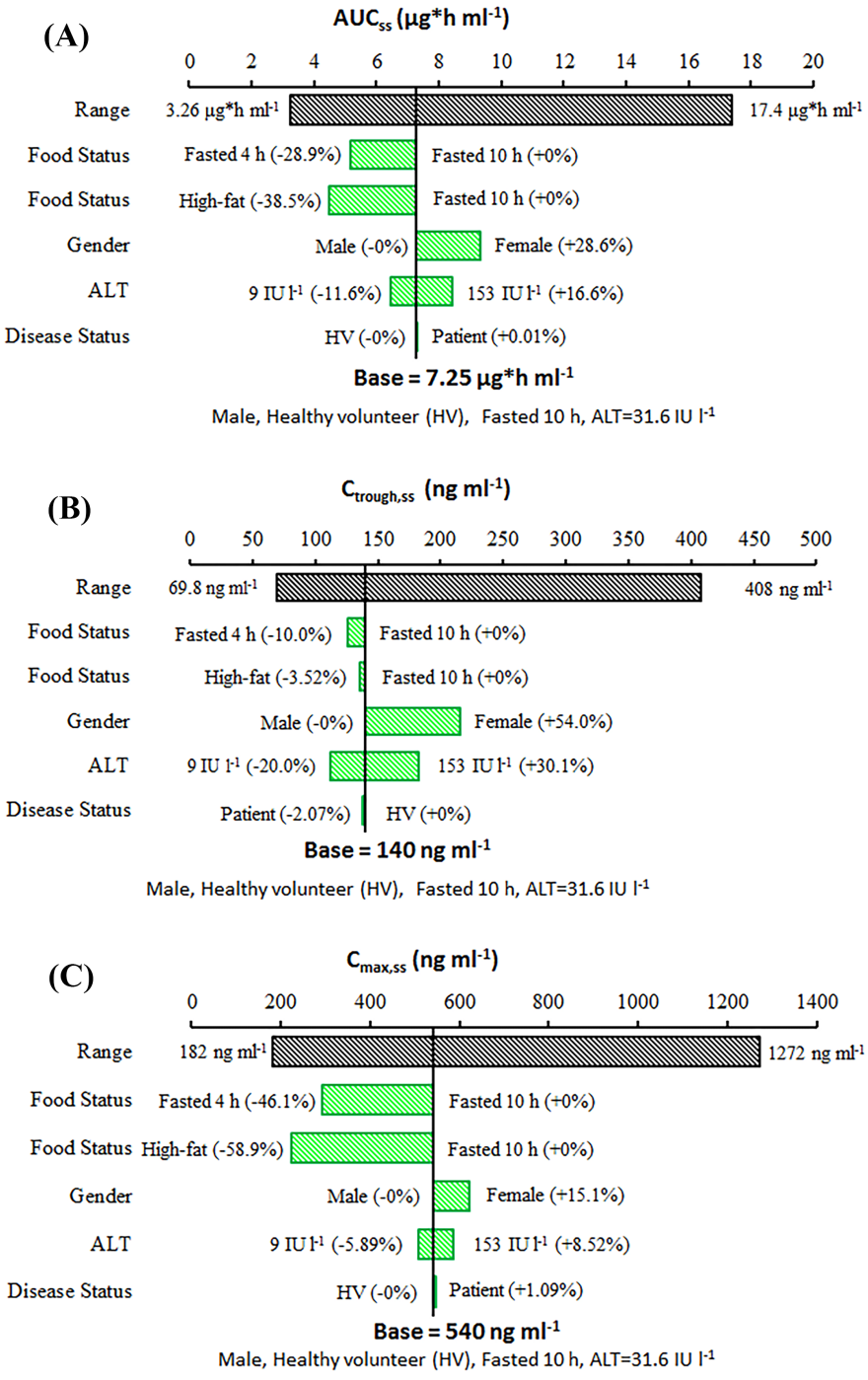
Figure 2. Goodness-of-fit plots of final population pharmacokinetics model. (A) Observed drug concentration (DV) versus individual prediction (IPRED); (B) DV versus population prediction (PRED); (C) conditional weighted residual (CWRES) versus PRED; (D) CWRES versus time after dose (TAD). The black line is the line of unity or the zero reference line, and the red line is the result of locally weighted scatterplot smoothing (loess).

Figure 3. Prediction-corrected visual predictive check (pcVPC) plot stratified by study. Black circles are observed yimitasvir concentrations, red solid lines represent the median of predicted concentrations, and grey dashed lines represent the 5th and 95th percentiles of predicted concentrations.

Figure 4. Sensitive plot comparing the effect of covariates on yimitasvir steady state exposure. (A) AUC_{ss}; (B) $C_{trough,ss}$; (C) $C_{max,ss}$. A typical subject is a healthy male volunteer with ALT value of 31.6 IU l^{-1} taking yimitasvir under fasted state more than 10 h. The black bar represents the 5th to 95th percentile of the exposure calculated using empirical Bayes estimates of the population after administration of yimitasvir 100 mg once daily for 12 consecutive weeks. Continuous covariates were evaluated at the 5th to 95th percentile of the population.







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