A Novel Framework of Long-term Prediction of Integrase Inhibitors for Treatment Naïve Patients

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Abstract

Objectives: **Dolutegravir (DTG, S/GSK1349572) is an unboosted, once daily integrase inhibitor currently under development for the treatment of HIV infection. A mathematical representation of long-term viral responses for integrase inhibitors remains challenging because it must include phenomena that are difficult to model such as resistance, background therapy and adherence. The objective was to develop a framework that describes complicated interactions in long-term treatment with integrase inhibitors, and that predicts efficacy at 96 weeks in Phase 3 clinical trials.**

Methods: **A simple PK/PD model for virologic response, which was developed previously [1], was used to predict HIV-1 RNA time courses in treatment naïve patients. The model was modified for incorporating resistance, adherence, subject dropout and the effect of background therapy (dual nucleoside reverse transcriptase inhibitors). Viral load influenced the probability of resistance-associated mutations. The basic model parameters were based on the estimates from Phase 2a 10-day monotherapy studies. Some of model parameters were adjusted so that the model described the observed data for up to 24 weeks in SPRING-1 [2] and STARTMRK [3, 4]. The model was used for predicting long-term viral responses for up to 96 weeks to simulate the results for a treatment-naïve Phase 3 study.**

Results: **Predicted proportion (90% simulation interval) of patients with <50 copies/mL HIV-1 RNA at 24 weeks were simulated as 90.0% (83.9%-96.0%), 96.0% (90.0%-100.0%), and 96.0% (92.0%-100.0%) at 10, 25 and 50 mg QD of DTG, respectively, and 92.0% (85.9%-96.0%) at 400 mg BID of raltegravir (RAL). These predictions were reasonably consistent with the data in SPRING-1 and STARTMRK. DTG was predicted to suppress viral loads to less than 50 copies/mL over a long duration: 82.0% (73.9%-90.0%) at 10 mg QD, 90.0% (84.0%-96.0%) in the 25 mg QD, and 92.0% (86.0%-96.1%) at 50 mg QD at 96 weeks, while 84.0% (76.0%-92.0%) at 400 mg BID of RAL.**

Conclusions: **We propose a novel framework for long-term prediction of efficacy with integrase inhibitors. The simulation shows durable efficacy of DTG for treatment naïve patients and supports the dose selection of 50 mg QD in Phase 3 studies.**

Introduction

- **Dolutegravir (DTG, S/GSK1349572) is an unboosted, once daily integrase inhibitor (INI) currently under development for the treatment of HIV infection.**
- **Short-term viral dynamics models have been reported [1,5]. However, a mathematical representation of long-term viral responses for integrase inhibitors remains challenging because it must include phenomena that are difficult to model such as resistance, background therapy (NRTI, nucleoside reverse transcriptase inhibitors) and adherence.**

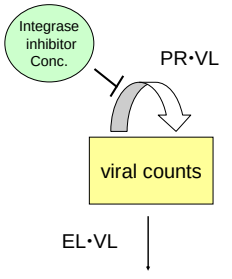
Objective

- **To develop a framework that describes complicated interactions in long-term treatment with integrase inhibitors, and that predicts efficacy at 96 weeks in Phase 3 clinical trials.**

Methods

- **The simple PK/PD model for virologic response, which was developed previously based on the estimates from Phase 2a 10-day monotherapy studies[1], was extended for long-term prediction in treatment naïve patients.**

Figure 1. A Model of Long-term prediction for Integrase Inhibitors



Log10-transformed HIV RNA count (VL) was computed as

$$\frac{dVL}{dt} = PR \cdot VL \cdot Inh - EL \cdot VL$$

Where PR: replication rate factor, **PR=EL*VL$_0$/VL^2**
VL$_0$: Initial VL
EL: viral depletion rate constant
Inh: Effects of INI and co-administered drugs assumed as the following equation.

$$Inh = \frac{1}{1 + \frac{f_{INI}(Cp)}{1 - f_{INI}(Cp)} + adj \cdot tlag \cdot Inh_{2NRTI}}$$

Where $f_{INI}(Cp)$: Drug effect of integrase inhibitors (DTG or RAL)

$$f_{INI}(Cp) = \frac{Cp}{IC50 \cdot (Fold\ Change) + Cp}$$

tlag: lag time required to exhibit anti-viral activity of NRTI
Initial value was 0.01 and changed to 1 according to a hazard rate of 1/12 week^{-1}
adj: Anti-HIV effects were adjusted by the number of fully active drugs. adj was given as follows.
adj: 0.3 while INI is active
adj 1 after mutation for INI occur
Inh$_{2NRTI}$: Drug effect of co-administered drug (2NRTI)
IC50: Concentration that achieves 50% of maximum inhibition.

$$Inh_{2NRTI} = \frac{IQ}{Scaling\_Factor}$$

IQ: inhibitory quotient derived from literature [6]
Scaling_Factor: in vitro-in vivo scaling parameter

- **Software: Trial Simulator Ver.2.2.1**
- **Pharmacokinetic model:**
  - **DTG: One compartment model with first-order absorption**
  - **RAL: Two compartment model with first-order absorption**
- **Resistance:**
  - **Condition of resistance against drug effect determined every week**
  - **Initial values of Fold Change:**
    - **1 (no resistance to a drug)**
  - **Following changes occurred under the probability in base scenario (resistance to a drug)**
    - **INI: Probability α*{ln(1+VL)}**
      - **Fold Change = 2.5 * Fold Changepre (DTG)**
      - **Fold Change = 80 * Fold Changepre (RAL)**
        - **Fold change values were assumed based on MONOGRAM data [7]**
    - **NRTI: Probability α'*{ln(1+VL)}**
      - **Inh2NRTI = 0**
- **Adherence:**
  - **INI: According to a 2 coin model**
    - **P(miss|take) 0.1, P(take|miss) 0.8**
  - **NRTI: According to a 1 coin model**
    - **P(miss) 0.1**
- **Dropout:**
  - **Hazard rates of dropout were assumed as follows**
    - **5% dropout up to week 48**
    - **1% dropout after week 48**

Table 1. Parameters in the Model

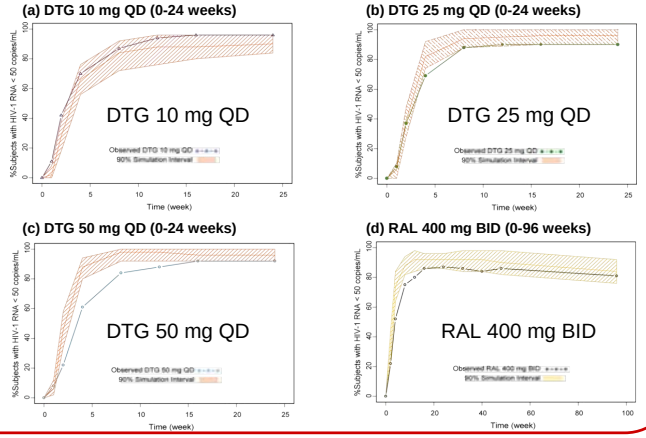
Parameters	Distribution	Mean	Variance
VL$_0$	Normal	4.5	1 (SD)
EL	Lognormal	0.00339 *	0.407 (sd(ln(x))) *
Scaling Factor (INI)	---	2.26 *	---
Scaling Factor (NRTI)	---	10	---
IC50 (ug/mL)	---	0.02957 *	---
α (INI)	---	0.003	---
α' (NRTI)	---	0.005	---

* Based on the estimates from Phase 2a 10-day monotherapy [1]

Results

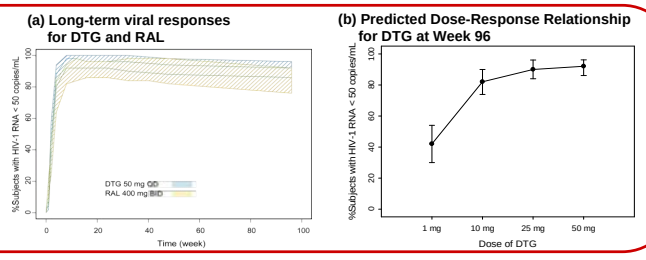
- **In Figure 2, the model performance was evaluated by superimposing the prediction intervals for proportion of <50 copies/mL of HIV-1 RNA counts with the observed data in SPRING-1 (N=50, 0-24 weeks so far)[2] for DTG and STARTMARK (N=281 , 0-96 weeks) [3,4] for RAL.**

Figure 2. Evaluation of the Simulation Performance



- **Predicted proportion (90% simulation interval) of patients with <50 copies/mL HIV-1 RNA at 24 weeks were simulated as 90.0% (83.9%-96.0%), 96.0% (90.0%-100.0%), and 96.0% (92.0%-100.0%) at 10, 25 and 50 mg QD of DTG, respectively, and 92.0% (85.9%-96.0%) at 400 mg BID of RAL.**
- **The model well described the observed virologic response for SPRING and STARTMARK.**

Figure 3. Long-term Prediction up to 96 Weeks



- **DTG was predicted to suppress viral loads to less than 50 copies/mL over the long duration.**
- **The simulation shows durable efficacy of DTG for treatment naïve patients and supports the dose selection of 50 mg QD in Phase 3 studies.**

Conclusions

- **We propose a novel framework for long-term prediction of efficacy with integrase inhibitors.**
- **The simulation shows durable efficacy of DTG for treatment naïve patients and supports the dose selection of 50 mg QD in Phase 3 studies.**

References

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