HIV-1 Attachment Inhibitor Prodrug BMS-663068: Exposure-Response Modeling to Predict QTcF Interval Prolongation Supporting Quantitative Dose Selection for the Phase 3 Program

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Disclosure

- Ishani Landry is a full time employee and stockholder of Bristol-Myers Squibb
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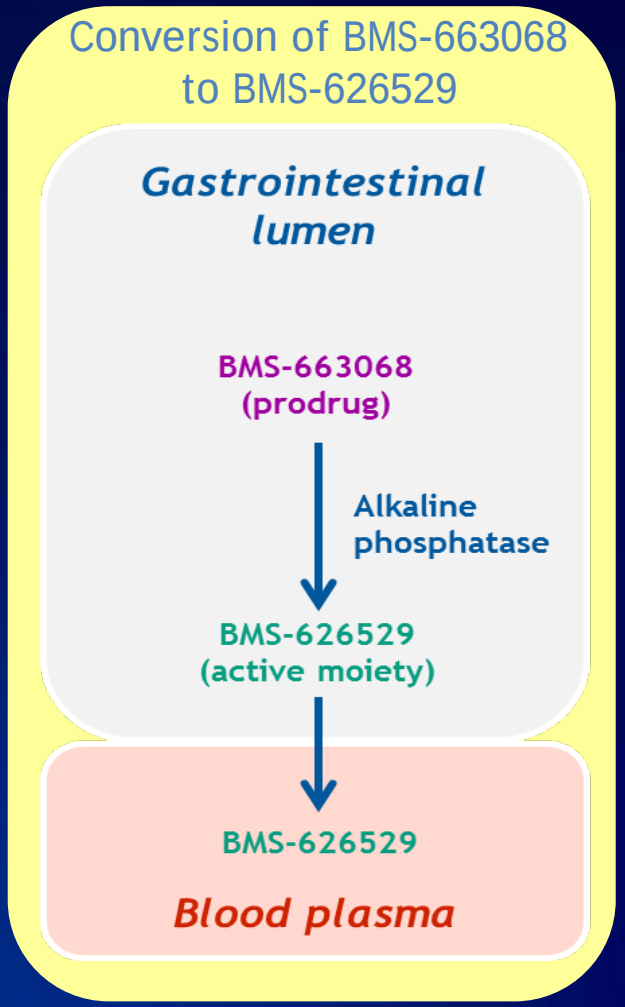
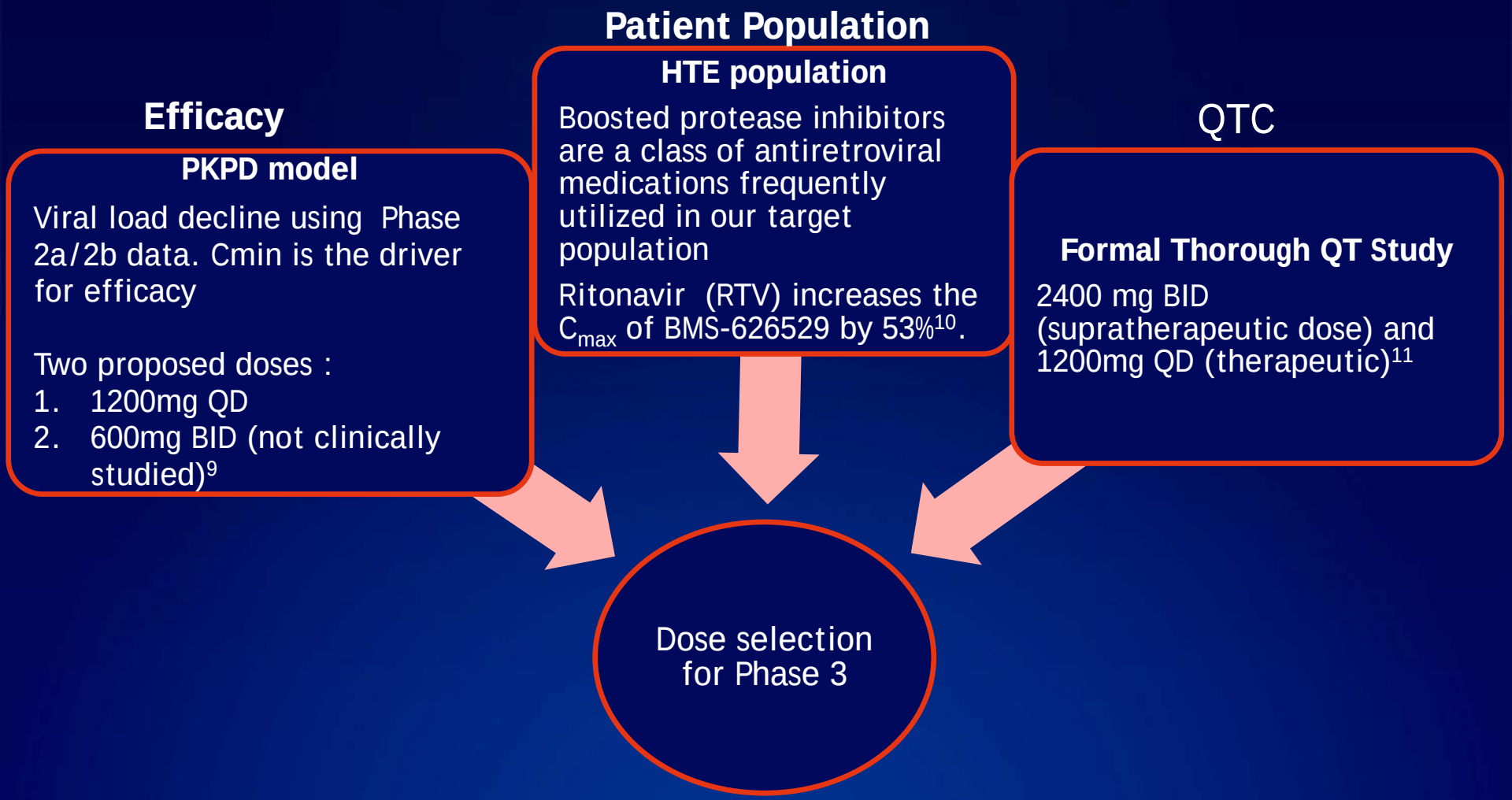
BMS-663068 Introduction

- BMS-663068 is a prodrug metabolized to the active moiety BMS-626529, a first-in-class attachment inhibitor that binds to HIV-1 gp120, preventing initial viral attachment and entry into the host CD4+ T cell, and:[1,2]
  - has a unique resistance profile with no *in vitro* cross-resistance to other classes of antiretrovirals[3,6]
  - has *in vitro* activity against HIV-1 viruses (except subtype AE and Group O)[3]
  - is active against CCR5-, CXCR4- and dual-tropic (R5X4) strains of HIV-1[3-6]
  - BMS-626529 inhibits virus entry at a step prior to that inhibited by CCR5 antagonists and fusion inhibitors and does not exhibit cross-resistance to viruses resistant to these agents.
- BMS-626529 is further metabolized by CYP3A4 and hydrolysis
- Virologic response rates (HIV-1 RNA <50 c/mL) appear to be similar across the BMS-663068 and ATV/r treatment arms.
- BMS-663068 is generally well tolerated with no dose-related safety signals or AEs led to discontinuation.



1. Langley DR *et al. Proteins;* 2015*; 83: 331*–350. 2. Brown J *et al. J Pharm Sci* 2013; 102: 1742–1751. 3. Nowicka-Sans B et al. Antimicrob Agents Chemother 2012; 56: 3498-3507. 4.Ray N *et al. JAIDS* 2013; 64: 7–15. 5. Zhou N *et al. JAC* 2014; 69: 573–581.6.Li Z *et al. AAC* 2013; 57: 4172–4180.

Model-Based Approach For Phase 3 Dose Selection



9. Savant Landry I CROI 2015.
10. Zhu L et al Antimicrob Agents Chemother 2015 April 13: Epub ahead of print
11. Hruska MW et al 15th IWCPHIV 19-21 May 2014 Washington DC, USA

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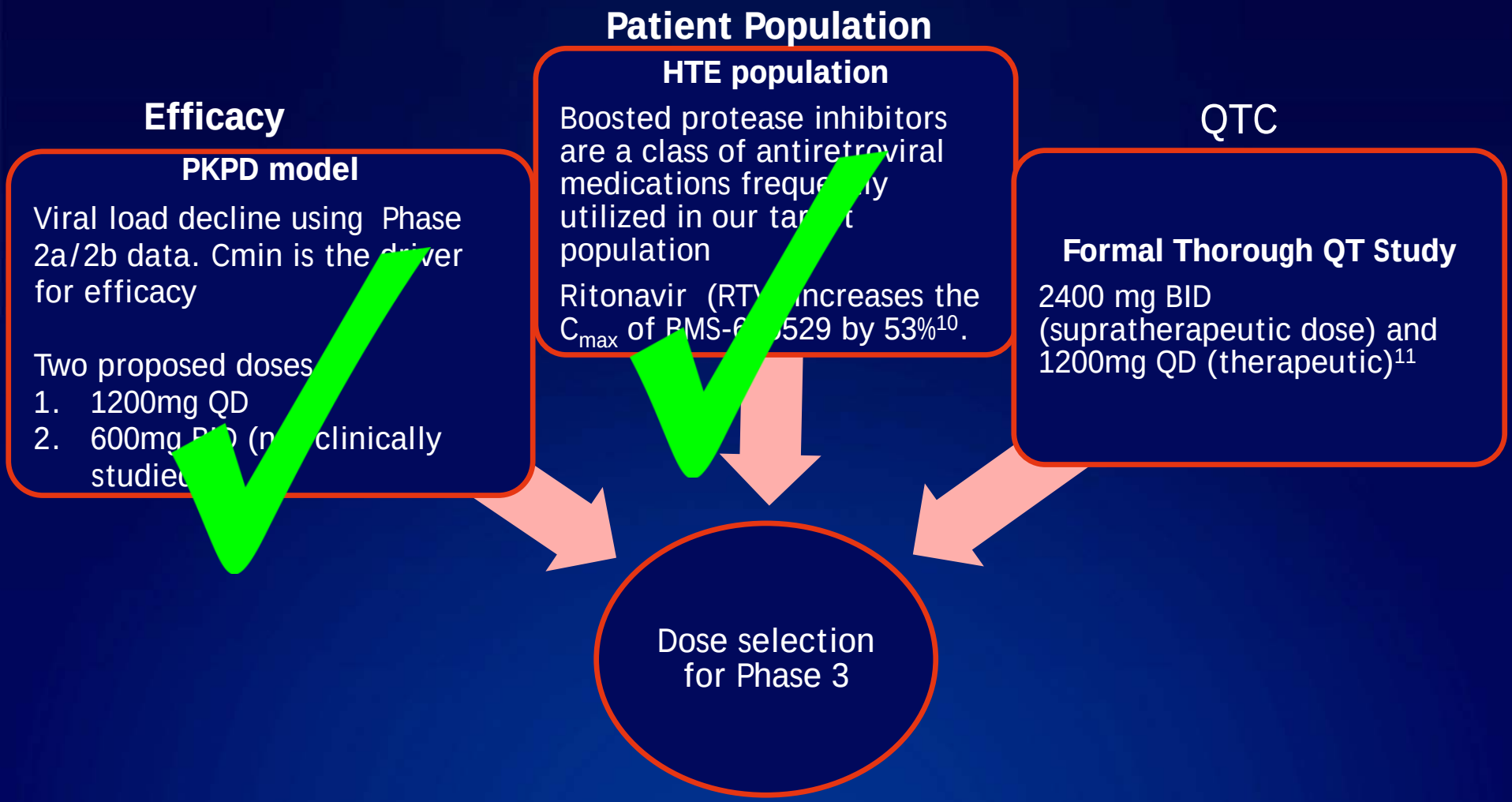

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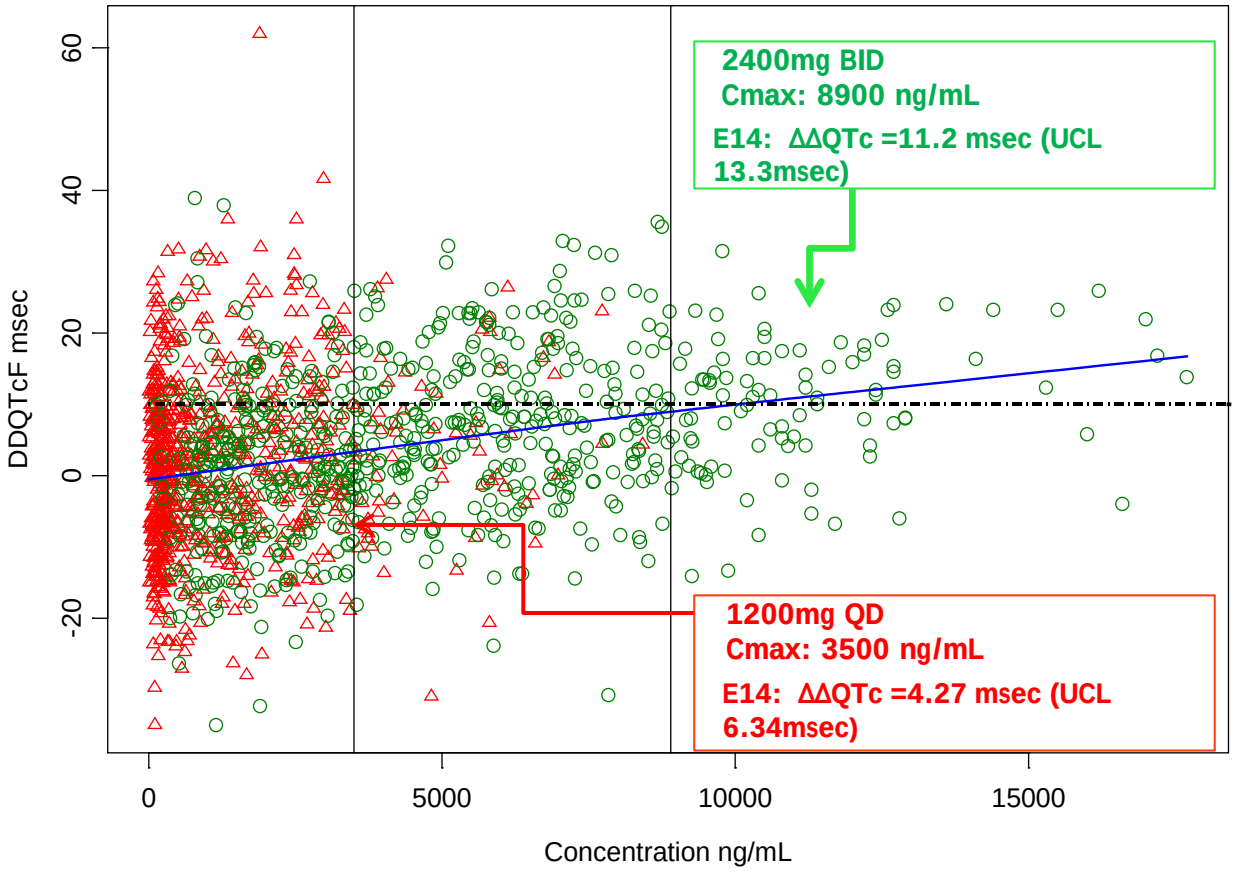
Formal Thorough QT Study Results



Per FDA guidance E14 analysis: a positive signal is when the mean QT/QTC > 5msec and 95% upper confidence limit (UCL) is ≥10 ms

Objectives

- To characterize the relationship between BMS-626529 systemic exposure and QTcF interval changes

- To predict QTcF effects of the two potential BMS-663068 Phase 3 doses (1200 mg QD; 600 mg BID) when administered with a boosted protease inhibitors using this model-based analysis

Methods

Four models exposure-QTc explored

Direct Response Models

- A model that assumed the relationship between BMS-626529 plasma concentration ΔΔQTcF was linear

$$E_{ij} = \left(slope * \exp\left(\eta_{2i}\right)\right) * \ CONC_{ij} \ + \epsilon_{ij}$$

- An Emax model that assumed a saturable relationship between BMS-626529 plasma concentration and ΔΔQTcF

$$E_{ij} = E_0 * exp\left(\eta_{4i}\right) + \frac{\left(E_{max} \ * exp\left(\eta_{5i}\right)\right) * CONC_{ij}}{\left(EC_{50} * exp\left(\eta_{6i}\right)\right) + CONC_{ij}} + \epsilon_{ij}$$

- A sigmoid Emax model

$$E_{ij} = E_0 * exp\left(\eta_{5i}\right) + \frac{\left(E_{max} \ * exp\left(\eta_{6i}\right)\right) ** \left(gamma * exp\left(\eta_{8i}\right)\right) * CONC_{ij} \ ** \left(gamma * exp\left(\eta_{8i}\right)\right)}{\left(EC_{50} * exp\left(\eta_{7i}\right)\right) ** \left(gamma * exp\left(\eta_{8i}\right)\right) + CONC_{ij} \ ** \left(gamma * exp\left(\eta_{8i}\right)\right)} + \epsilon_{ij}$$

- An indirect response model

$$\frac{DA}{DT} = K_{in}(1 + E\ ) - K_{out} * A(1)$$

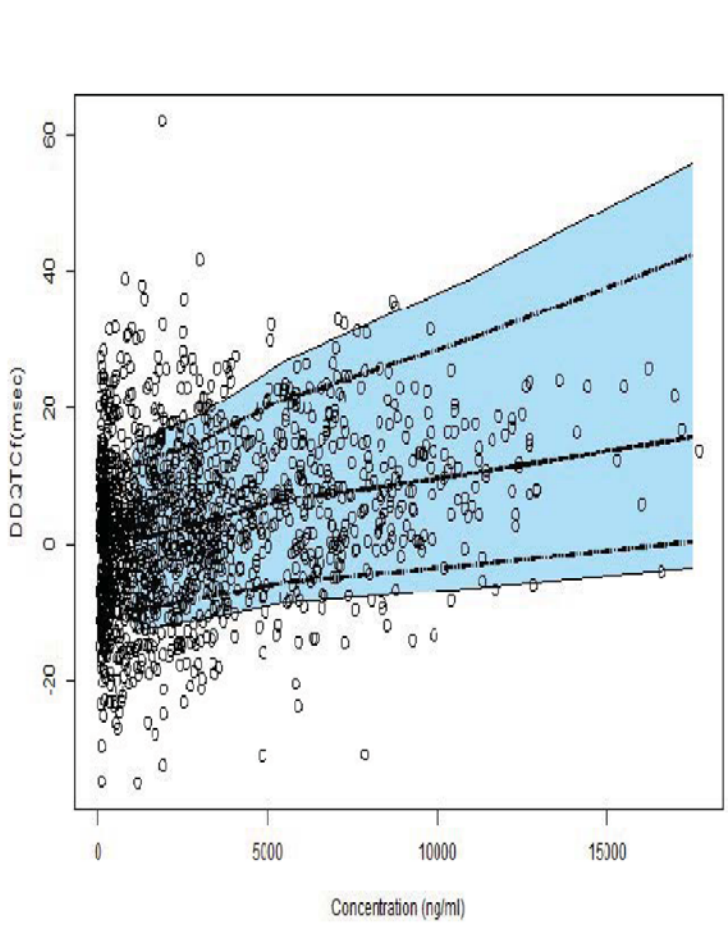
Methods

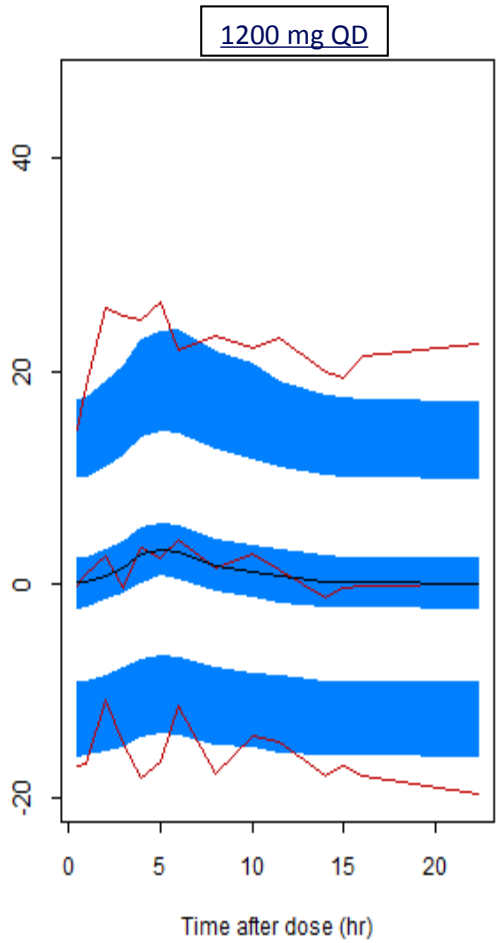
Final Model Chosen Based On:

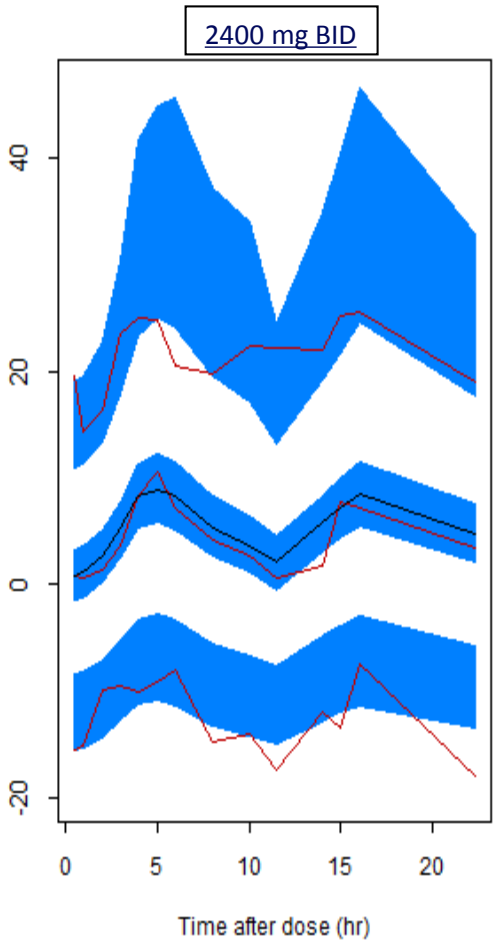
- Diagnostic plots, minimum objective function
- Visual predictive check
- Monte Carlo simulations conducted to predict estimates for the ΔΔQTcF with observed data from TQTc study

Final simulations conducted to predict ΔΔQTcF for the doses given with RTV boosted protease inhibitors

Evaluation of the Final Indirect Response Model (Visual Predictive Check)



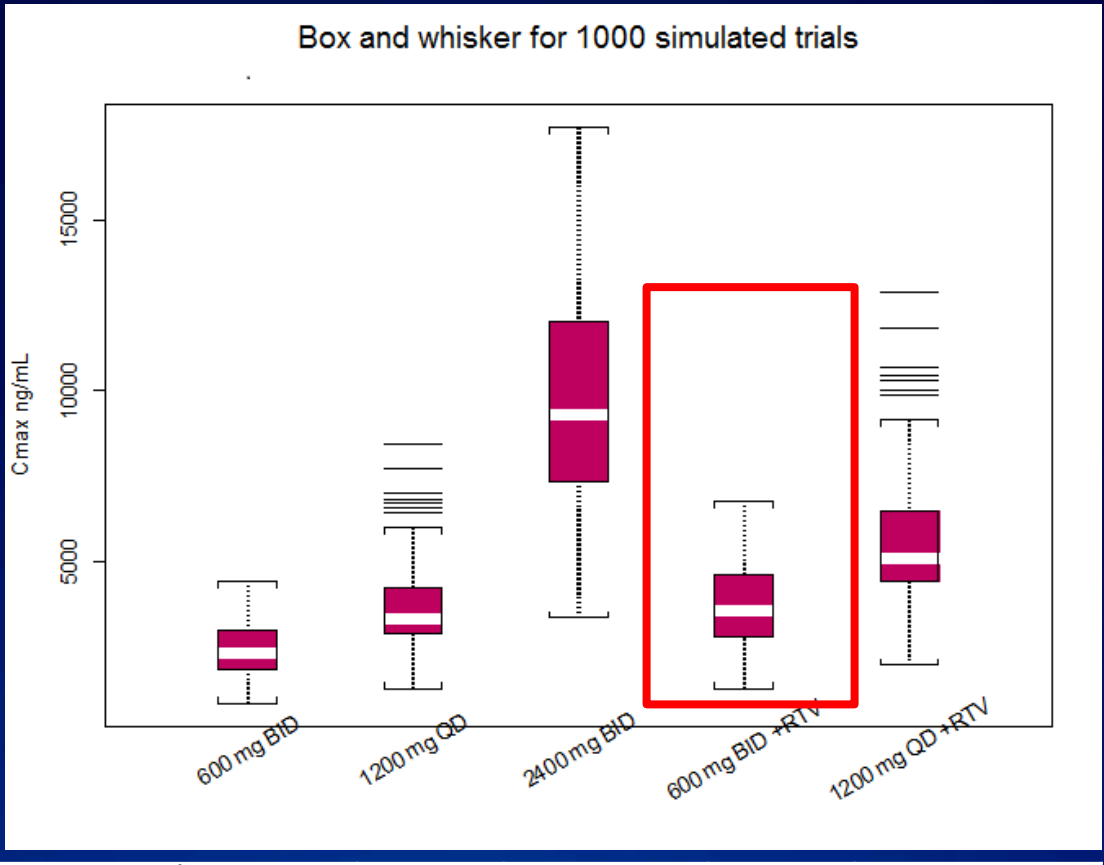




1200mg QD and 2400 mg BID : doses from TQTc study

Phase 3 Doses- BMS-663068 in combination with Boosted Protease Inhibitor: Cmax Simulation and Assessment of QTc risk

600mg BID with and without boosted protease inhibitor provides lower risk of Cmax approaching threshold where QTc risk may exist



Estimated ΔΔQTc at median Cmax	1.70	3.20	8.93	2.98	5.42
Upper confidence interval	4.15	5.61	12.15	5.58	7.94

Conclusions

- An indirect response sigmoid E_{max} model with Hill coefficient best described the relationship between individual observed ΔΔQTcF and plasma exposure of BMS-626529
  - BMS-663068 600 mg BID dose was predicted to have the optimum benefit–risk profile
- BMS-663068 600mg BID was chosen for the Phase 3 trial in treatment-experienced subjects based on quantitative modeling, clinical and safety observations