

# PHARMACOKINETIC-PHARMACODYNAMIC (PK/PD) MODELING OF THE EFFECT OF INTRAVENOUS (IV) DOSES OF ANZEMET® (DOLASETRON MESYLATE) AND ITS METABOLITE (HYDRODOLASETRON) ON THE QT INTERVAL IN HEALTHY SUBJECTS

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## INTRODUCTION

Dolasetron mesylate is a selective serotonin 5-hydroxytryptamine-3 (5-HT<sub>3</sub>) receptor antagonist, approved since September 1997 in the United States (US) in 2 formulations, injection and tablets. Parenteral dolasetron mesylate is indicated at dose of 100 mg IV for the: a) Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin; b) Prevention of postoperative nausea and vomiting; and c) Treatment of postoperative nausea and/or vomiting.

This study was intended to clarify the potential activity of dolasetron on ventricular repolarization, following the October 2005 ICH E14 Guidance for Industry [1].

The specific aim of this project is to present the PK modeling of the dolasetron and hydrodolasetron and the PD model of their relationship to the observed change from baseline QTcF ( $\Delta$ QTcF) effect to address a secondary objective of the study.

## METHODS

This study was a Phase I, randomized, single-dose, double-blind, placebo-controlled, cross-over, single-center trial; subjects were stratified by sex using a 4:1 male to female ratio. Dolasetron and hydrodolasetron plasma concentrations and electrocardiograph (ECG) data from 78 subjects who received 100 mg and 300 mg dolasetron were used for the PK and PK/PD modeling.

A 2-stage PK/PD modeling approach was undertaken.

### Stage 1:

- Developed a structural PK model for dolasetron and hydrodolasetron using the observed plasma concentration-time data
- Estimated individual hydrodolasetron PK parameters
- Predicted the plasma concentration-time profiles for dolasetron and hydrodolasetron

### Stage 2:

- Modeled the PK/PD relationship between the predicted hydrodolasetron concentration-time data and the observed QTcF data

The results of the second stage provided the basis for understanding the PK/PD relationship between dolasetron dose administration and the QTcF response. Several PK and PK/PD models were constructed and model comparisons were made using log-likelihood ratio tests with an  $\alpha = 0.01$ . The following models were explored to evaluate the PK/PD relationship between plasma hydrodolasetron concentrations and absolute QTcF or  $\Delta$ QTcF responses:

Linear model:  $y = m \cdot C + b$

$E_{max}$  model:  $y = \frac{E_{max} \cdot C}{EC_{50} + C}$

Sigmoidal  $E_{max}$  model:  $y = \frac{E_{max} \cdot C^\gamma}{EC_{50}^\gamma + C^\gamma}$

where  $y$  is the observed effect ( $E$ ) of the QTcF or  $\Delta$ QTcF response,  $C$  is the plasma hydrodolasetron concentration,  $m$  and  $b$  are the slope and the intercept of the linear model,  $E_{max}$  is the maximum QTcF or  $\Delta$ QTcF response,  $EC_{50}$  is the hydrodolasetron concentration which produces 50% of the maximum effect and  $\gamma$  is the Hill coefficient.

During the model development process, the following factors were considered to compare different candidate models:

- Log-likelihood ratio test for hierarchical models;
- Akaike's information criterion (AIC) for non-hierarchical models;
- Reduction in the residual error;
- Random distribution of the weighted residuals against the predicted concentration, and;
- Random distribution of the observed versus predicted concentration values across the identity line ( $y = x$ ).

All modeling was performed using mixed effect modeling as implemented in NONMEM version VI [2].

## RESULTS

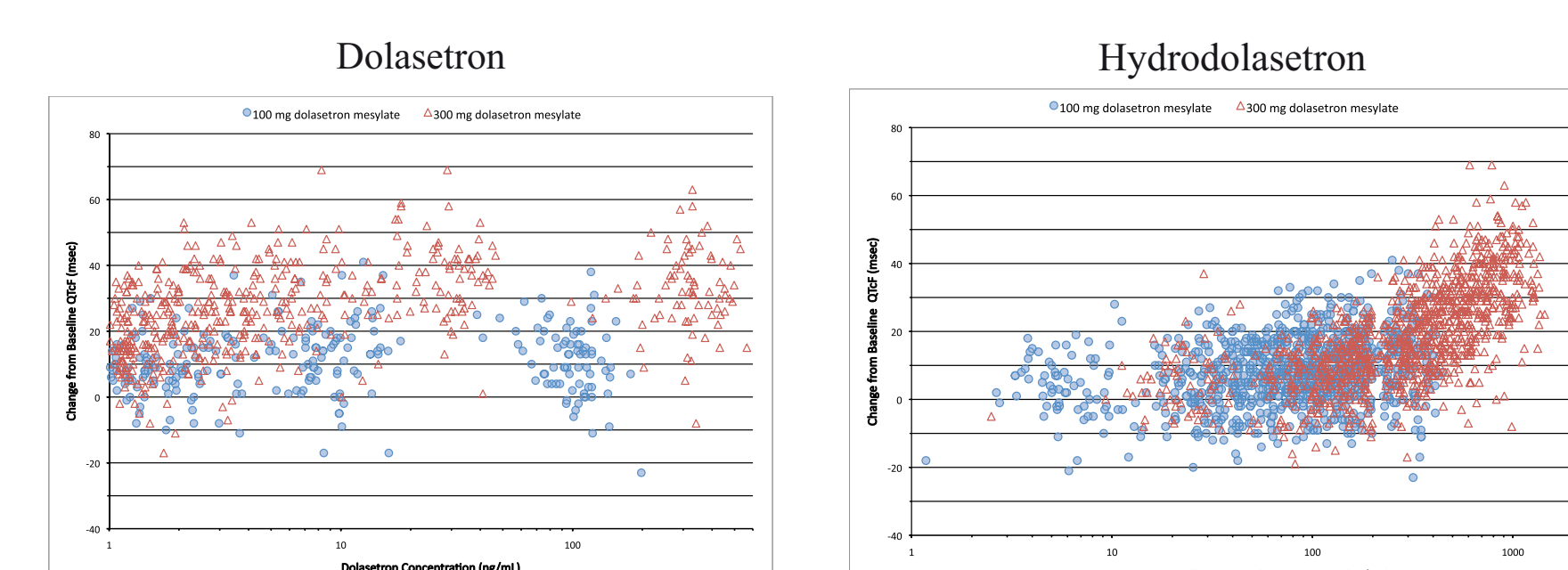
- Following a 15 minute IV infusion of 100 mg and 300 mg dolasetron mesylate doses, dolasetron was rapidly (mean half-life < 1 hour) converted to hydrodolasetron, resulting in mean dolasetron concentrations in plasma below the lower limit of quantitation of 1 ng/mL by 2 hours post dose for the 100 mg dose and by 4 hours post dose for the 300 mg dose.
- The PK relationship between dolasetron and hydrodolasetron was best described by a combined structural PK model, with 1 compartment for dolasetron and 2 compartments for hydrodolasetron, with a combined additive and proportional residual error model following an IV bolus administration. The population estimated PK parameters (assumed lognormal distribution) are presented in Table 1.
- A relationship between QTcF and hydrodolasetron concentrations was observed (Figure 1). Administration of dolasetron mesylate at the supratherapeutic dose (300 mg) resulted in a sustained and statistically significant increase in placebo-corrected QTcF change from baseline which was larger than that observed following the 100 mg dolasetron dose administration.

Table 1: Summary of Population Estimated PK Parameters from Final Structural PK Model

Parameter (units)	Population Estimate	Population Parameter Precision (%RSE)	Between-Subject Variability (%CV)
CLM (L/hr)	414	2.68	--
CLME (L/hr)	69.0	2.90	25.6
V1 (L)	88.5	3.51	10.7
V2 (L)	247	2.85	26.5
Q (L/hr)	82.8	3.86	--
V3 (L)	219	3.28	21.8
Residual variability	Proportional Component (%CV)		13.4
	Additive Component (SD)		2.72

CLM = clearance of parent to metabolite, CLME = excretory clearance of metabolite, V1 = volume of distribution of the parent (dolasetron) in the central compartment, V2 = volume of distribution of the metabolite (hydrodolasetron) in the central compartment, V3 = volume of distribution of the metabolite (hydrodolasetron) in the peripheral compartment, Q = intercompartmental exchange flow between the 2 compartments of the metabolite (hydrodolasetron), RSE = relative standard error, CV = coefficient of variation, SD = standard deviation, -- = not estimated

Figure 1: Observed Individual Change from Baseline QTcF Versus Dolasetron and Hydrodolasetron Following 100 mg or 300 mg Dolasetron Mesylate Administration



- A direct-response sigmoidal  $E_{max}$  model best described the relationship between the individual observed QTcF data and the individual predicted hydrodolasetron data, with an additive error term (Figure 2). The prediction estimates for the PD parameters (assumed lognormal distribution) are presented in Table 2.
- As plasma hydrodolasetron level increases, the QTcF value increases to a maximum change of 65.3 ms. Based on the model, plasma hydrodolasetron concentrations of 878 ng/mL will result in a change in QTcF of approximately 33 ms (50% of maximal change). Per the FDA Guidance, a Qtc change from baseline > 20 ms may have a substantially increased likelihood of being proarrhythmic [1]. Furthermore, the model indicates plasma hydrodolasetron concentrations above approximately 444 ng/mL will result in increases in QTcF that are approximately 20.0 ms or greater. (Figure 3).

Figure 2: Schematic of Final PK/PD Model

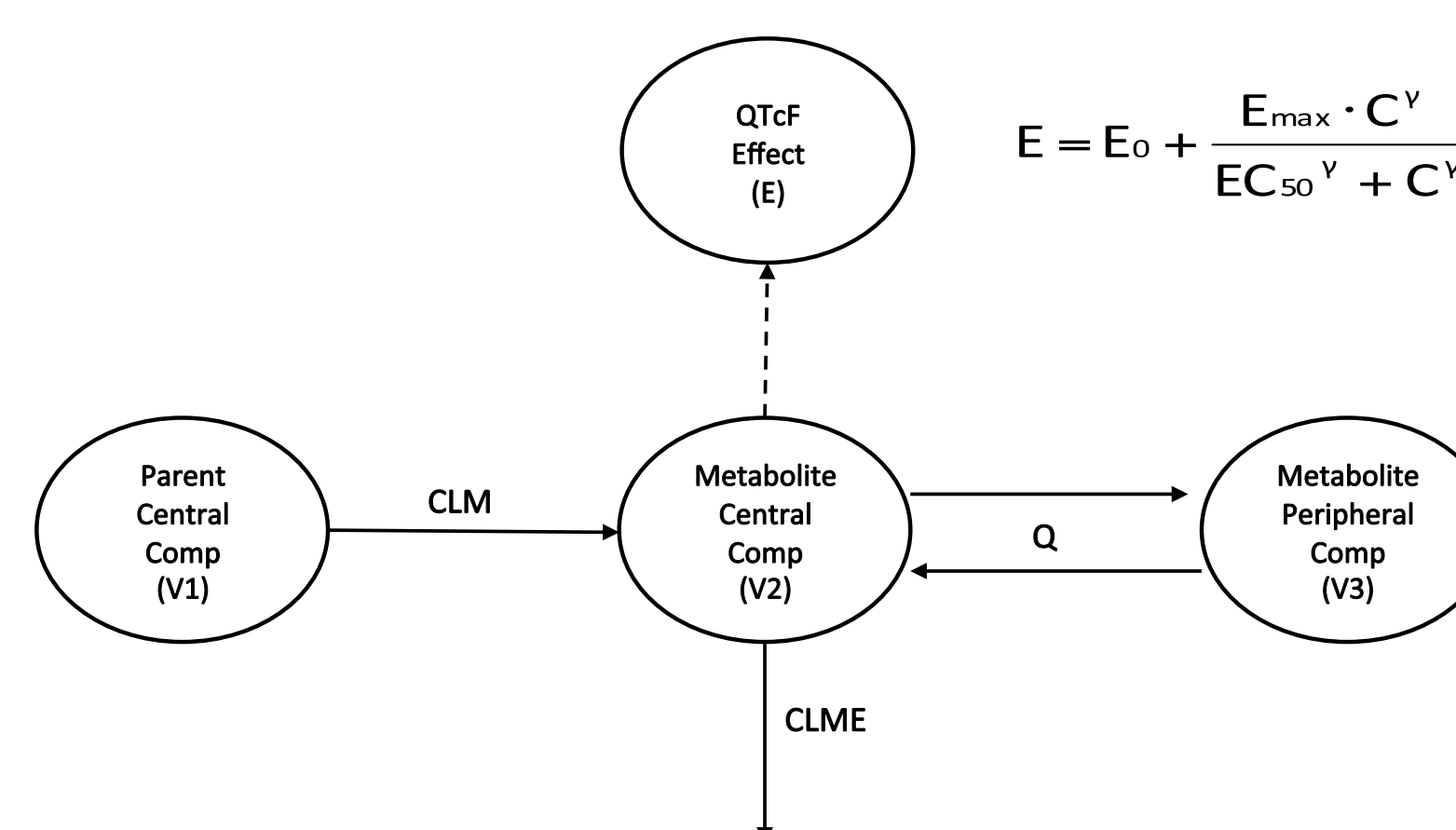


Figure 3: Individual Observed and Population Predicted QTcF Versus Individual Predicted Plasma Hydrodolasetron Concentrations

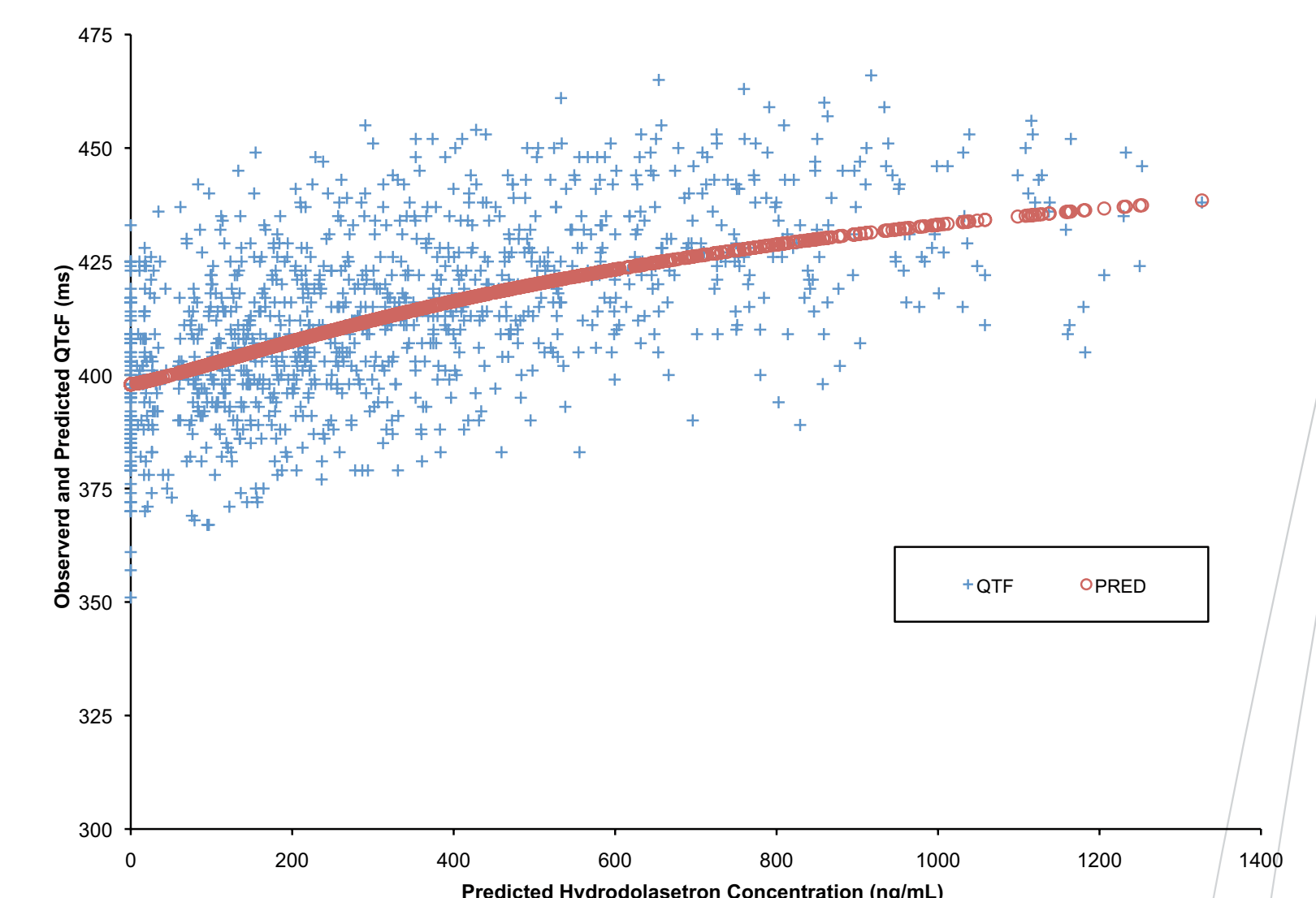


Table 2: Summary of Population Estimated PD Parameters from Final PK/PD Model

Parameter (units)	Population Estimate	Population Parameter Precision (%RSE)	Between-Subject Variability (%CV)
EC <sub>50</sub> (ng/mL)	878	21.5	--
E <sub>0</sub> (ms)	398	0.480	3.89
E <sub>max</sub> (ms)	65.3	15.6	29.2
HILL	1.20	7.10	--
Residual variability	Additive (SD)		6.35

EC<sub>50</sub> = plasma concentration which produces 50% of the maximum effect, E<sub>0</sub> = baseline QTcF value, E<sub>max</sub> = maximum change in effect, HILL = Hill coefficient, RSE = relative standard error, CV = coefficient of variation, SD = standard deviation, -- = not estimated

## DISCUSSION

The administration of dolasetron mesylate at the therapeutic dose (100 mg dolasetron mesylate) resulted in a moderate and transient but statistically significant increase in placebo-corrected QTcF change from baseline. Furthermore, the administration of dolasetron mesylate at the supratherapeutic dose (300 mg dolasetron mesylate) resulted in a statistically significant increase in placebo-corrected QTcF change from baseline which was numerically larger than that observed in dolasetron 100 mg. The increase in QTcF rapidly decreased, but was still statistically significant at Hour 12.0. The direct-response sigmoidal  $E_{max}$  model suggests that the relationship between QTcF and hydrodolasetron is one where there is an increase from baseline ( $E_0$ ) QTcF as a function of the plasma hydrodolasetron concentration,  $E_{max}$ , and the  $EC_{50}$ . As plasma hydrodolasetron level increases, the QTcF value increases to a population predicted maximum change of 65.3 ms. Using the observed hydrodolasetron  $C_{max}$  (range 156 ng/mL to 447 ng/mL) values following the administration of a 100 mg therapeutic dose of dolasetron the model predicts a  $\Delta$ QTcF ranging from 7.29 ms to 20.1 ms, while using the observed hydrodolasetron  $C_{max}$  values (range 616 ng/mL to 1440 ng/mL) following the supratherapeutic dose of 300 mg would result a  $\Delta$ QTcF ranging from 25.8 ms to 42.1 ms. The observed maximum  $\Delta$ QTcF values ranged from 1.00 ms to 41.0 ms following the 100 mg dose of dolasetron and from 9.00 ms to 69.0 ms following the 300 mg dose of dolasetron.

## CONCLUSION

- The PK relationship between dolasetron and hydrodolasetron was best described by a combined structural PK model, with 1 compartment for dolasetron and 2 compartments for hydrodolasetron, with a combined additive and proportional residual error model following an IV bolus.
- A direct-response sigmoidal  $E_{max}$  model best described the relationship between the individual observed QTcF data and the individual predicted hydrodolasetron data.
- The direct-response sigmoidal  $E_{max}$  model suggests that the relationship between QTcF and hydrodolasetron is one where there is an increase from baseline ( $E_0$ ) QTcF as a function of the plasma hydrodolasetron concentration,  $E_{max}$ , and the  $EC_{50}$ . The prediction estimates for the PD parameters were  $E_0 = 398$  ms,  $E_{max} = 65.3$  ms,  $EC_{50} = 878$  ng/mL, and a Hill coefficient of 1.2.
- The model indicates plasma hydrodolasetron concentrations above approximately 444 ng/mL will result in increases in QTcF that are 20 ms or greater.

## REFERENCES

- Guidance for Industry: E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, October, 2005. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf>.
- Nonlinear Mixed Effect Modeling (NONMEM) program (Version VI, Level 2.0, Icon Development Solutions, Ellicott City, MD).