Development and validation of a mechanism-based PK/PD model for the in vitro-in vivo prediction of QT prolongation by dofetilide

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Introduction
Drug-induced QT prolongation is an important biomarker for the risk of heart arrhythmias. Blockade of hERG currents is frequently used as an in vitro marker for this risk, but the relationship between hERG blockade and QT prolongation has not been determined in a quantitative manner. The aim of the present work was to establish an integrated PK/PD model relating the action of the selective Kᵦᵣ inhibitor dofetilide at the hERG potassium channel in vitro to its QT prolonging effects in man.

Methods
A joint analysis was performed to determine the affinity and activity of dofetilide concentrations were used to drive the PD model. By including semi-automated fashion. In the second step, the individually estimated

Results
A 3-compartment PK model with first-order absorption after oral administration and a lag time characterized the time course of dofetilide concentrations well. Three covariate relations were identified by using stepwise forward selection followed by backward elimination within NONMEM (Figure 2 and Table 2).

Fridericia-corrected QT observations were adequately described with the operational model including an effect compartment (Figure 3 and Table 3). Based on the in vitro affinity of 4.79 ng/ml, the estimate of t indicated the presence of a modest ion channel reserve. The development of tolerance upon chronic administration was best described by a decrease of t driven by the QT effect (Figure 1C).

Case deletion diagnostics did not indicate any structural between-study differences for the PK and PD parameters, except for those parameters that were supported by a single study only (Figure 4).

Conclusions
The quantitative relationship from the hERG assay to man was established using a selective Kᵦᵣ inhibitor. This PK/PD model scaled activity in the hERG model more accurately compared to extrapolation of dofetilide potency in the hERG assay. QT effects were adequately described for varying doses and administration routes and in both patients and healthy volunteers, demonstrating the general applicability of the proposed model.