

Title: Model Based Development of a Direct Factor Xa Inhibitor

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Objectives:

- Modeling and simulation (M&S) were employed to make dosage recommendations for human Phase 1 studies of CS-3030.
- Specific objectives were to:
 - Predict human PK-PD of CS-3030 based on animal to human projections,
 - Characterize sources of variability or safety concerns, and
 - Simulate potential clinical outcomes as compared to other anticoagulants.

Methods:

Predicted human pharmacokinetics (PK), biomarker responses (PD), and clinical outcomes were obtained using appropriate projection methods and PK/PD data from cynomolgus monkey, relative potency data and literature data. Allometric scaling was used to predict human pharmacokinetics. Models were developed for anti-FXa activity and fold-increase (compared to baseline) in PT using the following criteria to determine the target dose range: (1) anti-FXa activity within 0.5-0.8 IU/mL range (based on enoxaparin) and (2) 2- to 3-fold increase in PT (based on warfarin). It was assumed that PK-PD relationships observed in cynomolgus monkeys apply to humans.

PK/PD for a range of CS-3030 doses (10 to 320 mg), regimens (single dose, once daily (QD) and twice daily (BID)) and bioavailability fractions (4.5 to 50%) were simulated. Ranges of doses and bioavailability fractions were intended to compensate for any misspecification due to projection method or underlying assumptions. Influences of patient demographics and laboratory values were investigated on response to CS-3030. Comparison of clinical events was made using publicly available literature for three comparators: warfarin, enoxaparin sodium (Lovenox®) and fondaparinux sodium (Arixtra®).

Results:

No one dose met the dual criteria of anti-FXa activity and PT response. Rather, target levels were achieved only partially over the dosing interval. Proportions of the anti-FXa and PT profiles within the targeted range were consistently larger for BID regimens as compared to QD regimens. If a single criterion was used, e.g. anti-FXa activity only, then a dose of 40 mg provided 50% time within the target range. Renal impairment was expected to influence drug exposure, and therefore PD. The effect was smaller for PT response than anti-FXa activity. For a subject with severe renal impairment, average anti-FXa activity was approximately double that of a healthy subject. This may suggest that appropriate dose adjustment may be warranted if target anti-FXa activity were to be maintained close to target values. Human projections from animal FXa activity suggest doses up to 40 mg/day CS-3030 may provide similar efficacy (prevention of deep vein thrombosis) and safety (risk of bleeding) profiles to that of enoxaparin following hip and knees surgeries. However, doses of 10 – 80 mg show lower bioavailability and large intersubject variability.

Conclusions:

Integration of animal data and public literature allowed human PK-PD to be projected under certain plausible assumptions and scenarios. Human projections for CS-3030 identified dosing regimens which provided similar efficacy and safety profiles to that of comparators.

M&S was used to optimize the Phase 1 program to reduce uncertainty and test assumptions relating to bioavailability and variability, and further to provide a basis to: (1) Estimate the likely quality of Phase 2 dose-response in Phase 1 planning and (2) Quantify the effect of covariates, the magnitude and sources of uncertainty, and key assumptions. This example illustrates the application of M&S to guide drug development and inform the design of clinical trials.