Rivaroxaban Has Predictable Pharmacokinetics (PK) and Pharmacodynamics (PD) When Given Once or Twice Daily for the Treatment of Acute, Proximal Deep Vein Thrombosis (DVT)

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INTRODUCTION

Rivaroxaban is an oral, direct Factor Xa inhibitor in clinical development for the prevention and treatment of thromboembolic disorders. Two large, phase IIb, dose-finding studies investigating rivaroxaban for the treatment of acute, proximal DVT, showed that rivaroxaban once daily (od) and twice daily (bid) had similar efficacy and safety profiles to standard therapy. In order to characterize the population PK/PD of rivaroxaban for DVT treatment, a population model was developed based on data from healthy subjects.

METHODS

Sparse PK/PD samples from 870 patients across the two studies were analyzed using non-linear, mixed-effect population modeling (NONMEM), version V level 1.1. The program analyzed population data to give estimates of mean values and variability in the population. Prothrombin time (PT) was determined at a central laboratory and was used in the PD investigation. For the PK profile, data was pooled from both clinical trials and specific exposure parameters for rivaroxaban, such as area under the plasma concentration-time curve (AUC), maximum and minimum plasma concentrations (C_{max} and C_{trough}, respectively) were predicted for each patient according to the dosing regimen received.

CONCLUSION

The PK and PD of rivaroxaban were predictable with od and bid dosing, and affected by expected demographic factors in patients receiving it for DVT treatment. Combined with efficacy and safety results, this analysis aided the selection of an initial, intensified bid regimen followed by convenient, long-term rivaroxaban 20 mg od, for investigation in phase III studies in this indication.

RESULTS

The PK of rivaroxaban were well described by an oral, one-compartment model, with demographic factors influencing clearance (age, renal function) and volume of distribution (age, body weight, gender); variations due to these factors were moderate, suggesting fixed dosing may be possible. Co-medications (e.g. diuretics, NSAIDs, aspirin) had no relevant effects on the PK of rivaroxaban. Rivaroxaban C_{max} and C_{trough} concentrations increased dose dependently (Table). As expected, C_{max} was higher and C_{trough} was lower after od dosing compared with bid dosing, at equivalent total daily doses; however, 90% confidence intervals overlapped, suggesting that od dosing with rivaroxaban should not expose patients to a greater risk of bleeding (at C_{max}) or VTE (at C_{trough}) than bid dosing. Clinically relevant rivaroxaban plasma concentrations correlated linearly with PT, confirming that it would be suitable for measuring rivaroxaban exposure, if necessary.

Predicted rivaroxaban PK parameters

	Rivaroxaban total daily dose			
Parameter	**20 mg**	**30 mg**	**40 mg**	**60 mg**
n (od/bid)	134/117	134/--	252/114	--/119
od C_{max} (µg/L)*	270.6 (189.1-418.7)	324.6 (234.2-491.3)	406.5 (268.4-599.9)	--
bid C_{max} (µg/L)*	211.5 (130.3-360.7)	--	320.9 (209.9-517.9)	400.6 (244.2-749.5)
od C_{trough} (µg/L)*	25.5 (5.9-86.9)	33.8 (8.4-132.9)	42.3 (9.7-161.8)	--
bid C_{trough} (µg/L)*	65.1 (17.2-193.6)	--	104.2 (31.3-277.8)	143.1 (46.6-347.9)

*Values are shown as means (90% confidence intervals)

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