Development of a Paediatric Population-Based Model of the Pharmacokinetics of Rivaroxaban

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Electronic Supplementary Material: Section 1

Experimental Data Sets from Phase I Studies in Healthy Adult Subjects

Study A: Mass balance and safety

A single-centre, open-label, non-randomized, non-placebo-controlled study was conducted to investigate the metabolism, excretion pattern, mass balance, safety, tolerability and pharmacokinetics of a solution containing 10 mg of [^{14}C] rivaroxaban after a single oral administration to four healthy male subjects (aged 30–54 years) [1]. No major or pharmacologically active circulating metabolites were detected. The results showed that after absorption, rivaroxaban was metabolized via three different pathways. The drug and its metabolites were eliminated via renal (66 %) and biliary/faecal routes (28 %).

Study B: Absolute bioavailability

A single-centre, randomized, open-label, three-way crossover study evaluated the pharmacokinetics of rivaroxaban single 5 mg or 20 mg immediate-release tablet doses in comparison with rivaroxaban 1 mg administered as a 30-minute intravenous infusion in 12 healthy male subjects (aged 21–46 years) [2]. The drug was administered under fasted conditions. Compared with the 1 mg intravenous infusion, bioavailability of the 5 mg tablet dose was 112 % (95 % confidence interval [CI] 97–129), whereas that of the 20 mg dose was 66 % (95 % CI 57–76). When the 20 mg dose was compared with the 5 mg dose, bioavailability was 59 % (95 % CI 51–68). The higher than 100 % bioavailability of the 5 mg tablet compared with the intravenous infusion was not significant because 100 % is included in the CI and, therefore, bioavailability for the 5 mg tablet was considered to be complete. In addition, 112 % (i.e. >100 %) is considered a chance finding because detailed audits of dosing and bioanalytical procedures did not reveal any errors. Results of this study indicated that pharmacokinetic parameters (e.g. area under the plasma concentration–time curve [AUC], maximum [peak] plasma drug concentration [C_{max}] and time to reach maximum [peak] plasma concentration following drug administration [t_{max}]) increased with dose but were less than dose proportional [2]. The rates of treatment-emergent adverse events were similar between the three different dose groups.

Study C: Pharmacokinetics across a wide dose range

A placebo-controlled, dose-escalation study investigated plasma concentration–time profiles for rivaroxaban in 108 healthy male subjects (aged 19–45 years) after single oral doses of rivaroxaban ranging from 1.25 mg to 80 mg (dosage forms used were: 5 mg and 10 mg, both as tablet and solution, and 20 mg, as tablet) [3]. Rivaroxaban had predictable

pharmacokinetic characteristics for both formulations and across the wide range of doses. After administration, rivaroxaban was absorbed rapidly (t_{max} 2 hours for oral tablet).

Study D: Absorption from proximal and distal small bowel and ascending colon

For the evaluation of colonic absorption of rivaroxaban, a single-centre, non-randomized, non-placebo-controlled, non-blinded, crossover study investigated the pharmacokinetics of rivaroxaban 10 mg after single-dose applications: as two 5 mg oral tablets or as granules (from crushed tablets) administered via the Enterion™ capsule to the proximal small bowel, distal small bowel or ascending colon (Pharmaceutical Profiles Ltd., Nottingham, UK) [4]. This capsule enables remote-controlled, site-specific drug delivery and is used to investigate regional drug absorption in the gastrointestinal tract. In addition, a 5 mg solution prepared from rivaroxaban powder was administered to the ascending colon via the Enterion™ capsule [5].

Study E: Food effect on pharmacokinetics of two 5 mg tablets

This study was a randomized, open label, two-way crossover study to investigate the effect of a high-fat, high-calorie meal on safety, tolerability, pharmacodynamics and pharmacokinetics of rivaroxaban 10 mg given orally as two 5 mg tablets in 10 healthy male subjects (aged 19–45 years) [6]. Mean rivaroxaban t_{max} increased from 3 hours (fasted state) to 4 hours (fed state), indicative of slower absorption with the administration of food. Additionally, mean AUC and mean C_{max} values of rivaroxaban were significantly increased in the fed state.

Study F: Food effect on pharmacokinetics of four 5 mg tablets or one 20 mg tablet

In this single-dose, non-blinded, randomized, non-placebo-controlled crossover study, the effect of a high-fat, high-calorie or high-carbohydrate meal on the safety, tolerability, pharmacodynamics and pharmacokinetics of rivaroxaban 20 mg given either as four 5 mg tablets or one 20 mg tablet was investigated in 12 healthy male subjects (aged 19–44 years) [6]. No relevant pharmacokinetic differences were observed between the two dosing regimens (four 5 mg tablets vs one 20 mg tablet) or between the two types of meals (high fat, high calorie vs high carbohydrate). Mean t_{max} increased from 2.75 hours (fasted) to 4 hours (fed, both dosing regimens). Additionally, mean AUC and mean C_{max} values were significantly higher after food.

Study G: Food effect on pharmacokinetics of one 10 mg tablet or one 20 mg tablet

Two randomized, open-label, two-way crossover studies assessed the effect of a high-fat, high-calorie meal on the safety, tolerability and pharmacokinetics of a 10 mg (*n* = 24) and

20 mg rivaroxaban tablet (*n* = 22), respectively, in healthy male subjects (aged 19–45 years) [2]. In the 10 mg group, mean plasma AUC and mean C_{max} values were similar in fasted or fed states. The t_{max} was delayed by 0.5 hour after food. In the 20 mg group, AUC was increased by 39 % and C_{max} by 76 % after food. The t_{max} was delayed by 1.5 hours after food. Safety and adverse event profiles were similar between both doses.

Study H: Food effect on pharmacokinetics of 10 mg and 20 mg oral solution

In this single-dose, open-label, randomized, four-way crossover study, a 1 mg/mL oral solution of rivaroxaban at doses of 10 mg and 20 mg under fasting conditions and 20 mg under fed conditions were compared with a 10 mg tablet dose under fasting conditions in 16 healthy subjects (aged 19–45 years) [2]. Under fasting conditions, bioavailability (AUC/dose and C_{max}/dose) values were similar for the 10 mg oral solution and 10 mg tablet. Bioavailability of the 20 mg oral solution was lower in comparison with the 10 mg tablet (AUC/dose of 0.066 h/L and 0.095 h/L, and a mean dose-normalized C_{max}/dose of 0.006 1/L and 0.011 1/L, respectively). Under fed conditions, AUC values after the administration of the 20 mg oral solution increased by 47 % and C_{max} by 104 % compared with the same dose in the fasted state, indicating that the loss of bioavailability with this dose could be compensated by food intake.

Electronic Supplementary Material: Section 2

Parameters for Absorption from the Gastrointestinal Tract

Differences in the pH of the gastrointestinal tract may alter the absorption profile of acid and alkaline drugs. However, an effect of pH on solubility and permeability in the gastrointestinal tract is not expected for rivaroxaban. Therefore, the pH of the stomach and intestinal tract was not implemented as an age-dependent parameter, and default values of PK-Sim® were used.

The results of an independent reassessment of multiple data sets on gastric emptying time under fasted and fed conditions suggested that, when explicitly discriminating between both states, gastric emptying time is similar in children and adults [7–11]; however, gastric emptying is typically prolonged in neonates and infants aged 2–24 months owing to the almost constant presence of milk and/or formula in the stomach. The gastric emptying time functions for an average adult under fasted and fed conditions were used for simulations across the entire paediatric age range. In order to represent the average feeding state in the paediatric population, simulations in the fasted state (no lag) and in the fed state were carried out and subsequently pooled for the analysis (see Methods).

Reported small intestinal transit times in neonates and infants are similar to those in older children and adults [12–18]. Therefore, the small intestinal transit times were not implemented as an age-dependent parameter. By contrast, the large intestinal transit time is significantly shorter in children than in adults [19]. The reported differences are accounted for by using a scale factor for the velocity [cm/h] of drug transport along the large intestine that was established based on the data reported in the literature [19]. It was assumed that there were no differences in large intestinal transit time between male and female children.

Age-dependent differences in intestinal surface area may affect the proportion of absorption and/or the absorption profile of drugs in children. Information about anatomical changes of the intestine (length, radius) is available in the literature [19], whereas information about the ontogeny of the intestinal physiology (relevant for the estimation of the surface amplification owing to the presence of circular folds, villi and microvilli) is sparse. Therefore, the information required for scaling was derived from pharmacokinetic data of two reference compounds, acyclovir and ciprofloxacin, both given orally to children. For these compounds pharmacokinetic data for the children aged 3 days to 7 years were available [20, 21]. Analysis of these data suggested a scaling factor of 0.91 for the intestinal surface area of all

sections of the gastrointestinal tract for children aged 0–7 years. For children older than 7 years, the scaling factor was 1.

Specific intestinal permeability (i.e. the intestinal permeability normalized to the surface area) in infants aged 1 month to 3 years is similar to that in adults and is only high in infants in the first few days after birth [22–25]. Therefore, the specific intestinal permeability was held constant at all ages.

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