Evidence-Based Development and Rationale for Once-Daily Rivaroxaban Dosing Regimens across Multiple Indications

Dagmar Kubitza, Scott D. Berkowitz, Frank Misselwitz

SUPPLEMENTARY MATERIAL
Section 1: Preclinical Characterization of Rivaroxaban

Rivaroxaban was discovered as a result of a high-throughput screening program initiated in 1998 that sought to identify inhibitors of the coagulation serine protease Factor Xa. The compound is an oxazolidinone derivative (molecular weight 436)\(^1\) that binds directly (no cofactor requirement) and non-covalently to the active site of Factor Xa, with a selectivity >10,000-fold greater than for other related serine proteases.\(^2\) Initial biochemical characterization showed that rivaroxaban inhibited purified human Factor Xa in a competitive concentration-dependent manner with a \(K_i\) of 0.4 nM.\(^1\) Furthermore, rivaroxaban also inhibited Factor Xa within the prothrombinase complex\(^1\) and clot-associated Factor Xa,\(^3\) indicating that, in contrast to large molecule anticoagulants such as heparin, small molecules such as rivaroxaban could diffuse through the fibrin mesh of a clot. Rivaroxaban was shown to prolong prothrombin time and activated partial thromboplastin time in a concentration-dependent manner.\(^1\) In addition, rivaroxaban dose-dependently reduced thrombus formation in both a rat venous stasis model and in an arteriovenous-shunt model with no effect on rat tail or rabbit ear bleeding times at concentrations up to at least the median effective dose (ED\(_{50}\)), thus demonstrating in vivo antithrombotic potential.\(^1\)

Initial pharmacokinetic studies conducted in rats and dogs showed dose-dependent levels of area under the concentration–time curve (AUC) and maximum plasma drug concentration (C\(_{\text{max}}\)) following oral administration. Bioavailability was estimated at 57–66\% for rats and 60–86\% for dogs. In both species, time to C\(_{\text{max}}\) (T\(_{\text{max}}\)) was approximately 0.5 hours and elimination half-lives were approximately 1–2 hours.\(^4\) There was a high degree of plasma protein binding, primarily to albumin. Elimination of radiolabeled rivaroxaban in both species occurred via biliary and urinary pathways and no pharmacologically active metabolites were identified. Importantly, after both oral and intravenous administration, pharmacokinetics were predictable and dose proportional.\(^4\)
Section 2: Phase II Studies of Twice-Daily Dosing for Prevention of Venous Thromboembolism after Elective Total Hip or Knee Replacement

Two further twice-daily (BID) dose-ranging studies were also conducted. The double-blind, double-dummy ODIXa-HIP2 study evaluated doses of rivaroxaban from 2.5 to 30 mg BID versus enoxaparin 40 mg once daily (OD) subcutaneously in eligible patients undergoing total hip replacement. The primary efficacy endpoint occurred in 7–18% of patients receiving rivaroxaban compared with 17% in those receiving enoxaparin (Supplementary Table 1). There was no significant trend in the dose–response for efficacy, although the dose–response for major bleeding was significant (Supplementary Table 2). The ODIXa-KNEE phase II study was also double blind, double dummy, and evaluated the same rivaroxaban dose range of 2.5 mg to 30 mg BID in patients undergoing total knee replacement. However, this study used the North American enoxaparin regimen of 30 mg BID, commencing 12–24 hours after surgery. Efficacy and safety results are shown in Supplementary Tables 1 and 2, respectively. Again, there was no statistically significant dose–response for efficacy, but this was observed with respect to major bleeding.
Section 3: Posology Considerations in the Treatment of Venous Thromboembolism

Early Event Recurrence after Venous Thromboembolism – The THRIVE and van Gogh Studies

The THRIVE study evaluated 6 months of ximelagatran treatment, 36 mg BID, against standard of care (enoxaparin followed by dose-adjusted warfarin) in 2489 patients with acute deep vein thrombosis. Ximelagatran was non-inferior to standard care for efficacy, with similar rates of venous thromboembolic events in each treatment group. Bleeding rates were low and similar. Of note, the majority of the recurrent venous thromboembolic events occurred in the first few weeks of therapy, especially in the ximelagatran treatment group, suggesting a need for greater initial treatment intensity (Supplementary Figure 1). In the subsequent van Gogh studies that compared idraparinux with standard therapy, most of the recurrent events in patients with deep vein thrombosis occurred in the first 3 weeks, illustrated by the initial steep slope of the Kaplan–Meier curve (Supplementary Figure 2). These results also indicated that more intense initial therapy might be required for patients diagnosed with pulmonary embolism.

Pharmacokinetic Considerations

The proposed two-phase, single-drug regimen for the treatment of venous thromboembolism with rivaroxaban was also consistent with population pharmacokinetic analyses based on sparse sampling from patients in the phase II studies. As observed previously, results showed slightly higher $C_{\text{max}}$ and lower minimum plasma drug concentration ($C_{\text{trough}}$) for rivaroxaban with OD compared with BID dosing, but with substantial overlap (Supplementary Figure 3). Furthermore, both AUC and $C_{\text{max}}$ increased with dose for both OD and BID regimens. Conversely, although $C_{\text{trough}}$ levels of rivaroxaban also increased dose dependently with BID administration, the dose–response with OD administration was nearly flat (Supplementary Figure 3), suggesting that an OD regimen might be safer for long-term prevention of recurrence.
Section 4: Outcomes in Patients with Atrial Fibrillation with or without Moderate Renal Impairment

Please see Supplementary Table 3 for outcomes in patients with atrial fibrillation with or without moderate renal impairment.\textsuperscript{10}
Supplementary Table 1: Efficacy results in phase II studies of rivaroxaban for the prevention of venous thromboembolism after total hip replacement/total knee replacement surgery

| Procedure | Trial | BID dosing (%) | OD dosing (%) | Enoxaparin comparator (%) |
|-----------|-------|----------------|---------------|----------------------------|
|           |       | 2.5 mg 5 mg 10 mg 20 mg 30 mg | 5 mg 10 mg 20 mg 30 mg 40 mg | 40 mg OD |
| THR       | ODIXa-HIP<sup>a</sup> | 22.2 23.8 20.0 10.2 17.4 | – – – 15.1 – | 16.8 |
|           | ODIXa-HIP<sup>b</sup> | 15.4 13.8 11.9 18.2 6.9 | – – – – – | 17.0 |
|           | ODIXa-OD-HIP<sup>c</sup> | – – – – | 14.9 10.6 8.5 13.5 6.4 | 25.2 |
| TKR       | ODIXa-KNEE<sup>d</sup> | 31.7 40.4 23.3 35.1 25.4 | – – – – | 44.3 (30 mg BID) |

Results are per cent incidence of the primary efficacy endpoint: the composite of deep vein thrombosis, pulmonary embolism, and all-cause mortality.

a. Mandatory bilateral venography 5–9 days (median 7.5 days) after surgery. A total of 466 patients evaluable in the per protocol analysis.
b. Mandatory bilateral venography 5–9 days (mean 8 days) after surgery. A total of 548 patients evaluable in the per protocol analysis.
c. Mandatory bilateral venography 6–10 days (mean 7 days) after surgery. A total of 618 patients evaluable in the per protocol analysis.
d. Mandatory bilateral venography 5–9 days (mean 7 days) after surgery. A total of 366 patients evaluable in the per protocol analysis.

BID, twice daily; OD, once daily; THR, total hip replacement; TKR, total knee replacement.
Supplementary Table 2: Safety results in phase II studies of rivaroxaban for the prevention of venous thromboembolism after total hip replacement/total knee replacement surgery

| Procedure | Trial | BID dosing (%) | OD dosing (%) | Enoxaparin comparator (%) |
|-----------|-------|----------------|---------------|---------------------------|
|           |       | 2.5 mg | 5 mg | 10 mg | 20 mg | 30 mg | 5 mg | 10 mg | 20 mg | 30 mg | 40 mg | 40 mg OD |
| THR       | ODIX1 | 0      | 2.5  | 2.9   | 6.5   | 10.8  | –    | –    | –    | 4.5   | –    | 0       |
|           | HIPa  |        |      |       |       |       |      |      |      |       |      |         |
| TKR       | ODIXa | 0.8    | 2.2  | 2.3   | 4.5   | 5.4   | –    | –    | –    | –     | –    | 1.5     |
|           | HIP2b |        |      |       |       |       |      |      |      |       |      |         |
|           | ODIX  |        |      |       |       |       |      |      |      |       |      |         |
|           | OD-HIPc| –     | –    | –     | –     | –     | 2.3  | 0.7  | 4.3  | 4.9   | 5.1   | 1.9     |
| TKR       | ODIXa | 1.0    | 0    | 1.9   | 3.1   | 7.5   | –    | –    | –    | –     | –    | 1.9 (30 mg BID) |
|           | KNEEd |        |      |       |       |       |      |      |      |       |      |         |

Results are per cent incidence of the principal safety outcome: major postoperative bleeding up to 2 days after last dose of study drug.

- Mandatory bilateral venography 5–9 days (median 7.5 days) after surgery. A total of 625 patients in the safety population.
- Mandatory bilateral venography 5–9 days (mean 8 days) after surgery. A total of 704 patients in the safety population.
- Mandatory bilateral venography 6–10 days (mean 7 days) after surgery. A total of 845 patients in the safety population.
- Mandatory bilateral venography 5–9 days (mean 7 days) after surgery. A total of 613 patients in the safety population.

BID, twice daily; OD, once daily; THR, total hip replacement; TKR, total knee replacement.
**Supplementary Table 3:** Outcomes in patients with atrial fibrillation with or without moderate renal impairment\(^{10}\)

| Clinical endpoint                      | CrCl 30–49 mL/min |                  | CrCl ≥50 mL/min |                  |                  | P-value for interaction |
|----------------------------------------|-------------------|-----------------|-----------------|-----------------|-----------------|-------------------------|
|                                        | Rivaroxaban 15 mg (n = 1474)\(^n\) | Rivaroxaban 20 mg (n = 5637)\(^n\) | Warfarin (n = 1476)\(^n\) | Warfarin (n = 5640)\(^n\) |                  |                          |
| Primary efficacy endpoint (stroke and systemic embolism) | 2.32 | 0.84 (0.57–1.23) | 1.57 | 0.78 (0.63–0.98) | 0.76 |
| Principal safety endpoint              | 17.82 | 0.98 (0.84–1.14) | 14.24 | 1.04 (0.96–1.13) | 0.4496 |
| Major bleeding                         | 4.49 | 0.95 (0.72–1.26) | 3.39 | 1.07 (0.91–1.26) | 0.4800 |

Event rates as %/year.

CI, confidence interval; CrCl, creatinine clearance.
Supplementary Figure 1: Cumulative incidence of recurrent venous thromboembolic events in the THRIVE study.\textsuperscript{7}

Recurrent venous thromboembolic events in the ximelagatran and standard care treatment groups in the THRIVE study.
d, days; Enox, enoxaparin; Warf, warfarin.
Supplementary Figure 2: Cumulative incidence of recurrent venous thromboembolic events in the van Gogh studies.\textsuperscript{8}

Rates of recurrent venous thromboembolic events in the idraparinux and standard therapy groups: patients with deep vein thrombosis (the DVT study, left) and patients with pulmonary embolism (the PE study, right).

DVT, deep vein thrombosis; PE, pulmonary embolism.
Supplementary Figure 3: Rivaroxaban \(C_{\text{max}}\) (A) and \(C_{\text{trough}}\) (B) in the ODIXa-DVT and EINSTEIN DVT phase II study.\(^9\)

The horizontal line within each box is the mean; the top and bottom of each box represents the 25th and 75th percentiles, respectively. Whiskers are the 10th and 90th percentiles; circles are the 5th and 95th percentiles.

BID, twice daily; \(C_{\text{max}}\), maximum plasma drug concentration; \(C_{\text{trough}}\), minimum plasma drug concentration; OD, once daily.
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