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ANTITHROMBOTIC DRUGS

BLEEDING RISK ASSOCIATED WITH FACTOR XI MONOCLONAL ANTIBODIES IN COMBINATION WITH ASPIRIN IN HEALTHY VOLUNTEERS AND ORTHOPEDIC SURGERY PATIENTS: ANALYSIS FROM RECENT PHASE 1 AND PHASE 2 STUDIES

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Introduction. Standard-of-care anticoagulants effectively prevent venous thromboembolism but pose a high bleeding risk, particularly when combined with antiplatelet therapies (e.g., ASA). The two human monoclonal antibodies REGN9933^{A2} and REGN7508^{CAT} bind distinct FXI epitopes (the A2 and catalytic domains, respectively) and may confer an adjunctive benefit on top of ASA without increasing bleeding risk.

Aim. To evaluate the bleeding risk with combined antiplatelet and REGN9933^{A2} or REGN7508^{CAT} therapy using data from a Phase 1 study in healthy volunteers and post hoc analysis of phase 2 studies in post-operative knee arthroplasty patients.

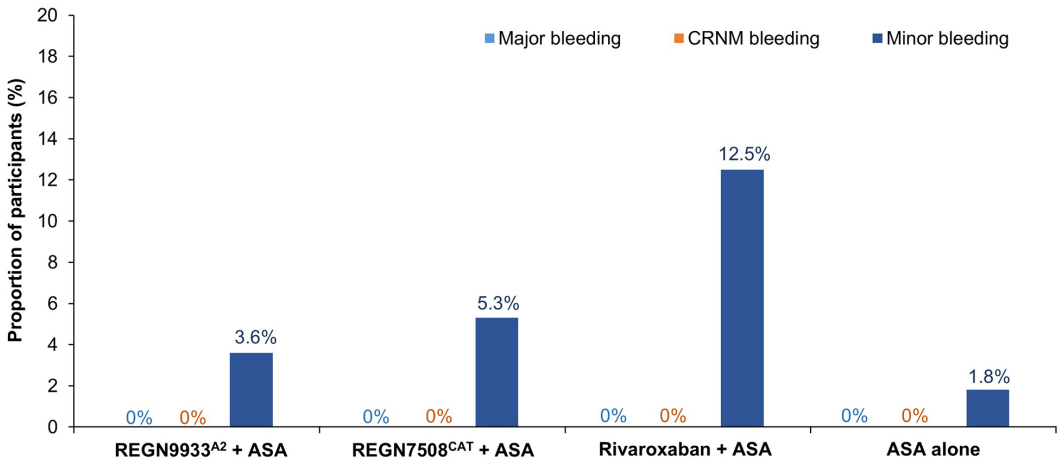
Materials and Methods. All studies were randomized and open label. In the Phase 1 study (NCT06444178), healthy volunteers received a single intravenous (IV) dose of REGN9933^{A2} 300 mg or REGN7508^{CAT} 250 mg + oral ASA 75 mg once daily (QD); oral rivaroxaban 20 mg QD + ASA 75 mg QD; or ASA 75 mg QD alone. The incidence of major and clinically relevant non-major (CRNM) bleeding was evaluated. In the Phase 2 ROXI-VTE-I (NCT05618808) and ROXI-VTE-II (NCT06454630) studies, patients post-total knee arthroplasty received a single IV dose of REGN9933^{A2} 300 mg, subcutaneous (SC) enoxaparin 40 mg QD, or oral apixaban 2.5 mg twice daily in ROXI-VTE-I, or a single IV dose of REGN7508^{CAT} 250 mg IV or SC enoxaparin 40 mg QD in ROXI-VTE-II; adjunctive ASA ≤100 mg/day was permitted in both studies. Post hoc analyses evaluated bleeding outcomes in the ASA cohort.

Results. In Phase 1 (n=224), there were no major or CRNM bleeding events in any treatment arm. Minor bleeding events occurred in 3.6% of participants in the REGN9933^{A2} + ASA group, 5.3% in the REGN7508^{CAT} + ASA group, 12.5% in the rivaroxaban + ASA group, and 1.8% with ASA alone (Figure 1). In ROXI-VTE-I (n=373) and ROXI-VTE-II (n=179), 58 (15.5%) and 11 (6.1%) patients received adjunctive ASA, respectively. There were no major, CRNM, or minor bleeding events.

Conclusions. Data from healthy volunteers and orthopedic surgery patients suggest that FXI inhibition with REGN9933^{A2} or REGN7508^{CAT} in combination with ASA does not increase the incidence of clinically relevant bleeding. Further studies are planned to evaluate the bleeding risk with FXI inhibitors in populations at higher risk of bleeding, including patients with cancer and those receiving antiplatelet therapy.

Antithrombotic Drugs

Figure. Bleeding rates in the Phase 1 study



There were no major, CRNM, or minor bleeding events in the Phase 2 ROXI-VTE-I and ROXI-VTE-II studies.

ASA, aspirin; CRNM, clinically relevant non-major.