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POSTER ABSTRACTS

322.DISORDERS OF COAGULATION OR FIBRINOLYSIS: CLINICAL AND EPIDEMIOLOGICAL

Updated Protocol for the Phase 3, Randomized, Double-Blinded Lex-210 Study of Four-Factor Prothrombin Complex Concentrate in Patients with Acute Major Bleeding on Factor Xa Inhibitor Therapy

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Background and Significance: Despite significantly reduced risk of intracranial hemorrhage compared with vitamin K antagonists, direct oral anticoagulant therapy with factor Xa inhibitors (FXaI) is associated with similar incidences of other major bleeds. Although hemostatic agents such as prothrombin complex concentrates (PCCs) are often used (off-label), the efficacy and safety of PCCs for managing FXaI-related bleeding requires further investigation. This study aims to evaluate superior hemostatic efficacy of high-dose vs low-dose four-factor (4F) PCC (Octaplex®; Octapharma) in adults with FXaI-related major bleeding.

Study Design and Methods: LEX-210 (NCT04867837) is a Phase 3, multicenter, prospective, randomized, double-blinded, group-sequential, parallel-group, adaptive design study. Significant modifications have recently been made to the study design.

Patients aged ≥18 years with acute major bleeding (e.g., gastrointestinal, intracranial) and baseline anti-factor Xa activity of ≥100 ng/mL are eligible. To increase rate of recruiting suitable patients into the study, the eligibility criteria have been optimized. For inclusion (full criteria in Table 1), baseline anti-factor Xa activity of ≥100 ng/mL may be either confirmed by locally available tests (including retrospectively by the central laboratory) or suspected by the investigator and later confirmed by the central lab. Prospective written informed consent will be obtained from all patients or patients' legally authorized representative prior to enrolment. If this is not possible, in countries outside the US where it is permitted under local regulations or approved by local ethics committees, deferred consent procedures may be applied.

Key exclusion criteria (Table 2) include acute trauma for which FXaI reversal alone would not be expected to control bleeding, and thromboembolic events in the last 3 months. In addition, hypersensitivity to heparin and platelet inhibitors are specified. Patients will be excluded if they score <7 on the Glasgow Coma Scale (with allowances for intubation), or have expected survival of <24 hours. While patients scheduled for surgery in <12 hours are excluded, minor surgeries and invasive procedures for diagnostic or therapeutic reasons are allowed, or if intended to address a second (non-index) bleeding event.

Patients will be randomized 1:1 to 50 or 15 IU/kg 4F-PCC. The primary objective is to demonstrate superior hemostatic efficacy of the higher dose in patients with major bleeding associated with FXaI. Hemostatic efficacy through 24 hours after receipt of 4F-PCC will be evaluated by an independent data monitoring and endpoint adjudication committee using objective criteria, with a binary outcome of effective or ineffective. Secondary endpoints include change in endogenous thrombin potential (baseline to 1 hour after 4F-PCC), 30-day rates of thromboembolic events, and all-cause mortality. The study is conducted in accordance with the ethical principles laid down in the Declaration of Helsinki

The proportion of patients with an effective outcome will be compared between groups using a one-sided z-test. The primary statistical model will be adjusted for the baseline anti-factor Xa activity as determined retrospectively by the central laboratory. A logistic regression model for the success rate using treatment group (dose level) and the anti-factor Xa activity as fixed effects will be used to determine the one-sided z-statistic.

LEX-210 launched in Q4 2021 and will be performed across ~60 sites in North America and the European Continent. Target enrollment is ~260 patients, assuming a 30% dropout rate. So far, 26 sites in the US, Italy, Germany, and Spain have been initiated, with 5 patients enrolled. Study completion is anticipated in Q3 2024.

Disclosures Sarode: *CSL Behring:* Consultancy; *Octapharma:* Consultancy; *Prothya:* Consultancy; *Sanofi:* Consultancy; *VarmX:* Consultancy; *Cerus:* Research Funding; *Siemens:* Research Funding; *Takeda:* Research Funding. **Maack:** *Octapharma AG:* Current Employment. **Solomon:** *Octapharma, AG:* Current Employment. **Knaub:** *Octapharma AG:* Current Employment. **Pezeshki:** *Octapharma USA:* Current Employment. **Schulman:** *Bayer:* Honoraria; *Hemostasis Reference Laboratory:* Honoraria; *International Society on Thrombosis and Haemostasis, treasurer:* Membership on an entity's Board of Directors or advisory committees; *Regeneron:* Honoraria; *Sanofi:* Honoraria; *Servier:* Honoraria; *Daiichi-Sankyo:* Honoraria; *Alexion:* Honoraria; *Octapharma:* Honoraria; *Boehringer-Ingelheim:* Honoraria.

Table 1. Inclusion Criteria in the LEX-210 Study

1	Patients on oral factor Xa inhibitor therapy and with known or suspected baseline anti-factor Xa activity of at least 100 ng/mL: • Patients who received or who are believed by the investigator to have received a dose of oral factor Xa inhibitor and who have a baseline anti-factor Xa activity of at least 100 ng/mL according to the locally available test (e.g., chromogenic assay) performed outside of the study as part of standard of care OR • Patients who received or who are believed by the investigator to have received their latest dose of oral factor Xa inhibitor (e.g., rivaroxaban ≥10 mg, apixaban ≥2.5 mg, edoxaban ≥30 mg) ≤8 hours prior to enrolment OR • Patients who received or who are believed by the investigator to have received their latest dose of oral factor Xa inhibitor (e.g., rivaroxaban ≥10 mg, apixaban ≥2.5 mg, edoxaban ≥30 mg) >8 hours prior to enrolment or at an unknown time, but for whom the investigator suspects a baseline anti-factor Xa activity of at least 100 ng/mL and assesses that the administration of 4F-PCC is clinically indicated
2	Aged ≥18 years
3	Patients who have given written informed consent or for whom written informed consent has been obtained from the patient's legally authorised representative on their behalf: • Wherever possible, prospective written informed consent will be obtained before enrolment from the patient or, if they are incapable of providing it, from their legally authorised representative • If prospective written informed consent is not possible, deferred consent procedures will be permitted outside the US if approved by the local ethics committee or otherwise permitted under local regulations • When deferred consent procedures are used outside the US, written informed consent should be obtained from the patient as soon as they recover the capacity to provide it, or otherwise from their legally authorised representative
4	Patients who have acute major bleeding defined as follows: • Bleeding that is life-threatening or uncontrolled, e.g., with signs or symptoms of haemodynamic compromise, such as severe hypotension, poor skin perfusion, or low cardiac output that cannot be otherwise explained OR • Symptomatic bleeding in critical organs (intracranial, intraspinal, intraocular, gastrointestinal, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome) OR • Acute overt bleeding associated with a fall in haemoglobin (Hgb) level of ≥2 g/dL, OR a Hgb level ≤8 g/dL if no baseline Hgb level is available, OR in the opinion of the investigator that the patient's Hgb level will fall to ≤8 g/dL with resuscitation

Table 2. Exclusion Criteria in the LEX-210 Study

1	Patients with 'Do not resuscitate' orders
2	Patients with acute trauma for which reversal of DOAC therapy with factor Xa inhibitor alone would not be expected to control the bleeding event
3	Hgb decrease without accompanying evidence of source of bleeding
4	Acute coronary syndrome, ischaemic stroke or venous thromboembolism (VTE) within the preceding 3 months
5	Patients with a history, within the last 3 months, of disseminated intravascular coagulation (DIC) or hyperfibrinolysis
6	Patients with a known congenital bleeding disorder
7	Known inhibitors to coagulation factors II, VII, IX, or X; heparin-induced, type II thrombocytopenia; or immunoglobulin A (IgA) deficiency with known antibodies against IgA
8	Known hypersensitivity to plasma-derived products or heparin
9	Patients who received haemostatic agents, including plasma, platelets, PCC, activated PCC (aPCC), recombinant factor VIIa, or recombinant factor Xa inactivated-zhzo (andexanet alfa), for the current bleeding event prior to enrolment (antifibrinolytic drugs and local haemostatic agents are allowed)
10	Patients who received ticlopidine within 14 days, prasugrel within 7 days, clopidogrel within 5 days, ticagrelor within 5 days, dipyridamole within 1 day or cangrelor within 1 hour preceding the bleeding event
11	Patients on enoxaparin therapy for thromboembolic prophylaxis
12	A score of less than 7 on the Glasgow Coma Scale in non-intubated patients or an estimated intracerebral haematoma volume of more than 60 mL. (Patients intubated or sedated at the time of screening may be enrolled if intubation or sedation were done for non-neurologic reasons)
13	Patients with expected survival of less than 24 hours, in the opinion of the investigator (in collaboration with other medical experts as appropriate per usual local practice)
14	Patients scheduled to undergo surgery in less than 12 hours, with the exception of minor surgeries and invasive procedures which are allowed for diagnostic or therapeutic reasons or if intended to address a second (non-index) bleeding event
15	Patients who are pregnant or breastfeeding at the time of enrolment
16	Patients previously enrolled in this study
17	Patients participating in another interventional clinical treatment study currently or during the past 1 month prior to study inclusion

Figure 1

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