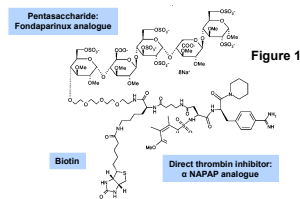


FIRST HUMAN STUDY WITH EP217609, A NEW SYNTHETIC PARENTERAL NEUTRALIZABLE DUAL ACTION ANTICOAGULANT

P. Gueret¹, C. Krezel², P. L. M. van Giersbergen³, E. Fuseau⁴, M. Petitou², E. Neuhart²
¹Hemostasis Department, University Hospital Rennes ²Endotis Pharma, Romainville
³Van Giersbergen Consulting, Wuenheim ⁴EMF Consulting, Aix en Provence, France

Background

EP217609 is a new synthetic parenteral dual action anticoagulant combining (Figure 1) an indirect factor Xa inhibitor (antithrombin binding pentasaccharide) and a direct thrombin inhibitor (peptidomimetic). EP217609 can be neutralized by avidin, an egg-derived glycoprotein, which binds with high affinity and specificity to the biotin moiety of EP217609.



EP217609 will be first developed as an anticoagulant for cardiac surgery patients undergoing a cardiopulmonary bypass. EP217609 will prevent clotting of the extracorporeal circuit, while avidin will neutralize the anticoagulant activity of EP217609 at the end of the procedure to prevent bleeding complications and avoid related transfusions. Then, EP217609 will be developed in patients with acute coronary syndromes undergoing a percutaneous coronary intervention, while avidin will be used in the treatment of major bleedings and prevention of major bleeding risks in this patient population. EP42675 is the non-biotinylated form of EP217609. EP42675 was well tolerated by 100 Phase I healthy young and elderly subjects. Its development will be discontinued.

Material and Methods

This phase I study assessed the pharmacokinetics (PK), pharmacodynamics (PD), safety and tolerability of a single intravenous (IV) bolus of EP217609 (1, 3, 10 mg) and an equimolar dose of EP42675 (2.6 mg) in 40 healthy male subjects (8 active and 2 placebo per group).

Plasma concentrations were measured by anti-factor Xa and anti-factor IIa specific bioassays (Biomnis, France). Pharmacodynamics was assessed by global thrombin generation test (TGT) and activated clotting time (ACT: ACT+ cartridge, Hemochron[®] Signature Elite, Gamida, France), and specific coagulation tests performed on a STA-R Evolution[®] automaton: prothrombin time (PT: Neoplastine[®] CI plus, Diagnostica Stago, France), activated partial thromboplastin time (aPTT: PTTA, Diagnostica Stago, France), ecarin clotting time (ECT: Ecarine, Diagnostica Stago, France), anti Xa activity expressed as $\Delta DO/min$ (Biophen[®] Heparin, Hyphen Biomed, France), and thrombin time (TT: Diagnostica Stago, France). TGT performed on platelet poor plasma (PPP) was triggered with PPP reagent high (20 pM recombinant human tissue factor and 4 μM phospholipids, Diagnostica Stago, France) on a Calibrated Automated Thrombogram (CAT[™]: Diagnostica Stago, France).

Noncompartmental PK and PD analyses were performed using WinNonlin. PK and PK/PD models were developed using the Nonmem[®] software. For the population PK/PD modeling the most relevant PD parameters ACT, ECT and anti-factor Xa activity were considered.

Conclusions

EP217609 was well tolerated. There were no drug-related adverse events, in particular no changes in liver function tests, over the 10-day study period.

The PD of EP217609, as expected, resulted in an increase in global and specific coagulation tests. Consistent with its half-life, the anticoagulant activity persisted for more than 72 hours after single-dose administration.

The PK and PD profiles were predictable with low inter-subject variability.

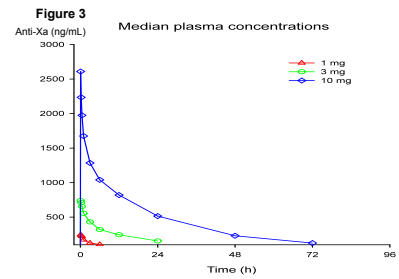
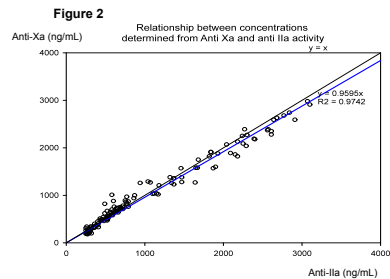
These data provide useful information for designing future clinical studies with a single-dose anticoagulant treatment in patients undergoing cardiac surgery. PK/PD simulations will help predicting the anticoagulant effects of EP217609 in different patient populations.

Results

Pharmacokinetics

There was a strong correlation between EP217609 plasma concentrations as measured by the anti-Xa and IIa bioassays (Figure 2). This indicates the absence of dissociation of the two active moieties. Therefore, either bioassay can be used to measure EP217609 plasma concentrations.

EP217609 concentrations were maximal immediately following IV administration and then rapidly decreased. For all 3 doses, the concentration-time profiles displayed a 2-compartmental disposition pattern (Figure 3). The EP217609 PK showed a dose-proportional increase in exposure. On average, the terminal half-life was 20.4 hours, the clearance was 0.26 L/h and the volume of distribution was 6.9 L. The inter-subject variability was low. The renal clearance of EP217609 was between 0.12 and 0.19 L/h. Between 32.9 and 49.0% of an administered dose were recovered unchanged in urine during the 72-hour collection period indicating that urinary excretion is a major elimination pathway. The PK profiles of EP217609 and EP42675 at equimolar doses (3 and 2.6 mg, respectively) were comparable (data not shown).

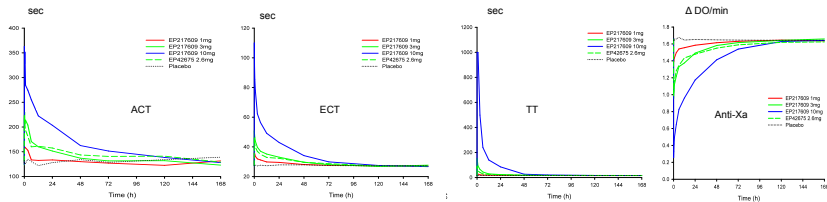


Pharmacodynamics

The IV administration of EP217609 resulted in dose-dependent increases in ACT, ECT, TT, anti-Xa activity, aPTT, PT/INR, and TGT lag time, whereas a decrease in TGT ETP was observed. These effects showed rapid onset after IV administration and lasted for more than 72 hours.

The PD of EP217609 was best defined by ACT, ECT, TT and anti-Xa activity (Figure 4). Interestingly, ACT is a bedside global coagulation test, while ECT and TT on the one hand and anti-Xa activity on the other hand explore the anti-factor IIa and anti-factor Xa active moieties of EP217609, respectively.

The PD profiles of EP217609 and EP42675 at equimolar doses (3 and 2.6 mg, respectively) were comparable (Figure 4).



Pharmacokinetic and pharmacodynamic relationships

The plasma concentration time profile of IV EP217609 was described by a 2-compartment disposition model. PK/PD models were developed for ACT (E_{max} model), ECT (linear model) and anti-factor Xa activity (E_{max} model).

The population predicted effects of EP217609 on these PD parameters indicated that the observed effects were well described by the developed models (Figure 5). There was a strong correlation between the population-predicted and observed values over the full range of tested doses (1 to 10 mg).

The PK and PD time profiles were parallel, indicating the absence of hysteresis.

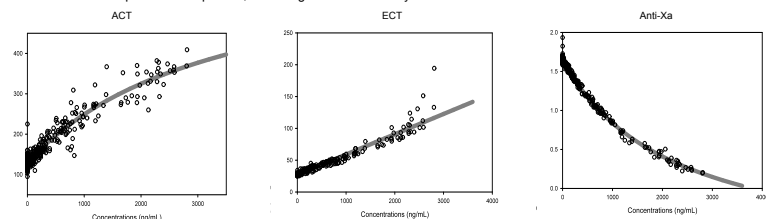


Figure 5
 Open dots: Observed values
 Continuous lines: Population-predicted values

Conflict of interest disclosure:

P. Gueret: Clinical Research Grant
 E. Fuseau, P. van Giersbergen: Endotis Consultants
 C. Krezel, E. Neuhart, M. Petitou: Endotis employees

Abstract 177
 ICT 2010, Milano, Italy