Session 332

#3351

Pharmacokinetics (PK) and Pharmacodynamics (PD) of a New Direct Thrombin Inhibitor (DPOC-4088) After Single Oral Doses of Two Prolonged Release Formulations in Healthy Male Subjects (NCT01347203)

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Background

- DPOC-4088 is an orally active, potent, rapidly binding, reversible direct thrombin inhibitor in clinical development as a once-daily oral treatment.
- DPOC-4088 inhibits plasma coagulation triggered via the intrinsic or extrinsic pathway and effectively interferes with whole blood clotting.
- The potency of DPOC-4088 is reflected by the concentrations that result in 2 x aPTT prolongation in human, rat, African Green monkey, and dog plasma: 810 nM, 870 nM, 520 nM, and 3000 nM, respectively.
- This Phase I clinical study was conducted in healthy subjects to determine PK/PD characteristics of single oral doses of 100 mg and 200 mg DPOC-4088 in two new prolonged-release (PR) formulations [16 and 20 hrs].

Study Objectives

- PRIMARY: Determine and compare plasma concentration ratios (C_{max}/C_{12h} and C_{max}/C_{24h}) following single oral dosing of 100 mg and 200 mg of DPOC-4088 in 16 and 20 hr PR formulations.
- SECONDARY: Standard PK parameters (C_{max}, AUC, $T_{1/2}$, T_{max}), the extent and duration of thrombin inhibition (aPTT, ECT, TT and PT), and safety of DPOC-4088.

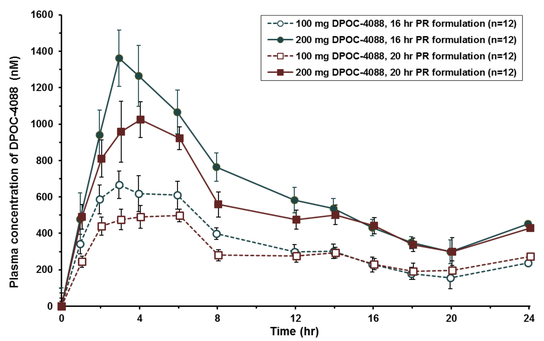
Methods

- Randomized, open-label, 4-period crossover, single oral dose study.
- 12 evaluable young (18-45 years of age) healthy male subjects.
- Each subject received 4 treatments (random order) with DPOC-4088 PR formulations in a fasting state with 5-10 days washout between doses:
  - 100 mg and 200 mg tablets (16 hr PR formulation)
  - 100 mg and 200 mg tablets (20 hr PR formulation)
- For each dose, plasma samples for DPOC-4088 PK were collected pre-dose and at 1, 2, 3, 4, 6, 8, 12, 14, 16, 18, 20, 24, 32, and 48 hrs post-dose.
- Plasma concentrations of DPOC-4088 were determined by validated liquid chromatography/mass spectrophotometry (LC/MS) methods
- Tests of blood coagulation were measured pre-dose and at 1, 2, 4, 6, 8, 12, 16, 24, 32 and 48 hrs post-dose.
- Prolongations in aPTT, ECT, TT and PT were evaluated by calculating absolute and fold-changes from baseline (defined as: values at Hr(i)/pre-dose values at each time point).
- Safety of DPOC-4088 was determined on the basis of adverse events (AEs), hematology, blood chemistry, coagulation parameters, urinalysis, ECG, vital signs and physical examination.

PK Results

- Twelve male subjects (mean age 32.9 ± 8.6 [SD]) were enrolled and completed all 4 treatments as planned.
- DPOC-4088 plasma concentrations are shown in **Figure 1**.

Figure 1. Mean (± SE) Plasma Concentrations of DPOC-4088 after Single Dose Oral Administration to 12 Healthy Male Subjects



Lower limit of quantitation (LLOQ) of DPOC-4088in the LC/MS assay was 0.100 ng/mL (0.221 nM).

- Increases in C_{max} and $AUC_{0-\infty}$ were dose proportional for both PR formulations.
- C_{max} of the 20 hr PR formulation was 79% (90% CI 66-95%) of the value of the 16 hr PR formulation for the 100 mg dose level and 73% (61-88%) for the 200 mg dose level.
- C_{max}/C_{12hr} and C_{max}/C_{24hr} ratios for a given dose were lower for the 20 hr PR formulation as compared to the 16 hr PR formulation (**Table 1**).
- Median T_{max} was 3-4 hrs. $T_{1/2\ terminal}$ ranged from 4.0 to 5.8 hrs.

Table 1: PK of Two Doses and Two PR Formulations of DPOC-4088

PK Parameter[a]	100 mg, 16 hr	200 mg, 16 hr	100 mg, 20 hr	200 mg, 20 hr
n	12[b]	12[c]	12[d]	12[e]
C_{max}, nM	720	1497	572	1099
Ratio $C_{max}/C_{12\ hr}$	2.6	2.9	2.2	2.6
Ratio $C_{max}/C_{24\ hr}$	4.4	3.9	2.5	3.1
T_{max}, hr (range)	3.0 (2.0-6.0)	3.0 (2.0-6.0)	4.0 (3.0-24.0)	3.0 (2.0-6.0)
$AUC_{0-\infty}$, nM.hr	9655	20070	9252	15940
$T_{1/2\ terminal}$, hr	5.1	5.8	5.3	4.0

[a]Values presented as geometric mean; T_{max}: median (range). For $AUC_{0-\infty}$ and $T_{1/2\ terminal}$: [b] n=11; [c] n=9; [d] n=10; [e] n=8.

PD Results

- Both ECT (**Figure 2A**) and aPTT (**Figure 2B**) followed closely the shape of the mean DPOC-4088 PK.
- Prolongation of ECT, aPTT, TT and PT (INR) was dose-dependent after single doses of 100 and 200 mg DPOC-4088 for both the16 hr and 20 hr PR formulations.
- The maximum fold-change in ECT from baseline for the 100 mg dose was 1.58 (16 hr) and 1.49 (20 hr). At the 200 mg dose, the maximum change in ECT was 1.93-fold (16 hr) and 1.77-fold (20 hr) (**Table 2**).
- The maximum fold-change in aPTT from baseline for the 100 mg dose was 1.34 (16 hr) and 1.27 (20 hr). At the 200 mg dose, the maximum change in aPTT was 1.51-fold (16 hr) and 1.44-fold (20 hr) (**Table 2**).

Figure 2A. Mean ECT of DPOC-4088 after Single Dose Oral Administration

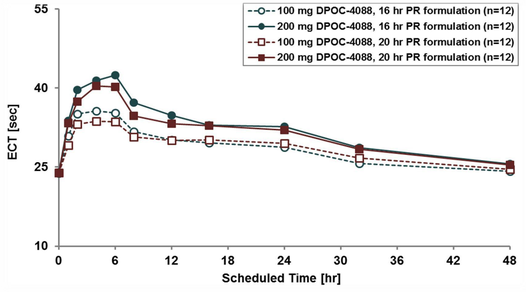


Figure 2B. Mean aPTT of DPOC-4088 after Single Dose Oral Administration

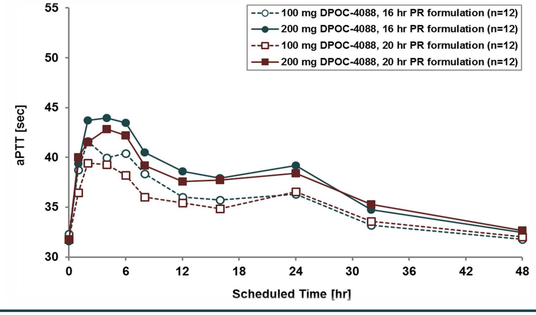


Table 2: PD of Two Doses and Two PR Formulations of DPOC - 4088

PD Parameter[a]	100 mg, 16 hr	200 mg, 16 hr	100 mg, 20 hr	200 mg, 20 hr
n	12	12	12	12
ECT, % max change	58	93	49	77
ECT, % change at 24 hr	21	36	23	35
aPTT, % max change	34	51	27	44
aPTT, % change at 24 hr	12	24	15	21

[a]Values of ECT and aPTT: mean % change compared to pre-dose.

Safety Results

- Single oral doses of 100 mg and 200 mg DPOC-4088 in both the 16 and 20 hr PR release formulations were well-tolerated.
- Overall, 27 AEs occurred in 9 subjects, all were grade 1 except for one grade 2 headache and one grade 2 neck pain, both unlikely to be treatment-related.
- Headache and oropharyngeal pain were the only AEs reported in more than 2 subjects.
- Grade 1 epistaxis occurred in one subject ~30 minutes post-dosing (200 mg, 20 hr) and resolved in 3 minutes; grade 1 blood in stools occurred in one subject 1 day post-dosing (200 mg, 16 hr).
- No SAEs occurred and no clinically significant abnormalities were observed in safety labs, ECGs, vital signs or physical examinations.

Conclusions

- Increasing the DPOC-4088 dose from 100 to 200 mg resulted in a dose proportional increase in C_{max} and exposure (AUC_{∞}) for both the 16 hr and 20 hr PR formulations.
- The 20 hr PR formulation exhibited a significantly lower C_{max} than the 16 hr PR formulation. The C_{max}/C_{12hr} and C_{max}/C_{24hr} ratios were lower for a given dose compared to the 16 hr PR formulation.
- The effect of DPOC-4088 on ECT, aPTT, TT and PT (INR) was dose-dependent for both the 16 hr and 20 hr PR formulations.
- The 20 hr PR formulation of DPOC-4088 was well-tolerated and is expected to show a favorable peak-to-trough ratio during multiple dosing.

Diakron Pharmaceuticals

Disclosures: LMVB, GVL, HVB (Employees of D.R.U.G); WH, ES (Employed by Kinesis Pharma); SR, VE, SR (Employed by Orchid Healthcare); SA (Consultant for Diakron)