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Pharmacokinetics and pharmacodynamics of lexaptepid, a novel anti-hepcidin molecule, in ESA-resistant haemodialysis patients

Iain C. Macdougall[1], Adam Rumjon[1], Jake Cinco[1], Leela Goldstein[1], Luciana Summo[2], Stéphanie Vauléon[2], Kai Riecke[2]

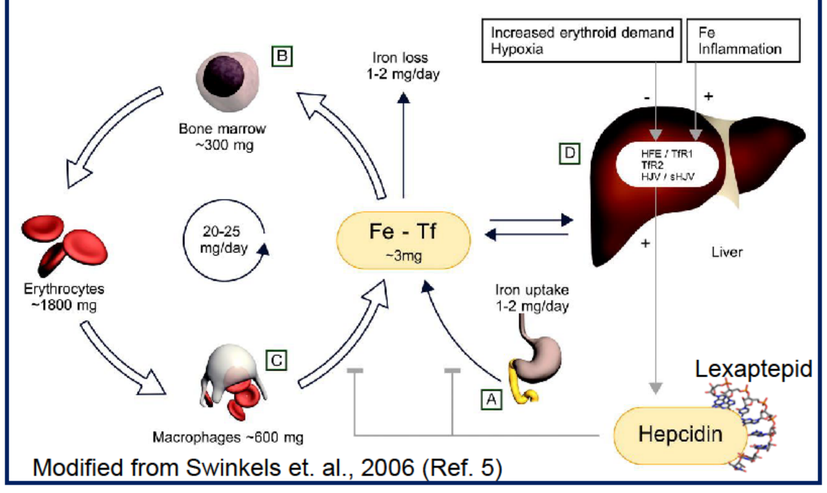
1: Department of Renal Medicine, King's College Hospital, London, UK; 2: Clinical Development, NOXXON Pharma AG, Berlin, Germany

Background

Lexaptepid pegol ("lexaptepid") is a PEGylated L-stereoisomer RNA aptamer (Spiegelmer®) that binds and neutralizes hepcidin, a 25-amino acid peptide regulating iron absorption and iron release from intracellular stores (Ref. 1).

Elevated hepcidin was identified as important contributor to anaemia of chronic disease in dialysis patients and is associated with functional iron deficiency and ESA-hypo-responsiveness (Figure 1, Ref. 2). Treatment with lexaptepid in a pilot study of cancer patients was generally well tolerated, decreased soluble transferrin receptor, increased reticulocyte haemoglobin, and led to clinically meaningful haemoglobin (Hb) increases ≥1 g/dL (Ref. 3). Here we report first data on the pharmacokinetics (PK) and pharmacodynamics of single lexaptepid doses in hemodialysis patients, Part I from an ongoing Phase IIa study.

Figure 1: Hepcidin, lexaptepid, and iron

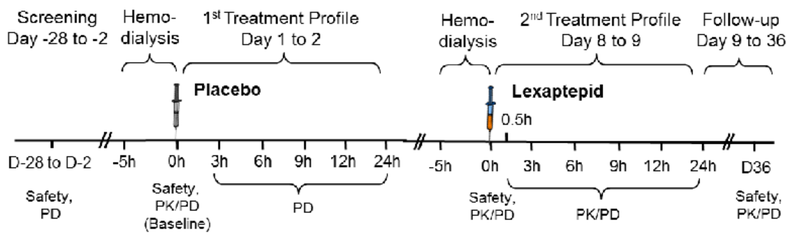


Modified from Swinkels et. al., 2006 (Ref. 5)

Methods

We studied anaemic (Hb 7-11 g/dL) hemodialysis patients with functional iron deficiency (TSAT <30%, ferritin ≥300 ng/mL) with weekly erythropoietin doses ≥12,000 IU. In a single-blind cross-over design, patients were treated with a single i.v. dose of placebo and lexaptepid (1.2 mg/kg) post-dialysis, separated by a 1-week washout period (Figure 2). For PK, PD, and safety assessments, blood samples were analysed among other parameters for lexaptepid, hepcidin, serum iron, TIBC, Hb, TSAT, ferritin, RBC, MCH, CHr, %HRC, and sTfR.

Figure 2: Study outline: single-dose, cross-over Part I



A 4-week follow-up period ensued after the 2nd administration until Day 36

Table 1: Patient characteristics at screening

N (male / female)	9 (3 / 6)
Age	58 (41-73) years
Time on dialysis	77 (12-187) months
Hb	10.6 (8.3-11.0) g/dL
Reticulocyte Hb	29.5 (28.0-34.8) pg
TSAT	15 (9-26) %
Ferritin	549 (320-1411) µg/L
Serum iron	6.2 (4.2-11.5) µmol/L
sTFR	40.5 (10.4-50.7) mg/L
CRP	12.9 (2.0-221) mg/L
Hepcidin	17.7 (9.0-35.5) nmol/L
IL-6	8.4 (3.7-63.0) pg/mL
Erythropoietin dose	15000 (12000-18000) IU/week

Data shown as median (range)

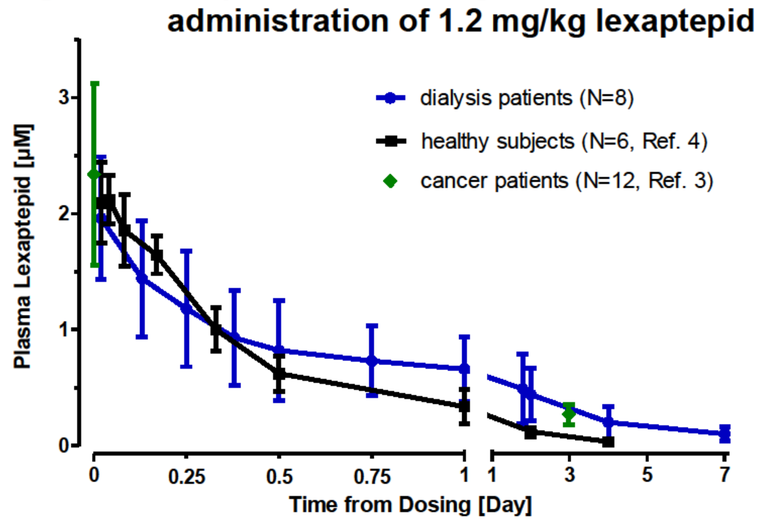
Results

Nine of 12 screened patients were enrolled in Part I. Eight patients completed the study as scheduled. One patient, who discontinued early for an unrelated AE, was replaced. Table 1 provides an overview of key baseline parameters.

Pharmacokinetics

The biphasic PK profile of lexaptepid in dialysis patients was similar to healthy subjects (Ref. 4) within the first 9 h, albeit with higher inter-individual differences. While the maximal plasma concentrations (C_{max}) and initial plasma half-life ($t_{1/2\alpha}$) were similar in the dialysis patients and healthy subjects, the terminal half-life ($t_{1/2\beta}$) was about 2-fold higher in patients. Correspondingly, systemic clearance was reduced by approximately half. This resulted in a less than 2-times higher systemic exposure (AUC_{0-96}) for the dialysis patients compared to healthy subjects (Figure 3, Table 2).

Figure 3: PK profiles after single i.v. administration of 1.2 mg/kg lexaptepid



Arithmetic mean ±SD

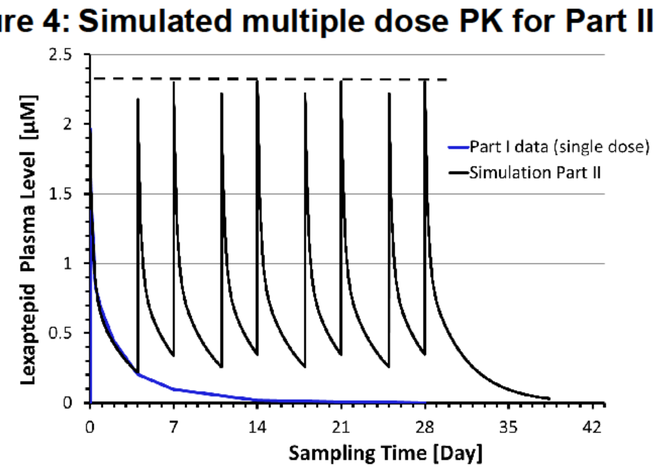
Table 2: PK parameters in dialysis patients and healthy subjects after i.v. administration

Population / Schedule		*Dialysis Patients* SD	*Dialysis Patients* MD/SS	*Healthy Subjects* SD	*Healthy Subjects* MD/SS
Cmax	[µM]	1.96*	2.31	2.16	2.23
Vss	[L]	6.53	-	4.08	-
AUC_{0-24}	[µM·h]	22.7	27.6	20.9	20.4
$t_{1/2\alpha}$	[h]	4.1	-	4.1	-
AUC_{0-96}	[µM·h]	45.7*	59.5	29.5	29.8
$t_{1/2\beta}$	[h]	50.4	-	22.4	-
CL	[L/h]	0.11	-	0.18	-

SD: single dose; MD/SS, multiple dose/steady-state (simulated for q2w i.v. dosing of 1.2 mg/kg);
Dialysis patients, N=8; Healthy subjects, N=6; *, N=5

The simulation of plasma concentrations after twice weekly administrations was done taking into account the actual single-dose PK in dialysis patients. It indicates that the peak concentrations and accumulation ratios in dialysis patients should be similar as in healthy subjects (Figure 4, Ref. 4).

Figure 4: Simulated multiple dose PK for Part II

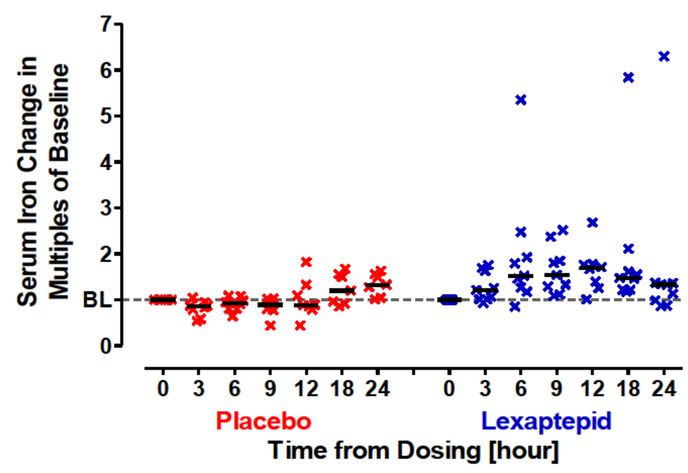


Pharmacodynamics

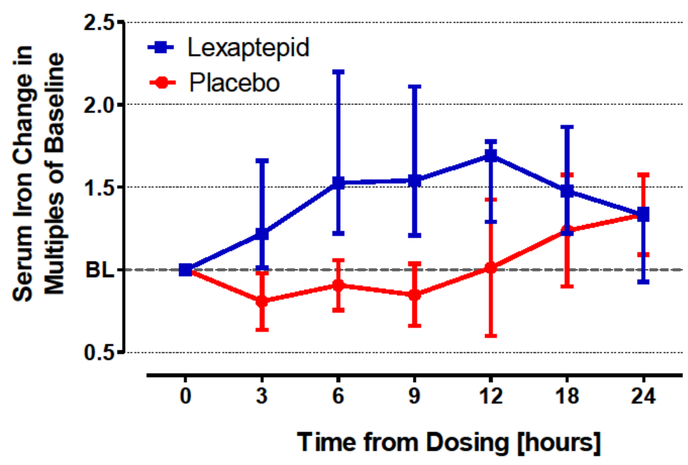
Baseline serum iron levels were similar prior to administration of placebo (7.7±2.5 µM) or lexaptepid (7.4±2.5 µM). Three hours after lexaptepid administration, serum iron started to increase, reaching peak levels at 12 hours with an increase of 69% above baseline; no significant changes were evident following placebo injection (Figure 5). The transferrin saturation showed corresponding changes.

Figure 5: Serum iron changes after single administration of lexaptepid or placebo

A: Individual data and medians



B: Group medians±interquartile range



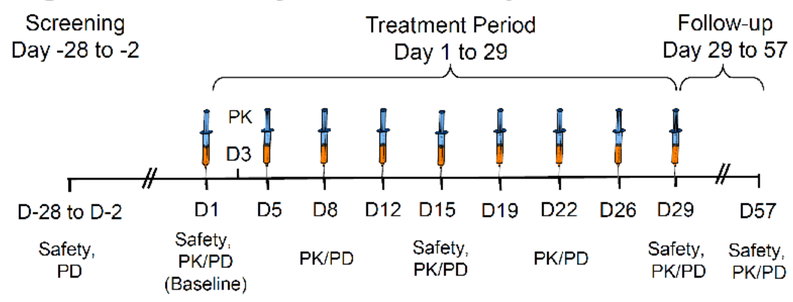
Safety

Treatment with single doses of 1.2 mg/kg lexaptepid was generally well tolerated without treatment-related AEs or other safety concern.

Conclusion

This study is the first to examine an anti-hepcidin strategy in haemodialysis patients. Analysis of single dose PK data with simulation of repeated administrations suggests that repeated administrations to dialysis patients, as scheduled for Part II (Figure 6), will result in similar plasma concentrations as previously observed in healthy subjects and cancer patients. Compared to placebo, there were significant increases in serum iron concentrations following lexaptepid administration, consistent with its anti-hepcidin action. Patient recruitment for the repeated dose part of this clinical study is currently ongoing.

Figure 6: Study outline: multiple dose Part II



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