Clinical Pharmacology, Efficacy, and Safety of the Anti-Hepcidin Spiegelmer® Lexaptepid Pegol (NOX-H94)

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High Hepcidin Causes Anemia of Chronic Disease

Hepcidin levels in patients on hemodialysis and in controls (Zaritsky 2010)

Hemoglobin and Hepcidin levels in patients with Hodgkin’s disease (Hohaus 2010)
Lexaptepid Pegol

- Single-stranded structured L-RNA oligonucleotide with 44 nucleotides
- Conjugation to 40kDa Polyethylene Glycol (PEG)
- Binds and inactivates human hepcidin

[Diagram of secondary structure of lexaptepid pegol (NOX-H94)]

Hepcidin bound to lexaptepid pegol
Three Clinical Trials Completed

Phase I:
Safety, pharmacokinetics, pharmacodynamics in healthy subjects
- Single ascending IV doses
- Repeated ascending IV doses
- Repeted SC doses

Phase I:
Pharmacodynamics in endotoxemia
- PK/PD in endotoxemia (single IV dose)

Phase II:
Proof of concept study in patients with cancer
- Efficacy on anemia of chronic disease (4-week IV treatment)
Pharmacokinetics in Healthy Subjects

Single IV doses

Repeated IV doses

Time from dosing start (days)

Lexaptepid (µM)

0 2 4 6 8 10

0.01
0.1
1
10

Time from dosing (hours)

Lexaptepid (µM)

0 3 6 9 12 15 18 21 24

0.01
0.1
1
10

0.6 mg/kg
1.2 mg/kg
2.4 mg/kg
4.8 mg/kg

0.3 mg/kg
0.6 mg/kg
1.2 mg/kg
2.4 mg/kg
4.8 mg/kg

*: pre-dose (trough-level)
Lexaptepid Increases Serum Iron in Healthy subjects

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Time (hours)</th>
<th>Change in Serum Iron from Baseline (µmol/L)</th>
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<td>D0 pre</td>
<td>-20</td>
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<td></td>
<td>4 pre</td>
<td>-10</td>
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<td>8 pre</td>
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<tr>
<td>5x 0.6 mg</td>
<td>D2 pre</td>
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<td>5x 1.2 mg</td>
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</tbody>
</table>

* Indicates pre-dose

Means±SEM

Time from last dosing (hours)
Lexaptepid Increases Serum Iron in Inflammation

**Graph:**
- **X-axis:** Time from LPS dosing (hours)
- **Y-axis:** Change in serum iron from baseline (µmol/L)
- **Legend:**
  - Lexaptepid 1.2 mg/kg
  - Placebo

**Data Points:**
- **Lexaptepid 1.2 mg/kg**
  - 0 hours: -20 µmol/L
  - 3 hours: +10 µmol/L
  - 6 hours: +20 µmol/L
  - 9 hours: +10 µmol/L
  - 12 hours: +10 µmol/L
  - 24 hours: +10 µmol/L
  - 48 hours: +10 µmol/L
  - 72 hours: +10 µmol/L

- **Placebo**
  - 0 hours: -20 µmol/L
  - 3 hours: -10 µmol/L
  - 6 hours: -10 µmol/L
  - 9 hours: -10 µmol/L
  - 12 hours: -10 µmol/L
  - 24 hours: -10 µmol/L
  - 48 hours: -10 µmol/L
  - 72 hours: -10 µmol/L

**Means±SD**

**Notes:**
- van Eijk et al. EIC Rennes 2012, Blood 2014
Plasma Hepcidin-25

- Analyzed by validated MALDI-TOF in Plasma
- Assay detects the sum of free and bound hepcidin
  - Hepcidin concentrations, bound hepcidin, increase in presence of lexaptepid
  - Production rate independent from lexaptepid dose
- Lexaptepid does not increases hepcidin production but decreases the excretion of bound hepcidin

A: Hepcidin and LXP after single IV dose

B: Hepcidin production rates after LXP ± LPS
Efficacy in Cancer Patients

- Pilot group of 12 patients with multiple myeloma / lymphoma
- Anemia 8.0 - 10.7 g/dL;
- Functional iron deficiency TSAT 6.5-25.2%, Ferritin 193-2800 µg/L

**Basal hepcidin in healthy subjects and patients**

**Hb increase after lexaptepid treatment**

**Individual data, medians**

**Individual data**
Efficacy in Cancer Patients

Reticulocyte hemoglobin

Soluble transferrin receptor

Median ± Range
Safety

- Healthy subjects
  - Only typical phase I adverse events
  - Local reactions after SC injection
  - Mild (<2x ULN) and transient ALT/AST increases at high doses

- Patients
  - No relevant adverse event

- Lexaptepid was safe and well tolerated
Summary and Outlook

Lexaptepid inhibits hepcidin activity in humans

- Pharmacodynamic activity in healthy subjects
- Pharmacodynamic activity in inflammation model

First signs of efficacy in cancer patients with functional iron deficiency

- Supported by pharmacodynamic markers
- Favorable safety profile

- Pilot study in dialysis patients ongoing
Thanks to: Investigators, Colleagues, Subjects, Patients