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The Anti-Hepcidin Spiegelmer® Lexaptepid Pegol (NOX-H94) as Treatment of Anemia of Chronic Disease in Patients with Multiple Myeloma, Low Grade Lymphoma, and CLL: a Phase II pilot Study

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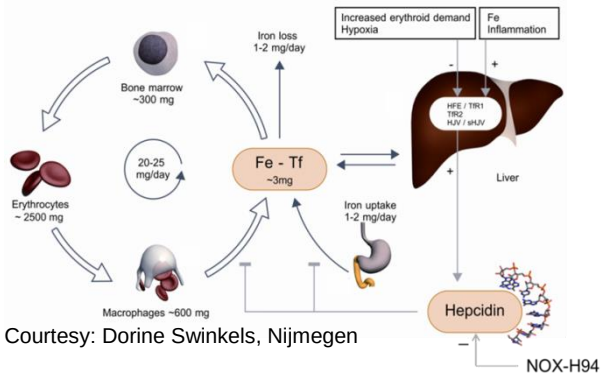
Background

Lexaptepid pegol is a PEGylated L-stereoisomer RNA aptamer that binds and neutralizes hepcidin. Hepcidin, a 25-amino acid peptide induced by inflammatory stimuli, is a pivotal regulator of iron resorption and iron release from intracellular stores. Iron uptake from the gut and iron release from macrophages are severely impaired in anemia of chronic disease (Figure 1). These disturbances in iron metabolism result in functional iron deficiency and are the key contributor to anemia of chronic disease, which frequently complicates malignant disease.

We evaluated the pharmacokinetics, pharmacodynamics, safety and efficacy of hepcidin blockade by lexaptepid pegol as sole treatment of anemia of chronic disease in patients with multiple myeloma, low grade non-Hodgkin lymphoma, or Hodgkin lymphoma.

Figure 1: Hepcidin, Lexaptepid (NOX-H94), and Iron



Courtesy: Dorine Swinkels, Nijmegen

Methods

Twelve patients with functional iron deficiency anemia, defined as Hb <10 g/dL, TSAT <50%, Ferritin >30 µmol/L at screening, were enrolled in this clinical study. Their baseline characteristics are shown in Table 1 as median (range) :

Table 1: Patient Baseline characteristics, median (range)

	Responder	Non-Responder	All Patients
n	5	7	12 (7F, 5M)
Age (years)	61 (41-74)	66 (35-77)	64 (35-77)
Hb (g/dL)	10.1 (8.0-10.2)	9.1 (8.6-10.7)	9.6 (8.0-10.7)
Ferritin (µg/L)	253 (206-2413)	1793 (192-2805)	317 (193-2805)
Iron (µg/dL)	25 (20-32)	31 (18-97)	29 (18-97)
TSAT (%)	19.3 (8.6-21.8)	11.1 (6.5-25.2)	12.3 (6.49-25.2)
MCH (pg)	23.7 (21.8-28.2)	28.8 (23.5-31.3)	26.6 (21.8-31.3)
CHr (pg)	21.8* (21.1-25.0)	30# (25.5-41.1)	25.5 (21.1-41.1)
sTFR (mg/L)	10.6* (8.4-11.0)	6.3# (4.3-6.6)	6.6 (4.3-11.0)
Hepcidin (nM)	8 (6.7-13.8)	21 (4.9-54.5)	12.7 (4.9-54.5)

*: n=3 #: n=4

Nine doses of 1.2 mg/kg lexaptepid pegol were injected twice weekly over 4 weeks (Figure 2).

Blood counts, serum biochemistry, and iron status were evaluated weekly until two weeks post treatment and at week four after the end of therapy.

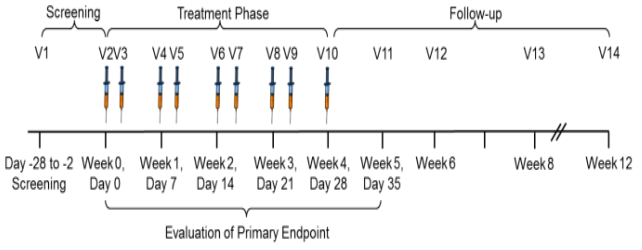
The primary endpoint was the number of treatment responders, defined by:

- Hb increase ≥1 g/dL OR reticulocyte index normalization (≥1%) at any time point until 1 week after the end of treatment

AND absence of the following treatment failure criteria until 1 week after the end of treatment:

- Erythrocyte transfusion, ESA or IV iron,
- Hb drop by ≥1 g/dL
- Treatment interruption due to adverse events

Figure 2: Study design



Results

Five of the 12 patients reached the target Hb increase of ≥1 g/dL and qualified as "responders". Three patients achieved this goal within 2 weeks from start of treatment. Another patient had a normalization of his reticulocyte index but also a Hb drop and therefore did not meet the responder criteria (Figure 3, Table 2).

Figure 3: Hemoglobin - Individual Change from Baseline

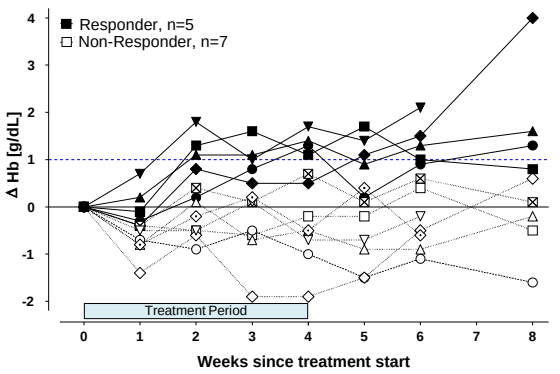
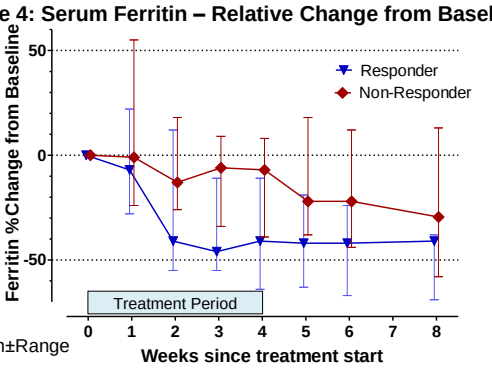


Table 2: Response Parameters and Treatment Response

Pat ID	Ferritin ↓	CHr / MCH ↑	Hb ↑ ≥1g	Ret-Idx norm^{zed}	HB ↓ ≥1g	Max Hb Δ [g/dL]	Rescue Treat^{mt}	Response
B2-2	–	–	–	–	–	< 0	–	–
B3-1	–	–	–	–	✓	< 0	–	–
R3-3	✓	✓	–	✓	✓	< 0	–	–
R3-2	✓	–	–	–	–	0.1	–	–
R4-1	✓	✓	–	–	–	0.1	–	–
R4-12	✓	–	–	–	–	0.4	–	–
B3-2	✓	✓	–	–	–	0.7	–	–
B2-3	✓	✓	✓	–	–	1.1	–	✓
B2-6	✓	–	✓	✓	–	1.3	–	✓
R3-1	✓	✓	✓	–	–	1.4	–	✓
R7-4	✓	✓	✓	✓	–	1.7	–	✓
R4-2	✓	✓	✓	✓	–	1.8	–	✓
Overall	10 / 12	7 / 12	5 / 12	4 / 12	2 / 12	n/a	0 / 12	5 / 12

Four of the 5 responding patients had hypochromic red cells (MCH 22-26 pg) and moderately increased baseline ferritin levels (200-350 µg/L). Median serum ferritin decreased from 317 to 232 µg/L (p=0.014) in the entire cohort of patients, and from 253 to 203 µg/L in responders. At baseline, serum ferritin levels were lower in subsequent responders and, as shown in Figure 4, had a more pronounced decrease in responders (-41%) compared to non-responders (-7%).

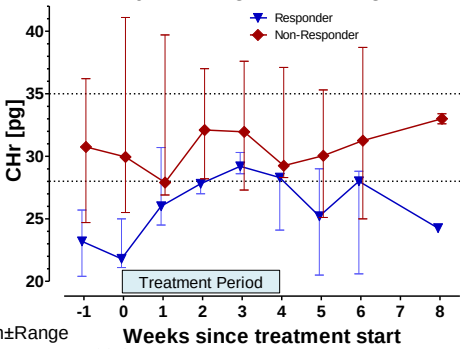
Figure 4: Serum Ferritin – Relative Change from Baseline



Median±Range

From baseline to end of treatment, the median reticulocyte hemoglobin (CHr) increased from 21.8 pg to 28.3 pg in responding patients, while in non-responders, who presented with CHr levels within the normal range, no increase was noted (Figure 5).

Figure 5: Reticulocyte Hemoglobin - Change from Baseline

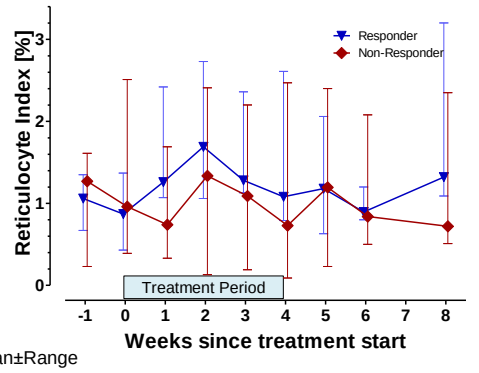


Median±Range
Reference range: 28-35 pg

Results (cont.)

Similarly, a tendency towards increased reticulocyte indices was observed only in the responding patients during the treatment period, with an increase of the median reticulocyte index from 0.9% up to 1.7% after 2 weeks of treatment. At the end of treatment the median reticulocyte index returned to 1.1% (Figure 6).

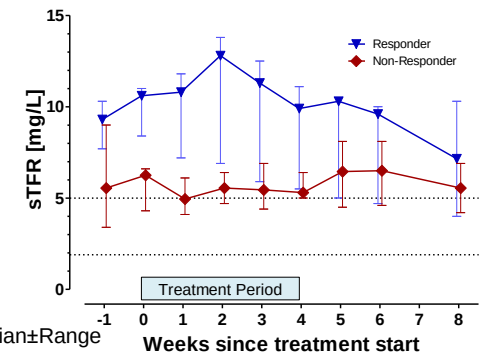
Figure 6: Reticulocyte Index



Median±Range

Soluble transferrin receptor (sTfR) levels were measured only for the 7 patients from Romania in a central laboratory. At baseline, sTFR was higher in the 3 responders than in the 4 non-responders. In responders it tended to decrease during the study period, while it remained unchanged in non-responders (Figure 7).

Figure 7: Soluble Transferrin Receptor



Median±Range

Baseline hepcidin concentrations of 12.7 nM (4.9-54.5) were increased in patients in comparison to those obtained in healthy subjects enrolled in previous clinical trials (1.78 nM, 0.37-7.26). Patients with mean corpuscular volume (MCV) or Chr baseline levels below the lower limit of the normal range (MCV < 82fL, Chr < 28pg) represent 75% of the responders, respectively, and all patients with high baseline sTfR levels (> 8 mg/L) reached the primary endpoint. Treatment with Lexaptepid was well tolerated without major adverse reactions.

Conclusions

Within a treatment period of 4 weeks, treatment with Lexaptepid resulted in a clinically meaningful hemoglobin increase of ≥1 g/dL in 5 of 12 patients. These results support the strategy of hepcidin inhibition as pharmacologic concept for treatment of chronic anemia of chronic disease in cancer patients. Responding patients also exhibited an increase in reticulocyte hemoglobin.

Disclosures

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