#2904

DXO-1801, A LIVER-TARGETED siRNA, ATTENUATES INFLAMMATION-DRIVEN IRON RESTRICTION AND ENHANCES ERYTHROPOIESIS IN NON-HUMAN PRIMATES

N. Madar-Balakirski[1], K. Moss[1], E. Weyl[1], N. Marbach-Bar[1], O. Penn[1], A. Laxer[1], L. Steiner[1], Y. Garbian[1], G. Yosef-Goldshtein[1], S. Sela[1] and E. Feinstein[1]

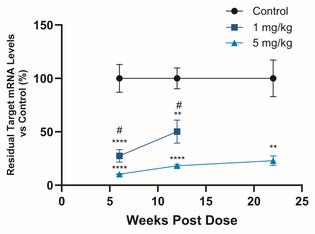
1. Dexoligo Therapeutics, Tel Aviv, Israel

INTRODUCTION

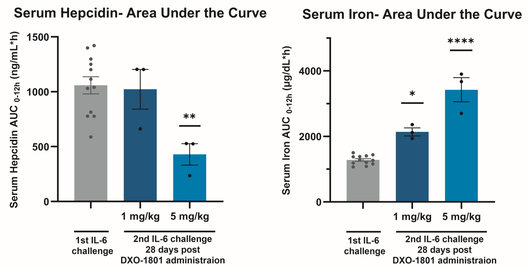
Anemia of inflammatory disease (AID) is a serious complication of chronic conditions[1] such as inflammatory bowel and autoimmune diseases, chronic kidney disease, advanced solid tumors and hematological malignancies (such as myelofibrosis[2]). AID is driven by elevated pro-inflammatory cytokines (e.g., IL-6) that trigger an increase in hepcidin levels. High hepcidin limits iron availability for erythropoiesis, by reducing dietary iron absorption and restricting its mobilization from tissue stores. Hepcidin is primarily produced by hepatocytes and is regulated by both inflammatory and iron-sensing pathways. The importance of hepcidin is further demonstrated in the context of genetic iron overload disorders such as hereditary hemochromatosis[3].Targeting hepcidin pathway is a valid therapeutic strategy for treating AID due to its pivotal role in regulating systemic iron homeostasis.

DXO-1801 is a first-in-class, fully chemically stabilized, liver targeted GalNAc-conjugated siRNA, silencing the expression of one of the key genes in the hepcidin-regulatory pathway in hepatocytes. Significant, dose dependent and sustained reduction in target gene mRNA has already been demonstrated in humanized liver mice (uPA-SCID PXB).

RESULTS



DXO-1801 SC single administration in NHP induced robust, dose-dependent and durable target mRNA knockdown.



The **first IL-6 challenge** (14 days prior to DXO-1801 administration) induced an acute hepcidin surge and deep hypoferremia.

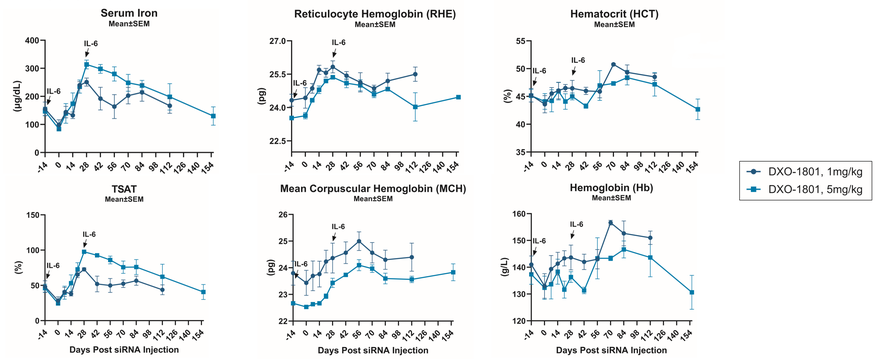
After the **second IL-6 challenge** (28 days post DXO-1801 administration), serum hepcidin increase was significantly reduced. Accordingly, the resulting hypoferremia was significantly and dose dependently attenuated.

DXO-1801 Efficacy

- **Serum hepcidin** declined markedly by week 3 and remained suppressed for over 8 weeks.
- Corresponding increases in **serum iron** and **transferrin saturation (TSAT)** (2–3 fold) peaked at week 4 and remained elevated through week 16.
- Early increases in **reticulocyte hemoglobin** and **mean corpuscular hemoglobin** were followed by elevations in **hematocrit and hemoglobin**.

DXO-1801 Safety

- Treatment was well tolerated at all dose levels.
- No complement activation, cytokine elevation or coagulation abnormalities were observed.
- Transient and minor post-dose liver enzyme elevation was seen at the super-pharmacologic dose (300mg/kg), consistent with a class effect.



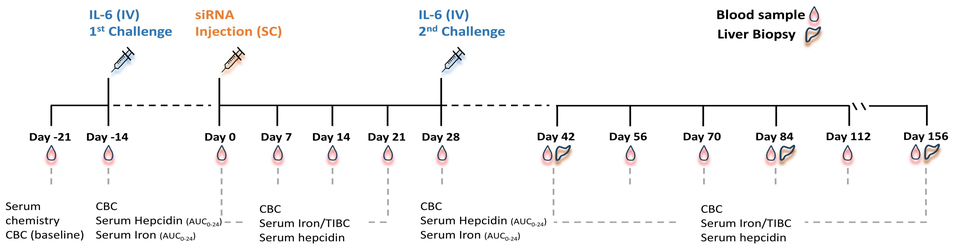
OBJECTIVES AND STUDY DESIGN

DXO-1801 evaluation in non-human primates (NHP):

Study Objectives

1. To evaluate DXO-1801 pharmacodynamic (PD) effect in non-human primates
2. To assess the impact of DXO-1801 on PD markers of the anemia induced by acute inflammation associated with the administration of IL-6

Methods: Animals (n=3 per group) received a single subcutaneous (SC) dose of DXO-1801 (1 or 5 mg/kg) and were followed for up to 12 (1mg/kg) and 22 weeks (5mg/kg and control). To model inflammation-driven anemia, animals were challenged with intravenous (IV) IL-6[4], 14 days before and 28 days after DXO-1801 administration.



CONCLUSIONS

- Doses as low as 1 or 5 mg/kg durably and deeply suppressed the target gene mRNA expression in the liver, leading to modulation of the hepcidin-iron axis that resulted in enhanced iron availability and improved erythropoiesis.
- Under acute inflammatory conditions associated with IL-6 dosing, DXO-1801 effectively attenuated the inflammation induced hypoferremia in a dose dependent manner.
- SC DXO-1801 treatment was well tolerated up to the highest tested dose of 300 mg/kg.
- These observations support DXO-1801 therapeutic potential for treating anemia of inflammatory disease. Further preclinical studies are ongoing in support of planned first in human study.

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CONTACT INFORMATION

Keren Moss, MD, Clinical Development Head, Dexoligo Therapeutics, keren.moss@dexoligo.com