# DXO-1801, a Hepatocyte-Targeted GalNAc-siRNA, Demonstrates Hepcidin Pathway Modulation, Iron Mobilization, and a Favorable Safety Profile in Non-Human Primates


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1. Dexoligo Therapeutics by Dexcel Pharma, Tel Aviv, Israel



EHA2026 Congress

June 11-14 Stockholm, Sweden


## INTRODUCTION

**Iron-restricted anemia** is a common complication of chronic inflammatory conditions, collectively termed anemia of inflammatory disease (AID), including inflammatory bowel and autoimmune diseases, chronic kidney disease, advanced solid tumors, and hematologic malignancies such as myelofibrosis[1,2]. AID is driven by pro-inflammatory cytokines that induce hepatic production of hepcidin, the central regulator of systemic iron homeostasis. Elevated hepcidin limits iron absorption and mobilization from tissue stores, thereby restricting iron availability for erythropoiesis. Consequently, hepcidin represents a key therapeutic target for inflammation-driven anemia.

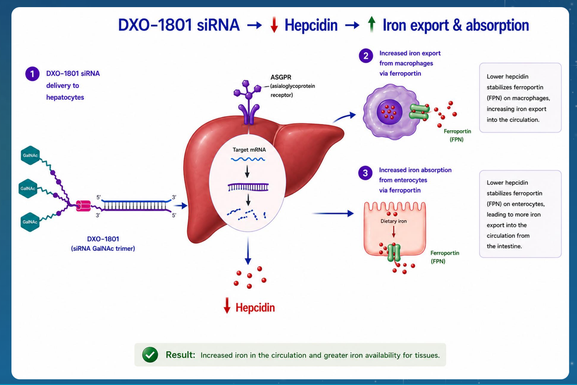
**DXO-1801** is a fully chemically stabilized, hepatocyte-targeted GalNAc-siRNA designed to silence a key gene in the hepcidin regulatory pathway, enabling precise and durable modulation of iron metabolism. In preclinical studies, DXO-1801 demonstrated robust, dose-dependent target knockdown in humanized liver (PXB) mice. In a non-human primate (NHP) interleukin-6 (IL-6) challenge model, DXO-1801 attenuated inflammation-induced hepcidin elevation and reduced hypoferremia in a durable, dose-dependent manner[3], supporting its potential as a novel therapeutic approach for AID.

### AIM

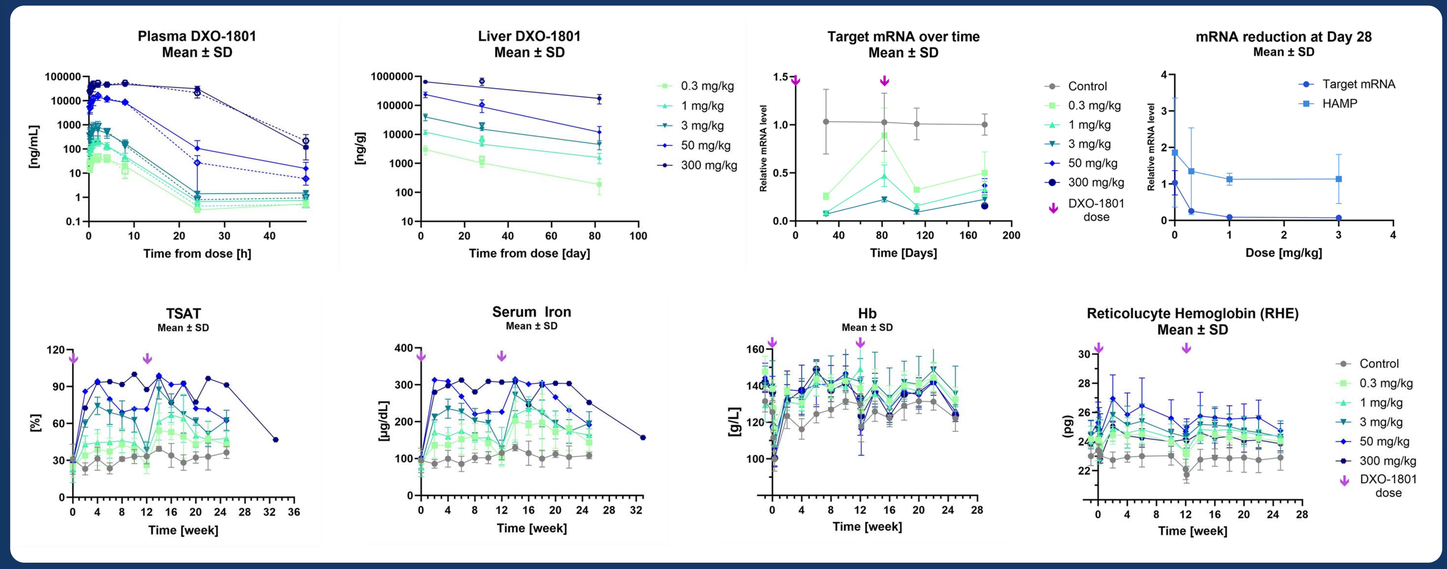
To characterize the pharmacokinetics (PK), dose–response relationship, durability, liver biodistribution, and safety of DXO-1801 in NHPs.

### METHOD

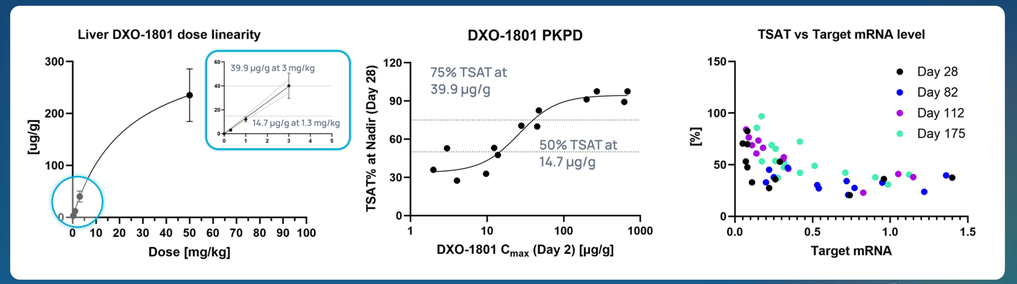
Healthy male cynomolgus monkeys received DXO-1801 at pharmacologically- (0.3, 1 or 3 mg/kg, n=3 per group) or at toxicologically relevant dose levels (50 or 300 mg/kg, n=2 per group)
via a subcutaneous (SC) injection on Study Days 0 and 84. Plasma PK, circulating hepcidin and iron parameters (including serum iron and transferrin saturation), hematology, clinical chemistry, coagulation, serum cytokines and complement activation biomarkers were assessed. Liver samples collected at selected time points were used to assess siRNA quantification, target gene knockdown (KD), and histopathology.




## RESULTS




Following SC administration, DXO-1801 exhibited rapid plasma clearance with preferential hepatic biodistribution, consistent with hepatocyte-targeted delivery. Suppression of the hepcidin pathway resulted in dose-dependent increases in serum iron and transferrin saturation (TSAT), indicating effective mobilization of iron. The dose– and concentration–response PK and PD (Emax) modeling of data demonstrated a clear and saturable plateau, enabling identification of the optimal dose required to achieve maximal PD and iron-related benefit.
DXO-1801 was well tolerated across the evaluated dose range. No changes were observed in cytokine levels, complement activation, or coagulation parameters. Transient, dose-dependent mild elevations of liver enzymes were detected shortly after dosing at ≥50 mg/kg, consistent with known siRNA class effect. No evidence of treatment-related liver injury or adverse hepatic iron accumulation was apparent by histopathology examination.




## CONCLUSIONS

In NHPs, DXO-1801 demonstrated durable and precise suppression of the hepcidin regulatory pathway, maintained for at least 3 months following a single dose. Treatment was associated with iron mobilization and improvements in hematological parameters.
DXO-1801 was well tolerated across a wide dose range, providing a >100-fold dose margin between the pharmacologically active dose and the highest evaluated, dose (300 mg/kg).These findings support the potential for infrequent dosing, predictable exposure–response relationship and favorable therapeutic index in future clinical studies.

## REFERENCES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