The FORCE™ Platform Does Not Cause Anemia in Repeat-Dose Toxicity Studies in Cynomolgus Monkeys

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BACKGROUND

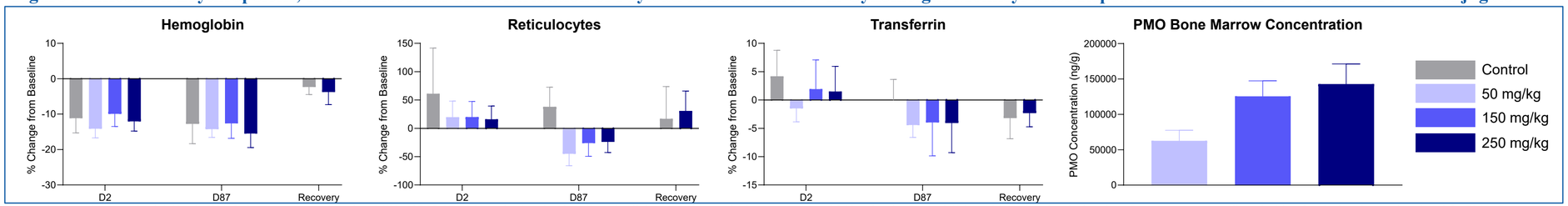
Oligonucleotides (ONTs) are a class of promising therapeutics for the treatment of genetic neuromuscular diseases. However, achieving efficacious concentrations in muscles and central nervous system (CNS) has hindered progress to success in the clinic. To overcome this limitation, we developed the FORCE platform, which consists of an antigen-binding fragment (Fab) highly specific for the human transferrin receptor 1 (TfR1), to which ONT payloads can be conjugated via a cleavable valine-citrulline linker. The FORCE platform is modular and can be conjugated to either neutral or charged ONTs to address the genetic defect. TfR1 plays an important role in iron uptake and erythropoiesis, and anemia has been reported nonclinically and clinically for biologics that leverage TfR1 to enable therapeutic delivery of payloads to muscle and CNS. In contrast, the FORCE platform was designed to avoid interference with iron uptake and its impact on anemia was tested in cynomolgus monkeys.

DESIGN OF TOXICITY STUDIES

Group	Dose (mg/kg)	Dose Frequency	Terminal	8W Recovery
			No. Monkeys	
Study 1: FORCE-Phosphorodiamidate Morpholino				
Vehicle	0	Q4W	6 (M)	4 (M)
Low	50	Q4W	6 (M)	-
Mid	150	Q4W	6 (M)	-
High	250	Q4W	6 (M)	4 (M)
Study 2: FORCE-Antisense Oligonucleotide				
Vehicle	0	Q3W	4/4 (M/F)	2/2 (M/F)
Low	50	Q3W	4/4 (M/F)	-
Mid	200	Q3W	4/4 (M/F)	-
High	356	Q3W	4/4 (M/F)	2/2 (M/F)
Study 3: FORCE-small interfering RNA				
Vehicle	0	Q4W	4/4 (M/F)	2/2 (M/F)
Low	32	Q4W	4/4 (M/F)	-
Mid	160	Q4W	4/4 (M/F)	-
High	288	Q4W	4/4 (M/F)	2/2 (M/F)

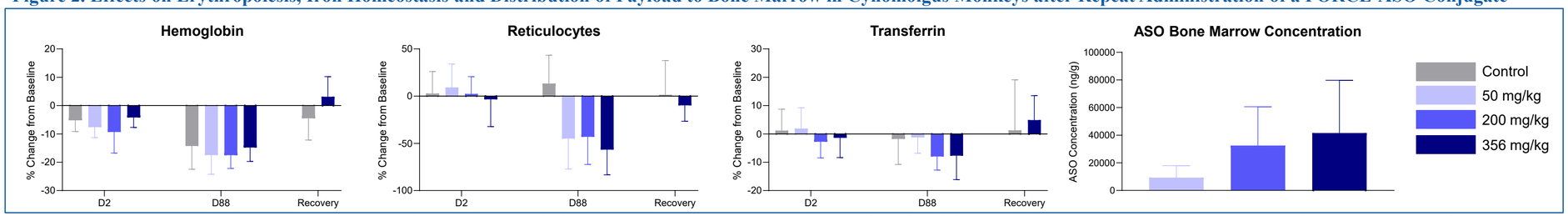
RESULTS

Figure 1. Effects on Erythropoiesis, Iron Homeostasis and Distribution of Payload to Bone Marrow in Cynomolgus Monkeys after Repeat Administration of a FORCE-PMO Conjugate



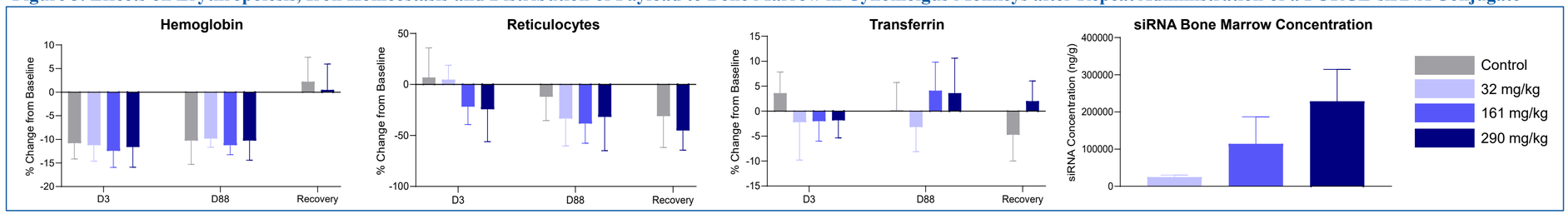
Cynomolgus monkeys received 4 60-min IV infusions once every 4 weeks (Q4W) of FORCE-PMO at the dose levels indicated. Clinical pathology endpoints were assessed 24 hr after the first and 48 hr and 8 weeks after the last dose. Bone marrow was collected 48 hr after the last dose and analyzed for PMO. Data are shown as mean ± S.D. PMO = phosphorodiamidate morpholino.

Figure 2. Effects on Erythropoiesis, Iron Homeostasis and Distribution of Payload to Bone Marrow in Cynomolgus Monkeys after Repeat Administration of a FORCE-ASO Conjugate



Cynomolgus monkeys received 5 60-min IV infusions once every 3 weeks (Q3W) of FORCE-ASO at the dose levels indicated. Clinical pathology endpoints were assessed 24 hr after the first and 72 hr and 8 weeks after the last dose. Bone marrow was collected 48 hr after the last dose and analyzed for ASO. Data are shown as mean ± S.D. ASO = antisense oligonucleotide.

Figure 3. Effects on Erythropoiesis, Iron Homeostasis and Distribution of Payload to Bone Marrow in Cynomolgus Monkeys after Repeat Administration of a FORCE-siRNA Conjugate



Cynomolgus monkeys received 5 60-min IV infusions once every 4 weeks (Q4W) of FORCE-siRNA at the dose levels indicated. Clinical pathology endpoints were assessed 48 hr after the first and 72 hr and 8 weeks after the last dose. Bone marrow was collected 72 hr after the last dose and analyzed for siRNA. Data are shown as mean ± S.D. siRNA = small interfering RNA.

CONCLUSIONS

Administration of FORCE conjugates to monkeys was well-tolerated

- Exposure of bone marrow to each payload increased in a dose-responsive manner
- There was no evidence of bone marrow toxicity at any dose level across the 3 studies

Administration of FORCE conjugates to monkeys does not result in anemia

- Reticulocytes were transiently decreased 24-72 hrs after administration of either FORCE-PMO or FORCE-ASO but not FORCE-siRNA
- Hemoglobin and other red cell parameters are unchanged
- Transferrin was unchanged indicating a lack of effect on iron metabolism

DISCLOSURE INFORMATION

All authors are employees or advisors of Dyne Therapeutics Inc. and may hold Dyne stock and/or stock options.

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