**ABSTRACT**

Facioscapulohumeral muscular dystrophy (FSHD) affects 800,000 globally with no cure available, current therapies only manage symptoms. Disease-causing DUX4 protein expression is encoded in the distal region of the D4Z4 chromosome from D4Z4 microsatellite array, which is hypomethylated in FSHD leading to DUX4 expression. At Epic Bio, we leveraged our proprietary GEMS platform to develop EPI-321, a treatment for FSHD that targets the D4Z4 epigenome and suppresses DUX4 expression. EPI-321 demonstrated dose-dependent re-methylation of the target sequence in vitro and in vivo allowing it to be packaged it into AAVrh74 vectors. In order to minimize the size of the payload, EPI-321 utilizes a proprietary GEMS screening platform identifying highly efficient effector-modulator pairs. EPI-321 shows no off-target robust delivery and expression in the humanized FSHD model in vivo, and no signs of toxicity or adverse events in non-GLP safety studies. EPI-321 is a promising gene therapy for FSHD that targets the D4Z4 epigenome and suppresses DUX4 expression for disease-modifying effect in patients with FSHD. **EPI-321: A Promising Gene Therapy for Facioscapulohumeral Muscular Dystrophy (FSHD) Targeting D4Z4 Epigenome**

**EPI-321 Represses DUX4 & Downstream Genes, and Rescues Apoptosis in FSHD Myoblasts Without Affecting Myogenic Genes**

**EPI-321 Overcomes the Limitations of Genetic Medicine**

**EPI-321 Represses DUX4 Expression through Re-methylation of D4Z4**

**EPI-321 Improves FSHD Muscle Cell Survival and Suppresses DUX4 In Humanized Mice**

**EPI-321 Shows No Signs of Toxicity or Adverse Events in Non-GLP Immunocompetent Mice and NHP Studies**

**EPI-321 Biodistribution in NHP Shows High Skeletal Muscle Expression**

**CONCLUSION**

Epic Bio’s GEMS screening platform identifies highly efficient effector-modulator combination suitable for treating genetic disease with unmet need like FSHD. EPI-321 is a compact AAV product that utilizes hypercompact nucleoside-dead Cas 9 molecule and modulates endogenous gene through methylation of target sequence in vivo. EPI-321 represses DUX4 target locus and decreases expression of downstream DUX4-pathway genes expression both in vitro FSHD patient derived myoblasts and in humanized mouse model. EPI-321 also rescues the apoptosis level in vitro in patient derived myoblast and improve FSHD myoblasts survival in humanized mouse model in vivo. EPI-321 has high skeletal muscle expression in NHP and shows peak blood DNA concentrations at 15 days (High Dose) and 41 days (Low dose) following i.v. administration.

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