# Preclinical Studies with HMI-104, an AAVHSC Vectorized C5 Monoclonal Antibody, for the Treatment of Paroxysmal Nocturnal Hemoglobinuria


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Abstract # 386

**AAVHSC GTx-mAb Therapy Targeting Complement Mediated Disorders**

- Adeno-associated virus (AAV) gene therapy has the potential to offer a long-term resolution for diseases that rely on chronic dosing of therapies such as monoclonal antibody (mAb)-based drugs.
- GTx-mAb platform is an extension of our gene therapy approach that aims to provide systemic and sustained levels of a therapeutic mAb with one-time intravenous (I.V.) dosing.
- Previously, we showed that GTx-mAb platform constructs achieved dose-dependent and sustained expression of a functional C5 monoclonal antibody (C5mAb) in NOD SCID mice, and humanized liver FRG® mice, supporting the use of a vectored approach for diseases relying on chronic anti-C5 dosing, such as Paroxysmal Nocturnal Hemoglobinuria (PNH).

**PNH is a Rare, Acquired, Life-Threatening Blood Disease Treatable with Complement Inhibitors**

- PNH is caused by acquired PIgma mutations in hematopoietic stem cells, leading to loss of surface expression of complement regulators.
- Blood cells derived from mutant PNH clones expand and are vulnerable to complement-induced hemolysis, leading to major complications such as anemia, thrombosis and bone marrow failure.
- Life expectancy in untreated PNH patients is 10-15 years after diagnosis.
- Treatment of PNH relies on chronic intravenous (I.V.) dosing of anti-C5 mAbs (eculizumab or ravulizumab every 2 or 8 weeks, respectively), or twice-a-week subcutaneous dosing of an anti-C3 inhibitor (pegcetacoplan).

**HMI-104 is a Single Dose GTx-mAb that Expresses a Vectorized Monoclonal Antibody Against C5 for the Treatment of PNH**

- HMI-104 is an AAVHSC vector and our developmental GTx-mAb candidate designed to elicit hepatic expression of a C5mAb for the treatment of PNH and alleviate the dependency on chronic dosing of anti-C5 therapeutics.
- HMI-104 is developed via a single (I.V.) injection and the expression of functional C5mAb levels in NOD SCID and humanized liver FRG® KO mice. These results support the use of vectorized approaches for diseases relying on chronic anti-C5 dosing.

**Nonclinical Studies with HMI-104**

- HMI-104 is an AAVHSC GTx-mAb platform construct that achieved dose-dependent and sustained expression of functional C5mAbs in NOD SCID and humanized liver FRG® KO mice.
- HMI-104 is developed via a single (I.V.) injection and the expression of functional C5mAbs in NOD SCID and humanized liver FRG® KO mice.

**Results**

- Dose-dependent changes in Vg in purified human hepatocytes were dose dependent.
- Vector genomes in purified human hepatocytes were dose dependent.
- Antibody levels in treated NOD SCID KO mice were greater than or equal to those obtained at steady state in the NOD SCID mouse model.

**References:**


**Conclusions**

In conclusion, we present nonclinical data with HMI-104 demonstrating sustained expression of functional C5mAb levels in NOD SCID and humanized liver FRG® KO mice. These results support the development of HMI-104, which is currently in IND-enabling studies, for the treatment of PNH and complement-mediated disorders.