No Evidence of Thrombocytopenia or Pro-inflammatory Effects

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Abstract

Thrombocytopenia and pro-inflammatory effects, including cytokine production, are commonly associated with nucleic acid-based therapeutics in a number of preclinical species and with clinical exposure to fully PS single-stranded antisense oligonucleotides. These effects are recapitulated with similarly designed GalNAc-siRNA conjugates (TTR-siRNA), which are being developed for the treatment of chronic HBV and CC5 liver diseases. Preclinical toxicology studies were conducted in SD male rats, SD female rats, NHP, and C57BL/6 female mice to evaluate the potential for thrombocytopenia or pro-inflammatory effects. No doses were toxic, and all doses were well tolerated.

Introduction

Thrombocytopenia and pro-inflammatory effects are commonly associated with nucleic acid-based therapeutics in a number of preclinical species and with clinical exposure to fully PS single-stranded antisense oligonucleotides. These effects are recapitulated with similarly designed GalNAc-siRNA conjugates (TTR-siRNA), which are being developed for the treatment of chronic HBV and CC5 liver diseases. Preclinical toxicology studies were conducted in SD male rats, SD female rats, NHP, and C57BL/6 female mice to evaluate the potential for thrombocytopenia or pro-inflammatory effects. No doses were toxic, and all doses were well tolerated.

No Evidence of Thrombocytopenia in Rats or NHPs Across Programs

No Platform-Wide Effects on Neutrophil Counts

No Evidence of Pro-inflammatory Effect in Spleen Weight

No Test Article-Related Effects on Serum Cytokines in NHP 4 or 24 Hours Post-Dose

No Test Article-Related Effects on Plasma Complement (Bb and C3a) Concentrations

No Platelet-Wide Effects on Plasma Complement (Bs and Cls) Concentrations

No Evidence of Immune-Mediated Glomerulopathy With siRNA Treatment

Summary

Eight high PS GalNAc-siRNA conjugates were evaluated in nonclinical and preclinical studies to assess the potential for immune-related glomerulopathy in either the liver or kidney.

References

No agreement on the need to develop a fully PS single-stranded antisense oligonucleotide targeting the liver-specific transcription factor TTR, enabling improved pharmacokinetics and improved efficacy.

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