Objective: Evaluate the stability of non-human primate pharmacokinetic and safety data of MRG-106, a phosphorothioate (PS) antimiR-105/106 antisense oligonucleotide, using intravenous bolus injections as the route of administration to patients in a cutaneous T cell lymphoma (CTCL) Phase I clinical trial.

Methods: The samples were analyzed by liquid chromatography with tandem mass spectrometry detection. Safety was monitored by physical exams, clinical laboratory tests, and clinical observations and assessment of adverse events in non-human primates and clinical trial participants.

Results: Preclinical studies in non-human primates (NHPs) were conducted to assess the pharmacokinetics (PK) and safety of a 30 mg/kg dose of MRG-106 administered subcutaneously (SC) injection, 2-hour IV infusion, or 1-minute IV bolus injection. All three routes of administration were well tolerated and not associated with any clinical safety concerns. The plasma drug Clearing Half-life in NHPs was 29.7 ± 12.1 hours following IV bolus injection. In the first clinical trial cohort, the previously reported thresholds of plasma concentrations (50-70 µg/mL) are not achieved with MRG-106 dosing in NHPs.

Abstract

Non Human Primate Pharmacokinetic Comparison of a Single 30 mg/kg IV Bolus, IV Infusion, or Subcutaneous Dose of MRG-106

- B-phase (or in-phase) plasma concentration vs time curves with short distribution phase followed by prolonged elimination phase
- Long terminal elimination half-life, representative of residual tissue elimination half-life
- High percent bioavailability AeUC(max)/Fmax=100%

Non Human Primate Safety Data: Single 30 mg/kg Subcutaneous or IV Bolus Dose

- IV bolus and subcutaneous injections were well tolerated in non-human primates.
- Transient increases of AST (1.0-1.4-fold), ALT (1.2-2.9-fold), CK (1.34-8.78-fold) and CRP (0.93-3.70-fold). No patients did not experience these transient effects.
- Clinical pathology findings were similar for the IV bolus and subcutaneous dosing groups. Increased ALT following IV bolus injection did not correlate with these transient effects.

Conclusions

- MRG-106 is well tolerated when administered via subcutaneous injection, intravenous infusion, or intravenous bolus injection in human subjects.
- Maximum achieved Cmax in human subjects is 63 µg/mL (IV Bolus).
- MRG-106 displays linear kinetics, with dose proportional increases in Cmax and AUC across dose groups.
- No adverse events on coagulation, complement activation, or clinical chemistry parameters were observed as a result of IV bolus dosing at 30 mg/kg.

References


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Disclosure

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