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Safety and Tolerability Study of an Intravenously Administered Small Interfering Ribonucleic Acid (siRNA) Post On-Pump Cardiothoracic Surgery in Patients at Risk of Acute Kidney Injury

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Introduction: Patients undergoing on-pump cardiac surgery are at an increased risk of acute kidney injury. QPI-1002, a small interfering ribonucleic acid, is under clinical development for the prevention of acute kidney injury. The safety, tolerability, and pharmacokinetics of QPI-1002 was evaluated in this first-in-man, Phase 1 study of a small, interfering ribonucleic acid in patients at risk of acute kidney injury after on-pump cardiac surgery.

Methods: In this phase 1 randomized, placebo-controlled dose-escalation study, a single i.v. dose of QPI-1002 was administered in subjects undergoing on-pump cardiac surgery. Subjects received placebo ($n = 4$), or QPI-1002 in increasing doses of 0.5 mg/kg ($n = 3$), 1.5 mg/kg ($n = 3$), 5 mg/kg ($n = 3$), and 10 mg/kg ($n = 3$).

Results: A total of 16 subjects were enrolled in the study. The average maximum concentration and area under the curve from the time of dosing to the last measurable concentration of QPI-1002 were generally dose proportional, indicating that exposure increased with increasing dose. The average mean residence time (mean residence time to the last measurable concentration) was 10 to 13 minutes in all 4 drug-dosing cohorts. Adverse events occurred at a similar rate in all study groups. Of the total 109 reported adverse events, the events were distributed as 26 in the placebo group and 21, 19, 24, and 19 in the QPI-1002 0.5, 1.5, 5.0, and 10.0 mg/kg groups, respectively. Eight of the 16 subjects experienced at least 1 serious adverse event: 4 (100%) in the placebo group and 4 (33.3%) in the combined QPI-1002 cohorts.

Discussion: QPI-1002 was rapidly eliminated from plasma. QPI-1002 was safe and well tolerated across all dose groups. Overall, no dose-limiting toxicities or safety signals were observed in the study. Further development of QPI-1002 for prophylaxis of acute kidney injury is warranted.

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Acute kidney injury (AKI) is a clinical syndrome characterized by deterioration of renal function that rapidly develops over hours to days. AKI complicates a significant proportion of hospital admissions and is associated with an increased risk of chronic kidney disease, major adverse cardiovascular events, increased length of hospital stay, and additional health care costs and mortality.[1–3] Despite recent advances in surgical techniques, the incidence of AKI remains high, ranging from 33% to 55%.[3]

Current attempts to treat AKI remain largely supportive, including the adjustment of medications, appropriate nutritional support, correcting volume

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status, electrolyte imbalance, and acidosis,[4] with or without renal replacement therapy. At present, there are no approved therapeutic agents available for the prevention or treatment of AKI.

QPI-1002 (active ingredient: I5NP), a small, interfering ribonucleic acid, is a synthetic, nuclease-resistant, double-stranded RNA oligonucleotide designed to temporarily inhibit the expression of the proapoptotic gene *p53* via activation of the RNA interference pathway. The rat analogue of QPI-1002, QM5, was shown to temporarily (<24 hours) suppress p53 protein-mediated apoptosis resulting from ischemia-reperfusion injury (IRI).[5] Inhibition of p53 in several preclinical models of ischemia-reperfusion injury demonstrated improved renal function post-injury and improved histology.[5] Small, interfering RNA inhibition of p53 may work by providing additional time during which nonlethal injury to renal tubular epithelial cells can be repaired before initiation of apoptosis.[6]

The objective of this study was to evaluate the safety, tolerability, and pharmacokinetics of QPI-1002 in this first in human study in patients at risk of the development of AKI while undergoing on-pump cardiac surgery.

MATERIALS AND METHODS

QRK-002 was a phase 1, double-blind randomized, placebo-controlled, dose-escalation study to evaluate the safety and tolerability of a single i.v. bolus injection of QPI-1002 to subjects scheduled to undergo nonemergent, on-pump cardiac surgery at 6 centers globally. Patients were eligible if they were 21 to 85 years of age and up-to-date on screening negative for cancer. Patients were excluded if their postoperative Cleveland Clinic Foundation AKI cumulative risk score was >8, they had received an organ transplant, they were receiving immunosuppressive therapy, or they were women of childbearing potential.

The randomization was performed manually via a centralized randomization system by unblinded Quark personnel, per the QRK.002 Pharmacy Manual and Patient Enrollment Guidelines, using the enrollment form. In each QPI-1002 dosing cohort, the first subject was dosed as single, followed by double-blind, placebo-controlled enrollment.

For each dose level, patients were allocated 3:1 to receive a single i.v. bolus injection of QPI-1002 in doses of 0.5, 1.5, 5.0, or 10.0 mg/kg or placebo (isotonic saline) at 4 ± 0.5 hours after discontinuation of cardiopulmonary bypass. The study protocol and informed consent were reviewed and approved by institutional review board or an independent ethics committee at each site. The study was conducted in accordance with the International Conference on Harmonization guidance on Good Clinical Practice based on the Declaration of Helsinki.

Pharmacokinetic plasma samples were collected just before administration of the study drug (QPI-1002 or placebo) and at 5, 15, and 30 minutes and 1, 2, 4, 8, and 24 hours post-dose. In addition to drug concentrations, these samples were also analyzed for complement activation products (Bb, C3a, C4a, and C5a) to monitor for the development of this previously described class effect, reported for the related, but structurally modified, phosphorothioate-substituted single-stranded oligodeoxyribonucleotides.[7,8] Baseline samples for complement activation were taken before surgery. Blood samples drawn into commercially available K_2-ethylenediamine tetraacetic acid–containing Vacutainer tubes (Becton, Dickinson and Company, Franklin Lakes, NJ) and were cold-centrifuged within 30 minutes of phlebotomy, and the plasma was frozen at −70 °C pending shipment on dry ice to a central laboratory (National Jewish Laboratory, Denver CO) for complement activation analyses and to Charles River Laboratories (Senneville, Quebec, Canada) for determination of QPI-1002 (I5NP) concentrations.

Additional blood and urine samples were collected at screening and postoperatively for routine determination of serum chemistry and hematology analytes, indices of coagulation, and measures of renal (blood urea nitrogen, serum creatinine), hepatic (aspartate transaminase, alanine transaminase, alkaline phosphatase, and total bilirubin), and pancreatic (serum amylase and lipase) function.

The QPI-1002 pharmacokinetic profile for each subject was evaluated by noncompartmental analysis of I5NP plasma data using commercially available computer software (WinNonlin Professional, version 5.3, Pharsight Corp., Mountain View, CA). Values below the limit of quantitation were treated as "missing." The area under the QPI-1002 plasma concentration versus time curve from time zero to the last quantifiable plasma concentration (AUC_{last}) was calculated using the linear trapezoidal method (linear interpolation). Other values determined, where possible, included maximum concentration (C_{max}), clearance (Cl), elimination half-life ($T_{1/2}$), Vss, AUC_{last} extrapolated to infinite time ($AUC_{0-\infty}$), and the mean residence time over the interval from time zero to the last quantifiable time point mean residence time (MRT_{last}).

Treatment emergent adverse events were defined as any adverse events occurring at any time from study drug administration through day 7, based on