QR-010 via inhalation is safe, well-tolerated, and achieves systemic concentrations in a single ascending dose study in subjects with cystic fibrosis homozygous for the F508del CFTR mutation

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Introduction
QR-010 is an antisense 23-mer RNA oligonucleotide with a phosphorothioate backbone and full 2’-O-methylation designed to hybridize to CFTR mRNA at the F508del exon junction to interfere with the function of the mutant CFTR protein in the airway epithelium, and potentially in other affected organs. Improved CFTR activity has been demonstrated in F508del animal models and in a clinical trial of 10 improved CFRD chloride and sodium transport. This was measured in F508del homozygous pattern by nasal potential difference following local administration to the nasal epithelium. QR-010 is an investigational product intended to be self-administered via nebulisation with the Alcon Nebulizer (Novo Pharma GmbH), an investigational device.

Objectives
• To evaluate the safety and tolerability of QR-010 administered via inhalation and identify the maximum tolerated dose (MTD)
• To evaluate the change from baseline for laboratory parameters and vital signs as well as the pharmacokinetics (PK) of QR-010 administered via inhalation.

Materials and Methods
Study PQ-050-001 is a multi-centre, randomized, double-blind, placebo-controlled, dose-escalation study to evaluate the safety, tolerability, and pharmacokinetics of inhalated QR-010. This study includes two portions: four single ascending dose (SAD) cohorts for QR-010 followed by four multiple ascending dose (MAD) cohorts; the results of the SAD cohorts are presented here.

Subjects were male or female, 18 years or older with a diagnosis of CF measured by sweat chloride confirmation of the CFTR gene homozygous for F508del mutation, and stable pulmonary function with a predicted FEV1 >70% at the screening visit, with no upper limit. Subjects taking CFTR modulators or correctors were excluded.

In each of 4 cohorts (p=4 planned), subjects were randomised 1:1 to receive a single dose of QR-010 6.25 mg, 12.5 mg, 25 mg, or 50 mg QR-010 and treated with placebo, or receive placebo and treated with QR-010. QR-010 was administered via nebulisation followed by a single breath hold. An Independent Data Monitoring Committee (IDMC) reviewed safety data prior to proceeding to subsequent dosing levels. QR-010 single ascending doses were 0.25, 1.25, 5, and 50 mg.

Safety and tolerability were assessed by monitoring adverse events, vital signs, laboratory data, chemistry, haematology and urinalysis, immunogenicity evaluations, ECGs, pulmonary function, and physical examinations. Spirometry to assess pulmonary function was performed per American Thoracic Society (ATS)/European Respiratory Society (ERS) Standards.

Results (continued)

Subjects Disposition
A total of 36 subjects were enrolled into four single ascending dose cohorts; 9 per cohort randomised 1:1:1:1 QR-010 to placebo; in one cohort 25-mg QR-010 placebo 4 additional subjects were added in response to the occurrence of moderate adverse events in one subject; these did not recur and following OCN review, dose escalation continued to the highest dose tested (50 mg QR-010 or placebo). All 36 subjects completed all study visits.

Safety
No deaths or serious adverse events occurred. There were no adverse events (AEs) resulting in subject discontinuations. Adverse events were reported in 16 (59.3%) subjects; all were mild or moderate. The most frequent adverse event occurred in the nervous system, headache, and was reported by 5 subjects (16.7%) across all treatment groups. The gastrointestinal and respiratory systems were the next most represented systems for AEs. Although respiratory adverse events were only reported in the highest dose (25 mg QR-010) dose-level, they occurred in 1 or 2 subjects each and did not present a dose relationship.

Review of unexpected safety data by the IDMC following each single ascending dose cohort confirmed that doses up to 50 mg of QR-010 administered via nebulisation were safe and well-tolerated, and a maximum tolerated dose was not established.

Pharmacokinetics
Serum concentrations of QR-010 peaked rapidly post nebulisation, and all 6 subjects receiving the 50 mg dose via inhalation demonstrated levels above the limit of quantitation. At 24 hours post dose all subjects had QR-010 serum concentrations below quantitation level. A mean (min, max) concentration of 1.37 ng/mL (0.11, 4.65) was achieved as the 30 minute nominal time point post dose. The median concentration of QR-010 at 30 minutes was 1.05 ng/mL.

Conclusions
• Single doses up to 50 mg of QR-010 administered via inhalation were safe and well-tolerated in subjects with cystic fibrosis homozygous for the F508del CFTR mutation
• A maximum tolerated dose was not established in the single ascending dose portion of study PQ-050-001
• Systemic concentrations of QR-010 were measured following a single dose administration, suggesting that QR-010 has the potential to treat both pulmonary and extra-pulmonary manifestations of CF

Acknowledgements
Thanks to all ProQR-050-001 Investigators and researchers for their support and hard work resulting in the successful completion and analysis of the single ascending dose study. The PQ-050-001 Study also received funding from the Cystic Fibrosis Foundation and from the European Union’s Horizon 2020 Research & Innovation programme under grant agreement Nos: 633546.