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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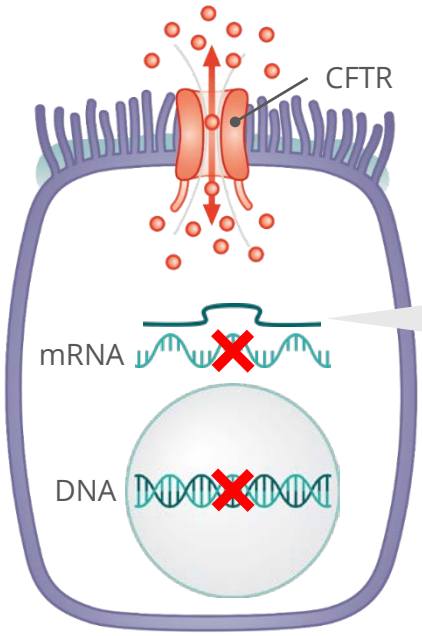
Background:

QR-010 is being developed as a novel RNA-based therapeutic for patients with CF carrying the F508del-*CFTR* mutation

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 analysis for laboratory parameters and vital signs as well as the pharmacokinetics (PK) of QR-010 administered via inhalation

QR-010 - a novel antisense RNA oligonucleotide



QR-010

- Single stranded 33-mer RNA oligonucleotide
- P=S and 2'Ome chemically modified for stability and uptake
- Designed to bind to mRNA region around F508-encoding deletion and to restore CFTR function
- Inhaled delivery by PARI eFlow nebulizer

- Improved CFTR activity has been demonstrated in F508del animal models
- In a clinical trial QR-010 improved CFTR chloride transport. This was measured in F508del homozygous patients by nasal potential difference following local administration to the nasal epithelium

Study Design

PQ-010-001 is a Randomized (3:1), Double-blinded, Placebo-controlled, Single Ascending Dose-escalation study with 8 patients per cohort.

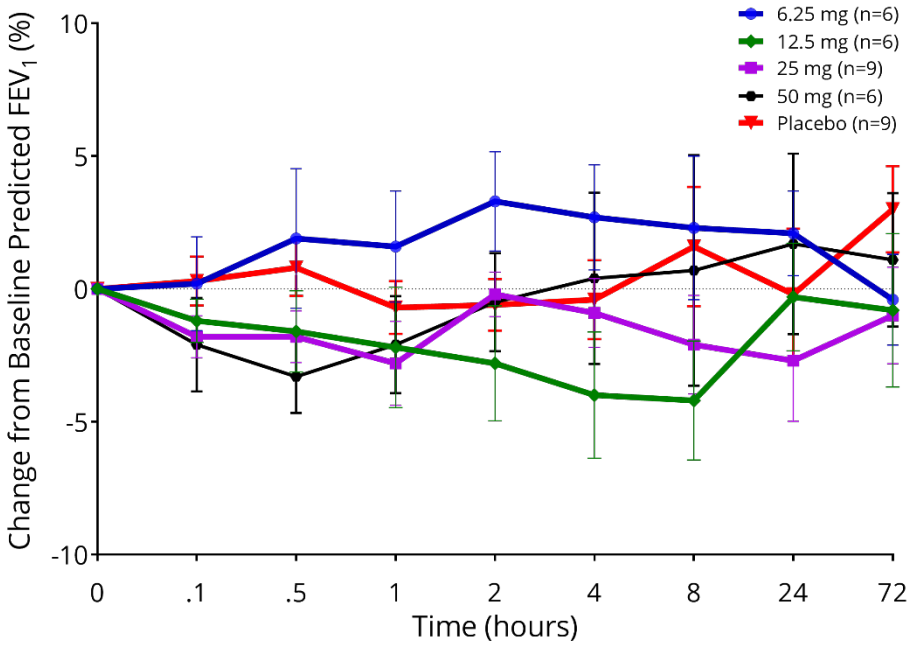
Study Population

- 36 subjects: male (17) and female (19) completed
- Age ≥ 18 years: mean 24.7 years
- CF measured by sweat chloride (mean 103.8 mmol/L), confirmation of the CFTR gene homozygous for F508del mutation
- Stable pulmonary function with a Screening predicted FEV_1 ≥70% : mean 91.4 % [67.6, 128.7] at baseline
- Subjects taking CFTR potentiators or correctors were excluded

Results: Safety

- No deaths or serious adverse events occurred. There were no subject discontinuations. Adverse events were reported in 16 (59.3%) subjects; all mild or moderate
- A post-inhalation leukocytosis returning to baseline at 24 hours post nebulization was observed in all cohorts including placebo
- DMC review following each SAD cohort confirmed doses up to 50 mg of QR-010 via nebulization were safe and well-tolerated, and a maximum tolerated dose was not established

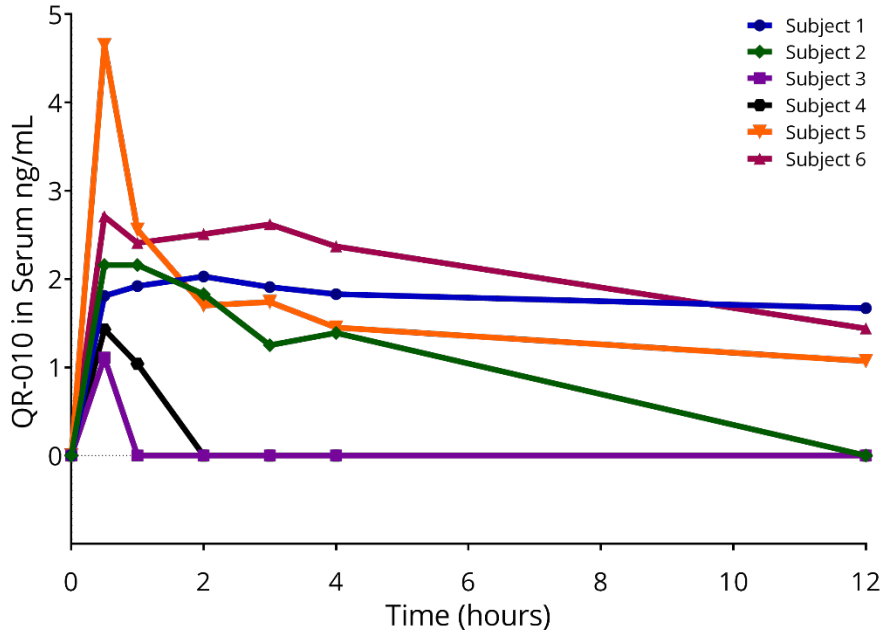
Mean (SEM) Change from Baseline in Predicted FEV_1 (%) Following a Single Dose of QR-010 or Placebo



Results: Pharmacokinetics

- Serum levels 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
- A mean [min, max] concentration of 2.3117 ng/mL [1.11, 4.65] was achieved at the 30 minute nominal time point post-dose
- The median serum concentration of QR-010 at 30 minutes was 1.985 ng/mL

Concentrations of QR-010 Measured in Serum Following a 50 mg Dose



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-010-001
- 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

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