QR-010 Significantly Improves CFTR function in Nasal Potential Difference Proof of Concept Study in Subjects with CF Homozygous for the F508del-CFTR mutation

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Introduction

- CF is a disease caused by mutations in the cystic fibrosis conductance regulator (CFTR) gene. The most common mutation is the F508del. Non-functional CFTR leads to dysregulated chloride transport in multiple organ systems, most notably in the respiratory tract
- QR-010 is a single-stranded RNA antisense oligonucleotide complementary to wild-type CFTR mRNA that aims to restore functional CFTR in CF patients with at least one copy of the F508del mutation. QR-010 is developed to be administered via inhalation
- Non-clinical studies show that QR-010 leads to increased CFTR function as assessed in vitro in CFPAC-1 cells and F508del-CF primary human bronchial epithelial cells, and in vivo in F508del CFTR mice by measuring saliva secretion and nasal potential difference (NPD)[1,2,8]
- As the only direct *in vivo* measure capable of separating sodium and chloride transport, NPD has been used as an important endpoint in clinical trials evaluating therapeutic agents, and provides a standardized, direct and sensitive measurement of CFTR activity[4,5,6,7]

Methods

Study design:
Exploratory, multi-center, open-label, proof of concept study at 5 NPD centers of excellence (3 US; 1 France, 1 Belgium).
- Cohort 1: 8 subjects with CF homozygous for the F508del mutation
- Cohort 2: 8 subjects with CF compound heterozygous for the F508del mutation

QR-010 10 mg (5 mg/250 µL per nostril) was dosed 3 times per week for 4 weeks by manual administration using the LMA MAD 300 Nasal™ Intranasal Mucosal Atomization Device.

NPD was conducted according to the standard operating procedure (SOP) used by the joint US Cystic Fibrosis Foundation Therapeutics Development Network/European Cystic Fibrosis Society Clinical Trials Network.
- One independent central reader, blinded to subject, genotype and time point evaluated all NPD tracings; all interpretable tracings were used in the analysis

Key eligibility criteria:
- Male or female ≥ 18 years of age
- Confirmed diagnosis of CF as defined by iontophoretic pilocarpine sweat chloride test of > 60 mmol/L
- Confirmation of CFTR gene mutation homozygous or compound heterozygous for the F508del mutation
- Baseline NPD with a classic CF phenotype characterized by a CFTR-mediated total chloride transport value of > -6.6 mV
- FEV1 ≥ 40% predicted [NHANES III]
- No recent or current exposure to CFTR modulating therapies

Endpoints:
- The primary endpoint was the within subject change from baseline in CFTR-mediated total chloride transport at Day 15, Day 26 (EoT), and Day 47, as measured by NPD, using the chloride-free plus isoproterenol (Cl-free+isoproterenol) parameter, and assessing the average of 2 nostrils per time point. Data were analyzed per cohort
- Secondary endpoints included the within subject change from baseline in the sodium channel parameter maximal basal potential difference (max basal PD) at Day 15, Day 26 (EoT), and Day 47, and were analyzed per cohort

Objectives

Primary:

To estimate the effect of topical administration of QR-010 on the nasal mucosa in the restoration of CFTR function, as measured by NPD, in the nasal epithelium of subjects with CF who have the F508del mutation.

Secondary:

- **To evaluate the safety and tolerability of intranasal administration of QR-010**
- **To assess the nasal symptoms measured by the patient-reported outcome (PRO) instrument called Sino-nasal Outcomes Test (SNOT-22)[3] and the Nasal Examination Rating Scale (NERS)**

Sodium and Chloride Transport Measured by NPD

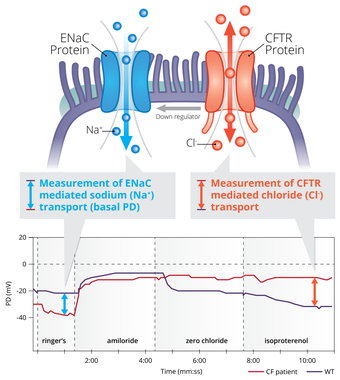

Figure 1. NPD tracing representing restoration of CFTR function by changing the chloride channel response to a more negative response and the sodium channel response to a more positive response. Adapted from: Rowe et al.[6]

Populations:
- Safety Population (N=10 for cohort 1; N=8 for cohort 2): All subjects who received one or more doses of QR-010; 2 additional subjects were enrolled in cohort 1
- Per Protocol Population (N=7 per cohort): All subjects with a Cl-free+isoproterenol response >-6.6 mV at baseline with at least one interpretable post-dose Cl-free+isoproterenol value

Analysis:
- Primary analysis method: the average of left and right nostril per time point; this is the recommended consensus method
- Sensitivity analyses included the analysis of: left and right nostril separately, the least polarized nostril at baseline carried forward, and the most polarized nostril per time point
- Baseline was defined as the average of the two most recent pre-dose values for each method
- Paired t-test alpha 5% level one-sided
- Data were analyzed per cohort

Results

Demographics & Baseline Characteristics

	Homozygous Cohort (Cohort 1)	Heterozygous Cohort (Cohort 2)
Characteristic	**Safety Population** (N=10)	**Safety Population** (N=8)
Age (years) Mean (SD) Min, Max	 25.8 (6.7) 19, 36	 36.0 (15.8) 18, 63
Sex, n (%) Male Female	 6 (60%) 4 (40%)	 4 (50.0%) 4 (50.0%)
Race, n (%) Caucasian	10 (100%)	8 (100.0%)
BMI (kg/m²) Mean (SD) Min, Max	 22.8 (2.8) 19.8, 28.2	 23.1 (3.3) 19.8, 28.4
Predicted FEV1 (%) Mean (SD) Min, Max	 74.2 (17.4) 45.2, 108.8	 74.9 (16.9) 52.3, 98.1
Sweat Chloride (mmol/L) Mean (SD) Min, Max	 98.7 (15.0) 78.0, 117.5	 103.9 (18.0) 86.0, 134,0
Baseline Cl-Free+Isoproterenol (mV) Mean (SD) Min, Max	 -1.2 (5.8) -11.1, 6.4	 -2.4 (5.9) -13.9, 6.3
Baseline SNOT-22 Total Score Mean (SD) Min, Max	 14.9 (5.9) 8.0, 24.0	 19.1 (17.7) 5.0, 59.0

Preliminary Safety & Tolerability Data for All Subjects

Treatment-Emergent Adverse Events Occurring in >10% Subjects by Preferred Term	Safety Population (Pooled Cohorts); N=18 N (%)
Subjects with Serious Adverse Events	0 (0)
Subjects with at least one TEAE	15 (83.3)
Gastrointestinal disorders Nausea	 3 (16.7)
General disorders and administration site conditions Fatigue Pyrexia	 4 (22.2) 4 (22.2)
Nervous System Disorders Headache	 2 (11.1)
Respiratory, thoracic and mediastinal disorders Cough Epistaxis Respiratory Tract Congestion Rhinorrhoea Sinus Congestion Nasal Congestion	 4 (22.2) 2 (11.1) 2 (11.1) 3 (16.7) 2 (11.1) 2 (11.1)

No clinical meaningful changes in nasal symptoms as assessed by the sino-nasal outcomes test SNOT-22 and the nasal examination rating scale (NERS) were observed throughout the study.

QR-010 signficantly improved CFTR activity in subjects with CF homozygous for the F508del mutation as assessed by NPD

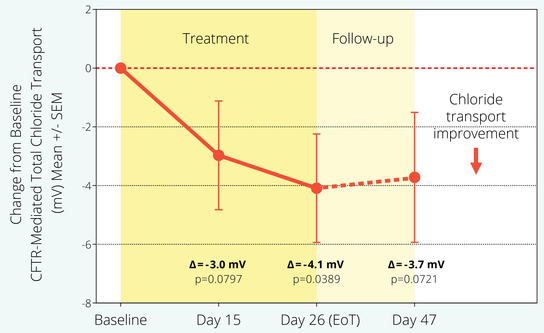

Figure 2. Per Protocol Population Cohort 1 (N=7). Mean (± SEM) change from baseline in CFTR-mediated total chloride transport (Cl-free+isoproterenol) at Day 15, Day 26 (EoT), and Day 47. Cl-free+isoproterenol is a direct measure of CFTR activity assessed by NPD.

Improved CFTR-activity was associated with improved max basal PD

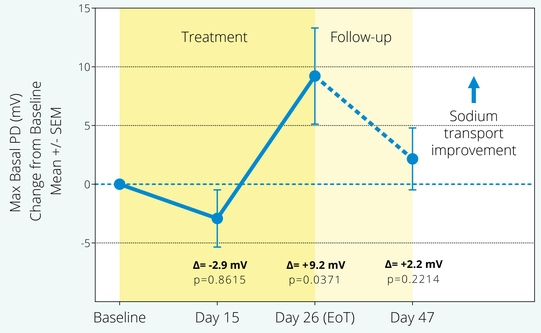

Figure 4. Per Protocol Population Cohort 1 (N=7). Mean (± SEM) change from baseline of max basal PD at Day 15, Day 26 (EoT), and Day 47. Max basal PD assessed by NPD is a measure of sodium channel activity, which is (indirectly) regulated by CFTR, and thus a supportive parameter for CFTR activity.

Sensitivity analyses supporting the primary analysis outcome of increased CFTR activity in subjects with CF homozygous for the F508del mutation

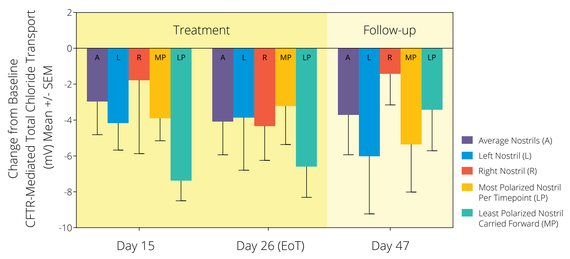

Figure 3. Per Protocol Population Cohort 1 (N=7). Comparison of predefined analysis methods (definitions in Methods section). Mean (± SEM) Change from Baseline in CFTR-mediated total chloride transport (Cl-free+isoproterenol) at Day 15, Day 26 (EoT), and Day 47.

QR-010 did not improve CFTR activity in subjects with CF compound heterozygous for the F508del mutation as assessed by NPD

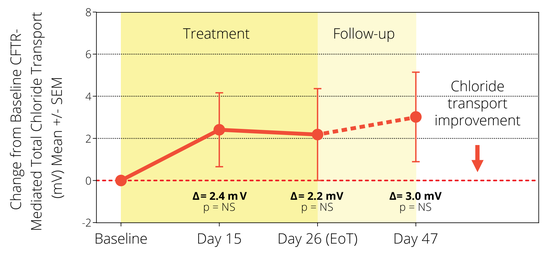

Figure 5. Per Protocol Population Cohort 2 (N=7). Mean (± SEM) change from baseline in CFTR-mediated total chloride transport (Cl-free+isoproterenol). CFTR gene mutations were: Q493X, 621+1 G>A, Y1092X, 1717-1 G>A (all Class I), N1303K, I336K, G628R (all Class II), and 2789+5 G>A (Class V).

Conclusions

These topline data show that QR-010 significantly improved CFTR function in subjects with CF homozygous for the F508del mutation.

- **Findings are supported by sensitivity analysis**
- **Findings are further supported by a positive sodium transport signal (max basal PD)**

QR-010 did not improve CFTR function in subjects with CF compound heterozygous for the F508del mutation.

- **Further preclinical work will be pursued to better understand the impact of the second allele before exploring the potential clinical potential of QR-010 in this population**

These findings demonstrate proof of concept has been established for QR-010 in restoring CFTR activity and support the potential of this new therapy to treat CF patients homozygous for the F508del mutation.

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