**Background**

Eluxastat (PQ-010) is an oral non-ribonucleotide investigational product designed to be complementary to the F508del correcting CFTR minigene. Eluxastat improved CFTR activity in F508del animal models and in CF subjects homozygous for the F508del mutation. Eluxastat has demonstrated clinical benefit with statistically significant changes in pulmonary function and lung infection compared to placebo in a Phase 3 clinical trial in patients with F508del homozygous disease. A biomarker for the PQ-010-001 study was identified as HE-4, a cystic fibrosis-homogeneous biomarker on the basis of the approval of the CLMA-NL expert panel. HE-4 was included as an exploratory biomarker to assess the potential treatment effects on sputum and serum levels of this biomarker with the compound in an intervention clinical study, through evaluation of healthy and CF patients, including those treated with eluxastat.

**Objective**

The objective of the exploratory immune assays was to assess immune responses in CF patients compared to healthy controls and the biomarkers for the PQ-010-001 study were evaluated through evaluation of baseline values at screening and check-in. Sample distribution was checked in PQ-010-001 screening and check-in samples as compared to averaged baseline concentrations (calculated by averaging screening and check-in concentrations from CF and non-CF individuals, and subsequently validated in a multi-centre, randomised, double-blind, placebo-controlled dose escalation study of eluxastat (PQ-010-001)). A panel of spu tum immune markers were measured using qualified ELISA. Results from immune measurements were correlated with patient baseline characteristics, and PQ-010-001 was conducted with the serum and sputum samples for the pilot study.

**Methods**

Samples (sputum and serum) from patients treated with eluxastat were measured by ELISA. Sputum and serum samples were collected at screening and check-in. The biomarkers assayed were selected based on literature proposing them as relevant.

**Results**

**Assay characteristics**

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<tr>
<th>Assay characteristics</th>
<th>Characteristics</th>
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<tbody>
<tr>
<td>ELISA</td>
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<td>Using qualified ELISA</td>
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<td>Biomarkers</td>
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<td>CF patients</td>
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<td>Healthy controls</td>
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<tr>
<td>Biomarkers</td>
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**Study Schematic PQ-010-001**

**Table 1: Assay characteristics (optimization and qualification using UCL pilot cohorts of CF and non-CF individuals)**

**Table 3: Correlation of serum and sputum biomarkers with HE-4 and YKL-40 in serum over time in SAD and MAD cohorts receiving different doses of eluxastat. (A) HE-4 evaluated on MAD5 (n=16), MAD7 (n=16), and MAD8 (n=16) at screening and check-in. (B) YKL-40 evaluated on MAD5 (n=16), MAD7 (n=16), and MAD8 (n=16) at screening and check-in. (C) HE-4 evaluated on MAD5 (n=16), MAD7 (n=16), and MAD8 (n=16) at screening and check-in. (D) YKL-40 evaluated on MAD5 (n=16), MAD7 (n=16), and MAD8 (n=16) at screening and check-in. (E) HE-4 evaluated on MAD5 (n=16), MAD7 (n=16), and MAD8 (n=16) at screening and check-in. (F) YKL-40 evaluated on MAD5 (n=16), MAD7 (n=16), and MAD8 (n=16) at screening and check-in. (G) HE-4 evaluated on MAD5 (n=16), MAD7 (n=16), and MAD8 (n=16) at screening and check-in. (H) YKL-40 evaluated on MAD5 (n=16), MAD7 (n=16), and MAD8 (n=16) at screening and check-in.

**Correlation of serum and sputum biomarkers with HE-4 and YKL-40 in serum over time in SAD and MAD cohorts receiving different doses of eluxastat. (A) HE-4 evaluated on MAD5 (n=16), MAD7 (n=16), and MAD8 (n=16) at screening and check-in. (B) YKL-40 evaluated on MAD5 (n=16), MAD7 (n=16), and MAD8 (n=16) at screening and check-in. (C) HE-4 evaluated on MAD5 (n=16), MAD7 (n=16), and MAD8 (n=16) at screening and check-in. (D) YKL-40 evaluated on MAD5 (n=16), MAD7 (n=16), and MAD8 (n=16) at screening and check-in. (E) HE-4 evaluated on MAD5 (n=16), MAD7 (n=16), and MAD8 (n=16) at screening and check-in. (F) YKL-40 evaluated on MAD5 (n=16), MAD7 (n=16), and MAD8 (n=16) at screening and check-in. (G) HE-4 evaluated on MAD5 (n=16), MAD7 (n=16), and MAD8 (n=16) at screening and check-in. (H) YKL-40 evaluated on MAD5 (n=16), MAD7 (n=16), and MAD8 (n=16) at screening and check-in.

**Conclusions**

- **Assays to measure HE-4 and YKL-40 in serum as well as SPUUNC1 and TIMP-1 in sputum were successfully optimized, qualified in a UCL pilot study of CF and non-CF cohorts, and validated in a clinical study of eluxastat in subjects with CF homozygous for the CTR-F508del mutation.
- **HE-4 and YKL-40 biomarkers were significantly elevated in CF patients compared to non-CF individuals.** HE-4 distinguished exceptionally well between non-CF and CF populations.
- **Overall, sputum biomarker SPUUNC1 was decreased and TIMP-1 was increased in CF patients compared to non-CF individuals; however, sputum sample availability in the PQ-010-001 study was low. Further clinical studies would provide more consistent collection and population characterisation.
- **Other known sputum immune inflammatory markers were successfully measured and showed high response variability at baseline.**
- **A trend towards decreased serum analyte concentrations was observed in some patients receiving eluxastat, but overall, response variability was high.** Further longitudinal studies to establish the marker development over time will help to distinguish true biomarker signals from ‘noise’.

**Acknowledgements**

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