CFTR modulators modify exhaled breath of children with cystic fibrosis within a week.

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AIMS

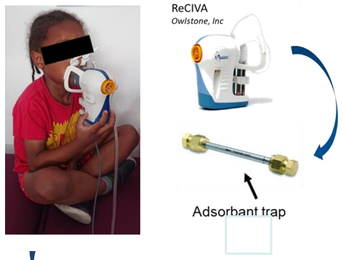
- The combination of cystic fibrosis transmembrane conductance regulator (CFTR) modulators ivacaftor/ tezacaftor/ elexacaftor (ETI) transform clinical status for many people with cystic fibrosis (CF).
- Clinical status and therapeutic response are classically assessed through respiratory function tests, sweat chloride concentration, microbiology assays, etc.
- New endpoints are now needed as pwCF will expectorate less and less and maintain a high lung function.
- CFTR modulators modifies the composition of breath within 3 months (Neerincx *et al. ERJ Open Res*. 2021).

Hypothesis: ETI modifies the lungs' metabolism leading to significant changes in exhaled breath.

Objective: Assess the value of breath analysis to monitor short-term response to ETI and better understand underlying lung biology.

COHORT AND STUDY DESIGN

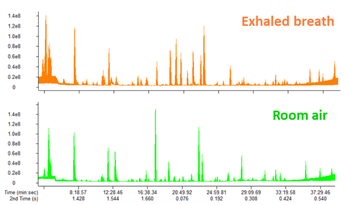
Breath collection with ReCIVA®



- Prospective open-label study, Necker-Enfants Malades hospital (Paris, France).
- 11 children (3 females), F508del-heterozygous, initiating ETI.
- 8.6 years (6 – 12).
- Timeline: baseline (day 0), 1 week (day 7), 1 month of ETI treatment (day 30).
- Clinical readouts: weight; sweat test (Cl-); lung function tests (FEV1, FVC).
- Collection of exhaled breath samples on sorbent tubes using a ReCIVA ® device.
- Off-line analysis by bidimensional gas chromatography (TD-GCxGC-MS, Leco).

Bidimensional GC-MS

GCxGC chromatograms



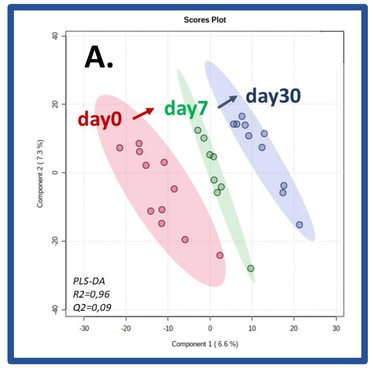
Clinical characteristics	Day 0	Day 30
Weight	26 kg	26 kg
FEV1%	87%	96%
FVC%	97%	102%
FEF_{25-75}%	60%	73%
Sweat Cl^-	107 mmol/L	50 mmol/L

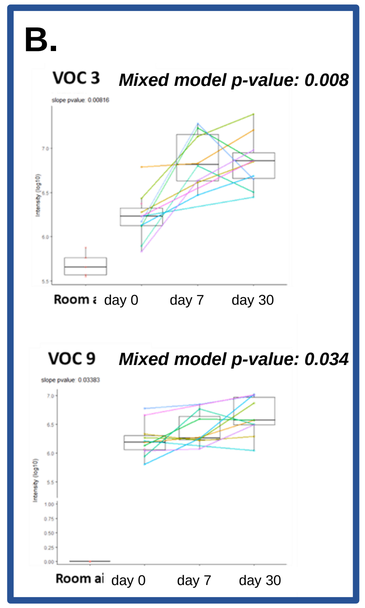
RESULTS

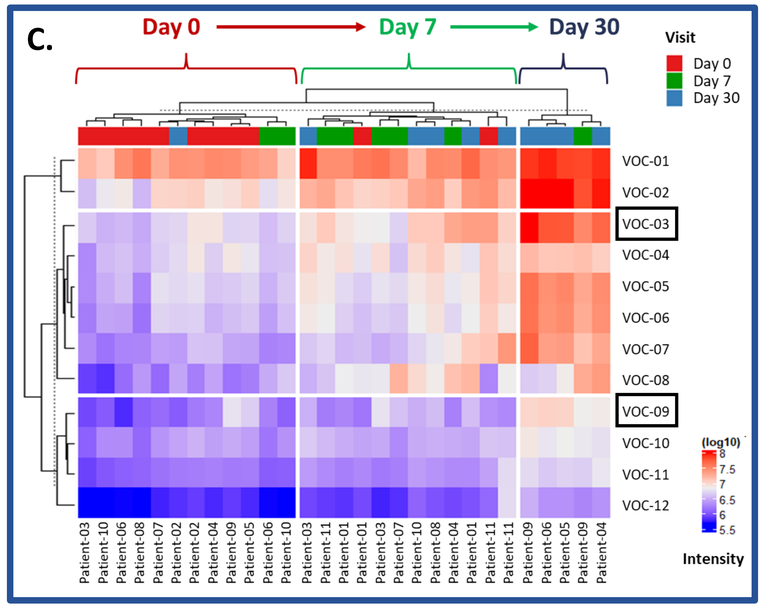
A. Supervised partial least square-discriminant analysis (PLS-DA) separates breath profiles detected at each visit.

B. Longitudinal analysis identified 12 volatile organic compounds (VOCs) significantly increased across pwCF during the first month of treatment.

C. These 12 VOCs allow a relative clustering of samples according to treatment duration.







CONCLUSIONS

There is a systemic and progressive shift in breath composition upon ETI treatment initiation: changes were detected from one week of treatment.and evolution was progressive throughout the 1st month. The metabolic origin of the impacted VOCs is being investigated; these may contribute to unveil mechanisms of action of ETI and serve as a a non-invasive tool for clinical and therapeutic monitoring in patients with normal lung function.

ACKNOWLEDGEMENTS

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