



Evaluation of QR-010

on CFTR function in CF subjects
with the F508del-*CFTR* mutation

ECFS Sevilla, 7 June 2017

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SM Rowe Disclosures

Clinical trial contracts

- ProQR
- Vertex Pharmaceuticals
- Novartis
- Bayer
- Astra/Zenica
- Celtaxsys

Research contracts

- Bayer
- Synedgen
- Galapagos/Abbvie
- Silurian
- Renovion
- Astra/Zenica

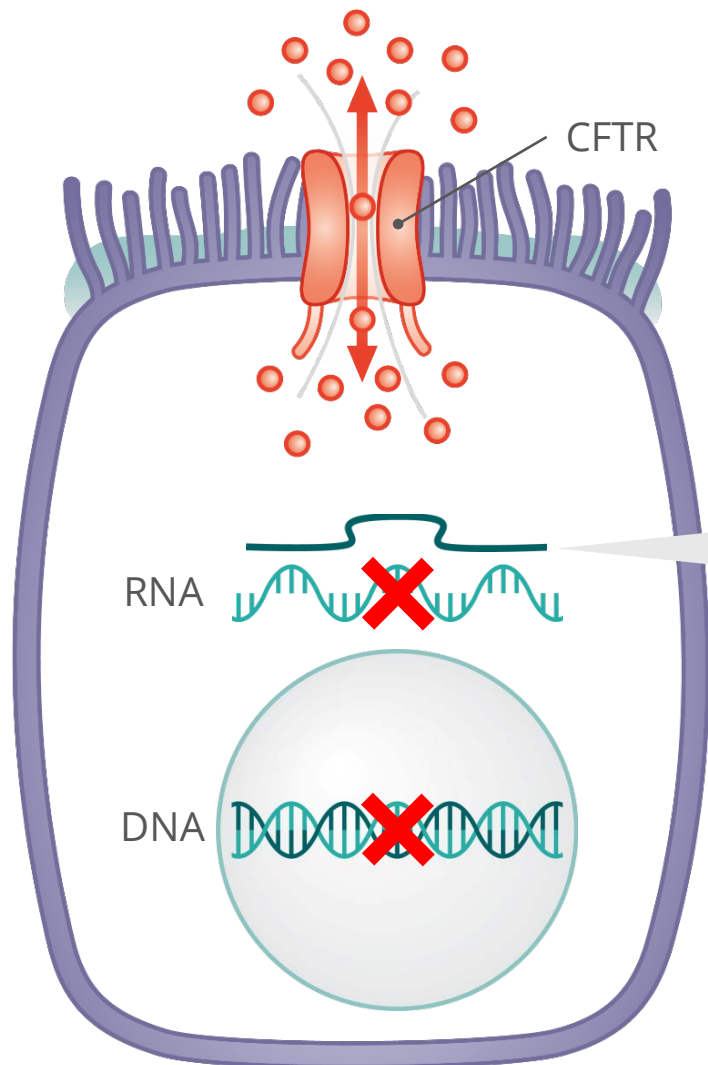
Consulting

- ProQR
- Vertex Pharmaceuticals
- Novartis
- Bayer
- Galapagos/Abbvie
- Synedgen
- Celtaxsys

Grant funding

- NIH
- CFFT
- CFF
- American Lung Association

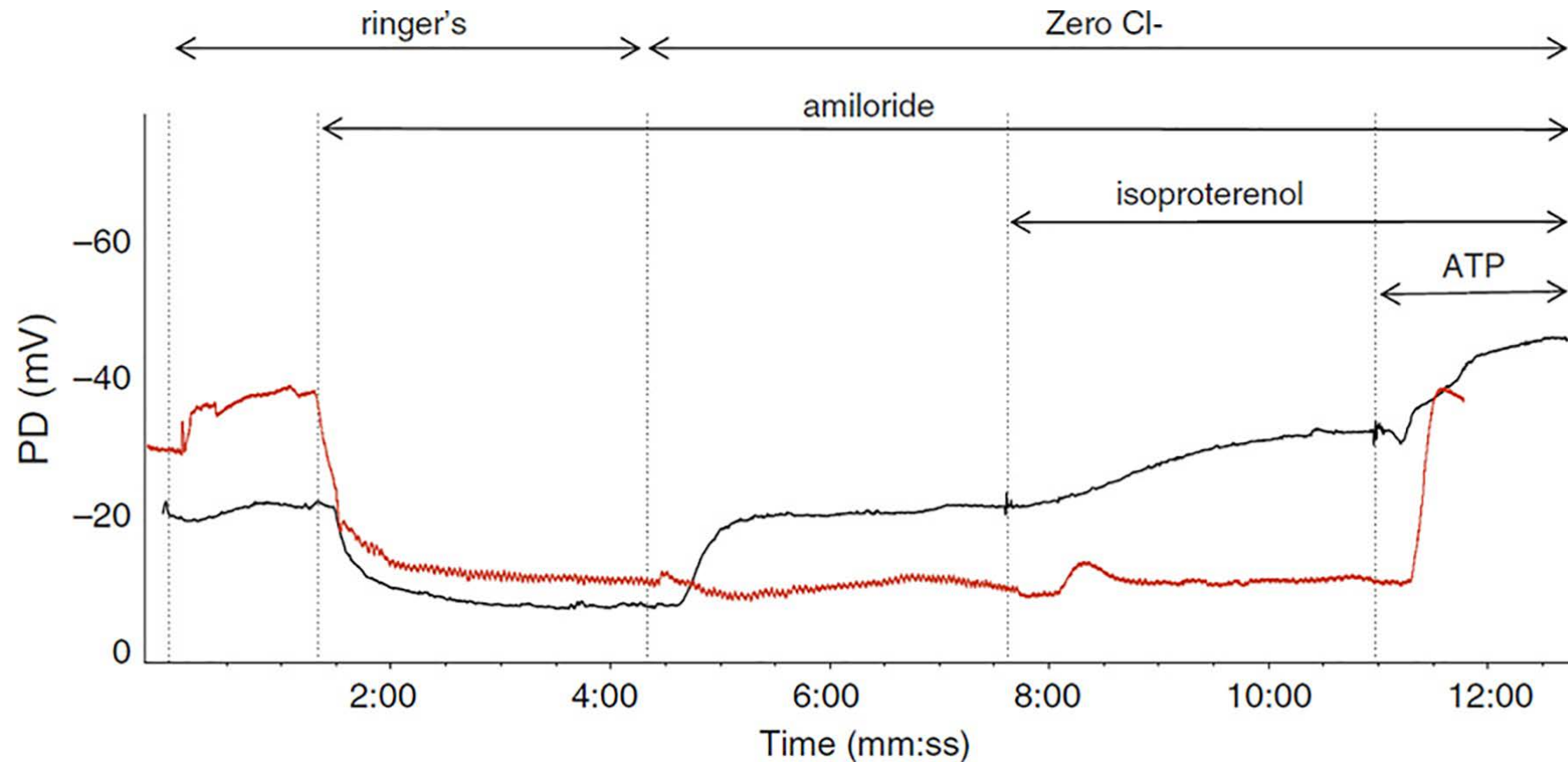
QR-010 for F508del Cystic Fibrosis



QR-010

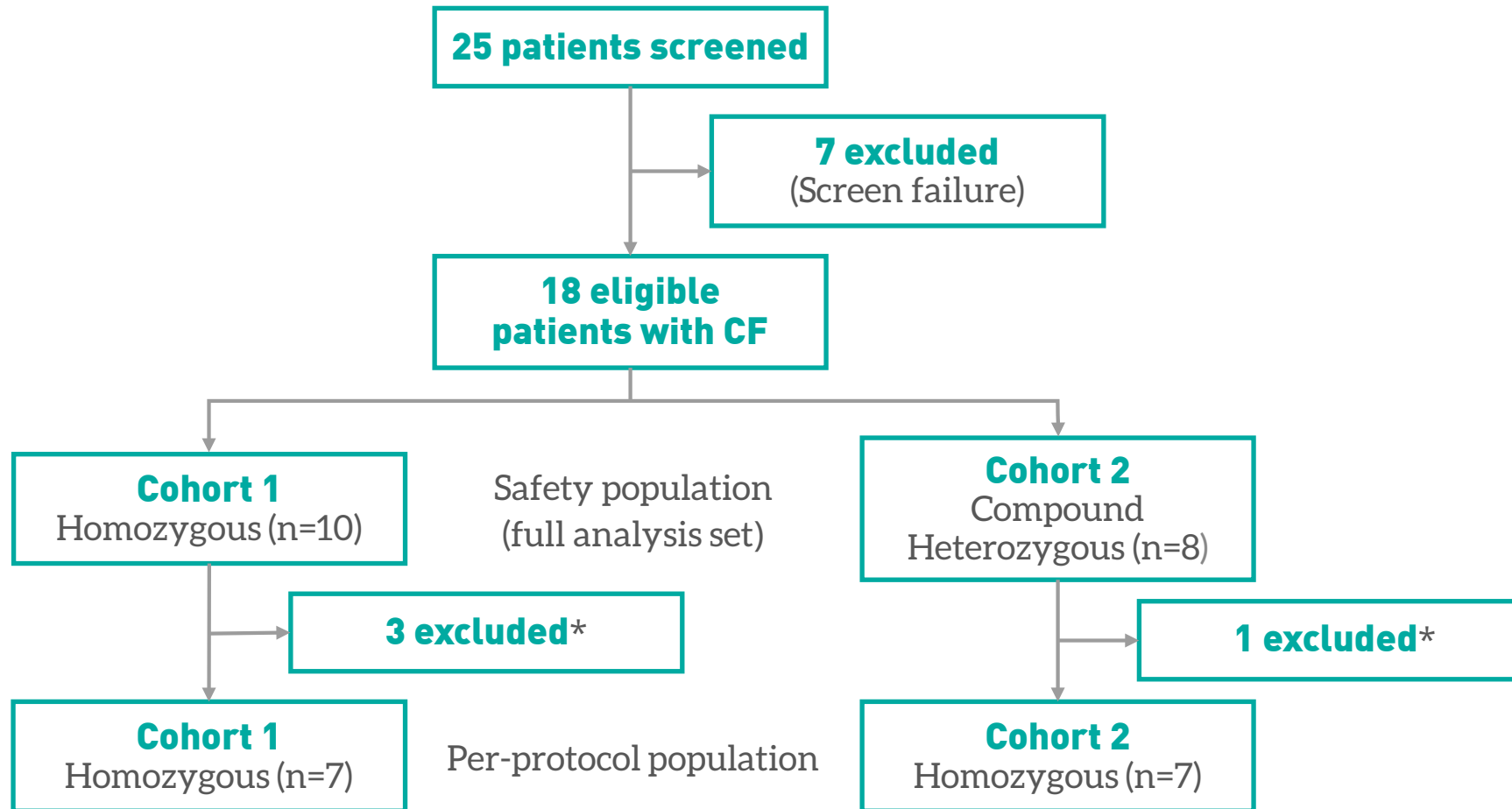
- Single stranded 33-mer RNA oligonucleotide
- P=S and 2'Ome chemically modified for stability and uptake
- Designed to bind to mRNA region around F508-encoding deletion and to restore CFTR function
- Inhaled delivery by PARI eFlow nebulizer

Nasal Potential Difference

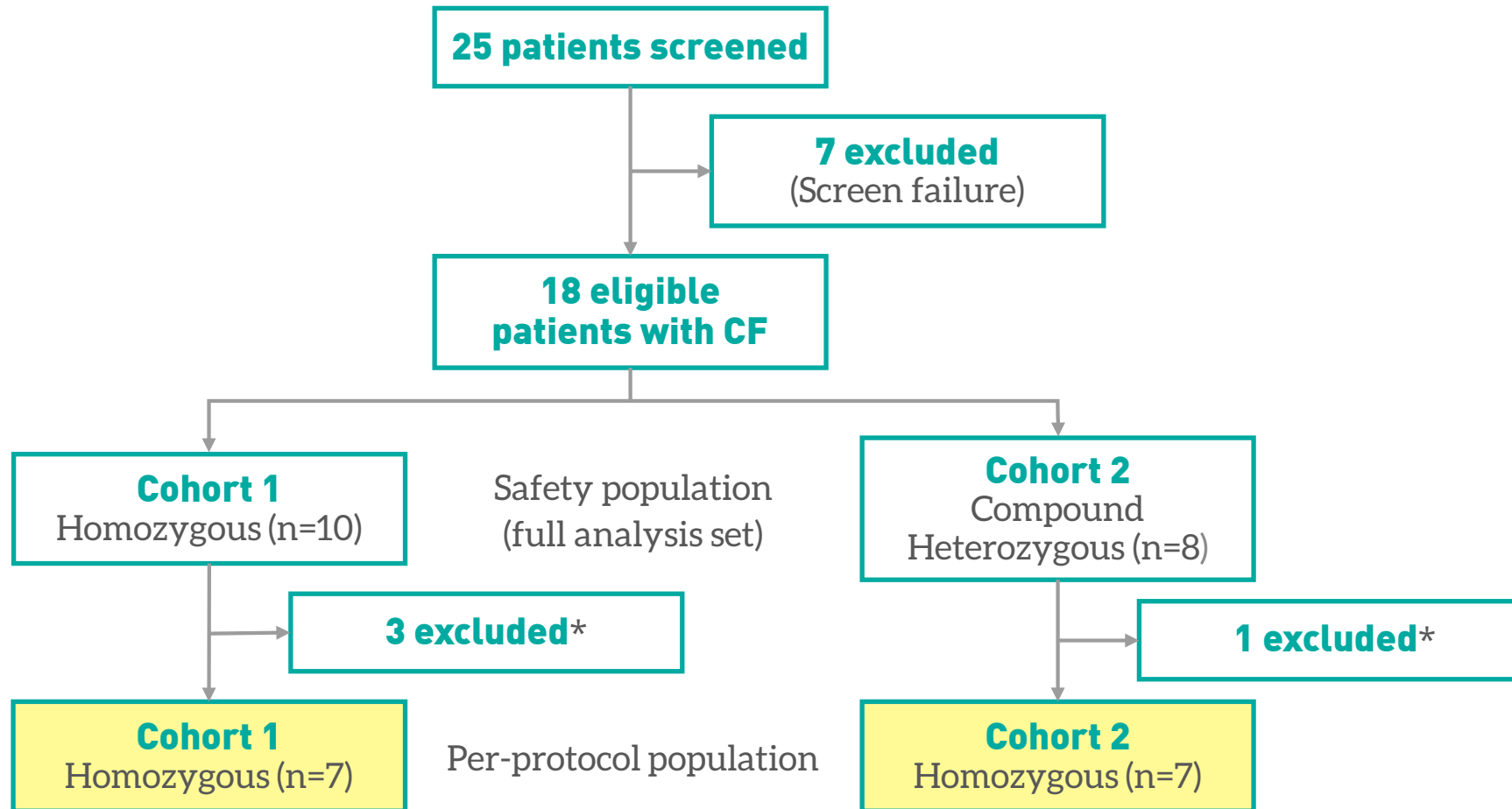


*From Rowe et al. Methods Mol Bio 2011
Representative nasal difference tracings from a normal (black) and a CF (red) subject.
Contents and duration of each perfused solution is designated above.*

Study Disposition



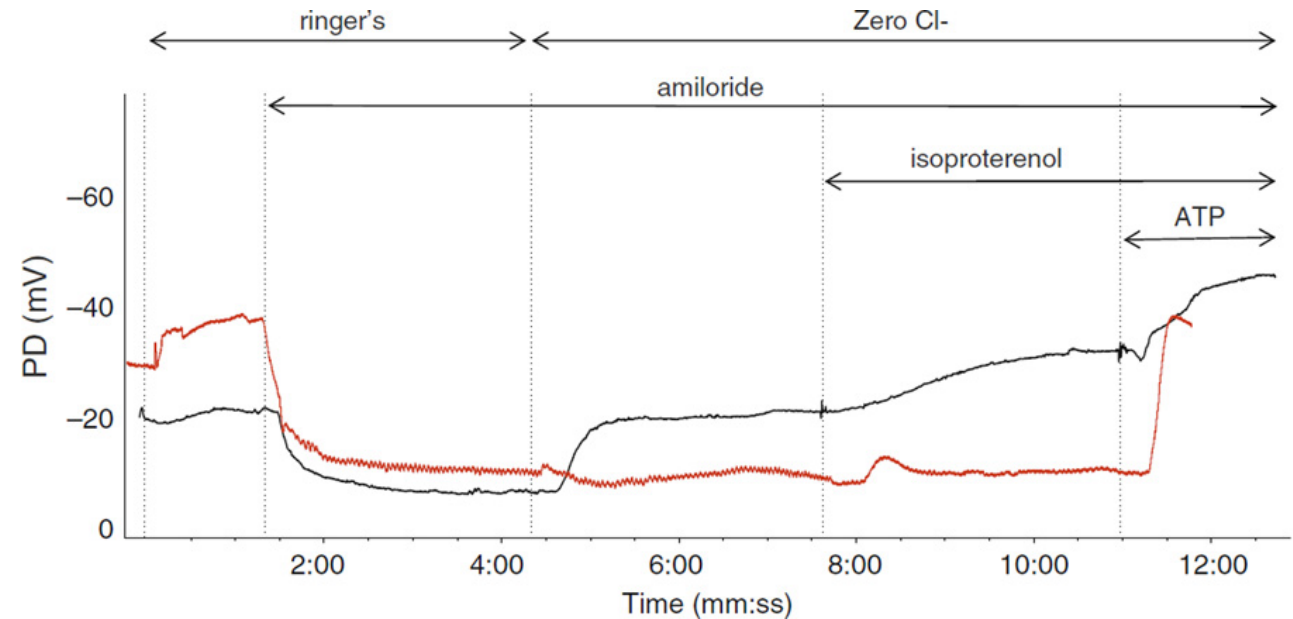
Study Disposition



* Did not meet inclusion criteria; their total chloride transport value was more negative than -6.6 mV at baseline, as determined by central reader after subject-initiated treatment

Standardized NPD Procedure

- Standardized SOP by joint US TDN and EU CTN
- Central supply of NPD solutions
- Final quality review and scoring by one blinded central reader
 - Blinded to genotype, subject ID and time point
- Less than 4% of tracings uninterpretable



Subject Demographics

	Homozygous cohort (n= 7)	Compound heterozygous cohort (n=7)
Age (years)	27 [20 ; 36]	36 [18 ; 63]
Sex		
Male	5 (71%)	3 (43%)
Female	2 (29%)	4 (57%)
Race		
White	7 (100%)	7 (100%)
BMI (kg/m ²)	22 [20 ; 26]	23 [20 ; 28]
Predicted FEV ₁ (%)	72.7 [45.2 ; 108.8]	72.7 [52.3 ; 93.8]
Sweat Chloride (mmol/L)	104.3 [80.0 ; 117.5]	104.6 [86.0 ; 134.0]
SNOT-22 total score	14.7 [8.0 ; 23.0]	21.1 [8.0 ; 59.0]
Cl-free+iso (mV)	1.9 [-4.0 ; 6.4]	-0,8 [-5.0 ; 6.3]
Average basal PD (mV)	-31.9 [-44.3 ; -16.4]	-27.0 [-45.0 ; -15.8]

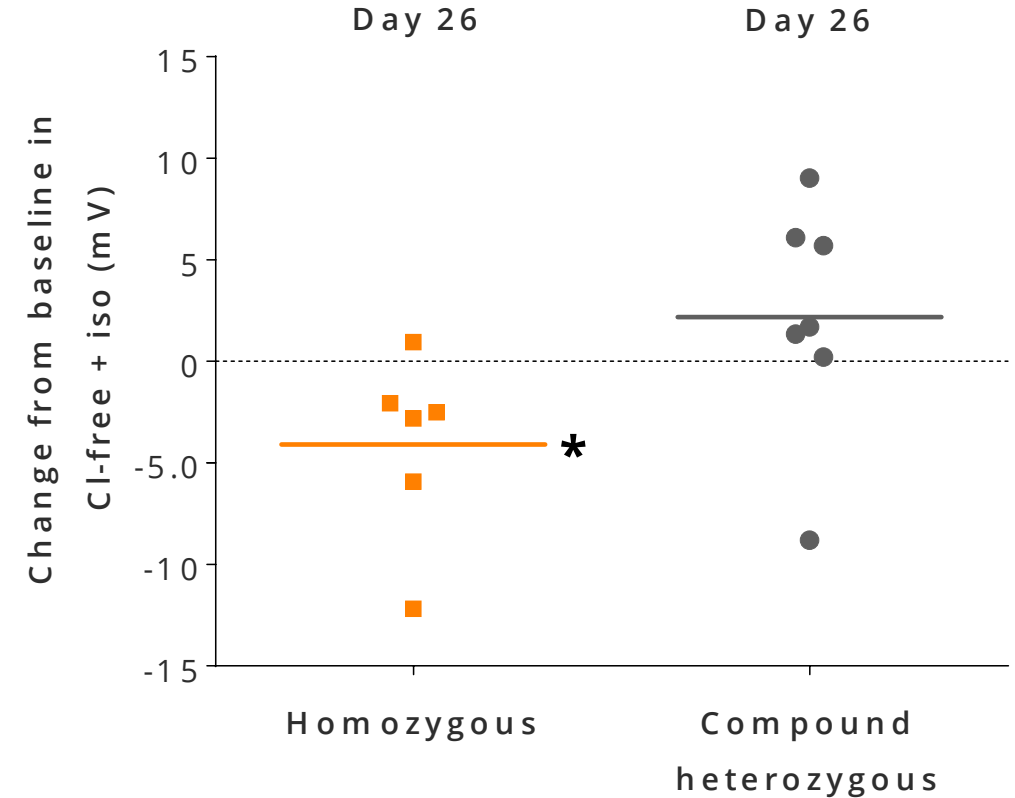
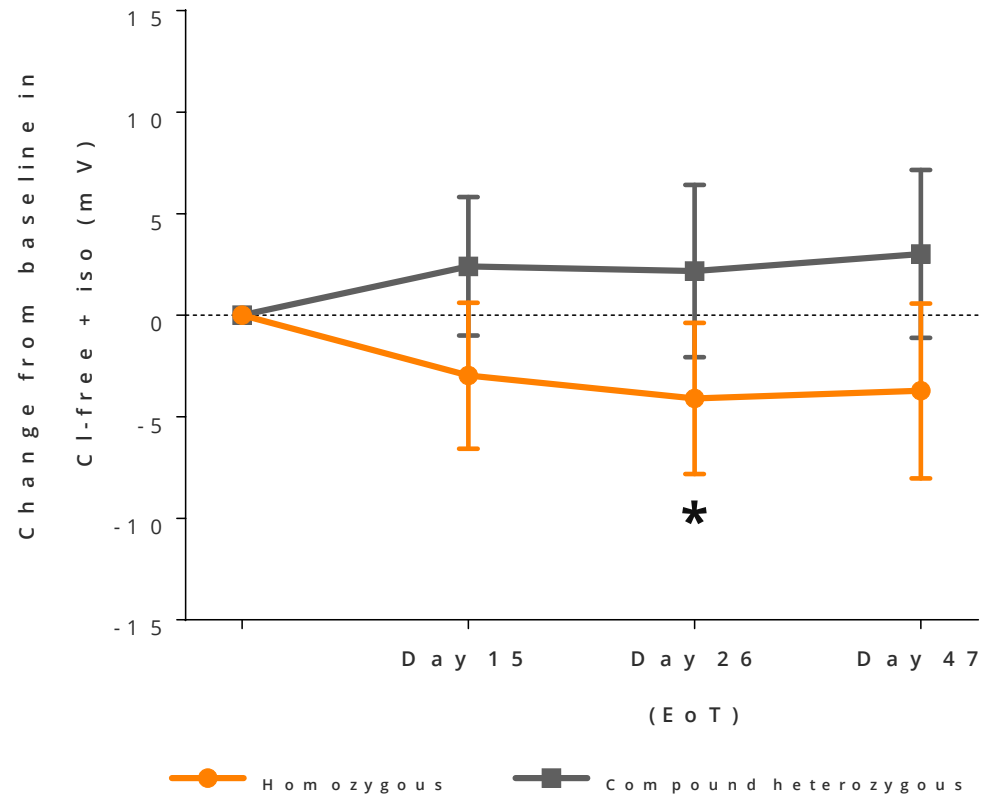
Data are mean (range) unless otherwise specified

QR-010 was safe and well tolerated

TEAEs occurring in >10% of subjects by preferred term	Safety population (pooled cohorts) (N=18) N (%)
Subjects with serious TEAEs	0 (0)
Subjects discontinuing due to TEAE	0 (0)
Subjects with at least one TEAE	16 (88.9)
Gastrointestinal disorders	
Nausea	3 (16.7)
General disorders and administration site conditions	
Fatigue	4 (22.2)
Pyrexia	4 (22.2)
Nervous System Disorders	
Headache	2 (11.1)
Respiratory, thoracic and mediastinal disorders	
Cough	5 (27.8)
Epistaxis	2 (11.1)
Nasal congestion	2 (11.1)
Respiratory tract congestion	2 (11.1)
Rhinorrhoea	3 (16.7)
Sinus congestion	2 (11.1)
Sputum increased	2 (11.1)

Total Chloride Transport (Cl-free+iso)

PD following chloride-free + isoproterenol perfusion

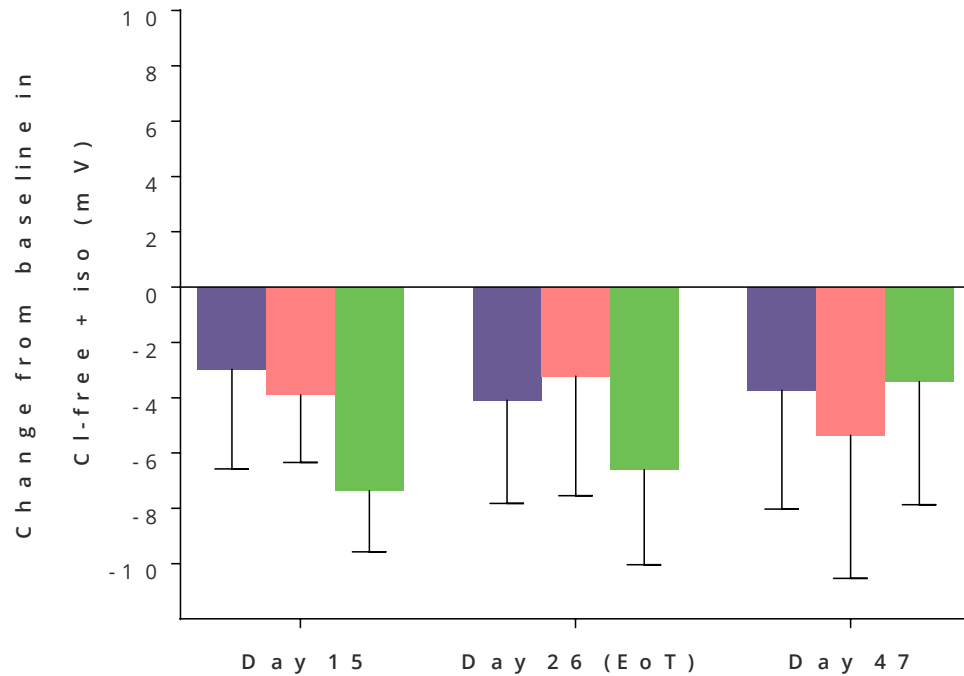


* Mean change Cl-free+iso at Day 26 = -4.1 mV [90% CI -7.8 ; -0.4], P = 0.04

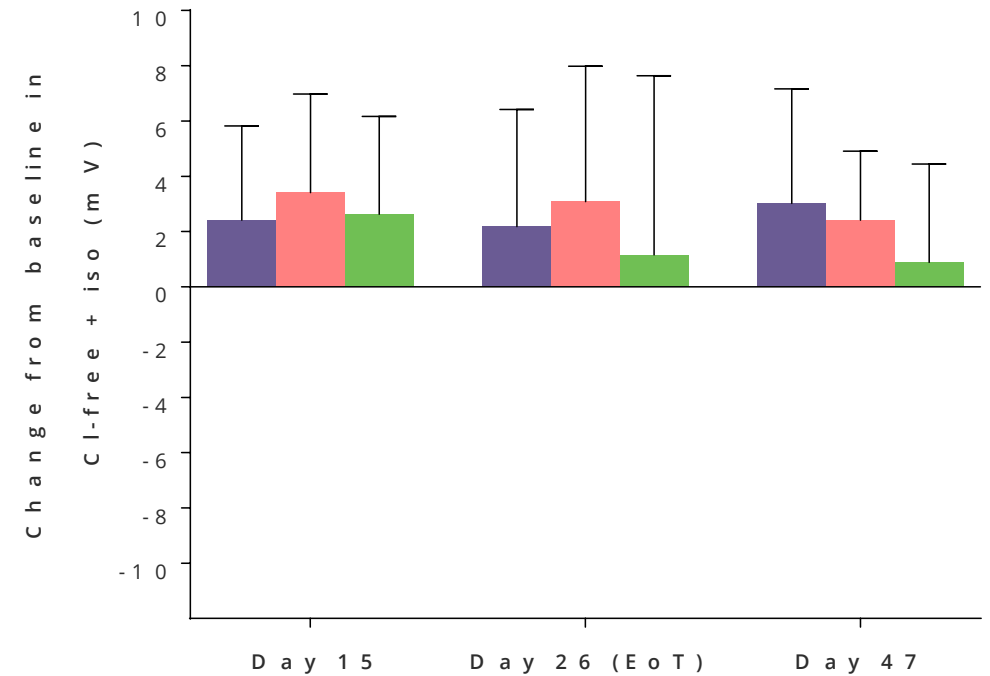
Total Chloride Transport (Cl-free+iso)

Sensitivity analysis

H o m o z y g o u s c o h o r t

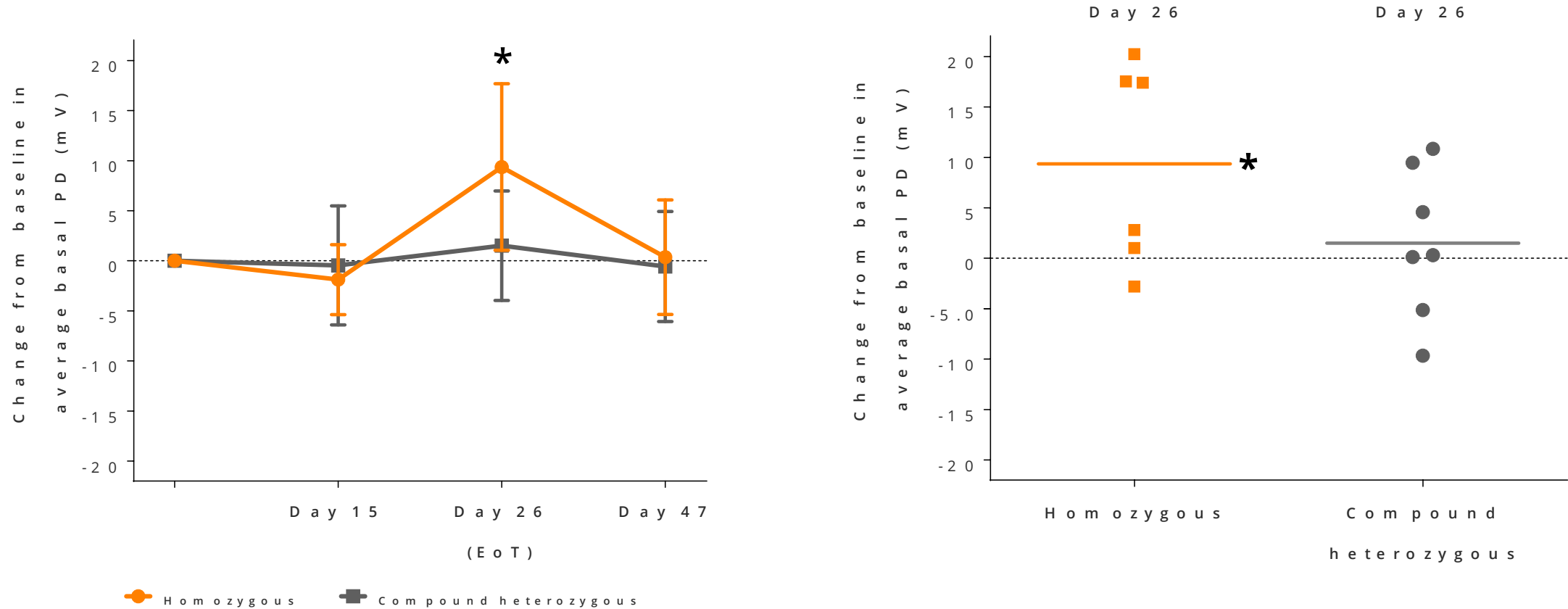


C o m p o u n d h e t e r o z y g o u s c o h o r t



■ Average nostrils ■ Most polarized nostril at each time point ■ Least polarized nostril carried forward

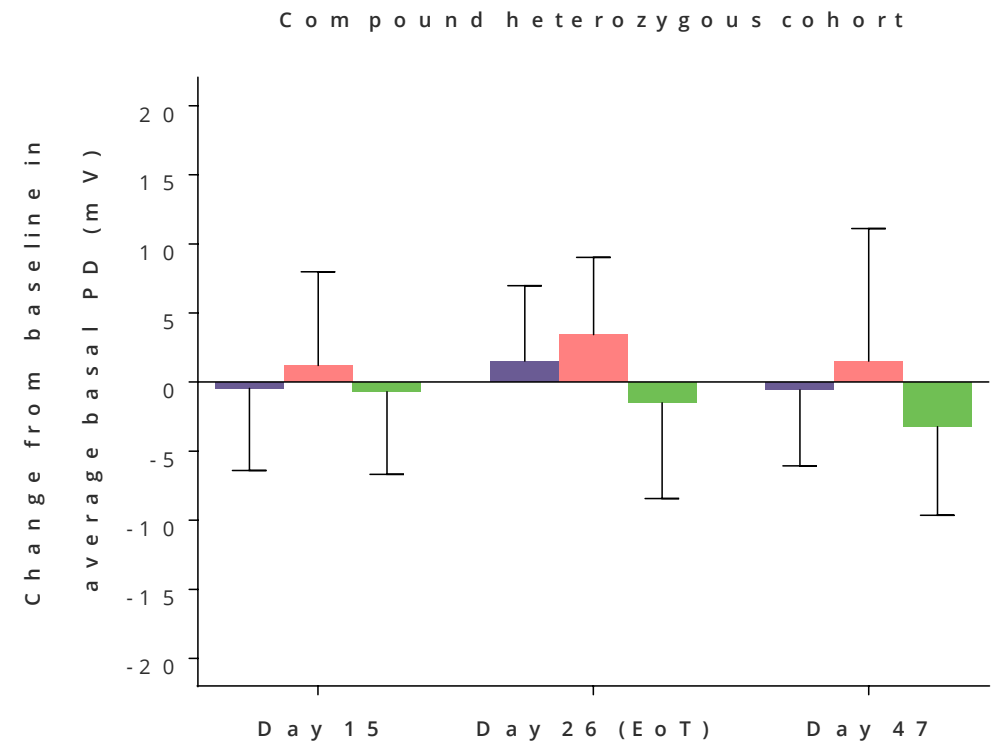
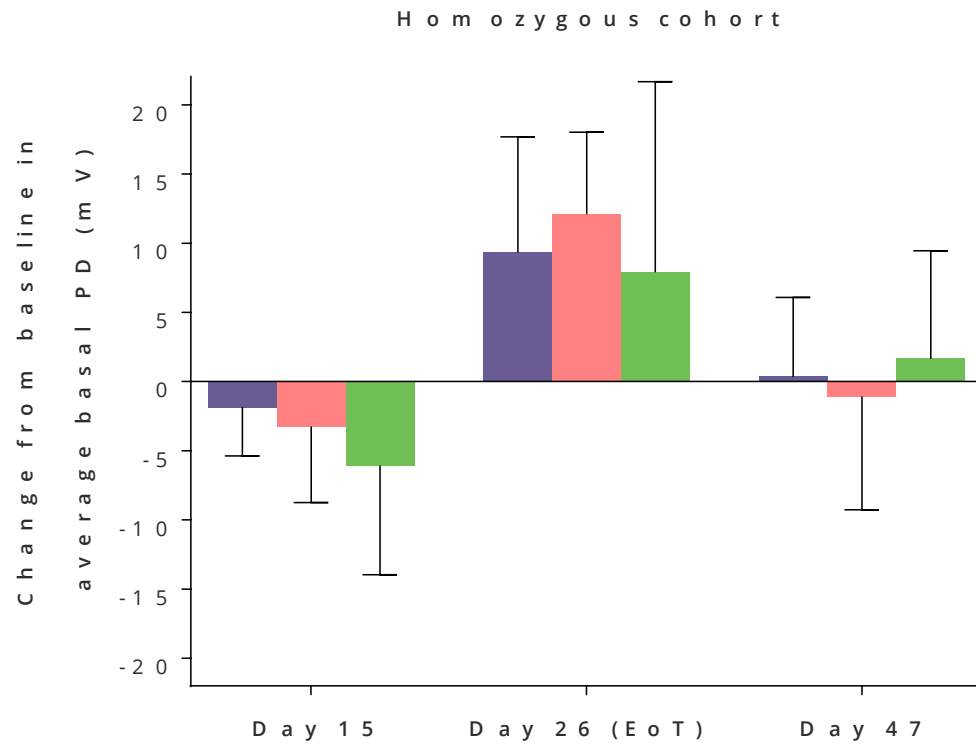
Sodium Transport: Average Basal PD



* Mean change average basal PD at Day 26 = +9.4 mV [90% CI 1.1 ; 17.7], P = 0.04

Sodium Transport: Average Basal PD

Sensitivity analysis



■ Average nostrils ■ Most polarized nostril at each time point ■ Least polarized nostril carried forward

Conclusions

- Repeated administration of the antisense oligonucleotide QR-010 resulted in evidence of improved CFTR biological activity in the nasal epithelium of homozygous F508del CF subjects. This is supported by various sensitivity analyses and improved (i.e. decreased) sodium transport
- The improved CFTR function observed for the homozygous F508del cohort is consistent with preclinical NPD data obtained in F508del CF mice and supports proof of concept of QR-010 biologic activity
- The cohort of compound heterozygous subjects evaluated did not respond to the QR-010 dose and regimen tested in this study
- These data support development of this novel RNA oligonucleotide approach for the F508del homozygous patient population

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