

New therapies and an update on organoids

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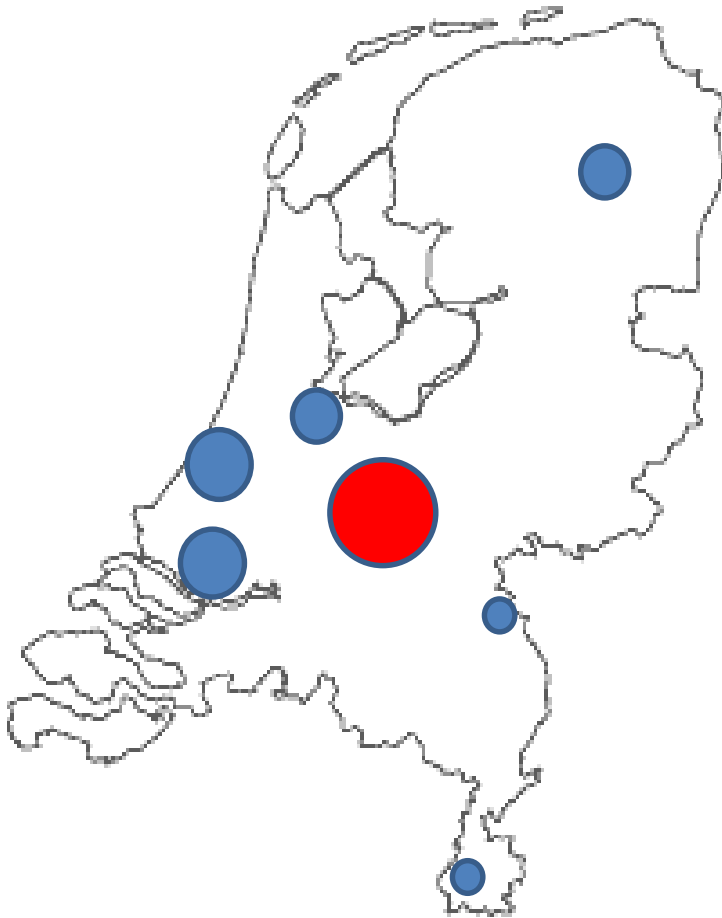
University Medical Center Utrecht

The Netherlands



UMC Utrecht

CF in The Netherlands (2017)



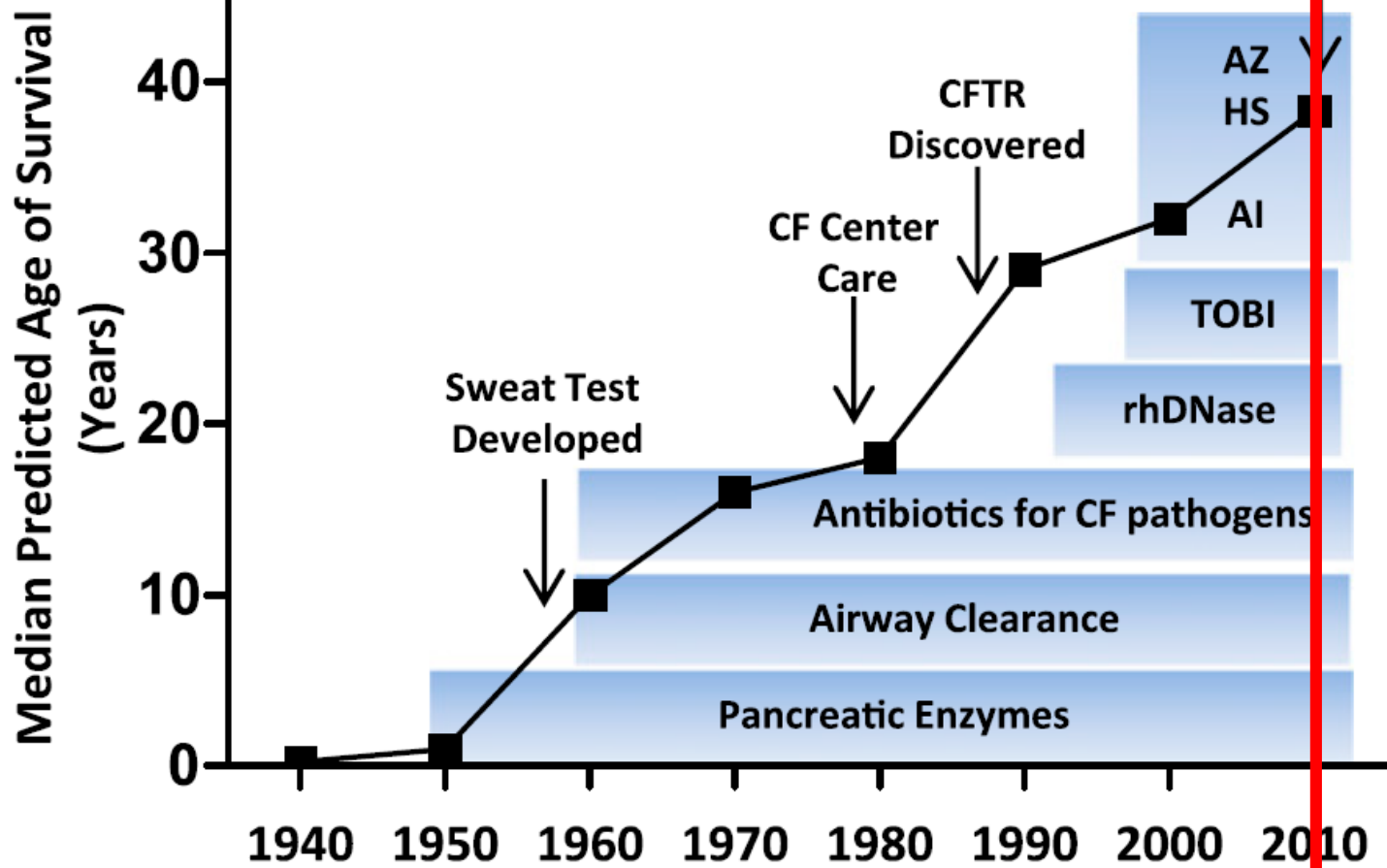
1600 patients with CF

2017: 900 patients > 18 years (56%)

Utrecht: 250 adults
215 children

3 paediatricians
3 adult pulmonologists
4 CF specialised nurses

2017: start of our Lifespan clinic
IV homecare system
2019: start E-health outpatient clinic



Complications

Cause

Ivacaftor

AZ

HS

AI

TOBI

rhDNase

Antibiotics for CF pathogens

Airway Clearance

Pancreatic Enzymes

CFTR
Discovered

CF Center
Care

Sweat Test
Developed

1940

1950

1960

1970

1980

1990

2000

2010

Cause and Aim

Normalisation of CFTR function in all mutations

Adults



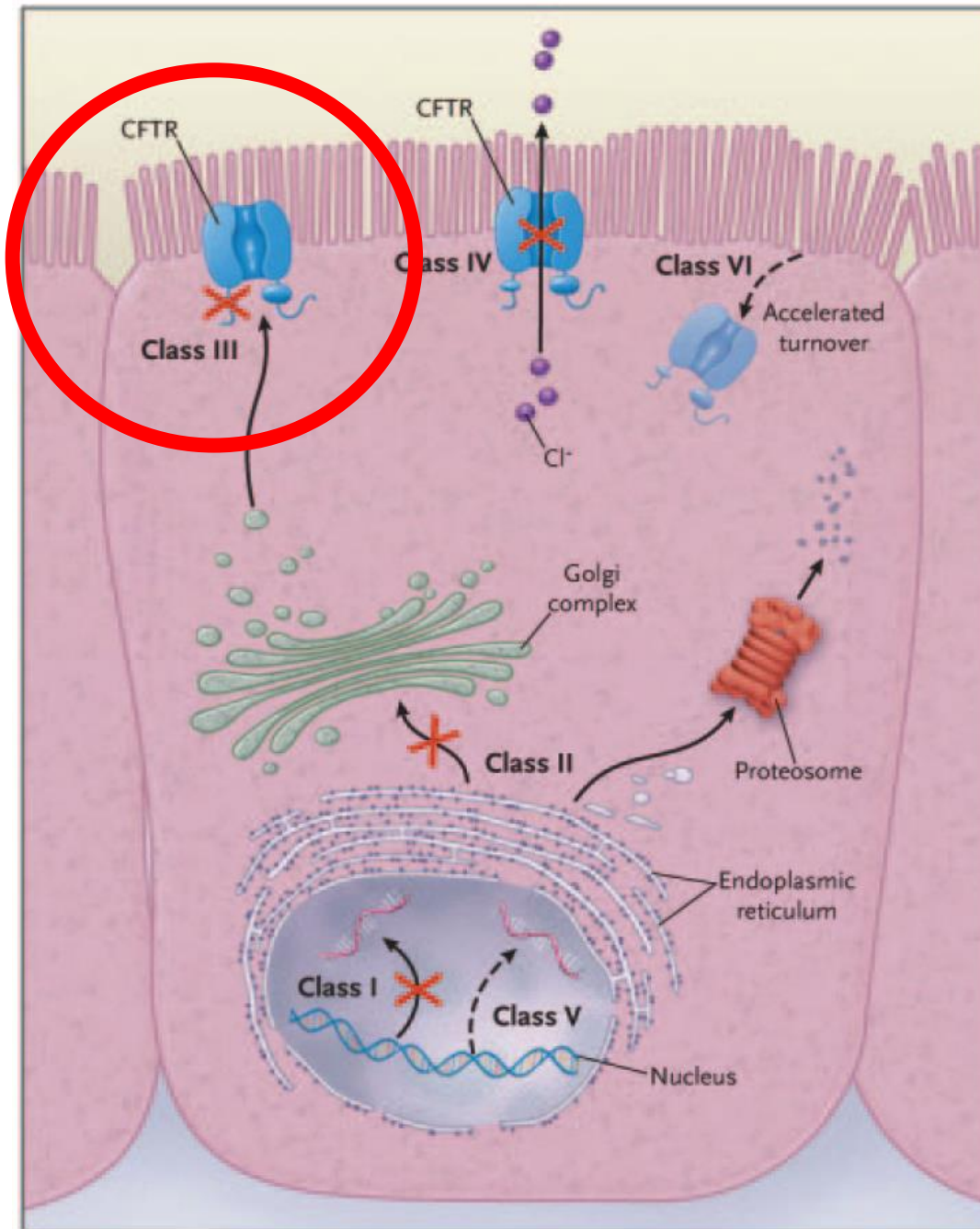
Children



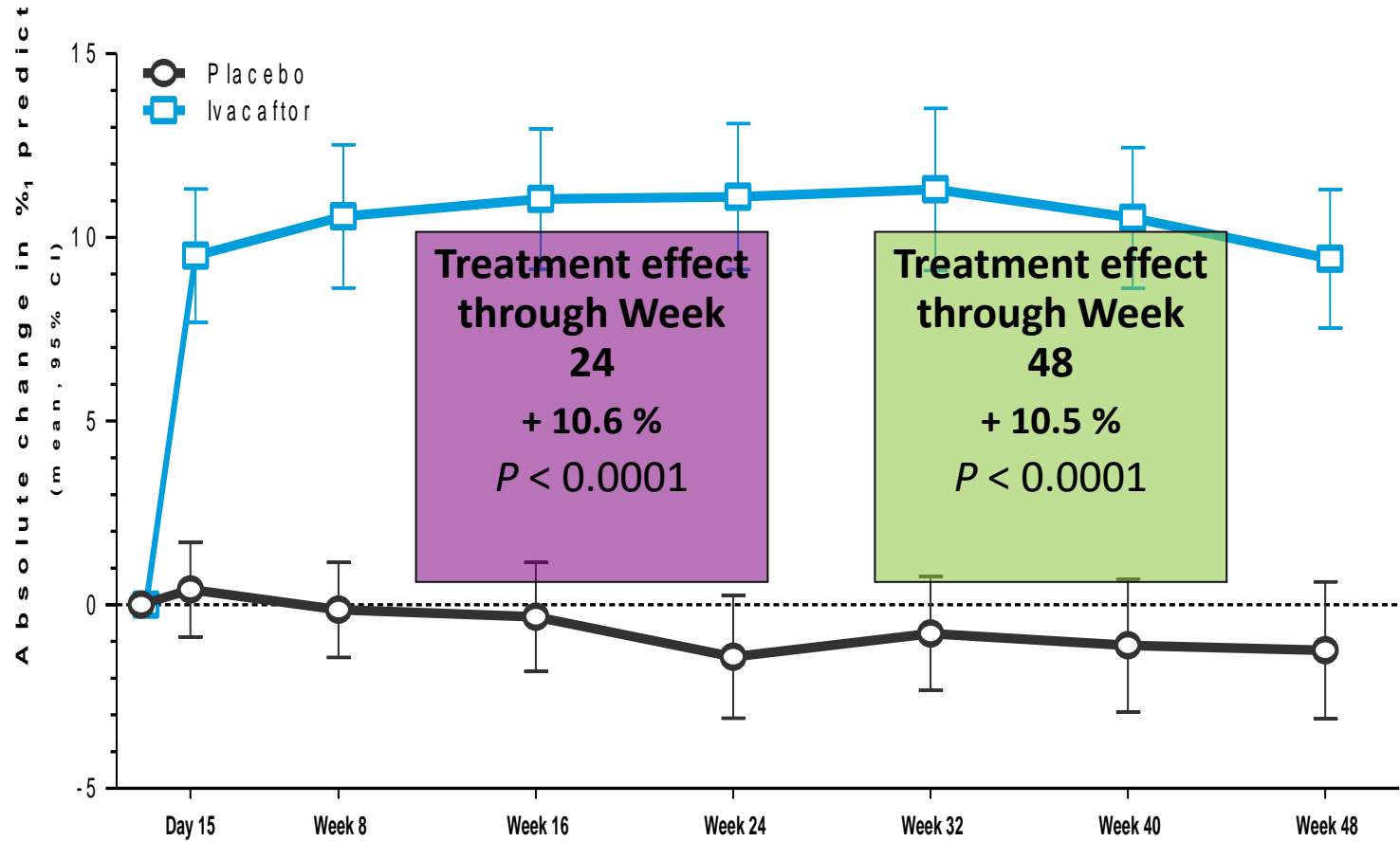
Newborns



?

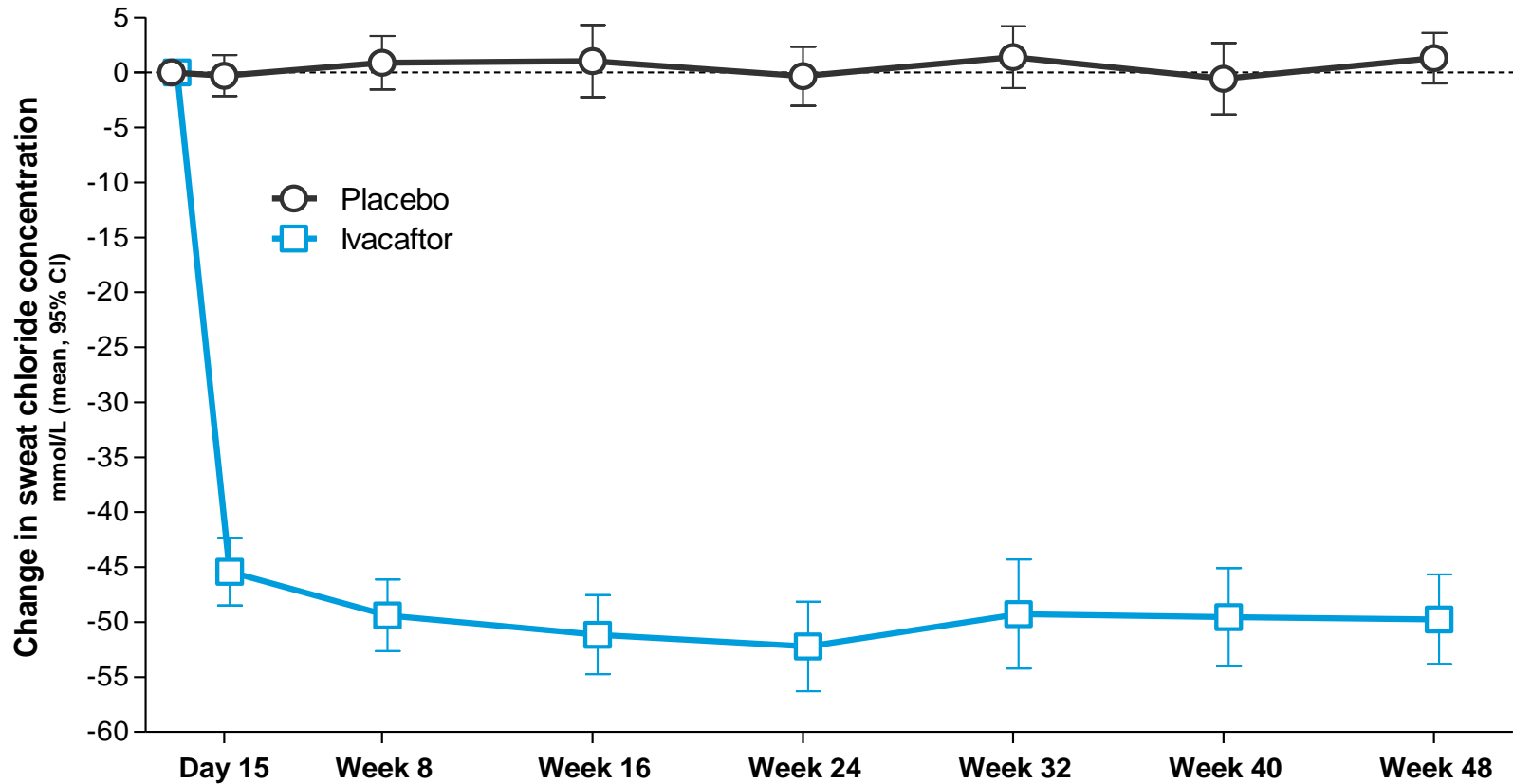


Ivacaftor, changes in FEV1



Class III

Ivacaftor, changes in sweat chloride



A Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamics of Ivacaftor in Subjects With Cystic Fibrosis Who Are Less Than 24 Months of Age and Have a CFTR Gating Mutation

Group 1: Participants 12 to < 24 months

Group 2: Participants 6 to < 12 months (enrollment begins after an assessment of data from Group 1)

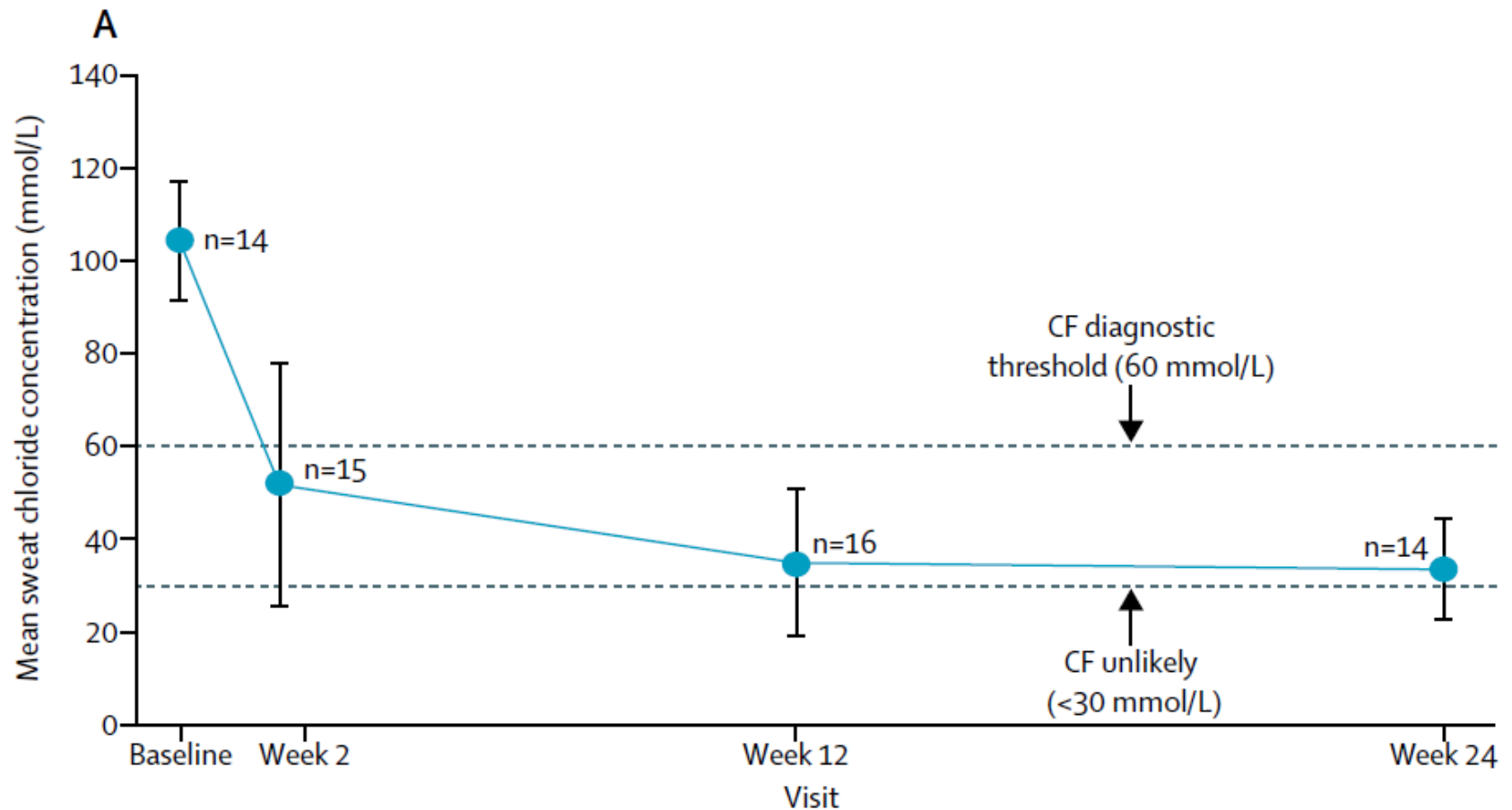
Group 3: Participants 3 to < 6 months (enrollment begins after an assessment of data from Group 2)

Group 4: Participants 0 to < 3 months (enrollment begins after an assessment of data from Group 3)

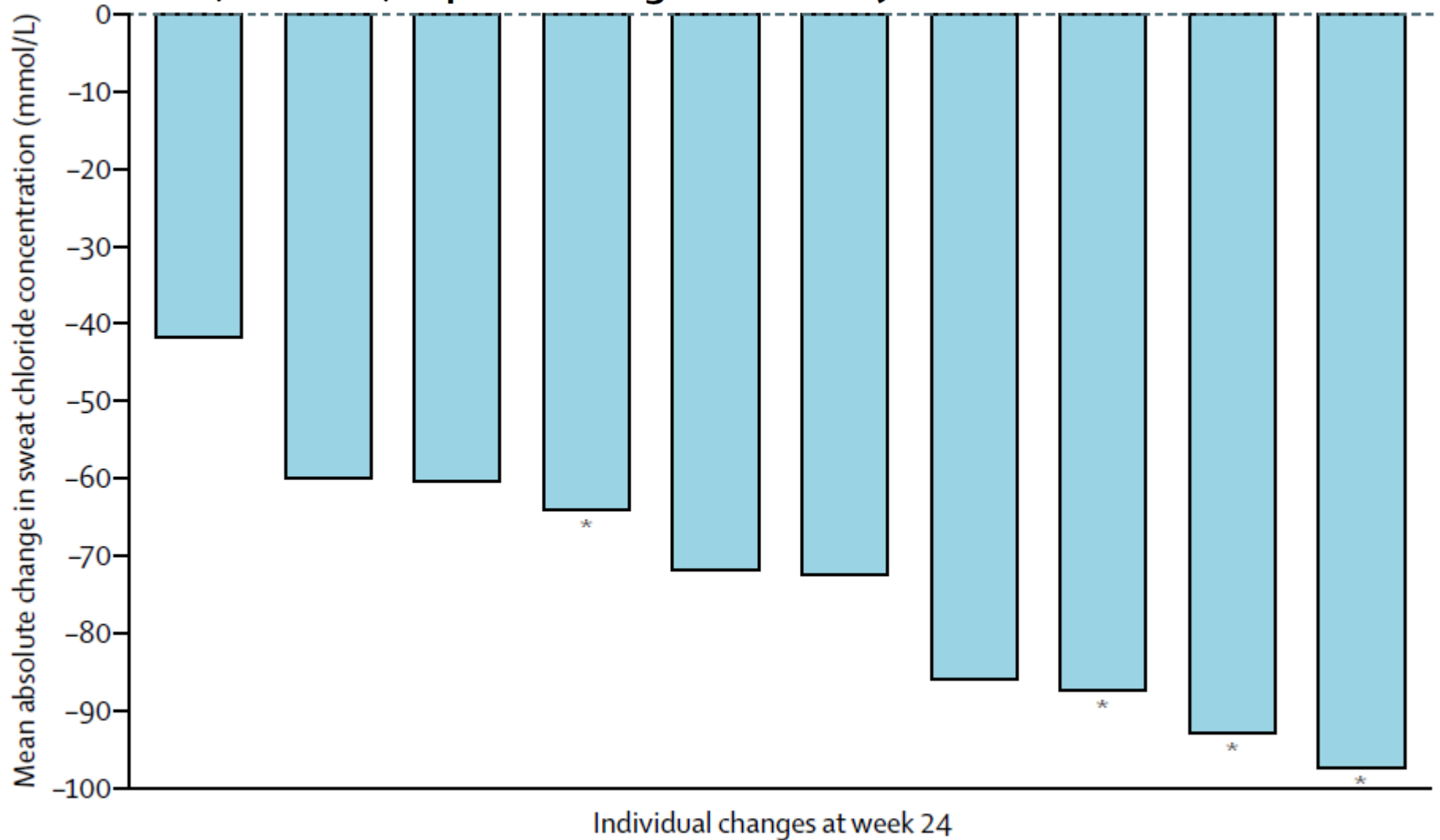
Started 2016, expected ending 2020 (Vertex)
(USA, Canada, UK, Ireland, Australia)

END points: Sweat chloride, side effects (ocular), pharmacokinetics

Ivacaftor treatment of cystic fibrosis in children aged 12 to <24 months and with a *CFTR* gating mutation (ARRIVAL): a phase 3 single-arm study

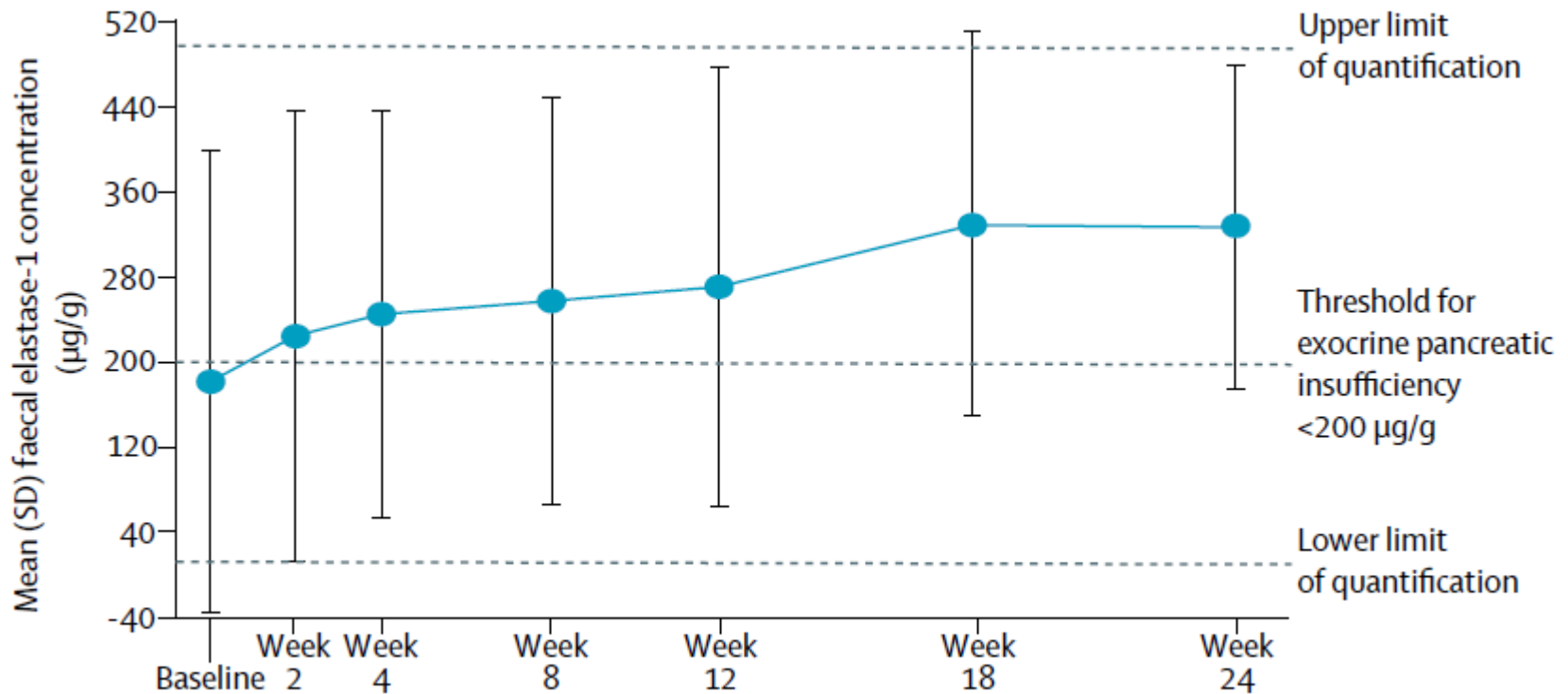


Ivacaftor treatment of cystic fibrosis in children aged 12 to <24 months and with a *CFTR* gating mutation (ARRIVAL): a phase 3 single-arm study



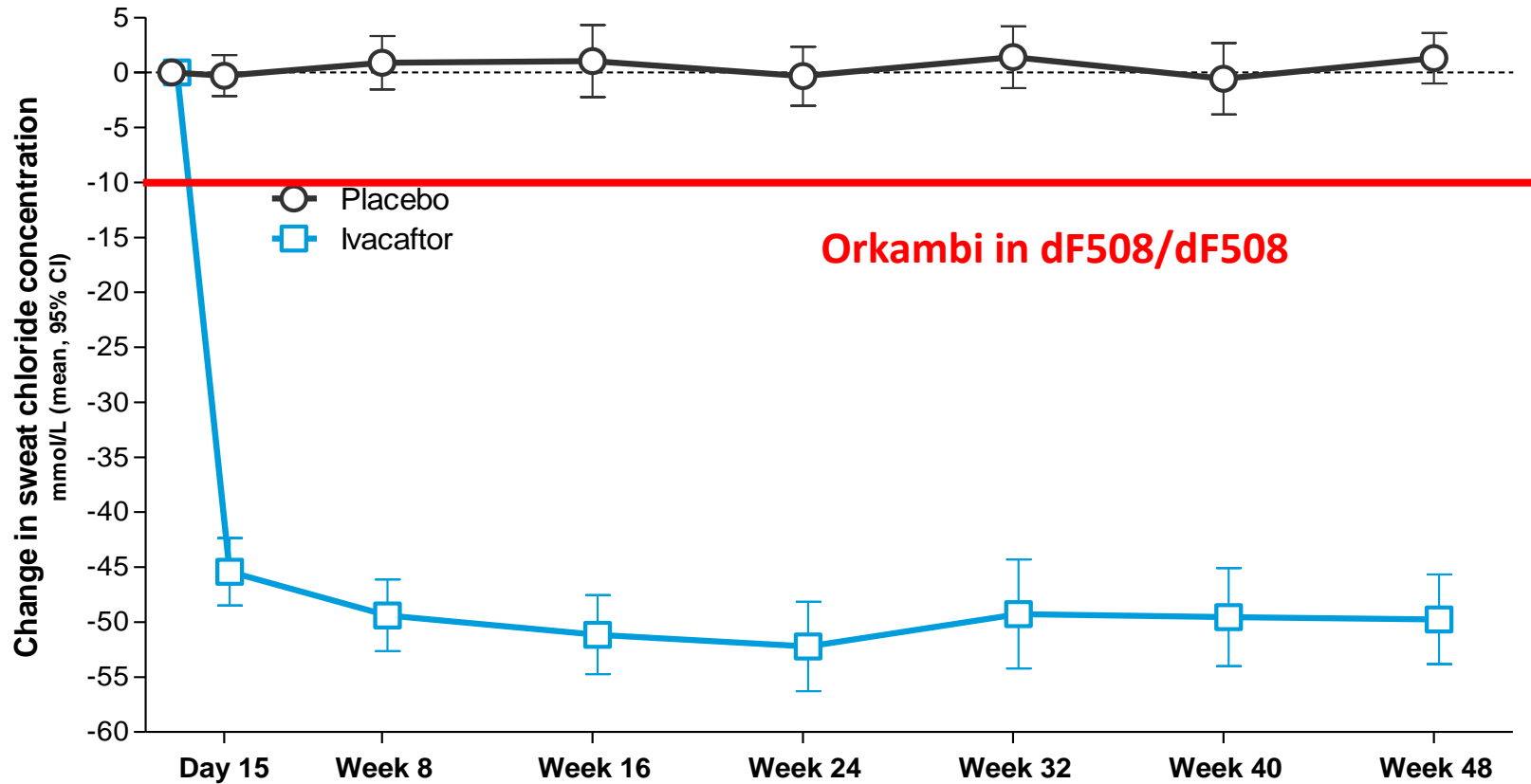
*Sweat chloride concentrations <30 mmol/L at week 24.

Ivacaftor treatment of cystic fibrosis in children aged 12 to <24 months and with a *CFTR* gating mutation (ARRIVAL): a phase 3 single-arm study

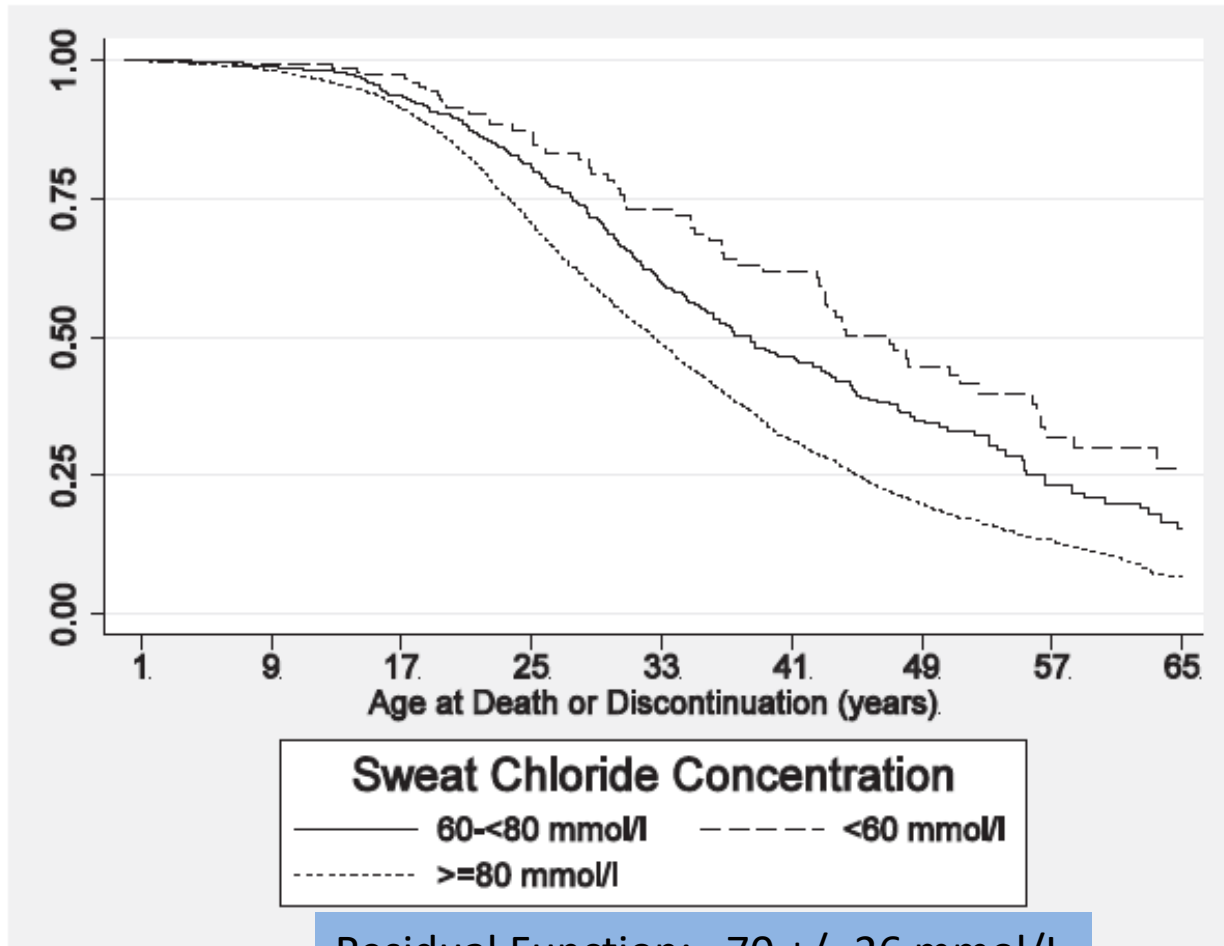


Class III

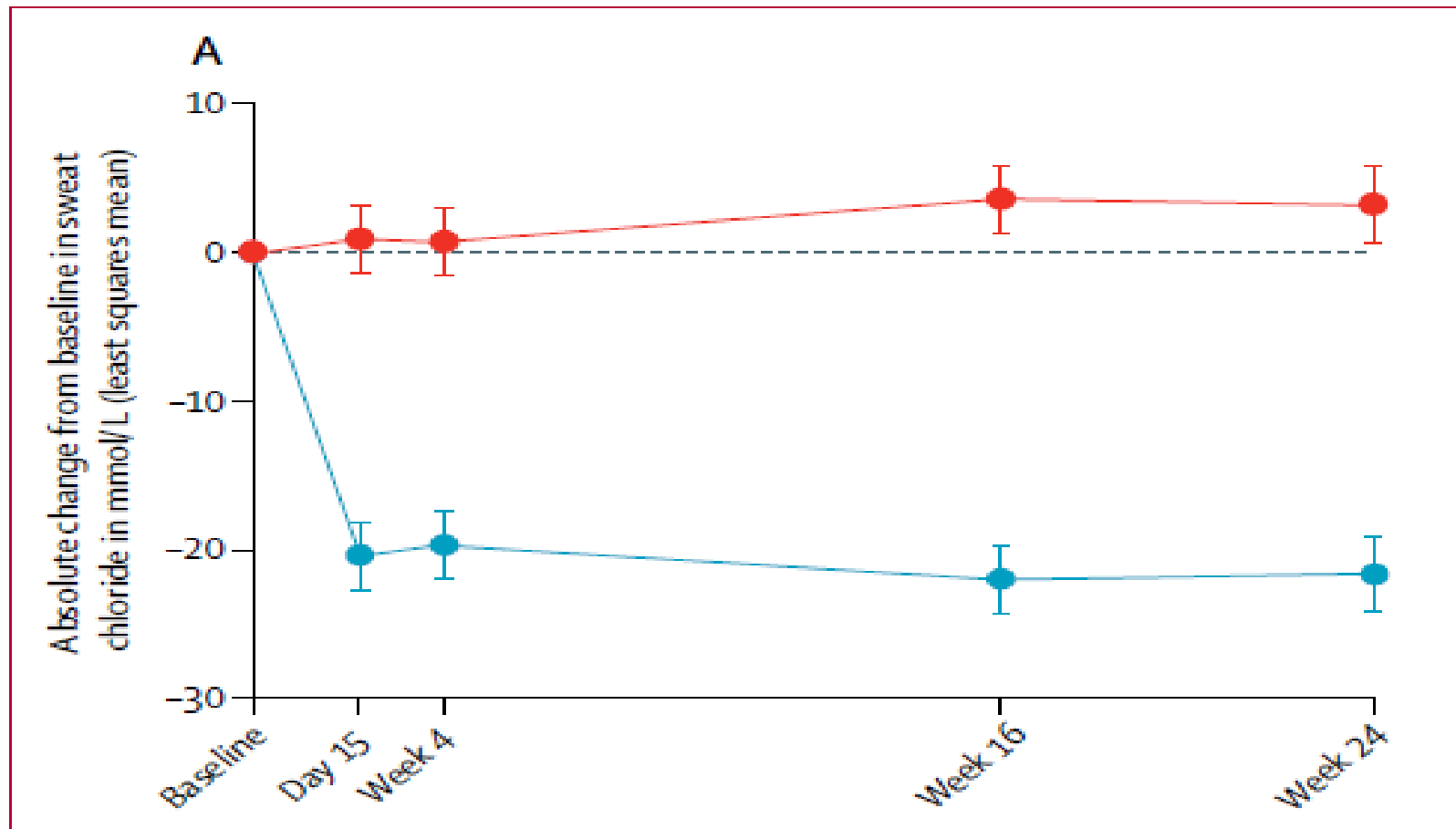
Ivacaftor, changes in sweat chloride



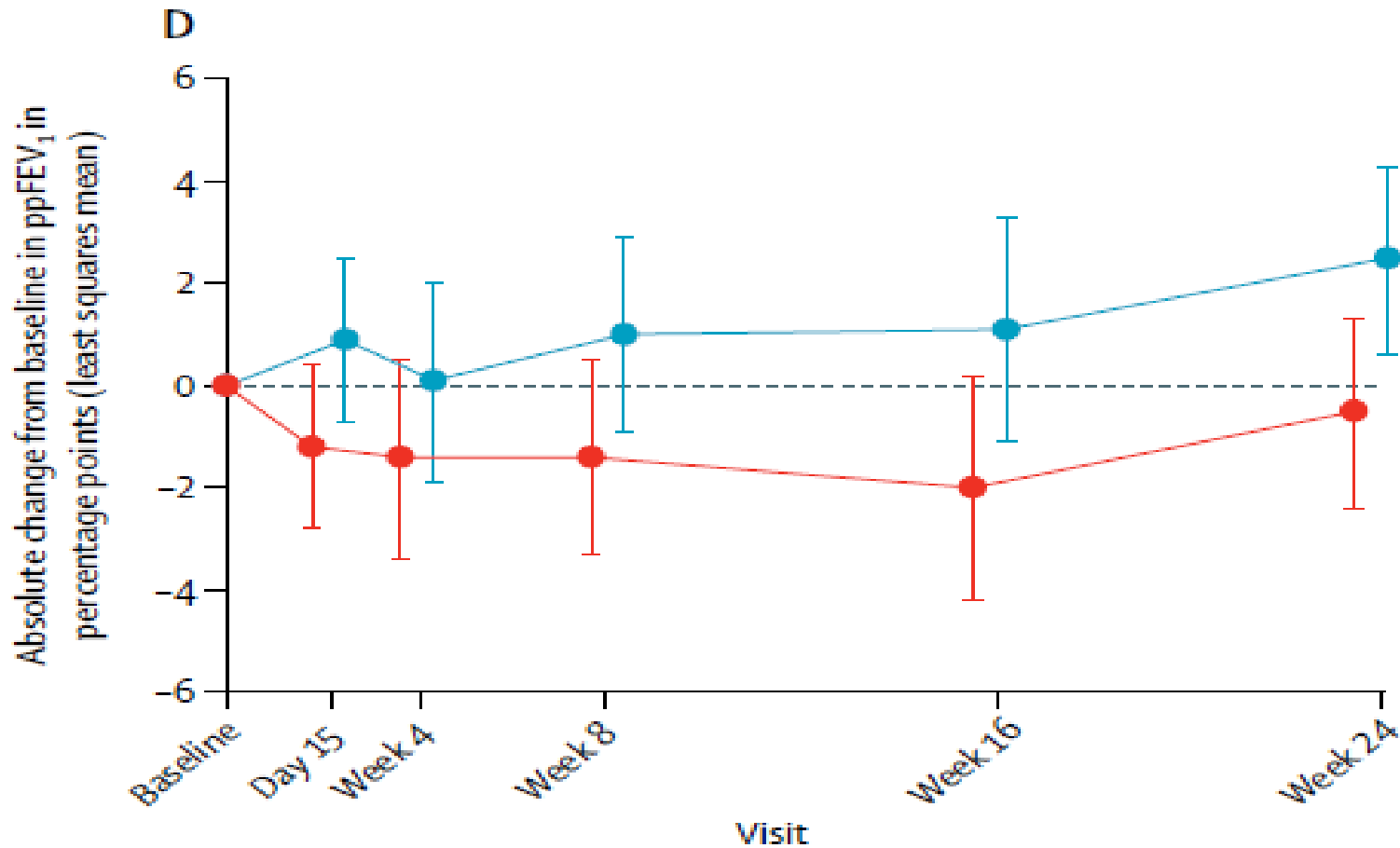
Mortality according to level of sweat chloride at baseline



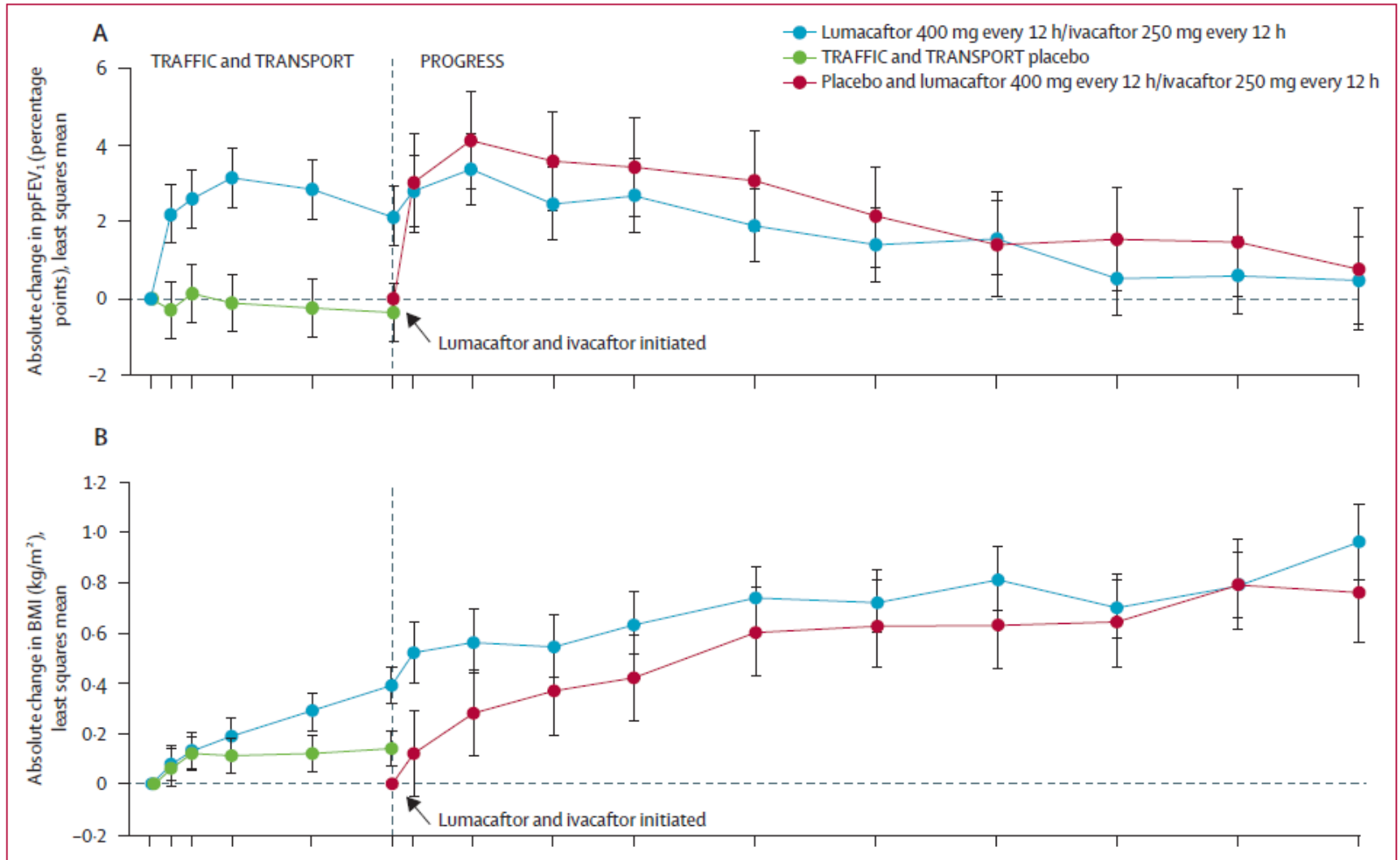
Efficacy and safety of lumacaftor and ivacaftor in patients aged 6–11 years with cystic fibrosis homozygous for *F508del-CFTR*: a randomised, placebo-controlled, phase 3 trial



Efficacy and safety of lumacaftor and ivacaftor in patients aged 6–11 years with cystic fibrosis homozygous for *F508del-CFTR*: a randomised, placebo-controlled, phase 3 trial



Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study.



Personal experiences

- Overall a significant change in our CF population (110 patients on Orkambi since nov 2017)
 1. More energy
 2. Lung function improvement, very variable
 3. Less exacerbations (hospitalizations)
 4. Decrease in the dosing of insulin (variable)
 5. Side effects in patients with worse lung disease.
 6. Change in sweat chloride (very variable)

Daily practice

Female 20 years:

	October 2016	October 2017:	October 2018
BMI	17.4	16.6	18.2
FVC:	73%	74%	98%
FEV1:	57	53%	73%

SweatCl:	103	56 mmol/L
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Male 26 years:

	October 2016	October 2017:	June 2018
BMI	24,5	25,4	25,5
FVC:	71%	74%	76%
FEV1:	49%	47%	50%

SweatCl: 90 96 mmol/L

Problems with gastric emptying.
Disappeared after stopping Orkambi

Lumacaftor/Ivacaftor reduces pulmonary exacerbations in patients irrespective of initial changes in FEV1☆

Table 2

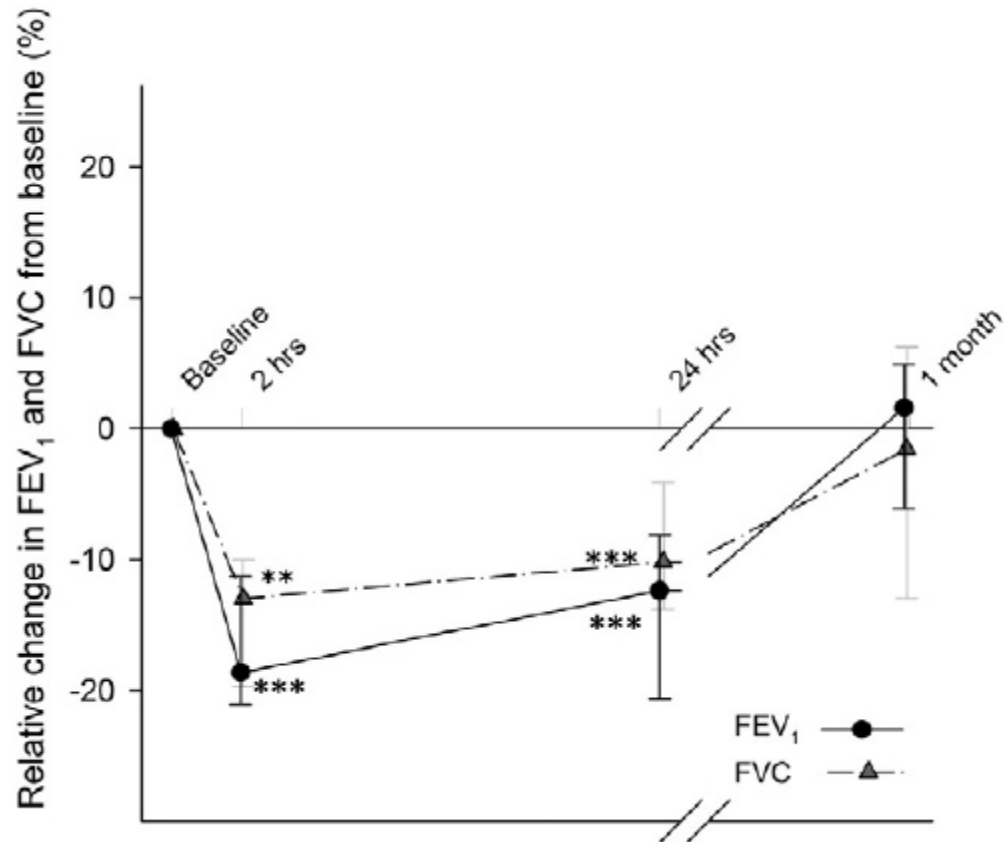
Mean number of days of PEx by treatment with LUM 400 mg q12h/IVA 250 mg q12h or placebo and change in ppFEV₁ threshold category. *

	Placebo (n = 371)	LUM 400 mg q12h/IVA 250 mg q12h			
		Absolute change ≤ 0 (n = 146)	Absolute change > 0 (n = 223)	Relative change < 5% (n = 228)	Relative change ≥ 5% (n = 141)
Mean days with PEx (SD)	15.7 (24.8)	11.5 (23.1)	5.9 (11.9)	8.9 (19.8)	6.9 (12.6)
P value vs placebo	–	<0.0001	<0.0001	<0.0001	<0.0001
Mean days on IV antibiotics for PEx (SD)	10.1 (20.5)	5.4 (15.8)	2.8 (8.2)	3.8 (13.1)	3.7 (9.5)
P value vs placebo	–	<0.0001	<0.0001	<0.0001	<0.0001
Mean days hospitalized for PEx (SD)	7.6 (18.8)	3.6 (13.7)	1.8 (6.3)	2.6 (11.3)	2.4 (7.2)
P value vs placebo	–	<0.0001	<0.0001	<0.0001	0.0005

IV, intravenous; IVA, ivacaftor; LUM, lumacaftor; PEx, pulmonary exacerbation; ppFEV₁, percent predicted forced expiratory volume in 1 s; q12h, every 12 h; SD, standard deviation.

**Side effects of Orkambi
and
how to prevent them.**

Immediate effects of lumacaftor/ivacaftor administration on lung function in patients with severe cystic fibrosis lung disease



N= 12

FEV1 <40% predicted

Immediate effects of lumacaftor/ivacaftor administration on lung function in patients with severe cystic fibrosis lung disease

Table 1

Respiratory-related adverse events reported at 4-hours, 24-hours and 1 month in twelve individuals.

	4-hours	24-hours	1-month
Respiratory-related adverse event n (%)	5 (41.6%)	10 (83.3%)	8 (66.6%)
Dyspnoea n (%)	2 (16.6%)	6 (50.0%)	7 (58.3%)
Chest-tightness n (%)	4 (33.3%)	8 (66.6%)	5 (41.6%)
Increased sputum production n (%)	0	2 (16.6%)	1 (8.3%)
Pulmonary exacerbation	NA	NA	6 (50.0%)

n = number of participants.

N= 12 , 3 discontinued treatment
FEV1 <40% predicted

Real-life initiation of lumacaftor/ivacaftor combination in adults with cystic fibrosis homozygous for the Phe508del CFTR mutation and severe lung disease

N= 53 FEV1 < 40%

Respiratory adverse events (AEs) were reported by 27 of 53 subjects (51%) and 16 (30%) discontinued treatment.

The mean absolute change in FEV1 was +2.06% after one month of treatment (P = 0.086) and +3.19% after 3 months (P = 0.009).

Orkambi is less tolerated in patients who need this treatment most!

Personal Experience / Observations with Orkambi and TEZ/IVA

- At present about 110 adults treated with Orkambi since November 2017
- Side effects:
 - dyspnea, chest tightness.
 - occur in a lot of patients.
 - are transient in about 3 weeks
 - patients with worse lung disease can't bridge these weeks.
 - some patients needed admission due to pulmonary deterioration and/or respiratory insufficiency.
 - TEZ/IVA: experience in clinical trial (n=12)
 - no side effects.

How to start treatment with Orkambi in patients with severe lung disease?

Male: 39 years

2016: start Compassionate use Orkambi: FEV1: 1,38L, (29 %)

Chest tightness, dyspnoea,
intolerant for Orkambi: stopped: FEV1: 1,27 (26%)

Screened for LOTx. 30-5-2018 FEV1: 1,04 (23%)

Restart Orkambi?????

Yes, we did, but how?

20-08-2018 FEV1: 1,46 (32%)

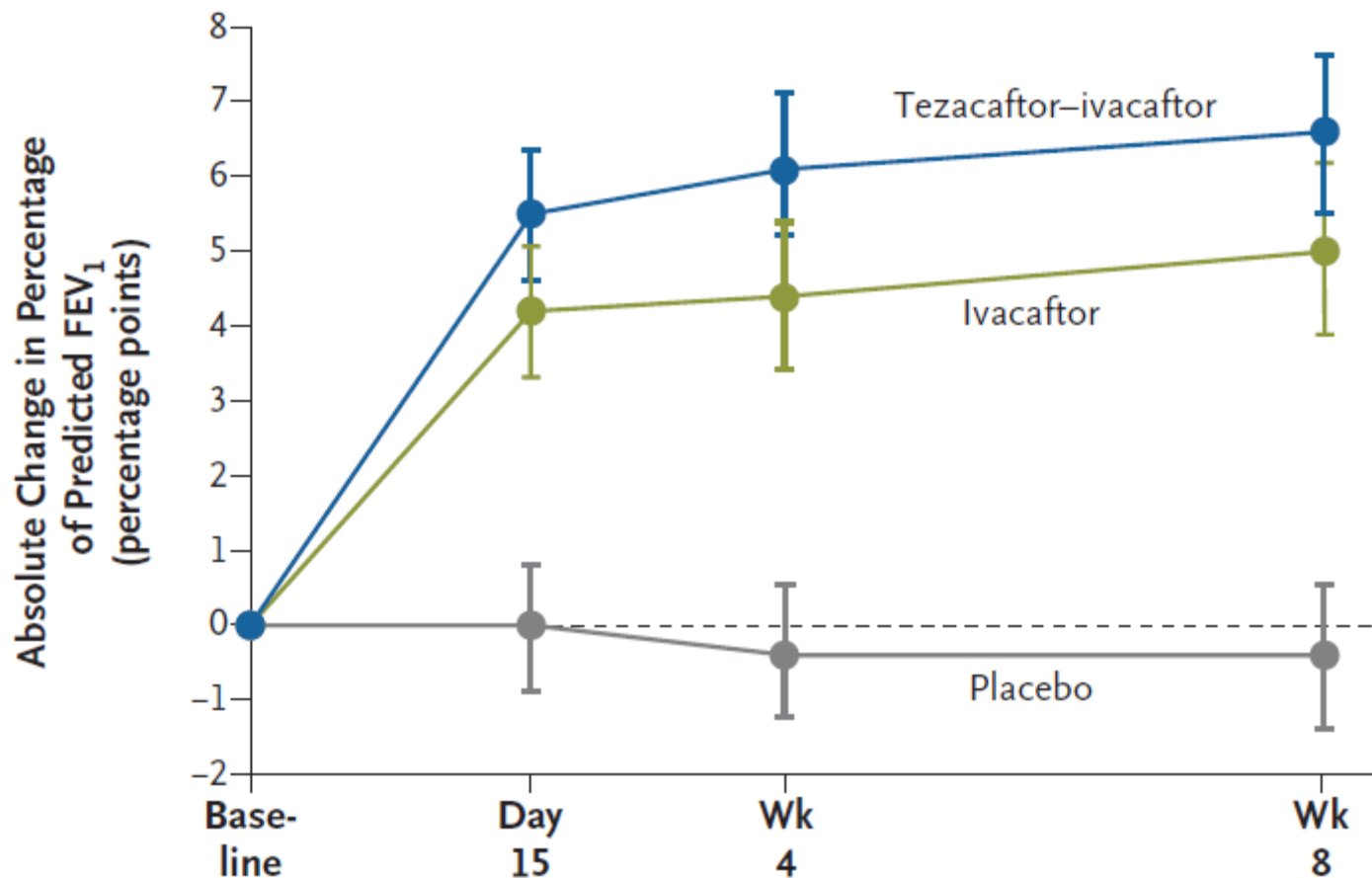
Works again, full time.

Learning from the compassionate use programme.

Patients with FEV1 < than 50%

Start with 1 tablet Orkambi and increase with 1 tablet every week.

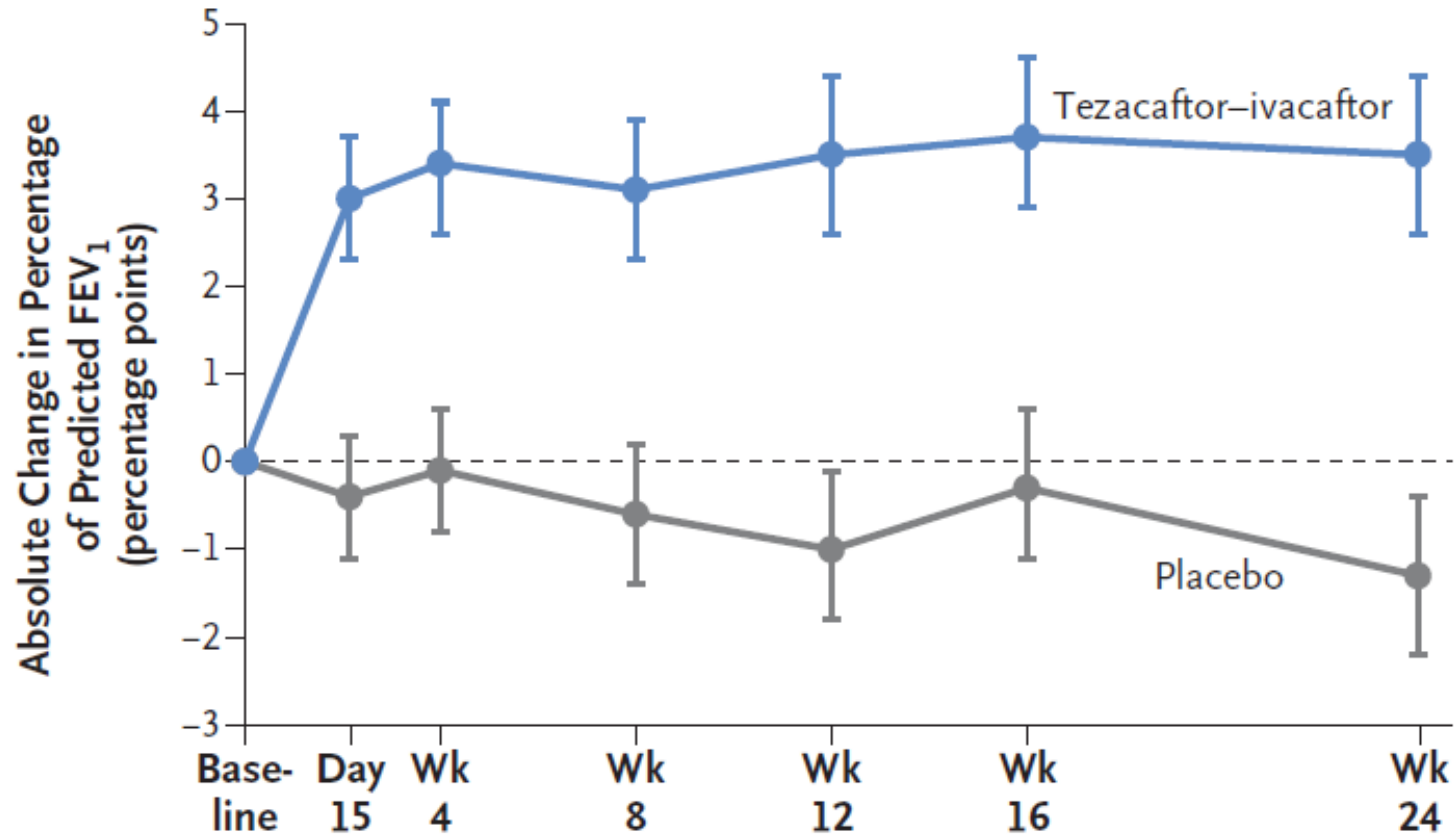
Tezacaftor–Ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis (in The Netherlands = 9% of all patients n=140)



Delta sweat chloride: -9,5mmol/L

No adverse events! (= comparable to placebo)

Tezacaftor–Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del



Delta sweat chloride: -10,1 mmol/L

No adverse events! (= comparable to placebo)

Triple therapies

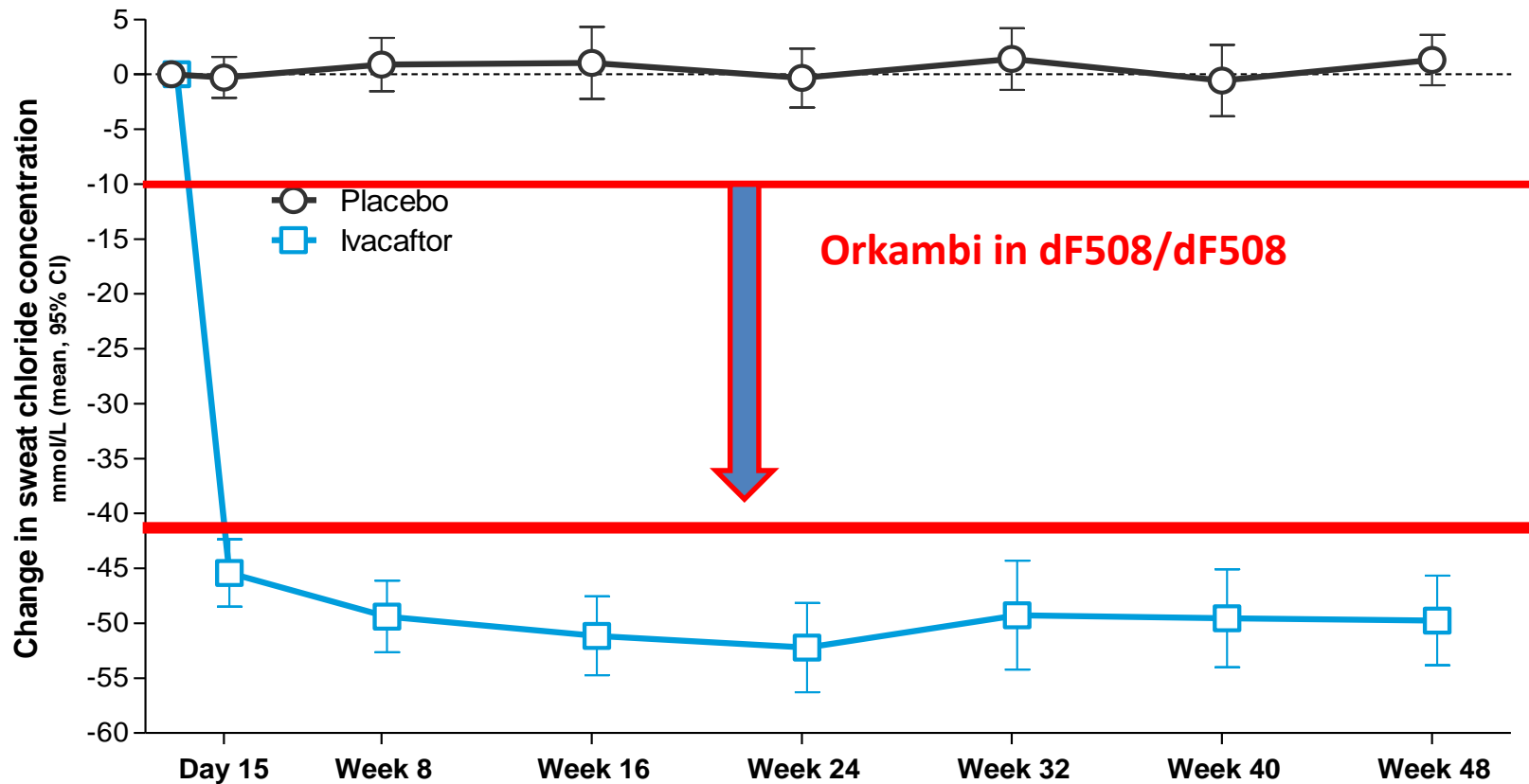
1. tezacaftor/ivacaftor + extra corrector VX 659 (fase II, eind: mrt 2018)
Patients: 1 x DF508 and one minimal function mutation
Fase II: onderzoek 4 weken: FEV1 + 13,3% , Chloor – 51,4mmol/L
2. tezacaftor/ivacaftor + extra corrector VX 445
Patients: 1 x DF508 and one minimal function mutation
Phase II: 4 weeks: FEV1 + 13,8%, Chloride – 39,1mmol/L

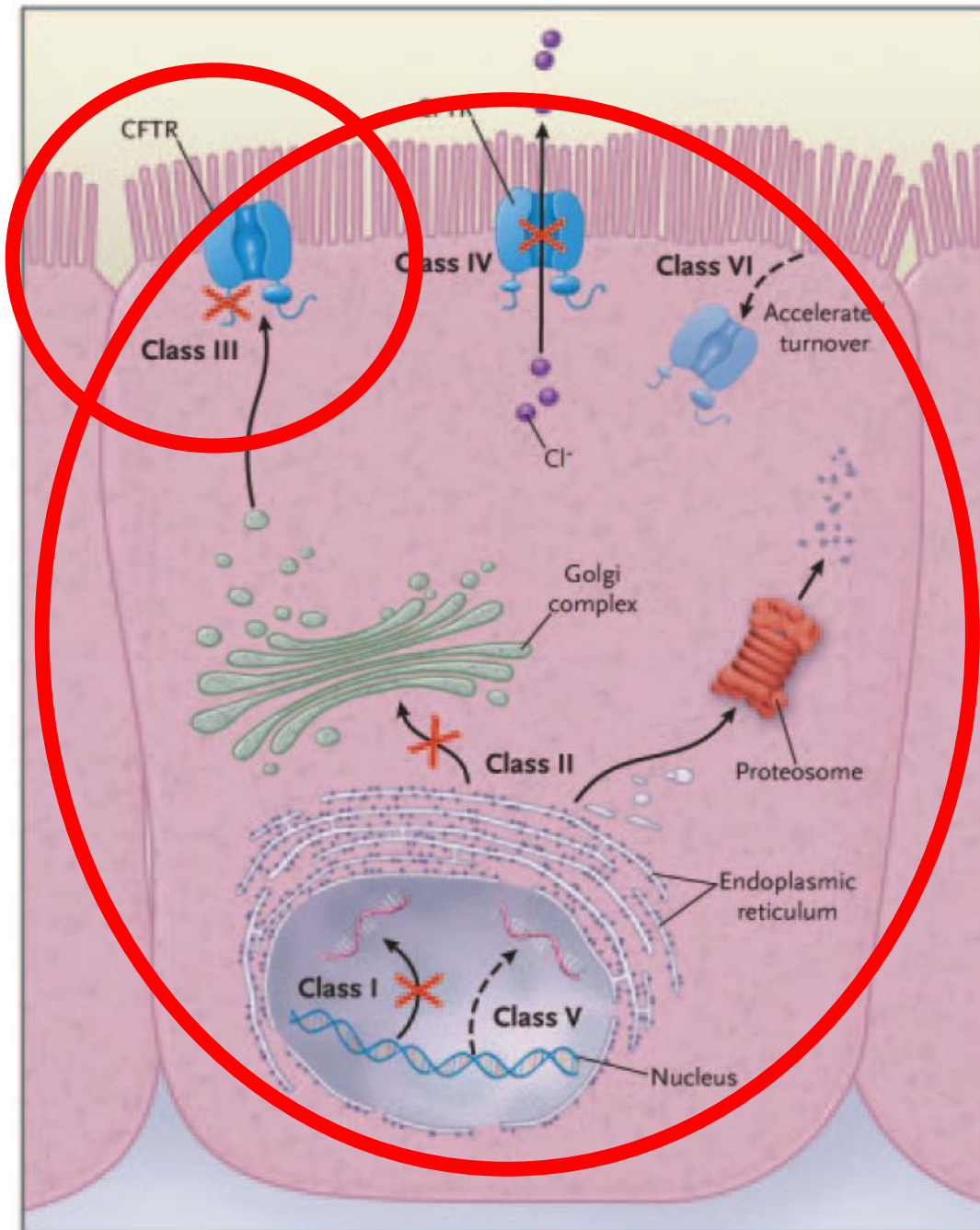
AND

These triple medications seem equally effective in homozygous patients and in homozygous dF508 together with a minimal function mutation.



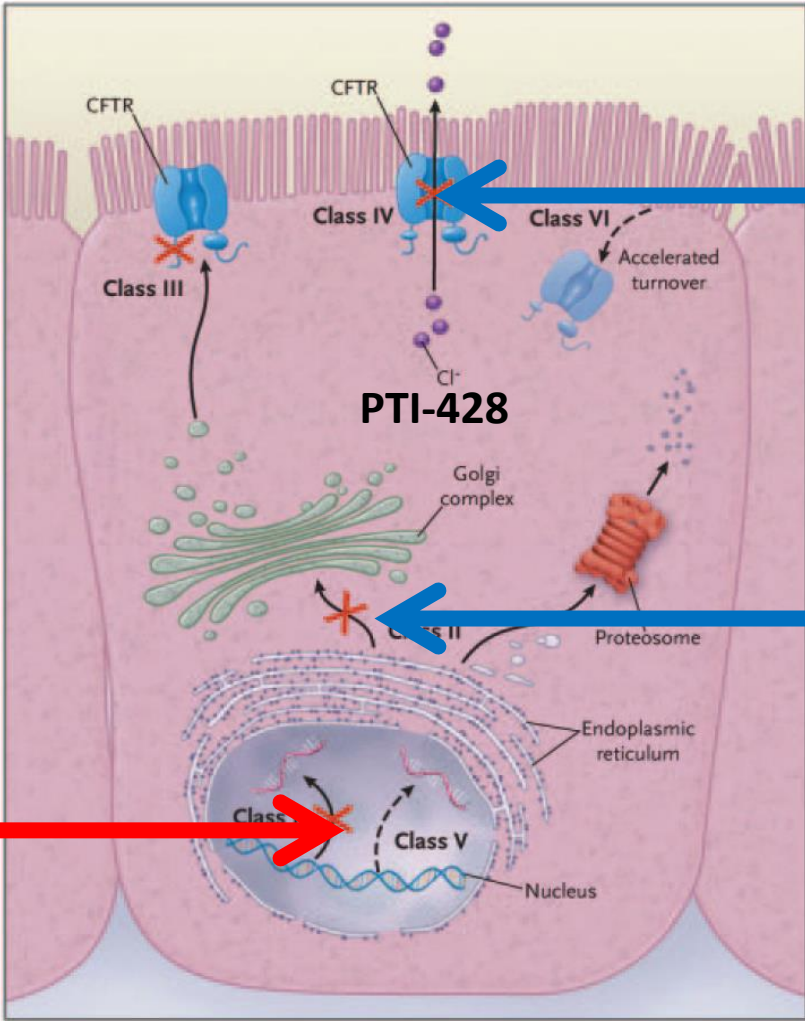
Tezacaftor Ivacaftor + VX 445/VX659 dF508/dF508 en dF508/minimale functie mutatie





What else is coming?

Amplifiers



Potentiator

Corrector

Amplifier

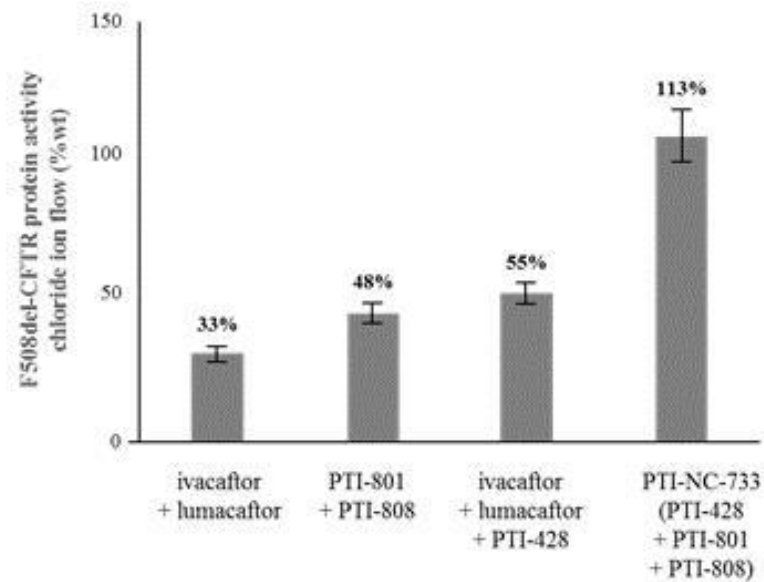
Proteostasis

PTI-428: Amplifier

Press release dec 2017:

Fase 2 onderzoek: Orkambi plus PTI-428

Toename FEV1 van 5,2% t.o.v. baseline.

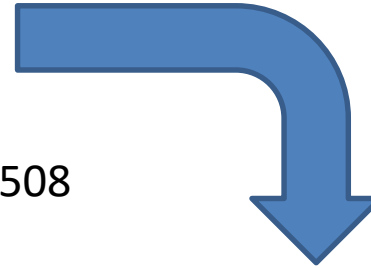


Proteostasis

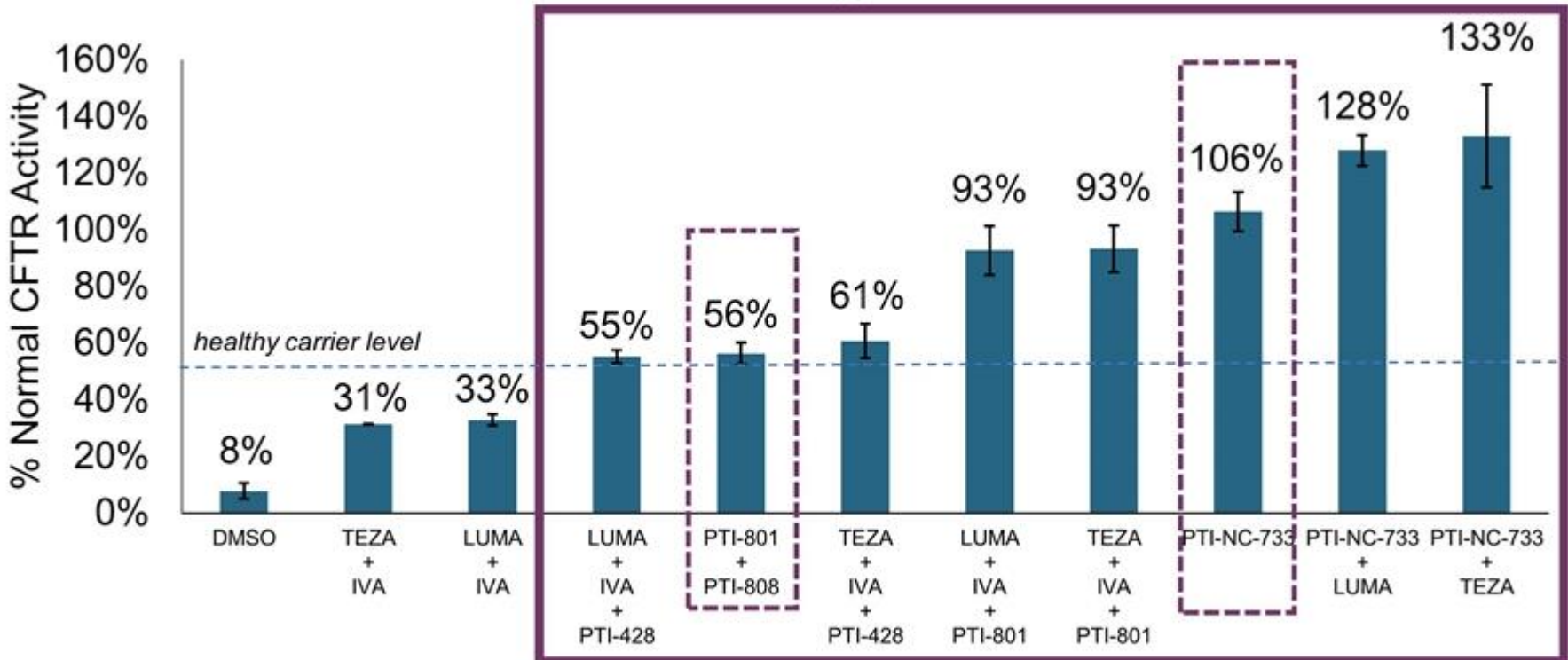
PTI-428: Amplifier

PTI-801: Corrector

PTI-808: Potentiator



In vitro data: dF508/dF508

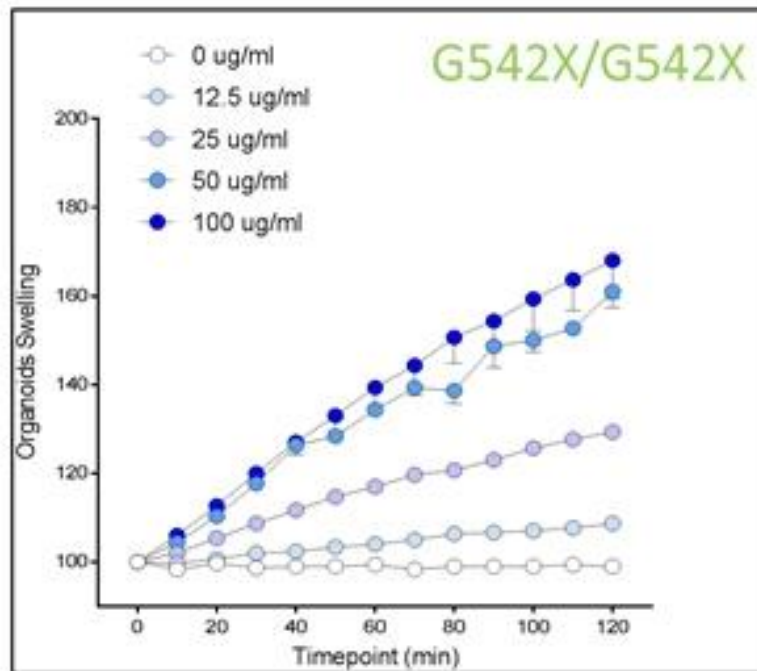


Concentrations of compounds: 3uM TEZA, 1uM IVA, 3uM LUMA, 10uM PTI-428, 10uM PTI-801, 1uM PTI-808

PTI-NC-733 is PTI-428 + PTI-801 + PTI-808

Class I/Ithe most difficult one

ELX-02: seems to work in vitro on organoids



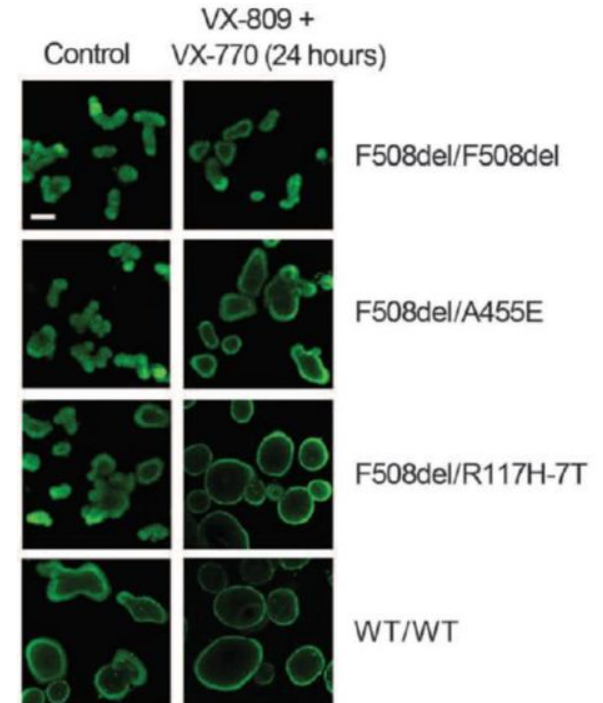
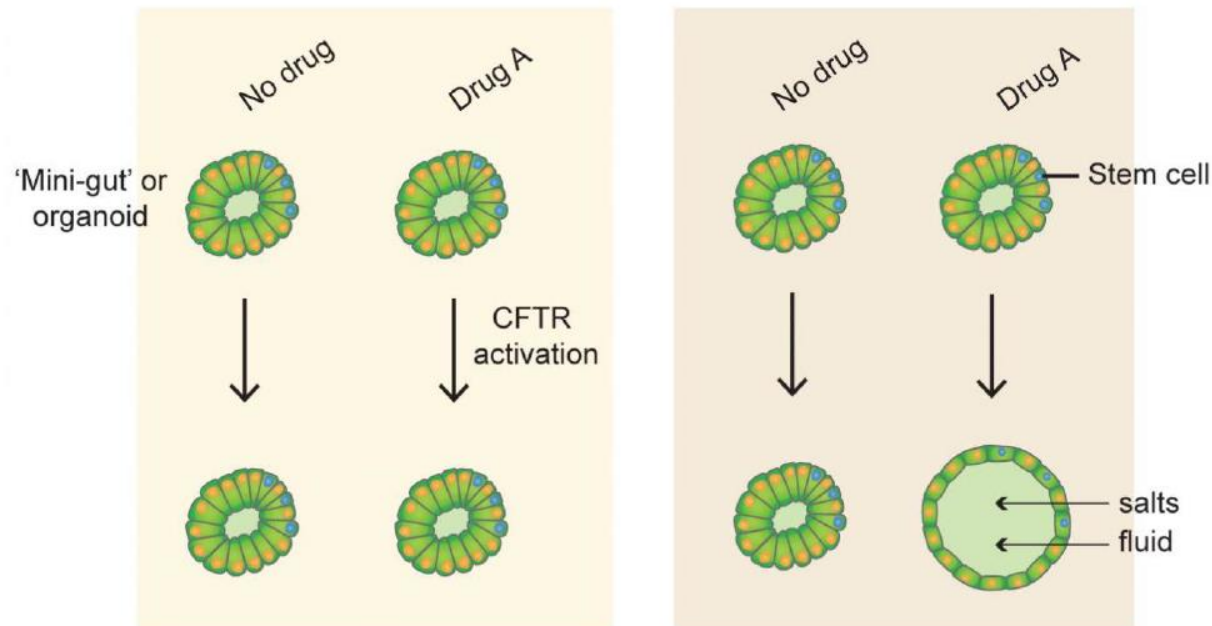
2019:Phase I and II trials

Organoids

Organoid response to therapy

Patient 1: Non-responder

Patient 2: Drug responder

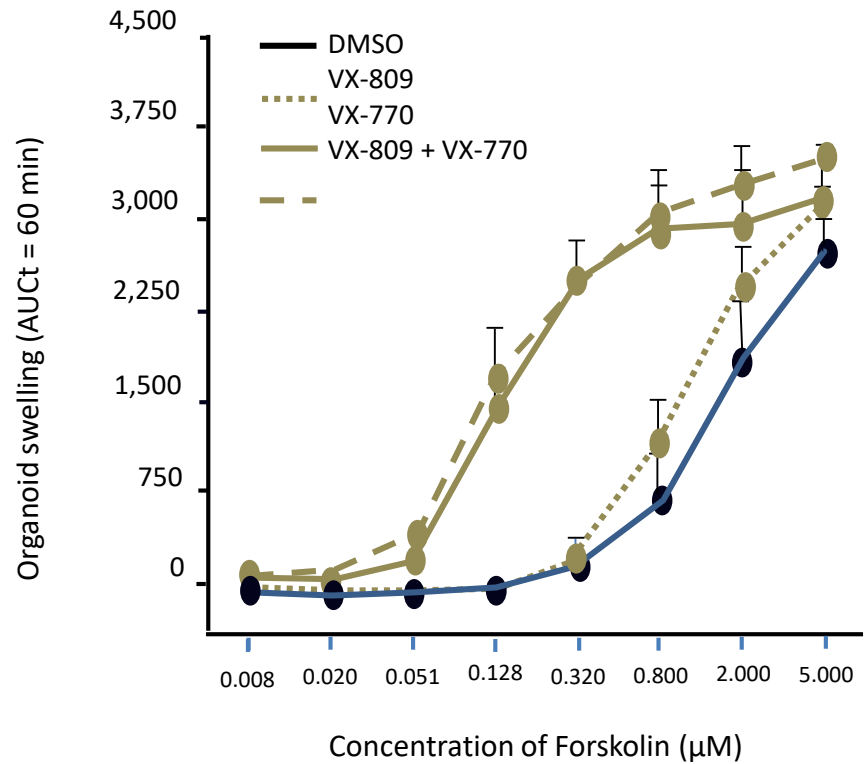


Use of Organoids in the individual patient

Female 39

	Baseline	4 weeks Ivacaftor	4-week washout
Weight	66.5	67.2	67.5
FEV ₁ (% predicted)	52	65	59
Raw	144	95	125
Sweat chloride	89	57	91

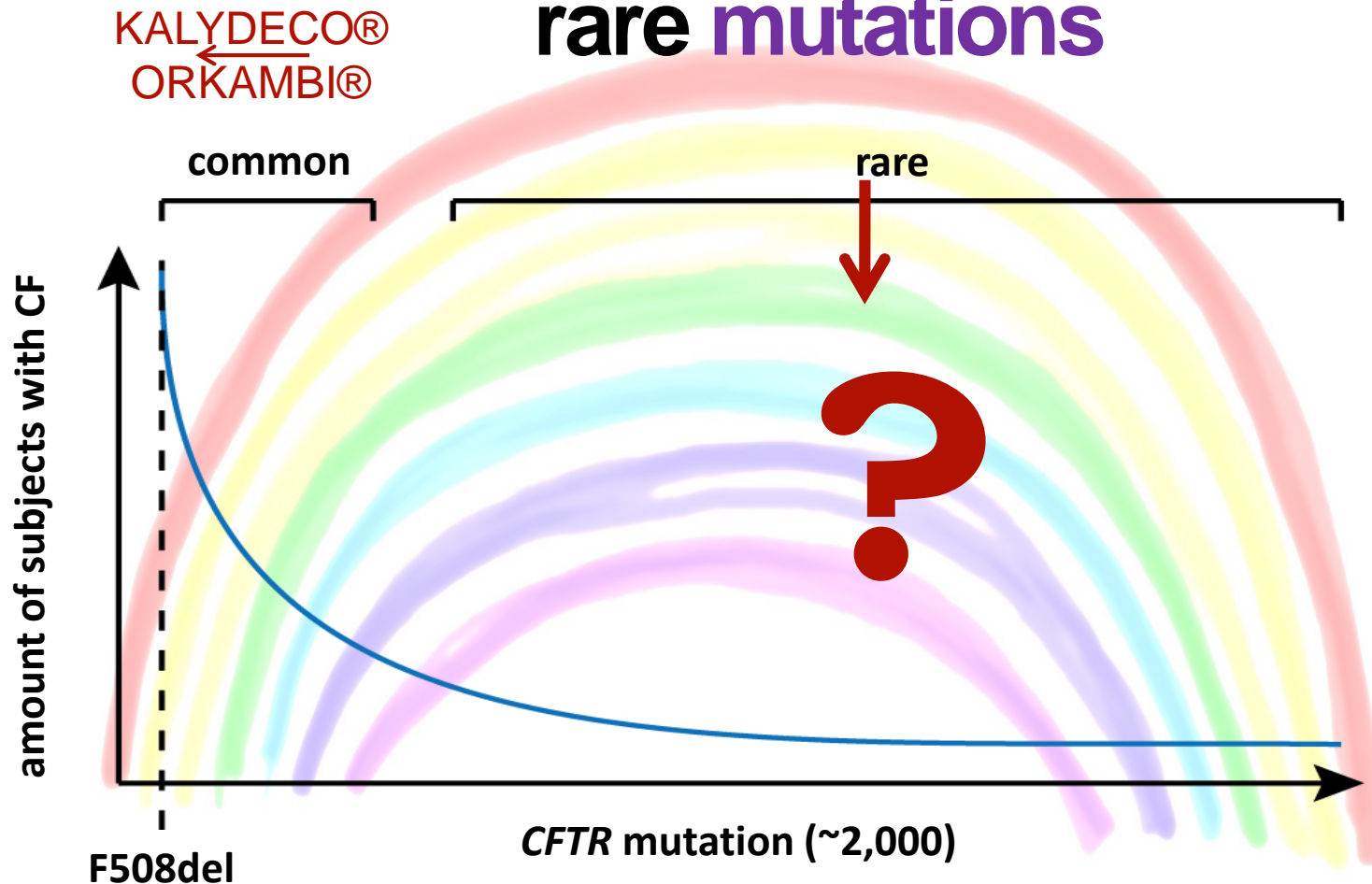
dF508/G1249R



AUCt, area under the curve; DMSO, dimethyl sulphoxide; FEV₁, forced expiratory volume in 1 second

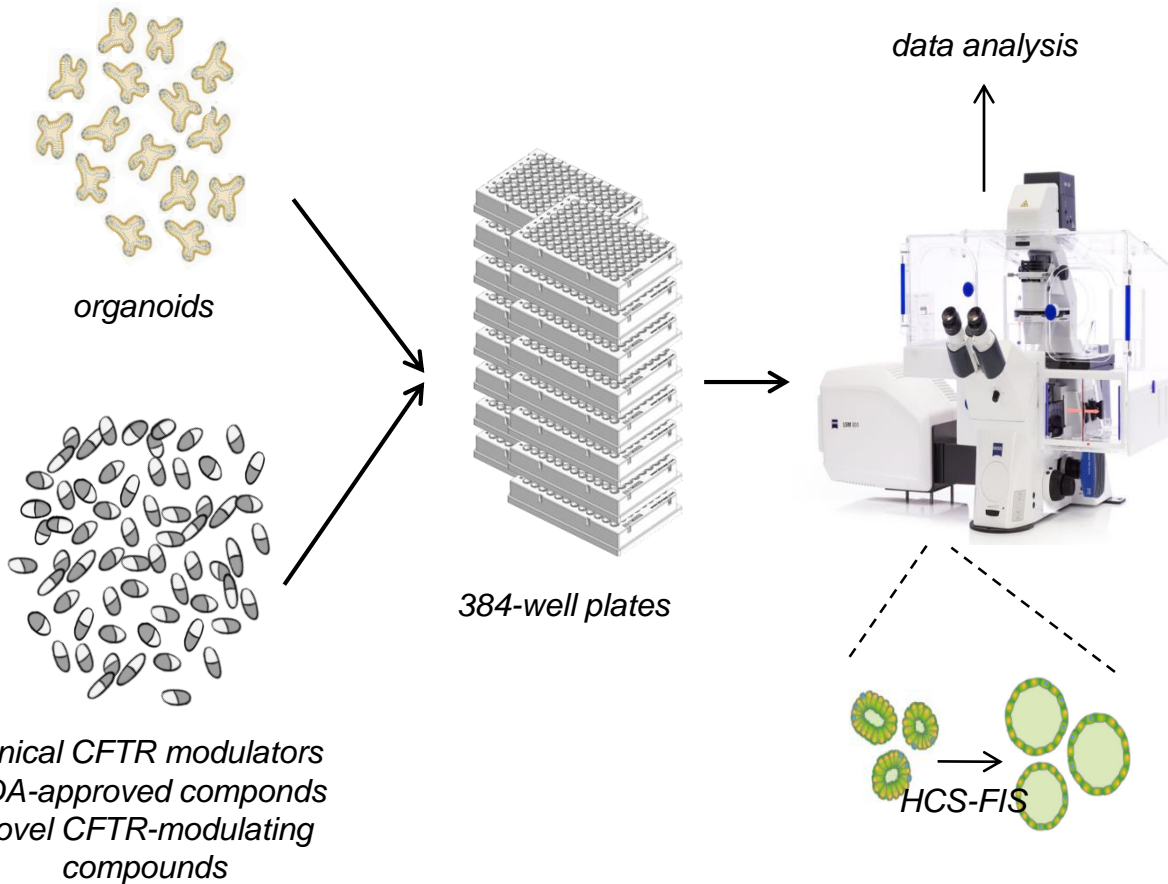
Individual drug screening in subjects with

rare mutations



Identification of novel CFTR-restoring compounds for CF patients with an extremely rare *CFTR* mutation

High-content FIS screening assay (HCS-FIS)

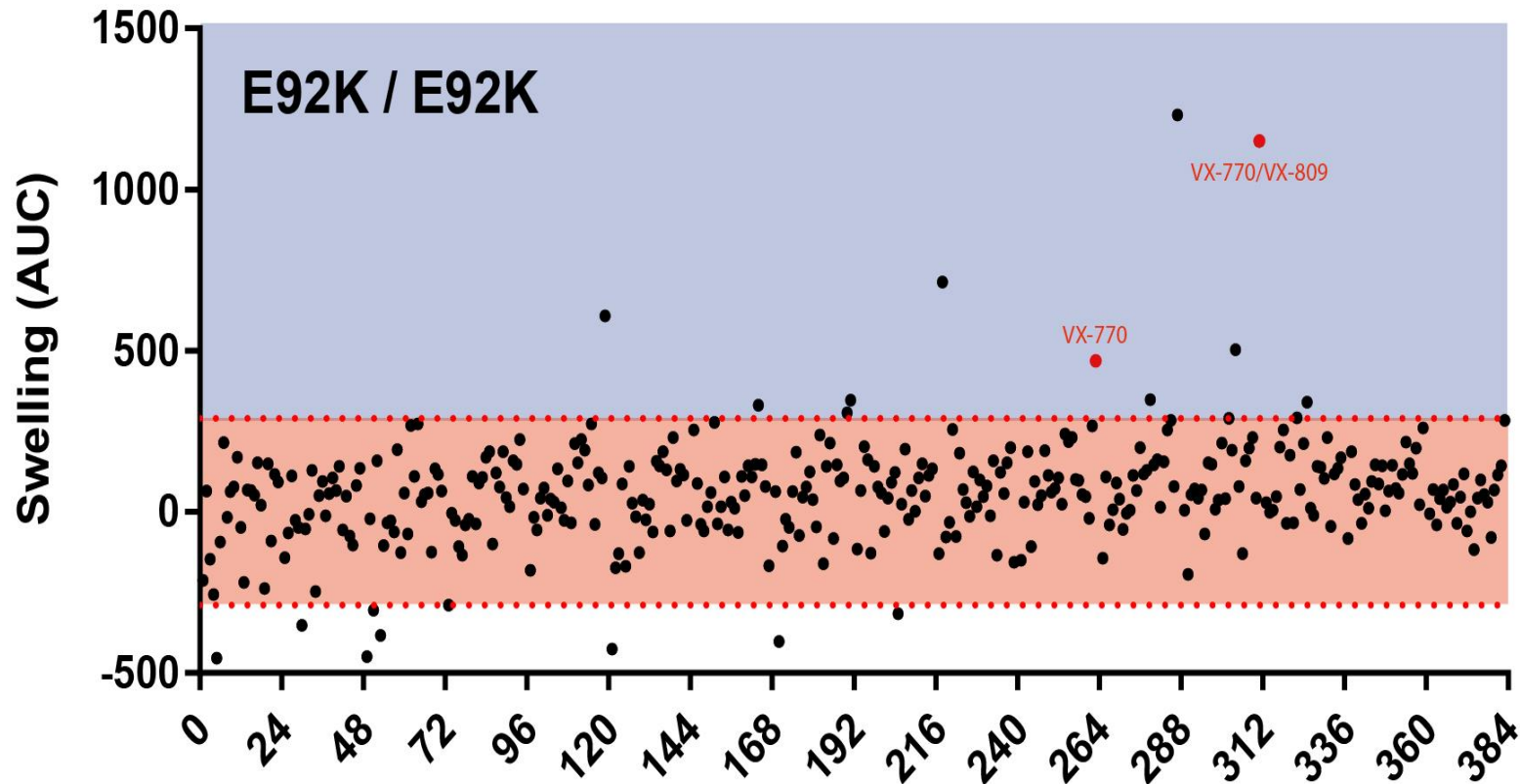


Screening 1 plate ~1hr FIS (HCS)
6 min acquisition time / 384 wells

APPLICATIONS

- Responders to CFTR modulators:
 - Existing and novel ones;
- Repurpose FDA treatments:
 - CFTR protein modulators;
 - CFTR activation modulators;
 - CFTR expression modulators.

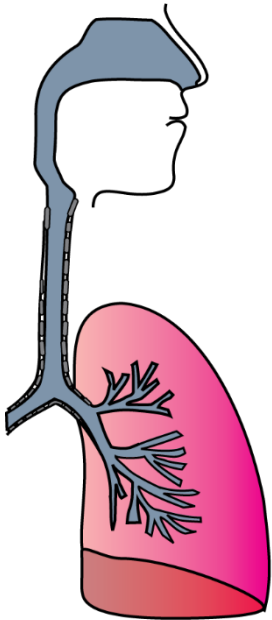
Identifying HITs using HCS-FIS screening platform



Repurposing of existing clinically available drugs is a very promising strategy to identify novel CFTR-restoring compounds

UMCU Airbank

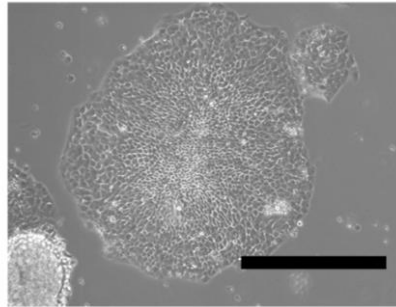
Living biobank of airway cells



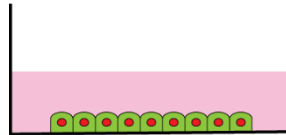
Nasal:
- Brushing
- Polyps
- Resected tissues

Bronchial:
- Brushing
- Biopsy
- Bronchoalveolar lavage fluid

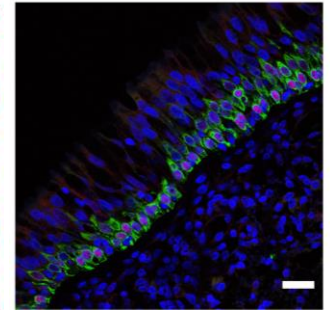
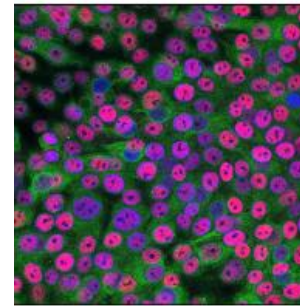
Nasal brushings: ~ 100 donors in 2 years



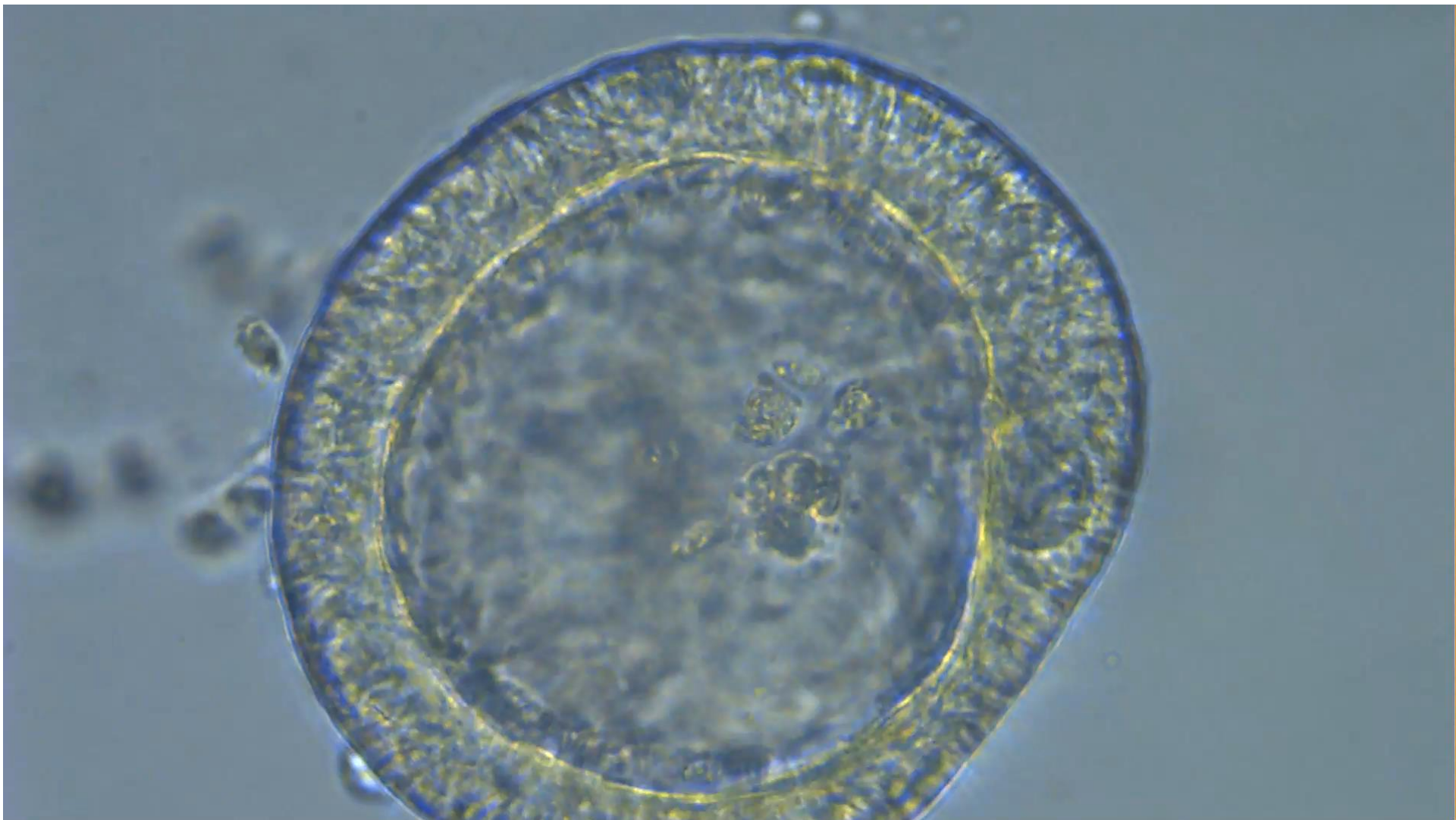
Feeder-free
2D expansion



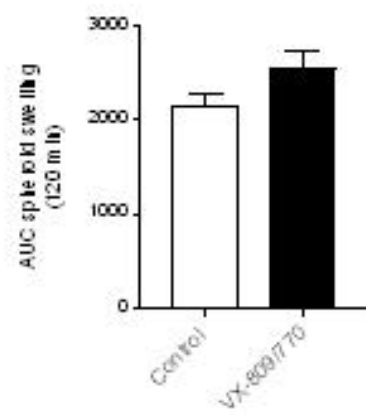
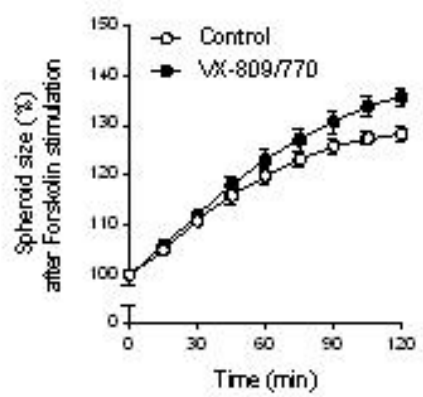
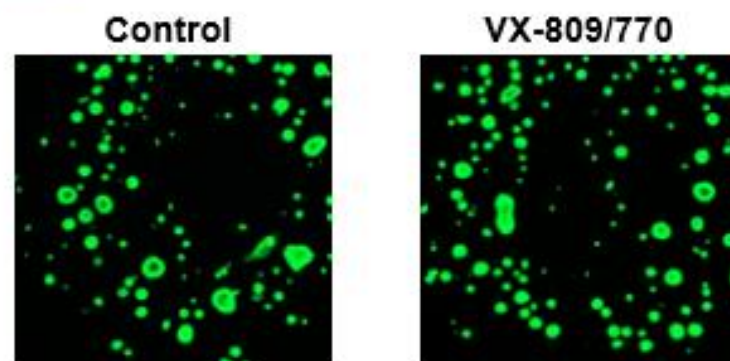
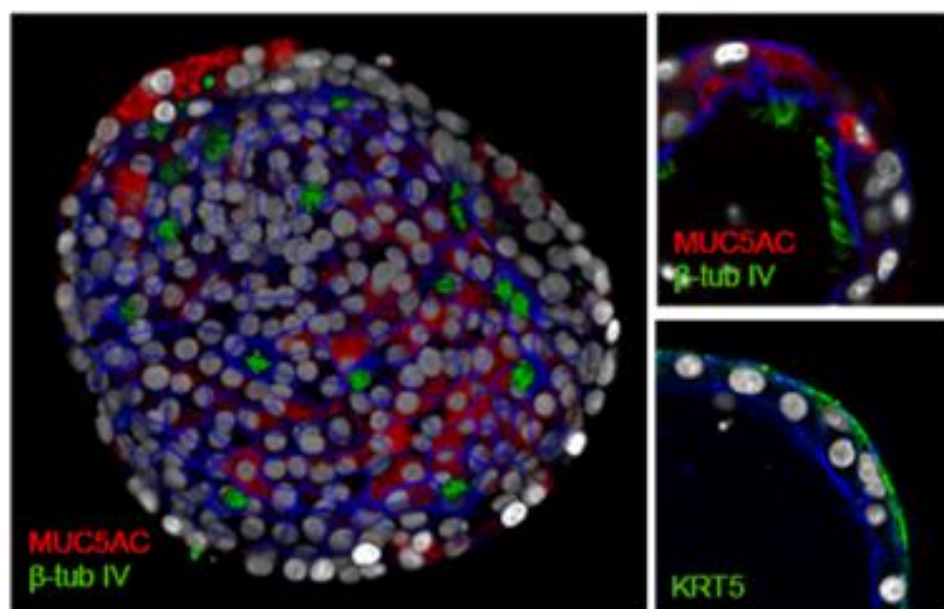
p63 KRT5



Basal stem cells



CFTR modulator responses in nasal organoids from F508del homozygous CF patients



Amatngalim et al., unpublished data

**“ The best way to
predict the future
is to create it.”**