NOVEL CFTR MODULATOR COMBINATIONS: EVALUATION OF THE CORRECTOR PTI-801, POTENTIATOR PTI-808, AND AMPLIFIER PTI-428 IN CF SUBJECTS

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Imperial College London

13° AUSTRALASIAN CYSTIC FIBROSIS CONFERENCE
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Relationships

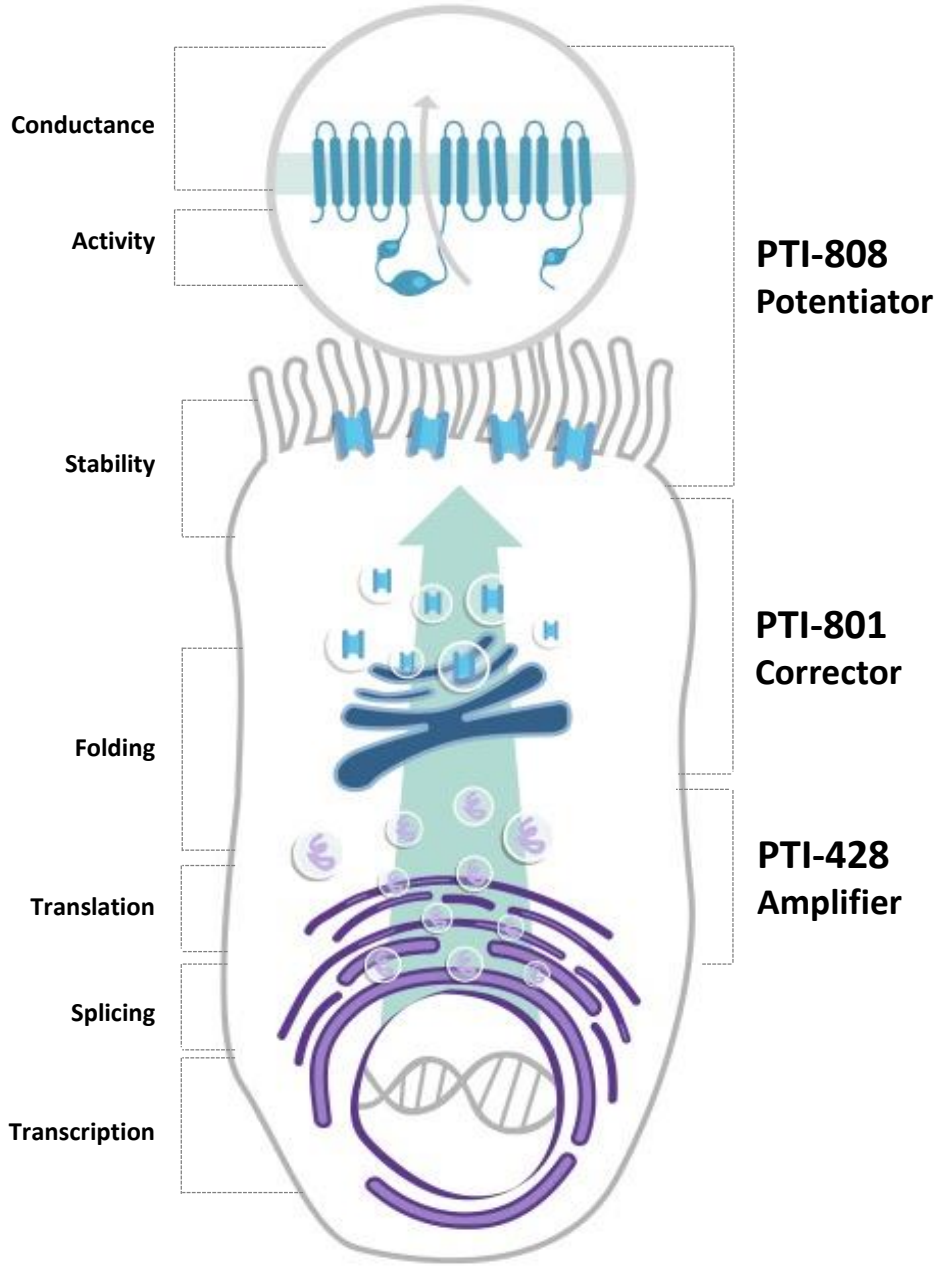
- ✓ Fees received by Imperial College London for participation in Advisory Boards and Clinical trial leadership:

  Proteostasis Therapeutics, Vertex Pharmaceuticals, AbbVie, Galapagos and Flatley

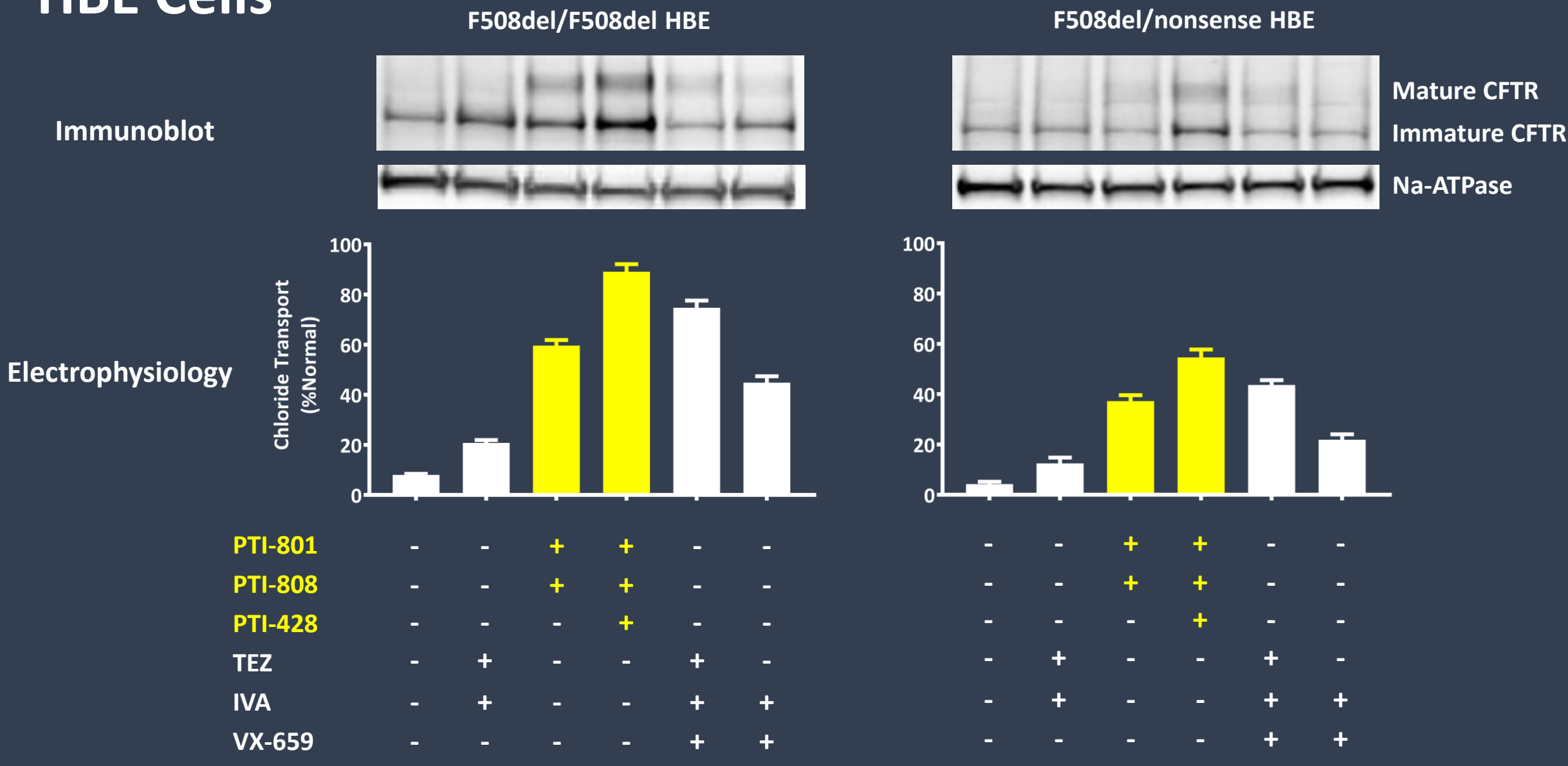
Proteostasis Therapeutics' Approach to Restoration of CFTR Activity

Novel CFTR modulators have been tested in multiple clinical paridigms

	Regulatory Designation	Add-on to approved modulators	Double combination	Triple combination
Potentiator PTI-808	Fast Track (FDA)		✓	✓
Corrector PTI-801	Fast Track (FDA)	✓	✓	✓
Amplifier PTI-428	Breakthrough Therapy (FDA) Orphan Drug (FDA, EMA)	✓		✓

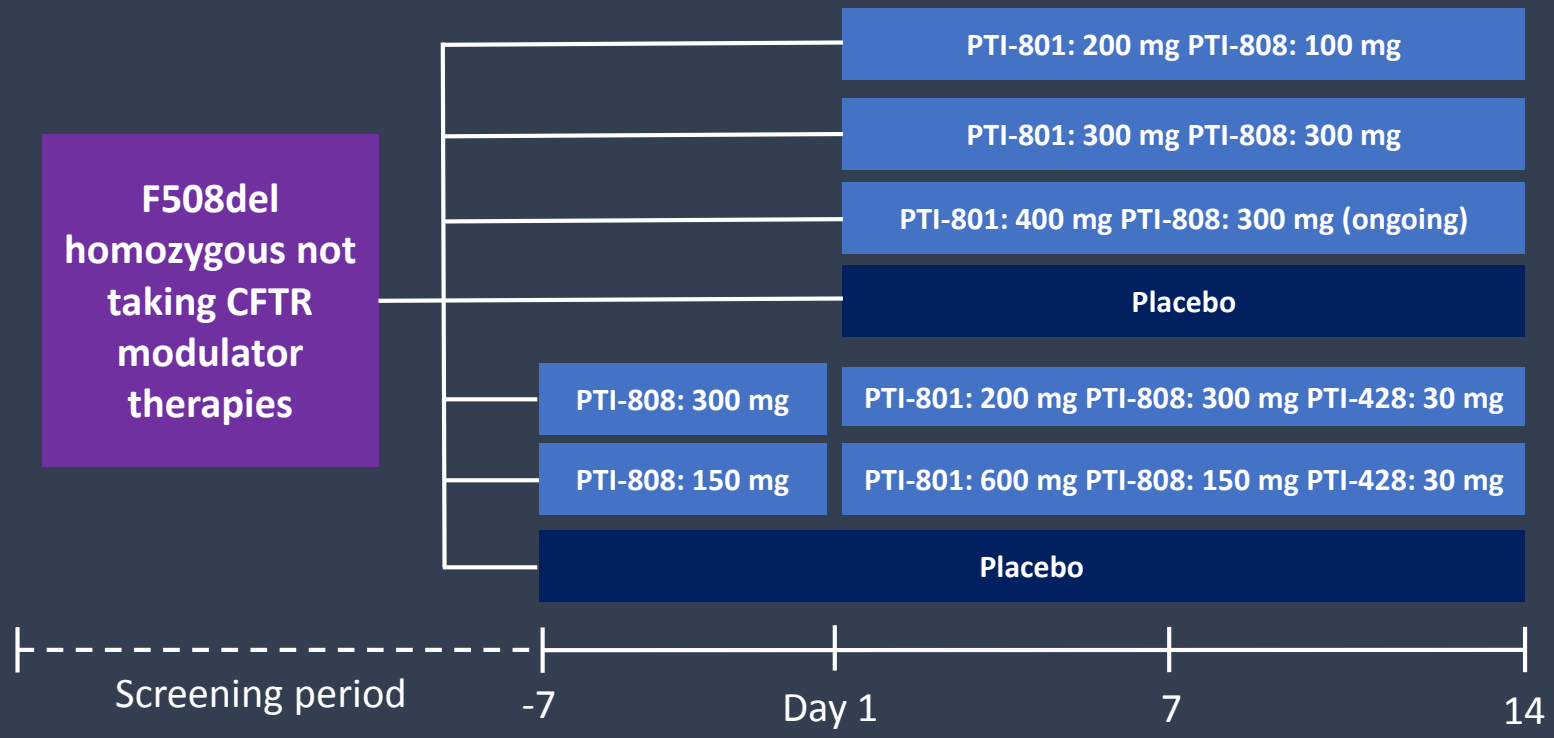


Exploring the Capacity for More in Homo- and Heterozygous HBE Cells



Double and Triple Combination Study Design

- **CF Subjects** ≥ 18 years of age
- **Lung function** 40-90% (ppFEV1).
- **Not taking CFTR modulator therapies**
- Not excluding subjects with lung colonization with organisms associated with a more rapid decline in pulmonary status



Primary Objectives

- Safety and tolerability of dose combinations of **PTI-801**, **PTI-808** and **PTI-428**

Secondary Objectives

- PK profile of multiple dose combinations
- Treatment effect on FEV_1 over time

Exploratory Objectives

- Treatment effect on sweat chloride

Over 50 Subjects Completed Combination Studies in North America and in Europe

Double and Triple Combination Study Demographics

	Triple combination			Double combination		
	Cohort 1 n=12	Cohort 2 n=13	Placebo n=6	Low dose double n=9	Mid dose double n=5	Placebo n=4
PTI-801 dose	200 mg	600 mg	-	200 mg	300 mg	-
PTI-808 dose	300 mg	150 mg	-	100 mg	300 mg	-
PTI-428 dose	30 mg	30 mg	-	-	-	-
Age, year (mean SD)	29.7 (9.6)	35.3 (10.6)	27.8 (7.0)	36.1 (12.4)	26.0 (8.8)	26.3 (4.5)
Baseline ppFEV$_1$ (mean, SD)	54.1 (10.3)	66.6 (13.4)	65.0 (12.6)	57.0 (16.6)	50.7 (12.7)	69.6 (7.1)
Baseline sweat chloride mmol/L (mean, SD)	104.5 (9.2)	100.3 (8.1)	93.8 (8.1)	99.9 (10.6)	98.7 (13.4)	109.5 (1.4)
Height, cm (mean, SD)	168.0 (9.2)	168.0 (7.6)	171.4 (7.2)	167.8 (10.4)	172.8 (4.9)	161.3 (9.4)
BMI, kg/m^2 (mean, SD)	20.1 (2.0)	22.9 (4.2)	19.9 (2.2)	22.2 (2.1)	22.3 (0.9)	22.7 (2.3)
Subjects with lung colonization status*	1	2	2	0	0	1

*Lung Colonization status associated with a more rapid decline in pulmonary status (e.g., *Burkholderia cenocepacia* and *Mycobacterium abscessus*) excluded in the ad hoc subset analysis

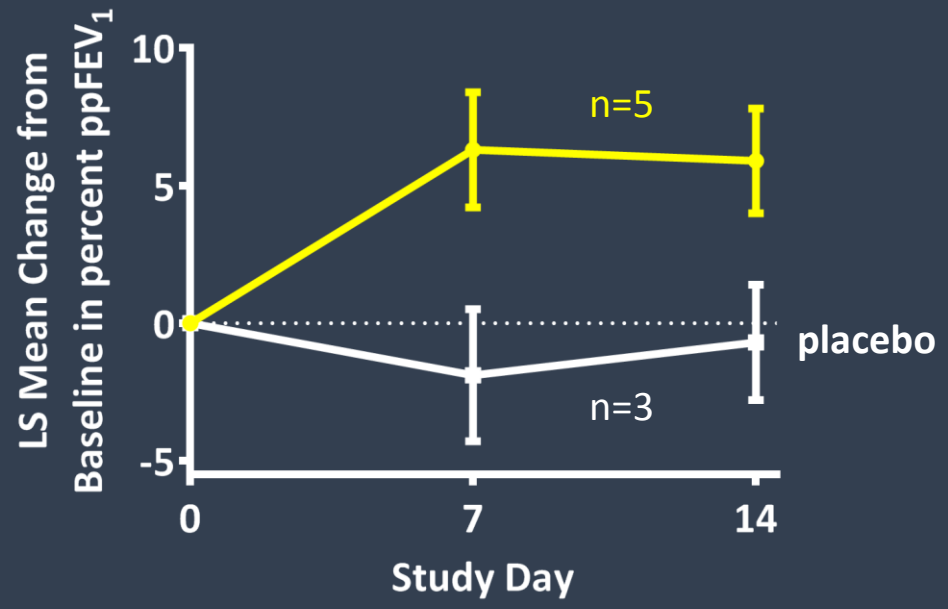
Double and Triple Combinations Generally Well Tolerated

	Triple combination			Double combination		
	Cohort 1 n=12	Cohort 2 n=13	Placebo n=6	Low dose double n=9	Mid dose double n=5	Placebo n=4
PTI-801 dose	200 mg	600 mg	-	200 mg	300 mg	-
PTI-808 dose	300 mg	150 mg	-	100 mg	300 mg	-
PTI-428 dose	30 mg	30 mg	-	-	-	-
Subjects completed study (n)	11	13	6	8	5	4
	Safety summary and key respiratory adverse events (n)					
At least one AE	11	9	5	8	3	4
Pulmonary exacerbation*	1	0[+]	1	0	0	0
Cough	0	0	1	1	0	0
Chest discomfort	0	0	0	1	1	0
Dyspnoea	0	1	0	0	0	0
	Other adverse events (n)					
Nausea (most frequent AE in triple study)	1	1	2	0	0	0
Headache (most frequent AE in double study)	1	0	1	2	0	1

*Excluded in the ad hoc subset analysis [+]1 PE post treatment period

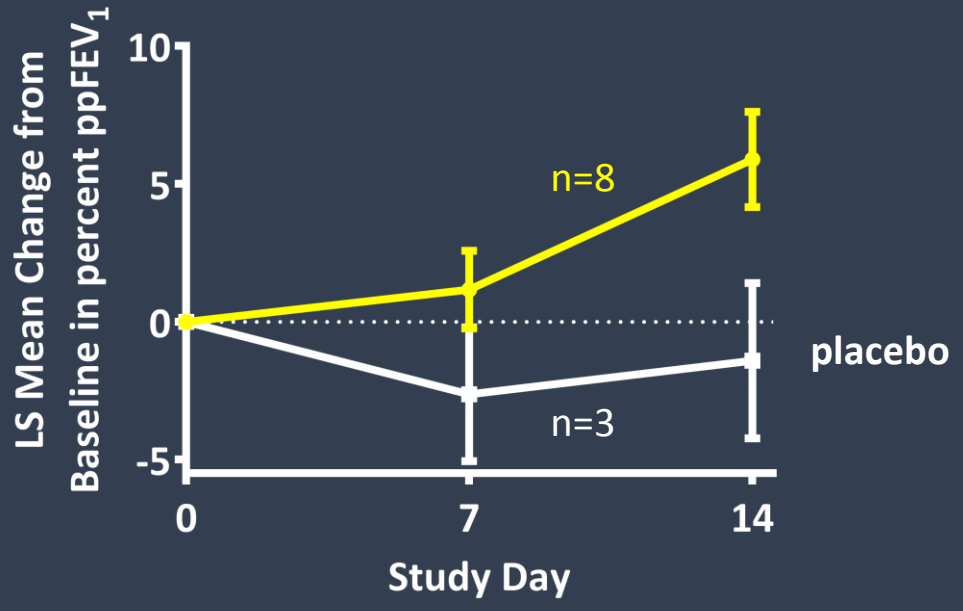
Statistical Significance in Improvement in Lung Function Achieved with both Double and Triple Combinations

PTI Double Combination
PTI-801: 300 mg, PTI-808: 300 mg



Double combination resulted in a +6.6 $ppFEV_1$ improvement compared to placebo*

PTI Triple Combination
PTI-801: 600 mg, PTI-808: 150 mg, PTI-428: 30 mg



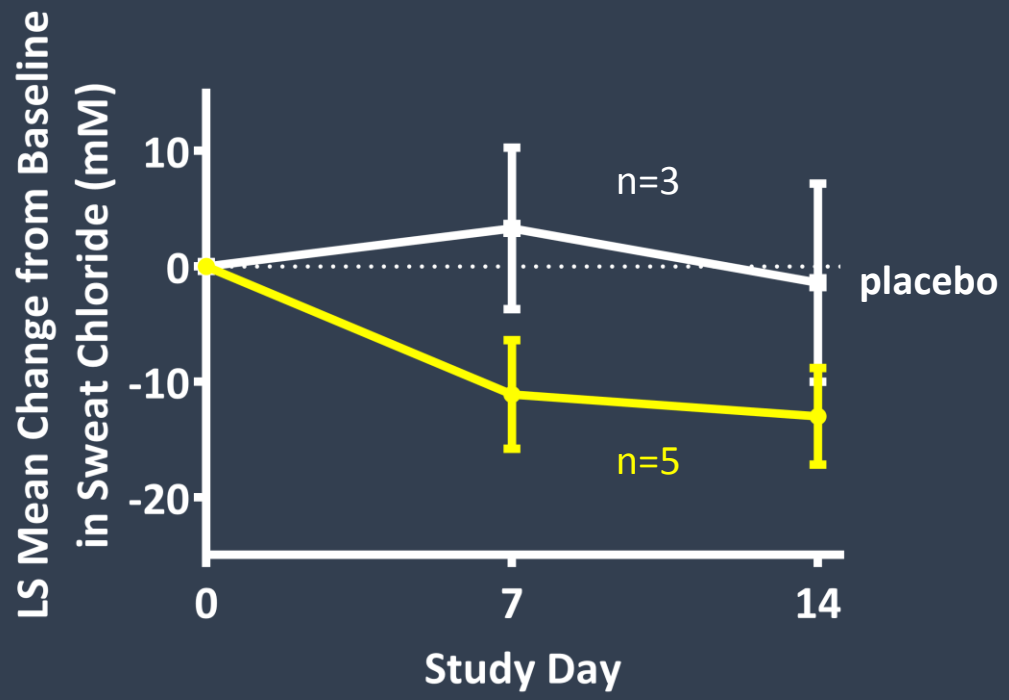
Triple combination resulted in a +8 $ppFEV_1$ improvement compared to placebo*

No plateau in $ppFEV_1$ response was observed at the end of 14 day treatment period with the PTI triple

**Previously disclosed data on October 17, 2018 and March 25, 2019*

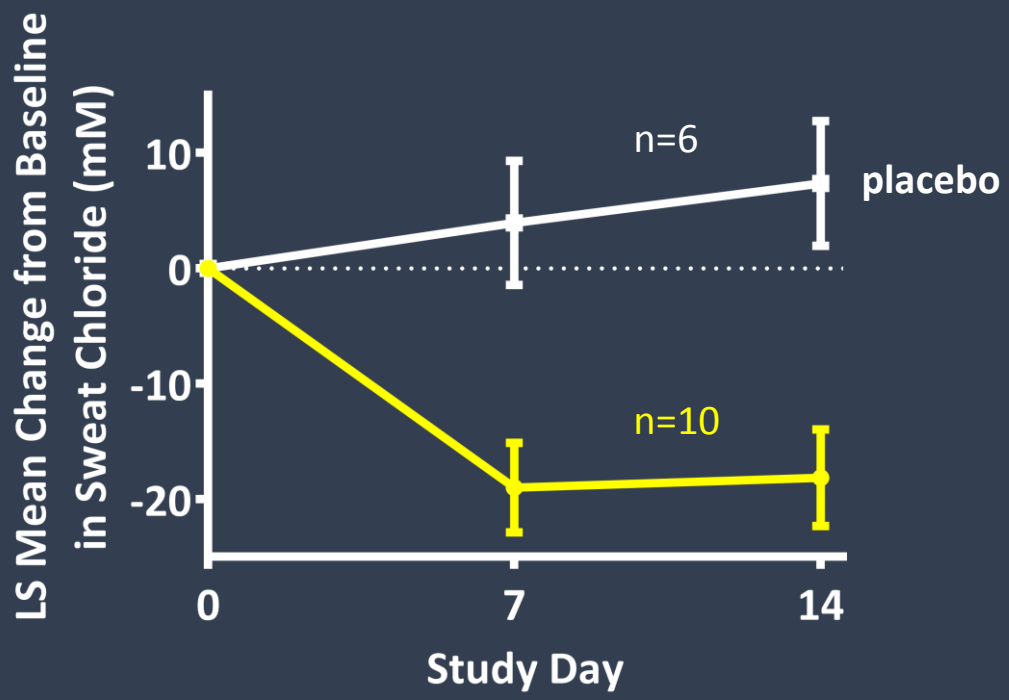
Statistical Significance in Sweat Chloride Improvement Achieved in both Double and Triple Combinations

PTI Double Combination
PTI-801: 300 mg, PTI-808: 300 mg



Double combination resulted in -12 mM improvement in sweat chloride compared to placebo*

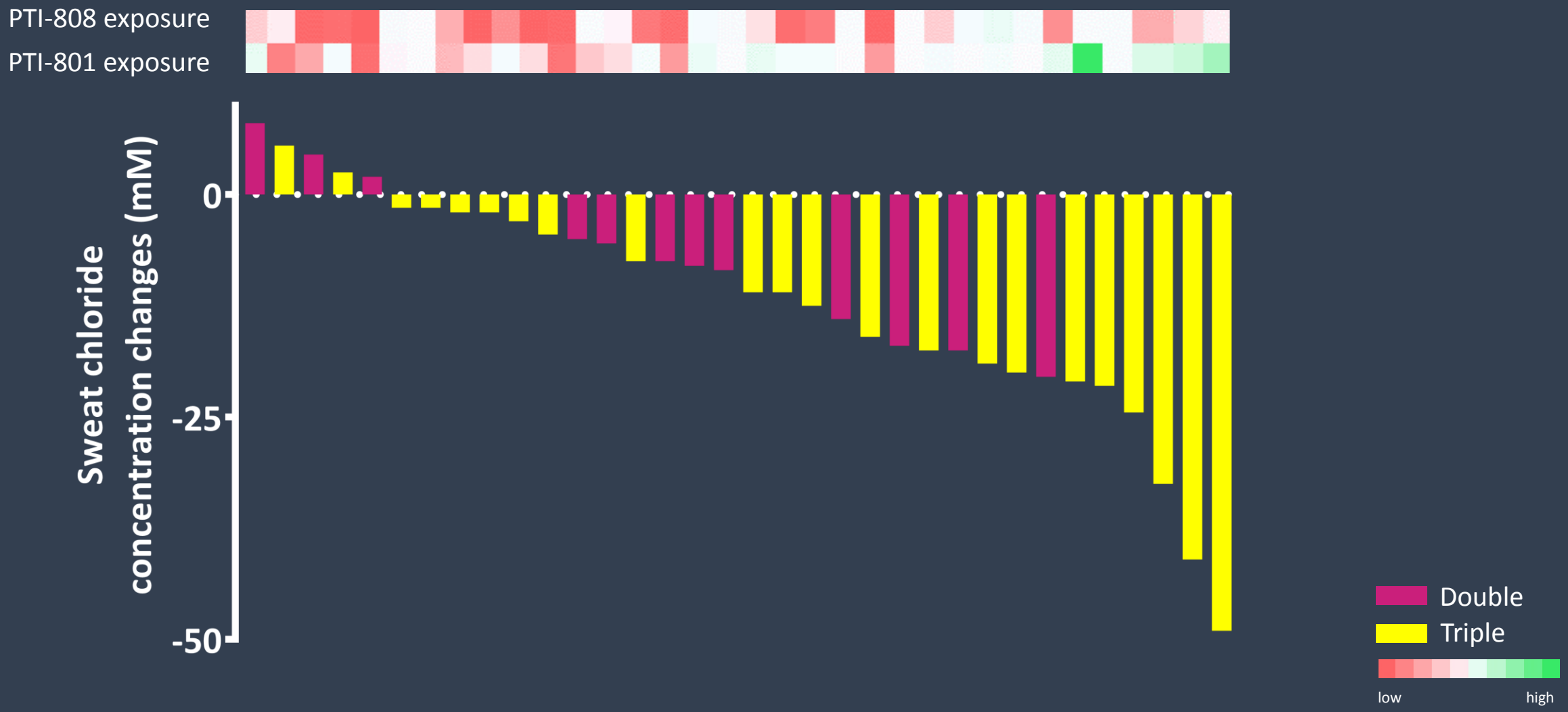
PTI Triple Combination
PTI-801: 600 mg, PTI-808: 150 mg, PTI-428: 30 mg



Triple combination resulted in -24 mM improvement in sweat chloride compared to placebo*

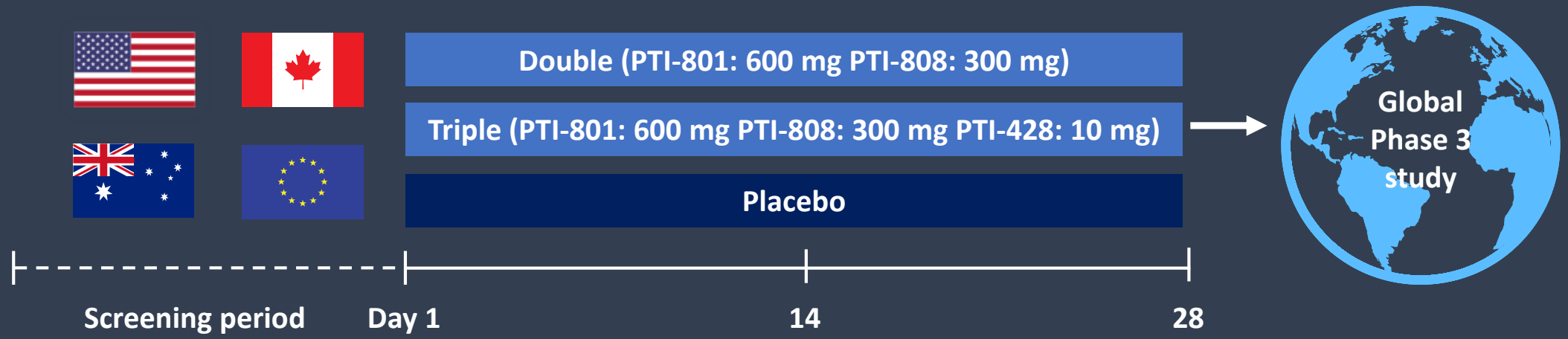
**Previously disclosed data on October 17, 2018 and March 25, 2019*

Drug Exposure Driven Sweat Chloride Improvement in Subjects Treated with PTI-801 and PTI-808



Potential Best-in-Class Double Backbone Serves as a Next Step in a Global Phase 2 Leading into Phase 3 Study Program

Double and Triple Combination Phase 2 Study Design for Patients with at least one F508del Mutation



Primary Objectives
- Safety and tolerability

Secondary Objectives
- PK profile of double and triple drug combinations
- Treatment effect on FEV_1
- Treatment effect on sweat chloride

Exploratory Objectives
- CFQ-R

- CF Subjects ≥ 18 years of age
  Homo- or heterozygous for the F508del mutation
- Lung function 40-90% ($ppFEV_1$)
- BMI ≥ 16 and ≤ 30
- Respiratory stability at least 28 days prior to dosing
- Targeted enrollment of 30 homozygous subjects and 30 heterozygous subjects

THANK YOU

Lead investigators Damian Downey, MD, Patrick Flume, MD, and Manu Jain, MD, global study teams and all participating people with Cystic Fibrosis and their families

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