Proteostasis Therapeutics, Inc. (PTI)

January 2018 Investor Deck

PROTEOSTASIS THERAPEUTICS, INC.

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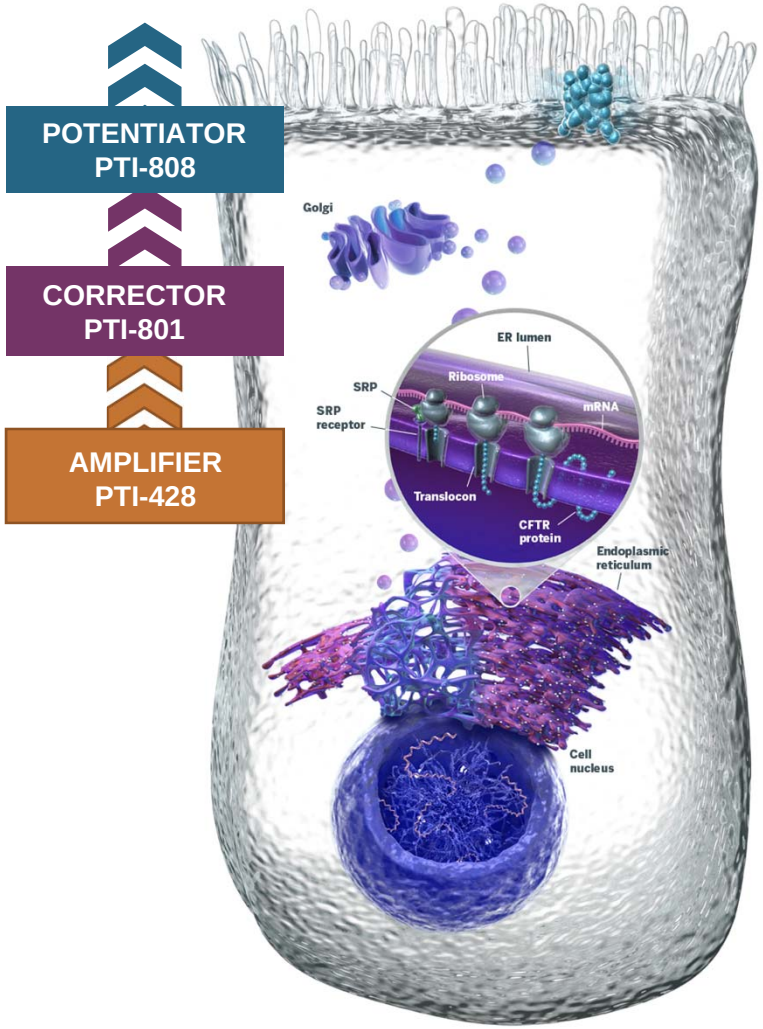
PTI Overview

- Clinical stage biopharma developing novel therapeutics for cystic fibrosis (CF) and other diseases caused by dysfunctional protein processing
- Focus on increasing CFTR activity in patients with CF
- Developing novel small molecules for CF combination therapy
  - PTI-808: Novel Potentiator
  - PTI-801: New Generation Corrector that is additive *in vitro* to first and second generation correctors
  - PTI-428: Novel Class of CFTR Modulator: Amplifiers
- Leveraging potential therapeutic benefit of multiple stand-alone combination options including PTI-801 and PTI-808 as a doublet and PTI-808, PTI-801, and PTI-428 as a triplet
  - PTI-801 and PTI-428 can potentially be developed as add-on therapies to current and future standard of care CFTR modulator therapies

PTI Approach to Restoration of CFTR Activity is Uniquely Orthogonal to Approved Modulators



Potentiators, such as PTI-808 and KALYDECO® (ivacaftor), act by increasing the opening time of the CFTR channel, resulting in higher ion flow

Correctors, such as PTI-801 and ORKAMBI® (lumacaftor/ ivacaftor), are thought to facilitate the processing of mutated CFTR protein substrate, leading to improved delivery to the cell membrane

Amplifiers, such as PTI-428, selectively increase the amount of immature CFTR protein in the cell, providing additional substrate for correctors and potentiators to act upon

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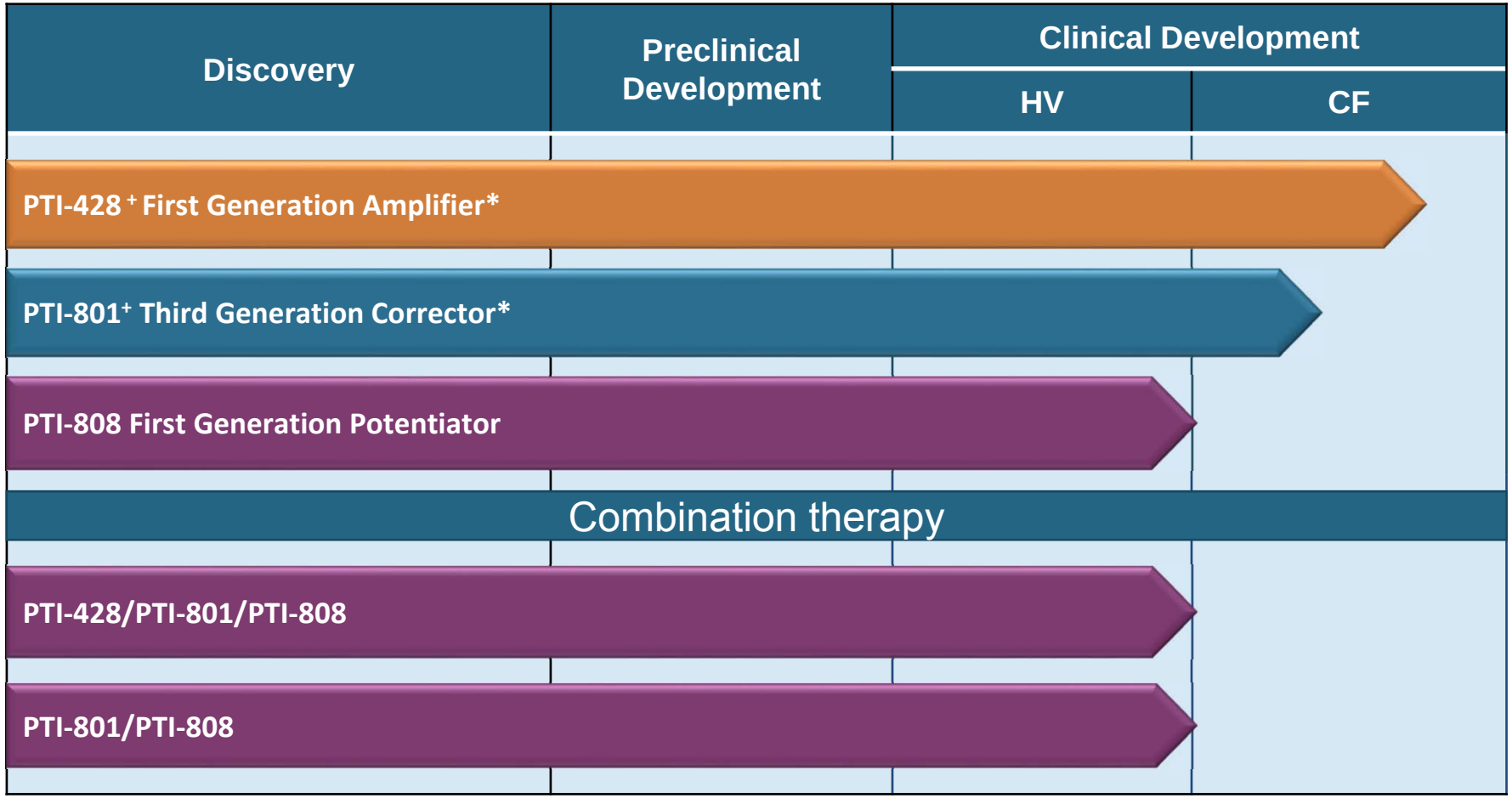
PTI Cystic Fibrosis Clinical Pipeline



* Received Fast Track designation from FDA

\+ Additive *in vitro* to first and second generation correctors

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2017 Key Accomplishments

2017

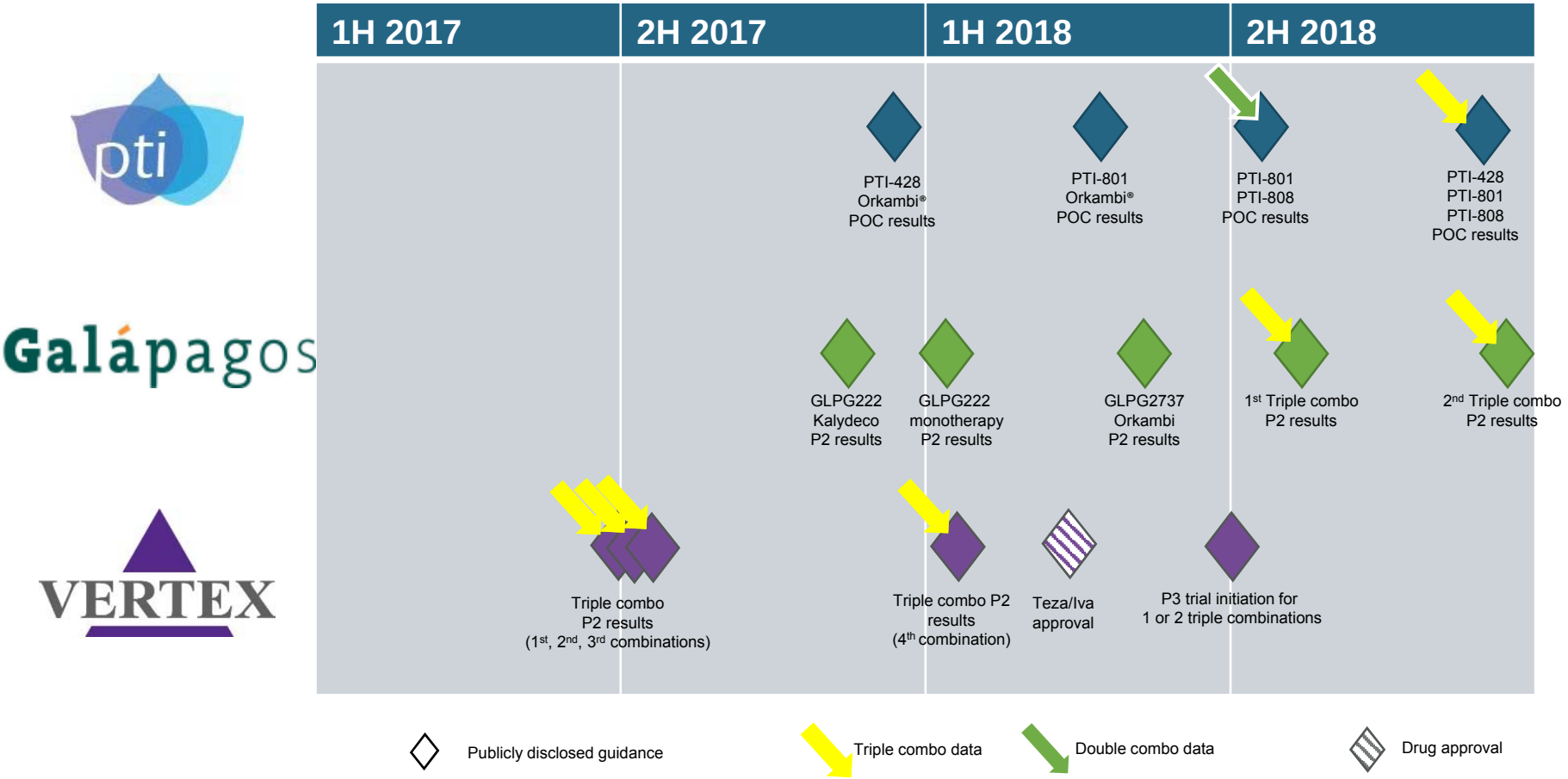
- PTI-801 IND submission
- PTI-428 preliminary data
- PTI-808 IND submission
- PTI-808 Phase 1 initiation
- PTI-801 Phase 1 initial data
- PTI-428 28 day dosing, preliminary data in CF subjects on Orkambi®
- PTI-801 14 day dosing, initial data in CF subjects on Orkambi®
- PTI-808 SAD and MAD clinical data in HV
- PTI-808/PTI-801/PTI-428 combination clinical safety data in HV

2018 Key Milestones

2018

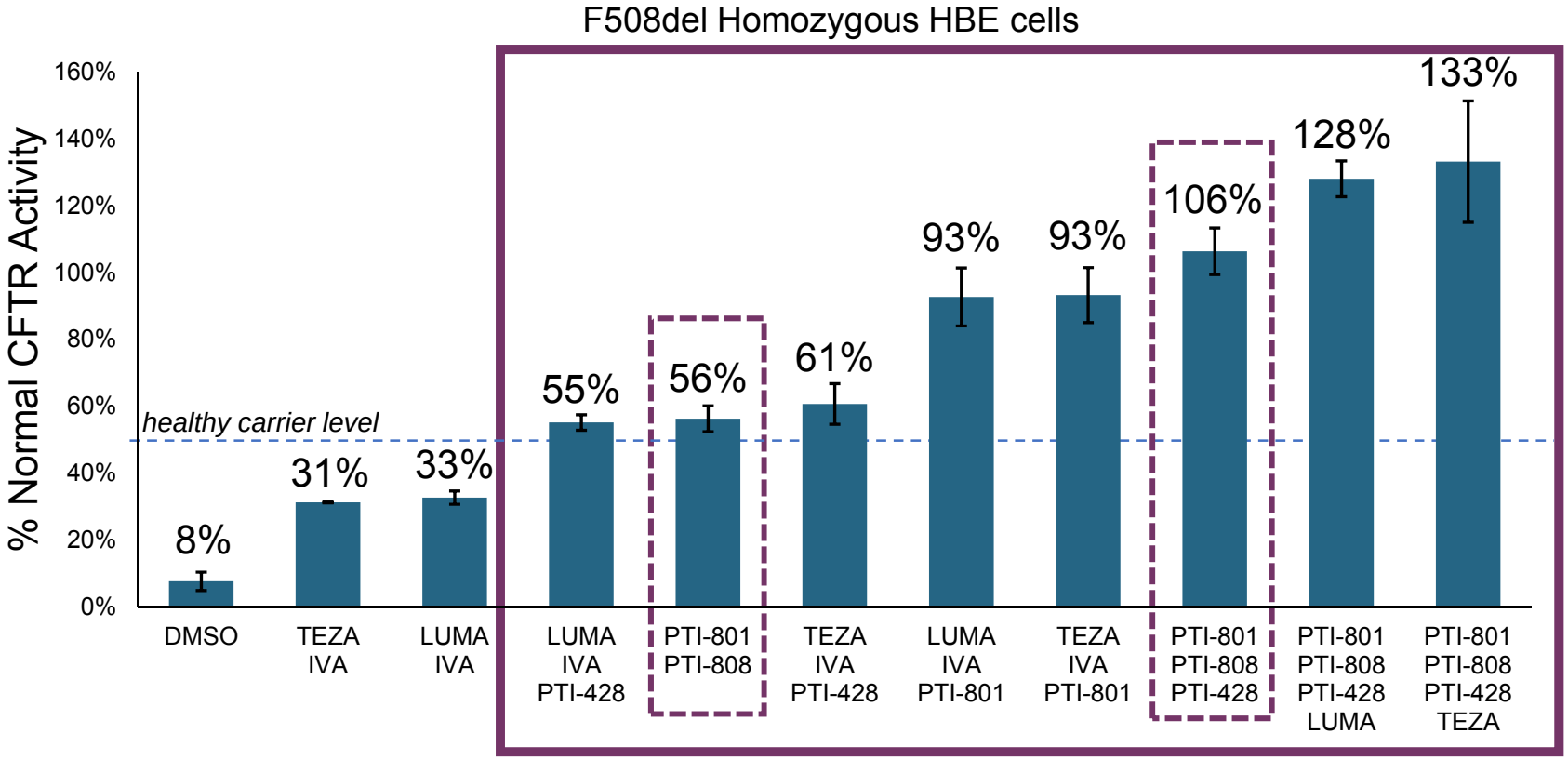
- ✓ PTI-808/PTI-801/PTI-428 combination study protocol endorsed with high strategic fit score by CF patient advocacy groups in the U.S. and Europe
- PTI-801/PTI-808 combination study dosing planned in CF patients
- PTI-808/PTI-801/PTI-428 combination studies initiated in CF subjects
- PTI-801 14 day dosing, additional data in CF subjects on Orkambi®
- PTI-808/PTI-801 initial data from combination study in CF subjects
- PTI-808/PTI-801/PTI-428 combination study preliminary data in CF subjects

PTI On Track for Triple Combination Data in 2018



PTI-428 and PTI-801 are Differentiated in Doublet, Triplet and Quadruplet Combination Formats *in vitro*

- PTI-801 and PTI-428 are additive to approved or late stage modulators *in vitro*
- Doublet and triplet combinations of PTI investigational drugs restored CFTR activity to at least healthy carrier levels *in vitro*



TEZA-tezacaftor, IVA-ivacaftor, DMSO-vehicle control

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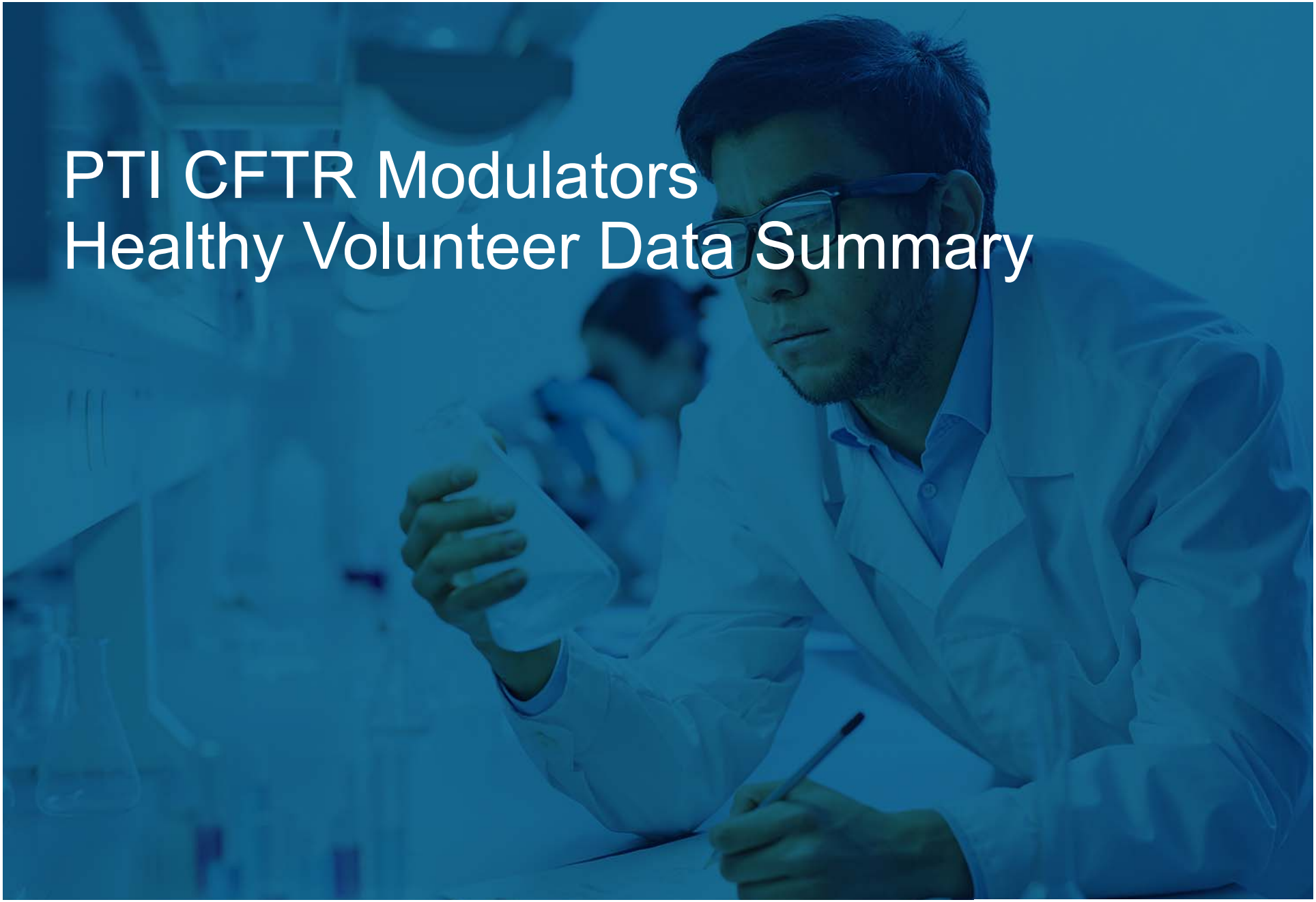
PTI CFTR Modulators
Healthy Volunteer Data Summary



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Healthy Volunteer Data Suggested Drug Candidates Generally Well Tolerated and May Be Amenable for Once a Day Dosing

	PTI-428	PTI-801	PTI-808
Number of HV subjects	134	48	48
Highest dose tested	300 mg	450 mg	300 mg
SAE	no	no	1*
AE severity	mild/moderate	mild/moderate	mild/moderate
Dose level achieving >EC_{50}	50 mg	100 mg	50 mg
Potential for once-a-day dosing	yes	yes	yes
DDI probability	low	low	low
Transitioned into CF subject studies	yes	yes	SRC approved

* From pre-existing condition (transverse myelitis), SRC – safety review committee

AE – adverse events, SAE – serious adverse events, DDI – drug drug interaction, EC_{50} - half maximal effective concentration

PTI-808, PTI-801, PTI-428 Co-Administration Was Generally Well Tolerated Across HV Cohorts

Multiple Dose Cohorts in HV Subjects

- In all co-administration cohorts a total of 11 subjects out of 20 experienced a TEAE
  - No severe AEs, SAEs or AEs leading to discontinuation of treatment were reported
- No clinically significant trends in safety labs, ECGs, physical exam, vital signs data

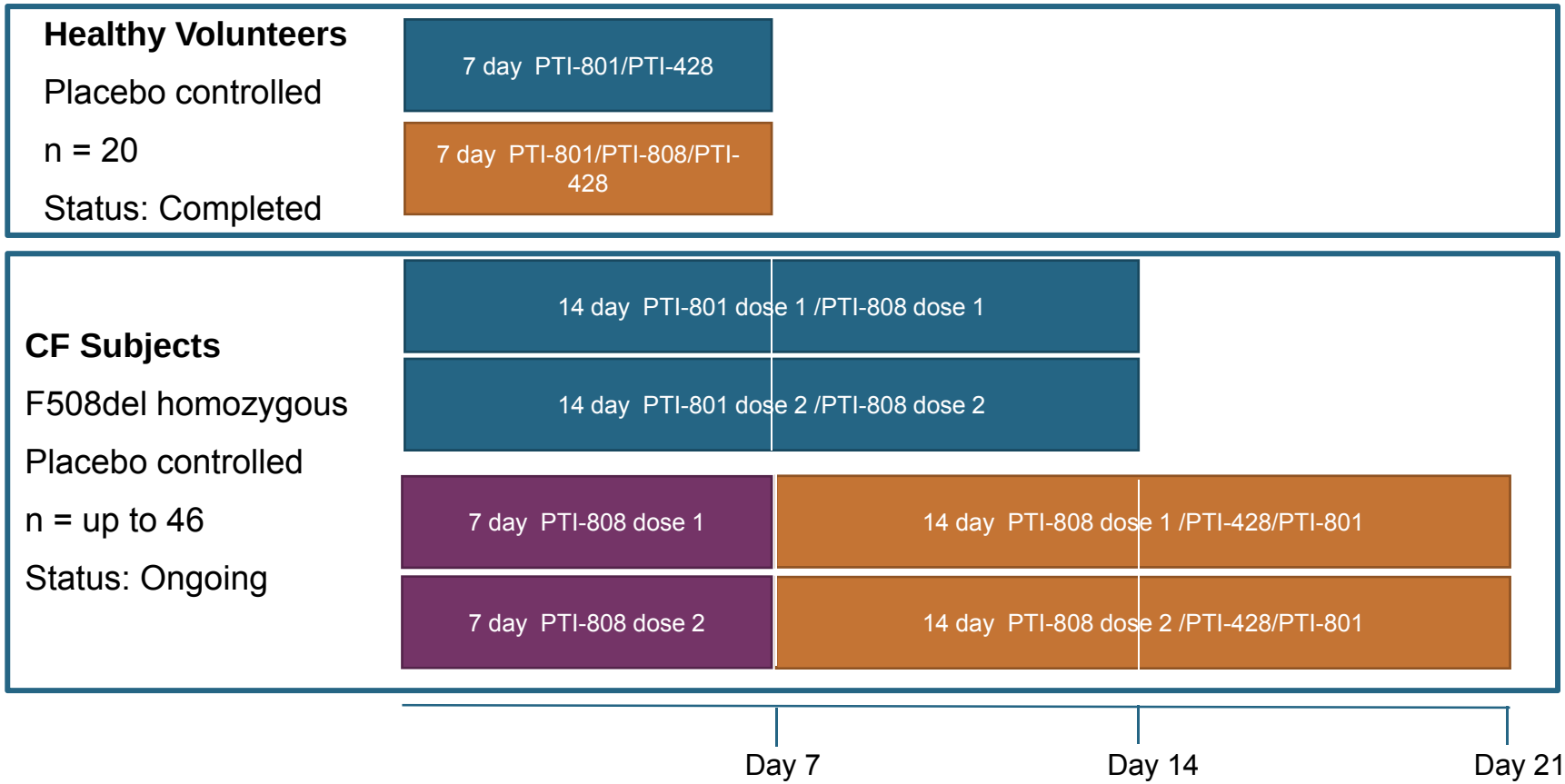
Exposures in excess of EC_{70} were achieved at steady state with co-administration of PTI-428 (50 mg), PTI-801 (100 mg) and PTI-808 (50 mg)

Co-administration of PTI-428, PTI-808 and PTI-801 in CF subjects on track to initiate in 1H 2018 with initial clinical data in 2H 2018

- Co-administration study protocol for CF subjects received endorsement and high strategic fit score from the TDN and CTN

TEAE – treatment emergent adverse events, AE – adverse events, SAE – serious adverse events, ECG – electrocardiogram, MAD – multiple ascending dose, SAD – single ascending dose

PTI Clinical Path to Proprietary Combination Therapies in CF Patients



28 day GLP preclinical combination safety studies completed

placebo | single agent | dual combination | triple combination

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PTI-801and PTI-428
CF Clinical Data Summary

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PTI-801 CF Study Overview

14 day MAD Cohort in CF Subjects (4:1 randomization)

Dose 1 – 100 mg	Dose 2 – 200 mg	Dose 3 - TBD

100 mg Dose Cohort in CF Subjects (Orkambi® Population)

- In the first 5 subjects dosed through day 14, a total of 3 out of 5 subjects experienced a TEAE
  - No severe AEs, SAEs or AEs leading to discontinuation of treatment were reported
- No unexpected PK interactions observed to date among PTI-801, ivacaftor, and lumacaftor
- Average PTI-801 exposure at steady state in excess of EC_{50} at 100 mg dose in CF

MAD – multiple ascending dose, TEAE – treatment emergent adverse events, AE – adverse events, SAE – serious adverse events, EC50 - half maximal effective concentration

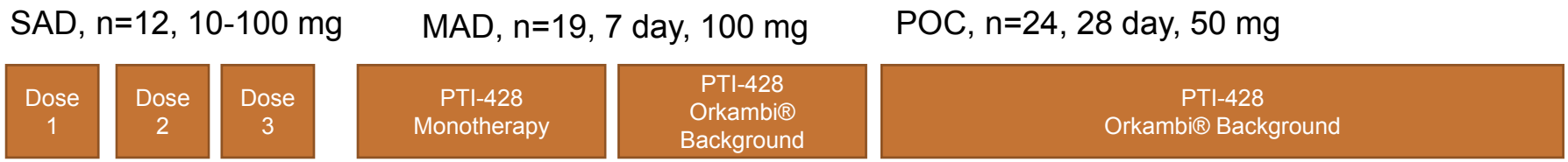
Initial Clinical Data for PTI-801 from *Ad Hoc* Interim Analysis

Initial clinical data with 100 mg PTI-801 in CF Patient Population Suggests Potential Add-on Therapy to Orkambi®

- Average baseline ppFEV1 in the first 5 subjects (4:1 randomization) was approximately 65%
- Preliminary review of the initial data from the first 5 patients in the first cohort showed all patients experienced improvement in lung function measured as absolute change in $ppFEV_1$
- Mean absolute improvements in $ppFEV_1$ of approximately 4 percentage points from baseline, with mean relative improvements of approximately 7 percent, were observed in all PTI-801 subjects who had completed 2 weeks of dosing

PTI-428 CF Study Overview

PTI-428 studies below showed PTI-428 was generally well tolerated by CF patients



- 55 CF subjects with highest dose level tested 100 mg
- Completed POC study with PTI-428, 50 mg, once-a-day for 28 days, in CF patients on background Orkambi®
  - No unexpected PK interactions observed to date among PTI-428, ivacaftor, and lumacaftor
  - Average PTI-428 exposure at steady state was in excess of EC_{50} at 50 mg

SAD – single ascending dose, MAD – multiple ascending dose, POC – proof-of-concept, EC50 - half maximal effective concentration

Data in CF Subjects on Background Orkambi® Suggested that PTI-428 is Generally Well Tolerated and Provided Statistically Significant Improvement in Lung Function

Preliminary data suggests PTI-428 efficacy as add-on therapy to Orkambi

- PTI-428 led to statistically significant mean absolute improvements in ppFEV1 of 5.2 percentage points from baseline compared to placebo ($p<0.05$)
  - Average lung function prior to dosing was 59% ppFEV1

2-year, PROGRESS study of long term Orkambi efficacy showed CF patients continue to experience lung function decline despite treatment

- Information on historical Orkambi® usage was available for 79% of the subjects enrolled in the 28-day study and of those, 95% were on Orkambi® therapy for an average of 1.8 years

*Michael W et al. The Lancet Respiratory Medicine, 2017, Volume 5 , Issue 2 , 107 – 118
Orkambi® is a registered trademark from Vertex Pharmaceuticals, Inc. POC – proof-of-concept

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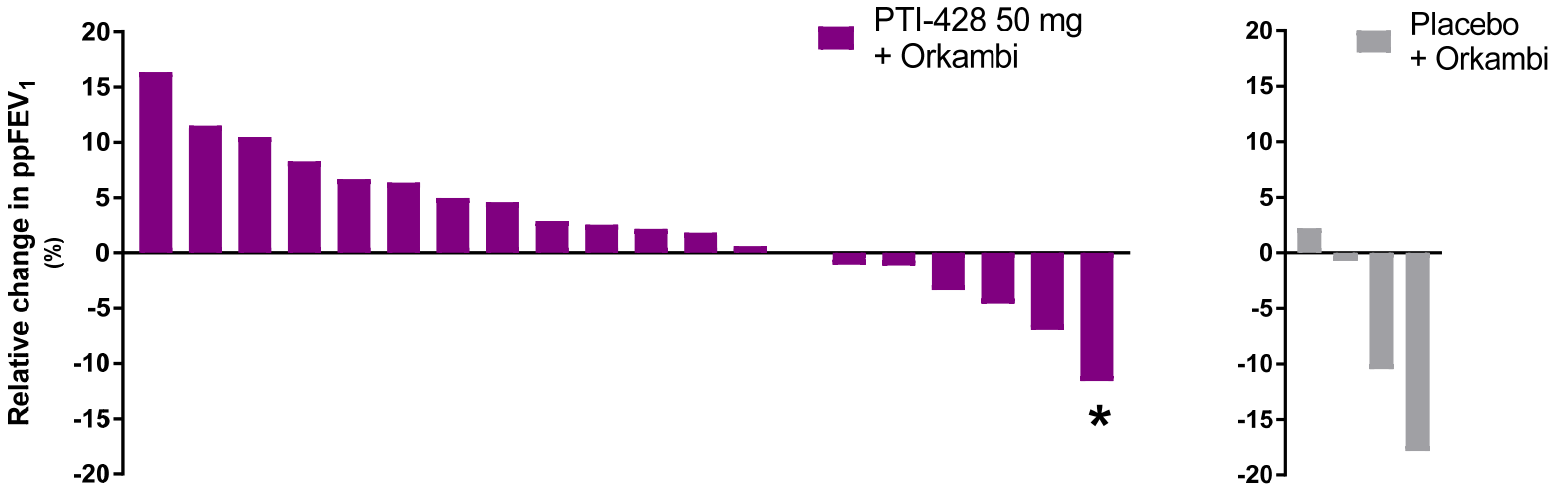
Individual Responses Showed Majority of PTI-428 Treated Patients Experienced Lung Function Improvement

Individual subject relative change in $ppFEV_1$ from baseline through the 28 day treatment period



* Subject did not comply with inhaled antibiotic treatment regimen as defined in the study protocol

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PTI-428 Led to Mean Absolute Improvements in $ppFEV_1$ of 5.2 percentage points from Baseline Compared to Placebo ($p<0.05$)

	PTI-428 50 mg Treatment Effect (PTI-428 n=20, Placebo n=4)		
	Day 7	***Day 14***	***Day 28***
Mean absolute change in $ppFEV_1$ percentage points (95% CI)	+4.9 (-0.2, 10.1)	+5.2 (0.4, 10.0)	+5.2 (0.3, 10.1)
p value	n.s.	**p<0.05**	**p<0.05**
Mean relative change in $ppFEV_1$ (95% CI)	+8.3% (-0.9, 17.6)	+9.0% (1.2, 16.9)	+9.2% (1.2, 17.2)
p Value	n.s.	**p<0.05**	**p<0.05**

$ppFEV_1$ changes expressed as least-square mean vs placebo

- Treatment effect of PTI-428 was achieved by day 14 and sustained through 28 days of dosing
- Changes in sweat chloride levels in PTI-428 treated patients did not correlate with changes in lung function

CF Patients with Less than 70% ppFEV$_1$ Baseline Lung Function Were Responders to Orkambi® Plus PTI-428

	50 mg PTI-428 + Orkambi®		Orkambi®* TRAFFIC/TRANSPORT study	
	ppFEV$_1$ <70 (n=17)	ppFEV$_1$ ≥70 (n=3)	ppFEV$_1$ <70 (n=245)	ppFEV$_1$ ≥70 (n=114)
Absolute change in ppFEV$_1$ from baseline compared to placebo				
Mean change in percentage points	+6.6	-1.1	+3.3	+1.9
p value	p<0.05	n.s.	p<0.0001	n.s.
Relative change in ppFEV$_1$ from baseline compared to placebo				
Mean change	+11.8%	+0.0%	+5.9%	+2.5%
p value	p<0.05	n.s.	p<0.0001	n.s.

ppFEV$_1$ changes expressed as least-square mean vs placebo

*reported data, not part of a head-to-head study

*J Stuart Elborn, Bonnie W Ramsey, Michael P Boyle, et al., "Efficacy and safety of lumacaftor/ivacaftor combination therapy in patients with cystic fibrosis homozygous for Phe508del CFTR by pulmonary function subgroup: a pooled analysis", The Lancet Respiratory Medicine, Volume 4, Issue 8, August 2016

Financial Status

- December 2017 Public Offering:
  - 9.2 M shares of common stock at $5 per share
  - Net proceeds ~$42.9 M
- Cash position estimated to be sufficient to fund operations into early 2019

2018 Key Milestones

2018

- ✓ PTI-808/PTI-801/PTI-428 combination study protocol endorsed with high strategic fit score by CF patient advocacy groups in the U.S. and Europe
- PTI-801/PTI-808 combination study dosing planned in CF patients
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