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VX-864 PHASE 2 RESULTS AND ALPHA-1 ANTITRYPSIN DEFICIENCY (AATD) PROGRAM UPDATE

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VX-864 PHASE 2 RESULTS AND ALPHA-1 ANTITRYPSIN DEFICIENCY (AATD) PROGRAM UPDATE

AGENDA

Reshma Kewalramani, M.D.,
Vertex's CEO and President

For Q&A

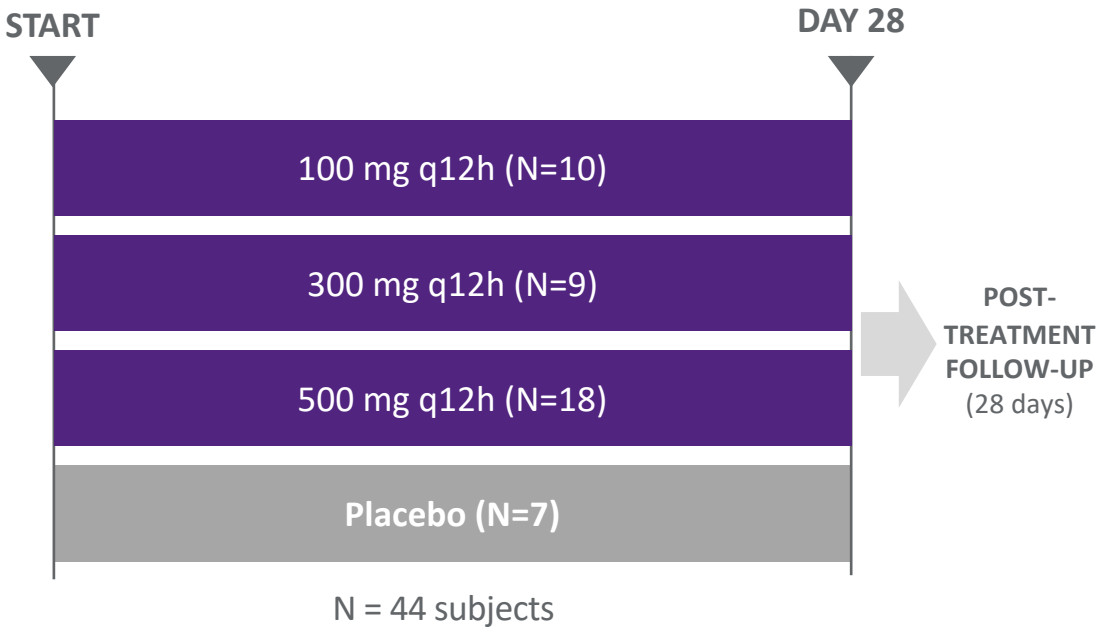
David Altshuler, M.D., Ph.D.,
Vertex's EVP, Global Research, and Chief Scientific Officer

SAFE HARBOR STATEMENT

This presentation contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, including, without limitation, (i) the company's intention to apply insights from this study and its plan to advance novel small molecule correctors with the potential for increased clinical efficacy in 2022 and (ii) the company's expectations regarding the clinical path for future molecules. While Vertex believes the forward-looking statements contained in this presentation are accurate, these forward-looking statements represent the company's beliefs only as of the date of this presentation and there are a number of risks and uncertainties that could cause actual events or results to differ materially from those expressed or implied by such forward-looking statements. Those risks and uncertainties include, among other things, risks related to the company's AATD research programs, that data from the company's research and development programs may not support registration or further development of its compounds due to safety, efficacy, or other reasons, and other risks listed under the heading Risk Factors in Vertex's annual report filed with the Securities and Exchange Commission and available through the company's website at www.vrtx.com and on the SEC's website at www.sec.gov. You should not place undue reliance on these statements. Vertex disclaims any obligation to update the information contained in this presentation as new information becomes available.

VX-864 PHASE 2 RESULTS

PHASE 2 STUDY AIMED TO ASSESS THE ABILITY OF VX-864 TO INCREASE LEVELS OF FUNCTIONAL AAT IN PLASMA AND SAFETY/TOLERABILITY



Primary Endpoints

- Change from baseline in plasma functional AAT levels at Day 28
- Safety and tolerability

Secondary Endpoints

- Change from baseline in plasma antigenic AAT levels at Day 28
- Pharmacokinetic parameters of VX-864

VX-864 PHASE 2 STUDY: DEMOGRAPHICS & BASELINE CHARACTERISTICS

	Placebo (N=7)	VX-864 100mg (N=10)	VX-864 300mg (N=9)	VX-864 500mg (N=18)
Age, years; mean (SD)	63.4 (10.5)	55.1 (5.3)	53.2 (16.2)	57.4 (9.9)
Baseline functional AAT (μM); mean (SD)	4.7 (1.3)	4.0 (0.7)	3.8 (0.9)	4.1 (0.6)
Baseline antigenic AAT (μM); mean (SD)	5.4 (1.2)	4.5 (0.9)	4.6 (1.1)	4.8 (0.9)

SD = standard deviation

Inclusion criteria

- PiZZ genotype (2 copies of Z allele)
- AAT levels in the blood (plasma) indicating severe deficiency
- Ages 18-80 years

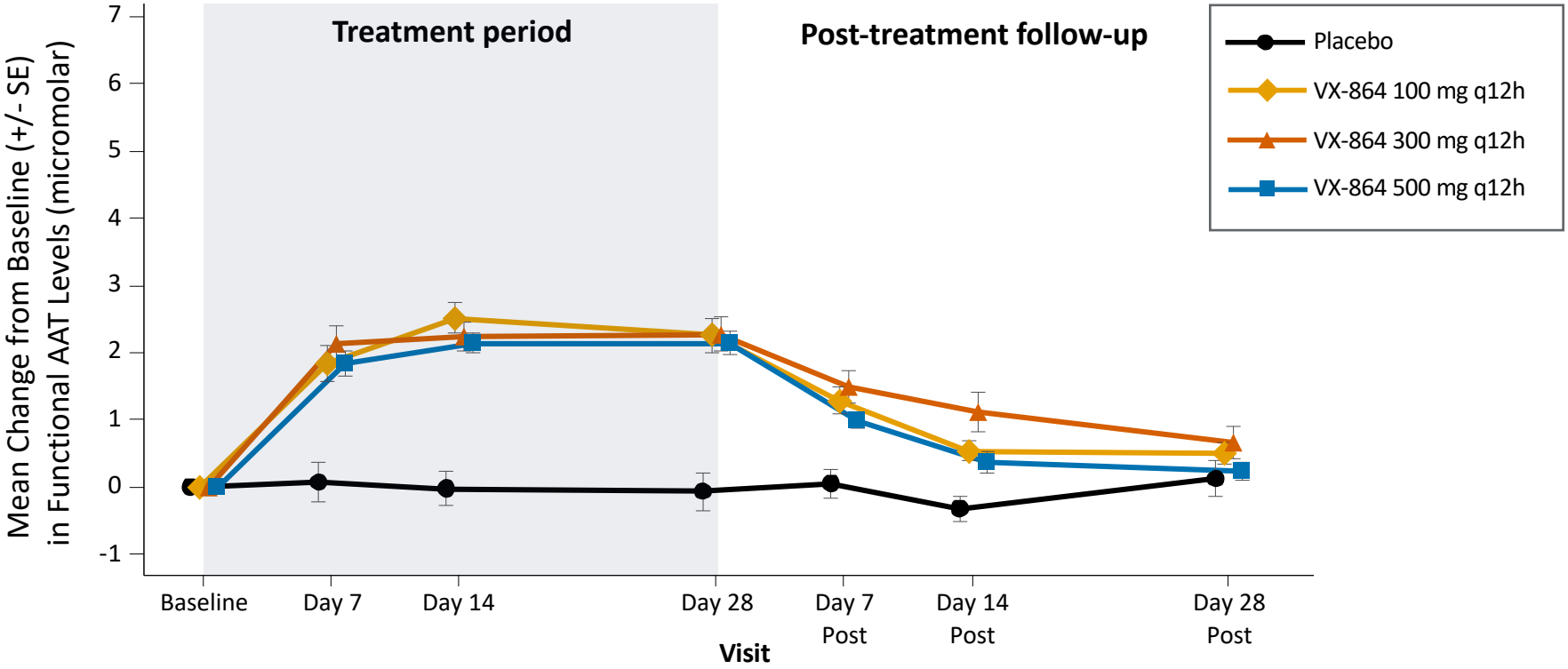
30 clinical sites across the U.S., Europe and Canada

STATISTICALLY SIGNIFICANT INCREASE IN MEAN FUNCTIONAL AND ANTIGENIC AAT OBSERVED AT DAY 28 COMPARED TO PLACEBO

	Change in **Functional AAT** from Baseline at Day 28 (μM; mean (SE))	P value vs placebo	Change in **Antigenic AAT** from Baseline at Day 28 (μM; mean (SE))	P value vs placebo
Placebo (N=7)	-0.1 (0.3)	-	-0.1 (0.4)	-
VX-864 100 mg q12h (N=10)	+2.3 (0.3)	<0.0001	+3.4 (0.4)	<0.0001
VX-864 300 mg q12h (N=9)	+2.3 (0.2)	<0.0001	+2.9 (0.4)	<0.0001
VX-864 500 mg q12h (N=18)	+2.1 (0.2)	<0.0001	+2.6 (0.2)	<0.0001

SE = standard error

RAPID AND SUSTAINED INCREASE IN MEAN FUNCTIONAL AAT LEVELS FROM BASELINE IN ALL DOSE GROUPS COMPARED TO PLACEBO



ABSOLUTE MEAN FUNCTIONAL AND ANTIGENIC AAT LEVELS AT BASELINE AND AT DAY 28

	Functional AAT (μM; mean (SD))		**Antigenic AAT** (μM; mean (SD))	
	Baseline	**Day 28**	**Baseline**	**Day 28**
Placebo (N=7)	4.7 (1.3)	4.6 (1.0)	5.4 (1.2)	5.3 (1.3)
VX-864 100 mg q12h (N=10)	4.0 (0.7)	6.3 (1.4)	4.5 (0.9)	7.9 (1.5)
VX-864 300 mg q12h (N=9)	3.8 (0.9)	6.1 (1.1)	4.6 (1.1)	7.5 (1.7)
VX-864 500 mg q12h (N=18)	4.1 (0.6)	6.2 (1.2)	4.8 (0.9)	7.5 (1.9)

SD = standard deviation

THERAPY WAS GENERALLY WELL TOLERATED REGARDLESS OF DOSE LEVEL

- No discontinuations due to adverse events (AEs)
- No serious adverse events (SAEs) considered related to study drug
- Majority of AEs were mild or moderate and not treatment limiting
- The most common AEs (>15%) in VX-864 treated patients in the study were diarrhea and nausea
- Liver function test (LFT) results were similar between placebo and VX-864 treated groups
- No evidence of any impact on LFTs with VX-864 treatment

CONCLUSIONS AND NEXT STEPS

We have established the Z-AAT corrector mechanism of action in the clinic

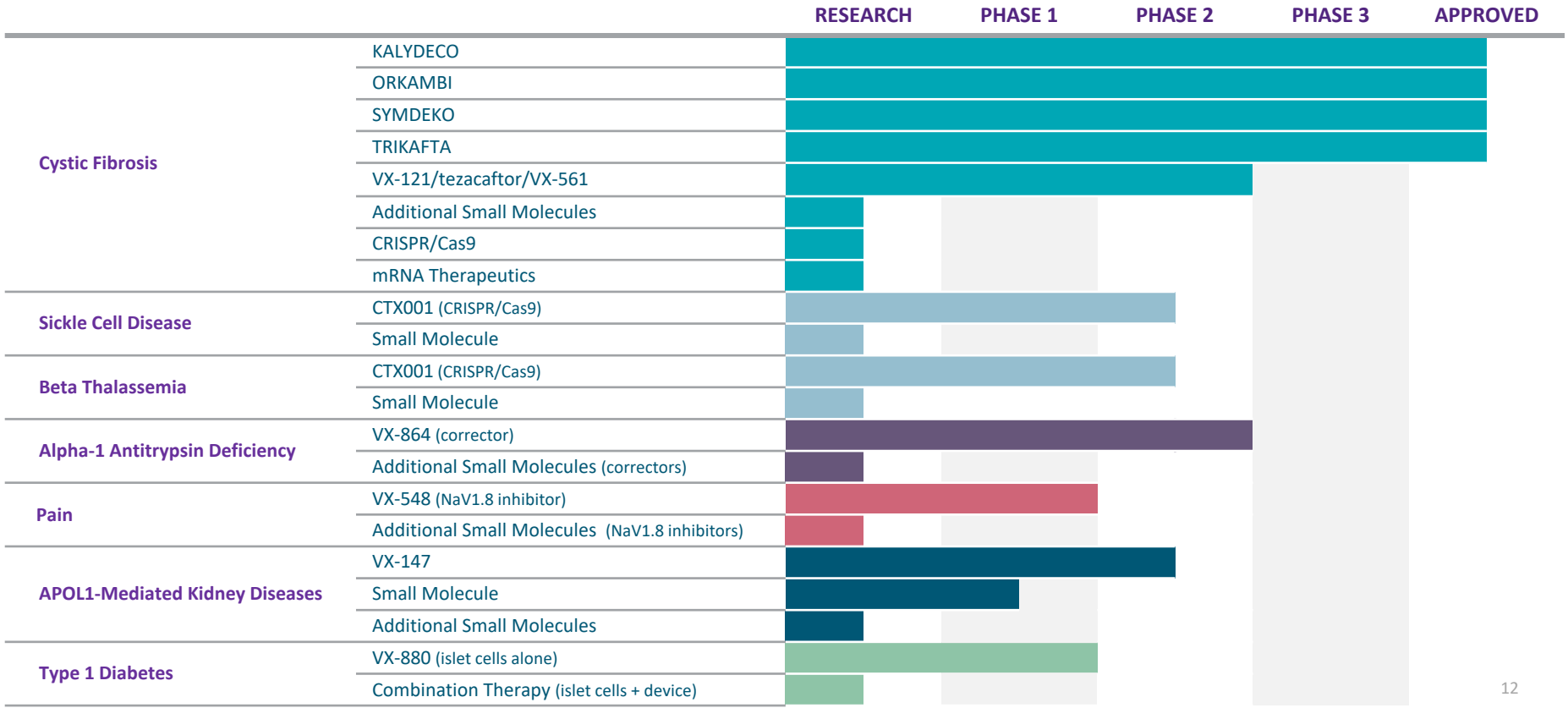
There is no evidence for on-mechanism toxicity; VX-864 was generally well tolerated

We will apply insights from the VX-864 Phase 2 study and plan to advance novel small molecule correctors with the potential for increased clinical efficacy in 2022

We expect that the clinical path of future molecules will be efficient, with rapid progression to proof-of-concept and late-stage development

DISEASE AREAS ACTIVE IN CLINICAL DEVELOPMENT

PORTFOLIO APPROACH WITH LEAD MOLECULES AND RAPIDLY ADVANCING FOLLOW-ON PROGRAMS



Thank you to all of the people living with AATD who participated in the trial & to the clinical study investigators