



FIRST-QUARTER 2021 FINANCIAL RESULTS

APRIL 29, 2021

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AGENDA

Introduction

Michael Partridge, Senior Vice President, Investor Relations

CEO Perspective and R&D Update

Reshma Kewalramani, M.D., CEO and President

Commercial Update

Stuart Arbuckle, Executive Vice President and Chief Commercial and Operations Officer

Financial Results

Charlie Wagner, Executive Vice President and Chief Financial Officer

SAFE HARBOR STATEMENT & NON-GAAP FINANCIAL MEASURES

This presentation contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, including, without limitation, the information provided regarding future financial performance and operation, the section captioned "Full-Year Updated 2021 Financial Guidance" and statements regarding (i) anticipated regulatory filings, data submissions, and approvals, (ii) future label expansions, (iii) the expectations, development plans and anticipated timelines for the company's therapies and pipeline programs, including clinical site activations, patient enrollment and data availability, (iv) the company's expectations regarding the effects COVID-19 will have on its business and operations, (v) expectations for the continued launch, uptake and reimbursement of KAFTRIO, (vi) expectations for the collaborations with CRISPR, including expectations regarding completion of enrollment in the CTX001 clinical studies, anticipated benefits of the collaborations and anticipated timing of product access for future patients, (vii) expectations for uptake of and expanded access to the company's medicines, including additional reimbursement agreements, (viii) expectations for an increase in the number of CF patients treated with our medicines, (ix) expectations for VX-548, including our plans to advance VX-548 into Phase 2 proof-of-concept studies in the second half of 2021, (x) expectations for the transactions contemplated by the amended collaboration with CRISPR, including satisfaction of closing conditions, antitrust clearance, anticipated upfront and milestone payments to CRISPR, and anticipated future activities of the parties, (xi) expected effect on our expenses upon the closing of the transaction contemplated by the amended collaboration with CRISPR, and (xii) anticipated internal and external development. 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, that the company's expectations regarding its 2021 product revenues, expenses and effective tax rates may be incorrect (including because one or more of the company's assumptions underlying its expectations may not be realized), that COVID-19 may have different or more significant impacts on the company's business or operations than the company currently expects, that data from preclinical testing or early clinical trials, especially if based on a limited number of patients, may not be indicative of final results, that the closing of the transaction contemplated by the amended collaboration with CRISPR may not occur in a timely manner, or at all, that data from the company's development programs may not be available on expected timelines, or at all, support registration or further development of its potential medicines due to safety, efficacy or other reasons, and other risks listed under 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.

In this presentation, Vertex's financial results and financial guidance are provided in accordance with accounting principles generally accepted in the United States (GAAP) and using certain non-GAAP financial measures. In particular, non-GAAP financial results and guidance exclude from Vertex's pre-tax income (i) stock-based compensation expense, (ii) revenues and expenses related to collaborative milestones and upfront payments, (iii) gains or losses related to the fair value of the company's strategic investments, (iv) increases or decreases in the fair value of contingent consideration, (v) acquisition-related costs and (vi) other adjustments. The company's non-GAAP financial results also exclude from its provision for income taxes the estimated tax impact related to its non-GAAP adjustments to pre-tax income described above and certain discrete items. These results should not be viewed as a substitute for the company's GAAP results and are provided as a complement to results provided in accordance with GAAP. Management believes these non-GAAP financial measures help indicate underlying trends in the company's business, are important in comparing current results with prior period results and provide additional information regarding the company's financial position that the company believes is helpful to an understanding of its ongoing business. Management also uses these non-GAAP financial measures to establish budgets and operational goals that are communicated internally and externally, to manage the company's business and to evaluate its performance. The company adjusts, where appropriate, for both revenues and expenses in order to reflect the company's operations. The company's calculation of non-GAAP financial measures likely differs from the calculations used by other companies. The company provides guidance regarding combined R&D and SG&A expenses and effective tax rate on a non-GAAP basis. The guidance regarding combined GAAP R&D and SG&A expenses does not include estimates associated with any potential future business development activities. The company does not provide guidance regarding its GAAP effective tax rate because it is unable to forecast with reasonable certainty the impact of excess tax benefits related to stock-based compensation and the possibility of certain discrete items, which could be material. A reconciliation of the GAAP financial results to non-GAAP financial results is included in the appendix hereto and in the company's Q1 2021 press release dated April 29, 2021.

VERTEX Q1 2021:

Strong revenue growth driven by our continued **leadership in CF**; multiple **pipeline programs** advancing through all stages of clinical development

Leadership in CF

- TRIKAFTA/KAFTRIO positioned to address 90% of CF patients
- Increasing number of patients treated; new approvals and reimbursement agreements across our CF portfolio
- Novel triple combination therapy advancing to Phase 3 in 2021
- Continued focus on genetic therapies to address remaining 10% of patients

Pipeline Programs Advancing

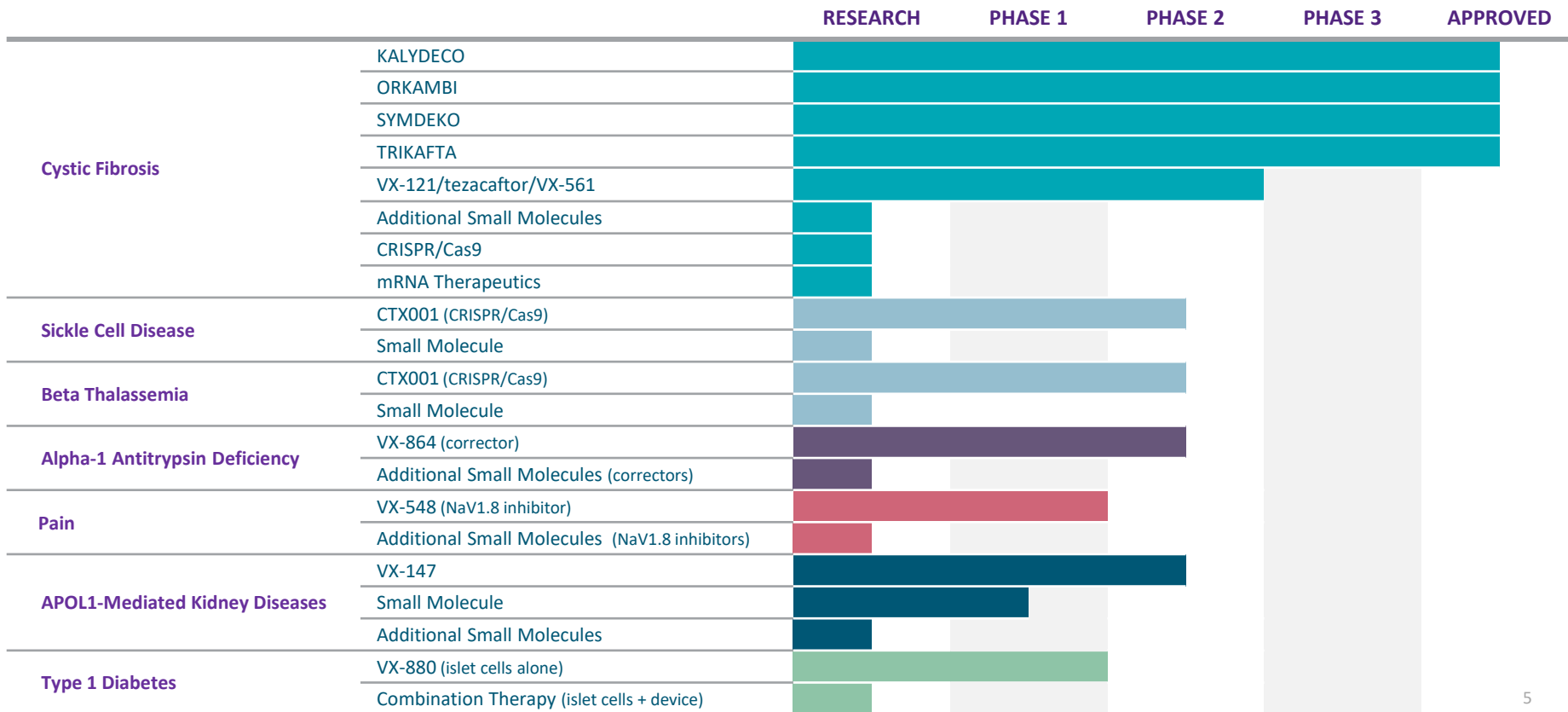
- Broad clinical pipeline spans seven diseases and three therapeutic modalities
- Significant progress in Q1 across all programs
- Potential for multiple clinical data readouts in the next 6 to 12 months

Revenue Growth & Capital Deployment

- \$1.7B in Q1 '21 revenues, a 14% increase, driven by strong international uptake of KAFTRIO and continued performance of TRIKAFTA
- Two new agreements highlight investment in external innovation to complement our internal pipeline and drive future growth

SEVEN DISEASE AREAS ACTIVE IN CLINICAL DEVELOPMENT

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



DEVELOPMENT ADVANCING IN MULTIPLE POTENTIALLY TRANSFORMATIVE PROGRAMS OUTSIDE OF CF

SMALL MOLECULES



Alpha-1 Antitrypsin Deficiency VX-864 in Phase 2

Small molecule correctors of Z-AAT protein misfolding, enabling secretion from the liver and increased functional AAT in serum

Phase 2 study completed dosing, safety follow-up ongoing
Potential POC data anticipated 2Q21



APOL1-Mediated Kidney Diseases VX-147 in Phase 2

Small molecule inhibitors of APOL1 function, an underlying genetic cause of FSGS and other proteinuric kidney diseases

Potential POC data in APOL1-mediated FSGS anticipated 2H21



NaV1.8 inhibitor for Pain VX-548 progressing to Phase 2 studies

Small molecule inhibitors of NaV1.8, a pharmacologically validated target for the treatment of pain

2 studies planned to start in 2H 2021 — acute pain following bunionectomy and acute pain following abdominoplasty

CELL AND GENETIC THERAPIES



Sickle Cell Disease & Beta Thalassemia CTX001 in Phase 2

Ex vivo gene editing with goal of providing a one-time curative therapy

> 30 patients dosed across two studies
Completion of enrollment anticipated in 2021
Potential for regulatory submission in 18-24 mo.



Type 1 Diabetes VX-880 (cells alone program) in Phase 1/2

Cell therapy that uses fully-differentiated functional islet cells derived from stem cells

Clinical trial sites open for enrollment
Cells + device program in late preclinical

ON THE PATH TO TREATING UP TO 90% OF CF PATIENTS WITH CFTR MODULATORS



TRIKAFTA

- Nearly all patients eligible for TRIKAFTA ages 12+ with at least one *F508del* mutation in the U.S. have initiated TRIKAFTA therapy
- Following the rare mutations approval in late December, many of the ~600 new patients in the U.S. have initiated therapy
- U.S. approval for children ages 6-11 anticipated mid-year



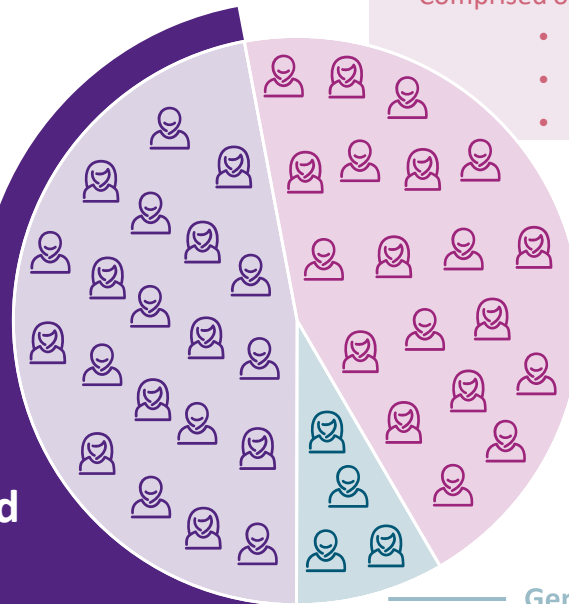
KAFTRIO

- KAFTRIO approved in the EU for people ages 12+ with at least one *F508del* mutation in the EU
- Strong uptake across all countries where patients have access, including the larger markets of England and Germany
- Regulatory submission filed in Europe for children ages 6-11

OPPORTUNITY FOR FURTHER SUBSTANTIAL GROWTH IN CF

83,000 people with CF in U.S., Europe, Australia and Canada.

Nearly 50% of Patients Currently Treated with Vertex Medicines



>30,000 Patients Currently Untreated & Addressable with Triple Combination

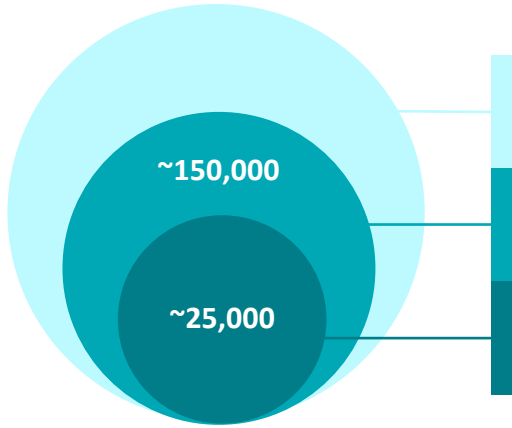
Comprised of:

- Countries not yet reimbursed
- Countries awaiting approval
- Younger ages not yet approved

Genetic Therapies Needed

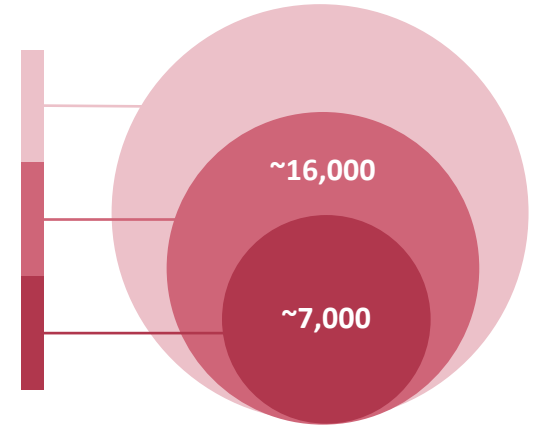
NEAR-TERM CTX001 MARKET OPPORTUNITY IS MORE THAN 30,000 PATIENTS

SICKLE CELL DISEASE



- Expansion into other international markets
- Total patients in the U.S. and EU – *potential for expansion with gentler conditioning regimens*
- Likely candidates for gene-editing therapy in the U.S. and EU based on disease severity

BETA THALASSEMIA



Potential to treat patients with severe forms of these diseases in the U.S. and EU in the near-term with CTX001

Q1 2021 FINANCIAL HIGHLIGHTS

<i>(\$ in millions except as noted, per share data and percentages)</i>	Q1 20	FY 20	Q1 21
Total CF product revenues	<u>\$1.52B</u>	<u>\$6.20B</u>	<u>\$1.72B</u>
TRIKAFTA/KAFTRIO	895	3.86B	1.19B
SYMDEKO/SYMKEVI	173	629	125
ORKAMBI	234	908	219
KALYDECO	213	803	186
Combined non-GAAP R&D and SG&A expenses	<u>477</u>	<u>1.98B</u>	<u>530</u>
Non-GAAP operating income	877	3.49B	1.00B
Non-GAAP operating margin	58%	56%	58%
Non-GAAP net income	674	2.72B	781
Non-GAAP net income per share - diluted	\$2.56	\$10.32	\$2.98
Cash, cash equivalents & marketable securities (period-end)	\$4.2B	\$6.7B	\$6.9B

Notes: An explanation of non-GAAP financial measures and reconciliation of combined non-GAAP R&D and SG&A expenses, non-GAAP operating income and non-GAAP net income to corresponding GAAP measures are included in the company's Q1 2021 press release dated April 29, 2021. Non-GAAP financial measures are presented compared to corresponding GAAP measures in the appendix of this presentation. Totals above may not add due to rounding.

FULL-YEAR 2021 UPDATED FINANCIAL GUIDANCE

	Current FY 2021 Guidance	Previous FY 2021 Guidance	FY 2021 Commentary
Total CF Product Revenues	Unchanged	\$6.7 - \$6.9B	Guidance does not include potential new reimbursement agreements that may be reached in 2021
Combined GAAP R&D and SG&A Expenses	\$3.8 to 3.95 billion	\$2.9 - \$3.05B	Increase in combined GAAP R&D and SG&A expenses guidance reflects the expected impact of the company's transaction with CRISPR Therapeutics announced in April
Combined Non-GAAP R&D and SG&A Expenses	Unchanged	\$2.25 - \$2.3B	
Non-GAAP Effective Tax Rate	Unchanged	21-22%	



FIRST-QUARTER 2021 FINANCIAL RESULTS

RESHMA KEWALRAMANI, M.D.
CEO AND PRESIDENT

APRIL 29, 2021

APPENDIX

GAAP TO NON-GAAP FINANCIAL INFORMATION

	Q1 20	FY 20	Q1 21
<i>(\$ in millions except as noted, per share data and percentages)</i>			
Combined R&D and SG&A expenses			
GAAP	631	2.60B	648
Non-GAAP	477	1.98B	530
Operating income			
GAAP	720	2.86B	888
Non-GAAP	877	3.49B	1.00B
Operating Margin %:			
GAAP	48%	46%	51%
Non-GAAP	58%	56%	58%
Net income			
GAAP	603	2.71B	653
Non-GAAP	674	2.72B	781
Net income per share - diluted			
GAAP	\$2.29	\$10.29	\$2.49
Non-GAAP	\$2.56	\$10.32	\$2.98