


VERTEX

THE SCIENCE *of* POSSIBILITY

FOURTH-QUARTER 2020 FINANCIAL RESULTS

RESHMA KEWALRAMANI, M.D.

CEO AND PRESIDENT

FEBRUARY 1, 2021

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 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 2021 Financial Guidance" and statements regarding (i) anticipated regulatory filings and data submissions, (ii) future label expansions, (iii) the expectations, development plans and anticipated timelines for the company's therapies and pipeline programs, including the expected initiation of a Phase 1/2 clinical trial evaluating VX-880, (iv) the company's expectations regarding the effects COVID-19 will have on its business and operations, (v) expectations for the continued launch of and access to KAFTRIO, (vi) expectations for the uptake of and expanded access to the company's medicines, including additional reimbursement agreements, (vii) expectations for the collaboration with CRISPR, including expectations regarding completion of enrollment, and (viii) 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, the FDA may not approve VX-880 on a timely basis, 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 and subsequent quarterly reports 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) an adjustment to product revenues and related cost of sales to reflect the conclusion of the early access program for ORKAMBI in France in the fourth quarter of 2019, (iii) revenues and expenses related to collaboration agreements, (iv) gains or losses related to the fair value of the company's strategic investments, (v) increases or decreases in the fair value of contingent consideration, (vi) acquisition-related costs and (vii) 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 a 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 Q4 2020 press release dated February 1, 2021.

2020:
A YEAR OF SIGNIFICANT ACCOMPLISHMENTS ACROSS THE CF PORTFOLIO AND CLINICAL PIPELINE WITH INCREASED FINANCIAL STRENGTH

ACHIEVE OUR VISION IN CYSTIC FIBROSIS

- ✓ **EU approval of triple combination regimen for ages 12+**
- ✓ **EU approval of SYMKEVI for ages 6 to 11**
- ✓ **Submit sNDA for triple combination regimen in the U.S. for ages 6 to 11**

DEVELOP NEW TRANSFORMATIVE MEDICINES FOR SERIOUS DISEASES

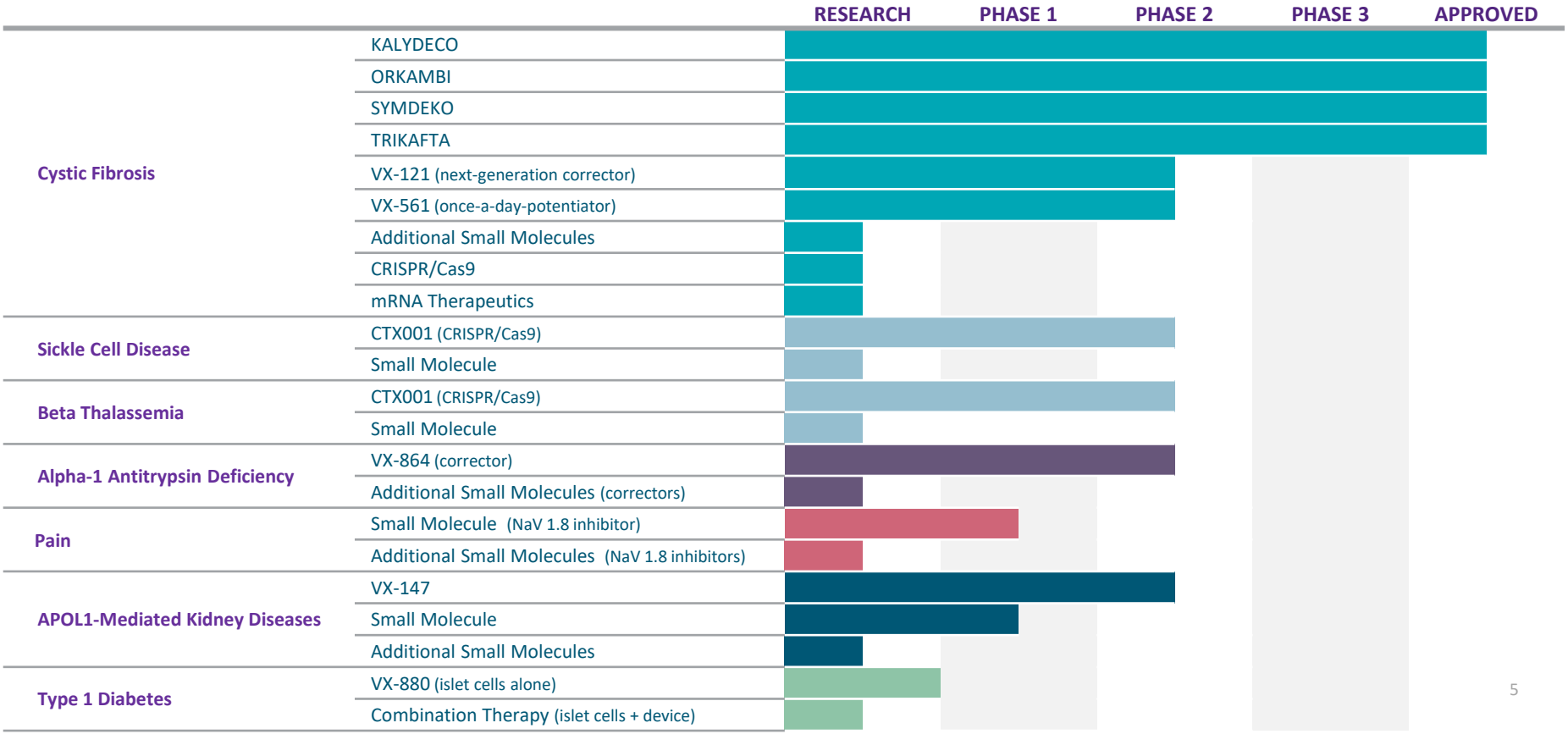
- ✓ **Generate proof-of-concept data for both sickle cell disease and beta thalassemia**
- ✓ **Advance cell tx. for type 1 diabetes into clinical dev. in late 2020/early 2021**
- ✓ **Advance two new compounds into clinical development**

DELIVER FINANCIAL PERFORMANCE

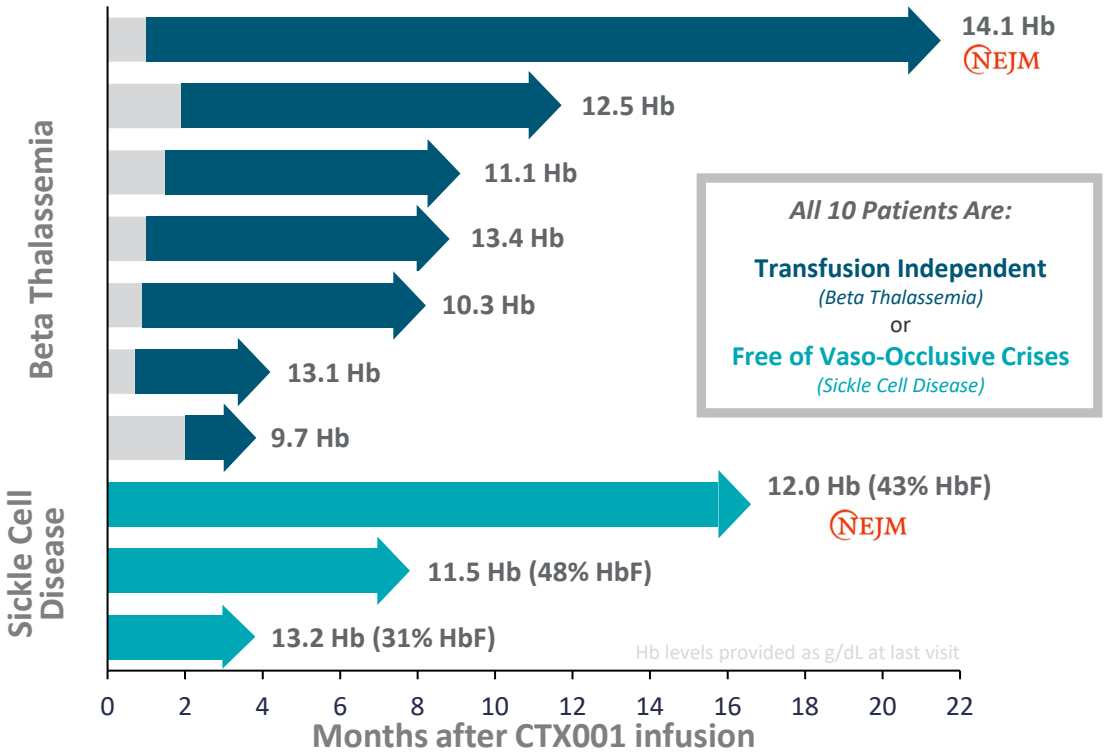
- ✓ **Continued CF product revenue growth**
- ✓ **Further expansion of non-GAAP operating margins and cash flows**
- ✓ **Effectively deploy capital to pursue future growth opportunities**

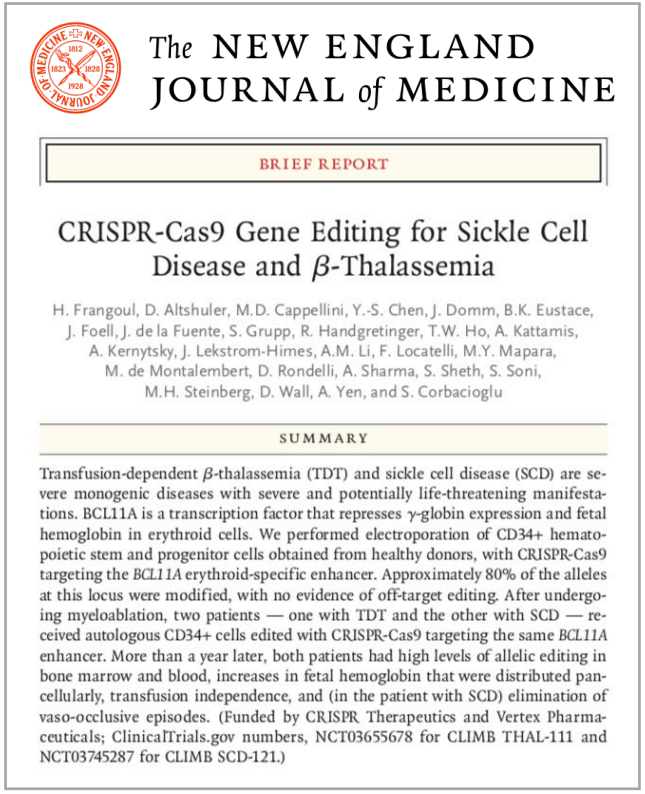
SEVEN DISEASE AREAS ACTIVE IN CLINICAL DEVELOPMENT

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



CTX001: PROOF OF CONCEPT ESTABLISHED IN BOTH BETA THALASSEMIA & SICKLE CELL DISEASE DEMONSTRATING A FUNCTIONAL CURE IS POSSIBLE





The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β-Thalassemia

H. Frangoul, D. Altshuler, M.D. Cappellini, Y.-S. Chen, J. Domm, B.K. Eustace, J. Foell, J. de la Fuente, S. Grupp, R. Handgretinger, T.W. Ho, A. Kattamis, A. Kernytsky, J. Lekstrom-Himes, A.M. Li, F. Locatelli, M.Y. Mapara, M. de Montalembert, D. Rondelli, A. Sharma, S. Sheth, S. Soni, M.H. Steinberg, D. Wall, A. Yen, and S. Corbacioglu

SUMMARY

Transfusion-dependent β-thalassemia (TDT) and sickle cell disease (SCD) are severe monogenic diseases with severe and potentially life-threatening manifestations. BCL11A is a transcription factor that represses γ-globin expression and fetal hemoglobin in erythroid cells. We performed electroporation of CD34+ hematopoietic stem and progenitor cells obtained from healthy donors, with CRISPR-Cas9 targeting the *BCL11A* erythroid-specific enhancer. Approximately 80% of the alleles at this locus were modified, with no evidence of off-target editing. After undergoing myeloablation, two patients — one with TDT and the other with SCD — received autologous CD34+ cells edited with CRISPR-Cas9 targeting the same *BCL11A* enhancer. More than a year later, both patients had high levels of allelic editing in bone marrow and blood, increases in fetal hemoglobin that were distributed pancellularly, transfusion independence, and (in the patient with SCD) elimination of vaso-occlusive episodes. (Funded by CRISPR Therapeutics and Vertex Pharmaceuticals; ClinicalTrials.gov numbers, NCT03655678 for CLIMB THAL-111 and NCT03745287 for CLIMB SCD-121.)

MULTIPLE POTENTIALLY TRANSFORMATIVE PROGRAMS IN DEVELOPMENT

SMALL MOLECULES

Alpha-1 Antitrypsin Deficiency

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

VX-864 in Phase 2
Potential POC data anticipated 1H21

Second molecule in the clinic in 2021

APOL1-Mediated Kidney Diseases

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

VX-147 in Phase 2
Potential POC data anticipated 2021

Second molecule in Phase 1

Pain

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

Novel NaV1.8 inhibitor in Phase 1

Second molecule in the clinic in 2021

CELL AND GENETIC THERAPIES

Sickle Cell Disease & Beta Thalassemia

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

CTX001 in Phase 2
POC achieved for sickle cell disease & beta thalassemia programs
Completion of enrollment anticipated 2021

Type 1 Diabetes

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

IND cleared for VX-880
Initiation of Phase 1/2 trial expected 1H21

Cells + device program in late preclinical

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

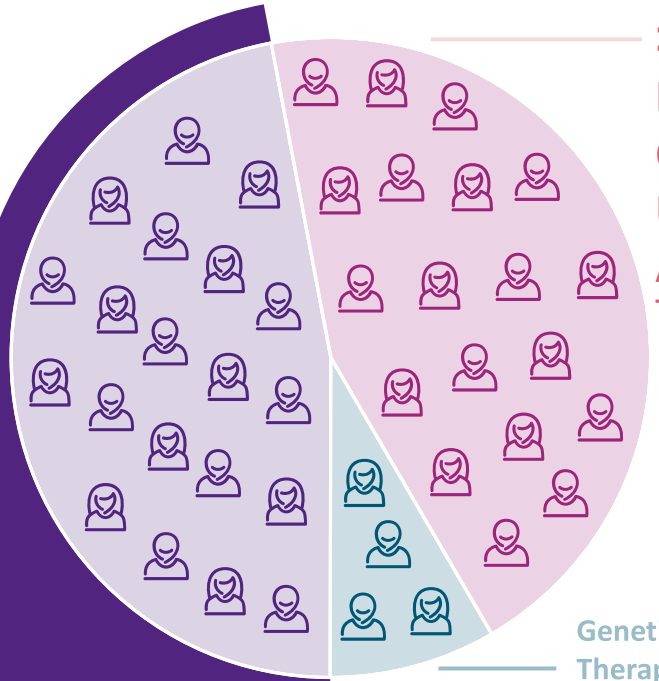
- More than 1 year since launch of TRIKAFTA in the U.S. for people ages 12+ who have at least one *F508del* mutation
- Vast majority of the ~18,000 eligible patients in the U.S. have initiated therapy
- sNDA accepted for children ages 6-11; approval anticipated mid-year

- Early EC approval for KAFTRIO in the EU received on August 21, 2020 for people ages 12+ who have two *F508del* mutations or one *F508del* mutation and one minimal function mutation
- Strong uptake across all countries where patients have access, including the larger markets of England and Germany
- Focus on continuing the launch in countries where patients have access and completing new reimbursement agreements across the EU

FUTURE OPPORTUNITY FOR SIGNIFICANT GROWTH IN CF

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

Nearly 50% of Patients Currently Treated with Vertex Medicines



Q4 2020 FINANCIAL HIGHLIGHTS

($ in millions except where noted or per share data and percentages)	Q4 19	FY 19	Q1 20	Q2 20	Q3 20	Q4 20	FY 20
Total non-GAAP CF product revenues	$1.26B	**$4.00B**	$1.52B	$1.52B	$1.54B	$1.63B	**$6.2B**
TRIKAFTA/KAFTRIO	420	**420**	895	918	960	1.09B	**3.86B**
SYMDEKO/SYMKEVI	332	**1.42B**	173	172	156	128	**629**
ORKAMBI	270	**1.18B**	234	232	226	215	**908**
KALYDECO	236	**991**	213	203	194	193	**803**
Combined non-GAAP R&D and SG&A expenses	496	**1.69B**	477	467	497	539	**1.98B**
Non-GAAP operating income	593	**1.79B**	877	874	854	887	**3.49B**
Non-GAAP operating margin	47%	**45%**	58%	57%	56%	54%	**56%**
Non-GAAP net income	444	**1.39B**	674	687	697	661	**2.72B**
Non-GAAP net income per share - diluted	$1.70	**$5.33**	$2.56	$2.61	$2.64	$2.51	**$10.32**
Cash, cash equivalents & marketable securities (period-end)		**$3.8B**					**$6.7B**

Notes

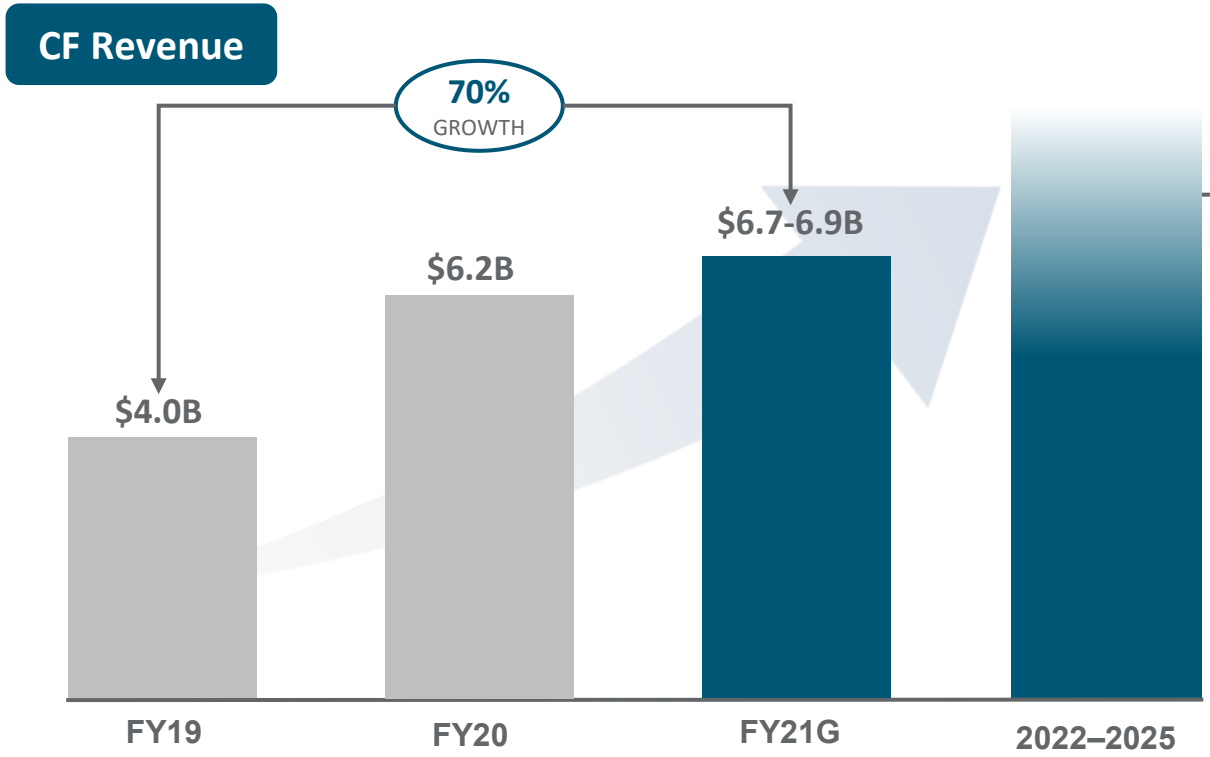
- An explanation of non-GAAP financial measures and reconciliation of combined non-GAAP R&D and SG&A expense and non-GAAP net income to corresponding GAAP measures are included in the company's Q4 2020 press release dated February 1, 2021.
- Reconciliation of non-GAAP CF product revenues and non-GAAP operating income to corresponding GAAP measures, as well as non-GAAP operating margin and net income per share - diluted are presented compared to corresponding GAAP measures in the appendix of this presentation; totals may not add due to rounding.

FULL-YEAR 2021 FINANCIAL GUIDANCE

	FY 2020 Actuals	FY 2021 Guidance	FY 2021 Commentary
Total CF Product Revenues	$6.2B	**$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	$2.6B	**$2.9 -$3.05B**	Year-over-year growth largely driven by investment in our pipeline programs
Combined Non-GAAP R&D and SG&A Expenses	$1.98B	**$2.25 -$2.3B**	
Non-GAAP Effective Tax Rate	21%	**21-22%**	

Note: An explanation of non-GAAP financial measures and a reconciliation between the company's full-year 2021 combined GAAP R&D and SG&A expenses and combined non-GAAP R&D and SG&A expenses guidance is included in the company's Q4 2020 press release dated February 1, 2021.

AFTER EXCEPTIONAL PROGRESS IN 2020, VERTEX IS POISED FOR CONTINUED GROWTH IN 2021 AND BEYOND



Future Revenue Growth Driven By:

Continued Growth in CF

- Younger Age Groups
- Label Expansions
- New Reimbursements

Commercialization in Disease Areas Beyond CF

Notes: 2019 CF Revenues are non-GAAP; see appendix for a reconciliation; 2021 reflects the midpoint of the total CF revenue guidance; 2022 – 2025 potential growth in CF revenues provided as a graphical representation and not intended as financial guidance; 70% growth represents year-over-year increase at the midpoint of 2021 guidance range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APPENDIX

RECONCILIATION OF GAAP TO NON-GAAP FINANCIAL INFORMATION

($ in millions except where noted or per share data and percentages)	Q4 19	FY 19	Q1 20	Q2 20	Q3 20	Q4 20	FY 20
GAAP total product revenues	$1.41B	**$4.16B**	$1.52B	$1.52B	$1.54B	$1.63B	**$6.20B**
ORKAMBI adjustment	(156)	**(156)**	-	-	-	-	**-**
Non-GAAP total product revenues	1.26B	**4.00B**	1.52B	1.52B	1.54B	1.63B	**6.20B**
GAAP operating income	551	**1.20B**	720	718	672	746	**2.86B**
Stock compensation expense	92	**360**	116	117	100	97	**429**
Other adjustments	(50)	**228**	41	39	82	44	**205**
Non-GAAP operating income	593	**1.79B**	877	874	854	887	**3.49B**
Operating Margin %:							
GAAP	39%	**29%**	48%	47%	44%	46%	**46%**
Non-GAAP	47%	**45%**	58%	57%	56%	54%	**56%**
Net income							
GAAP	583	**1.18B**	603	837	667	604	**2.71B**
Non-GAAP	444	**1.39B**	674	687	697	661	**2.72B**
Net income per share - diluted							
GAAP	$2.23	**$4.51**	$2.29	$3.18	$2.53	$2.30	**$10.29**
Non-GAAP	$1.70	**$5.33**	$2.56	$2.61	$2.64	$2.51	**$10.32**

Note: Reconciliation of non-GAAP net income to corresponding GAAP measures is included in the company's Q4 2020 press release dated February 1, 2021; totals may not add due to rounding.