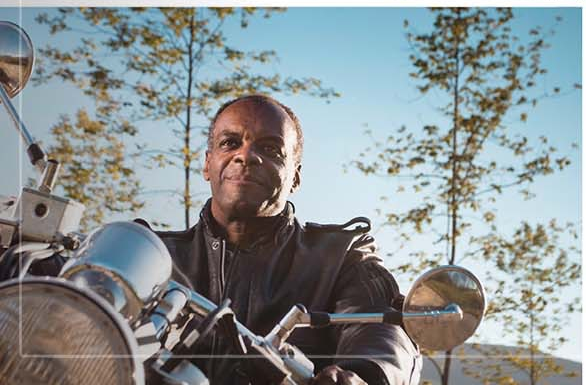







VERTEX

THE SCIENCE *of* POSSIBILITY

FOURTH QUARTER AND FULL YEAR 2021 FINANCIAL RESULTS

JANUARY 26, 2022

AGENDA

Introduction

Michael Partridge, Senior Vice President, Investor Relations

CEO Perspective and Pipeline Update

Reshma Kewalramani, M.D., CEO and President

Commercial Update

Stuart Arbuckle, Executive Vice President and Chief Operating 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 operations, and statements regarding (i) the expectations, development plans, anticipated timelines for and potential benefits of the company's therapies and pipeline programs, including study designs, clinical site initiations, patient enrollment, data availability, anticipated regulatory filings, approvals, and timing thereof, (ii) expectations for the CTX001 program, including the potential of CTX001 to be a curative approach for patients with TDT and SCD, the expectation of regulatory filings in 2022, expectations for program approval and launch, and potential commercial opportunity, (iii) expectations for uptake of and expanded access to the company's medicines, including additional reimbursement agreements, label expansions and approvals in new markets, (iv) expectations for continued growth in the number of CF patients treated with our medicines, including reaching all CF patients who can benefit from TRIKAFTA/KAFTRIO, expansion of treatment options for the patients who do not benefit from CFTR modulators and anticipated size of patient populations, (v) our plans to treat additional CF patients with mRNA, including plans for a CFTR mRNA IND filing in 2022, (vi) expectations for our pain program, including for available data in the first quarter of 2022, (vii) beliefs about delivering treatments and potential cures for more patients in multiple new disease areas, including potential commercial opportunities in the disease areas in which we focus, (viii) expectations for our T1D program, including dosing additional patients with VX-880, data from additional patients and longer duration follow up, and an IND submission for our T1D cells and device program in 2022, (ix) expectations for our next-in-class, once-daily triple regimen for CF patients, including our Phase 3 program expectations, enrollment plans and related economics, (x) plans to initiate and advance the VX-147 pivotal program in AMKD in the first quarter 2022 and potential commercial opportunity, and (xi) our plans to continue to invest in internal and external innovation. 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 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 future financial and operating performance may be incorrect (including because one or more of the company's assumptions underlying its expectations may not be realized), that the company may not be able to submit anticipated regulatory filings on expected timelines, or at all, 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 clinical trials, especially if based on a limited number of patients, may not be indicative of final results, that actual patient populations able to participate in our trials or eligible for our products may be smaller than we anticipated, that data from the company's development programs may not be available on expected timelines, or at all, and may not 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 filings 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 or the scientific data presented. 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 upfront and milestones payments, including a $900 million upfront payment to CRISPR, and certain other business development activities, (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. Non-GAAP financial measures are presented compared to corresponding GAAP measures in the appendix hereto. A reconciliation of the GAAP financial results to non-GAAP financial results is included in the company's Q4 2021 press release dated January 26, 2022.

VERTEX Full Year 2021 Results:

Important progress across our business and exceptional financial performance

Expanded leadership in CF

- Treating more patients
- TRIKAFTA real-world performance continues to raise the bar
- Advanced next-gen therapies:
  - Phase 3 studies underway with next-in-class triple combination regimen
  - CFTR mRNA IND filing planned for 2022

Advanced the mid- and late-stage pipeline

- CTX001 pivotal trial enrollment for SCD and beta thalassemia complete
- Proof-of-concept for VX-147 in APOL1-mediated FSGS
- Promising early results with VX-880 in T1D
- Proof-of-concept studies for VX-548 in acute pain underway

Further strengthened our financial position

- Q4’21 product revenues: $2.07B, +27% year-over-year
- 2021 product revenues: $7.57B, +22% year-over-year
- 2021 GAAP operating income: $2.78B; non-GAAP operating income: $4.34B
- Cash & Investments (Dec.31, 2021): $7.5B

Notes: An explanation of non-GAAP financial measures and reconciliation of GAAP operating income to non-GAAP operating income is included in the company’s Q4 2021 press release dated January 26, 2022.

VERTEX MEDICINES ARE TRANSFORMING THE LIVES OF CF PATIENTS

Real-world data from >16,000 U.S. patients treated with TRIKAFTA show:

87% ↓
Reduction in risk of lung transplant*

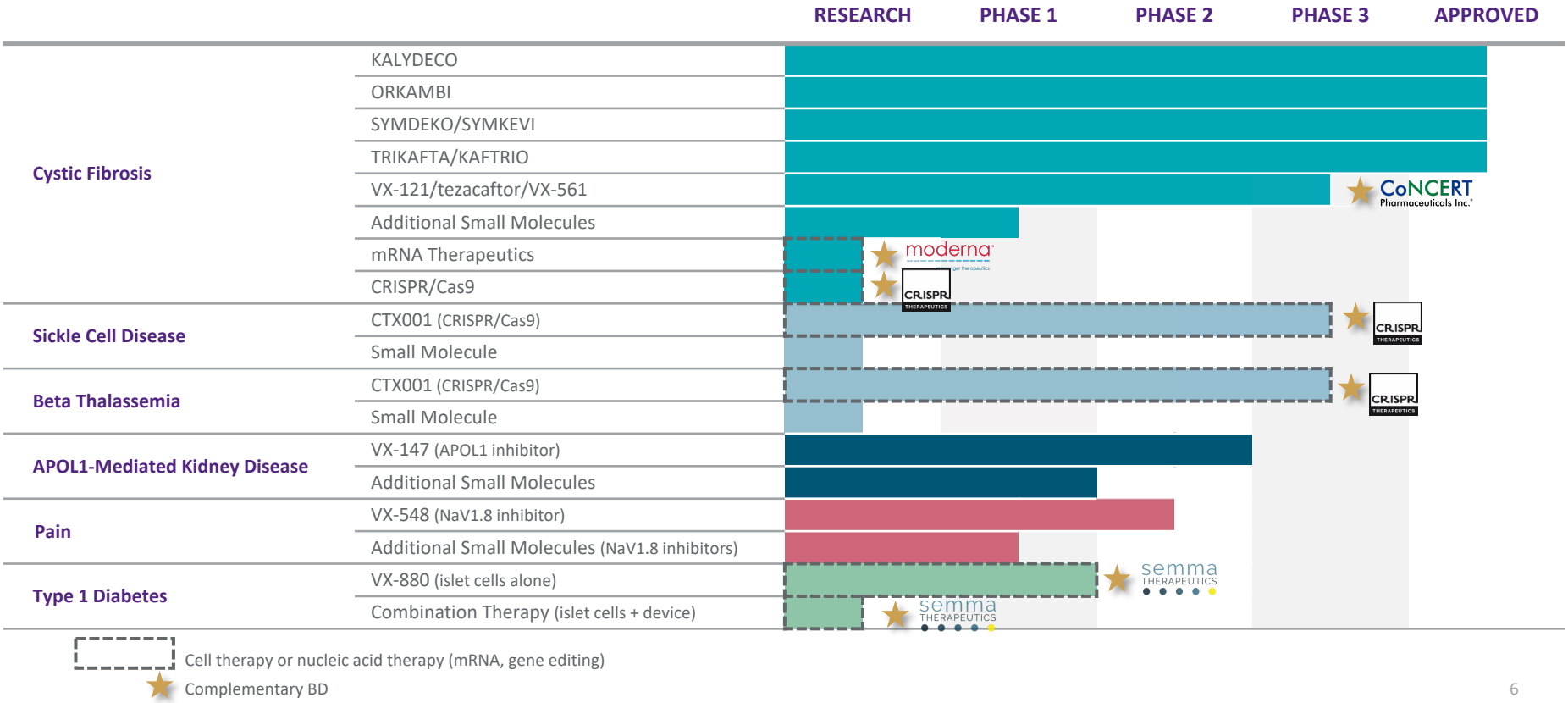
77% ↓
Fewer pulmonary exacerbations**

74% ↓
Reduction in risk of death*

In addition, TRIKAFTA 96-week follow-up data from pivotal trials showed no reduction in lung function

* Unadjusted estimate relative to historical 2019 U.S. Cystic Fibrosis Foundation registry data for patients older than 12 with at least one copy of F508del mutation
** Relative to 12-month period prior to TRIKAFTA treatment initiation
Data from observational post-authorization safety study on >16,000 TRIKAFTA-treated patients with mean of ~9 months of exposure, from U.S Cystic Fibrosis Foundation patient registry.

VERTEX IS ADVANCING A BROAD AND DEEP CLINICAL PIPELINE ACROSS MULTIPLE MODALITIES

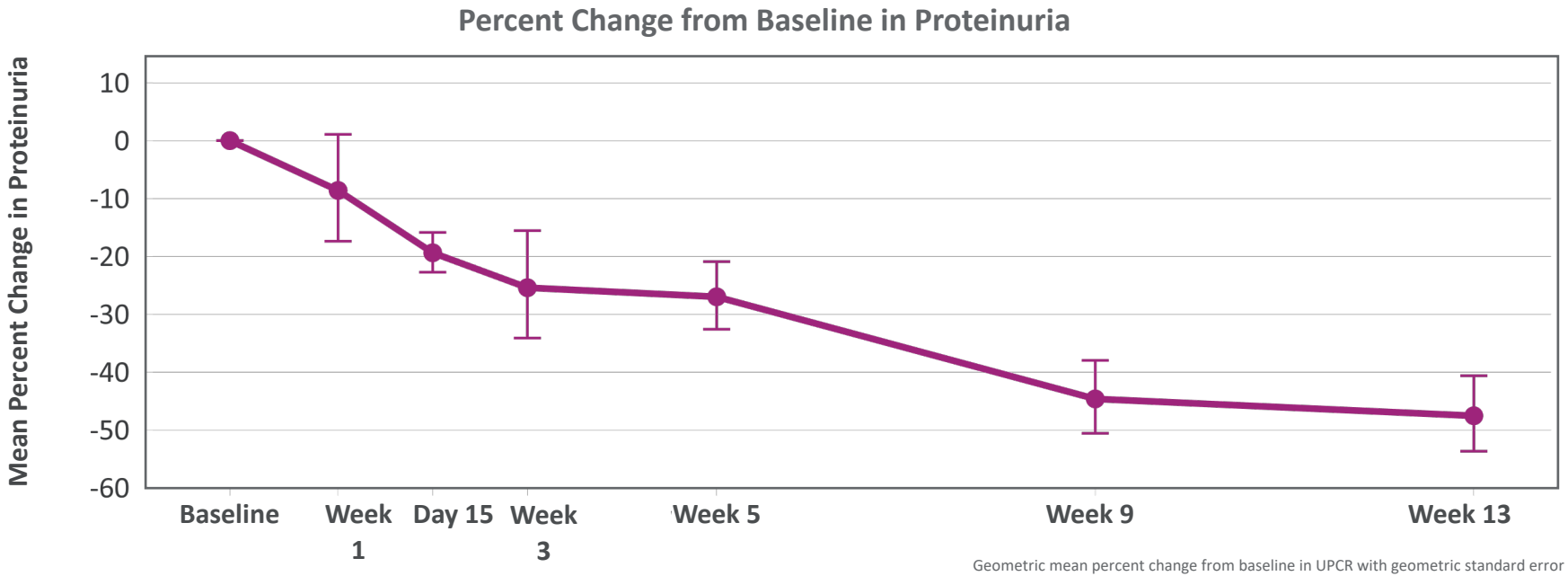


KEY PIPELINE ADVANCES IN 2021 CREATE HIGH-VALUE CATALYSTS IN 2022

Completed in 2021	Planned for 2022
Completed enrollment in pivotal studies of CTX001 and dosed >70 patients	Plan to file for regulatory approval by year-end 2022
First type 1 diabetes patients dosed with VX-880	• Dose more patients with VX-880 • File IND for cells+device approach in 2022
Proof-of-concept established for VX-147, small molecule for APOL1-mediated kidney disease	Advancing to pivotal development in Q1 2022
Initiation and rapid enrollment of two Phase 2 POC studies of VX-548 in acute pain	POC readouts in Q1 2022 could establish basis for advancing to pivotal development

VX-147: FIRST MEDICINE TARGETING APOL1-MEDIATED KIDNEY DISEASE

Phase 2 results in APOL1-mediated FSGS show 47.6% mean reduction in proteinuria, on top of standard-of-care



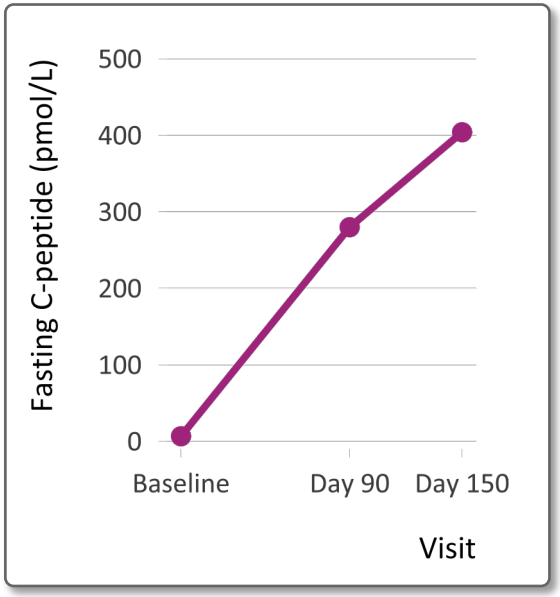
Geometric mean percent change from baseline in UPCR with geometric standard error

Plan to initiate VX-147 pivotal program in AMKD in Q1 2022

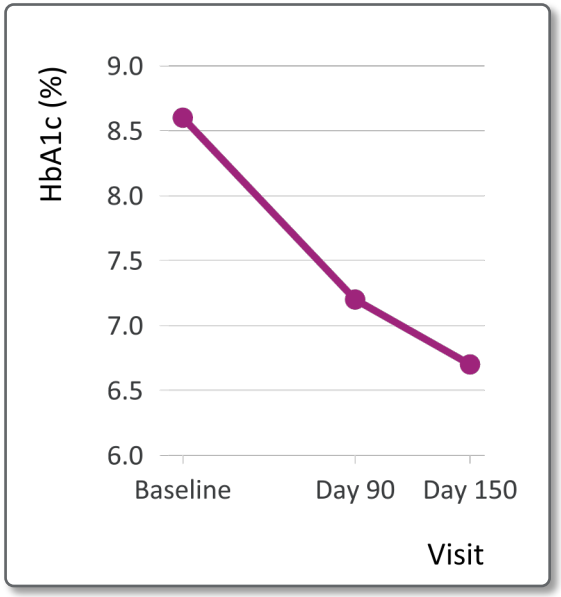
VX-880: POTENTIALLY TRANSFORMATIVE CELL THERAPY FOR TYPE 1 DIABETES

Day 150 data: 92% reduction in exogenous insulin use, simultaneous rapid improvement in glycemic control in 1st patient

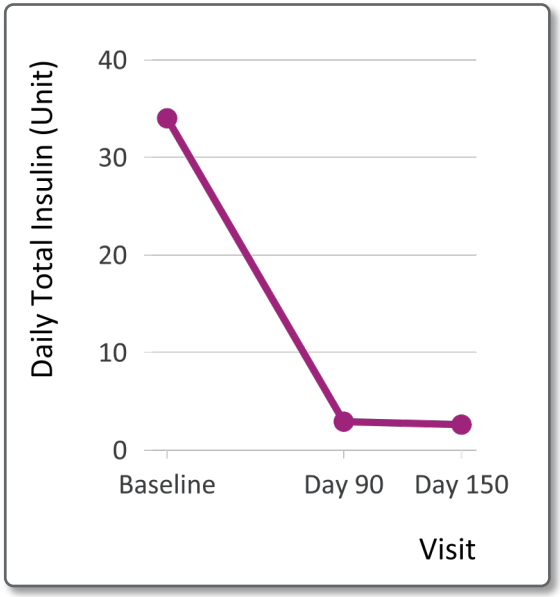
Fasting C-peptide increase to 404 pmol/L



HbA1c decline to 6.7%



92% reduction in daily insulin use



CONTINUED UPTAKE OF OUR CFTR MODULATORS AROUND THE WORLD

UNITED STATES

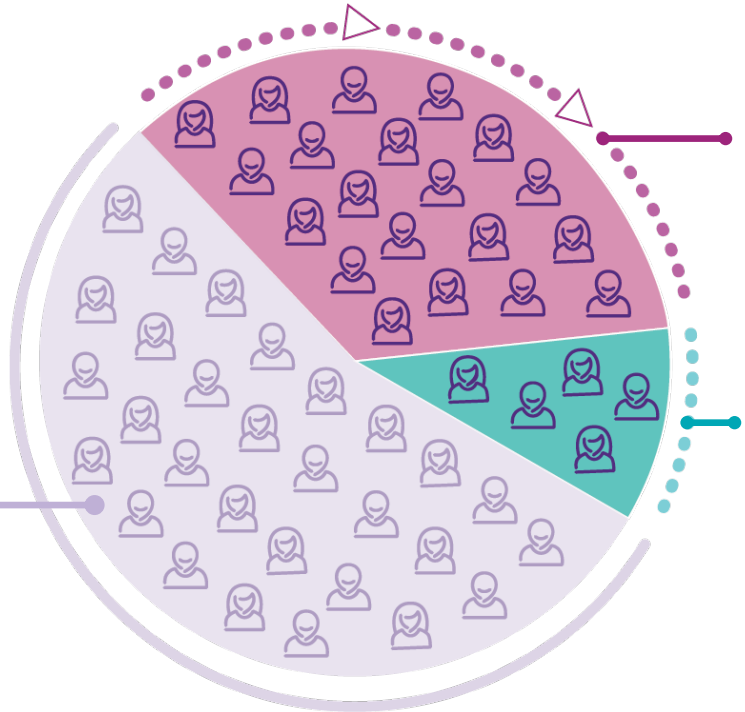
- Continued strong demand, high persistence and compliance rates with TRIKAFTA in the U.S.
- Successfully launched TRIKAFTA in U.S. for children ages 6-11 following approval in June 2021

EUROPE and OTHER MARKETS

- New reimbursement agreements for KAFTRIO/TRIKAFTA in 16 countries in 2021
- Approval for KAFTRIO in Europe and the UK in children ages 6-11, with at least one *F508del* mutation, in January 2022

CONTINUED GROWTH AHEAD IN CF

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



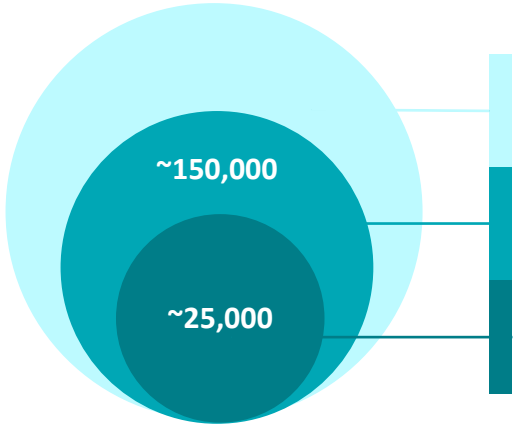
Rapid uptake for our CF medicines in currently eligible patients

Growth Opportunities

1. **>25,000 patients** that are addressable with triple combination are still untreated
   - Continued uptake
   - New reimbursements
   - Label expansion to younger ages
2. **NEW:** potential to treat additional **5,000+** patients with mRNA; IND planned for 2022

CTX001: INITIAL MULTIBILLION-DOLLAR OPPORTUNITY IN 32,000 SEVERE DISEASE PATIENTS

SICKLE CELL DISEASE

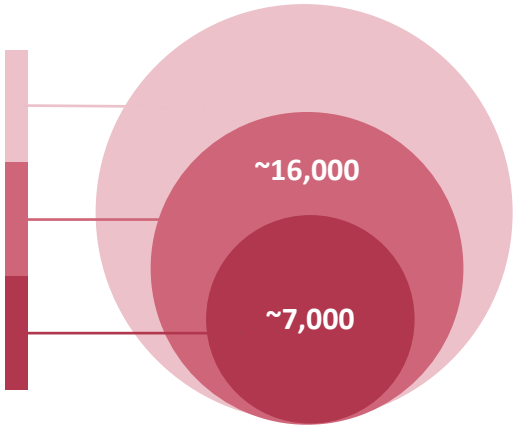


Expansion into other international markets

Total patients in the U.S. and Europe – *potential for expansion with gentler conditioning regimens*

Likely candidates for gene-editing therapy in the U.S. and Europe based on disease severity

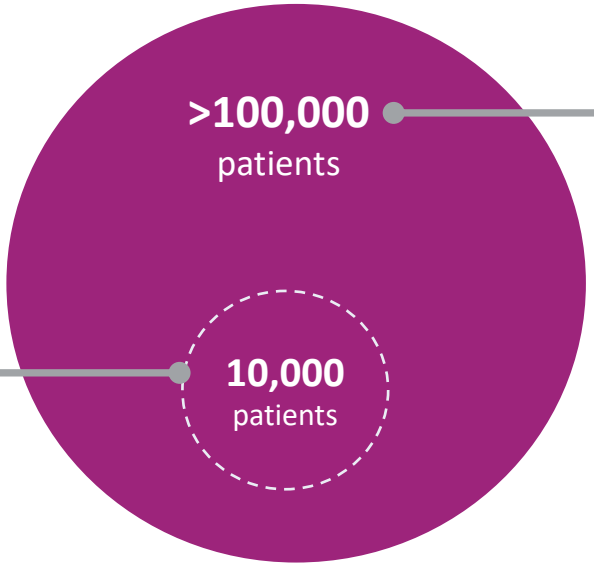
BETA THALASSEMIA



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

VX-147: APOL1-MEDIATED KIDNEY DISEASE REPRESENTS A SIGNIFICANT OPPORTUNITY

APOL1-mediated kidney disease includes different clinical/histological presentations with the same genetic cause



APOL1-MEDIATED KIDNEY DISEASE

- **Broader** population
  - Includes APOL1-mediated FSGS
- Moderate to heavy proteinuria
- Clinically diagnosed
- Two APOL1 mutations

APOL1-MEDIATED FSGS

- **Narrower** population
- Heavy proteinuria
- Biopsy-diagnosed
- Two APOL1 mutations

Q4 AND FULL YEAR 2021 FINANCIAL HIGHLIGHTS

($ in millions except where noted or per share data and percentages)	Q4 20	FY 20	Q1 21	Q2 21	Q3 21	Q4 21	FY 21
Total CF product revenues	$1.63B	**$6.2B**	$1.72B	$1.79B	$1.98B	$2.07B	**$7.57B**
TRIKAFTA/KAFTRIO	1.09B	**3.86B**	1.19B	1.26B	1.56B	1.69B	**5.70B**
SYMDEKO/SYMKEVI	128	**629**	125	134	81	80	**420**
ORKAMBI	215	**908**	219	221	185	147	**772**
KALYDECO	193	**803**	186	183	162	152	**684**
Combined non-GAAP R&D and SG&A expenses	539	**1.98B**	530	537	561	703	**2.33B**
Non-GAAP operating income	887	**3.49B**	1.00B	1.03B	1.19B	1.12B	**4.34B**
Non-GAAP operating margin	54%	**56%**	58%	57%	60%	54%	**57%**
Non-GAAP net income	661	**2.72B**	781	811	926	866	**3.38B**
Non-GAAP net income per share - diluted	$2.51	**$10.32**	$2.98	$3.11	$3.56	$3.37	**$13.02**
Cash, cash equivalents & marketable securities (period-end)		**$6.7B**					**$7.5B**

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 Q4 2021 press release dated January 26, 2022. 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.

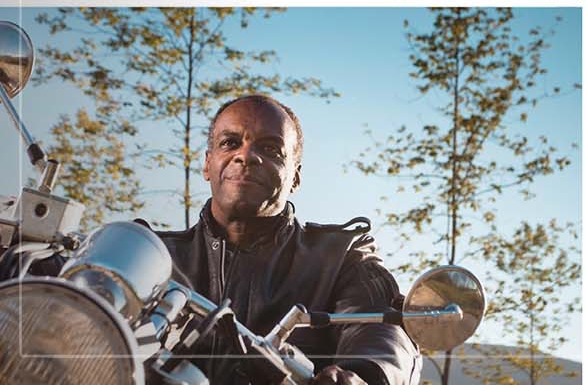
FULL YEAR 2022 FINANCIAL GUIDANCE

	FY 2021 Actuals	FY 2022 Guidance	FY 2022 Commentary
Total CF Product Revenues	$7.6B	$8.4 - $8.6B	Anticipate continued CF revenue growth; many more patients left to treat
Combined GAAP R&D and SG&A Expenses	$3.89B	$3.3 -$3.45B	FY 2021 GAAP R&D expense included $900 million payment to CRISPR in Q2 2021
Combined Non-GAAP R&D and SG&A Expenses	$2.33B	$2.7 -$2.75B	Increased investment to support advancement of our clinical pipeline
Non-GAAP Effective Tax Rate	21%	21%-22%	

Note: An explanation of non-GAAP financial measures, 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 and a note describing the difference between the company's full year 2022 combined GAAP R&D and SG&A expense guidance and combined non-GAAP R&D and SG&A expense guidance is included in the company's Q4 2021 press release dated January 26, 2022.








VERTEX

THE SCIENCE *of* POSSIBILITY

FOURTH QUARTER AND FULL YEAR 2021 FINANCIAL RESULTS

JANUARY 26, 2022

APPENDIX

GAAP TO NON-GAAP FINANCIAL INFORMATION

($ in millions except as noted, per share data and percentages)	Q4 20	FY 20	Q1 21	Q2 21	Q3 21	Q4 21	FY 21
Combined R&D and SG&A							
GAAP	678	**2.60B**	648	1.60B	692	950	**3.89B**
Non-GAAP	539	**1.98B**	530	537	561	703	**2.33B**
Operating income							
GAAP	746	**2.86B**	888	(38)	1.05B	878	**2.78B**
Non-GAAP	887	**3.49B**	1.00B	1.03B	1.19B	1.12B	**4.34B**
Operating Margin %:							
GAAP	46%	**46%**	51%	(2%)	53%	42%	**37%**
Non-GAAP	54%	**56%**	58%	57%	60%	54%	**57%**
Net income							
GAAP	604	**2.71B**	653	67	852	770	**2.34B**
Non-GAAP	661	**2.72B**	781	811	926	866	**3.38B**
Net income per share - diluted							
GAAP	$2.30	**$10.29**	$2.49	$0.26	$3.28	$3.00	**$9.01**
Non-GAAP	$2.51	**$10.32**	$2.98	$3.11	$3.56	$3.37	**$13.02**

Note: 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 Q4 2021 press release dated January 26, 2022.