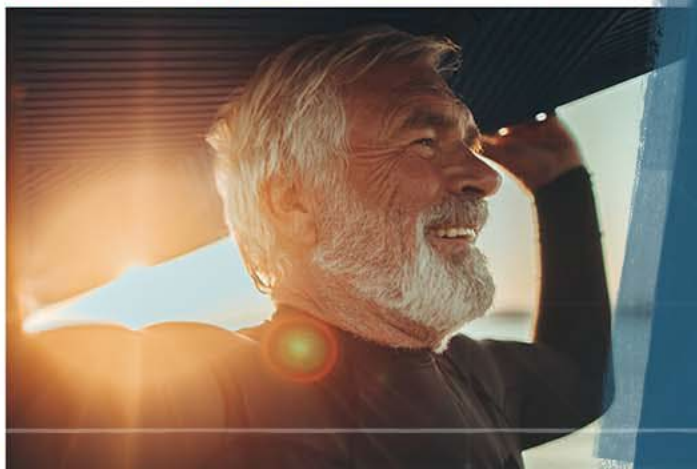


VERTEX

THE SCIENCE *of* POSSIBILITY

THIRD QUARTER 2022 FINANCIAL RESULTS

OCTOBER 27, 2022

AGENDA

Introduction

Susie Lisa, CFA, Senior Vice President, Investor Relations

CEO Perspective and Pipeline Update

Reshma Kewalramani, M.D., Chief Executive Officer 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, as amended, including, without limitation, the information provided regarding future financial performance and operations, fiscal year 2022 financial guidance, and statements regarding our (i) expectations, development plans, anticipated timelines for and potential benefits of the company's products and product candidates, including study designs, clinical site initiations, patient enrollment, data availability, anticipated regulatory filings, approvals, and timing thereof, (ii) outlook for sustained growth in the number of CF patients treated with our products, including reaching more CF patients who can benefit from our marketed products, (iii) plans to treat additional CF patients with mRNA and views on treatable patient population, expectations for a CFTR mRNA IND filing before the end of 2022 with clinical trials thereafter, (iv) expectations for our next-in-class, once-daily, oral triple regimen for CF patients, including beliefs on enhanced patient benefit and development of Phase 3 trials and program expectations, (v) expectations for our exa-cel program, including the continued potential for exa-cel to be a curative approach for patients with TDT and SCD and our views on treatable patient population, plans to initiate regulatory filings in the U.S. in November with completion expected in Q1 2023, and submit regulatory filings in Europe and the U.K. before the end of 2022, as well as potential commercial opportunities and preparations, (vi) expectations regarding the potential benefits of our pain program, including the belief that VX-548 could reduce in prevalence of opioids in the treatment of pain, the continued advancement of VX-548 into its Phase 3 trial in acute pain, commercial opportunities, preparations, and market analysis for VX-548, and plans to study VX-548 in a Phase 2 dose-ranging proof-of-concept study for neuropathic pain towards year-end 2022, as well as enrollment expectations in both studies, (vi) our plans regarding our pivotal program underway for inaxaplin in AMKD, including enrollment expectations, and our beliefs regarding anticipated results of the study and the possibility for accelerated approval in the U.S., (vii) expectations for the development of our T1D programs, including the potential benefits and safety of VX-880 and treatable patient population, plans to continue to progress the Phase 1/2 program for VX-880, and plans and expectations regarding our additional T1D programs, including intentions to file an IND before the end of 2022 for our "cells + device" program and how the recent acquisition of ViaCyte may accelerate the development of our T1D program, (viii) views on the continued uptake of and expanded access to the company's products, including additional reimbursement agreements, as well as label extensions for younger patients, (ix) plans for continued advancement of VX-634 and VX-864, (x) beliefs about rapid development of treatments and potential cures for more patients in multiple new disease areas, and plans to continue to invest in our pipeline and commercial readiness activities for our programs, and (xi) expectations regarding the company's tax rates, revenue growth, and the impact of foreign exchange rates on revenue growth. 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 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 external factors 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 patient enrollment in our trials may be delayed, 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 quarterly reports filed with the Securities and Exchange Commission (SEC) 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) gains or losses related to the fair value of the company's strategic investments, (iii) increases or decreases in the fair value of contingent consideration, (iv) acquisition-related costs, (v) an intangible asset impairment charge 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's calculation of non-GAAP financial measures likely differs from the calculations used by other companies. The company provides guidance regarding combined R&D, Acquired IPR&D and SG&A expenses and effective tax rate on a non-GAAP basis. The guidance regarding combined GAAP and non-GAAP R&D, Acquired IPR&D and SG&A expenses does not include estimates associated with any potential future business development transactions, including collaborations, asset acquisitions and/or licensing of third-party intellectual property rights. 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 Q3 2022 press release dated October 27, 2022.

STRATEGIC INFLECTION POINT FOR VERTEX

Unique and differentiated R&D strategy delivers success

Expanding CF leadership

- Treating more patients with our CF medicines
- On track to file TRIKAFTA for 2–5-year-olds globally by YE 2022
- Next-gen CFTR regimen Phase 3 enrollment for 12 years and up, to complete by YE 2022
- On track to file IND for CFTR mRNA therapy by YE 2022

Accelerating broad and deep R&D pipeline

- Proof-of-concept established in five disease areas outside CF
- Multiple programs in pivotal development
- Next wave of therapies approaching the clinic

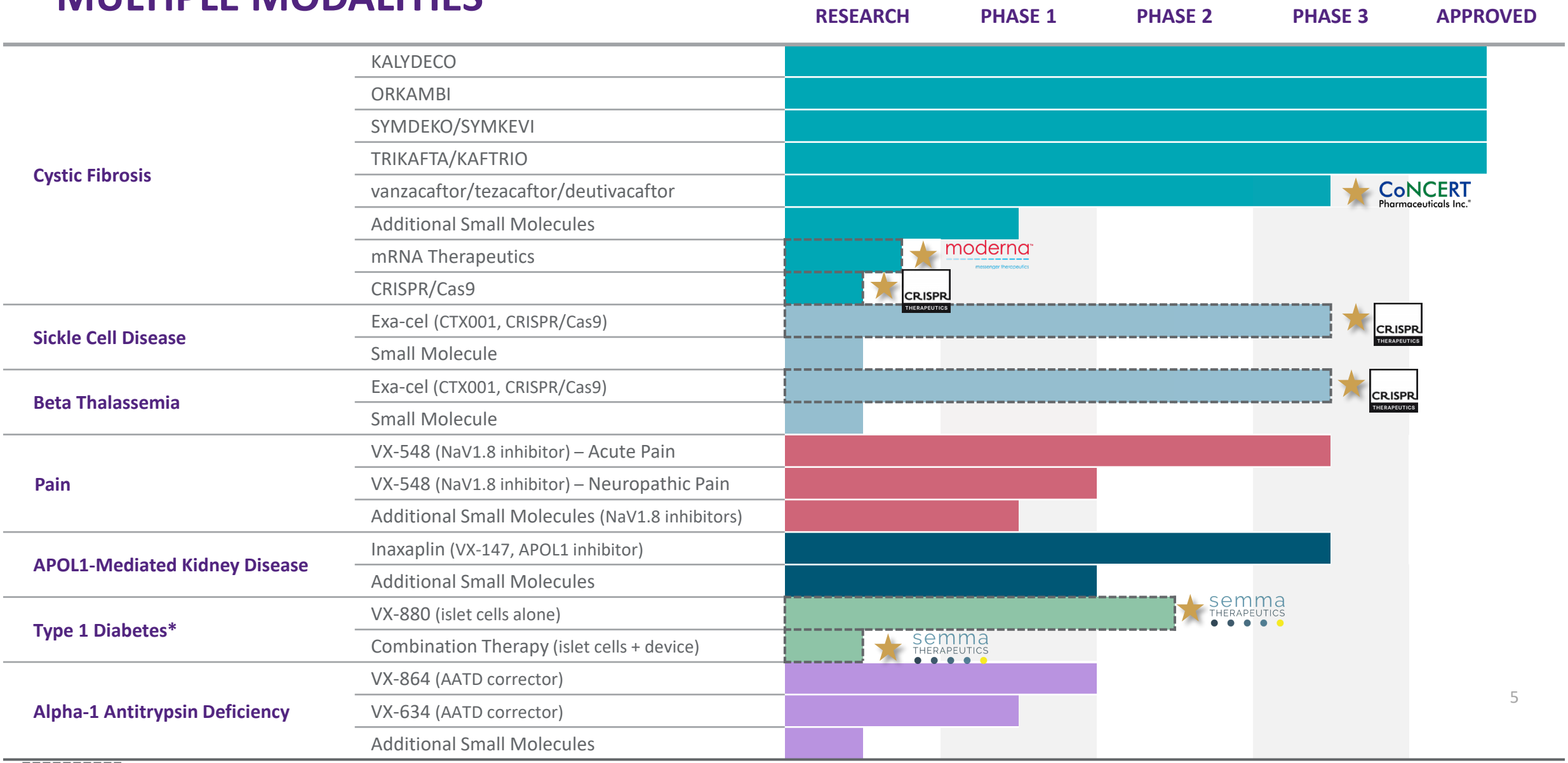
Preparing for near-term commercial opportunities

- Exa-cel for SCD and TDT in U.S., EU and UK
  - Submissions initiate in Q4 2022
  - Engaging with ~75 targeted authorized treatment centers, payers, and policy makers
- VX-548 in acute pain
  - Pivotal development initiated
  - Go-to-market strategy and planning underway

Strong financial profile

- On track for 8th consecutive year of double-digit revenue growth
- Industry-leading profitability
- Strong balance sheet and cash flow enable flexibility to re-invest in innovation

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



Cell therapy or nucleic acid therapy (mRNA, gene editing)

Complementary BD

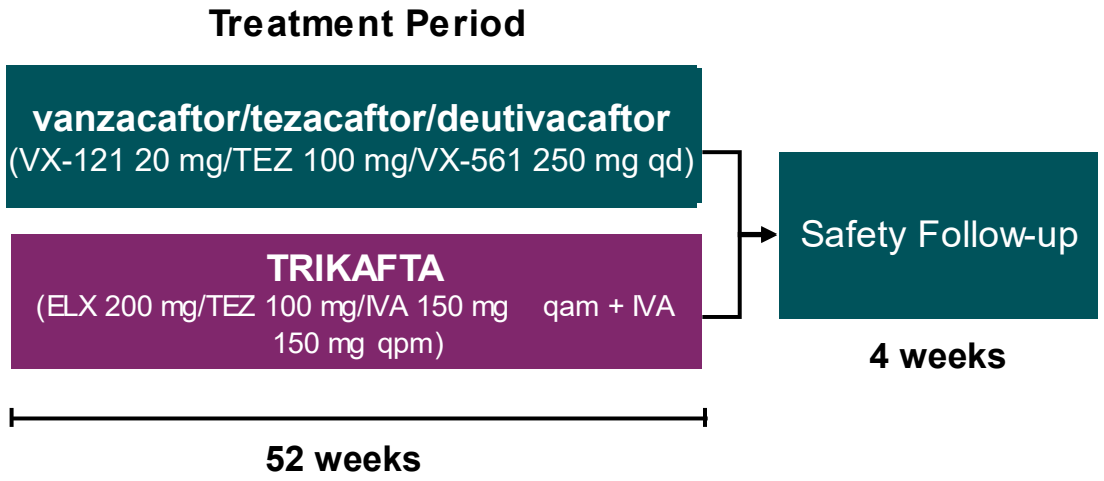
**ViaCyte acquired 9/27/22; pipeline graphic does not yet reflect ViaCyte programs in T1D.*

VANZACAFTOR/TEZACAFTOR/DEUTIVACAFTOR REGIMEN MAY FURTHER ENHANCE PATIENT BENEFIT IN CYSTIC FIBROSIS

Phase 3 enrollment now projected to complete before year end 2022

Two Phase 3 global, randomized, double-blind, active-controlled trials underway (N=950 total):

SKYLINE SKYLINE



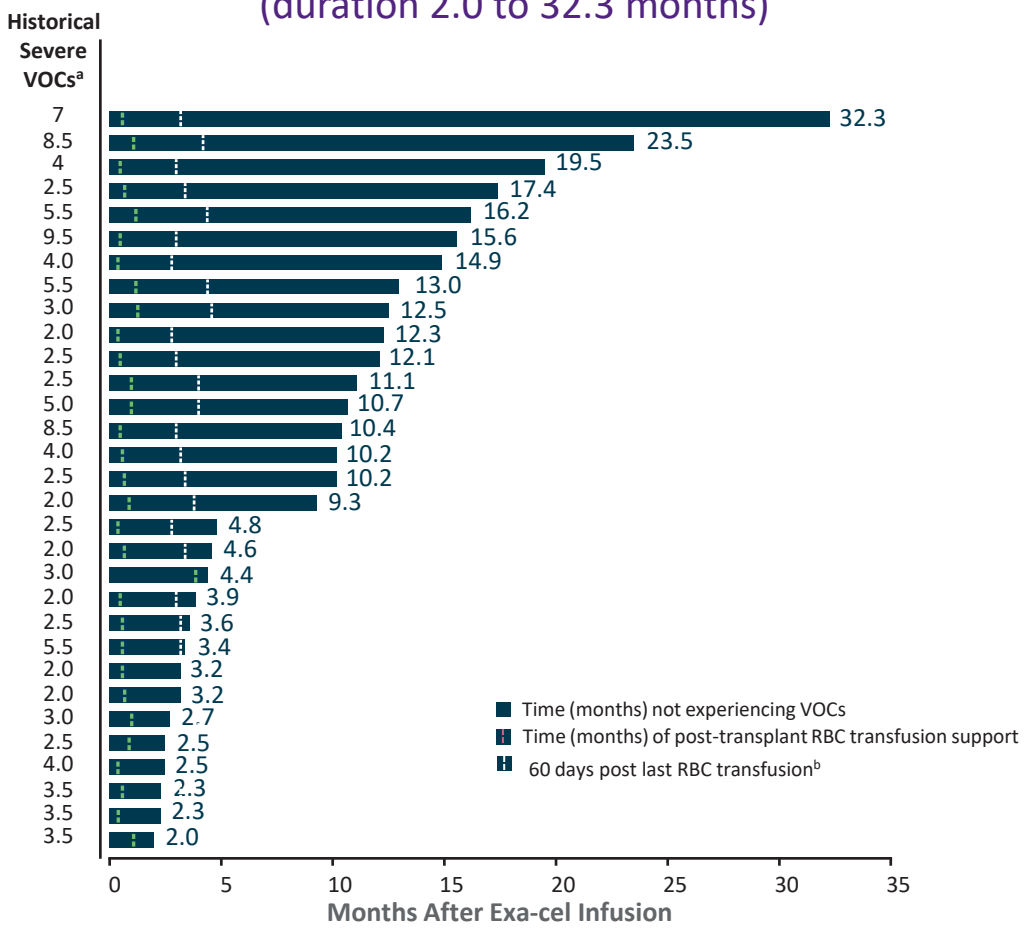
Next-in-Class, Once-Daily, Oral Triple Regimen

- Preclinical and Phase 2 data demonstrate potential for greater clinical benefit over TRIKAFTA
- Once-daily regimen
- Improved royalty profile
- RIDGELINE study in patients ages 6 to 11 also underway

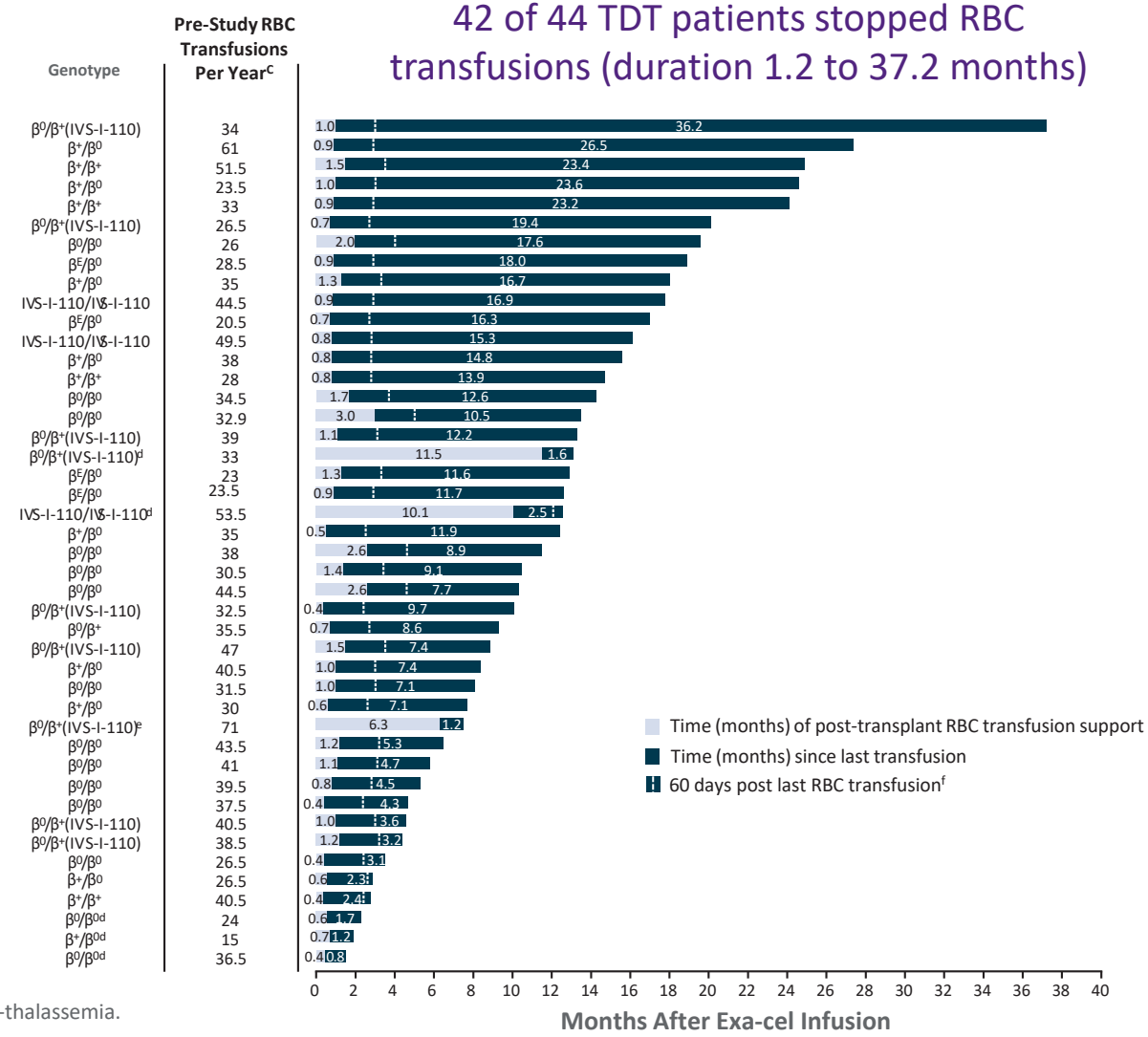
EXA-CEL: COMPELLING EFFICACY IN PATIENTS WITH SCD AND TDT; GLOBAL REGULATORY SUBMISSIONS TO BEGIN BY YEAR END 2022

Initiate U.S. BLA submission for rolling review in Nov 2022; targeted completion Q1:23; EU & UK submissions targeted YE 2022

31 of 31 SCD patients were VOC-free (duration 2.0 to 32.3 months)



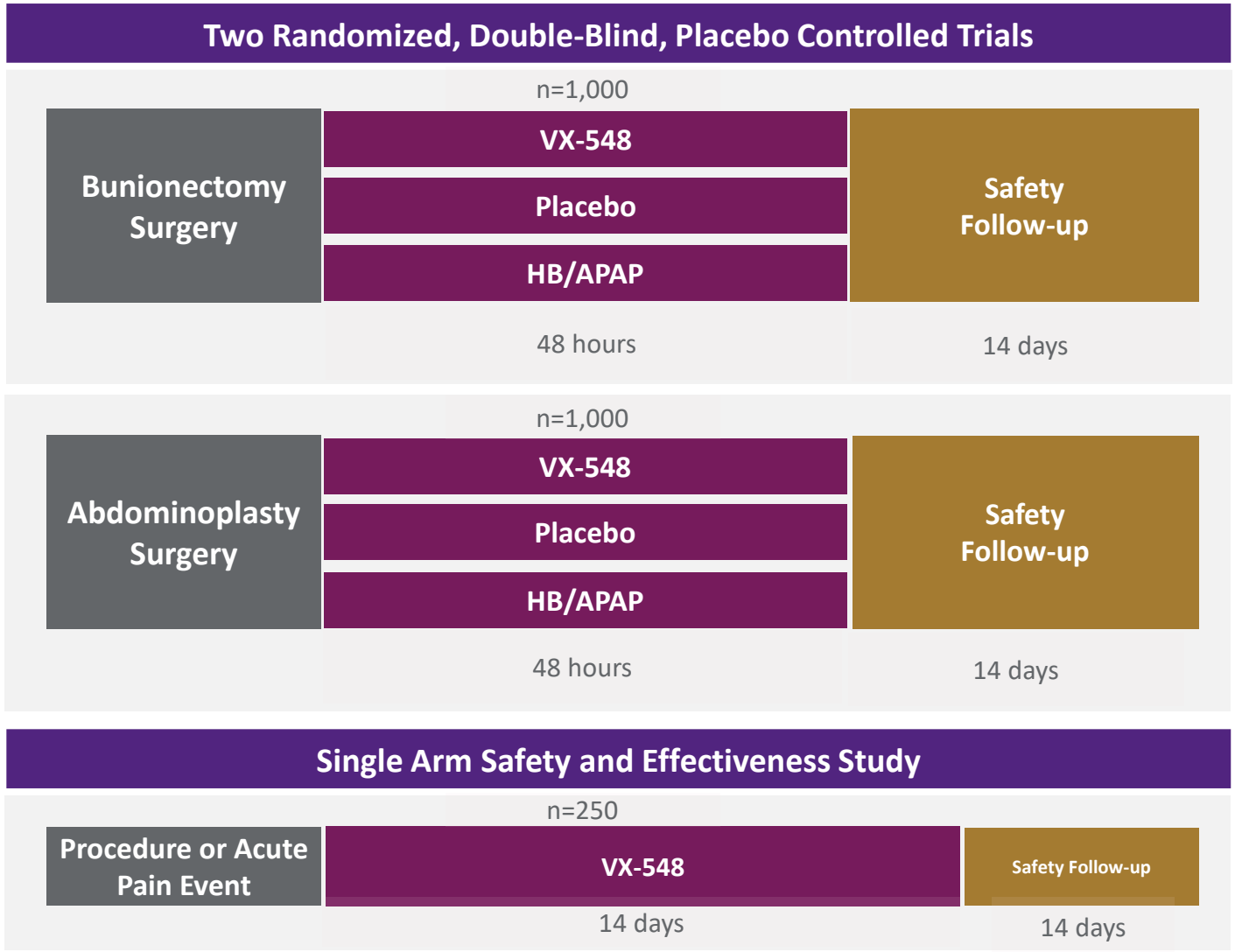
42 of 44 TDT patients stopped RBC transfusions (duration 1.2 to 37.2 months)



RBC, red blood cell; SCD, sickle cell disease; VOC, vaso-occlusive crisis; Hb, hemoglobin; TDT, transfusion-dependent β-thalassemia.
Each row in the figures represents an individual patient. Data previously presented at EHA in June 2022.
[a]Pre-study severe VOCs annualized over 2 years; [b]Patients are evaluated for elimination of VOCs starting 60 days after their last transfusion. [c]Number of transfusion units annualized over 2 years; [d]Received RBC transfusions at or after data cut; [e]Patient stopped transfusions after data cut; [f]Patients are evaluable for elimination of transfusions starting 60 days after their last transfusion.

VX-548: INITIATED PIVOTAL DEVELOPMENT FOR ACUTE PAIN IN Q3

Near-term significant commercial opportunity targeting moderate to severe acute pain in the U.S.



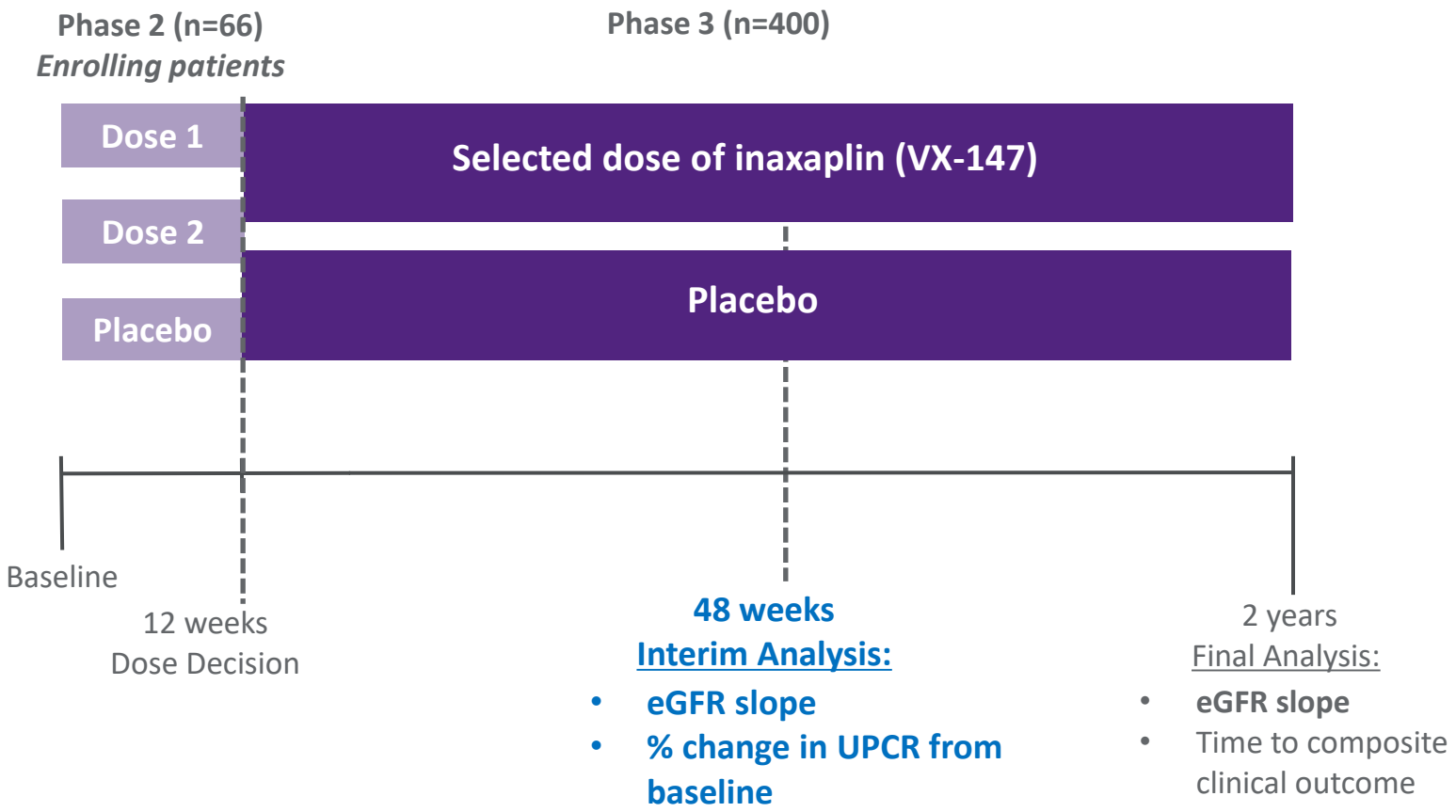
VX-548: 100 mg load, 50 mg q12h; HB/APAP = hydrocodone bitartrate/acetaminophen: 5 mg/325 mg q6h

Novel, Selective NaV1.8 Inhibitor for Pain

- Two Phase 3 RCTs expected to enroll efficiently given similarity to Phase 2:
  - Same pain states: post bunionectomy and abdominoplasty
  - Same treatment duration: 48 hours
  - Same primary endpoint: SPID48 of VX-548 vs. placebo
- A third, single-arm study will study multiple other types of moderate to severe acute pain with up to 14 days of treatment

INAXAPLIN IS IN PIVOTAL DEVELOPMENT; POTENTIAL FIRST MEDICINE TO TREAT THE UNDERLYING CAUSE OF APOL1-MEDIATED KIDNEY DISEASE (AMKD)

Program targets broad AMKD label; interim analysis at 48 weeks may provide path to accelerated U.S. approval



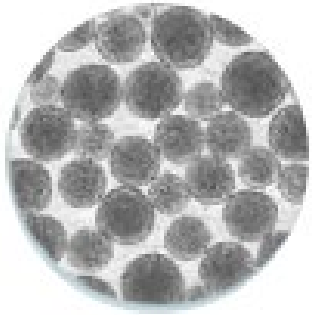
Small Molecule Targeting the Underlying Cause of AMKD

- Single, adaptive Phase 2/3 study in patients with AMKD
- More than 50 sites open for enrollment with goal of opening more than 150 sites total
- **Interim analysis at 48 weeks**: if data are positive, potential to file for accelerated approval
- Breakthrough Therapy designation in the U.S. and Orphan Drug and PRIME designation in Europe

ADVANCING POTENTIALLY CURATIVE TREATMENTS
~2.5 MILLION PEOPLE LIVING WITH TYPE 1 DIABETES IN U.S. AND E.U. ALONE

VX-880

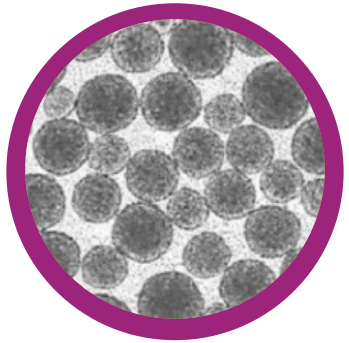
Stem cell-derived islets with standard immunosuppression



Phase 1/2 trial: POC achieved with first two patients at half dose, multiple patients treated at full-dose in Part B

Cells + device

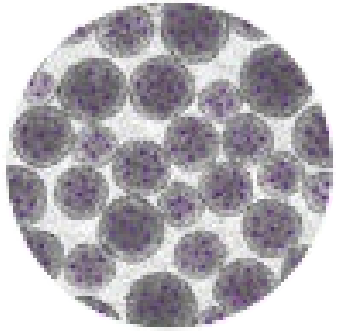
Stem cell-derived islets with encapsulation



On track to file IND by YE 2022

Hypoimmune cells

Stem cell-derived islets with hypoimmune gene editing



In preclinical development

CONTINUED GROWTH OF OUR CFTR MODULATORS AROUND THE WORLD

Global filings for TRIKAFTA in patients 2-5 years of age expected by year end 2022

UNITED STATES

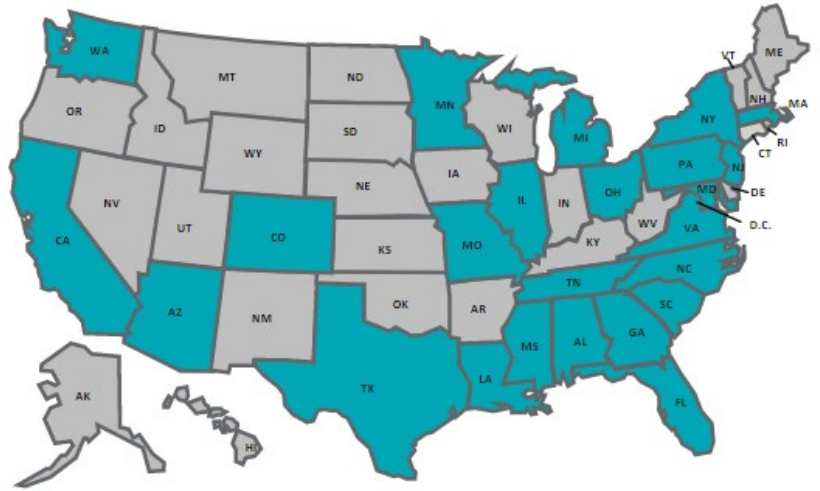
- Steady performance with high persistence and compliance rates in the U.S.
- ORKAMBI recently approved in patients ages 12 months to less than 24 months

EUROPE and OTHER MARKETS

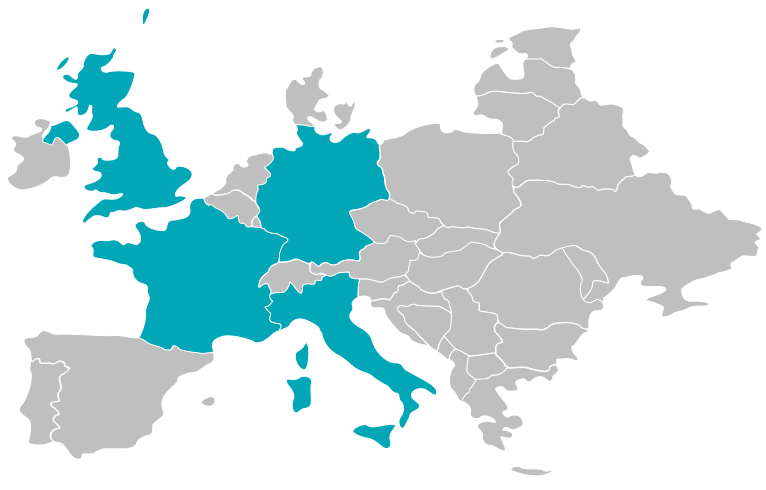
- Rapid uptake of KAFTRIO/TRIKAFTA in markets with recent reimbursement agreements, such as France, Spain, Italy, Australia, and Canada
- Strong uptake of KAFTRIO in children ages 6-11 in countries where this group has reimbursed access

SIGNIFICANT PROGRESS WITH EXA-CEL LAUNCH PREPARATION ACTIVITIES

~24 States with ~90% of SCD/TDT Patients



4 Countries in Europe with ~75% of SCD/TDT Patients



Commercial Readiness Efforts

- Initial launch will focus on ~32,000 patients with severe forms of SCD and TDT in the U.S. and Europe/UK
  - U.S.: ~50 ATCs can serve ~90% of all SCD and TDT patients (living in 24 states)
  - Europe/UK: ~25 ATCs in the UK, Germany, France, Italy can serve ~75% of all SCD and TDT patients (living in Europe/UK)
- On track with hiring and training of the Commercial and Medical Science Liaison teams. Field teams are engaging ATCs on administrative and logistical capabilities
- In active discussions with policymakers and payors to ensure access for eligible patients

ATC, authorized treatment center.

ACUTE PAIN: LARGE MARKET, CONCENTRATED PRESCRIBING, UNMET NEEDS CREATES SIGNIFICANT OPPORTUNITY FOR VX-548

185M Visits to Hospitals Annually

~35M
In-Patient Visits

~150M
Out-Patient & Emergency Department Visits

Rx.

Hospital Discharge Prescriptions

Office Visits

1.5B Treatment Days

>1B Treatment Days Driven by Hospital Treatment or Prescribing

Hospital-based prescribing aligns with specialty sales force model

~500K Treatment Days from Office Visits

Q3 2022 FINANCIAL HIGHLIGHTS

($ in millions except where noted or per share data and percentages)	Q3 21	FY 21	Q3 22
Total CF product revenues	$1.98B	$7.57B	**$2.33B**
TRIKAFTA/KAFTRIO	$1.56B	$5.70B	**$2.01B**
SYMDEKO/SYMKEVI	81	420	**38**
ORKAMBI	185	772	**146**
KALYDECO	162	684	**139**
Combined non-GAAP R&D, acquired IPR&D and SG&A expenses	588	3.44B	**758**
Non-GAAP operating income	1.16B	3.23B	**1.29B**
Non-GAAP operating margin %	59%	43%	**55%**
Non-GAAP net income	912	2.51B	**1.04B**
Non-GAAP net income per share – diluted	$3.51	$9.67	**$4.01**
Cash, cash equivalents & marketable securities (period-end)	$7.0B	$7.5B	**$9.8B**

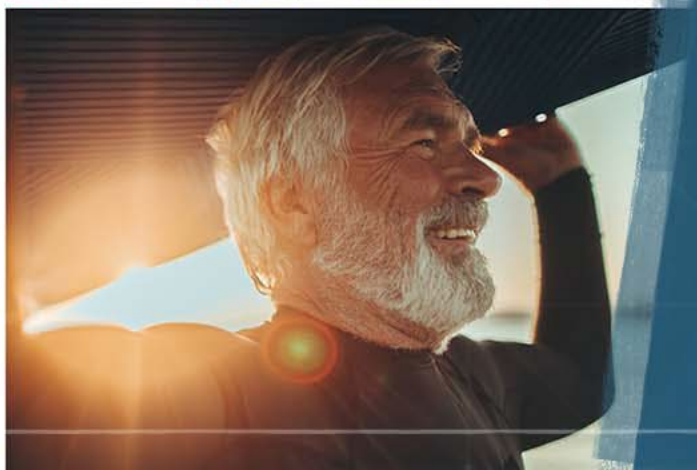
Notes: Starting in the first quarter of 2022, Vertex no longer excludes research and development charges resulting from upfront or contingent milestone payments in connection with collaborations, asset acquisitions and/or licensing of third-party intellectual property rights from its Non-GAAP financial measures. These charges are included as "Acquired in-process research and development expenses," and were previously included in "Research and development expenses," in Vertex's consolidated statements of operations. Non-GAAP financial measures for the third quarter of 2021 and FY 2021 have been recast to reflect this change. An explanation of non-GAAP financial measures and reconciliation of combined non-GAAP R&D, Acquired IPR&D and SG&A expenses, non-GAAP operating income and non-GAAP net income to corresponding GAAP measures are included in the company's Q3 2022 press release dated October 27, 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.

RAISING FULL YEAR 2022 REVENUE GUIDANCE TO $8.8 TO 8.9 BILLION, REPRESENTING 17% GROWTH AT THE MIDPOINT

	Current FY 2022 Guidance	Previous FY 2022 Guidance	FY 2022 Commentary
Total CF Product Revenues	**$8.8 - $8.9B**	**$8.6 - $8.8B**	Strong uptake of KAFTRIO/ TRIKAFTA in markets with recent reimbursement agreements, continued performance in the U.S.
Combined GAAP R&D, Acquired IPR&D and SG&A Expenses	**Unchanged**	**$3.48 - $3.63B**	
Combined Non-GAAP R&D, Acquired IPR&D and SG&A Expenses	**Unchanged**	**$3.0 - $3.1B**	
Non-GAAP Effective Tax Rate	**Unchanged**	**21% - 22%**	

RECENT ADVANCES POSITION VERTEX FOR MULTIPLE MILESTONES IN THE MONTHS AHEAD

Recent Highlights	Anticipated Key Milestones
Completed Phase 3 study of TRIKAFTA in patients with CF ages 2 to 5	**Submit global regulatory filings** by YE 2022
More than 250 sites active in **vanzacaftor/tezacaftor/deutivacaftor Phase 3** studies	**Complete enrollment** by YE 2022
IND-enabling studies completed for CFTR mRNA program	On track to **file IND** by YE 2022
Completed global regulatory discussions for exa-cel in both SCD and TDT	**Submit for regulatory approval** in Europe and the U.K. by YE 2022; begin rolling submission in the U.S. in November and target completion Q1:23
Initiated Phase 3 development of VX-548 in acute pain	Ramp **enrollment in Phase 3 trial**
Completed Phase 2 readiness for VX-548 in neuropathic pain	Initiate **Phase 2 dose-ranging study in neuropathic pain** by YE 2022
Initiated pivotal development of inaxaplin (VX-147) in broad AMKD population	Ramp **enrollment in Phase 2/3 trial**
Achieved proof of concept for VX-880 in type 1 diabetes; Part B ongoing	Complete **Part B**
IND-enabling studies ongoing for cells + device program in type 1 diabetes	On track to **file IND** by YE 2022
Two AATD programs advanced into the clinic	**Sites activated and enrolling** for VX-634 in healthy volunteers
	Initiate Phase 2 trial for VX-864 in patients with AATD by YE 2022



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THIRD QUARTER 2022 FINANCIAL RESULTS

OCTOBER 27, 2022

APPENDIX

GAAP TO NON-GAAP FINANCIAL INFORMATION

($ in millions except as noted, per share data and percentages)	Q3 21	FY 21	Q3 22
Combined R&D, Acquired IPR&D and SG&A			
GAAP	692	3.89B	**921**
Non-GAAP	588	3.44B	**758**
Operating income			
GAAP	1.05B	2.78B	**1.13B**
Non-GAAP	1.16B	3.23B	**1.29B**
Operating Margin %:			
GAAP	53%	37%	**48%**
Non-GAAP	59%	43%	**55%**
Net income			
GAAP	852	2.34B	**931**
Non-GAAP	912	2.51B	**1.04B**
Net income per share - diluted			
GAAP	$3.28	$9.01	**$3.59**
Non-GAAP	$3.51	$9.67	**$4.01**

Note: Starting in the first quarter of 2022, Vertex no longer excludes research and development charges resulting from upfront or contingent milestone payments in connection with collaborations, asset acquisitions and/or licensing of third-party intellectual property rights from its Non-GAAP financial measures. These charges are included as "Acquired in-process research and development expenses," and were previously included in "Research and development expenses," in Vertex's consolidated statements of operations. Non-GAAP financial measures for the third quarter of 2021 and FY 2021 have been recast to reflect this change. An explanation of non-GAAP financial measures and reconciliations of combined non-GAAP R&D, Acquired IPR&D and SG&A expenses, non-GAAP operating income and non-GAAP net income to corresponding GAAP measures are included in the company's Q3 2022 press release dated October 27, 2022.