




VERTEX

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SECOND QUARTER 2023 FINANCIAL RESULTS

AUGUST 1, 2023

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 expectations for future financial and operating performance, full-year 2023 financial guidance, and statements regarding our (i) expectations, development plans, and timelines for the company's products, product candidates, and pipeline programs, including expectations for five potential launches in five years, multiple clinical-stage programs with launch potential by 2030, anticipated benefits of new products, patient populations, study designs, study enrollment, data availability, anticipated regulatory filings, regulatory approvals, and timing thereof, (ii) expectations for continued growth in the number of CF patients treated with our existing therapies, including expected KAFTRIO/TRIKAFTA approval in patients aged 2 to 5 years in the EU by the end of 2023 and new reimbursement agreements, (iii) expectations to reach all CF patients eligible for CFTRm and the last ~5,000 CF patients (ineligible for a CFTRm) with VX-522, our plans to complete a single ascending dose study and initiate multiple ascending dose study for VX-522 in 2023, (iv) expectations for the benefits of vanzacaftor triple combination therapy, plans to complete Phase 3 studies in 2023, expectations for data in early 2024, and expectations for near-term launch, commercial potential and lower royalty burden, (v) expectations for the exa-cel program, including the potential of exa-cel to be a one-time, functional cure for patients with SCD and TDT and potential of exa-cel regulatory approval(s), and expectations for near-term launch and commercial potential, including potential participation in early access programs, expected patient population and expectations regarding providers and payers, (vi) expectations for our pain program, including its potential to treat acute pain without the limitations of opioids, the anticipated timeline to complete Phase 3 pivotal program for VX-548 in acute pain and complete Phase 2 studies of VX-548 in neuropathic pain, expectations for timelines of pain data, and plans for near-term commercial launch in moderate-to-severe acute pain, (vii) our expectations and beliefs regarding our pivotal program for inaxaplin, including its potential to treat the underlying cause of AMKD, plans to complete Phase 2B portion of studies in 2023, and our beliefs regarding anticipated results of the study, (viii) expectations for the development of our T1D programs, including the patient population, potential curative benefits and safety of VX-880, plans to present updated clinical data in October 2023, plans to begin Part C with concurrent dosing with VX-880 at full target dose, expectations for enrollment and dosing in VX-264 study, and expected use of CRISPR/Cas9 gene editing in our hypoimmune program, (ix) plans for continued advancement of VX-634 and VX-864, (x) plans for our DMD and DM1 programs, including expectations to file INDs, 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 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 our regulatory submissions could be delayed and our products may not receive regulatory approval on expected timelines, or at all, that external factors may impact the company's business or operations differently 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 anticipated, that reimbursement for our therapies may be more difficult to obtain or maintain than expected, 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 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. Unless otherwise noted, 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 Q2 2023 press release dated August 1, 2023.

CONTINUED STRONG MOMENTUM IN THE SECOND QUARTER

Continue the journey in cystic fibrosis (CF)

- Serially innovate to bring highly efficacious CFTRm to all eligible patients
- Reach the last ~5,000 patients (ineligible for a CFTRm) with mRNA therapy
- Continue to build unparalleled portfolio of real-world and long-term data

Prepare for potential near-term commercial launches

- Exa-cel in SCD and TDT: FDA granted Priority Review for SCD (PDUFA: December 8, 2023); TDT (PDUFA: March 30, 2024); reviews in the EU and U.K. are well underway
- VX-548 in moderate to severe acute pain: all Phase 3 studies expected to complete by end of 2023
- Vanzacaftor triple in CF: Phase 3 studies expected to complete by end of 2023

Accelerate diversified R&D pipeline

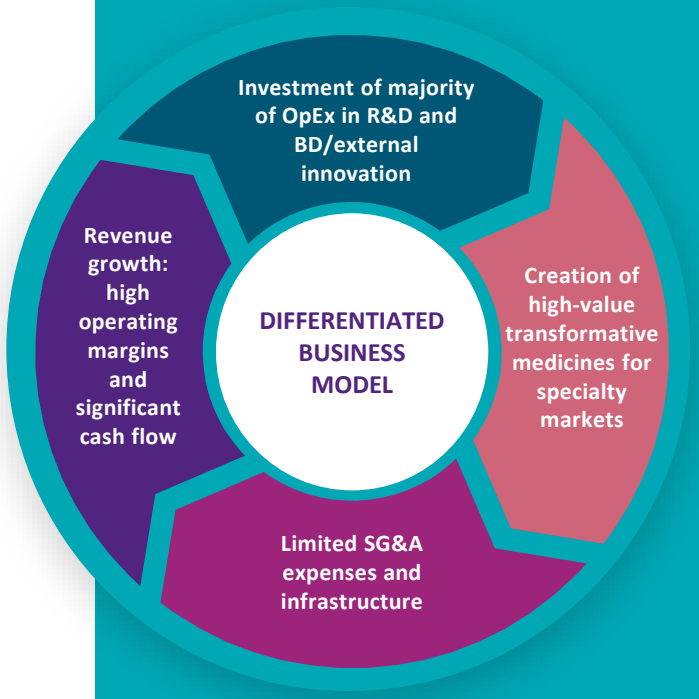
- Five potential launches in the next five years

Deliver financial performance

- Strong results; raising 2023 revenue guidance $100-150M on continued revenue growth from treating more patients with CF; raising 2023 non-GAAP OpEx guidance $200M on higher YTD acquired IPR&D expenses from new business development
- Specialty model sustains strong operating margins while allowing for significant investments in the pipeline and commercial capabilities

EXECUTING ON VERTEX BUSINESS MODEL AND R&D STRATEGY WITH RAPID PROGRESS ON A ROBUST PIPELINE

FIVE POTENTIAL LAUNCHES IN THE NEXT FIVE YEARS



We focus on

- **Validated targets** that address causal human biology
- **Predictive lab assays** and clinical biomarkers
- **Rapid path to registration and approval**

In order to deliver a portfolio with

- **transformative benefit,** regardless of modality
- **greater likelihood of clinical success**

4 **Approved medicines in cystic fibrosis**

kalydeco® ORKAMBI® symdeko™ trikafta™

8 **Programs in mid- or late-stage development**

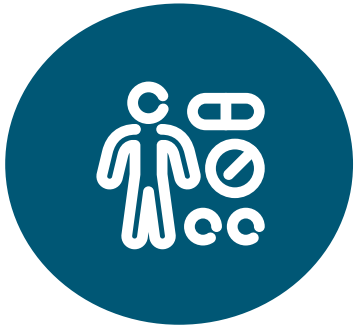
Near-term commercial opportunities
- Exa-cel (SCD)
- Exa-cel (TDT)
- Vanzacaftor triple (CF)
- VX-548 (acute pain)

Mid/late-stage clinical pipeline
- Inaxaplin (AMKD) - Post PoC
- VX-880 (T1D) - Post PoC
- VX-548 (neuropathic pain) – Phase 2
- VX-864 (AATD) – Phase 2

PoC: proof of concept; SCD: sickle cell disease; TDT: transfusion-dependent beta thalassemia; AMKD: APOL1-mediated kidney disease; T1D: type 1 diabetes; AATD: Alpha-1 Antitrypsin Deficiency

CONTINUING OUR SERIAL INNOVATION IN CYSTIC FIBROSIS

VANZACAFTOR TRIPLE STUDIES TO COMPLETE AT END OF 2023 WITH DATA IN EARLY 2024



Vanzacaftor Triple

- Next-in-class CFTR modulator triple therapy
- Now expect to complete all three Phase 3 studies by the end of 2023: SKYLINE 102 and SKYLINE 103 in patients ages 12+, and RIDGELINE in patients ages 6-11 years
- Expect to release data for all three studies in early 2024
- Convenient, once-daily dosing
- Meaningfully lower royalty burden

VX-522

- CFTR mRNA therapy in development for ~5,000 CF patients who cannot benefit from CFTR modulators
- Continue to enroll and dose CF patients in the single ascending dose (SAD) study
- Expect to complete SAD study and initiate Multiple Ascending Dose study in 2023
- Program developed in partnership with Moderna

NEAR-TERM LAUNCH POTENTIAL: EXA-CEL

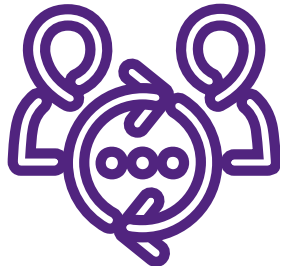
FDA HAS GRANTED PRIORITY REVIEW FOR EXA-CEL BLA IN SICKLE CELL DISEASE

Exa-cel holds potential for one-time, functional cure

The first CRISPR-based gene-editing treatment potentially to be approved

New EHA data, which were the basis for EMA and MHRA filings, showed both trials met the primary and key secondary endpoints as of the data cut

Safety profile consistent with myeloablative conditioning and autologous stem cell transplant



SCD PDUFA: December 8, 2023
TDT PDUFA: March 30, 2024

Regulatory reviews in the EU and U.K. well underway

EHA: European Hematology Association

NEAR-TERM LAUNCH POTENTIAL: VX-548 FOR MODERATE TO SEVERE ACUTE PAIN

ON TRACK TO COMPLETE PIVOTAL PROGRAM BY THE END OF 2023

Significant Unmet Needs

- Millions in the U.S. each year suffer from acute pain
- Existing therapies have challenging side effects and/or abuse potential

Validated Target

- $Na_V1.8$ is genetically and pharmacologically validated
- 5 successful Proof-of-Concept studies across both VX-150 and VX-548 in major pain types

Pivotal Program Ongoing

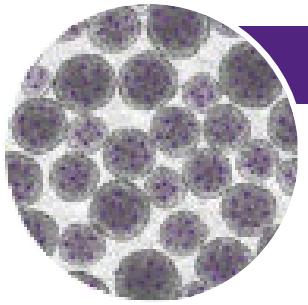
- Phase 3 pivotal program design, duration and endpoints similar to Phase 2
- **Pivotal program to complete by end of 2023**
- **Results from all three Phase 3 studies expected in late 2023 or early 2024**

Near-Term Commercial Opportunity

- Positive interactions with FDA
- Granted Fast Track and Breakthrough Therapy designations

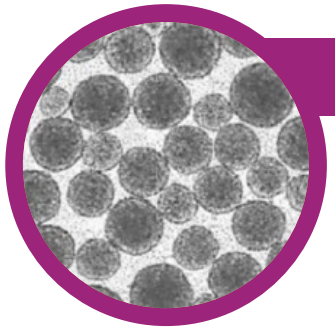
TYPE 1 DIABETES: ADA DATA DEMONSTRATE CONFIDENCE IN FOUNDATIONAL VX-880 CELLS

3 PROGRAMS TO ADDRESS ~2.5M T1D PATIENTS IN NORTH AMERICA & EUROPE



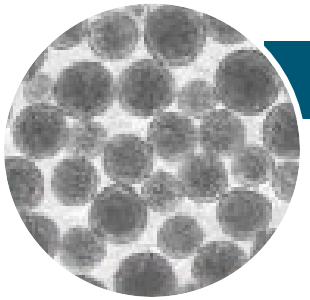
EDITED, FULLY DIFFERENTIATED, HYPOIMMUNE CELLS

- The same cells as VX-880
- Research program continues to progress
- $70M milestone to CRSPR Q2 2023



VX-264: FULLY DIFFERENTIATED CELLS + DEVICE

- The same cells as VX-880
- Encapsulates cells in a device that is designed to eliminate the need for immunosuppressants
- First patient dosed in the Phase 1/2 trial
  - Trial sites currently active in the U.S., Canada and the Netherlands



VX-880: FULLY DIFFERENTIATED CELLS WITH STANDARD IMMUNOSUPPRESSION

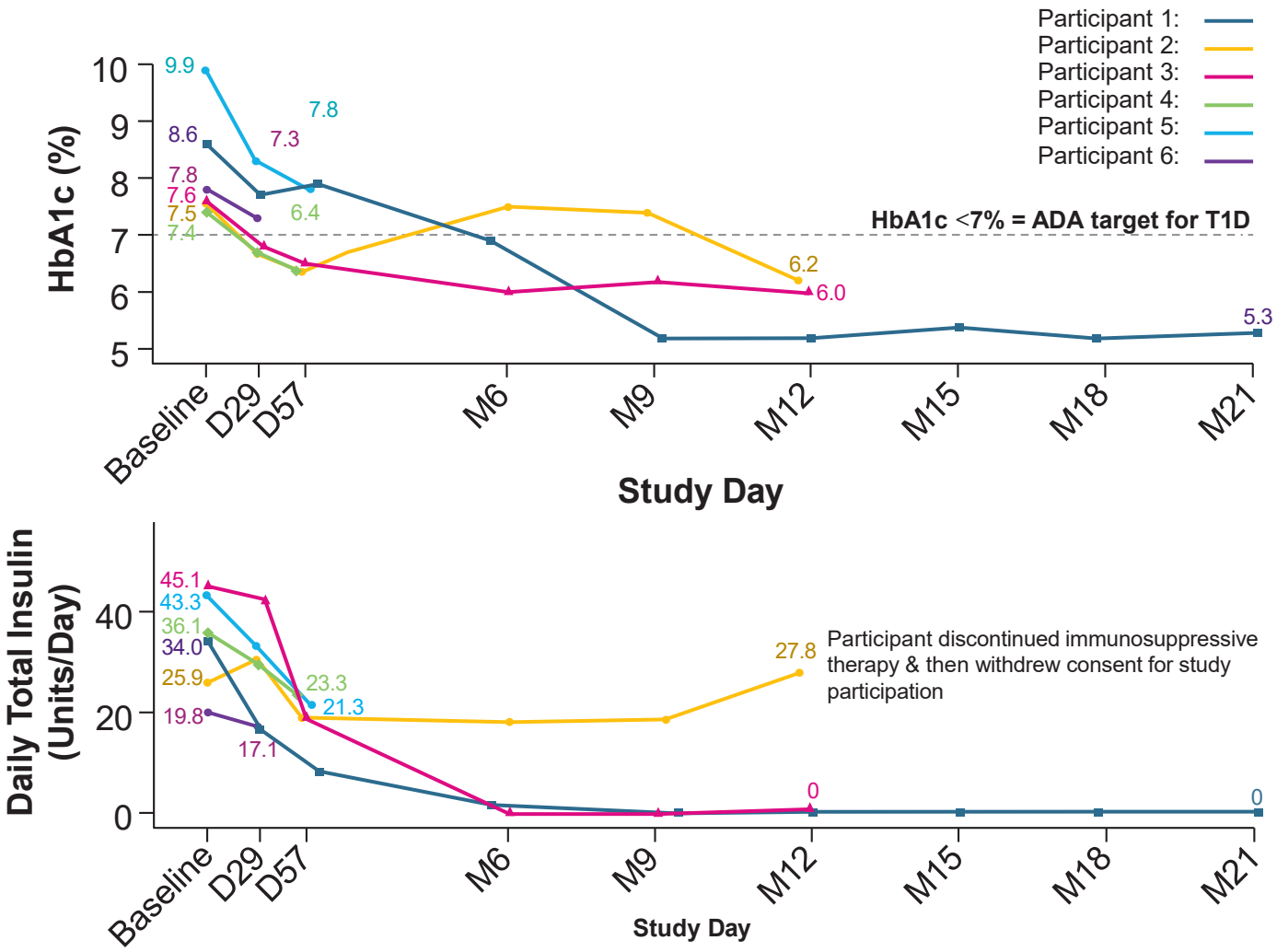
- Phase 1/2 trial:
  - Completed Part A and Part B; presented positive updated clinical data at ADA in June 2023
  - Initiated Part C with concurrent dosing
    - Trial sites currently active in the U.S., Canada and Europe

ADA: American Diabetes Association

VCTX-211, a hypoimmune program that originated under ViaCyte, has finished enrollment and dosing in Group 1 of the Phase 1/2 trial.

POSITIVE VX-880 RESULTS FROM ADA

INITIATED PART C WITH CONCURRENT DOSING AT FULL TARGET DOSE



AE: adverse event; D: day; HbA1c: hemoglobin A1c; M: month; SHEs: severe hypoglycemic events; T1D: Type I diabetes

Efficacy Highlights

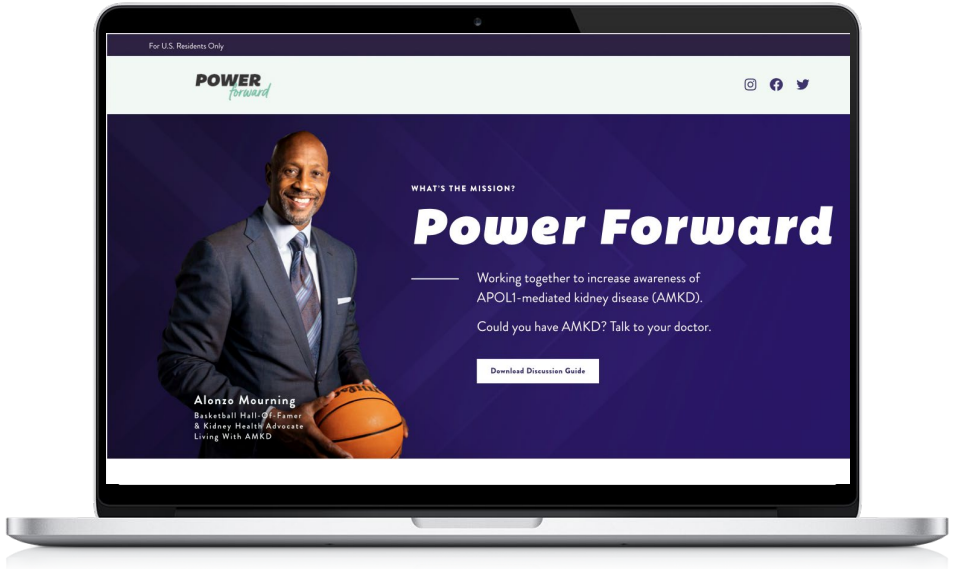
- All 6 participants demonstrated:
  - Production of endogenous insulin (C-peptide)
  - Reduction in HbA1c
  - Reductions in exogenous insulin use
- Two patients with >1 year of follow-up met criteria for primary endpoint, saw a complete elimination of severe hypoglycemic events, maintained HbA1c levels below 7.0, and achieved insulin independence
- Patients earlier on their course of therapy were on a similar trajectory as the two patients with long-term follow-up

Safety

- VX-880 has been generally well tolerated in all patients
- Majority of AEs were mild or moderate
- No serious AEs related to VX-880

INAXAPLIN: FIRST POTENTIAL MEDICINE TO TARGET THE UNDERLYING CAUSE OF AMKD

100,000
patients in the
U.S. and Europe



APOL1-MEDIATED KIDNEY DISEASE

- Two APOL1 variants
- Proteinuric kidney disease
- Rapid progression to ESKD

PIVOTAL TRIAL UNDERWAY

- On track to complete Phase 2B portion of Phase 2/3 pivotal trial in 2023
- Path to accelerated approval with interim analysis at 48 weeks of treatment
- Final analysis at ~2 years of treatment

RAISING DISEASE AWARENESS AND ONGOING GENETIC TESTING EFFORTS

- Education outreach with physicians and patients
- Building trust with historically underserved communities
- Multiple ongoing initiatives, including new partnerships, to increase awareness of the importance of genetic testing for AMKD

Power Forward is a Vertex disease education campaign launched November 2022 in partnership with basketball Hall-of-Famer and kidney health advocate Alonzo Mourning, who has AMKD and received a kidney transplant in 2003.

CLINICAL PORTFOLIO IS BROAD, DIVERSE AND RAPIDLY ADVANCING; RESEARCH PIPELINE PROGRESSING TO DELIVER NEXT WAVE OF INNOVATION

Next Wave Discovery Research	Phase 1 In Healthy Volunteers	Phase (1)/2 in Patients	Pivotal Development	Regulatory Submissions Completed	Launched
Vertex hypoimmune cells Type 1 diabetes	**Follow-on small molecules:** • CF • Pain • AMKD • AATD	**VX-880** Type 1 diabetes *PoC achieved*	**VX-548** Acute Pain	**Exa-cel** Sickle Cell Disease	trikafta™
DMD	**VX-634** AATD	**VX-264 cells + device** Type 1 diabetes	**Vanzacaftor triple** Cystic Fibrosis	**Exa-cel** TD Beta Thalassemia	symdeko™
DM1		**VCTX-211 (ViaCyte) hypoimmune cells** Type 1 diabetes	**Inaxaplin** AMKD		ORKAMBI®
Huntington's		**VX-548** Peripheral neuropathic pain			kalydeco®
ADPKD		**VX-864** AATD			
Exa-cel Improved conditioning		**VX-522*** CFTR mRNA			
Na_V 1.7 Pain					

Next Wave = select assets in preclinical development

DMD: Duchenne Muscular Dystrophy; DM1: Myotonic Dystrophy Type 1; ADPKD: Autosomal Dominant Polycystic Kidney Disease; FIH: First In Human

**Phase 1, single ascending dose study in patients with CF*

SUSTAINING AND EXPANDING LEADERSHIP IN CF WITH SERIAL INNOVATION

RECEIVED EU APPROVAL FOR ORKAMBI FOR AGES 1-2
EXPECT TRIKAFTA/KAFTRIO APPROVALS IN EU, U.K. AND CANADA FOR AGES 2-5 BY END OF 2023

88,000 PATIENTS WITH CF

vs. 83,000 estimated in 2021

U.S., Europe, Australia and Canada

TREATED TODAY WITH CFTRm

>20,000 REMAINING ADDRESSABLE WITH CFTRm

~5,000 ADDRESSABLE WITH VX-522

DRIVERS OF GROWTH

1. Treating younger patients and securing additional reimbursements

- Strong U.S. launch of TRIKAFTA in children ages 2-5 years
- Outside the U.S., strong KAFTRIO growth in patients ages 6 years and older following approval, reimbursement and launch across multiple countries

2. More people with CF, living longer

- Interim results from the largest real-world study of TRIKAFTA shared at ECFS showed sustained improvement in lung function, a reduction in pulmonary exacerbations frequency and lower rates of lung transplantation and death compared to historical rates in a comparable CF population

3. Raising the bar

- Vanzacaftor triple: all pivotal studies in CF patients ages 12+ and 6-11 years expected to complete by the end of 2023

4. Advancing therapies for all patients

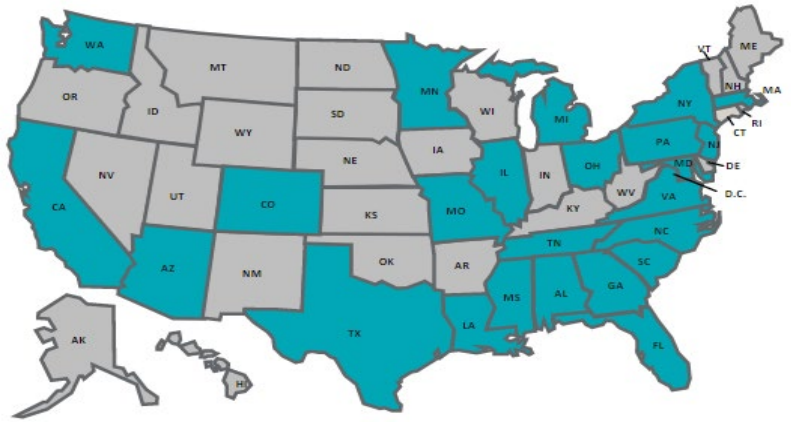
- Ongoing VX-522 CFTR mRNA Phase 1 (SAD/MAD) trial in CF patients who cannot benefit from CFTR modulators

Note: estimated CF patient population and population breakdown as of January 2023
ECFS: European Cystic Fibrosis Society

NEAR-TERM LAUNCH POTENTIAL: EXA-CEL

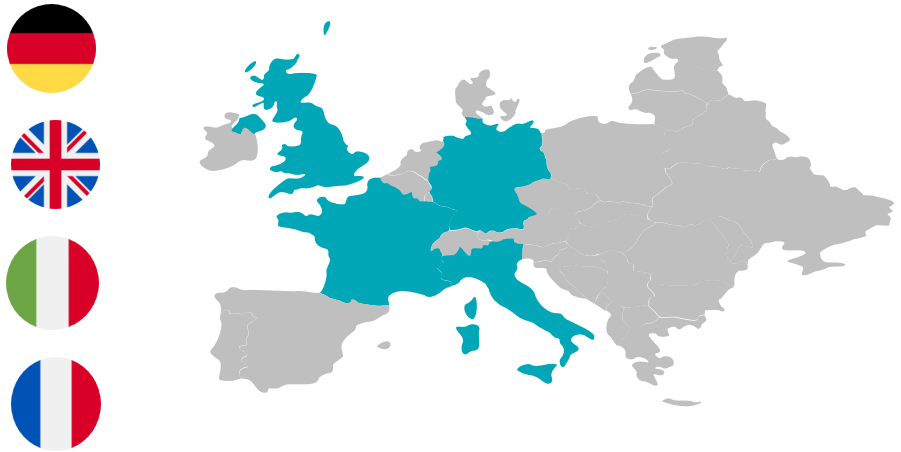
PROGRESS WITH ACCESS AND REIMBURSEMENT: STRONG INTEREST IN EXA-CEL AND INTENT TO PROVIDE COVERAGE QUICKLY UPON APPROVAL

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



- **Government payers** (~65% of U.S. payer mix, largely Medicaid):
  - Engaged with **Medicaid** administrators in all 50 states and positive **Medicare** meetings with CMS
    - Ongoing discussions focused on disease burden, prevalence, clinical data and mechanisms for coverage
- **Commercial payers** (~35% of U.S. payer mix): high level of engagement across top 4 payers (~80% of covered lives) and working to ensure timely access to exa-cel

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



- Engaging with European health systems to secure reimbursed access and educating as to significant disease burden upon patients, healthcare systems, and society
- Working with European health authorities to discuss different payment models and value of a one-time, potential functional cure

Q2 2023 FINANCIAL HIGHLIGHTS

($ in millions except where noted or per share data and percentages)	Q2 22	FY 22	Q2 23
Total CF product revenues	$2.20B	$8.93B	**$2.49B**
TRIKAFTA/KAFTRIO	1.89B	7.69B	**2.24B**
Other CF products	303	1.24B	**253**
Combined non-GAAP R&D, acquired IPR&D and SG&A expenses	750	3.07B	**1.04B**
Non-GAAP operating income	1.19B	4.79B	**1.15B**
Non-GAAP operating margin %	54%	54%	**46%**
Non-GAAP net income	930	3.86B	**1.01B**
Non-GAAP net income per share – diluted	$3.60	$14.88	**$3.89**
Cash, cash equivalents & total marketable securities (period-end)	$9.3B	$10.9B	**$12.6B**

Notes: 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 Q2 2023 press release dated August 1, 2023. 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 2023 UPDATED FINANCIAL GUIDANCE

	Current FY 2023 Guidance	Previous FY 2023 Guidance	Commentary
Total CF Product Revenues	$9.7 - $9.8B	$9.55 - $9.7B	Increase primarily reflects the strong uptake of TRIKAFTA/KAFTRIO in multiple countries internationally and continued performance of TRIKAFTA in the U.S.
Combined GAAP R&D, Acquired IPR&D and SG&A Expenses	$4.55 - $4.8B	$4.35 - $4.6B	Now includes ~$500 million of upfronts and milestones from existing or recently completed BD transactions
Combined Non-GAAP R&D, Acquired IPR&D and SG&A Expenses	$4.1 - $4.2B	$3.9 - $4.0B	
Non-GAAP Effective Tax Rate	Unchanged	21%-22%	

A STRONG CADENCE OF CATALYSTS THROUGH EARLY 2024

Recent Highlights	Anticipated Key Milestones
Received FDA approval in U.S. for TRIKAFTA in patients with CF ages 2 to 5	Expect TRIKAFTA/KAFTRIO **approvals in EU, U.K. and Canada** in patients ages 2-5 years by end of 2023
Fully enrolled vanzacaftor/tezacaftor/deutivacaftor Phase 3 studies (ages 6-11 and 12+)	**Complete all Phase 3 studies (6+)** by end of 2023; **data in early 2024**
Enrolling and dosing SAD study for VX-522 CFTR mRNA in CF patients	**Complete SAD study and initiate MAD study by end of 2023**
FDA accepted BLAs for SCD (Priority Review) and TDT (Standard Review) **Regulatory reviews in EU and U.K. ongoing**	**SCD PDUFA: December 8, 2023** **TDT PDUFA: March 30, 2024** **Completion of UK and EU regulatory reviews**
Rapid enrollment in Phase 3 trials for VX-548 in acute pain	**Complete all Phase 3 studies by end of 2023; data in late 2023 or early 2024**
Rapid enrollment in Phase 2 dose-ranging study for VX-548 in diabetic peripheral neuropathy	**Complete Phase 2 study by end of 2023; data in late 2023 or early 2024**
Enrolling and dosing pivotal trial of inaxaplin in broad AMKD population	**Complete Phase 2B portion** of Phase 2/3 pivotal study by end of 2023
Presented updated positive clinical data at ADA (Part A + Part B) in type 1 diabetes **Initiated Part C** for VX-880 with concurrent dosing	**Enroll and dose Part C**
Initiated Phase 1/2 trial in both U.S. and Canada for VX-264, the cells + device program in type 1 diabetes; first patient dosed	**Enroll and dose Phase 1/2 trial**
Enrolling and dosing Phase 2 trial for VX-864 in patients with AATD and FIH trial for VX-634	**VX-864: Complete Phase 2 enrollment in 2023** **VX-634: Complete FIH study in 2023**
IND-enabling studies ongoing for DMD and DM1	**Complete IND-enabling studies; File INDs**



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AUGUST 1, 2023

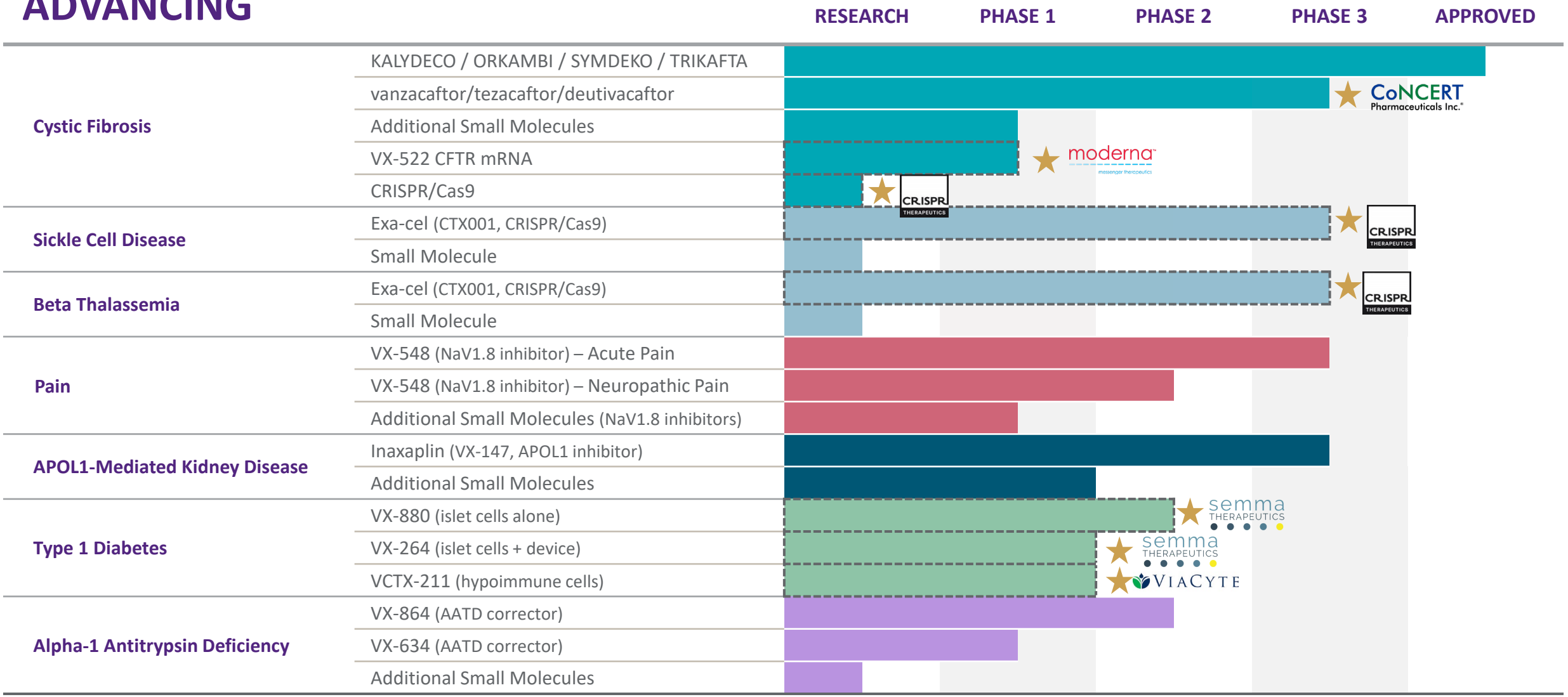
APPENDIX

GAAP TO NON-GAAP FINANCIAL INFORMATION

($ in millions except as noted, per share data and percentages)	Q2 22	FY 22	Q2 23
Combined R&D, Acquired IPR&D and SG&A			
GAAP	877	3.60B	**1.16B**
Non-GAAP	750	3.07B	**1.04B**
Operating income			
GAAP	1.11B	4.31B	**1.03B**
Non-GAAP	1.19B	4.79B	**1.15B**
Operating Margin %:			
GAAP	50%	48%	**41%**
Non-GAAP	54%	54%	**46%**
Net income			
GAAP	810	3.32B	**916**
Non-GAAP	930	3.86B	**1.01B**
Net income per share - diluted			
GAAP	$3.13	$12.82	**$3.52**
Non-GAAP	$3.60	$14.88	**$3.89**

Note: 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 Q2 2023 press release dated August 1, 2023.

R&D STRATEGY DESIGNED TO DELIVER SERIAL INNOVATION WITH HIGH PROBABILITY OF SUCCESS; CLINICAL-STAGE PIPELINE IS BROAD, DEEP AND ADVANCING



Cell therapy or nucleic acid therapy (mRNA, gene editing) ★ Complementary BD