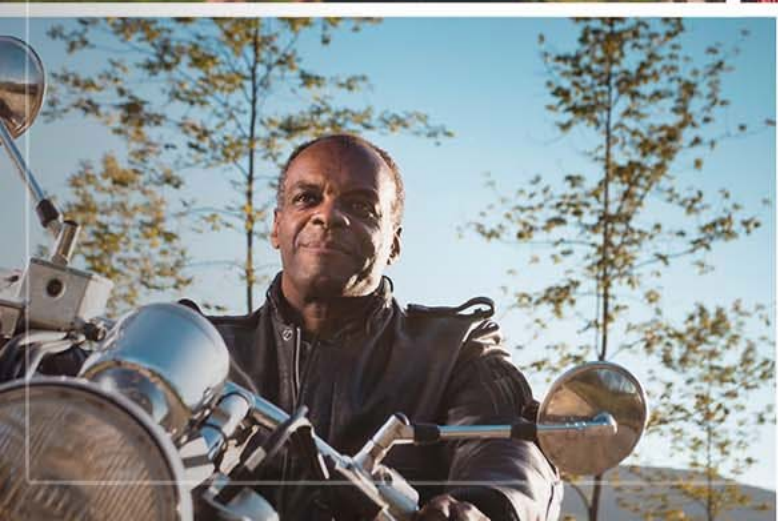




FOURTH QUARTER AND FULL YEAR 2022 FINANCIAL RESULTS

FEBRUARY 7, 2023

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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 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, clinical site initiations, patient enrollment, data availability, anticipated regulatory filings, approvals, and timing thereof, (ii) expectations for continued growth in the number of CF patients treated with our existing therapies, including targeted 2023 global launch of TRIKAFTA/KAFTRIO in patients aged 2-5, (iii) expectations to reach all CF patients eligible for CFTRm, including 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 on continued innovation in CF, including the benefits of vanzacaftor triple combination therapy, our plan to complete Phase 3 studies in 2023, and plans for near-term launch and commercial potential, (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, expectations to complete U.S. regulatory submissions in the first quarter of 2023, expectations for near-term launch and commercial potential, (vi) expectations for our pain program, including its potential to broadly and effectively treat acute pain without the limitations of opioids, the market size and opportunity for VX-548, the anticipated timeline to complete the Phase 3 pivotal program for VX-548 in acute pain and progress enrollment in Phase 2 studies of VX-548 in neuropathic pain, 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 studies in 2023, our beliefs regarding anticipated results of the study and the potential to seek accelerated approval in the U.S., (viii) expectations for the development of our T1D programs, including the patient population, potential curative benefits and safety of VX-880, plans to continue to progress the Phase 1/2 program for VX-880 and availability of updated clinical data in 2023, plans to initiate VX-264 in Canada, and expectations that our recent ViaCyte acquisition may accelerate the development of our T1D program, (ix) plans for continued advancement of VX-634 and VX-864, (x) plans for our DMD program, including expectations to file an IND, (xi) 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 (xii) 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. 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 Q4 2022 press release dated February 7, 2023.

**STRONG PROGRESS IN
2022 SETS UP
PROMISE FOR
EXPANDED
LEADERSHIP IN CF,
MULTIPLE NEAR-TERM
LAUNCHES,
IMPORTANT CLINICAL
MILESTONES, AND
CONTINUED GROWTH**

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 sickle cell disease and transfusion-dependent beta thalassemia
- VX-548 in moderate-to-severe acute pain
- Vanzacaftor triple in CF

Accelerate diversified R&D pipeline

- Five launches possible in next five years
- Multiple clinical-stage programs with launch potential by 2030

Deliver financial performance

- Continued significant revenue growth from treating more CF patients and upcoming launches in new disease areas, starting with exa-cel
- Specialty model and operating expense discipline sustain strong operating margins while allowing for significant investments in the pipeline and commercial capabilities

DIFFERENTIATED VERTEX BUSINESS MODEL AND R&D STRATEGY HAVE DELIVERED TRANSFORMATIVE CYSTIC FIBROSIS MEDICINES AND A ROBUST PIPELINE

FIVE POTENTIAL LAUNCHES IN THE NEXT FIVE YEARS



4 Approved medicines in cystic fibrosis

Near-term commercial opportunities

- Exa-cel (SCD)
- Exa-cel (TDT)
- VX-548 (acute pain)
- Vanzacaftor triple (CF)

8 Programs in mid- or late-stage development

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 TO SERIALY INNOVATE IN CYSTIC FIBROSIS



Vanzacaftor Triple

- Next-in-class CFTR modulator triple therapy
- Holds potential for greater clinical benefit
- Convenient, once-daily dosing
- Meaningfully lower royalty burden
- Completed enrollment in pivotal program in patients ages 12+
 - Phase 3 study in patients ages 6-11 ongoing



VX-522

- CFTR mRNA approach in development for more than 5,000 CF patients who cannot benefit from CFTR modulators
- Expect to complete Single Ascending Dose (SAD) study and initiate Multiple Ascending Dose (MAD) study in 2023
- Program developed in partnership with Moderna



NEAR-TERM LAUNCH POTENTIAL: EXA-CEL

DELIVERING A POTENTIAL ONE-TIME, FUNCTIONAL CURE FOR SICKLE CELL DISEASE (SCD) AND TRANSFUSION-DEPENDENT BETA THALASSEMIA (TDT) PATIENTS



Sickle Cell Disease and Beta Thalassemia

Genetic diseases caused by mutation in the beta-globin gene

Causal human biology well understood

- Mutation in beta-globin gene leads to impairment in quality or quantity of hemoglobin

Severe, symptomatic diseases

- Highly symptomatic with frequent hospitalizations due to vaso-occlusive pain crises (SCD) and severe anemia (TDT)
- Reduced life expectancy



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



- ✓ Precise and durable edit to BCL11A gene to increase production of fetal hemoglobin



- ✓ Regulatory submissions for SCD and TDT completed and validated in the EU and UK
- ✓ Rolling submission initiated in the U.S.; on track to complete Q1:23

NEAR-TERM LAUNCH POTENTIAL: VX-548

ADDRESSING CRITICAL GAP IN TREATMENT OF MODERATE TO SEVERE ACUTE PAIN



Significant Unmet Needs

- Millions in the U.S. each year suffer from acute pain
- Existing therapies have challenging side effects and/or abuse potential
- Pain often poorly managed and inadequately treated as a result

Validated Target

- NaV1.8 is genetically and pharmacologically validated
- 5 Proof of Concept studies across VX-150 and VX-548 in major pain types:
 - Acute
 - Peripheral neuropathic (PNP)
 - Musculoskeletal

Pivotal Program Ongoing

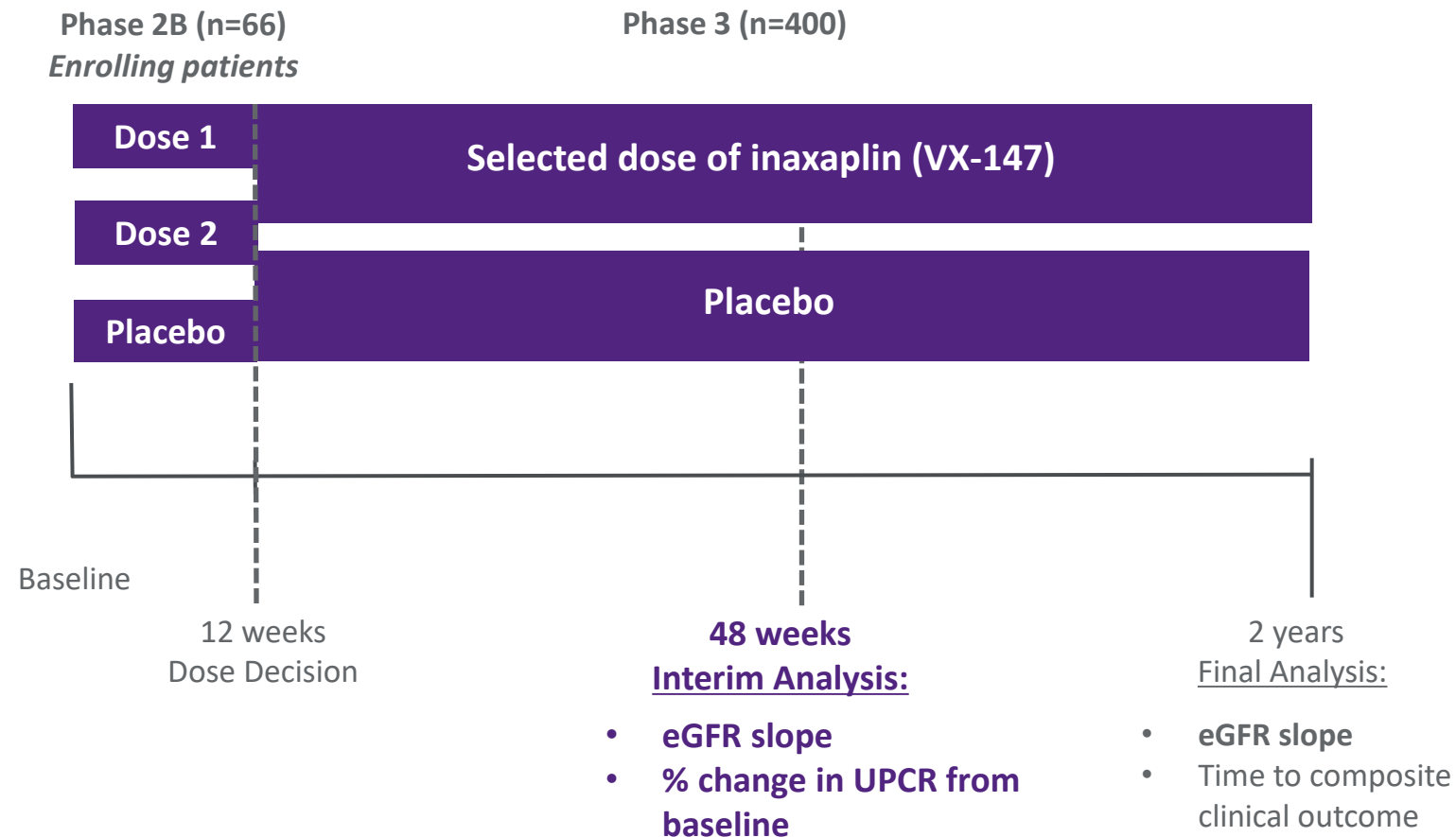
- Phase 3 program similar to Phase 2:
 - Two RCTs: same pain states, duration and endpoints
 - Single-arm study for other types of acute pain
 - Seeking broad, moderate-to-severe, acute pain label

Near-Term Commercial Opportunity

- Phase 3 enrollment well underway in high-volume procedures
- Short treatment duration facilitates efficient timelines
- Positive interactions with FDA
 - Fast Track and Breakthrough Therapy designations granted

Anticipate completing the Phase 3 pivotal program by late 2023/early 2024

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



Small molecule targeting the underlying cause of AMKD

- Single, adaptive Phase 2/3 study in patients with AMKD
- **Interim analysis at 48 weeks:** if data are positive, potential to file for U.S. accelerated approval
- Breakthrough Therapy designation in the U.S. and Orphan Drug and PRIME designation in Europe
- Expect to complete Phase 2B dose-ranging portion in 2023

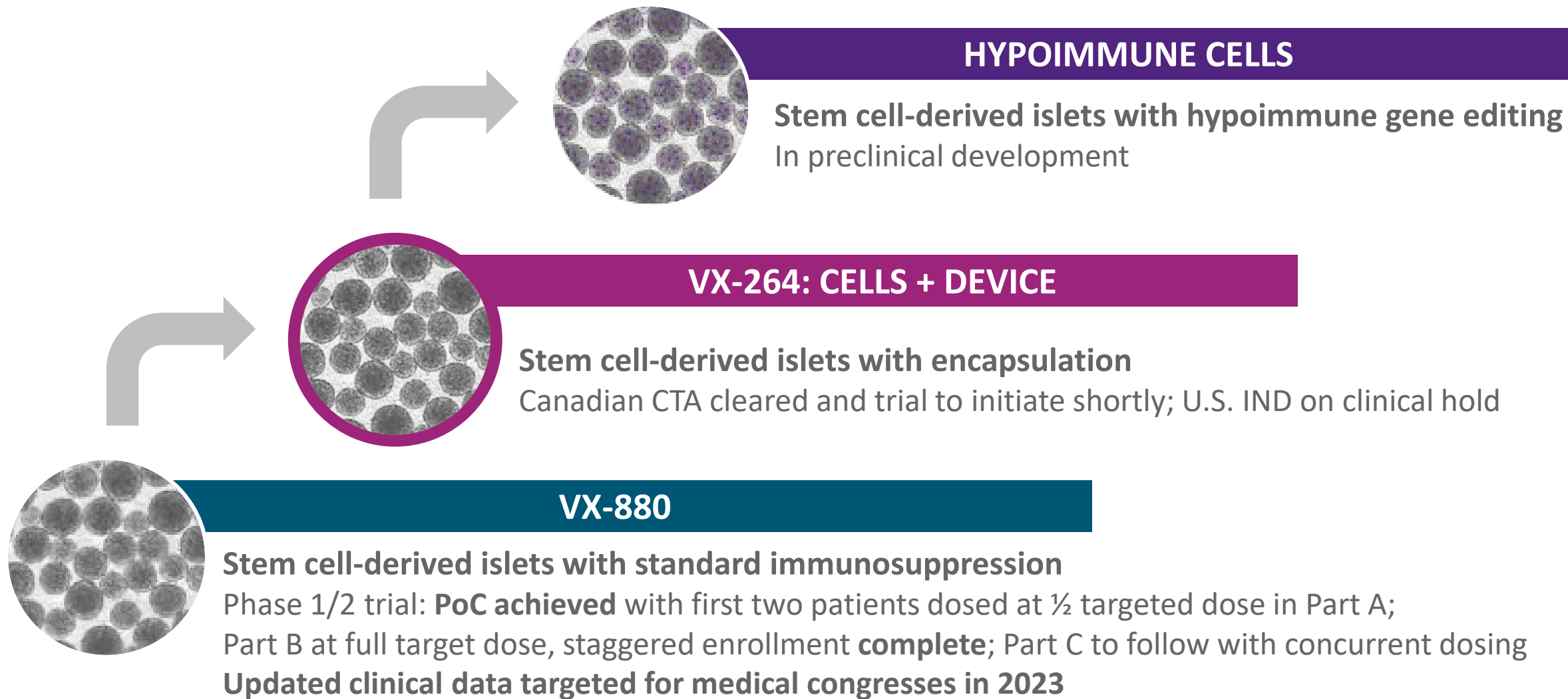
eGFR: estimated glomerular filtration rate

UPCR: urine protein creatinine ratio

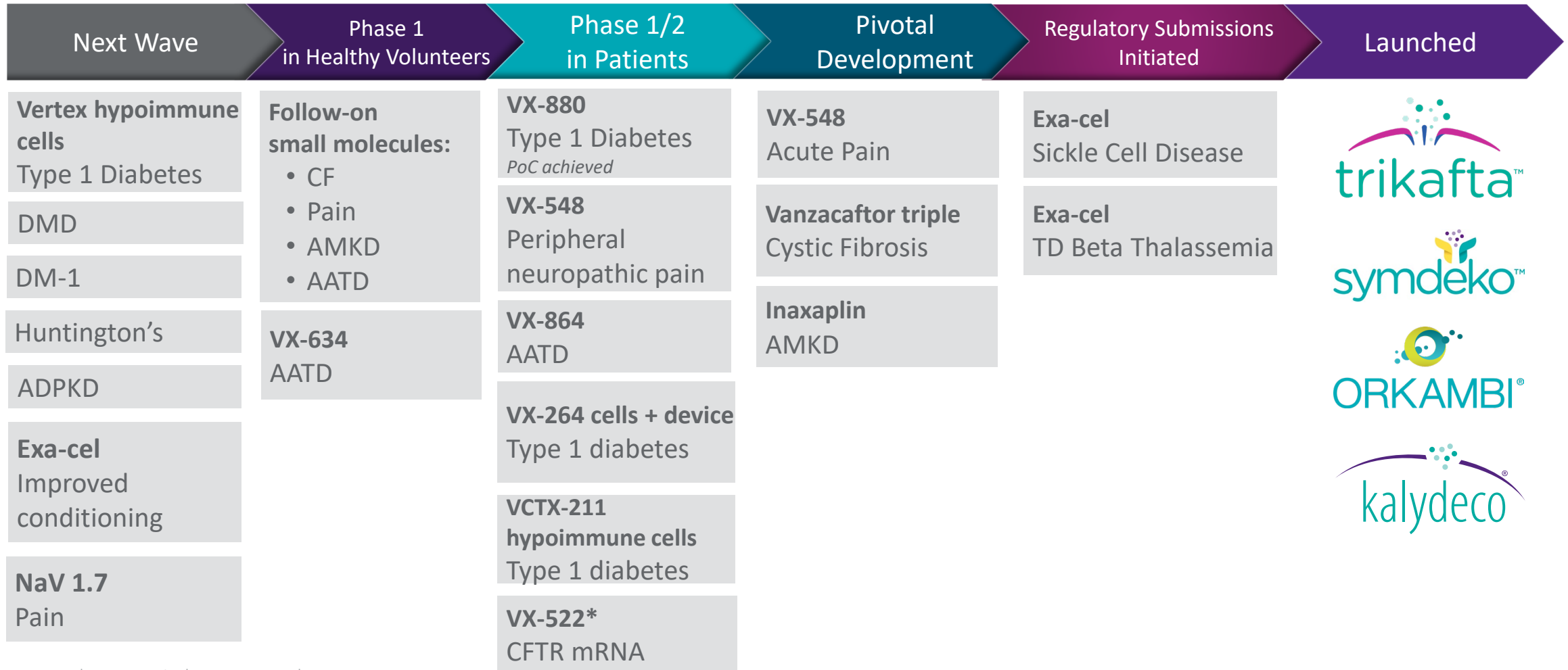
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TYPE 1 DIABETES: ADVANCING POTENTIALLY CURATIVE TREATMENTS

~2.5 MILLION PEOPLE LIVING WITH T1D IN NORTH AMERICA AND EUROPE



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



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DMD: Duchenne Muscular Dystrophy; DM-1: 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

INCREASING EPIDEMIOLOGY ESTIMATES TO 88,000 PATIENTS WITH CF



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. More people with CF, living longer**
Median predicted age of survival is ~65 years*
- 2. Treating younger patients**
Targeting 2023 TRIKAFTA/KAFTRIO global launch in patients ages 2-5 years
- 3. Raising the bar**
Completed Phase 3 enrollment for vanzacaftor triple; studies to complete by YE 2023
- 4. Advancing therapies for all patients**
Initiated VX-522 CFTR mRNA clinical trial in CF patients who cannot benefit from CFTR modulators; received Fast Track designation

* Cystic Fibrosis Foundation Patient Registry 2021 Annual Data Report

NEAR-TERM LAUNCH POTENTIAL: EXA-CEL

THE POTENTIAL FOR A ONE-TIME, FUNCTIONAL CURE IS A COMPELLING OPTION FOR PATIENTS

Severe, symptomatic diseases

- Highly symptomatic with frequent hospitalizations due to vaso-occlusive pain crises (SCD) and severe anemia (TDT)
- Reduced life expectancy

High healthcare utilization and economic burden

- \$4.2M-\$6.2M projected lifetime costs for U.S. SCD patient with recurrent vaso-occlusive pain crises*
- \$4.2M-\$5.7M projected lifetime costs for U.S. TDT patient**

Geographic concentration enables specialty model

- ~32,000 patients with severe SCD and TDT in the U.S. and Europe
- ~50 ATCs in U.S. and ~25 ATCs in Europe to serve eligible patients

*Udeze et al., presented at AMCP Nexus 2022, October 11–14, 2022, National Harbor, MD, USA

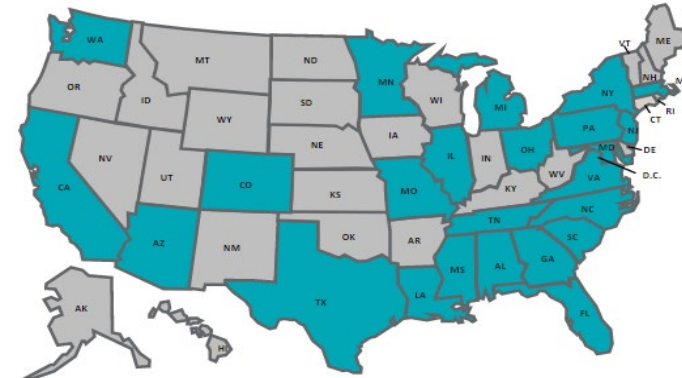
** Udeze et al., presented at EHA 2022, June 9-17, 2022, Vienna, Austria

ATC: Authorized Treatment Center

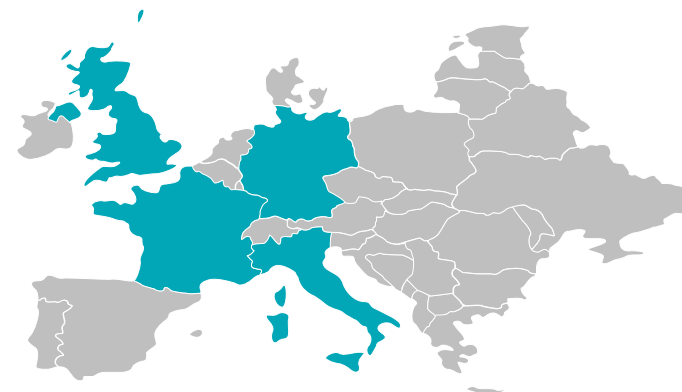


MULTI-BILLION \$ OPPORTUNITY, SPECIALTY MODEL

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



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



VX-548: POTENTIAL FOR KEY ROLE IN BROAD TREATMENT OF ACUTE PAIN, WITHOUT LIMITATIONS OF OPIOIDS, INCLUDING ABUSE POTENTIAL



SIGNIFICANT
UNMET NEED

VX-548

NSAIDs, acetaminophen

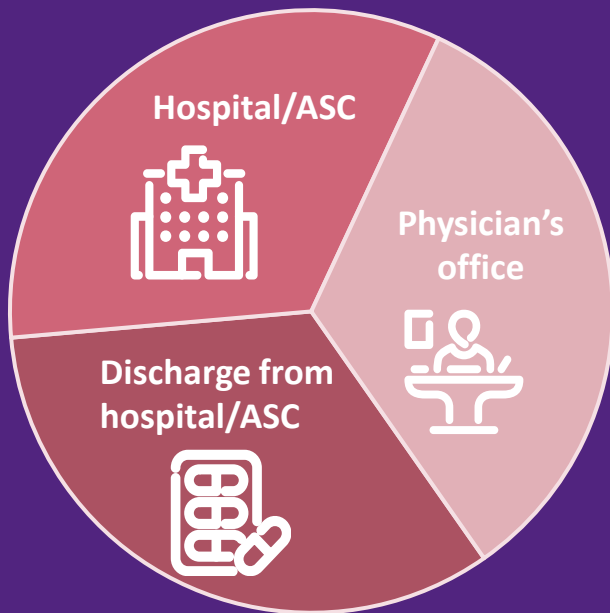
- Ineffective at severe pain relief
- GI side effects – NSAIDs
- Liver toxicity – acetaminophen
- + Non-addicting

- + Effective pain relief
- + Without abuse potential
- + Manageable side effects

Opioids

- Many patients unable to tolerate
- Highly addictive
- Constipation
- Somnolence
- Dizziness
- Nausea/vomiting
- + Effective pain relief

NEAR-TERM LAUNCH POTENTIAL: VX-548 IN ACUTE PAIN



Targeting a broad
moderate to severe
acute pain label

MULTI-\$B MARKET OPPORTUNITY ACCESSIBLE VIA VERTEX SPECIALTY MODEL



Large existing U.S. market, despite being highly generic

- Acute pain ~\$4B market today (with 90% of prescriptions generic)
- 1.5B treatment days

Specialty market given concentration of hospital prescribing

- 2/3 of prescribing volume is generated in hospitals/ASCs
 - Vast majority concentrated in ~1,700 hospitals within ~220 IDNs

Stakeholder-wide recognition of high unmet need

- Policies limiting opioid use have been implemented by many hospitals and IDNs
- All 50 states have opioid prescribing guidelines
 - 16 states have statutory requirements mandating prescriber consideration of non-opioid alternatives

Clear path to access & reimbursement

- NOPAIN Act directs CMS to provide add-on payments for non-opioid treatments (in addition to bundled payments) in hospital/ASC outpatient setting
- **Hospital/ASC:** Benefit/risk profile will drive placement on hospital formulary
- **Discharge and physician's office:** Dispensed at retail and reimbursed through standard pharmacy benefit

Q4 AND FULL YEAR 2022 FINANCIAL HIGHLIGHTS



















<i>(\$ in millions except where noted or per share data and percentages)</i>	Q4 21	FY 21	Q1 22	Q2 22	Q3 22	Q4 22	FY 22
Total CF product revenues	<u>\$2.07B</u>	<u>\$7.57B</u>	<u>\$2.10B</u>	<u>\$2.20B</u>	<u>\$2.33B</u>	<u>\$2.30B</u>	<u>\$8.93B</u>
TRIKAFTA/KAFTRIO	1.69B	5.70B	1.76B	1.89B	2.01B	2.02B	7.69B
SYMDEKO/SYMKEVI	80	420	65	43	38	34	180
ORKAMBI	147	772	132	122	146	111	511
KALYDECO	152	684	139	139	139	136	553
Combined non-GAAP R&D, acquired IPR&D and SG&A expenses	<u>830</u>	<u>3.44B</u>	<u>687</u>	<u>750</u>	<u>758</u>	<u>872</u>	<u>3.07B</u>
Non-GAAP operating income	997	3.23B	1.17B	1.19B	1.29B	1.15B	4.79B
Non-GAAP operating margin %	48%	43%	56%	54%	55%	50%	54%
Non-GAAP net income	777	2.51B	907	930	1.04B	978	3.86B
Non-GAAP net income per share - diluted	\$3.02	\$9.67	\$3.52	\$3.60	\$4.01	\$3.76	\$14.88
Cash, cash equivalents & marketable securities (period-end)		\$7.5B					\$10.8B

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 fourth 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 Q4 2022 press release dated February 7, 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 FINANCIAL GUIDANCE

	FY 2022 Actuals	FY 2023 Guidance	FY 2023 Commentary
Total CF Product Revenue	\$8.9B	\$9.55 - \$9.7B	Continued performance of TRIKAFTA in ages 6+, approval and launch of TRIKAFTA in ages 2-5
Combined GAAP R&D, Acquired IPR&D and SG&A Expenses	\$3.60B	\$4.35 - \$4.6B	Includes expectations for continued investment in our multiple mid- and late-stage clinical development programs, commercial and manufacturing capabilities, and approximately \$300 million of upfront and milestone payments from existing collaborations and our anticipated transaction with Entrada Therapeutics
Combined Non-GAAP R&D, Acquired IPR&D and SG&A Expenses	\$3.07B	\$3.9 - \$4.0B	
Non-GAAP Effective Tax Rate	20.8%	21%-22%	

PROGRESS IN 2022 SETS UP MEANINGFUL CLINICAL CATALYSTS IN 2023

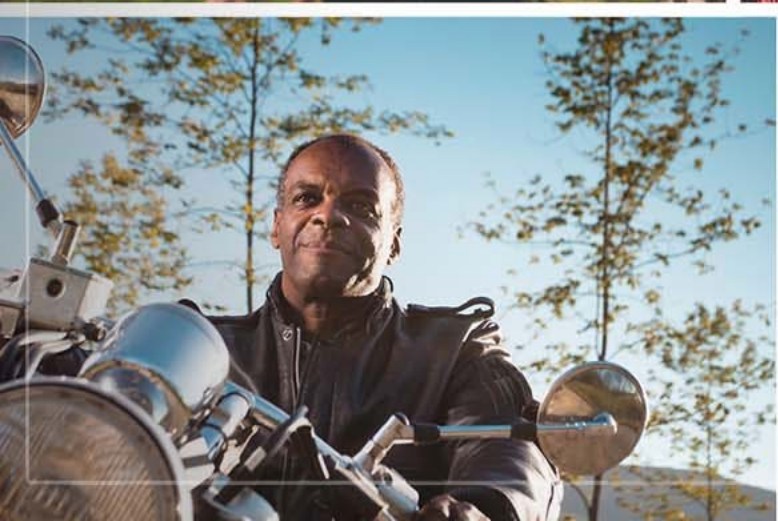
Recent Highlights		Anticipated Key Milestones	
	Submitted global regulatory filings of TRIKAFTA in patients with CF ages 2 to 5		Priority Review granted; PDUFA April 28
	Fully enrolled vanzacaftor/tezacaftor/deutivacaftor Phase 3 studies		Complete Phase 3 studies
	IND cleared for VX-522 CFTR mRNA program; SAD study in CF patients initiated		Complete SAD and initiate MAD study
	Submitted for regulatory approval of exa-cel in EU and the UK and submissions validated; rolling submission in the U.S. initiated		Complete rolling BLA submission to FDA by Q1:23
	All Phase 3 trials underway for VX-548 in acute pain		Complete Phase 3 trials late 2023/early 2024
	Initiated Phase 2 dose-ranging study of VX-548 in neuropathic pain		Ramp enrollment in Phase 2 trial
	Initiated pivotal development of inaxaplin in broad AMKD population		Complete Phase 2B (dose-ranging) portion of Phase 2/3 pivotal study
	Completed enrollment of Part B for VX-880 in type 1 diabetes		Initiate Part C (concurrent dosing); present updated clinical data
	Cleared CTA in Canada for VX-264, the cells + device program in type 1 diabetes		Initiate Phase 1/2 trial
	Initiated Phase 2 trial for VX-864 in patients with AATD and FIH trial for VX-634		Ramp enrollment
	IND-enabling studies ongoing for DMD		File IND



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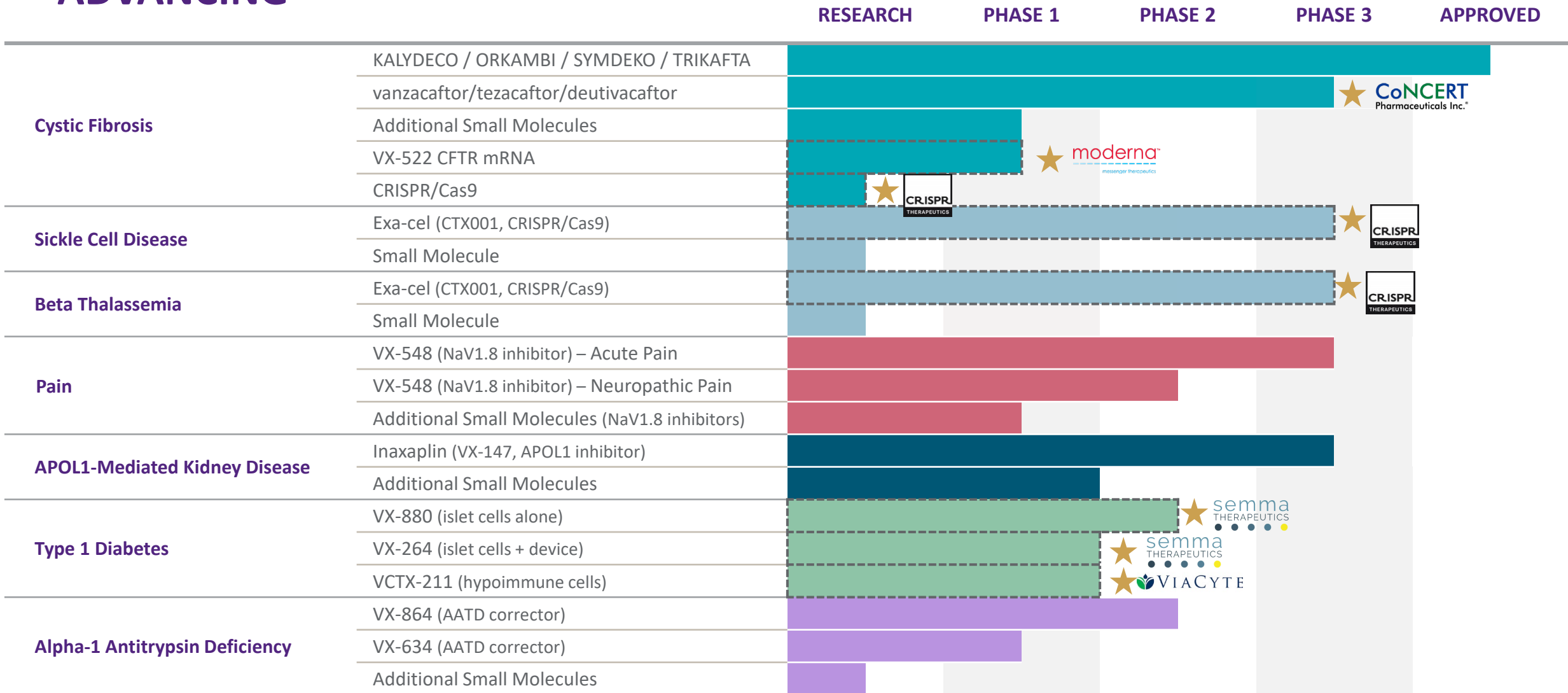
APPENDIX

GAAP TO NON-GAAP FINANCIAL INFORMATION

	(\$ in millions except as noted, per share data and percentages)						
	Q4 21	FY 21	Q1 22	Q2 22	Q3 22	Q4 22	FY 22
Combined R&D, Acquired IPR&D, and SG&A							
GAAP	950	3.89B	818	877	921	984	3.60B
Non-GAAP	830	3.44B	687	750	758	872	3.07B
Operating income							
GAAP	878	2.78B	1.04B	1.11B	1.13B	1.03B	4.31B
Non-GAAP	997	3.23B	1.17B	1.19B	1.29B	1.15B	4.79B
Operating Margin %:							
GAAP	42%	37%	50%	50%	48%	45%	48%
Non-GAAP	48%	43%	56%	54%	55%	50%	54%
Net income							
GAAP	770	2.34B	762	810	931	819	3.32B
Non-GAAP	777	2.51B	907	930	1.04B	978	3.86B
Net income per share - diluted							
GAAP	\$3.00	\$9.01	\$2.96	\$3.13	\$3.59	\$3.15	\$12.82
Non-GAAP	\$3.02	\$9.67	\$3.52	\$3.60	\$4.01	\$3.76	\$14.88

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 fourth 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 Q4 2022 press release dated February 7, 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