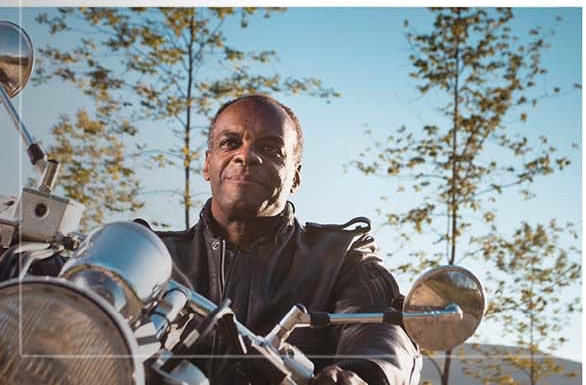







VERTEX

THE SCIENCE *of* POSSIBILITY

SECOND QUARTER 2022 FINANCIAL RESULTS

AUGUST 4, 2022

AGENDA

Introduction

Charlie Wagner, Executive Vice President and Chief Financial Officer

CEO Perspective and Pipeline Update

Reshma Kewalramani, M.D., Chief Executive Officer and President

Business 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, the section captioned "Full-Year 2022 Financial Guidance", and statements regarding (i) the 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) expectations for continued growth in the number of CF patients treated with our products, including reaching more CF patients who can benefit from our marketed products, (iii) our plans to treat additional CF patients with mRNA, including plans for a CFTR mRNA IND filing in 2022, (iv) expectations for our next-in-class, once-daily, oral triple regimen for CF patients, including further enhancements of patient benefit, our Phase 3 program expectations, enrollment plans and related economics, (v) expectations for the exa-cel program, including the continued potential of exa-cel to be a curative approach for patients with TDT and SCD, expectations for program approval and launch, and potential commercial opportunity, (vi) our plans regarding our pivotal program underway for inaxaplin in AMKD, and our beliefs regarding anticipated results of the study and the possibility for accelerated approval in the U.S., (vi) expectations regarding the potential benefits of our pain program and products, and plans for the advancement of VX-548 into a Phase 3 program in acute pain in the fourth quarter of 2022 and into Phase 2 dose-ranging study for neuropathic pain by year-end 2022, and our beliefs regarding the possibility for accelerated approval in the U.S., (vii) expectations for uptake of and expanded access to the company's products, including additional reimbursement agreements, label expansions and approvals in new markets, (viii) the potential benefits and safety of VX-880, and our plans to continue to progress the Phase 1/2 program for VX-880, (ix) our plans and expectations regarding our additional programs in T1D, including the completion of IND-enabling studies for the encapsulated islet cell program and anticipated regulatory filings in 2022, (x) plans to advance one or more novel small molecule Z-AAT correctors into the clinic in 2022, (xi) our plans regarding our DMD program, and (xii) our investments and expectations in external innovation, including collaborations and acquisitions, and (xiii) 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. 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 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 Q2 2022 press release dated August 4, 2022.

A NEW INFLECTION POINT FOR VERTEX

Unique and differentiated R&D strategy delivers success

Accelerating CF leadership

- Treating more patients with our CF medicines
- TRIKAFTA real-world data continue to raise the bar
- Advancing our next-gen CFTR regimen through Phase 3
- Plan to file IND for CFTR mRNA therapy in 2H22

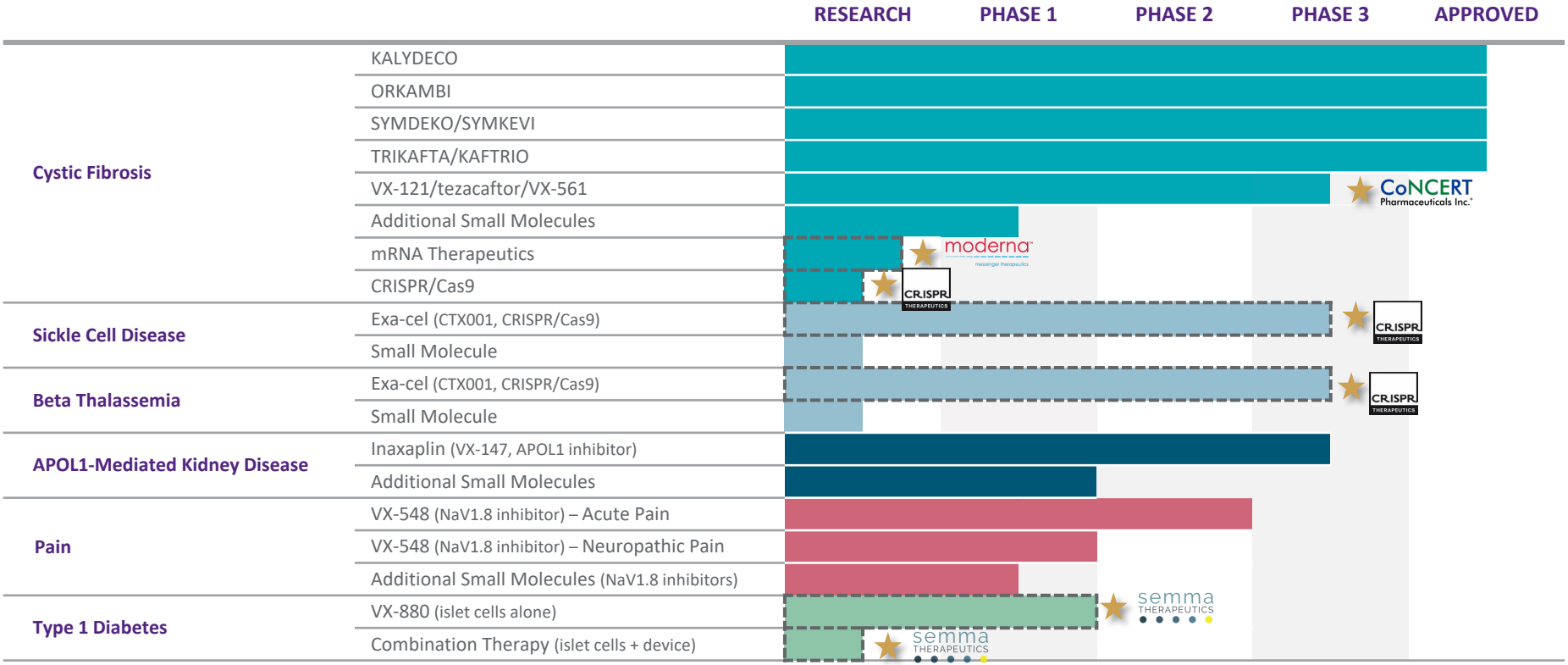
Advancing broad and deep R&D pipeline

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

Strong financial profile

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

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

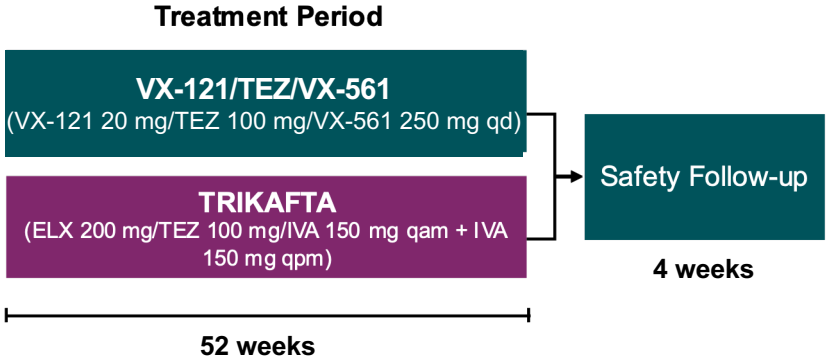


VX-121/TEZACAFTOR/VX-561 TRIPLE REGIMEN MAY FURTHER ENHANCE PATIENT BENEFIT IN CYSTIC FIBROSIS

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

SKYLINE 102 STUDY

SKYLINE 103 STUDY



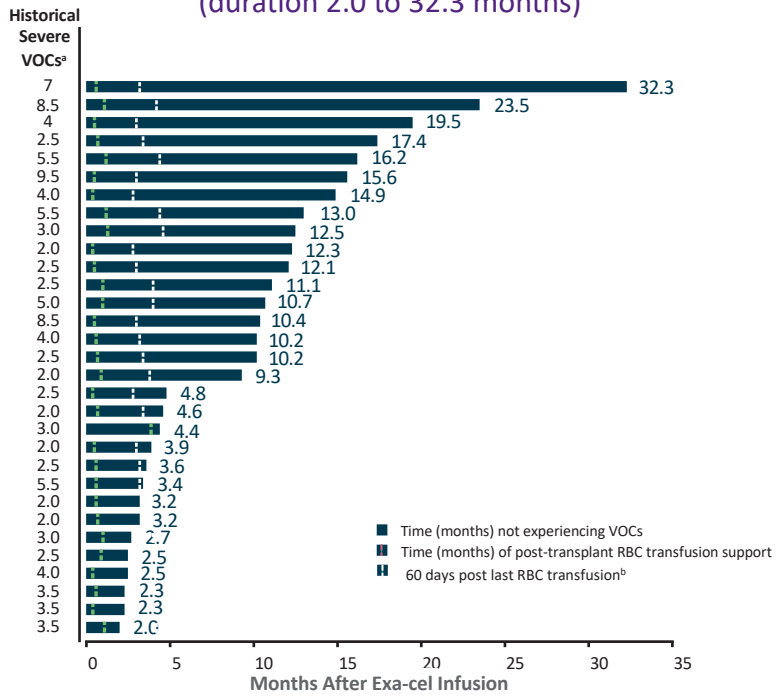
Next-in-Class, Once-Daily, Oral Triple Regimen

- Preclinical and Phase 2 clinical data demonstrate potential for superior efficacy over TRIKAFTA
- Once-daily regimen
- Enhanced economics
- More than 250 clinical sites active across both studies
- On track to complete pivotal program enrollment by late 2022/early 2023
- RIDGELINE study initiated in patients ages 6 to 11

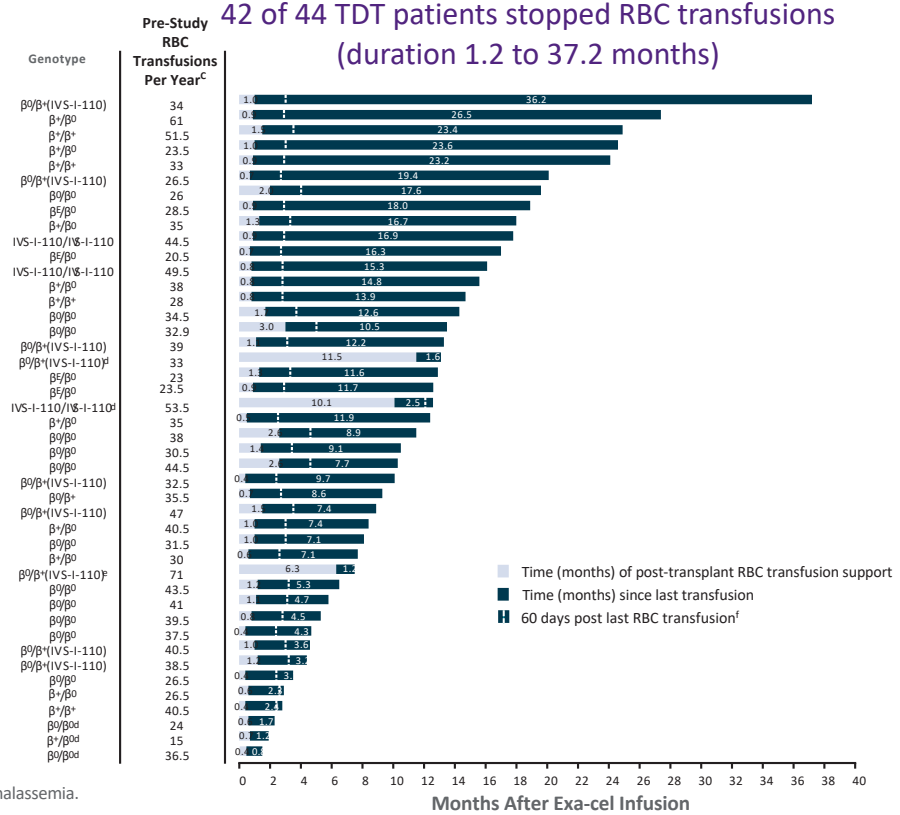
EHA 2022: EXA-CEL DATA CONTINUE TO DEMONSTRATE CURATIVE POTENTIAL

Data from 75 patients with follow up to 37 months show compelling efficacy in patients with SCD and TDT

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)

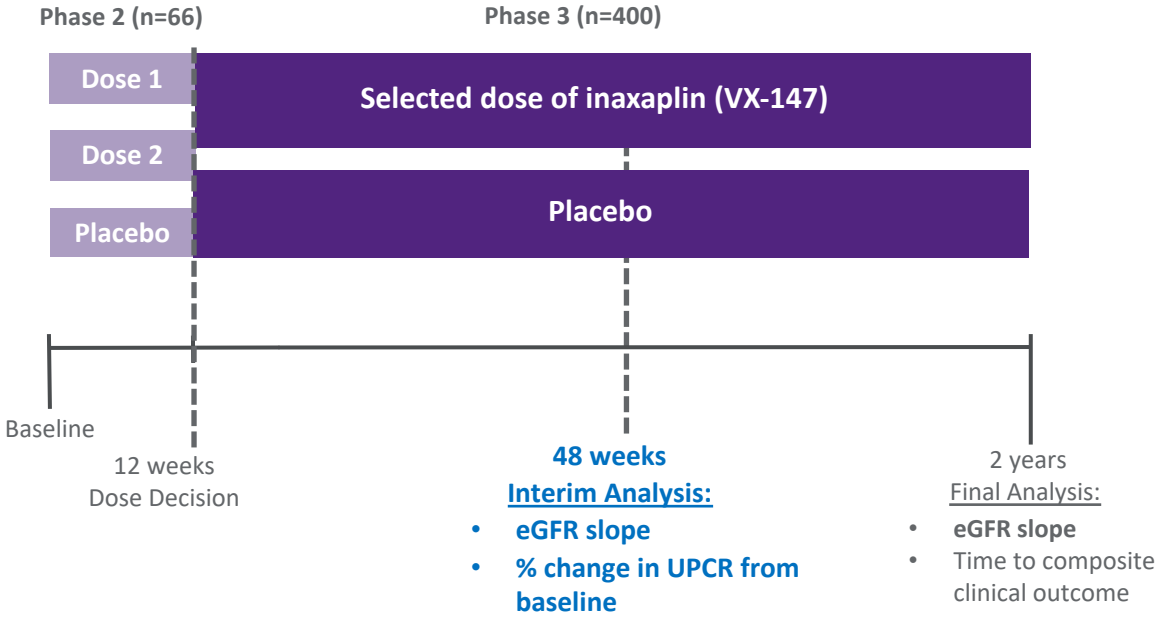


RBC, red blood cell; SCD, sickle cell disease; VOC, vaso-occlusive crisis; Hb, hemoglobin; TDT, transfusion-dependent β-thalassemia.
Each row in the figures represents an individual patient.

[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.

INAXAPLIN PIVOTAL PROGRAM UNDERWAY FOR PATIENTS WITH APOL1-MEDIATED KIDNEY DISEASE (AMKD)

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

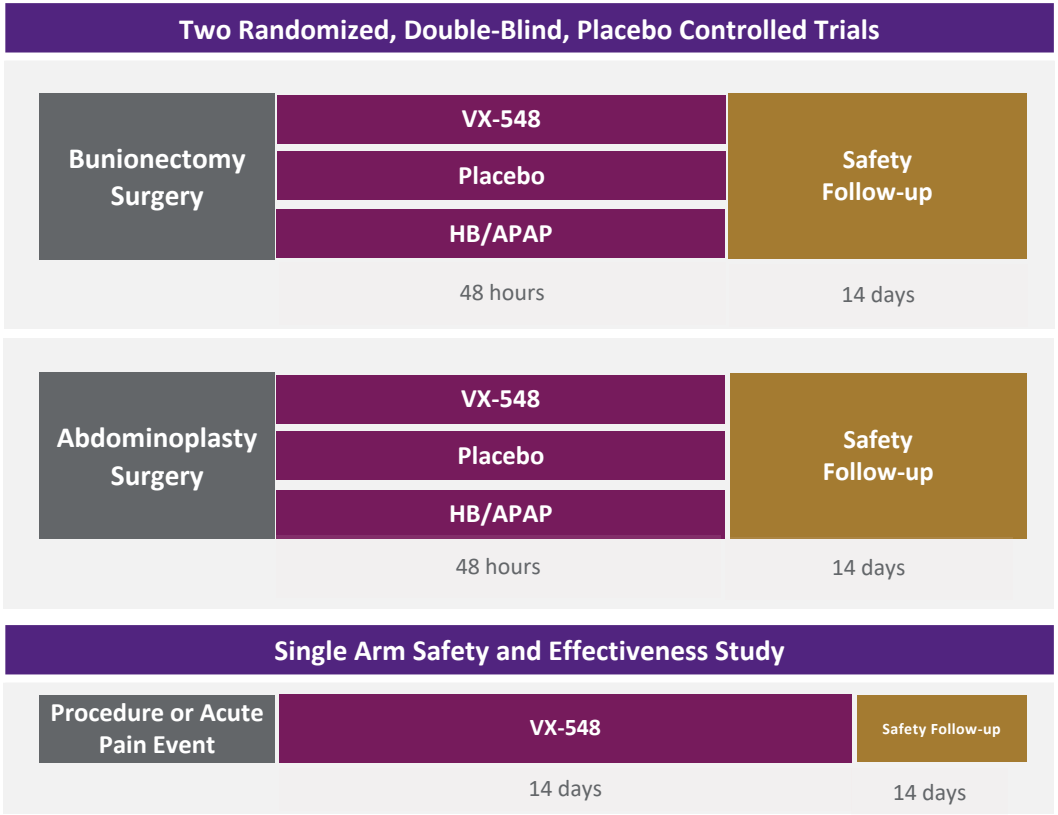


Small Molecule Targeting the Underlying Cause of AMKD

- Single, adaptive Phase 2/3 study in patients with AMKD
- 150 sites planned globally
- **Interim analysis at 48 weeks**: if data are positive, potential to file for accelerated approval
- Breakthrough Therapy designation in the U.S. and PRIME designation in Europe

VX-548: INITIATING PIVOTAL DEVELOPMENT FOR ACUTE PAIN

Program targets broad moderate to severe acute pain label in the U.S.; studies to include an opioid treatment arm



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

Novel, Selective NaV1.8 Inhibitor for Pain

- Novel MOA with potential to redefine the treatment of pain
- Breakthrough Therapy designation secured and Phase 3 program for acute pain to initiate in Q4 2022
- Phase 2 dose-ranging study for neuropathic pain to initiate by year-end 2022

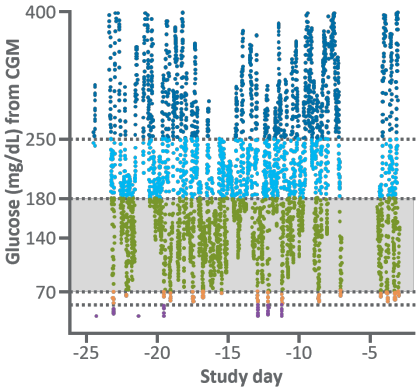
ADA 2022: ADDITIONAL DATA FROM FIRST TWO VX-880 PATIENTS CONTINUE TO SHOW TRANSFORMATIVE POTENTIAL

Significant increases in time in range (TIR); both patients have demonstrated glucose-responsive insulin production

Patient 1 (1/2 dose of VX-880)

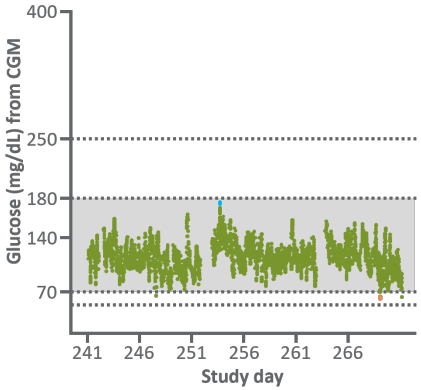
Insulin independent, 99.9% TIR (day 241-270)

Baseline



Daily Insulin	34 units
Time in Range	40.1%
HbA1c	8.6%

Day 241 – 270

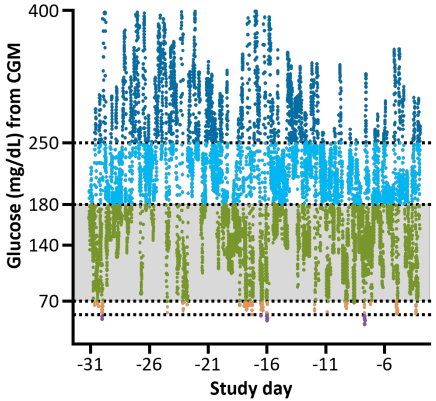


0 units
99.9%
5.2%

Patient 2 (1/2 dose of VX-880)

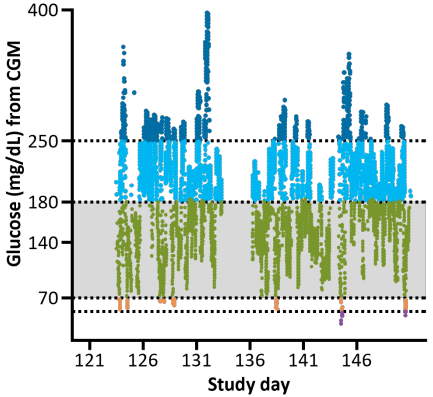
30% insulin reduction, 51.9% TIR (day 121-150)

Baseline



Daily Insulin	25.9 units
Time in Range	35.9%
HbA1c	7.5%

Day 121 - 150



18.2 units
51.9%
7.1%

CGM, continuous glucose monitoring; TIR, time in range. Data from the latest cut evaluated, Day 241-270 for patient 1 and Day 121-150 for patient 2.
*Time in range 70-180 mg/dL.

NEXT WAVE OF INNOVATION ADVANCING RAPIDLY

Recent Highlights	Key Milestones Ahead
IND-enabling studies completed for CFTR mRNA program	On track to **file IND** in 2H22
Continued **advancement of IND-enabling studies for cells + device** program in type 1 diabetes	On track to **file IND** in 2H22
IND-enabling studies initiated for next-generation **small molecules for AATD**	On track to **file IND** in 2H22
IND-enabling studies initiated for **gene editing program for DMD**	Plan to **file IND in 2023**
Advancement of **follow-on and next-generation molecules** across the pipeline	Progression to **IND-enabling studies and first-in-human clinical trials throughout 2022**

CONTINUED UPTAKE OF OUR CFTR MODULATORS AROUND THE WORLD

UNITED STATES

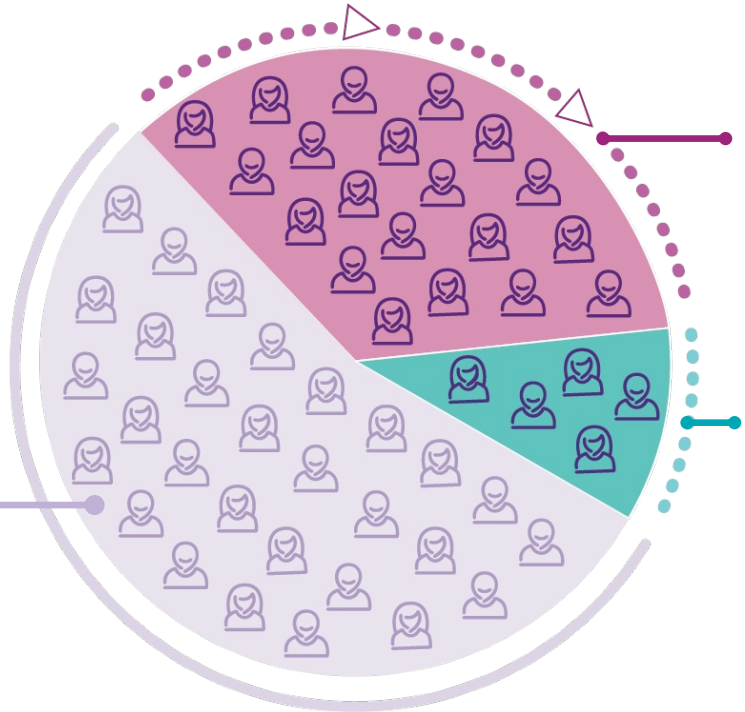
- Q2 TRIKAFTA growth in younger age groups (ages 6-11)
- Consistently strong performance, high persistence and compliance rates for TRIKAFTA in the U.S.

EUROPE and OTHER MARKETS

- Rapid uptake of KAFTRIO/TRIKAFTA in markets with recent reimbursement
- KAFTRIO/TRIKAFTA available and reimbursed in more than 25 countries

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 approximately **5,000** additional patients with CFTR mRNA; IND planned for 2H 2022

Note: Estimated CF patient population and population breakdown as of January 2022.

COMMERCIALIZATION HIGHLIGHTS FOR PROGRAMS IN PIVOTAL DEVELOPMENT

Sickle Cell Disease and Beta Thalassemia

32,000 Patients in U.S. and EU

Vast Majority of 25,000 Patients with Severe Sickle Cell Disease are in the U.S.

- *Identified "centers of excellence"*
- *Teams in place across multiple functions*
- *Engaging with payors*

MAAs expected in 4Q22
Discussions with FDA ongoing

APOL1-Mediated Kidney Disease

100,000 Patients in U.S. and EU

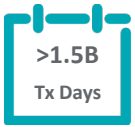
Vast Majority (>80%) of AMKD Patients are in the U.S.

- *Raising disease awareness among physicians and patients*
- *Initiatives to increase genetic testing for APOL1*

Phase 2/3 Ongoing

Acute Pain

>1.5B Treatment Days (U.S.)



$4B U.S. Market
Despite 90% Generic RXs

- *2/3 of the acute pain market in the U.S. is related to hospital stays or discharges*

Phase 3 to Initiate in Q4 2022

Q2 2022 FINANCIAL HIGHLIGHTS

($ in millions except where noted or per share data and percentages)	Q2 21	FY 21	Q2 22
Total CF product revenues	$1.79B	$7.57B	**$2.20B**
TRIKAFTA/KAFTRIO	$1.26B	$5.70B	**$1.89B**
SYMDEKO/SYMKEVI	134	420	**43**
ORKAMBI	221	772	**122**
KALYDECO	183	684	**139**
Combined non-GAAP R&D, acquired IPR&D and SG&A expenses	1.50B	3.44B	**750**
Non-GAAP operating income	71	3.23B	**1.19B**
Non-GAAP operating margin %	4%	43%	**54%**
Non-GAAP net income	43	2.51B	**930**
Non-GAAP net income per share – diluted	$0.17	$9.67	**$3.60**
Cash, cash equivalents & marketable securities (period-end)	$6.7B	$7.5B	**$9.3B**

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 second 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 Q2 2022 press release dated August 4, 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 UPDATED FINANCIAL GUIDANCE

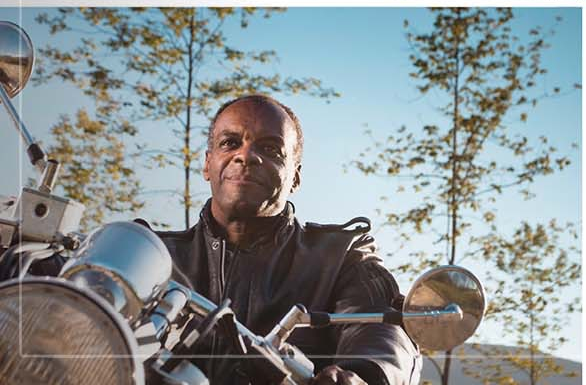
	Current FY 2022 Guidance	Previous FY 2022 Guidance	FY 2022 Commentary
Total CF Product Revenues	**$8.6 - $8.8B**	**$8.4 - $8.6B**	Increase primarily reflects recent reimbursements and uptake of KAFTRIO/ TRIKAFTA in countries outside the U.S.
Combined GAAP R&D, Acquired IPR&D and SG&A Expenses	**$3.48 - $3.63B**	**$3.30 - $3.45B**	Increase driven by the clinical pipeline advancement and incremental expenses from BD activity
Combined Non-GAAP R&D, Acquired IPR&D and SG&A Expenses	**$3.0 - $3.1B**	**$2.82 - $2.92B**	
Non-GAAP Effective Tax Rate	**Unchanged**	**21% - 22%**	

RECENT ADVANCES POSITION VERTEX FOR MULTIPLE CLINICAL MILESTONES AHEAD

Recent Highlights	Key Milestones Ahead
Submitted regulatory filings for ORKAMBI in patients with CF ages 12 to <24 months	**Regulatory approval** in the U.S. expected in 2H22
Completed Phase 3 study of TRIKAFTA in patients with CF ages 2 to 5	**Submit global regulatory filings** by the end of 2022
Positive data in 75 patients dosed in **the pivotal studies of exa-cel**	**Submit for regulatory approval** in Europe and the U.K. by the end of 2022; complete discussion with U.S. FDA
More than 250 sites active in **VX-121/tezacaftor/VX-561 Phase 3** studies	**Complete enrollment** by late 2022 or early 2023
Initiated pivotal development of inaxaplin (VX-147) in broad AMKD population	Ramp **enrollment in pivotal program**
Proof of concept for VX-548 in two types of acute pain, **reached agreement with FDA** on pivotal program design for acute pain	Initiate **pivotal development in acute pain** in 4Q22
	Initiate **Phase 2 study in neuropathic pain** by year end 2022
Proof of concept for VX-880 in type 1 diabetes; 1st patient in Part B (full target dose) has been dosed	Complete **Part B enrollment**, **additional data** from Part B of the trial





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AUGUST 4, 2022

APPENDIX

GAAP TO NON-GAAP FINANCIAL INFORMATION

($ in millions except as noted, per share data and percentages)	Q2 21	FY 21	Q2 22
Combined R&D, Acquired IPR&D and SG&A			
GAAP	1.60B	3.89B	**877**
Non-GAAP	1.50B	3.44B	**750**
Operating income			
GAAP	(38)	2.78B	**1.11B**
Non-GAAP	71	3.23B	**1.19B**
Operating Margin %:			
GAAP	(2)%	37%	**50%**
Non-GAAP	4%	43%	**54%**
Net income			
GAAP	67	2.34B	**810**
Non-GAAP	43	2.51B	**930**
Net income per share - diluted			
GAAP	$0.26	$9.01	**$3.13**
Non-GAAP	$0.17	$9.67	**$3.60**

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 second 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 Q2 2022 press release dated August 4, 2022.