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J.P. MORGAN HEALTHCARE CONFERENCE

RESHMA KEWALRAMANI, M.D.

CEO AND PRESIDENT

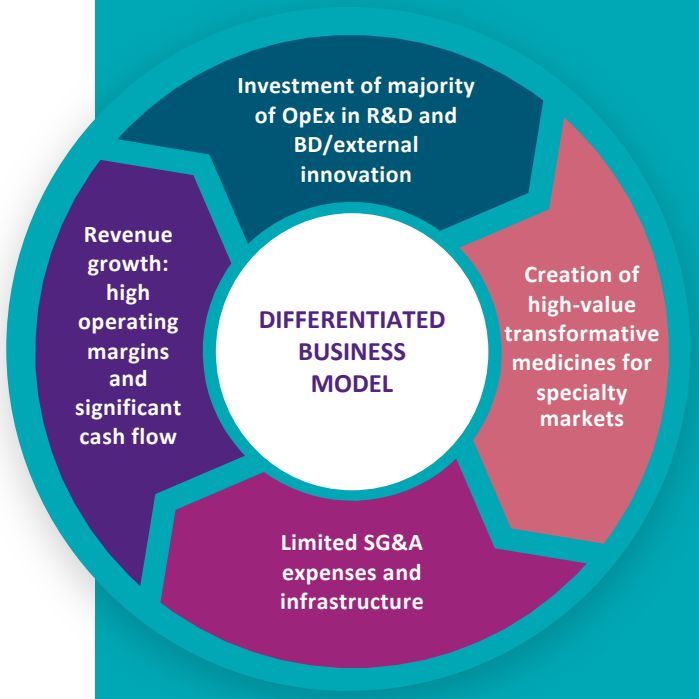
JANUARY 2023

SAFE HARBOR STATEMENT & NON-GAAP FINANCIAL MEASURES

This presentation contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, including, without limitation, the information provided regarding future financial and operating performance and statements regarding (i) expectations, development plans and timelines for the company's medicines, drug 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 and relevant patient populations, (ii) expectations for uptake of and expanded access to the company's medicines (iii) expectations for continued growth in the number of CF patients treated with our therapies, including targeted 2023 global launch of TRIKAFTA/KAFTRIO in patients aged 2-5, anticipated serial innovation to reach all CF patients eligible for CFTRm and plans to reach the last >5,000 CF patients with mRNA therapy, (iv) 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 for completion of US regulatory submissions in the first quarter of 2023, expectations for near-term launch and commercial potential, (v) expectations for our pain program, including enrollment plans in the acute pain and neuropathic pain studies and plans for near-term launch and commercial potential in acute pain, and expectation for treatment of acute pain without limitations of opioids, (vi) expectations for our T1D program, including availability of VX-880 clinical data in 2023 and Phase 1/2 clinical trial for VX-264 anticipated to begin in Canada in the first half of 2023, (vii) expectations for vanzacaftor triple combination therapy, including our plan to complete dosing by end of 2023 and potential commercial launch, (viii) expectations for inaxaplin, including completion of Phase 2 portion and enrollment plans for Phase 3 portion and potential commercial opportunity, (ix) expectations for VX-864, including enrollment, (ix) expectations for our DMD program, including plans to file an IND, and (x) our plans to continue to invest in internal and external innovation. While Vertex believes the forward-looking statements contained in this presentation are accurate, these forward-looking statements represent the company's beliefs as of the date of this presentation and there are risks and uncertainties that could cause actual events or results to differ materially from those expressed or implied by such forward-looking statements. Those risks and uncertainties include, among other things, that the company's expectations regarding future revenues may be incorrect, data from clinical trials, especially if based on a limited number of patients, may not to be indicative of final results, the company may not be able to scale up manufacturing of our product candidates, actual patient populations able to participate in our trials or eligible for our products may be smaller than anticipated, data from the company's development programs may not be available on expected timelines, or at all, support registration or further development of its potential medicines due to safety, efficacy or other reasons, and other risks listed under the heading "Risk Factors" in Vertex's annual report and subsequent quarterly reports filed with the Securities and Exchange Commission at www.sec.gov and available through the company's website at www.vrtx.com. You should not place any undue reliance on these statements, or the data presented. Vertex disclaims any obligation to update the information contained in this presentation as new information becomes available.

In this presentation, Vertex references financial guidance and results that have been provided in accordance with US GAAP and certain non-GAAP financial measures. 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. A reconciliation of the GAAP financial results to non-GAAP financial results is included in the appendix hereto.

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



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**

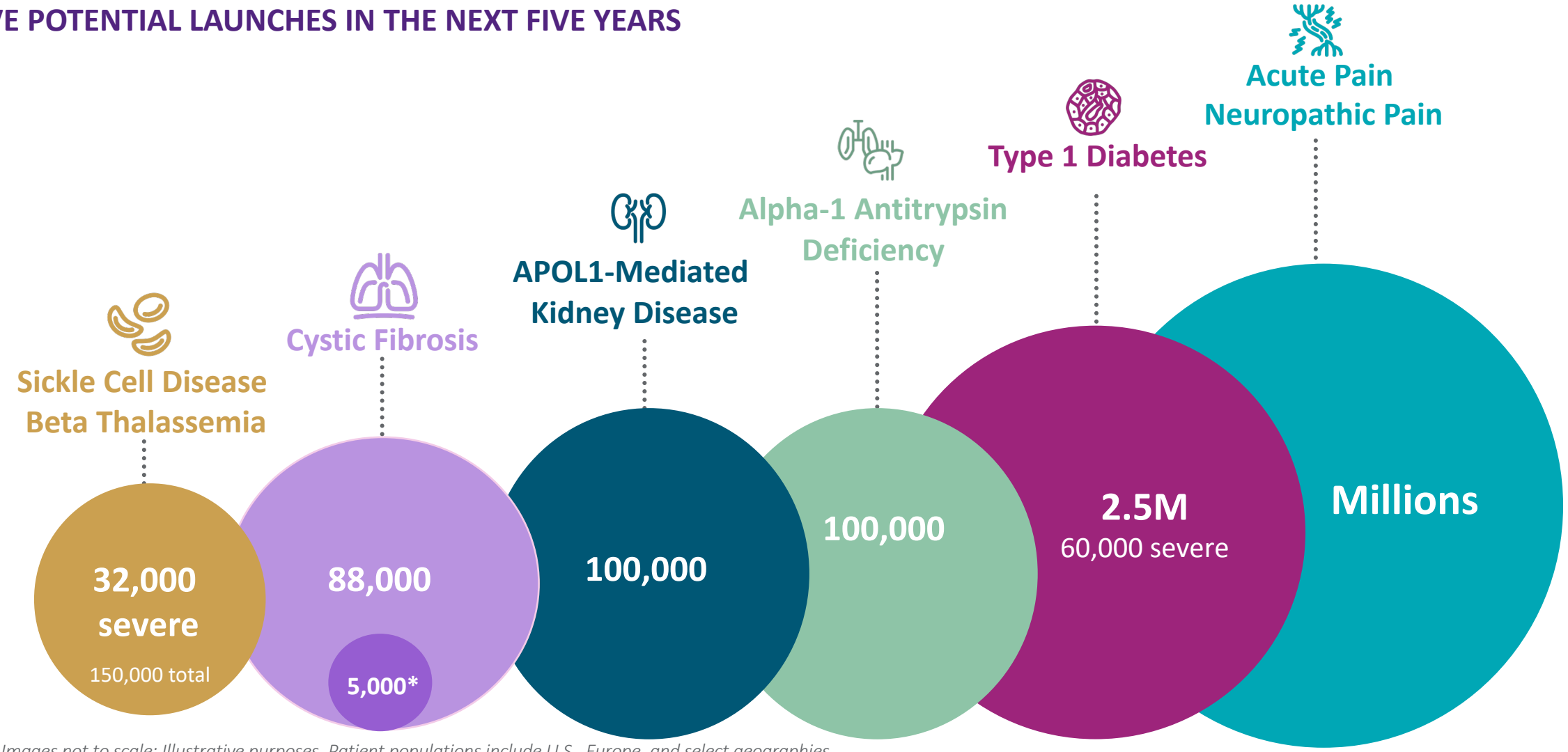
Near-term commercial opportunities
- Exa-cel (SCD)
- Exa-cel (TDT)
- VX-548 (acute pain)
- Vanzacaftor triple (CF)

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

ADVANCED, CLINICAL-STAGE PROGRAMS TARGET TRANSFORMATIVE BENEFITS ACROSS EIGHT SPECIALTY DISEASE AREAS

FIVE POTENTIAL LAUNCHES IN THE NEXT FIVE YEARS



Images not to scale; Illustrative purposes. Patient populations include U.S., Europe, and select geographies.
**Approximately 5,000 people with CF cannot benefit from CFTR modulators and thus may potentially benefit from VX-522, our mRNA program.*

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

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

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**

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

- ✓ Precise and durable edit to BCL11A gene to increase production of fetal hemoglobin
- ✓ Exa-cel submission completed Q4:22 in EU and UK for both SCD and TDT
- ✓ Rolling submission initiated in the U.S.; on track to complete Q1:23

*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

NEAR-TERM LAUNCH POTENTIAL: EXA-CEL

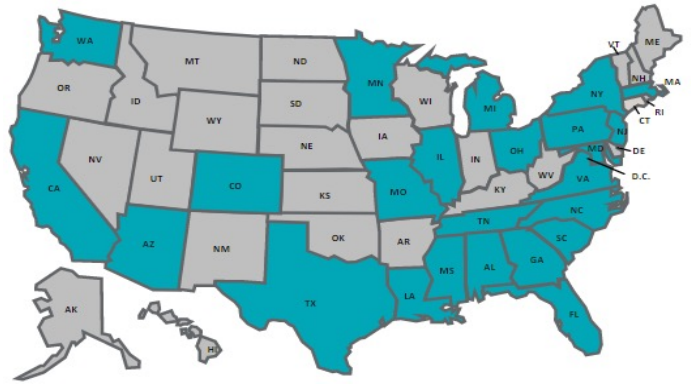
PATIENT GEOGRAPHIC CONCENTRATION ENABLES SPECIALTY MODEL; LAUNCH PREP WELL UNDERWAY

- ~32,000 patients with severe SCD and TDT in the U.S. and Europe
- Geographic concentration of patients enables specialty model
  - ~50 ATCs in U.S. and ~25 ATCs in Europe to serve eligible patients
- Field teams engaging ATCs on administrative and logistical capabilities
- Commercial and medical teams hired, trained and actively engaging with key stakeholders

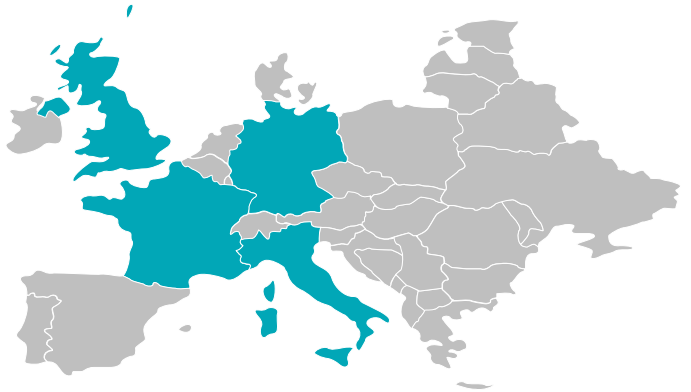
ATC: Authorized Treatment Center

MULTI-BILLION $ OPPORTUNITY, SPECIALTY MODEL

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



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



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

ADDRESSING CRITICAL GAP IN THE 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

RCT: Randomized controlled trial

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

SIGNIFICANT UNMET NEED

NSAIDs, acetaminophen

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

VX-548

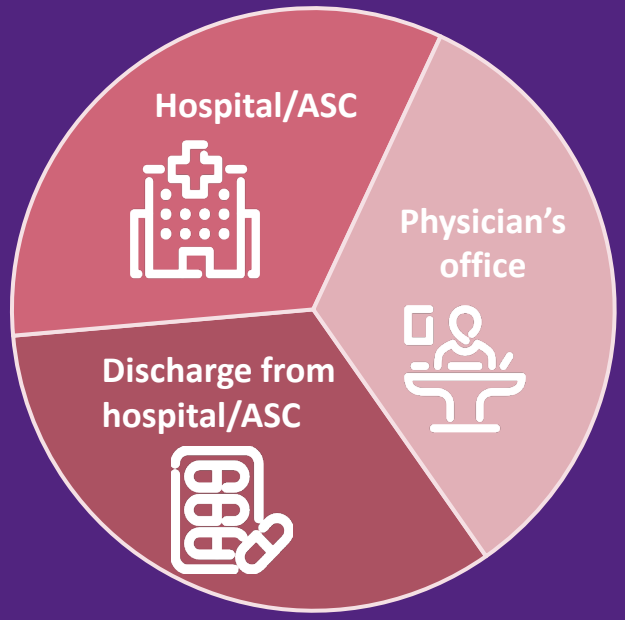
- Effective pain relief
- Without abuse potential
- Manageable side effects

Opioids

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

NSAID: Non-steroidal anti-inflammatory drugs

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

ASC: ambulatory surgery center; IDN: integrated delivery network

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

- 47.6% reduction in proteinuria in Phase 2 in APOL1-mediated FSGS
- Dose selection portion of Phase 2/3 pivotal trial expected to complete in 2023
- Path to accelerated approval with interim analysis at 48 weeks of treatment
- Final analysis at ~2 years of treatment

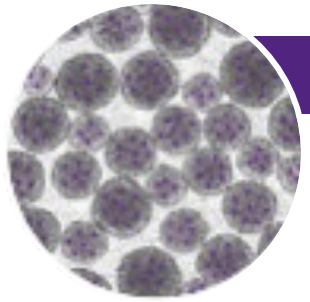
RAISING DISEASE AWARENESS

- Education outreach with physicians and patients
- Building trust with historically underserved communities
- Initiatives to increase genetic testing for APOL1

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. *ESKD: End-stage kidney disease; FSGS: Focal segmental glomerulosclerosis*

TYPE 1 DIABETES: ADVANCING POTENTIALLY CURATIVE TREATMENTS

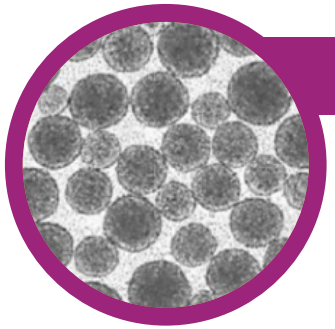
~2.5 MILLION PEOPLE LIVING WITH T1D IN NORTH AMERICA AND EUROPE



HYPOIMMUNE CELLS

Stem cell-derived islets with hypoimmune gene editing

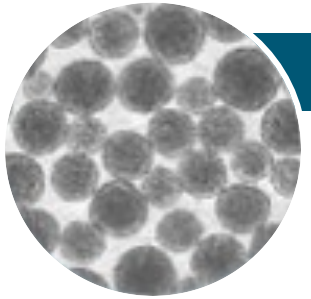
In preclinical development



VX-264: CELLS + DEVICE

Stem cell-derived islets with encapsulation

Filed U.S. IND and Canadian CTA



VX-880

Stem cell-derived islets with standard immunosuppression

Phase 1/2 trial: **PoC achieved** with first two patients dosed at ½ targeted dose in Part A; Part B enrollment **complete**; Part C to follow with concurrent dosing

Updated clinical data targeted for medical congresses in 2023

ViaCyte programs not included

R&D PIPELINE IS BROAD, DIVERSE AND RAPIDLY ADVANCING

Select Preclinical	Phase 1 in Healthy Volunteers	Phase 1/2 in Patients	Pivotal Development	Regulatory Submissions Initiated	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-548** Peripheral neuropathic pain	**Vanzacaftor triple** Cystic Fibrosis	**Exa-cel** TD Beta Thalassemia	symdeko™
DM-1		**VX-864** AATD	**Inaxaplin** AMKD		ORKAMBI®
Huntington's		**VX-264 cells + device** Type 1 diabetes			kalydeco®
ADPKD		**ViaCyte hypoimmune cells** Type 1 diabetes			
Exa-cel Improved conditioning		**VX-522*** CFTR mRNA			
NaV 1.7 Pain					

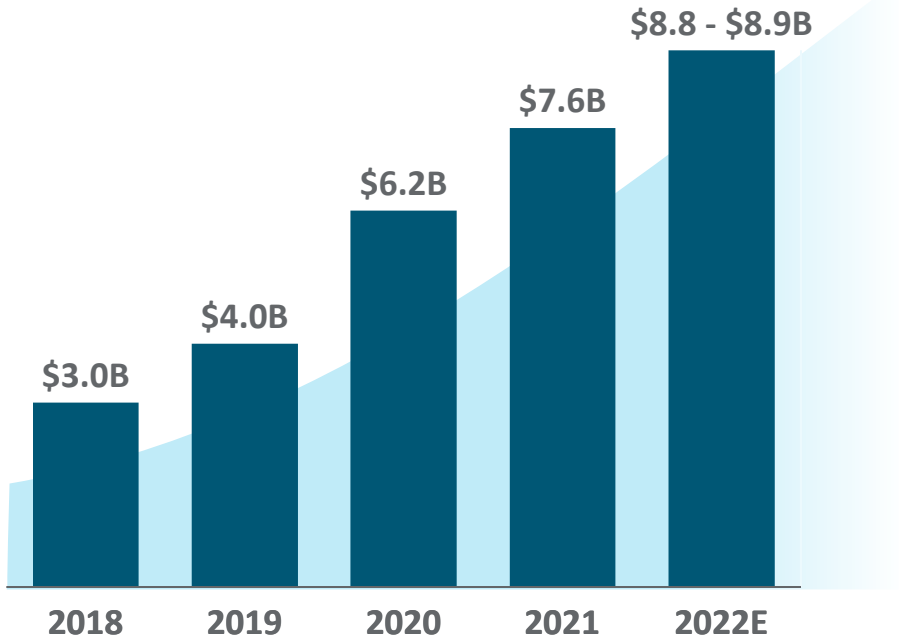
DMD: Duchenne Muscular Dystrophy; DM-1: Myotonic Dystrophy Type 1; ADPKD: Autosomal Dominant Polycystic Kidney Disease; FIH: First In Human
**Phase 1, single ascending dose study in patients with CF*

DIFFERENTIATED BUSINESS MODEL DRIVES GROWTH, INVESTMENT IN INNOVATION AND ATTRACTIVE PROFITABILITY

Strong, sustained CF revenue growth

Significant R&D investment augmented with external innovation

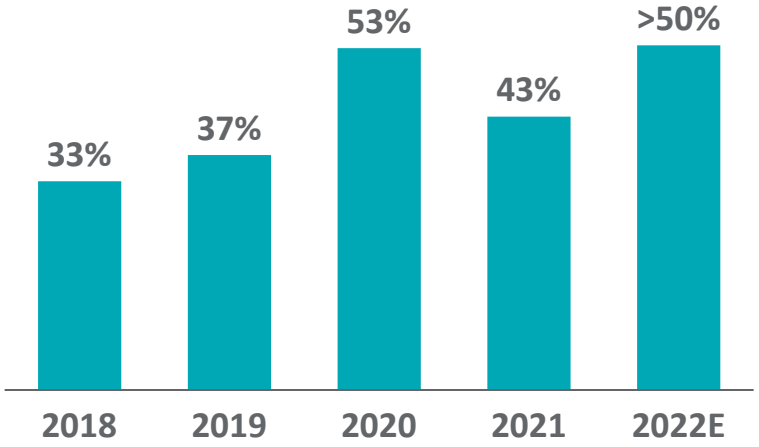
Industry-leading profitability



CF Revenue

moderna™ messenger therapeutics
CRISPR THERAPEUTICS
exonics THERAPEUTICS
verve THERAPEUTICS
VIACYTE
semma THERAPEUTICS
entrada THERAPEUTICS

R&D + Acquired IPR&D ⇨ **≥70%** of OpEx



Non-GAAP Operating Margin

Note: 2019 CF revenues are non-GAAP; See appendix for reconciliations of GAAP to non-GAAP 2019 CF revenues and GAAP to non-GAAP 2018-2022E Operating Margin; 2022E CF revenue reflects the product revenue guidance provided on 10/27/22; 2022E non-GAAP operating margin reflects the midpoint of the product revenue and combined non-GAAP R&D, AIPR&D & SG&A expense guidance ranges provided on 10/27/22 and an estimate of 12% for cost of sales based on Vertex's non-GAAP cost of sales for the nine months ended Sept. 30, 2022; not intended as a reiteration of guidance.

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 study**
Submitted for regulatory approval of exa-cel in EU and the UK; 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**

DIFFERENTIATED BUSINESS MODEL AND R&D STRATEGY WILL CONTINUE TO DRIVE VALUE FOR PATIENTS AND SHAREHOLDERS

Continue the journey in cystic fibrosis

- 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 launches in new disease areas, starting with exa-cel
- Specialty model and operating expense discipline sustain strong operating margins

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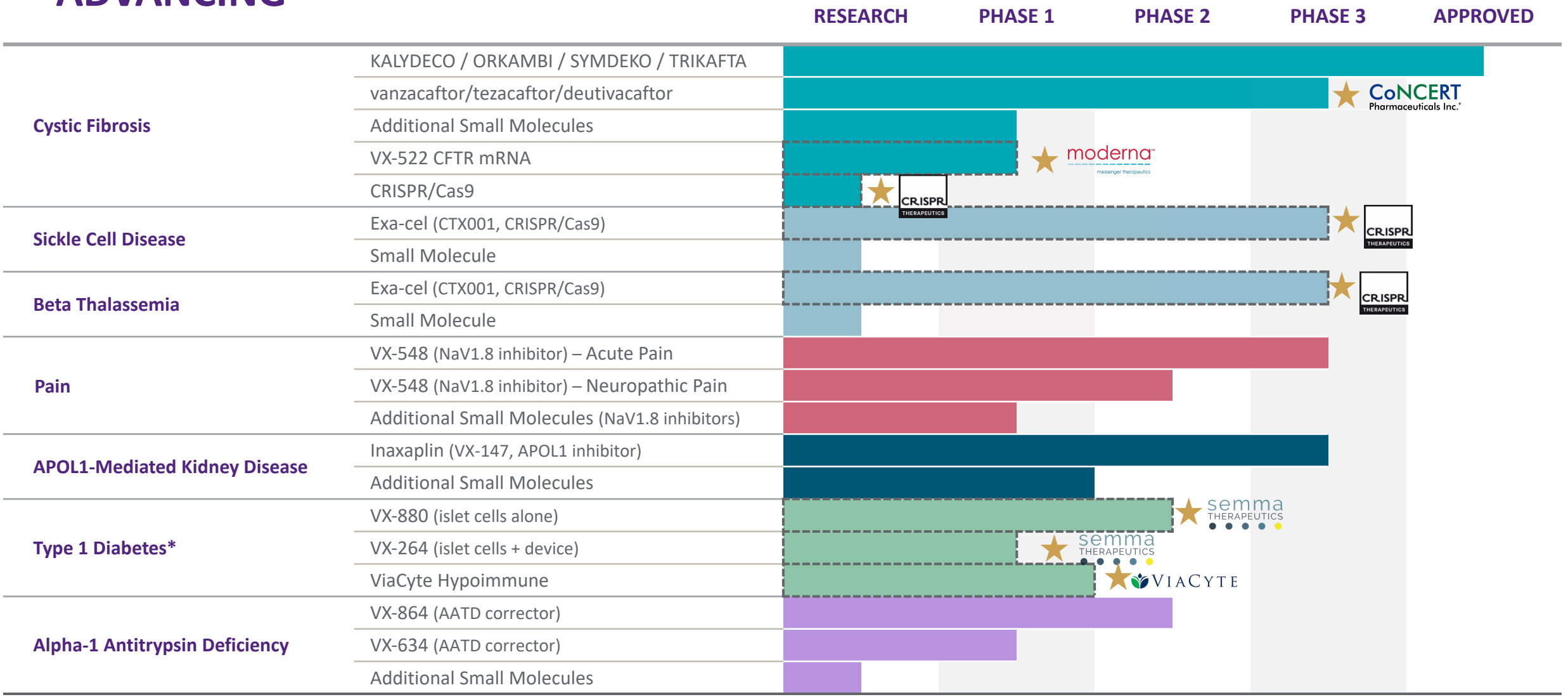
APPENDIX

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

RECONCILIATION OF GAAP TO NON-GAAP FINANCIAL INFORMATION

	2018	2019	2020	2021	Q3'22YTD
GAAP operating income	$635	$1.20B	$2.86B	$2.78B	$3.27B
GAAP operating margin	*21%*	*29%*	*46%*	*37%*	*49%*
Stock compensation expense	325	360	430	441	380
Other adjustments	40	(90)	21	7	(11)
Non-GAAP operating income	1.00B	1.47B	3.31B	3.23B	3.64B
Non-GAAP operating margin	*33%*	*37%*	*53%*	*43%*	*55%*

	2019
GAAP total revenues	$4.16B
ORKAMBI adjustment	(156)
Non-GAAP total revenues	4.01B

All numbers in the above reconciliation tables are in millions except where noted.

Note: Starting in 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. The non-GAAP operating income and corresponding percentages for 2018-2021 above have been recast to reflect this change. "ORKAMBI adjustment" represents a 2019 adjustment to reflect the conclusion of Vertex's early access program for ORKAMBI in France. Prior to 2019, Vertex had only recognized a portion of net product revenues related to ORKAMBI distributed through the early access program in France. As a result, Vertex recognized an adjustment to increase net product revenues, which related to prior period shipments of ORKAMBI distributed through the early access program in France. Vertex removed this amount from its 2019 non-GAAP product revenues.