VERTEX

THE SCIENCE *of* POSSIBILITY

J.P. MORGAN HEALTHCARE CONFERENCE

RESHMA KEWALRAMANI, M.D.

CEO AND PRESIDENT

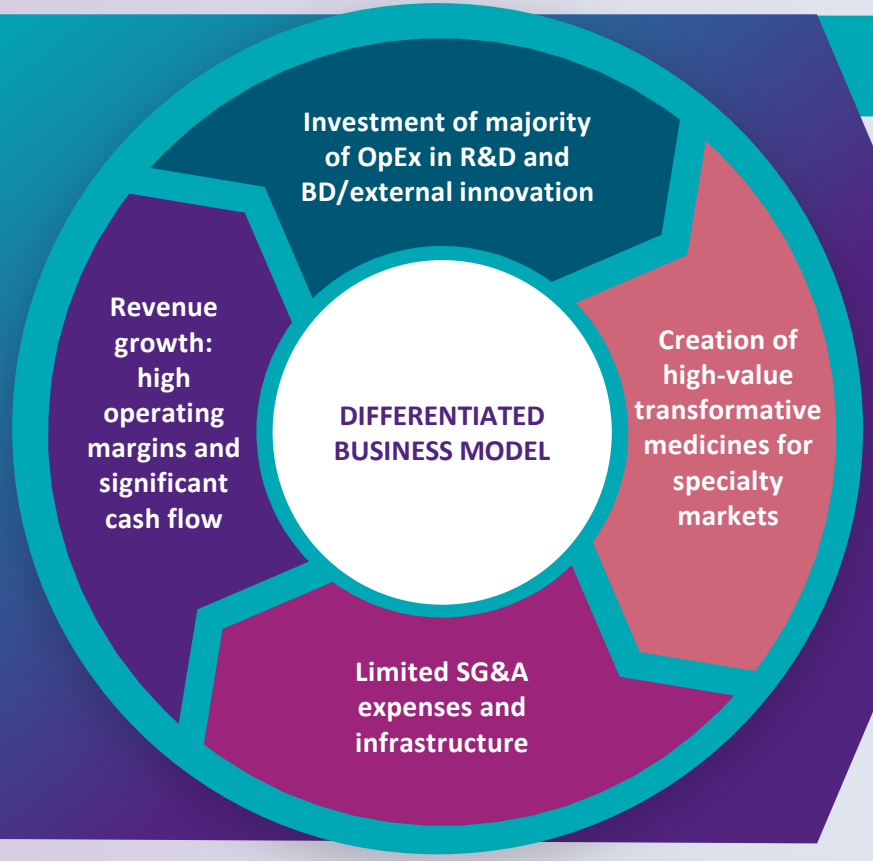
JANUARY 2024

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 and expectations for future financial and operating performance and statements regarding (i) expectations, development plans and timelines for the company's medicines and pipeline programs, including anticipated 10 disease areas in clinical development in 2024, expectations for five potential launches in five years, anticipated near-term commercial opportunities in TDT, CF and acute pain, anticipated benefits of new products and relevant patient populations, and plans to broaden and deepen R&D pipeline across modalities, (ii) plans to launch CF medicines in younger age groups globally and to bring additional molecules to market to get CF patients to carrier levels of SwCl, (iii) plans to advance VX-522 to reach the >5,000 CF patients who cannot benefit from a CFTR modulator, (iv) expectations for CASGEVY, including the potential benefits for patients with SCD and TDT, expectations for broad access in the US, expectations for ex-US access initially through Early Access Programs and efforts for long-term reimbursement agreements, plans to obtain approvals in additional geographies, and plans to complete dosing in younger age groups, (v) expectations for our pain program, including plans for near-term launch and commercial potential in acute pain, expectation for treatment of acute pain without side effects of addictive properties of opioids, plans to share data from the acute pain pivotal program and submit regulatory filings, plans to advance VX-993 into Phase 2 for acute pain and to initiate Phase 1 for VX-993 intravenous formulation, plans to engage in meetings with regulators with goal of broad PNP label, advance VX-548 in DPN into pivotal development in 2024, and to enroll and dose VX-548 Phase 2 study in LSR, and plans to advance NaV 1.7 and NaV1.8 inhibitors, (vi) expectations for our T1D program, including plans for VX-880 and VX-264 studies, (vii) expectations for vanzacaftor triple combination therapy, including our plan share Phase 3 data in early 2024, (viii) expectations for inaxaplin, including dose selection and movement into Phase 3 in Q1 2024, expectations for accelerated approval in US, and potential commercial opportunity, (ix) expectations for our ability to reinvest in our pipeline, (ix) expectations for our DM1 program, and (x) plans to file an IND and CTA for VX-407 and initiate first in human trial. 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 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 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



WE FOCUS ON

- Diseases where causal human biology is known
- Validated targets
- Biomarkers that translate from bench to bedside
- Best modality (i.e., modality agnostic)
- Efficient development & regulatory pathways

IN ORDER TO DELIVER

- Transformative medicines for patients
- Greater likelihood of clinical success
- Sustained innovation
- Shareholder value

EXPANDING LEADERSHIP IN CF AND ENTERING A NEW ERA OF DIVERSIFICATION IN MULTIPLE SERIOUS DISEASES

Approved medicines
across CF, sickle cell disease and beta thalassemia

kalydeco®
ORKAMBI®
symdeko™
trikafta™
casgevy™ (exagamglogene autotemcel)

Multiple near-term commercial opportunities*

- CASGEVY™ (TDT – U.S.; SCD and TDT – EU, KSA)
- Vanzacaftor triple (CF)
- VX-548 (acute pain)

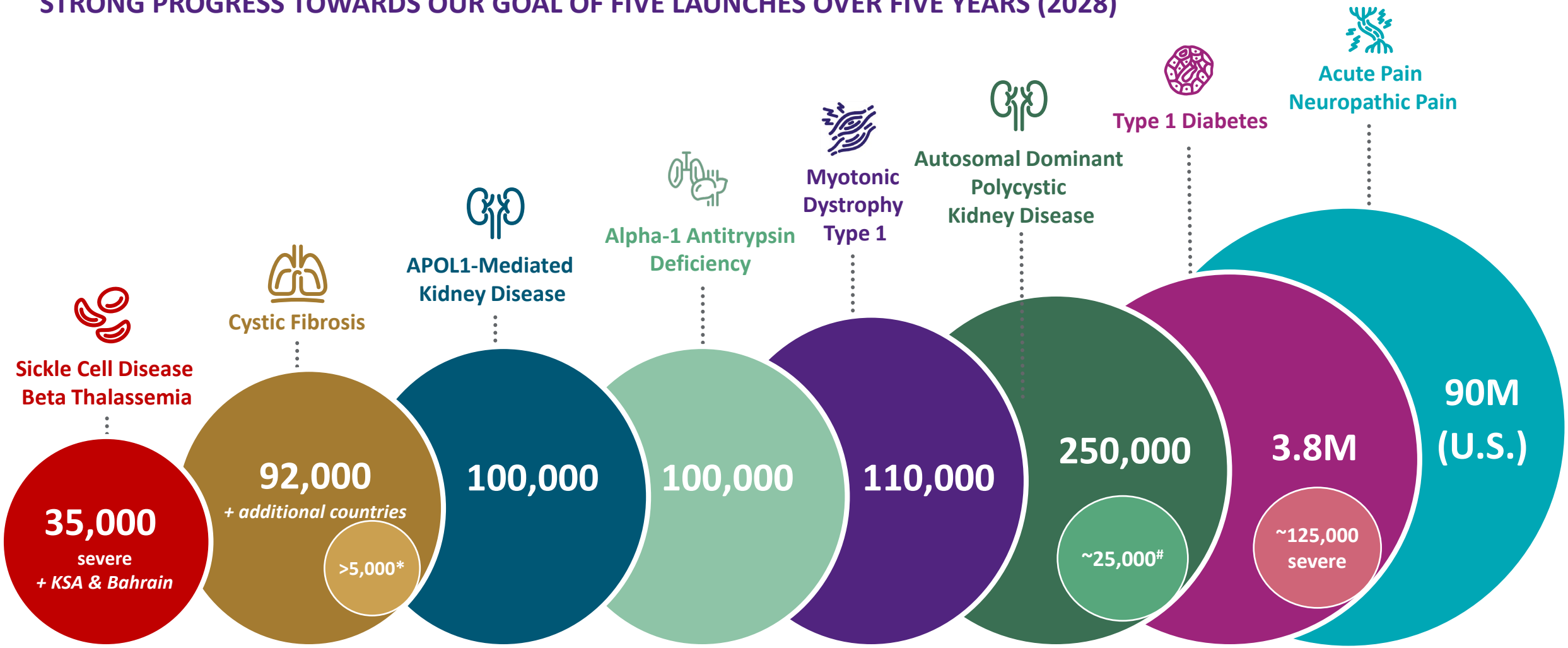
Broad, diversified pipeline in clinical development

- Inaxaplin (AMKD)
- VX-548 (DPN)
- VX-548 (LSR)
- VX-880 (T1D)
- VX-264 (T1D)
- VX-522 (CF - mRNA)
- VX-670 (DM1)

TDT: transfusion-dependent beta thalassemia; AMKD: APOL1-mediated kidney disease; T1D: type 1 diabetes; DPN: diabetic peripheral neuropathy; LSR: lumbosacral radiculopathy; DM1: myotonic-dystrophy type 1
*Subject to regulatory approval

IN 2024, WE ANTICIPATE 10 DISEASE AREAS IN CLINICAL DEVELOPMENT

STRONG PROGRESS TOWARDS OUR GOAL OF FIVE LAUNCHES OVER FIVE YEARS (2028)



Images not to scale; Illustrative purposes. Patient populations include U.S., Europe, and select geographies.
*Over 5,000 people with CF cannot benefit from CFTR modulators and thus may potentially benefit from VX-522, our mRNA program.
#Select PKD1 mutations.

EXPANDING LEADERSHIP IN CF AND RAISING THE BAR WITH SERIAL INNOVATION

~92,000
patients with CF*

~20,000
eligible patients not on CFTR modulators

DURABLE GROWTH DRIVERS

- ✓ Treating younger patients
- ✓ Patients living longer
- ✓ Serial CFTRm innovation
- ✓ mRNA for last >5,000 patients

Cystic Fibrosis Approvals

kalydeco® symdeko™ ORKAMBI® trikafta™

Vanzacaftor triple

- Next-in-class CFTR modulator with potential for improved benefit
- Convenient, once-daily dosing
- Meaningfully lower royalty burden
- Phase 3 studies completed; results in early 2024

VX-522 mRNA

- For CF patients who cannot benefit from CFTR modulators
- Completed dosing SAD and initiated MAD portion of study in people with CF

Best-in-class medicines

Goal: carrier levels of CFTR function

*Patient populations include North America, Europe, and Australia.

CASGEVY (EXA-CEL): NEW ERA OF DIVERSIFICATION WITH LAUNCHES IN TWO DISEASES OUTSIDE CF

casgevy™
(exagamglogene autotemcel)

The first precise, durable, CRISPR/Cas9 gene-edited therapy, delivering a potential one-time functional cure for patients with SCD and TDT.

Rapid pace of global approvals:

- By the **FDA** for eligible patients ages 12+ with sickle cell disease
- By the **MHRA** and **BFDA** for eligible patients ages 12+ with sickle cell disease or transfusion-dependent beta thalassemia

MHRA: Medicines and Healthcare Products Regulatory Agency (Great Britain); BFDA: Bahrain FDA
CRISPR/Cas9 precisely targets the erythroid-specific enhancer region of the BC11A gene.

CASGEVY REPRESENTS A POTENTIAL MULTI-$B OPPORTUNITY FOR VERTEX

FOUNDATIONAL YEAR IN 2024

Patients

~35,000

Severe patients in U.S., Europe
+ additional in KSA, Bahrain

~25%

of surveyed SCD and TDT patients strongly believe genetic therapy is right choice for them[1]

Victoria Gray, Sickle Cell Warrior
First SCD patient dosed

Providers

75

ATCs targeted in U.S. and Europe;
9 U.S. and 3 Europe ATCs activated

~75%

of surveyed U.S. providers prefer a gene-edited approach over other gene therapy mechanisms[1]

Payers

U.S.

Anticipate broad access with government and commercial payers

OUS

Anticipate Early Access Programs initially; pursuing long-term reimbursement agreements

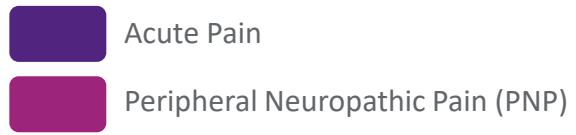
ATC: Authorized Treatment Center

[1]Source: Vertex market research, April-June 2022; patient research is U.S./Europe

VERTEX IS COMMITTED TO TRANSFORMING THE TREATMENT OF PAIN

SERIAL INNOVATION, BROAD/DEEP PIPELINE FOR LEADERSHIP IN MULTIPLE PAIN STATES GIVEN HIGH UNMET NEED

	FORMULATION	RESEARCH	PHASE 1	PHASE 2	PHASE 3	APPROVED
VX-548 NaV1.8 inhibitor* - Acute pain	Oral					
VX-548 NaV1.8 inhibitor - DPN	Oral					
VX-548 NaV1.8 inhibitor - LSR	Oral					
VX-993 NaV1.8 inhibitor	Oral					
VX-973 NaV1.8 inhibitor	Oral					
VX-993 NaV1.8 inhibitor	IV					
Additional NaV1.8 inhibitors	Oral and IV					
NaV1.7 inhibitors	Oral					

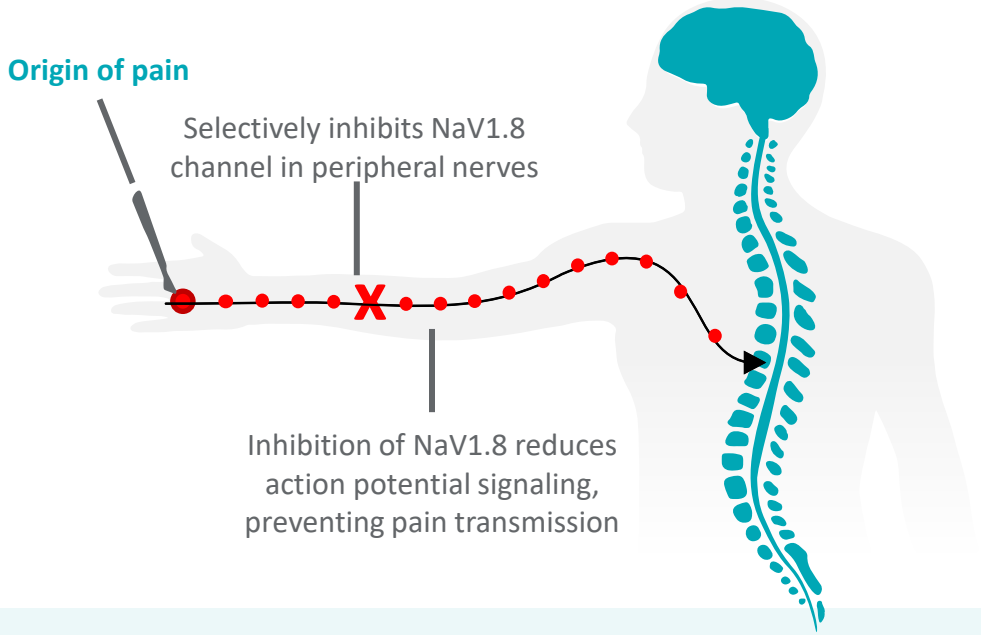


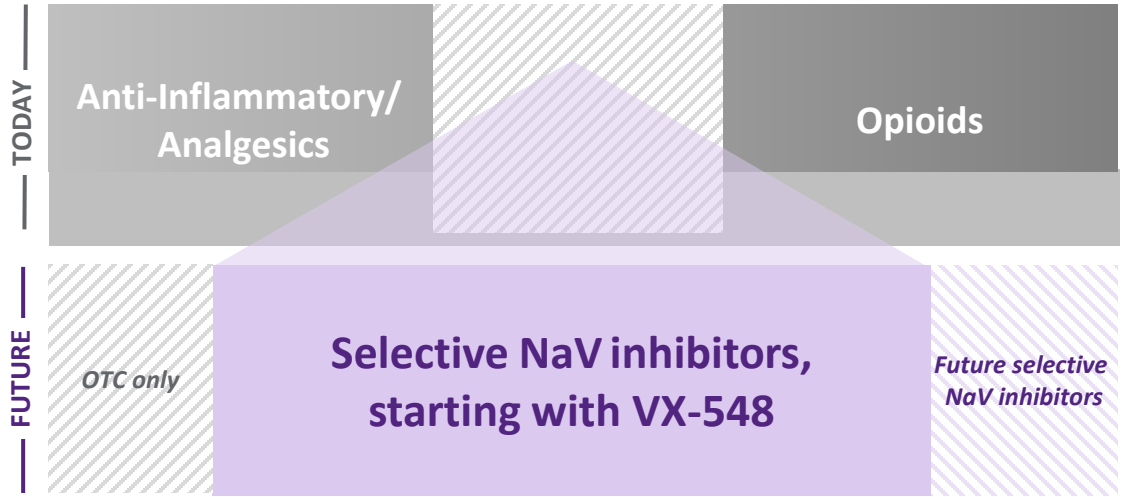
DPN: diabetic peripheral neuropathy; LSR: lumbosacral radiculopathy; IV: intravenous

* Phase 3 program in acute pain has completed; data expected in early 2024.

VX-548 FOR ACUTE PAIN: POTENTIAL FOR EFFECTIVE PAIN RELIEF WITHOUT THE SIDE EFFECTS OR ADDICTIVE PROPERTIES OF OPIOIDS

PIVOTAL PROGRAM COMPLETE; RESULTS EXPECTED EARLY 2024





- NaV1.8 and 1.7 are **validated targets** for pain
- **Phase 3 trials of VX-548** in abdominoplasty, bunionectomy and a single arm safety and effectiveness trial – **all complete**; results early 2024
- **Program targets a broad label** in moderate to severe acute pain

- **Acute pain is a multi-billion-dollar market** today with significant unmet need; 80M patients annually U.S.
- **Existing treatment options have limitations** around efficacy, side effects and addiction potential
- We aim to **transform the treatment of acute pain** with effective and well-tolerated **non-opioid** options

VX-548 FOR PERIPHERAL NEUROPATHIC PAIN: LARGE MARKET WITH HIGH UNMET NEED; 10M PATIENTS ANNUALLY IN U.S.

POSITIVE PHASE 2 RESULTS IN DPN ARE FIRST DEMONSTRATION OF SAFETY & EFFICACY IN THE CHRONIC SETTING

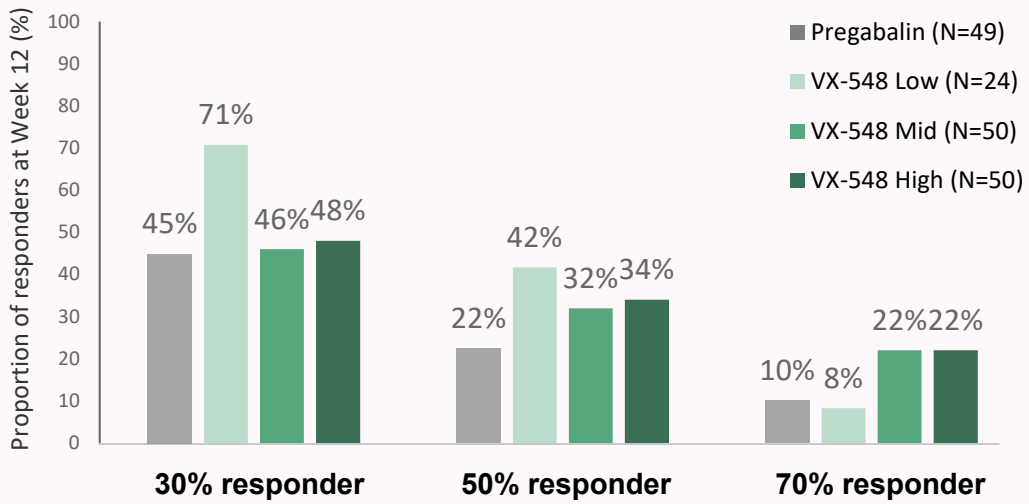
STATISTICALLY SIGNIFICANT AND CLINICALLY MEANINGFUL RESULTS

Primary endpoint

Change from baseline in weekly average NPRS at 12 weeks	Pregabalin 100mg TID N=47	VX-548 Low Dose N=24	VX-548 Mid Dose N=48	VX-548 High Dose N=48
LS Mean (SE)	**-2.09** (0.29)	**-2.18** (0.39)	**-2.11** (0.28)	**-2.26** (0.28)

P value <0.0001 in all arms of the study

HIGH LEVELS OF 30%, 50%, AND 70% PAIN REDUCTION



LS Mean = least square mean, SE = standard error; Low Dose = 23 mg qd, Mid Dose = 46 mg qd, High Dose = 69 mg qd; qd = once a day, TID = three times a day.
The pregabalin arm serves as a reference. Study was not designed or powered for comparisons between the VX-548 arms or between VX-548 and pregabalin.

NEXT STEPS FOR OUR PAIN PROGRAM

Acute Pain

- Share VX-548 Phase 3 trial results in acute pain
- Advance VX-993 into Phase 2 in acute pain – oral formulation
- Initiate VX-993 Phase 1 study in acute pain – intravenous formulation

Peripheral Neuropathic Pain

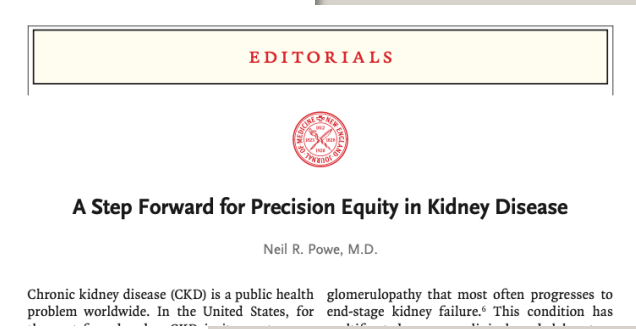
- Engage in VX-548 End-of-Phase 2 meeting with regulators; goal is broad PNP label
- Advance VX-548 into pivotal development in diabetic peripheral neuropathy
- Enroll and dose VX-548 Phase 2 study in lumbosacral radiculopathy
- Advance VX-993 into Phase 2 study for peripheral neuropathic pain

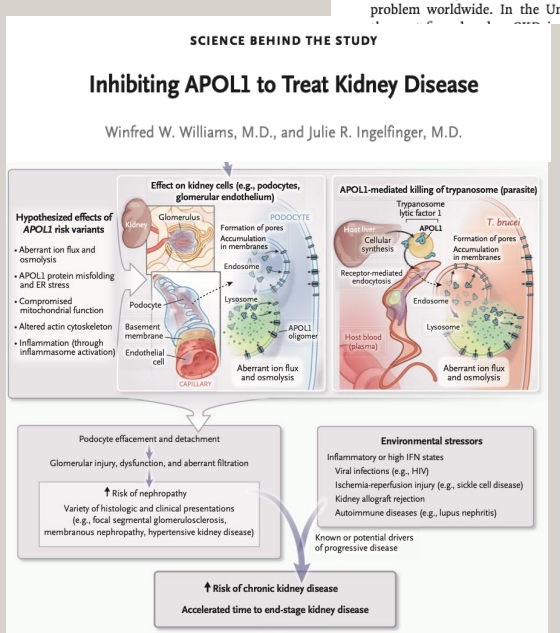
Research

- Advance NaV1.7 inhibitors, alone or in combination
- Advance follow-on NaV1.8 inhibitors

INAXAPLIN: FIRST POTENTIAL MEDICINE TO TARGET THE UNDERLYING CAUSE OF APOL1-MEDIATED KIDNEY DISEASE (AMKD)

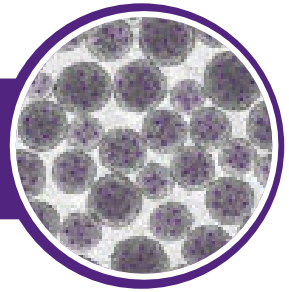
- Enrollment complete in Phase 2B dose-ranging portion of the Phase 2/3 pivotal trial
- Expect to select a dose and begin the Phase 3 portion in Q1:24
- Opening more sites in additional countries for Phase 3
- Pre-planned interim analysis at 48 weeks with potential path to file for accelerated approval in the U.S.
- Final analysis at 2 years of treatment





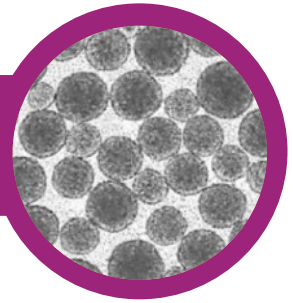
TYPE 1 DIABETES: ADVANCING POTENTIALLY CURATIVE TREATMENTS FOR ~3.8M PATIENTS IN NORTH AMERICA & EUROPE

EDITED, FULLY DIFFERENTIATED, HYPOIMMUNE CELLS



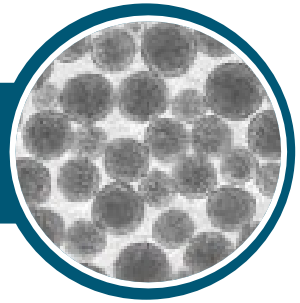
- Same cells as VX-880, edited to eliminate need for immunosuppressants
- Research program continues to progress

VX-264: FULLY DIFFERENTIATED CELLS + DEVICE



- Same cells as VX-880, encapsulated in a device designed to eliminate the need for immunosuppressants
- Phase 1/2 multi-part study ongoing:
  - Part A has been initiated and has enrolled and dosed multiple patients
  - Preparing for Part B

VX-880: FULLY DIFFERENTIATED CELLS WITH STANDARD IMMUNOSUPPRESSION



- Phase 1/2 trial fully enrolled
- *Efficacy*: Remains consistent with EASD results presented Q4:23 and continues to show curative potential
- *Safety*: Consistent with immunosuppressives, perioperative period, and past medical history; two deaths unrelated to VX-880; Vertex has placed the study on protocol-specified pause

CLINICAL PORTFOLIO IS BROAD, DIVERSE AND RAPIDLY ADVANCING

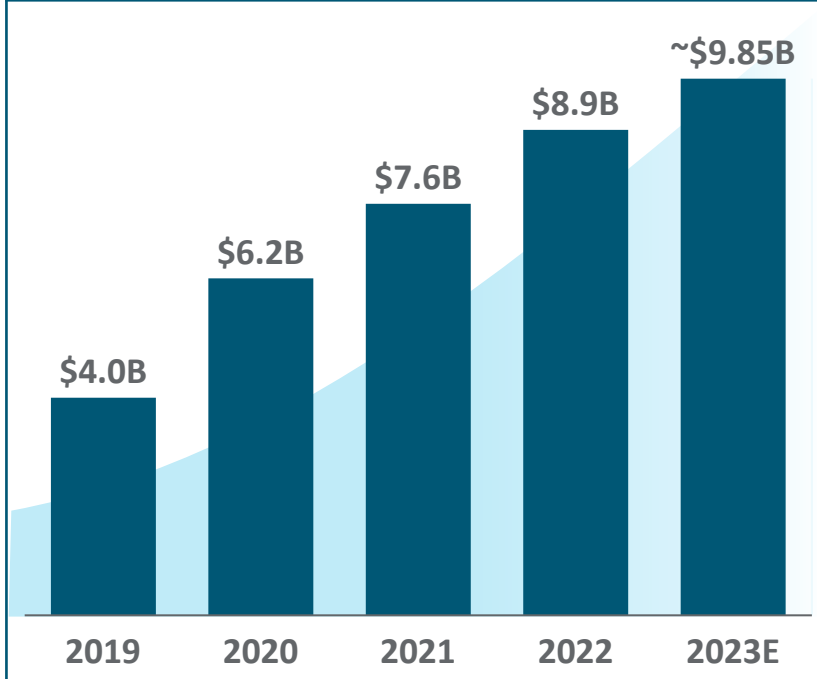
STRONG PROGRESS TOWARDS OUR GOAL OF FIVE LAUNCHES OVER FIVE YEARS (2028)

Select, Next Wave Research-stage Programs	Phase 1 in Healthy Volunteers	Phase (1)/2 in Patients	Pivotal Development	Regulatory Submissions Completed	Approved
Hypoimmune cells Type 1 diabetes	**Follow-on molecules:** • CF • Pain • AMKD • AATD	**VX-880** Type 1 diabetes	**VX-548** Acute Pain	**Exa-cel additional geographies***** SCD & TDT	trikafta™
Small molecule Huntington's		**VX-264 cells + device** Type 1 diabetes	**Vanzacaftor triple** Cystic Fibrosis		symdeko™
Improved conditioning Casgevy – SCD & TDT		**VX-548** Peripheral Neuropathic Pain - DPN	**Inaxaplin** AMKD		ORKAMBI®
NaV1.7 inhibitor Pain		**VX-548** Peripheral Neuropathic Pain - LSR			kalydeco®
VX-407* ADPKD		**VX-522** CFTR mRNA			casgevy™ (exagamglogene autotemcel)
		VX-670** DM1			

ADPKD: autosomal dominant polycystic kidney disease; DM1: myotonic dystrophy type 1; DPN: diabetic peripheral neuropathy; LSR: painful lumbosacral radiculopathy.
*Anticipate first-in-human clinical trial to initiate H1:24 **CTAs cleared in Canada and UK. Trial initiated and enrolling in Canada. On clinical hold in the U.S.
***Under regulatory review in the U.S. for TDT; under regulatory review for SCD and TDT in EU, Switzerland and KSA.

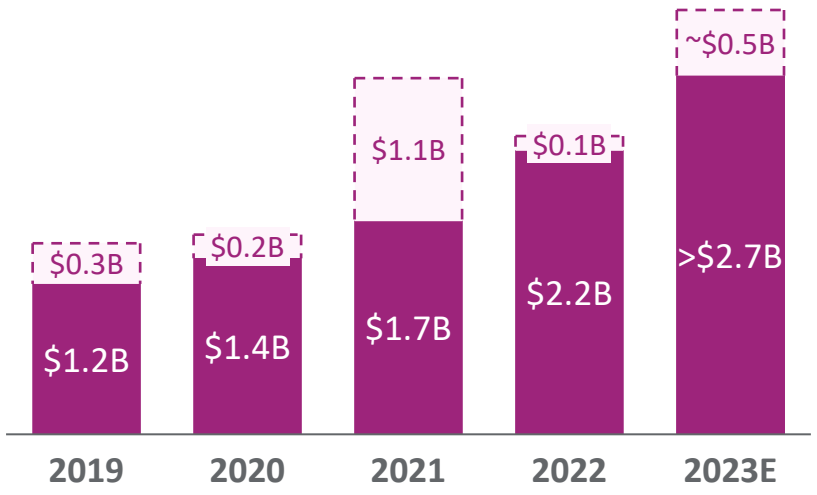
DIFFERENTIATED BUSINESS MODEL DELIVERS PROFITABLE REVENUE GROWTH, FUELING CONTINUED INVESTMENT IN INNOVATION

Strong, sustained **CF revenue growth….**



CF Revenue

….enables significant investment in **internal** and **external innovation**



Non-GAAP R&D | Acquired IPR&D

BD Activity

moderna™ messenger therapeutics
exonics THERAPEUTICS
CRISPR THERAPEUTICS
immunogen
ViaCyte
verve THERAPEUTICS
entrada THERAPEUTICS
semma THERAPEUTICS

Note: 2019 CF revenues are non-GAAP; See appendix for reconciliations of GAAP to non-GAAP 2019 CF revenues and GAAP to non-GAAP 2019-2023E research and development ("R&D") expenses; 2023E CF revenue reflects the product revenue guidance provided on 11/6/23; 2023E non-GAAP R&D and Acquired IPR&D expenses are based on combined non-GAAP R&D, Acquired IPR&D and SG&A expenses guidance provided on 11/6/23; this slide is intended to be illustrative and is not intended to be a reiteration of guidance.

OUR GOAL IS TO CONSISTENTLY DELIVER TRANSFORMATIVE THERAPIES AND SHAREHOLDER VALUE

Expand our leadership and raise the bar in CF

- ❑ Launch in younger age groups globally
- ❑ Bring additional molecules to market to get CF patients to carrier levels of CFTR function
- ❑ Advance VX-522 to reach the >5,000 patients who cannot benefit from a CFTR modulator

Drive era of diversification with multiple commercial launch opportunities

- ❑ Launch CASGEVY; obtain approvals in additional geographies
- ❑ Prepare to file and launch VX-548 in moderate to severe acute pain
- ❑ Complete late-stage clinical development programs in support of five launches in five years (2028) goal

Broaden and deepen R&D pipeline across modalities

- ❑ Advance multiple programs across multiple modalities into pivotal development
- ❑ Achieve proof-of-concept for additional sandbox disease areas
- ❑ Progress next wave of innovation into the clinic, starting with DM1 and ADPKD

Deliver financial performance

- ❑ Continue CF product revenue growth; incremental sales from launches in new disease areas
- ❑ Sustain strong operating margins and continue to invest in pipeline, with focus on specialty model

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APPENDIX

MULTIPLE CATALYSTS THROUGHOUT 2024 AND BEYOND

RECENT HIGHLIGHTS	ANTICIPATED KEY MILESTONES
• **Received approvals for TRIKAFTA in EU, U.K. and Canada** in patients with CF ages 2 to 5 • **Completed vanzacaftor/tezacaftor/deutivacaftor Phase 3** studies (ages 6-11 and 12+) • **VX-522 CFTR mRNA study: completed dosing SAD portion, initiated MAD portion** in CF patients	• **Launch TRIKAFTA/KAFTRIO OUS** in ages 2-5 years • **Share vanza triple Phase 3 data early 2024** • **Complete MAD portion of the VX-522 CFTR mRNA study**
• **Received approval for CASGEVY in U.S. for SCD; in U.K. and Bahrain for TDT and SCD** • **Received CHMP positive recommendation** for exa-cel in SCD and TDT in EU • **Regulatory reviews ongoing** in U.S. for TDT; in KSA and Switzerland for SCD and TDT • **Enrollment completed in global Phase 3 studies** in patients with SCD or TDT **ages 5 to 11**	• **Launch CASGEVY in U.S., U.K., Bahrain** • **Secure additional global regulatory approvals:** • **U.S. (TDT); EU, KSA, Switzerland (SCD and TDT)** • **Complete dosing in younger age group**
• **Completed VX-548 Phase 3 trials in acute pain** • **Reported VX-548 positive Phase 2 PNP results in diabetic peripheral neuropathy (DPN)** • **Initiated VX-548 Phase 2 PNP study in lumbosacral radiculopathy (LSR)** • **Completed VX-993 Phase 1 study (oral); completed IND-enabling studies (IV)**	• **VX-548: share acute pain data early 2024;** prepare for filing, launch • **VX-548: DPN End-of-Phase 2 meeting Q1:24**; initiate pivotal trials • **VX-548: LSR trial – continue enrollment and dosing** • **VX-993: initiate acute pain studies – Phase 2 oral** and **Phase 1 IV** • **VX-993: initiate neuropathic pain studies – Phase 2 oral**
• **Completed enrollment in Phase 2B portion of Phase 2/3 pivotal trial of inaxaplin in AMKD**	• Select dose and **advance to Phase 3 portion** of study in Q1: 24
• **VX-880: Phase 1/2 trial fully enrolled** (Parts A, B, C) for T1D • **VX-264** (the "cells + device" program)**: enrolling and dosing in Phase 1/2 trial**	• **VX-880**: Review Phase 1/2 data, **resume trial when appropriate** • **VX-264: Complete Part A of Phase 1/2 trial**, proceed to Part B
• **CTAs cleared in Canada and U.K. for VX-670 in DM1; study initiated in Canada**	• **Enroll and dose VX-670 study** in DM1 patients in Canada, start U.K. • **Work with FDA to address comments, lift hold, initiate study** in the U.S.
• **Completed IND-enabling studies for VX-407 in ADPKD**	• **File IND and CTA; initiate first-in-human trial**

RECONCILIATION OF GAAP TO NON-GAAP FINANCIAL INFORMATION

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

	2019	2020	2021	2022	Q3'23YTD
GAAP Research and Development ("R&D") Expenses	$1.44B	$1.64B	$1.94B	$2.54B	$2.34B
Stock-based compensation expense	(225)	(263)	(268)	(298)	(232)
Other adjustments	(41)	(10)	(11)	(38)	(9)
Non-GAAP R&D Expenses	1.17B	1.37B	1.66B	2.20B	2.10B

Note: Beginning 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 R&D expenses for 2019-2021 above have been recast to reflect this change.

Non-GAAP R&D expenses for 2023 are based on the nine-months ended September 30, 2023.

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

Note: "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.