VERTEX

THE SCIENCE *of* POSSIBILITY

WILLIAM BLAIR 44TH ANNUAL GROWTH STOCK CONFERENCE

RESHMA KEWALRAMANI, M.D.

CEO AND PRESIDENT

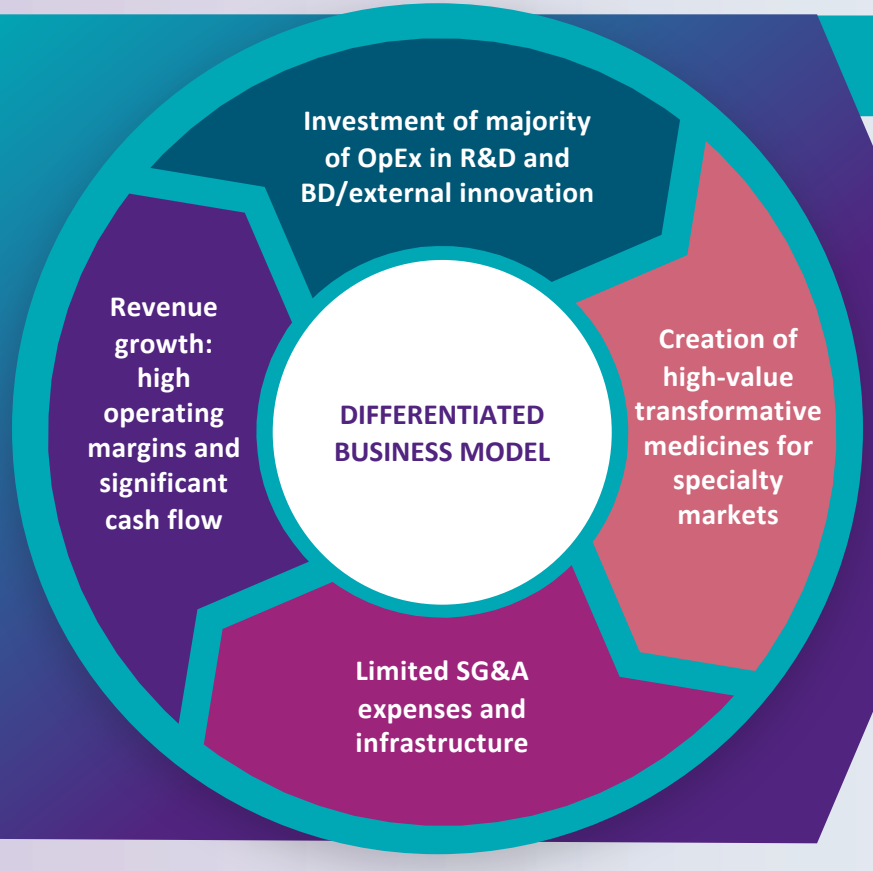
JUNE 4, 2024

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 expectations for five potential launches over five years, anticipated near-term commercial opportunities for the vanzacaftor triple in CF and suzetrigine in acute pain, anticipated benefits of potential 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 CFTR function, (iii) expectations for the vanzacaftor triple, including expectations for a substantially lower royalty burden, (iv) plans to advance VX-522 mRNA to reach the >5,000 CF patients who cannot benefit from CFTR modulators, (v) expectations for CASGEVY, including the potential benefits for patients with SCD or TDT, and plans to obtain approvals in additional geographies, (vi) expectations for our pain program, including plans for near-term launch and commercial potential in acute pain, expectation for treatment of acute pain without non-opioid medicine, expectations related to acute pain regulatory filings and potential for a broad label in acute pain, and our plans and expectations for our VX-993 studies, (vii) expectations for our T1D program, including expectations to complete dosing in the 17-patient trial for VX-880, expectations for the VX-264 studies and plans to share updated data at a conference in June 2024, and (viii) expectations for povetacicept, including expectations for the Phase 3 trial to begin in the second half of 2024, and expectations that povetacicept offers "pipeline-in-a-product" opportunities, and plans to accelerate povetacicept development. 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, regulatory submissions may not be completed on the anticipated timeline, or at all, expected benefits of the Alpine acquisition may not be achieved, 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)

Additional near-term commercial opportunities*

- Vanzacaftor triple (CF)
- Suzetrigine (acute pain)

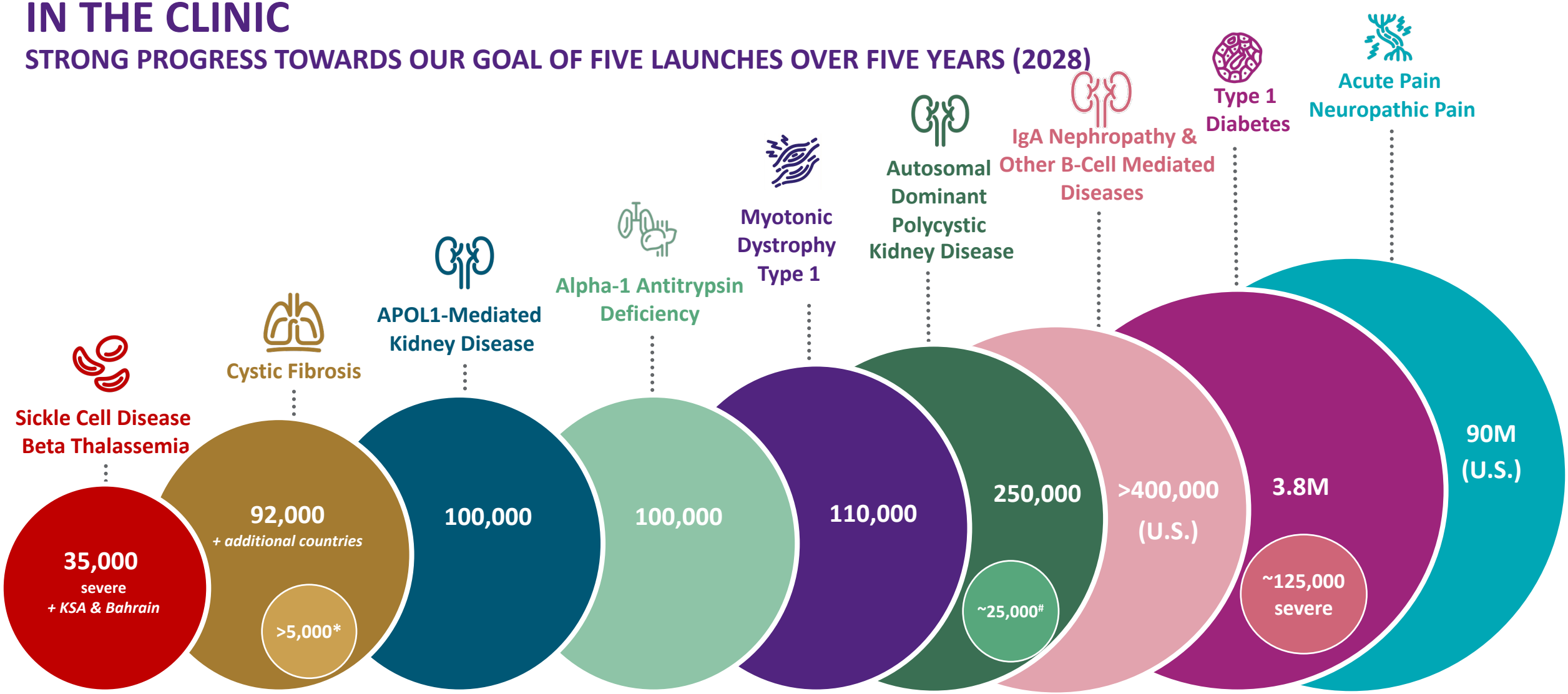
Broad, diversified pipeline in patients in mid- and late- stage clinical development

- Inaxaplin (AMKD)
- Suzetrigine (DPN)
- Povetacicept (IgAN)
- Suzetrigine (LSR)
- VX-880 (T1D)
- VX-264 (T1D)
- VX-522 (CF - mRNA)
- VX-670 (DM1)
- Povetacicept (additional indications)

AMKD: APOL1-mediated kidney disease; T1D: type 1 diabetes; DPN: diabetic peripheral neuropathy; IgAN: IgA nephropathy; LSR: lumbosacral radiculopathy; DM1: myotonic-dystrophy type 1
*Subject to regulatory approval

WE HAVE A BROAD PORTFOLIO OF DISEASE AREAS UNDER EVALUATION IN THE CLINIC

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

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

- Completed regulatory submissions for ages 6+ in the U.S. and the EU
- Non-inferior on lung function, superior on sweat chloride vs. TRI in 12+
- Convenient, once-daily dosing
- Substantially lower royalty burden

VX-522 mRNA

- For the last >5,000 patients who cannot benefit from CFTR modulators

Best-in-class medicines

Goal: carrier levels of CFTR function

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

CASGEVY: BEGINNING OF NEW ERA OF DIVERSIFICATION

casgevy™
(exagamglogene autotemcel)

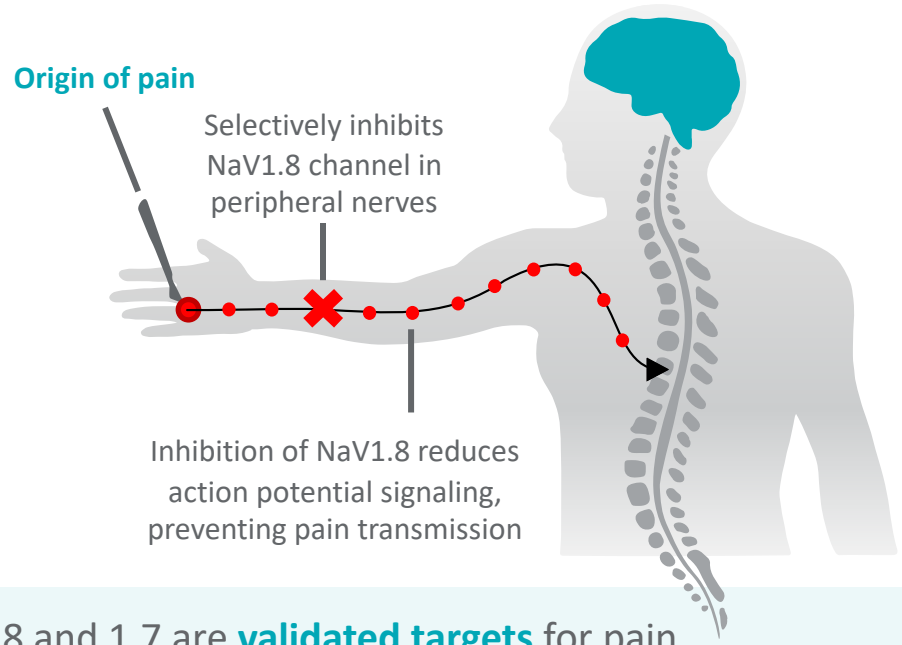
The first precise, durable, CRISPR/Cas9 gene-edited therapy, delivering a potential one-time functional cure for patients with SCD and TDT

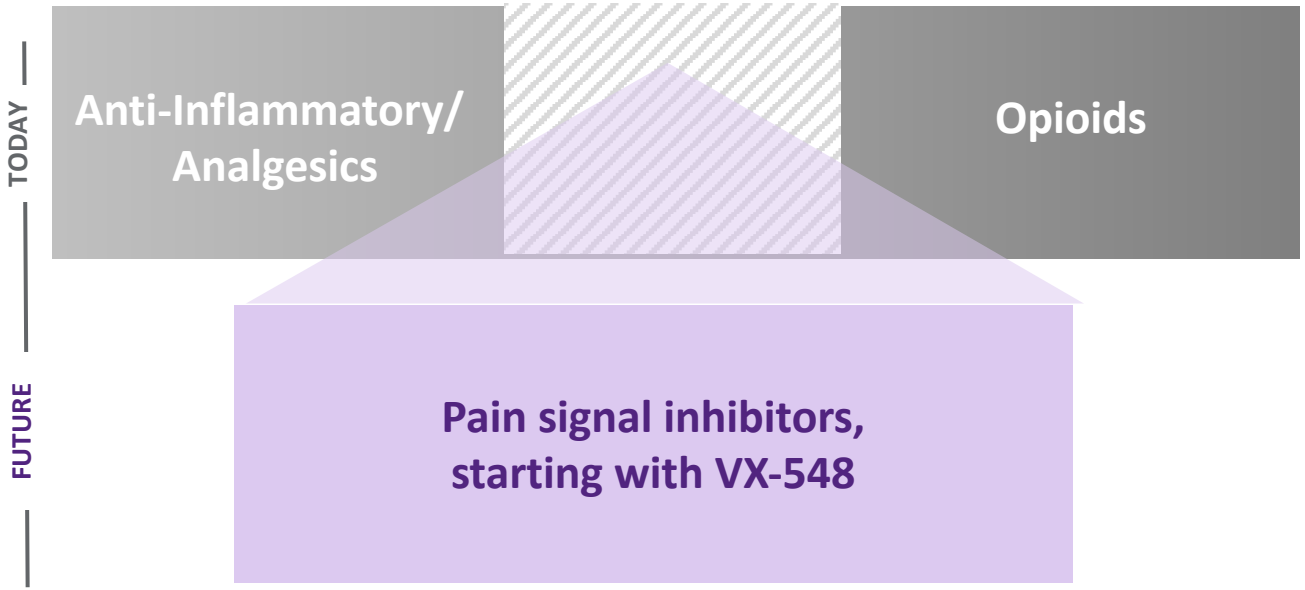
Rapid pace of global approvals:

- Approved for eligible patients ages 12+ with sickle cell disease or transfusion-dependent beta thalassemia by
  - ✓ **U.S.**
  - ✓ **Great Britain**
  - ✓ **European Union**
  - ✓ **Kingdom of Saudi Arabia**
  - ✓ **Kingdom of Bahrain**
- Completed regulatory submissions for CASGEVY in Switzerland and Canada

CRISPR/Cas9 precisely targets the erythroid-specific enhancer region of the BC11A gene.

WE AIM TO TRANSFORM TREATMENT OF ACUTE PAIN WITH SUZETRIGINE, A NON-OPIOID POTENTIAL MEDICINE AND FIRST NEW CLASS OF PAIN MEDICINES IN >2 DECADES



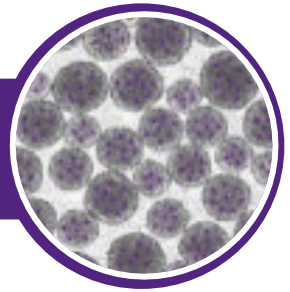


- NaV1.8 and 1.7 are **validated targets** for pain
- Compelling combination of **strong efficacy and safety** in Phase 3 results
- **Rolling NDA submission progressing as planned**; suzetrigine has Fast Track and Breakthrough Therapy designations
- **Seeking a broad label** in moderate to severe acute pain

- **Acute pain is a multi-billion-dollar market** today: 80M patients annually and over 1B calendar days of treatment in the U.S.
- **Significant unmet need:** Existing treatment options have limitations around efficacy, side effects and addiction potential
- High concentration of prescribing, will target with specialty infrastructure and **commercial team build-out well underway**

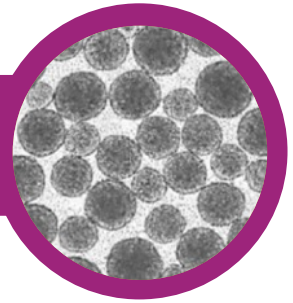
TYPE 1 DIABETES: ADVANCING POTENTIALLY CURATIVE TREATMENTS FOR ~3.8M PATIENTS IN NORTH AMERICA & EUROPE

EDITED, FULLY DIFFERENTIATED, HYPOIMMUNE ISLET CELLS



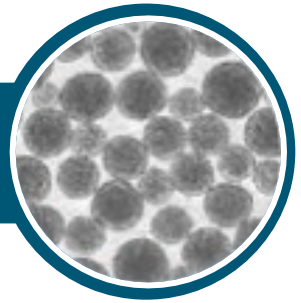
- Same cells as VX-880, edited to eliminate need for immunosuppressants
- **Research program continues to progress**

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 completed
  - **Part B ongoing in multiple countries**

VX-880: FULLY DIFFERENTIATED CELLS WITH STANDARD IMMUNOSUPPRESSION



- **Phase 1/2 trial: 17-patient trial fully enrolled and expect to complete dosing soon**
- Plan to share updated data at American Diabetes Association 84th Scientific Sessions Conference in June 2024

ACQUISITON OF ALPINE IMMUNE SCIENCES:
~$5B CASH

- Compelling fit with the Vertex strategy of investing in serial innovation to create transformative medicines that target serious diseases with high unmet need in specialty markets
- Alpine's lead asset, povetacicept ("pove"), is a Phase 3-ready, innovative, and potentially transformative approach to IgAN, a serious, progressive, autoimmune kidney disease
    - Best-in-class potential; Phase 3 trial to begin H2:24
- Povetacicept, given dual BAFF/APRIL inhibition, also offers promise of "pipeline-in-a-product" in multiple other serious autoimmune renal diseases and cytopenias
- Vertex capabilities will accelerate povetacicept development in IgAN and other indications, while Alpine adds protein engineering and immunotherapy expertise to Vertex

BAFF: B-cell activating factor; APRIL: a proliferation-inducing ligand; IgAN: immunoglobulin A nephropathy; pMN: primary membranous nephropathy; LN: lupus nephritis
Transaction closed on May 20, 2024.

CLINICAL PORTFOLIO IS BROAD, DIVERSE AND RAPIDLY ADVANCING

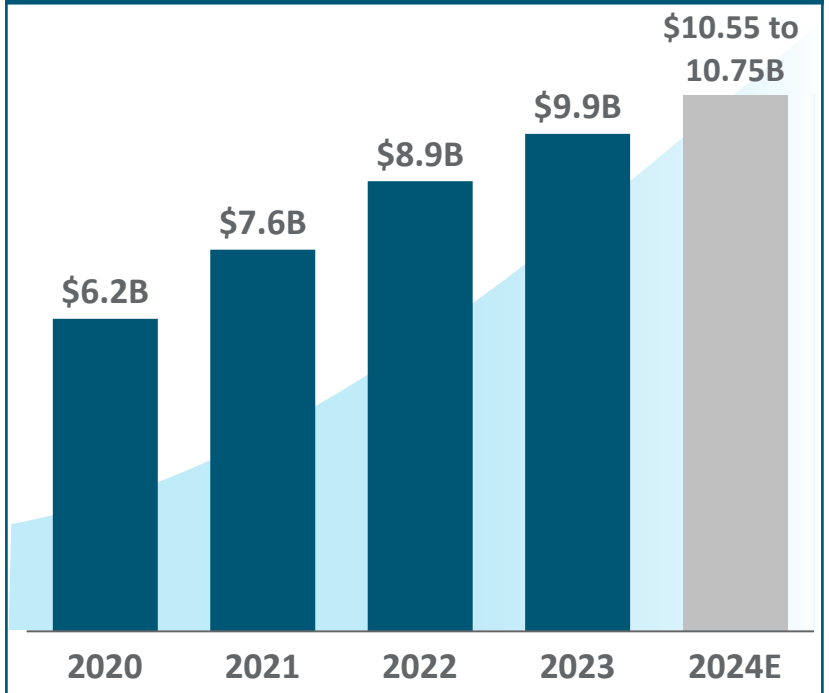
STRONG PROGRESS TOWARDS OUR GOAL OF FIVE LAUNCHES OVER FIVE YEARS (2028)

Select, Next Wave Research-stage Programs	Phase 1 in Healthy Volunteers	Phase (1)/2 in Patients	Pivotal Development Ongoing or ’24 initiation	Regulatory Submissions Completed or Underway	Approved
Hypoimmune islet cells Type 1 diabetes	**Follow-on molecules:** • CF • Pain • AMKD • AATD	**VX-880** Type 1 diabetes	**Inaxaplin** AMKD	**Exa-cel add’l geographies** SCD & TDT	trikafta®
Small molecule Huntington’s	**VX-407** ADPKD	**VX-264 cells + device** Type 1 diabetes	**Suzetrigine** Peripheral Neuropathic Pain - DPN	**Suzetrigine** Acute Pain	symdeko®
Improved conditioning CASGEVY – SCD & TDT	**VX-993** IV	**Suzetrigine** Peripheral Neuropathic Pain - LSR	**Povetacicept** IgA nephropathy	**Vanzacaftor triple** Cystic Fibrosis	ORKAMBI®
NaV1.7 inhibitor Pain		**VX-993** Acute pain (H2:24E start)			kalydeco®
		VX-993 DPN (H2:24E start)			casgevy™ (exagamglogene autotemcel)
		VX-522 CFTR mRNA			
		VX-670 DM1			
		Povetacicept, RUBY3 (pMN, LN, AAV)			
		Povetacicept, RUBY4 (ITP, AIHA, CAD)			

ADPKD: autosomal dominant polycystic kidney disease; DM1: myotonic dystrophy type 1; DPN: diabetic peripheral neuropathy; LSR: painful lumbosacral radiculopathy; pMN: primary membranous nephropathy; LN: lupus nephritis; AAV: ANCA-associated vasculitides; ITP: idiopathic thrombocytopenia; AIHA: warm autoimmune hemolytic anemia; CAD: cold agglutin disease.

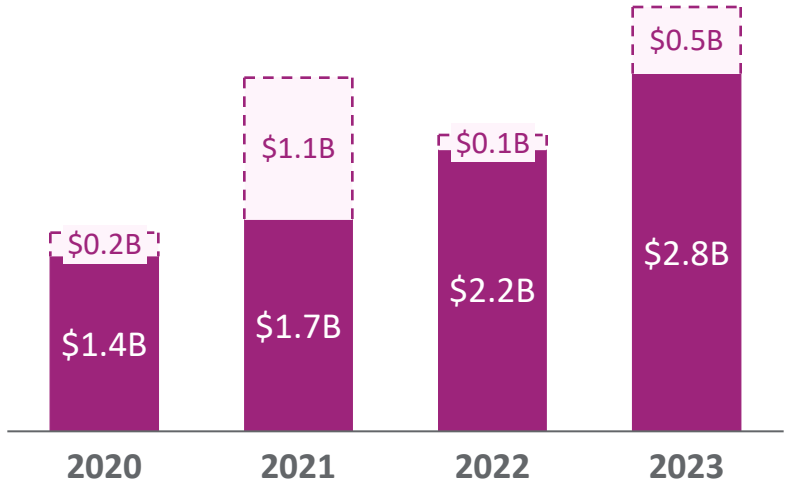
DIFFERENTIATED BUSINESS MODEL DELIVERS PROFITABLE REVENUE GROWTH, FUELING CONTINUED INVESTMENT IN INNOVATION

Strong, sustained **revenue growth….**



Total Revenue

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



Non-GAAP R&D | Acquired IPR&D

Select BD Activity

*Alpine Immune Sciences acquired in 2024.

Note: See appendix for reconciliations of GAAP to non-GAAP 2020-2023 research and development ("R&D") expenses; 2024E total revenue reflects the product revenue guidance provided on 5/6/24; 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
- ❑ File for approval and prepare to launch suzetrigine 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

RECONCILIATION OF GAAP TO NON-GAAP FINANCIAL INFORMATION

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

	2020	2021	2022	2023	2024 YTD*
GAAP Research and Development ("R&D") Expenses	$1.64B	$1.94B	$2.54B	$3.16B	$0.79B
Stock-based compensation expense	(263)	(268)	(298)	(355)	(119)
Other adjustments	(10)	(11)	(38)	(11)	-
Non-GAAP R&D Expenses	1.37B	1.66B	2.20B	2.80B	0.67B

Note: In 2022, Vertex stopped excluding 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 2020-2021 above have been recast to reflect this change.

*Non-GAAP R&D expenses for 2024 are based on the three-months ended March 31, 2024.