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SECOND QUARTER 2024 FINANCIAL RESULTS

AUGUST 1, 2024

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 that are subject to risks, uncertainties and other factors. All statements other than statements of historical fact are statements that could be deemed forward-looking statements, including all statements regarding the intent, belief, or current expectation of Vertex and members of the Vertex senior management team. Forward-looking statements are not purely historical and may be accompanied by words such as “anticipates,” “may,” “forecasts,” “expects,” “intends,” “plans,” “potentially,” “believes,” “seeks,” “estimates,” and other words and terms of similar meaning. Such statements include, without limitation, the information provided regarding and expectations for future financial and operating performance, the section captioned “Raising Full Year 2024 Produce Revenue Guidance,” and statements regarding (i) expectations, development plans and timelines for the company’s products and pipeline programs, including expectations for anticipated near-term commercial launch opportunities, anticipated benefits of new products and relevant patient populations, and plans to broaden, diversify and rapidly advance our R&D pipeline across modalities, (ii) expectations for the vanzacaftor triple, including with respect to the preparations for commercial launch in multiple geographies and a substantially lower royalty burden, (iii) expectations regarding VX-522 to reach the >5,000 CF patients who cannot benefit from a CFTR modulator, VX-522 study progress and plans to have VX-522 data in the first half of 2025, (iv) expectations for our acute pain program, including beliefs regarding the potential benefits of suzetrigine as a non-opioid treatment option and that suzetrigine holds the potential to reshape the treatment of acute pain in the U.S., plans to seek a broad acute pain label, expectations regarding the target profile and treatment settings for suzetrigine, updates on the clinical statuses of the intravenous and oral formulations of VX-993, our expectations and plans for near-term launch and beliefs regarding the commercial potential of suzetrigine, including as multi-billion dollar opportunity, our estimates on the treatable patient population and potential impactful legislation, (v) expectations for our PNP pain program, including plans to seek a broad PNP label, plans to advance suzetrigine in DPN into Phase 3 pivotal development in the third quarter of 2024, status of the Phase 2 study of suzetrigine in LSR and expectations for study results in late 2024, plans to advance an oral formulation of VX-993 into a Phase 2 study in PNP in Q3 2024, and plans to advance additional NaV 1.7 and NaV1.8 inhibitors, (vi) expectations for our T1D program, including beliefs for a potentially curative treatment and the treatable patient population, the potential benefits of VX-880, the status of the global VX-880 study and expectations for VX-880 data, (vii) expectations with respect to the therapeutic scope and potential benefits of povetacicept, including the "pipeline-in-a-product" potential, our beliefs regarding povetacicept’s target patient population, and our beliefs regarding the clinical progress and availability of clinical data for Alpine's pipeline, (viii) expectations regarding our CF program, (ix) expectations for CASGEVY, including potential benefits for patients with SCD or TDT, expectations for ongoing commercial launch, including as a multi-billion dollar opportunity, our estimates on treatable patient population across geographies, expectations with respect to access and reimbursement, expectations for additional regulatory approvals, ATC activations and patient cell collections, and plans for studies in younger age groups. 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 successfully integrate or profit from the Alpine acquisition, the company's regulatory submissions may be delayed, 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. 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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) intangible asset amortization expense, (iii) gains or losses related to the fair value of the company's strategic investments, (iv) increases or decreases in the fair value of contingent consideration, (v) acquisition-related costs, 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 and SG&A expenses and effective tax rate on a non-GAAP basis. The guidance regarding combined Acquired IPR&D 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 2024 press release dated August 1, 2024.

CONTINUED MOMENTUM AND OUTSTANDING EXECUTION ACROSS THE BUSINESS IN Q2

Expand our leadership and raise the bar in CF

- Continue to reach more people living with cystic fibrosis
- **Vanzacaftor triple:** NDA accepted with Priority Review, Jan. 2, 2025 PDUFA
  - MAAs validated in EU and U.K.
- **VX-522:** MAD portion of study underway; for >5K pts who can't benefit from CFTRm

Drive multiple near-term commercial launch opportunities

- **CASGEVY**: Launched in SCD/TDT; more ATCs activated, growth in patient cell collections across all regions
- **Suzetrigine** for moderate to severe acute pain: NDA accepted with Priority Review; Jan. 30, 2025 PDUFA

Advance R&D pipeline

- **Suzetrigine:** DPN Phase 3 study to initiate Q3:24; LSR Phase 2 study completed enrollment, with results expected in late 2024
- **VX-880 (T1D):** Positive updated data at ADA; secured regulatory endorsement to expand enrollment to 37 patients
- **Povetacicept (IgAN):** Phase 3 trial to initiate Q3:24

Deliver financial performance

- Q2:24 product revenue $2.65B; increasing FY product revenue guidance to $10.65 - $10.85B
- Sustain strong operating margins while continuing to invest in pipeline and commercial capabilities for potential new launches
- Closed $5B purchase of Alpine Immune Sciences

MAD: Multiple Ascending Dose; CFTRm = cystic fibrosis transmembrane conductance regulator modulators; SCD: sickle cell disease; TDT: transfusion dependent beta thalassemia; LSR, lumbosacral radiculopathy; T1D, type 1 diabetes; IgAN, IgA nephropathy.

CF: EXPANDING LEADERSHIP & RAISING THE BAR WITH SERIAL INNOVATION

VANZACAFTOR TRIPLE: U.S. PDUFA: JANUARY 2, 2025 AND U.K. & EU REGULATORY SUBMISSIONS VALIDATED

Vanzacaftor Triple

- **Positive Phase 3 results met high expectations:**
  - non-inferior to TRIKAFTA on lung function
  - superior to TRIKAFTA on sweat chloride, a measure of CFTR protein function
- **Convenient**, once-daily dosing
- Substantially **lower royalty burden**
- NDA accepted with **priority review and PDUFA target action date of January 2, 2025**
- MAA submissions **validated in EU and U.K.**

VX-522

- **CFTR mRNA therapy** in development for >5,000 CF patients who cannot benefit from CFTR modulators
- Single ascending dose portion completed and **multiple ascending dose (MAD) portion of the Phase 1/2 study underway**
- **Expect to complete and share results from the study in H1:2025**

NOVEL, EFFECTIVE, NON-OPIOID THERAPIES FOR MODERATE TO SEVERE ACUTE PAIN

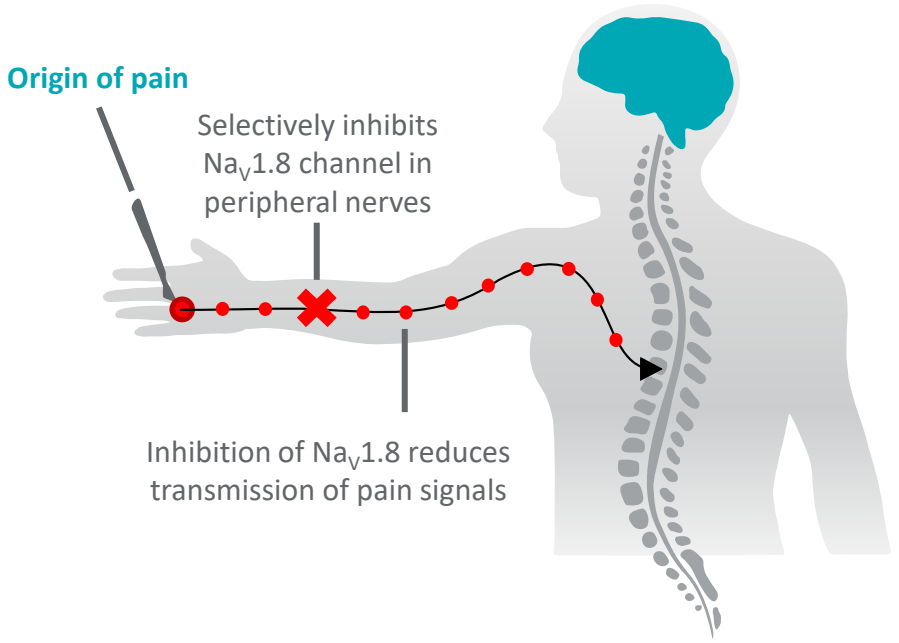
Suzetrigine (VX-548) is an oral, selective Nav1.8 pain signal inhibitor with the potential to treat acute pain types across multiple care settings

- ✓ Compelling combination of strong safety and strong efficacy in Phase 3
- ✓ NDA submission accepted with Priority Review; Jan. 30, 2025 PDUFA

VX-993 is the next generation selective Nav1.8 pain signal inhibitor in the acute pain pipeline

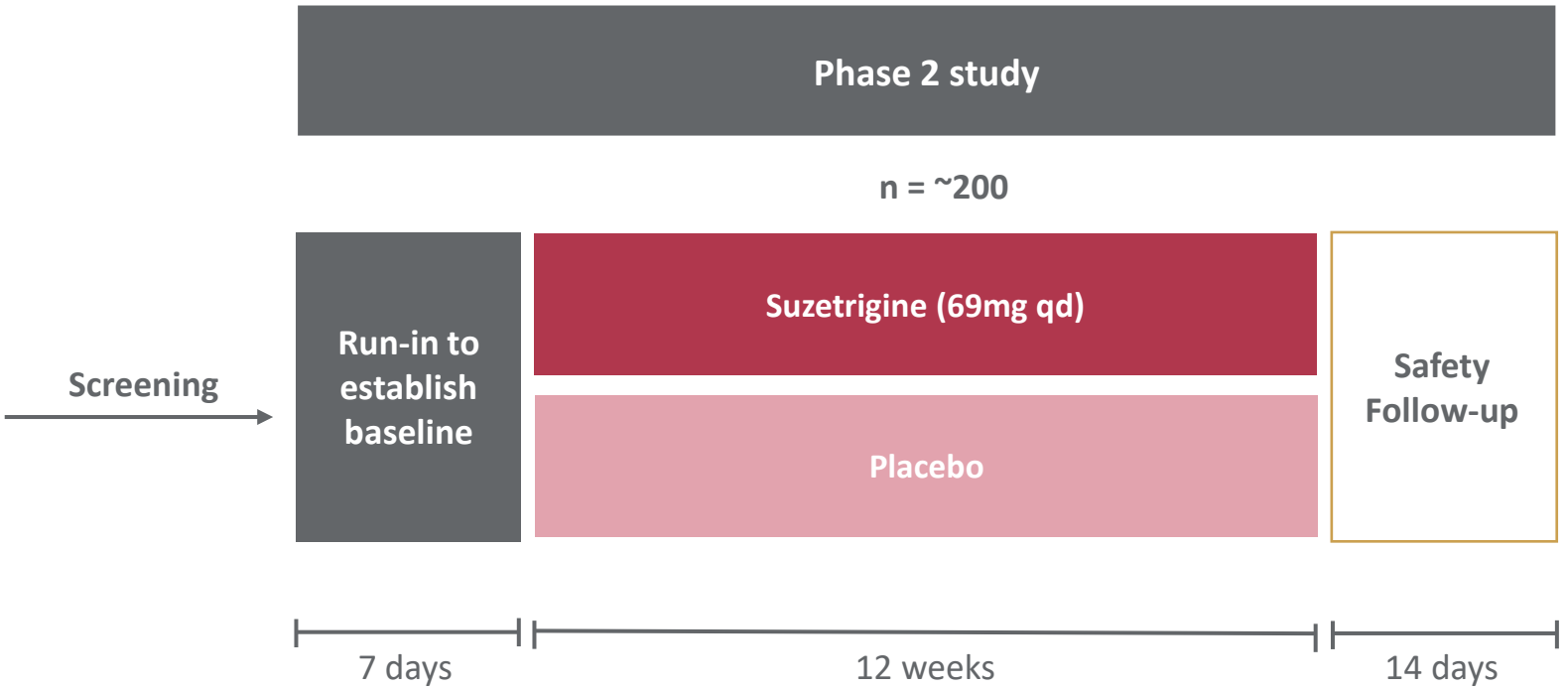
- ✓ Enrolling and dosing patients in Phase 1 trial with IV formulation
- ✓ Initiating Phase 2 study of oral formulation following bunionectomy surgery in Q3:24

First novel mechanism for acute pain in over 20 years



Seeking a broad moderate-to-severe acute pain label for suzetrigine

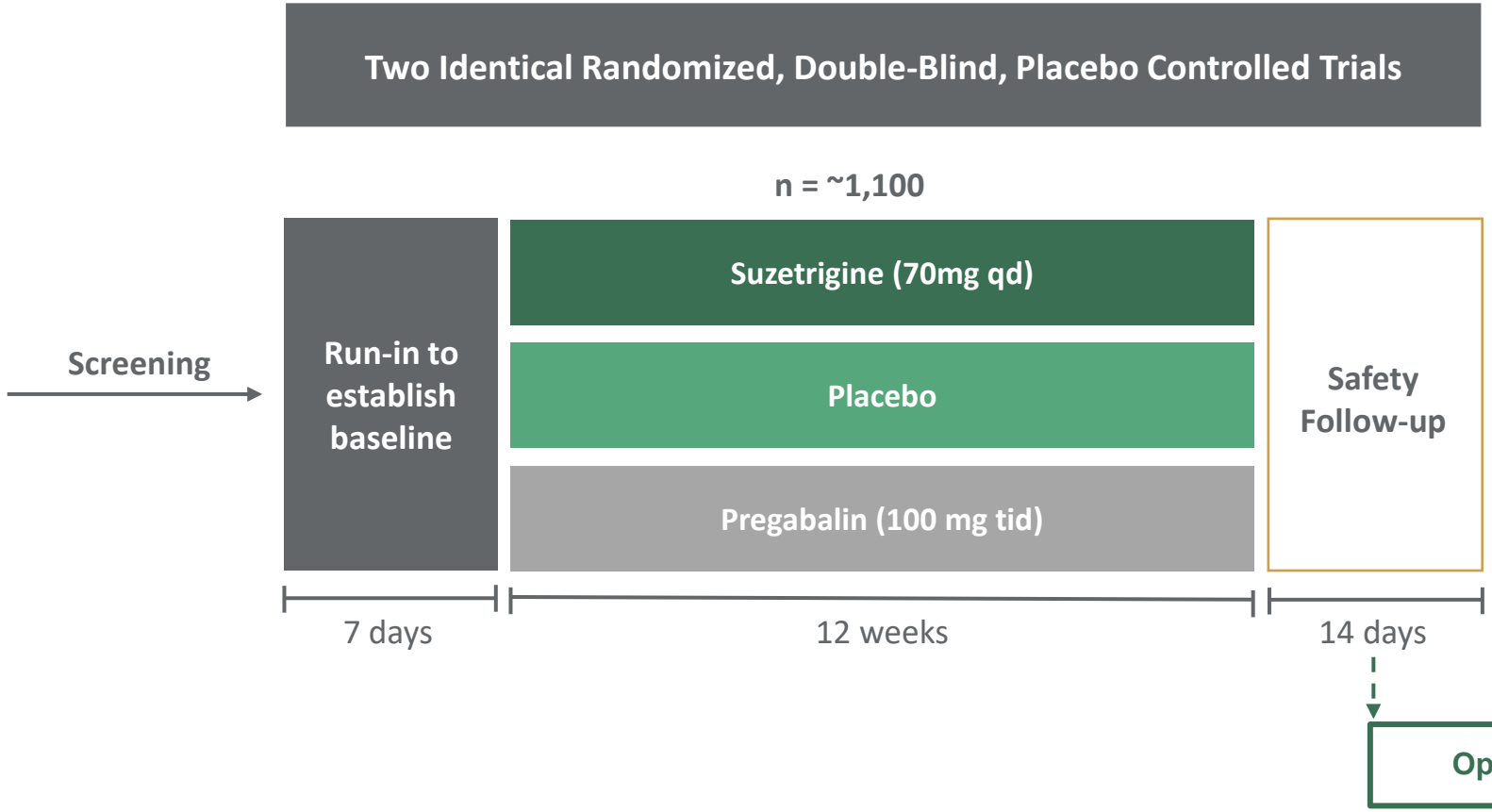
LUMBOSACRAL RADICULOPATHY (LSR): SUZETRIGINE PHASE 2 STUDY COMPLETED ENROLLMENT EARLY AND RESULTS EXPECTED BY END OF YEAR



- **Primary Endpoint**: within-group change from baseline to week 12 in the weekly average of daily leg pain intensity on the NPRS

LSR affects >4 million people in the U.S. with significant unmet need

DIABETIC PERIPHERAL NEUROPATHY (DPN): SUZETRIGINE PHASE 3 PIVOTAL PROGRAM TO BEGIN IN Q3



Efficacy Endpoints

- Based upon change from baseline at week 12:
  - **Primary**: SUZ vs placebo on weekly average of daily pain intensity scores (NPRS)
  - **1st key secondary**: SUZ vs. pregabalin (non-inferiority) on weekly average of daily NPRS
    - If successful, test for superiority

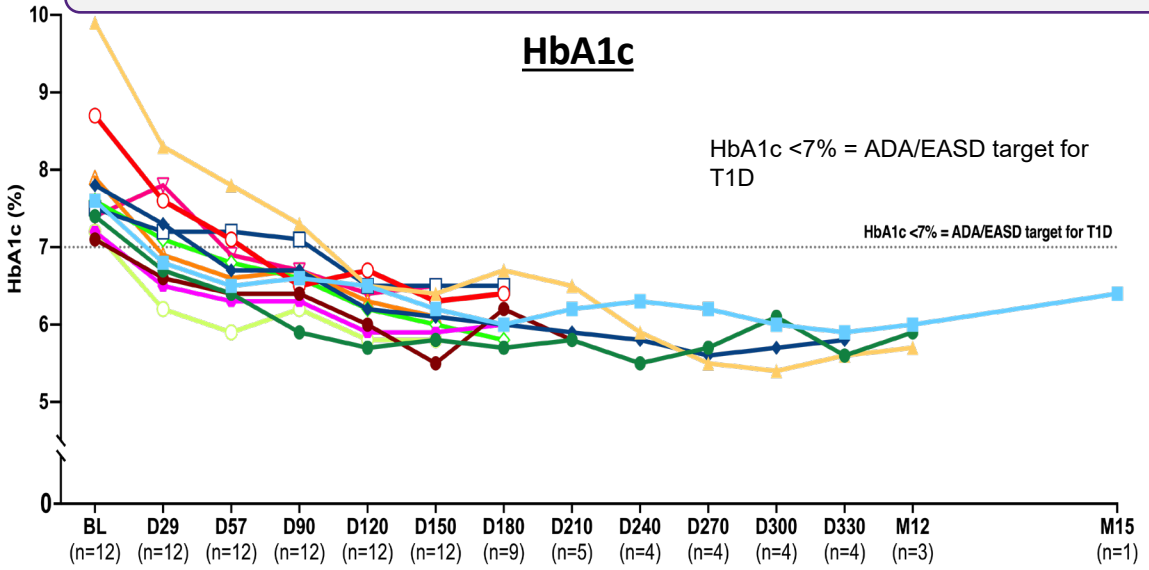
NPRS: numeric pain rating scale.

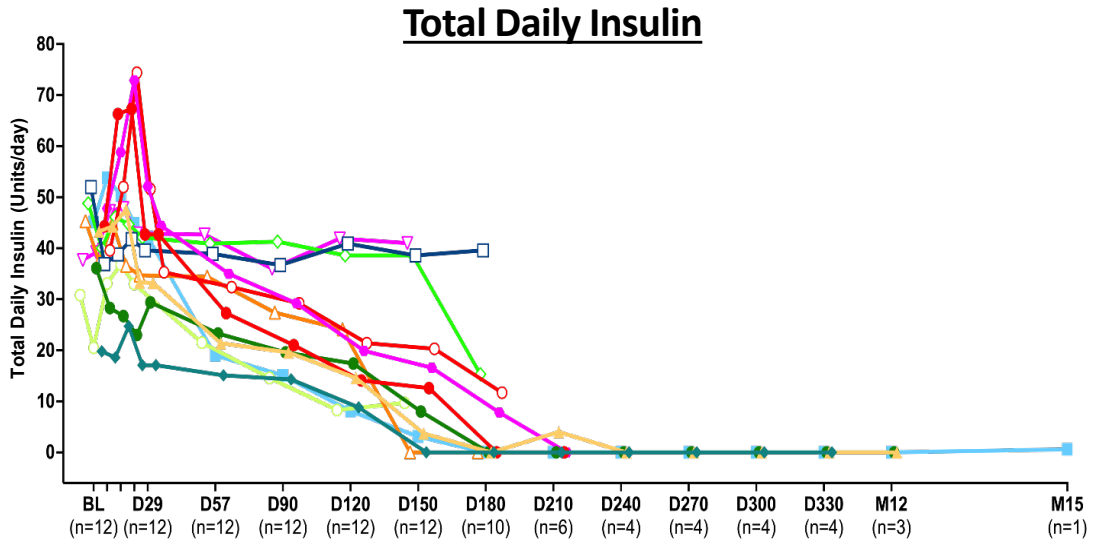
The U.S. FDA granted Breakthrough Therapy Designation to suzetrigine in DPN

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

UPDATED VX-880 PHASE 1/2 TRIAL DATA FROM ADA CONTINUE TO DEMONSTRATE POTENTIAL AS A FUNCTIONAL CURE

- All patients dosed demonstrated **islet cell engraftment and glucose-responsive insulin production**
- All 12 patients who received single, full-dose infusion achieved a **reduction in HbA1c** to <7%
  - All 12 participants had **elimination of severe hypoglycemic events (SHEs)** during the evaluation period (day 90 onward)
  - 11 of 12 patients had **reduction or elimination of exogenous insulin use at most recent visit**
  - All 3 evaluable patients with at least 12 months of follow-up met the primary endpoint of SHE elimination and HbA1c <7% and the secondary endpoint of insulin independence



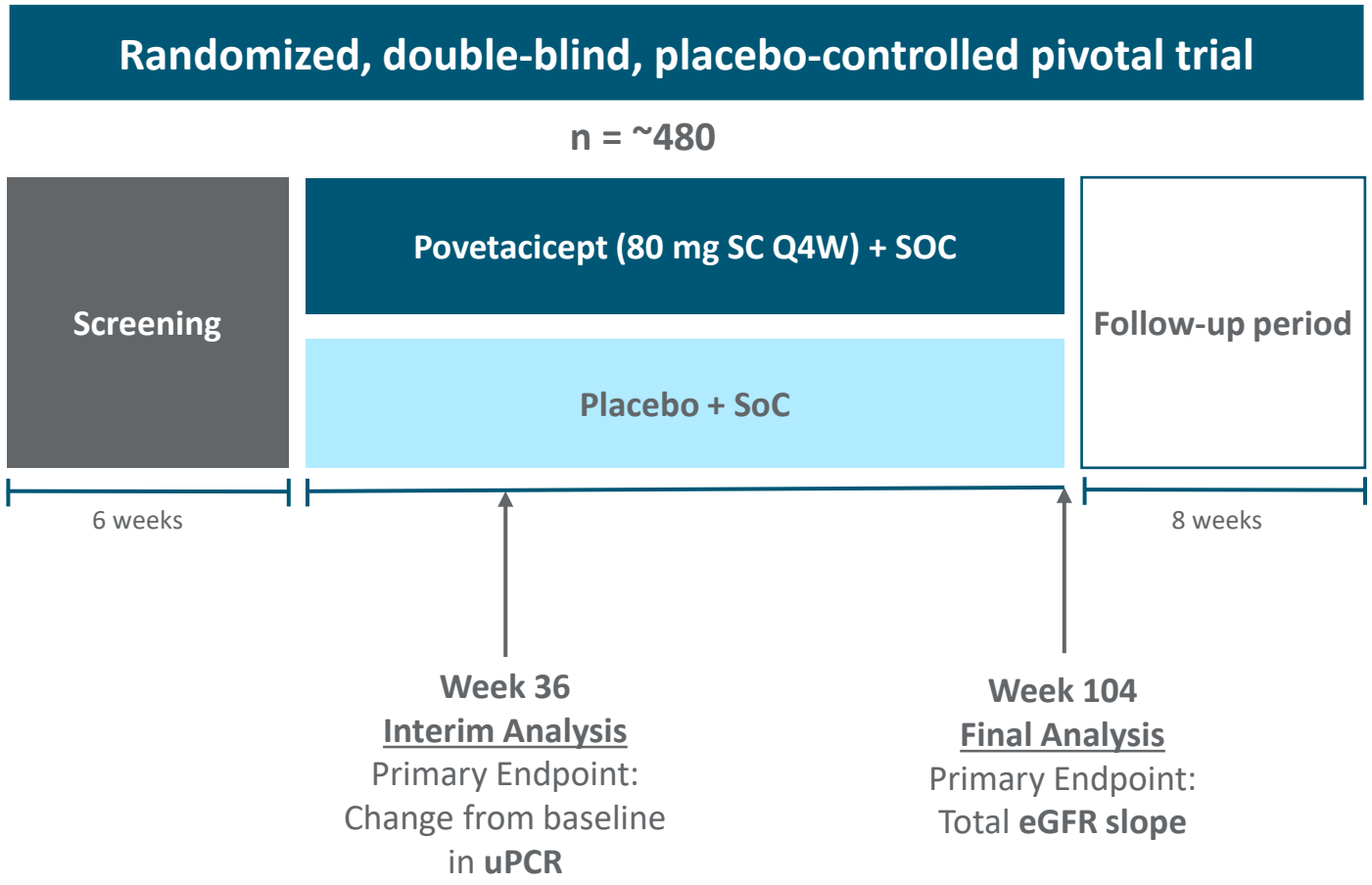


Original 17-patient Phase 1/2 study has completed enrollment and dosing;
Secured regulatory endorsement to expand study to 37 patients

D, day; HbA1c, hemoglobin A1c; M, month; SHEs, severe hypoglycemic events.
Data presented at the 84th American Diabetes Association; June 21-24, 2024.

POVETACICEPT: SUCCESSFUL EOP2 MEETINGS & ON TRACK TO INITIATE GLOBAL PHASE 3 IN IGAN LATER THIS MONTH

SIGNIFICANT UNMET NEED WITH ~130K PATIENTS IN THE U.S. ALONE



- **Best-in-class potential:** Pove is a dual APRIL/BAFF inhibitor; holds promise as a transformative approach for IgA nephropathy (IgAN), a serious, progressive, autoimmune kidney disease
- **A pre-planned interim analysis** will occur when a certain number of patients reach 36 weeks; if positive, potential to file for accelerated approval in the U.S.
- "**Pipeline-in-a-product**" potential with two Phase 2 basket studies ongoing:
  - RUBY-3: autoimmune renal diseases
  - RUBY-4: autoimmune cytopenias

EoP2: End-of-Phase 2; eGFR: estimated glomerular filtration rate; SC: subcutaneous; SOC: standard of care; uPCR: urine protein to creatinine ratio; Q4W, every 4 weeks.

CLINICAL PORTFOLIO IS BROAD, DIVERSE AND RAPIDLY ADVANCING

ON TRACK TO MEET 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 or Underway	Approved
Hypoimmune islet cells Type 1 diabetes	**Follow-on molecules:** • CF • Pain • AMKD	**VX-880** Type 1 diabetes	**Inaxaplin** AMKD	**Exa-cel add'l geographies** SCD & TDT	trikafta®
Small molecule Huntington's		**VX-264 cells + device** Type 1 diabetes	**Suzetrigine** Peripheral Neuropathic Pain - DPN (Q3:24E start)	**Suzetrigine** Acute Pain	symdeko®
Improved conditioning CASGEVY – SCD & TDT	**VX-407** ADPKD	**Suzetrigine** Peripheral Neuropathic Pain - LSR	**Povetacicept** IgA nephropathy (Q3:24E start)	**Vanzacaftor triple** Cystic Fibrosis	ORKAMBI®
NaV1.7 inhibitor Pain	**VX-993** IV	**VX-993** Acute pain (Q3:24E start)			kalydeco®
Small molecule AATD		**VX-993** DPN (Q3:24E 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.

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

- FDA accepted NDA; PDUFA target action date of January 2
- MAAs validated in EU and U.K.; submissions complete in Canada, Australia, Switzerland and New Zealand
- Commercial launch prep rapidly progressing

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 for all patients

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

CASGEVY REPRESENTS A POTENTIAL MULTI-$B OPPORTUNITY FOR VERTEX

STRONG PROGRESS WITH ATC ACTIVATION, PHYSICIAN & PATIENT ENGAGEMENT, AND ACCESS

Patients

~35,000

Severe patients in U.S., Europe

~23,000

Eligible patients in the Kingdom of Saudi Arabia and Bahrain

Victoria Gray, Sickle Cell Warrior
First SCD patient dosed,
now >5 years post-treatment

Providers

>35

ATCs activated; expect to activate ~75 ATCs globally over time

~20

Patients have had cells collected, as of mid-July. Growing number of patients initiating the treatment journey in every region where CASGEVY is approved

Payers

U.S.

Strong payer support across commercial, Medicaid and Medicare segments

OUS

Early Access Program in France for TDT & SCD; reimbursement in Austria, Bahrain, KSA

ATC: Authorized Treatment Center

ACUTE PAIN IS A MULTI-BILLION DOLLAR MARKET, WITH SIGNIFICANT UNMET NEED

- **80M patients** are prescribed a medicine for moderate to severe acute pain every year in the U.S.; **>1B calendar days** of treatment
- **Specialty market due to high concentration of prescribing**
  - **~2/3 of patients** treated in the institutional setting
  - **~50% of prescriptions** originate in the institutional setting
- Focus on **institutions, high volume procedures/conditions, key HCPs**
  - Earliest uptake expected in the **discharge segment**

- **Completed hiring of field team and strategic account leads**
- **Engaging with key decision-makers** across the access landscape
- **Range of initiatives for first year of launch** to support patient access
- **Federal and state legislative tailwinds:**
  - NOPAIN Act add-on payment takes effect Jan. 1, 2025*
  - Alternatives to PAIN Act introduced in both houses of Congress

Suzetrigine holds the potential to fundamentally reshape the treatment of acute pain in the U.S.

*For select medicines approved by CMS.

Q2 2024 FINANCIAL HIGHLIGHTS

($ in millions except where noted or per share data and percentages)	Q2 23	FY 23	Q2 24
Total product revenues	$2.49B	$9.87B	**$2.65B**
TRIKAFTA/KAFTRIO	2.24B	8.94B	**2.45B**
Other CF products	253	925	**196**
Combined non-GAAP R&D and SG&A expenses	928	3.71B	**978**
Acquired IPR&D expenses	111	527	**4.45B**
Non-GAAP operating income	1.15B	4.37B	**(3.15)B**
Non-GAAP operating margin %	46%	44%	**(119)%**
Non-GAAP net income	1.01B	3.97B	**(3.31)B**
Non-GAAP net income per share – diluted	$3.89	$15.23	**$(12.83)**
Cash, cash equivalents & total marketable securities (period-end)	$12.6B	$13.7B	**$10.2B**

Notes: An explanation of non-GAAP financial measures and reconciliation of combined non-GAAP R&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 2024 press release dated August 1, 2024. Non-GAAP financial measures are presented compared to corresponding GAAP measures in the appendix of this presentation.

RAISING FULL YEAR 2024 PRODUCT REVENUE GUIDANCE

	Current FY 2024 Guidance	Previous FY 2024 Guidance	Commentary
Total Product Revenues	$10.65 - $10.85	$10.55 - $10.75B	Includes expectations for continued growth in CF as well as contribution in the second half from the launch of CASGEVY in approved indications and geographies.
Combined GAAP R&D and SG&A Expenses	$5.0 - $5.2B	$4.8 - $5.0B*	Absorbing Alpine SG&A and R&D expenses for the remainder of 2024.
Combined Non-GAAP R&D and SG&A Expenses	Unchanged	$4.2 - $4.3B*	
Acquired IPR&D Expenses	$4.6B	$125 million*	Updated guidance includes the Alpine Acquired IPR&D charge of $4.4 billion in Q2:24.
Non-GAAP Effective Tax Rate	~100%**	20%-21%	Impacted by non-deductible Alpine acquired IPR&D charge, underlying FY 2024 effective tax rate would have remained in a range of 20% - 21%.

*Guidance ranges provided on May 6, 2024 included combined GAAP R&D, Acquired IPR&D and SG&A expenses of $4.9-$5.1 billion and combined Non-GAAP R&D, Acquired IPR&D and SG&A expenses of $4.3-$4.4 billion. Included in both ranges were approximately $125 million for Acquired IPR&D expenses.

**Full year non-GAAP tax rate is impacted by the Alpine Acquired IPR&D expense, which is non-deductible for tax.

MULTIPLE CATALYSTS THROUGHOUT 2024 AND BEYOND

RECENT HIGHLIGHTS	ANTICIPATED KEY MILESTONES
• **KALYDECO received European Commission approval** in infants with CF ages 1 mo to <4 mo • **Vanzacaftor triple: NDA accepted with Priority Review** • VX-522 CFTR mRNA study: SAD completed; MAD underway	• **Continue to reach more eligible patients;** expand into younger age groups • **Vanza triple: Potential FDA approval and launch (Jan. 2, 2025 PDUFA)** • **VX-522: Complete MAD portion** of the study and share data in H1:2025

• **CASGEVY:**
  • Continued **strong launch** progress across all regions
  • **Regulatory reviews ongoing** in Canada (priority review) and Switzerland for SCD and TDT
	• **CASGEVY:**
	  • **Reach more eligible patients across geographies with regulatory approval and access**
	  • **Secure additional global regulatory approvals and reimbursement agreements**

• **Suzetrigine:**
  • **Acute**: NDA accepted with **Priority Review**
  • **DPN: Successful End-of-Phase 2 meeting with FDA** ; preparing for **Phase 3**
  • **LSR: Completed enrollment** ahead of schedule in Phase 2 study
• **VX-993: Acute:** On track to **begin Phase 2 study (oral);** continue to **enroll and dose Phase 1 (IV)**
• **VX-993: DPN:** On track to **begin Phase 2 (oral)**
	• **Suzetrigine:**
	  • **Acute: Potential FDA approval and launch with (Jan. 30, 2025 PDUFA)**
	  • **DPN: Initiate Phase 3 program in Q3:2024**
	  • **LSR: Complete Phase 2 dosing and share results in late 2024**
	• **VX-993: Acute: Initiate Phase 2 study in Q3:24 for acute; complete Phase 1 study for acute pain (IV) / DPN: Initiate Phase 2 study in Q3:24 (oral)**

• **Inaxaplin (AMKD): Enrolling and dosing patients in Phase 3 portion of Phase 2/3 trial** • **VX-407 (ADPKD): Phase 1 clinical trial in healthy volunteers well underway**	• **Inaxaplin: Continue to enroll and dose patients in Phase 3 trial** • **VX-407: Complete Phase 1 study**
• **VX-880 (T1D): Positive data update at ADA; Enrollment and dosing complete in original 17-patient study; secured regulatory endorsement to expand Phase 1/2 trial to 37 patients** • **VX-264: Part A complete. Part B of Phase 1/2 trial underway**	• **VX-880: Enroll and dose additional patients; meet with regulators on pivotal development requirements** • **VX-264: Complete Part B**
• **VX-670 (DM1): Phase 1/2 clinical trial enrolling and dosing DM1 patients in SAD portion of the study**	• **Complete the SAD portion of the study by end of 2024; initiate the MAD portion**
• **Closed Alpine Immune Sciences acquisition** • **Successful EoP2 regulatory meetings for povetacicept in IgAN**	• **Initiate povetacicept Phase 3 trial in IgAN this month (August)** • **Continue to enroll and dose** Phase 2 basket studies in autoimmune renal diseases and cytopenias; **data readouts from some cohorts later in 2024/early 2025**

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AUGUST 1, 2024

APPENDIX

GAAP TO NON-GAAP FINANCIAL INFORMATION

($ in millions except as noted, per share data and percentages)	Q2 23	FY 23	Q2 24
Combined R&D and SG&A			
GAAP	1.05B	4.30B	**1.34B**
Non-GAAP	928	3.71B	**978**
Operating income			
GAAP	1.03B	3.83B	**(3.51)B**
Non-GAAP	1.15B	4.37B	**(3.15)B**
Operating Margin %:			
GAAP	41%	39%	**(133)%**
Non-GAAP	46%	44%	**(119)%**
Net income			
GAAP	916	3.62B	**(3.59)B**
Non-GAAP	1.01B	3.97B	**(3.31)B**
Net income per share - diluted			
GAAP	$3.52	$13.89	**$(13.92)**
Non-GAAP	$3.89	$15.23	**$(12.83)**

Note: An explanation of non-GAAP financial measures and reconciliation of combined non-GAAP R&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 2024 press release dated August 1, 2024.