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/KAFTOR 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 vanzacafor 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

Approved medicines in cystic fibrosis
- Kalydeco
- Orkambi
- Trikafta

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

- Type 1 Diabetes
- Acute Pain
- Neuropathic Pain
- APOL1-Mediated Kidney Disease
- Sickle Cell Disease
- Beta Thalassemia
- Alpha-1 Antitrypsin Deficiency
- Cystic Fibrosis

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.

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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

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

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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

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

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

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

Targeting a broad moderate-to-severe acute pain label

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
Stem cell-derived islets with hypoimmune gene editing
In preclinical development

Stem cell-derived islets with encapsulation
Filed U.S. IND and Canadian CTA

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
R&D PIPELINE IS BROAD, DIVERSE AND RAPIDLY ADVANCING

<table>
<thead>
<tr>
<th>Select Preclinical</th>
<th>Phase 1 in Healthy Volunteers</th>
<th>Phase 1/2 in Patients</th>
<th>Pivotal Development</th>
<th>Regulatory Submissions Initiated</th>
<th>Launched</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertex hypoimmune cells</td>
<td>Follow-on small molecules: • CF • Pain • AMKD • AATD</td>
<td>VX-880 Type 1 Diabetes PoC achieved</td>
<td>VX-548 Acute Pain</td>
<td>Exa-cel Sickle Cell Disease</td>
<td>Exa-cel TD Beta Thalassemia</td>
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<tr>
<td>DMD</td>
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<td>VX-548 Peripheral neuropathic pain</td>
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<td>DM-1</td>
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<td>VX-864 AATD</td>
<td>Vanzacaftor triple Cystic Fibrosis</td>
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<td>Huntington’s</td>
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<td>VX-264 cells + device Type 1 diabetes</td>
<td>Inaxaplin AMKD</td>
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<td>ADPKD</td>
<td>VX-634 AATD</td>
<td>ViaCyte hypoimmune cells Type 1 diabetes</td>
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<tr>
<td>Exa-cel Improved conditioning</td>
<td></td>
<td>VX-522* CFTR mRNA</td>
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<td>NaV 1.7 Pain</td>
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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

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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

2018 2019 2020 2021 2022E

$3.0B $4.0B $6.2B $7.6B $8.8 - $8.9B

R&D + Acquired IPR&D ≥70% of OpEx

Non-GAAP Operating Margin

2018 2019 2020 2021 2022E

33% 37% 53% 43% >50%

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

<table>
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<tr>
<th>Event</th>
<th>Details</th>
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<tbody>
<tr>
<td>Submitted global regulatory filings of TRIKAFTA</td>
<td>in patients with CF ages 2 to 5</td>
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<td>Fully enrolled vanzacaftor/tezacaftor/deutivacaftor Phase 3 studies</td>
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<tr>
<td>IND cleared for VX-522 CFTR mRNA program; SAD study in CF patients initiated</td>
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<tr>
<td>Submitted for regulatory approval of exa-cel</td>
<td>in EU and the UK; rolling submission in the U.S. initiated</td>
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<td>All Phase 3 trials underway for VX-548 in acute pain</td>
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<td>Initiated Phase 2 dose-ranging study of VX-548 in neuropathic pain</td>
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<td>Initiated pivotal development of inaxaplin</td>
<td>in broad AMKD population</td>
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<td>Completed enrollment of Part B for VX-880 in type 1 diabetes</td>
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<td>Cleared CTA in Canada for VX-264, the cells + device program in type 1 diabetes</td>
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<tr>
<td>Initiated Phase 2 trial for VX-864 in patients with AATD and FIH trial for VX-634</td>
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<td>IND-enabling studies ongoing for DMD</td>
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## Anticipated Key Milestones

<table>
<thead>
<tr>
<th>Milestone</th>
<th>Details</th>
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<tr>
<td>Priority Review granted; PDUFA April 28</td>
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<tr>
<td>Complete Phase 3 studies</td>
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<tr>
<td>Complete SAD study</td>
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<td>Complete rolling BLA submission to FDA by Q1:23</td>
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<tr>
<td>Complete Phase 3 trials late 2023/early 2024</td>
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<td>Ramp enrollment in Phase 2 trial</td>
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<tr>
<td>Complete Phase 2B (dose-ranging) portion of Phase 2/3 pivotal study</td>
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<tr>
<td>Initiate Part C (concurrent dosing); present updated clinical data</td>
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<tr>
<td>Initiate Phase 1/2 trial</td>
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<tr>
<td>Ramp enrollment</td>
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<td>File IND</td>
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**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
R&D STRATEGY DESIGNED TO DELIVER SERIAL INNOVATION WITH HIGH PROBABILITY OF SUCCESS; CLINICAL-_STAGE PIPELINE IS BROAD, DEEP AND ADVANCING

<table>
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<tr>
<th>Condition</th>
<th>Research</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Approved</th>
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<tr>
<td>Cystic Fibrosis</td>
<td>KALYDECO / ORKAMBI / SYMDEKO / TRIKAFTA</td>
<td>vanzacaftor/tezacaftor/deutivacaftor</td>
<td>VX-522 CFTR mRNA</td>
<td>CRISPR/Cas9</td>
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<td>Sickle Cell Disease</td>
<td>Exa-cel (CTX001, CRISPR/Cas9)</td>
<td>Small Molecule</td>
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<tr>
<td>Beta Thalassemia</td>
<td>Exa-cel (CTX001, CRISPR/Cas9)</td>
<td>Small Molecule</td>
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<tr>
<td>Pain</td>
<td>VX-548 (NaV1.8 inhibitor) – Acute Pain</td>
<td>VX-548 (NaV1.8 inhibitor) – Neuropathic Pain</td>
<td>Additional Small Molecules (Nav1.8 inhibitors)</td>
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<tr>
<td>APOL1-Mediated Kidney Disease</td>
<td>Inaxaplin (VX-147, APOL1 inhibitor)</td>
<td>Additional Small Molecules</td>
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<tr>
<td>Type 1 Diabetes*</td>
<td>VX-880 (islet cells alone)</td>
<td>VX-264 (islet cells + device)</td>
<td>ViaCyte Hypoimmune</td>
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<tr>
<td>Alpha-1 Antitrypsin Deficiency</td>
<td>VX-864 (AATD corrector)</td>
<td>VX-634 (AATD corrector)</td>
<td>Additional Small Molecules</td>
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<td><img src="https://example.com/viacyte.png" alt="Viacyte" /></td>
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Cell therapy or nucleic acid therapy (mRNA, gene editing)  | Complementary BD
## RECONCILIATION OF GAAP TO NON-GAAP FINANCIAL INFORMATION

<table>
<thead>
<tr>
<th></th>
<th>2018</th>
<th>2019</th>
<th>2020</th>
<th>2021</th>
<th>Q3’22YTD</th>
<th>2019</th>
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<tbody>
<tr>
<td><strong>GAAP operating income</strong></td>
<td>$635</td>
<td>$1.20B</td>
<td>$2.86B</td>
<td>$2.78B</td>
<td>$3.27B</td>
<td>$4.16B</td>
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<tr>
<td><strong>GAAP operating margin</strong></td>
<td>21%</td>
<td>29%</td>
<td>46%</td>
<td>37%</td>
<td>49%</td>
<td>49%</td>
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<tr>
<td>Stock compensation expense</td>
<td>325</td>
<td>360</td>
<td>430</td>
<td>441</td>
<td>380</td>
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<tr>
<td>Other adjustments</td>
<td>40</td>
<td>(90)</td>
<td>21</td>
<td>7</td>
<td>(11)</td>
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<tr>
<td><strong>Non-GAAP operating income</strong></td>
<td>1.00B</td>
<td>1.47B</td>
<td>3.31B</td>
<td>3.23B</td>
<td>3.64B</td>
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<tr>
<td><strong>Non-GAAP operating margin</strong></td>
<td>33%</td>
<td>37%</td>
<td>53%</td>
<td>43%</td>
<td>55%</td>
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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.