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) the expectations, development plans and timelines for the company’s medicines, drug candidates and pipeline programs, including expectations for program stage, patient enrollment and dosing, and available data, (ii) expectations for successfully advancing our pipeline and approved products beyond CF, (iii) anticipated regulatory filings and data submissions, including with respect to CTX001, (iv) anticipated regulatory approvals, including with respect to CTX001, and future label expansions, (v) expectations for expanded access to and uptake of the company’s medicines, including additional reimbursement agreements, (vi) expectations for the future commercial launch and anticipated benefits of new products, including CTX001, (vii) anticipated market opportunity for new products, including estimated eligible patient populations, and (viii) anticipated investment 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, that COVID-19 may have different impacts on the business or operations, data from preclinical testing or early clinical trials, especially if based on a limited number of patients, may not 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 we 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.
**ACHIEVE OUR VISION IN CYSTIC FIBROSIS**

- Successful launch of TRIKAFTA in the U.S. for ages 12+
- EU approval of triple combination regimen for ages 12+
- EU approval of SYMKEVI for ages 6 to 11
- Submit sNDA for triple combination regimen for ages 6 to 11

**DEVELOP NEW TRANSFORMATIVE MEDICINES FOR ADDTL. SERIOUS DISEASES**

- Generate proof-of-concept data for AAT program
- Generate proof-of-concept data for both sickle cell disease and beta thalassemia
- Advance cell tx. for type 1 diabetes into clinical dev. in late 2020/early 2021
- Advance two new compounds into clinical development

**DELIVER FINANCIAL PERFORMANCE**

- Continued CF product revenue growth
- Disciplined management of non-GAAP combined R&D and SG&A expenses
- Further expansion of non-GAAP operating margins and cash flows
- Effectively deploy capital to pursue future growth opportunities

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OUR STRATEGY AND BUSINESS MODEL
A BLUEPRINT FOR SERIAL INNOVATION

CORPORATE STRATEGY
Vertex invests in scientific innovation to create transformative medicines for people with serious diseases with a focus on specialty markets.

RESEARCH STRATEGY
Combine transformative advances in the understanding of human disease and in the science of therapeutics to dramatically advance human health.

- Focus on validated targets that address causal human biology
- Create predictive lab assays and clinical biomarkers
- Identify rapid path to registration and approval
- Discover and develop medicines that offer transformative benefit, regardless of modality
CF IS AN EXEMPLAR OF OUR STRATEGY AND BUSINESS MODEL

Preclinical Data Predicts Clinical Benefit
Transformative Medicines that Rapidly Advance to Registration and Approval
Revenue Growth, High Operating Margins and Reinvestment Back Into Internal and External Innovation

Notes: 2019 CF Revenues are non-GAAP; see appendix for a reconciliation; see slide 24 for an explanation of 2020 CF Revenues and non-GAAP Operating Income
IN ADDITION TO CF, OUR R&D STRATEGY HAS DELIVERED A BROAD AND DEEP PIPELINE

DISEASE
- Cystic Fibrosis
- Sickle Cell Disease
- Beta Thalassemia
- Pain
- Alpha-1 Antitrypsin Deficiency
- APOL1-Mediated Kidney Diseases
- Type 1 Diabetes (Cells Only)
- Type 1 Diabetes (Cells+Device)
- Duchenne Muscular Dystrophy
- Myotonic Dystrophy Type 1
- Huntington’s Disease
- Polycystic Kidney Disease
- Other Programs

STAGE OF LEAD PROGRAM
- 4 APPROVED MEDICINES
- PROOF-OF-CONCEPT ESTABLISHED
- PROOF-OF-CONCEPT EXPECTED IN 2021/2022
- PROGRAMS ADVANCING IN PRECLINICAL DEVELOPMENT
- DISCOVERY RESEARCH

EXCLUDED
- Alzheimer’s
- Depression
- NASH
- Influenza
- Hypertension
- & many more
WE HAVE APPLIED THE LESSONS FROM CF TO DRIVE OUR R&D PROGRAMS

**Identify the Right Disease Opportunity**
*Disciplined strategy to address causal human biology*

**Crack the Biology**
*Create predictive assays; get meaningful early clinical readouts as a gate to late-stage investments*

**Pour on the Chemistry (Therapeutics)**
*Multiple assets and approaches to maximize potential for early development success*

**Portfolio Approach to Development**
*Advance multiple assets to mitigate compound-specific risk and select the best for pivotal development*
# Six Disease Areas Active in the Clinic

**Portfolio Approach with Lead Molecules and Rapidly Advancing Follow-On Programs**

<table>
<thead>
<tr>
<th>Disease Area</th>
<th>Lead Molecules/Therapeutics</th>
<th>Research</th>
<th>Phase 1</th>
<th>Phase 2</th>
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<td>Kalydeco</td>
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<td></td>
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<tr>
<td></td>
<td>VX-121 (next-generation corrector)</td>
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<tr>
<td></td>
<td>VX-561 (once-a-day-potentiator)</td>
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<tr>
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<tr>
<td></td>
<td>CRISPR/Cas9</td>
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<tr>
<td></td>
<td>mRNA Therapeutics</td>
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<tr>
<td><strong>Sickle Cell Disease</strong></td>
<td>CTX001 (CRISPR/Cas9)</td>
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<td></td>
<td>Small Molecule</td>
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<tr>
<td><strong>Beta Thalassemia</strong></td>
<td>CTX001 (CRISPR/Cas9)</td>
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<td>Small Molecule</td>
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<tr>
<td><strong>Alpha-1 Antitrypsin Deficiency</strong></td>
<td>VX-864 (corrector)</td>
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<td>Additional Small Molecules (correctors)</td>
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<td><strong>Pain</strong></td>
<td>Small Molecule (NaV 1.8 inhibitor)</td>
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<td></td>
<td>Additional Small Molecules (NaV 1.8 inhibitors)</td>
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<tr>
<td><strong>APOL1-Mediated Kidney Diseases</strong></td>
<td>VX-147</td>
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<tr>
<td></td>
<td>Small Molecule</td>
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</tr>
<tr>
<td></td>
<td>Additional Small Molecules</td>
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</tbody>
</table>
WE CONTINUE TO EXPAND OUR TOOLKIT RECOGNIZING NEW MODALITIES MAY HOLD THE KEY TO TRANSFORMATIVE OUTCOMES

**VERTEX FIRSTS**

**Protein Folding Correctors**

Multiple CFTR modulators approved for cystic fibrosis

**Gene Editing**

Proof-of-concept clinical data in beta thalassemia and sickle cell disease; potential for functional cure

**NEW MODALITIES DIRECTED AT SPECIFIC DISEASES OF INTEREST**

**Targeted Protein Degradation**

**Small Molecules Targeting RNA**

**mRNA Therapy**

**Cell Therapy**

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Continue to Innovate in Cystic Fibrosis

• Reach CF patients who can benefit from TRIKAFTA/KAFTRIO
  • >30,000 patients currently untreated
• Develop medicines to bring 90% of CF patients to carrier levels and genetic therapies for the last 10% of patients

Advance the Pipeline Beyond CF

• Approval and launch of CTX001 in beta thalassemia and sickle cell disease
• Achieve proof-of-concept for small molecule Z-AAT corrector(s) in AATD
• Achieve proof-of-concept for small molecule inhibitor(s) of APOL1 function in FSGS
• Advance novel NaV 1.8 inhibitor to late-stage development in pain
• Advance cell-based therapy - cells alone and with device - for T1D into the clinic
• Continue to invest in internal and external innovation
  • Focus on mid and late clinical-stage assets that fit our strategy and technologies to expand our toolkit

Deliver Financial Performance

• Continued significant CF revenue growth
• Launch of new medicines to drive additional growth beyond CF
• Disciplined operating expense growth allowing continued high operating margins and cash flow
AN UPDATED AND EXPANDED VIEW OF THE LONG-TERM CF OPPORTUNITY

83,000 people with CF in U.S., Europe, Australia and Canada. New patients identified due to:

• Availability of transformational medicines
• Improved country-level registry data collection

Nearly 50% of Patients Currently Treated with Vertex Medicines

>30,000 Patients Currently Untreated
Addressable with Triple Combination

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WE WILL CONTINUE TO GROW IN CF IN THE NEAR-TERM WITH TRIKAFTA

KEY 2021 MILESTONES

Younger Patients & Rare Mutations
• Ages 6-11 U.S. approval
• Complete ages 2-5 study enrollment
• Rare mutations U.S. launch

Uptake in Newly Launched and Reimbursed Countries
• Uptake in England and other countries
• Expand EU label to patients with at least one F508del mutation

Global Reimbursement Agreements and Regulatory Approvals
• Regulatory approval in Australia, Canada and other regions
• Additional reimbursement agreements
# Long-Term Revenue Growth from Future CF Regimens

## Benefit & Value

<table>
<thead>
<tr>
<th>Next-In-Class</th>
<th>Best-In-Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High Efficacy</td>
<td>Next-in-Class Benefits Plus:</td>
</tr>
<tr>
<td>• Once-Daily Dosing</td>
<td>• Carrier-Like Efficacy</td>
</tr>
<tr>
<td>• Lower Royalty Obligation</td>
<td>• Low or No Royalty Obligation</td>
</tr>
<tr>
<td>• Duration of Exclusivity Extended</td>
<td></td>
</tr>
</tbody>
</table>

### Novel CFTR Modulator Combination Regimens

### Genetic Therapies

**mRNA, Gene Therapy and Gene-Editing Technologies**

*For the last 10% of CF patients who do not make CFTR protein*
SICKLE CELL DISEASE AND BETA THALASSEMIA

Severity of Disease

• Frequent hospitalizations due to vaso-occlusive pain crises (sickle cell disease) and severe anemia (beta thalassemia)
• Reduced life expectancy

Established Human Biology

• Disease caused by mutations in beta-globin gene that lead to impairment in quality or quantity of beta-globin
• Human genetics shows persistent expression of fetal hemoglobin (HbF) (>20%) mitigates manifestation of both sickle cell disease and beta thalassemia

Clinical Approach & Biomarkers

• CRISPR/Cas9 gene editing to reduce BCL11A expression and increase production of HbF
• Measure circulating Hb, HbF

OPPORTUNITY – Sickle Cell Disease

~25,000 patients with severe disease (U.S. and EU)

Current Treatment:
Standard of care is hydroxyurea; few patients receive curative treatment (<500 annually in U.S. and EU)

OPPORTUNITY – Beta Thalassemia

~7,000 patients with severe disease (U.S. and EU)

Current Treatment:
Vast majority of patients receive lifelong transfusions; few patients receive curative treatment (<500 annually in U.S. and EU)

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**GENE EDITING OF BCL11A ENHANCER INCREASES HBF Expression IN VITRO**

**Gene-Editing Strategy**

- Cas9
- DNA
- Guide RNA

**Erythroid enhancer**

**Reduced expression in erythroid lineage**

**HbF**

**β-globin locus**

(Chromosome 11)

**BCL11A**

(Chromosome 2)

**HbF Expression In Vitro**

- 76% of cells
- 16% of cells
- 8% of cells

**CALCULATED HbF/(HbF+HbA) (%)**

- Bi-Allelic Edited
- Mono-Allelic Edited
- Unedited

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CTX001: PROOF OF CONCEPT ESTABLISHED IN BOTH BETA THALASSEMAIA & SICKLE CELL DISEASE DEMONSTRATING A FUNCTIONAL CURE IS POSSIBLE

All 10 Patients Are:

- **Transfusion Independent** *(Beta Thalassemia)*
- or
- **Free of Vaso-Occlusive Crises** *(Sickle Cell Disease)*

**Beta Thalassemia**
- 14.1 Hb
- 12.5 Hb
- 11.1 Hb
- 13.4 Hb
- 10.3 Hb
- 13.1 Hb
- 9.7 Hb

**Sickle Cell Disease**
- 12.0 Hb (43% HbF)
- 11.5 Hb (48% HbF)
- 13.2 Hb (31% HbF)

Hb levels provided as g/dL at last visit

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Increased Momentum in Enrolling and Dosing Patients

>20 patients dosed to date

Multiple additional patients expected to be dosed by end of 1Q21

Anticipate completion of enrollment in 2021

Increased Regulatory Interaction

Multiple regulatory designations allow for constructive and frequent regulatory interactions and input

Consistent Manufacturing Processes

Robust manufacturing process designed to be facile and consistent from clinical development through to commercial product
CTX001 MARKET OPPORTUNITY IS SUBSTANTIAL

SICKLE CELL DISEASE

~150,000

~25,000

Expansion into other international markets

Total patients in the U.S. and EU – potential for expansion with gentler conditioning regimens

Likely candidates for gene-editing therapy in the U.S. and EU based on disease severity

Beta THALASSEMIA

~16,000

~7,000

Potential to treat patients with severe forms of these diseases in the U.S. and EU in the near-term with CTX001
ALPHA-1 ANTITRYPSIN DEFICIENCY (AATD)
SMALL MOLECULE CORRECTION OF DEFECTIVE PROTEIN

Severity of Disease
• Progressive lung and liver disease
• Reduced life expectancy

Established Human Biology
• >90% of patients with severe AATD carry ZZ mutation causing misfolded protein
• Misfolded Z-AAT unable to protect the lungs by inactivating proteinases (enzymes) that damage healthy tissue
• Misfolded Z-AAT proteins accumulate as polymers that damage the liver

Clinical Approach & Biomarkers
• Small molecule Z-AAT correctors to address the protein folding defect and thereby treat both lung and liver manifestations
• Measure circulating functional AAT in the plasma

OPPORTUNITY

~80,000 patients with symptomatic AATD lung disease (U.S. and EU)
~20,000 currently diagnosed with AATD lung disease (U.S. and EU)

Current Treatment: No disease-modifying treatment

Augmentation therapy was approved by U.S. FDA based on AAT levels
• ~8,000 patients currently treated (U.S. and EU)
• $1.3B annually (WW)

Weekly intravenous (IV) infusions

Limited benefits for AATD lung disease and no impact on liver disease

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ELEVATION IN AAT LEVELS IN PRECLINICAL PROOF-OF-CONCEPT NOW BEING EVALUATED; RESULTS FROM PHASE 2 STUDY EXPECTED 1H21

CIRCULATING FUNCTIONAL LEVELS OF AAT IN PIZ TRANSGENIC MOUSE

PHASE 2 PROOF-OF-CONCEPT STUDY DESIGN

START

(n=40)

PLACEBO

Multiple Doses

FOLLOW-UP PERIOD

Primary Endpoints

• Change from baseline in plasma functional AAT levels at day 28

• Safety and tolerability

Secondary Endpoints

• Change from baseline in plasma total (antigenic) AAT levels at day 28

• Pharmacokinetic parameters of VX-864

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TYPE 1 DIABETES

CELL THERAPY AND CELLS+DEVICE APPROACH

Severity of Disease

• Results from autoimmune destruction of pancreatic islet beta cells causing loss of insulin production, hyperglycemia, serious complications as well as end organ damage

Established Human Biology

• Replacement of pancreatic islets, by way of pancreas or islet cell transplant (with immunosuppression), can enable patients to achieve insulin independence

Clinical Approach & Biomarkers

• Produce fully-differentiated insulin-producing pancreatic islets from stem cells with two therapeutic opportunities:
  • Cells alone, using immunosuppression
  • Cells in a novel immunoprotective device that enables cell survival and function without immunosuppression

  • Measure glucose, HbA1c and C-peptide levels

Cells Alone:
~60,000 patients with severe disease or with organ transplant (U.S. and EU)

Cells+Device:
2.6M patients

Standard of Care: Frequent Glucose Monitoring and Exogenous Insulin
Patients continue to face relentless daily management of disease; external insulin pumps and continuous glucose monitors incompletely manage disease

Disease-Modifying Treatment: Islet or Pancreas/Kidney Transplant

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CADAVERIC PANCREAS & ISLET CELL TRANSPLANTATION PROVIDE PROOF-OF-CONCEPT AND POTENTIAL FOR TRANSFORMATIVE OUTCOMES

IMPETUS FOR STEM-CELL DERIVED ISLET CELL APPROACH FOR PEOPLE WITH TYPE 1 DIABETES

- Cadaveric transplantation limited by cell supply and variable quality (~75 transplants performed per year)
- Requires long-term immunosuppression

Result:
Elimination of severe hypoglycemic events, control of blood glucose levels and, in some patients, achievement of insulin independence
AFTER EXCEPTIONAL PROGRESS IN 2020, VERTEX IS POISED FOR CONTINUED GROWTH IN 2021 AND BEYOND

Future Revenue Growth Driven By:

Continued Growth in CF
- Younger Age Groups
- Label Expansions
- New Reimbursements

Commercialization in Disease Areas Beyond CF

Notes: 2019 CF Revenues are non-GAAP; see appendix for a reconciliation; 2020 reflects the midpoint of the total CF revenue guidance updated on 10/29/20; not meant as a reiteration of guidance; 2021 – 2025 potential growth in CF revenues provided as a graphical representation and not intended as financial guidance; CAGR calculated based on midpoint of guidance range.

CF Revenue

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<th>Revenue</th>
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<td>FY17</td>
<td>$2.2B</td>
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<tr>
<td>FY18</td>
<td>$3.0B</td>
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<tr>
<td>FY19</td>
<td>$4.0B</td>
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<tr>
<td>FY20</td>
<td>$6-6.2B</td>
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<tr>
<td>2021–2025</td>
<td>(41% \text{ CAGR})</td>
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VERTEX’S BUSINESS MODEL SUSTAINS HIGH LEVELS OF PROFITABILITY, CASH FLOW AND SIGNIFICANT RE-INVESTMENT IN INNOVATION

Non-GAAP Operating Income

<table>
<thead>
<tr>
<th>Year</th>
<th>Non-GAAP Operating Income</th>
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<tbody>
<tr>
<td>2017</td>
<td>$0.6B</td>
</tr>
<tr>
<td>2018</td>
<td>$1.1B</td>
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<tr>
<td>2019</td>
<td>$1.8B</td>
</tr>
<tr>
<td>2020</td>
<td>&gt;$3B</td>
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</table>

Capital Deployment

- Investment in Internal R&D
- Investment in External Innovation (Business Development)
- Share Repurchases to Offset Dilution

Areas of Focus

- Mid and late clinical-stage assets that fit our R&D strategy and expand our pipeline
- Tools and technologies that enable us to better address diseases of interest
- Assets that complement our existing CF pipeline

Notes: See appendix for a reconciliation of 2017-2019 GAAP Operating Income to non-GAAP Operating Income; 2020 Non-GAAP Operating Income reflects the midpoints of the total CF revenue and combined non-GAAP R&D & SG&A expenses guidance ranges provided on 10/29/20 and an estimate of approximately 13% for cost of revenues. Estimated 2020 GAAP Operating Income would be approximately $2.8b utilizing the same methodology. Not meant as a reiteration of guidance. ©2021 Vertex Pharmaceuticals Incorporated
KEY MILESTONES THAT WILL MARK OUR FORWARD PROGRESS

Continue to Innovate in Cystic Fibrosis
- Reach CF patients who can benefit from TRIKAFTA/KAFTRIO
  - >30,000 patients currently untreated
- Develop medicines to bring 90% of CF patients to carrier levels and genetic therapies for the last 10% of patients

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- Advance cell-based therapy - cells alone and with device - for T1D into the clinic
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Deliver Financial Performance
- Continued significant CF revenue growth
- Launch of new medicines to drive additional growth beyond CF
- Disciplined operating expense growth allowing continued high operating margins and cash flow
INVESTING IN SCIENTIFIC INNOVATION TO CREATE TRANSFORMATIVE MEDICINES FOR PEOPLE WITH SERIOUS DISEASES

Transformed CF

Advancing Toward Approval & Commercialization

“...the biggest impact I want to come from this study is hope.”

Victoria, first person treated with CRISPR/Cas9 gene-editing therapy for sickle cell disease

Commitment to Transform Many More Diseases
## APPENDIX

### RECONCILIATION OF GAAP TO NON-GAAP FINANCIAL INFORMATION

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<tr>
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<th>FY17</th>
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<td><strong>GAAP operating income</strong></td>
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<td>Stock compensation expense</td>
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<td>Other adjustments</td>
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<td><strong>Non-GAAP operating income</strong></td>
<td>564</td>
<td>1.11B</td>
<td>1.79B</td>
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<table>
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<td><strong>GAAP total revenues</strong></td>
<td>$4.16B</td>
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<td>ORKAMBI adjustment</td>
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<td><strong>Non-GAAP total revenues</strong></td>
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**Notes:** All numbers in the above reconciliation table are in millions except where noted.