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, (i) information pertaining to our medicines and the ongoing discovery, development and commercialization of Vertex’s product candidates, (ii) graphical representations of future financial performance and (iii) Vertex’s 2019 key milestones and goals. While the Company believes that these forward-looking statements are accurate, these statements are subject to risks and uncertainties that could cause actual outcomes to differ materially from the Company’s current expectations. These risks and uncertainties include, among other things, the risk that data from the Company’s development programs may not support registration or further development of its compounds due to safety, efficacy or other reasons, the Company’s expectations regarding future financial performance may be incorrect, and the risks and uncertainties listed under Risk Factors in the Company’s 10-K and other filings with the SEC.

In this presentation, Vertex references financial guidance and results that have been 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 (i) stock-based compensation expense, (ii) revenues and expenses related to business development transactions including collaboration agreements and asset acquisitions, (iii) revenues and expenses related to consolidated variable interest entities, including asset impairment charges and related income tax benefits and the effects of the deconsolidation of a variable interest entity and (iv) other adjustments. These results are provided as a complement to results provided in accordance with GAAP because 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. Management also uses these non-GAAP financial measures to establish budgets and operational goals that are communicated internally and externally and to manage the company’s business and to evaluate its performance. The company adjusts, where appropriate, for both revenues and expenses in order to reflect the company’s operations. The company provides guidance regarding product revenues in accordance with GAAP and provides guidance regarding expenses on both a GAAP and a non-GAAP basis. The most recent reconciliation of the GAAP financial results to non-GAAP financial results is included in the Company’s October 24, 2018 press release.
**Vertex Strategy and Business Model**

*A Blueprint for Serial Innovation*

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**CORPORATE STRATEGY**

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

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**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**.

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**DIFFERENTIATED BUSINESS MODEL**

- **Investment of majority of OpEX in R&D and BD/external innovation.**
- **Revenue growth: high operating margins and significant cash flow.**
- **Creation of high-value transformative medicines for specialty markets.**
- **Limited SG&A expenses and infrastructure.**
## 2018 Key Goals and Accomplishments

### Achieve Our Vision in Cystic Fibrosis

- Phase 2 data for triple combinations in CF patients
- Initiation of pivotal development of up to two triple combination regimens
- Approval for tezacaftor/ivacaftor combination in the U.S. (Europe anticipated in 2H 2018)
- Advance additional next-generation correctors into development

### Expand Pipeline Beyond CF

- Advance one or more compounds from research into clinical development
- Initiate clinical development of CRISPR/Cas9 treatment in sickle cell disease & beta thalassemia

### Build Financial Strength

- Significantly increase 2018 total CF product revenues
- Obtain reimbursement for ORKAMBI in additional countries outside the U.S.
- Continued management of non-GAAP combined R&D and SG&A expenses
- Continue to increase operating margins and cash flows

### Note:

2018 revenue projection reflects the midpoint of growth based on total CF revenue guidance updated on 7/25/18
2019 and Beyond

Completing the Journey in CF

Advancing the Pipeline Beyond CF

Revenue and Earnings Growth
2019 and Beyond

Completing the Journey in CF

Advancing the Pipeline Beyond CF

Revenue and Earnings Growth
Developing Medicines for All People with CF

KALYDECO
ORKAMBI
SYMDEKO

37,000 Patients
Currently Eligible

37,000 → 44,000
• Treating younger patients
• Label expansions

44,000 → 68,000
Triple Combination Regimens
F508del/ Minimal CFTR Function

68,000 → 75,000
Gene Editing mRNA
Potential to treat all people with CF
Multiple Medicines to Treat Underlying Cause of CF
Approved for Approximately Half of All CF Patients Worldwide

KALYDECO
• First approved in 2012 for patients ages 6+ with the G551D mutation

ORKAMBI
• First approved in 2015 for patients ages 12+ with two F508del mutations

SYMDEKO/SYMKEVI
• Approved in 2018 for patients ages 12+ with two F508del mutations or at least one residual function mutation

2018 Accomplishments:
• Approved for patients as young as 12 months old in U.S. and EU

2018 Accomplishments:
• Approved for patients ages 2+ in U.S. and ages 6+ in EU

2018 Accomplishments:
• U.S. launch; EU approval for ages 12+

- Full-year 2018 total CF product revenue guidance of $2.9 - $3.0 billion -

Notes:
• SYMKEVI EU indication is for F508del/F508del and F508del/residual function mutations
• 2018 revenue projection for total CF revenue guidance updated on 7/25/18

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Data from long-term observational safety study using CF Registries show multi-system benefits and transformational disease modification

- Mortality: -59%, 0.41 (0.20 - 0.86)
- Transplantation: -71%, 0.29 (0.13 - 0.67)
- Hospitalization: -33%, 0.67 (0.62 - 0.73)
- Pulmonary Exacerbation: -28%, 0.72 (0.66 - 0.79)

Notes
- Provided as Percent Reduction with corresponding Risk Ratio (95% CI);
- Analysis used 2016 registry data up to 5 years of KALYDECO use in U.S.
- Potential for confounding cannot be excluded but was partially addressed through matching and stratification

Volkova et al. Presented at 41st European Cystic Fibrosis Conference, June 2018
Triple Combination Regimens Have Potential to Treat Up to 90% of CF Patients

TRIPLE COMBINATION REGIMEN

ENHANCED EFFICACY

37,000 Patients
Currently Eligible

37,000 → 44,000

NEW PATIENTS

44,000 → 68,000

F508del / Minimal CFTR Function (all ages)

Gene Editing mRNA
Potential to treat all people with CF
On Track to Submit NDA for Triple Combination Regimen in 2019

### PRIMARY ENDPOINT
Absolute ppFEV₁ from baseline at week 4

<table>
<thead>
<tr>
<th>VX-659</th>
<th>F508del/ F508del (homozygous)</th>
<th>F508del/ Minimal Function (heterozygous)</th>
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<tbody>
<tr>
<td>N=111 F/F N=382 F/MF</td>
<td>Treatment Difference +10.0 (p&lt;0.0001)</td>
<td>+14.0 (p&lt;0.0001)</td>
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- Enrollment for VX-445 F/F and F/MF Phase 3 studies complete; Data expected in Q1’19 –
- Vertex will choose the best regimen to submit for regulatory approval; NDA planned for no later than mid-2019 –

**Notes:**
- F/F = F508del/F508del; F/MF = F508del/minimal function
- Change in ppFEV₁ provided as percentage points
2019 and Beyond

Completing the Journey in CF

Advancing the Pipeline Beyond CF

Revenue and Earnings Growth
Vertex Research Strategy Will Drive Growth Beyond CF

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
Beyond CF
Multiple Opportunities for Transformative Medicines

Alpha-1 Antitrypsin Deficiency
First molecule advanced into clinical development in December 2018;
Multiple additional molecules in late preclinical development

Pain
First selective NaV1.8 inhibitor (VX-150) to demonstrate proof-of-concept in acute,
inflammatory and neuropathic pain; Ongoing research to discover/develop additional
NaV1.8 inhibitors and other potential pain molecules

Focal Segmental Glomerulosclerosis
Novel approach to underlying biology of severe kidney disease;
Potential clinical candidate in 2019

Sickle Cell Disease / Beta Thalassemia
Initiated Phase 1/2 studies of gene editing therapy CTX001
Alpha-1 Antitrypsin Deficiency
Small Molecule Corrector

Genetic Disease
More than 90% of severe patients carry a single point mutation in \textit{SERPINA1}.

Protein Folding Defect
Point mutation causes a protein folding defect that leads to lung and liver disease.

Preclinical and Clinical Biomarkers
Preclinical: human cells and transgenic mice
Clinical: circulating levels of AAT

Approach
Oral small molecule corrector

**OPPORTUNITY**

- \(~100,000\) patients in the U.S. and EU

- Current Treatment
  A minority of patients treated with augmentation protein therapy; limited therapeutic benefit

- Life-Threatening
  Reduced life expectancy due to progressive lung and liver disease
Small Molecule Corrector for Alpha-1 Antitrypsin Deficiency
Proof of Mechanism in Preclinical Studies

RAISING CIRCULATING LEVELS OF AAT IN THE PiZ TRANSGENIC MOUSE

REDUCING TOXIC POLYMER FORMATION IN THE LIVER OF PiZ TRANSGENIC MOUSE

Vehicle 5 days
Treated 5 days

Potential to prevent disease progression in the lung
Potential to address pathology in the liver

- Clinical development of first molecule initiated in December 2018 -
- Multiple small molecule correctors in late preclinical development -

Note: Animal studies using PiZ transgenic mouse model that carries human Z-AAT gene
Mouse baseline in this experiment corresponds well with approximate average human ZZ baseline (~5 uM)
“Carrier range” corresponds to values above the “protective threshold” (11 uM)
Sickle Cell Disease and Beta Thalassemia

Gene Editing

Genetic Diseases
Caused by mutations in globin gene

Protein Defect
Hemoglobin defects lead to red cell disorders
Sickle cell: pain crises, organ damage
β thalassemia: severe anemia, iron overload

Preclinical and Clinical Biomarkers
Predclinical: human CD34+ primary cells
Clinical: circulating levels of fetal hemoglobin

Approach
CRISPR gene editing to delete BCL11A enhancer leading to increase in fetal hemoglobin

OPPORTUNITY

~150,000 people with sickle cell disease in U.S. and EU
~16,000 with transfusion dependent beta thalassemia in U.S. and EU

Current Treatment
Only helps certain patients

Life-Threatening
Complications and frequent hospitalizations; Reduced life expectancy
Sickle Cell Disease and Beta Thalassemia

Gene Editing

**HbF RATIO AFTER EDITING AND ERYTHROID DIFFERENTIATION**

**ESTIMATED HbF EXPRESSION AT THE CELLULAR LEVEL**

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

**Calculated HbF/HbA (%)**

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

**Protein Tetramer (%)**

- Control
- CTX001

*n=6 healthy donors*

- Phase 1/2 Studies Ongoing in Sickle Cell Disease and Beta Thalassemia -
- Enrollment Ongoing for Each Study -
2019 and Beyond

Completing the Journey in CF

Advancing the Pipeline Beyond CF

Revenue and Earnings Growth
CF Revenue Growth to Continue into 2019 and Beyond

Of ~37,000 patients currently eligible for an existing VRTX CF medicine, ~18,000 are currently on treatment.

The increase from ~37,000 to ~44,000 patients will be based on treating younger patients and label expansions with our current medicines.

With a triple combination regimen, VRTX has the potential to increase treatment from ~44,000 to ~68,000 patients worldwide.

Notes: 2018 reflects the midpoint of the total CF revenue guidance updated on 7/25/18; not meant as a reiteration of guidance; 2019 & 2025 potential growth in CF revenues provided as a graphical representation and not intended as financial guidance.
Increasing Cash Flow Enables Investment for Future Growth

Growing Cash Position Enables Continued Investment in Internal R&D and Execution of Business Development Strategy

Business Development and Capital Allocation Strategy
- Complement ongoing R&D in CF
- Access novel platform technologies and targets
- In-license or acquire pipeline assets

Year-End Net Cash includes cash, cash equivalents and marketable securities; 2018 Year-End Net Cash estimate represents the net cash balance at the end of Q3 2018; Not intended as financial guidance.
# 2019 Key Milestones and Goals

## ACHIEVE OUR VISION IN CYSTIC FIBROSIS

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<td>✓ Obtain reimbursement for ORKAMBI in additional countries outside the U.S.</td>
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## EXPAND PIPELINE BEYOND CF

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## BUILD FINANCIAL STRENGTH

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We Are Vertex
Transformative Medicines for People with Serious Diseases