J.P. Morgan Healthcare Conference

Jeffrey Leiden, M.D., Ph.D.

Chairman, President and CEO

VERTEX

THE SCIENCE *of* POSSIBILITY

January 7, 2019

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

CORPORATE STRATEGY

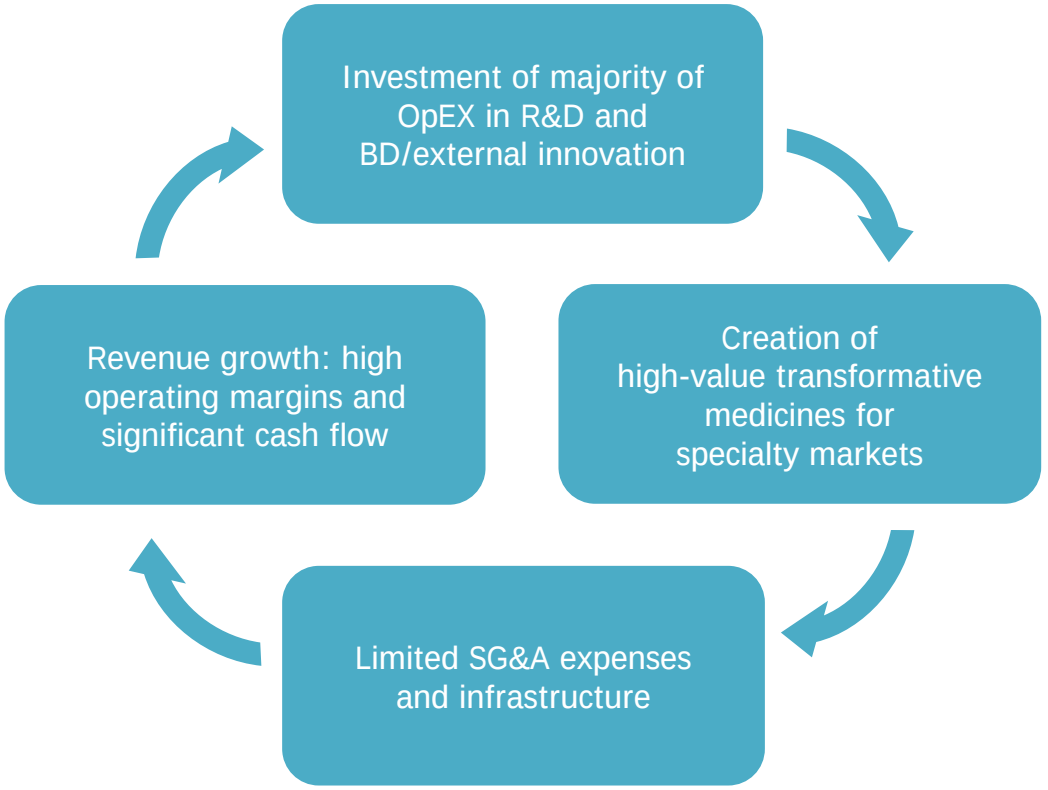
Vertex invests in **scientific innovation** to create **transformative medicines** for people with **serious diseases** with a focus on **specialty markets**

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**

DIFFERENTIATED BUSINESS MODEL



2018 Key Goals and Accomplishments

ACHIEVE OUR VISION IN CYSTIC FIBROSIS	☑ Phase 2 data for triple combinations in CF patients	*VX-659 Phase 3 topline data; VX-445 Phase 3 fully enrolled*
	☑ Initiation of pivotal development of up to two triple combination regimens	*SYMDEKO U.S. approval and launch in February 2018; EU approval received in November 2018*
	☑ Approval for tezacaftor/ivacaftor combination in the U.S. (Europe anticipated in 2H 2018)	*Initiated Phase 1/2 clinical study of next-generation corrector VX-121*
	☑ Advance additional next-generation correctors into development	
EXPAND PIPELINE BEYOND CF	☑ Advance one or more compounds from research into clinical development	*Clinical development underway of first small molecule corrector for AATD*
	☑ Initiate clinical development of CRISPR/Cas9 treatment in sickle cell disease & beta thalassemia	*Initiated Phase 1/2 studies of CTX001 in sickle cell disease and beta thalassemia*
BUILD FINANCIAL STRENGTH	☑ Significantly increase 2018 total CF product revenues	*>35% CF product revenue growth in 2018 v. 2017*
	☑ Obtain reimbursement for ORKAMBI in additional countries outside the U.S.	*Innovative, long-term access agreements in multiple countries*
	☑ Continued management of non-GAAP combined R&D and SG&A expenses	
	☑ Continue to increase operating margins and cash flows	

VERTEX

Note: *2018 revenue projection reflects the midpoint of growth based on total CF revenue guidance updated on 7/25/18*

2019 and Beyond

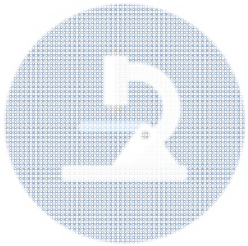
Completing the Journey in CF

Advancing the Pipeline Beyond CF

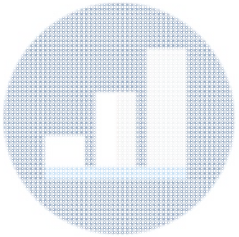
Revenue and Earnings Growth

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

2018 Accomplishments:

- *Approved for patients as young as 12 months old in U.S. and EU*

ORKAMBI

- First approved in 2015 for patients ages 12+ with two *F508del* mutations

2018 Accomplishments:

- *Approved for patients ages 2+ in U.S. and ages 6+ in EU*

SYMDEKO/SYMKEVI

- Approved in 2018 for patients ages 12+ with two *F508del* mutations or at least one residual function mutation

2018 Accomplishments:

- *U.S. launch; EU approval for ages 12+*

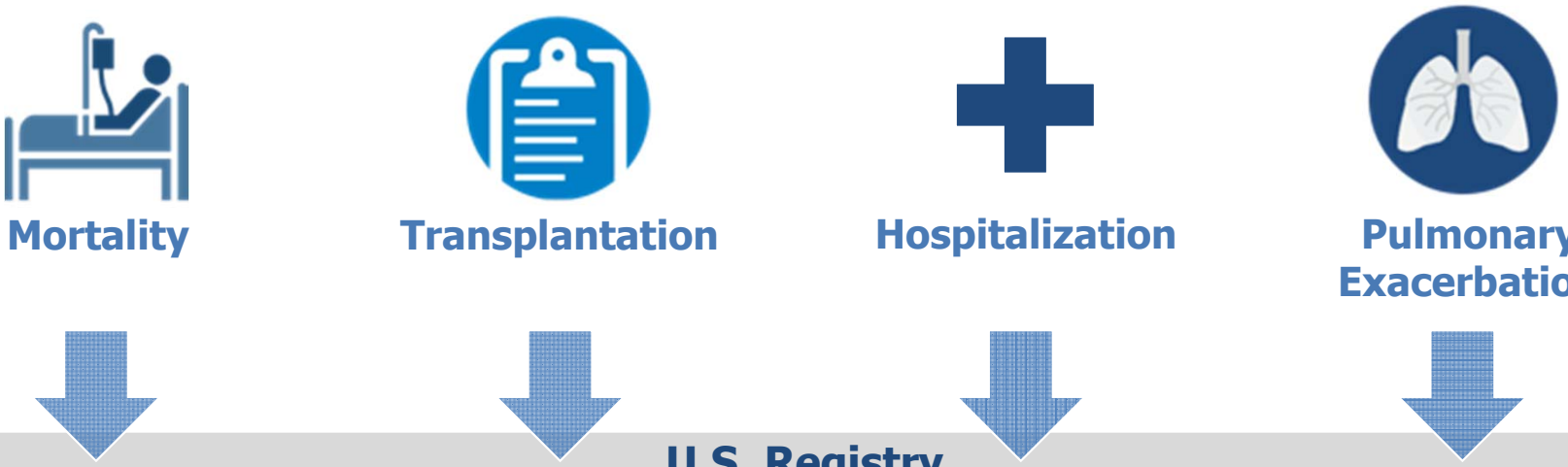
- Full-year 2018 total CF product revenue guidance of $2.9 - $3.0 billion -

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*

Long-Term Real-World Data for KALYDECO

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

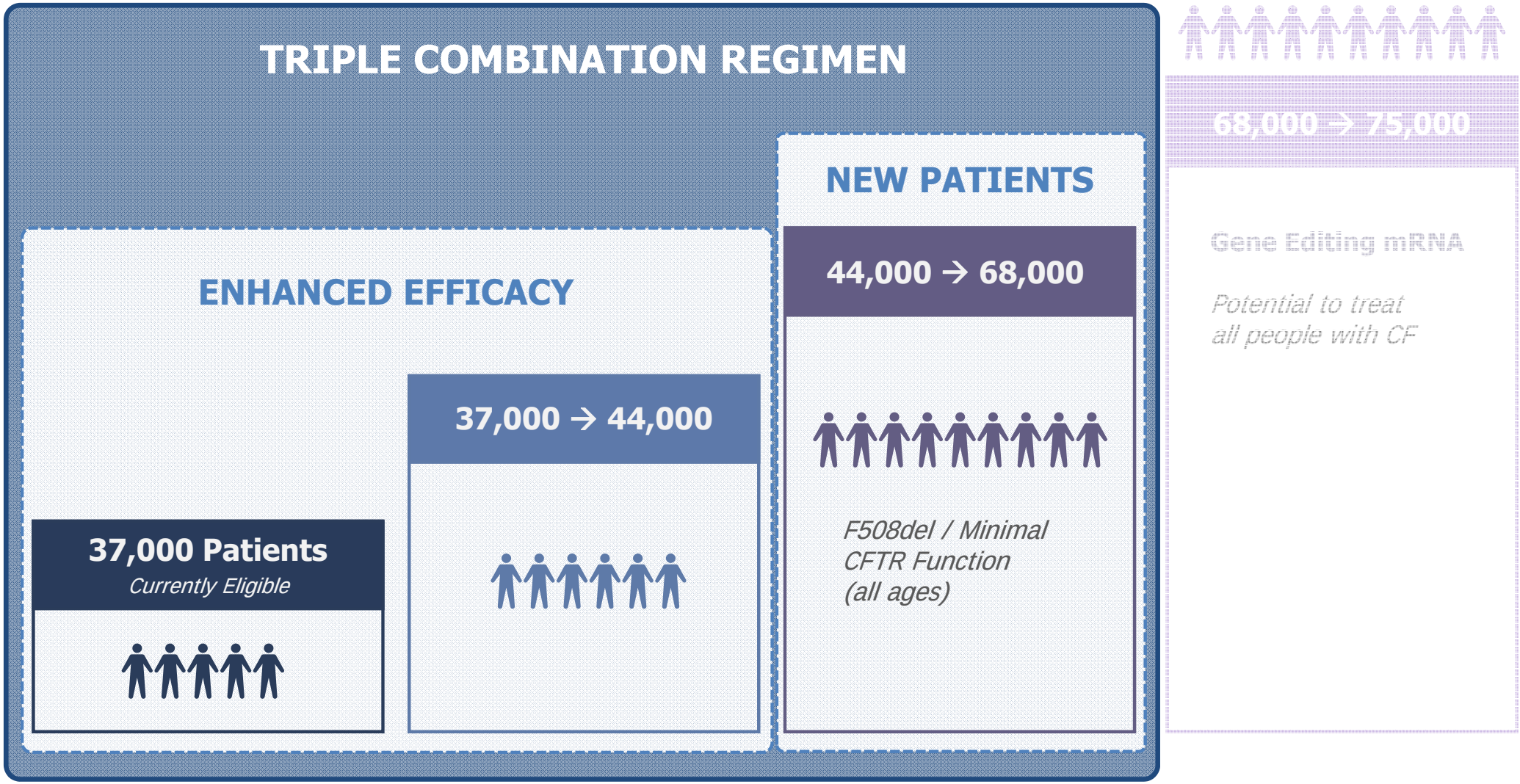


Notes

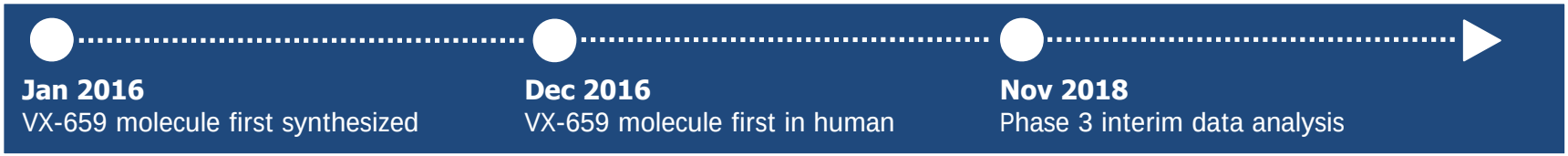
- *Provided as Percent Reduction with corresponding Risk Ratio (95% CI);*
- *Analysis used 2016 registry data up to 5 years of KALYDECO use in U.S.*
- *Potential for confounding cannot be excluded but was partially addressed through matching and stratification*

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



On Track to Submit NDA for Triple Combination Regimen in 2019



PRIMARY ENDPOINT Absolute ppFEV$_1$ from baseline at week 4		*F508del/ F508del* (homozygous) *(incremental to tez/iva treatment)*	*F508del/ Minimal Function* (heterozygous)
VX-659 *N=111 F/F* *N=382 F/MF*	Treatment Difference	**+10.0** (p<0.0001)	**+14.0** (p<0.0001)

- 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 ppFEV$_1$ 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

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

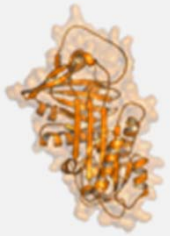
RESEARCH STRATEGY

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**

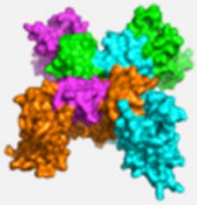
Beyond CF

Multiple Opportunities for Transformative Medicines



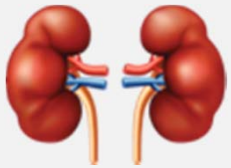
Alpha-1 Antitrypsin Deficiency

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

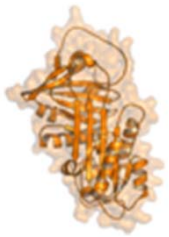


Focal Segmental Glomerulosclerosis

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 *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

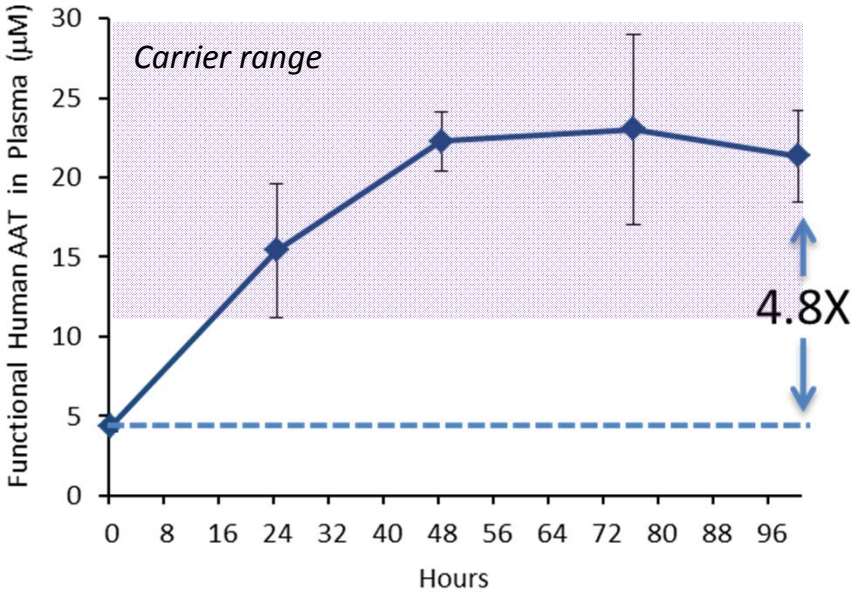
Life-Threatening
Reduced life expectancy due to progressive lung and liver disease

VERTEX

Small Molecule Corrector for Alpha-1 Antitrypsin Deficiency

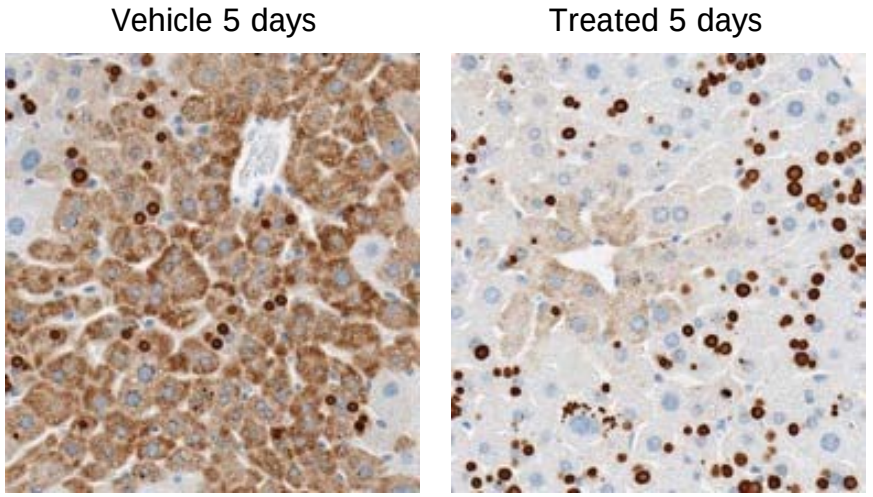
Proof of Mechanism in Preclinical Studies

RAISING CIRCULATING LEVELS OF AAT IN THE PiZ TRANSGENIC MOUSE



Potential to prevent disease progression in the lung

REDUCING TOXIC POLYMER FORMATION IN THE LIVER OF PiZ TRANSGENIC MOUSE



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 (~5uM)
"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

Preclinical: 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

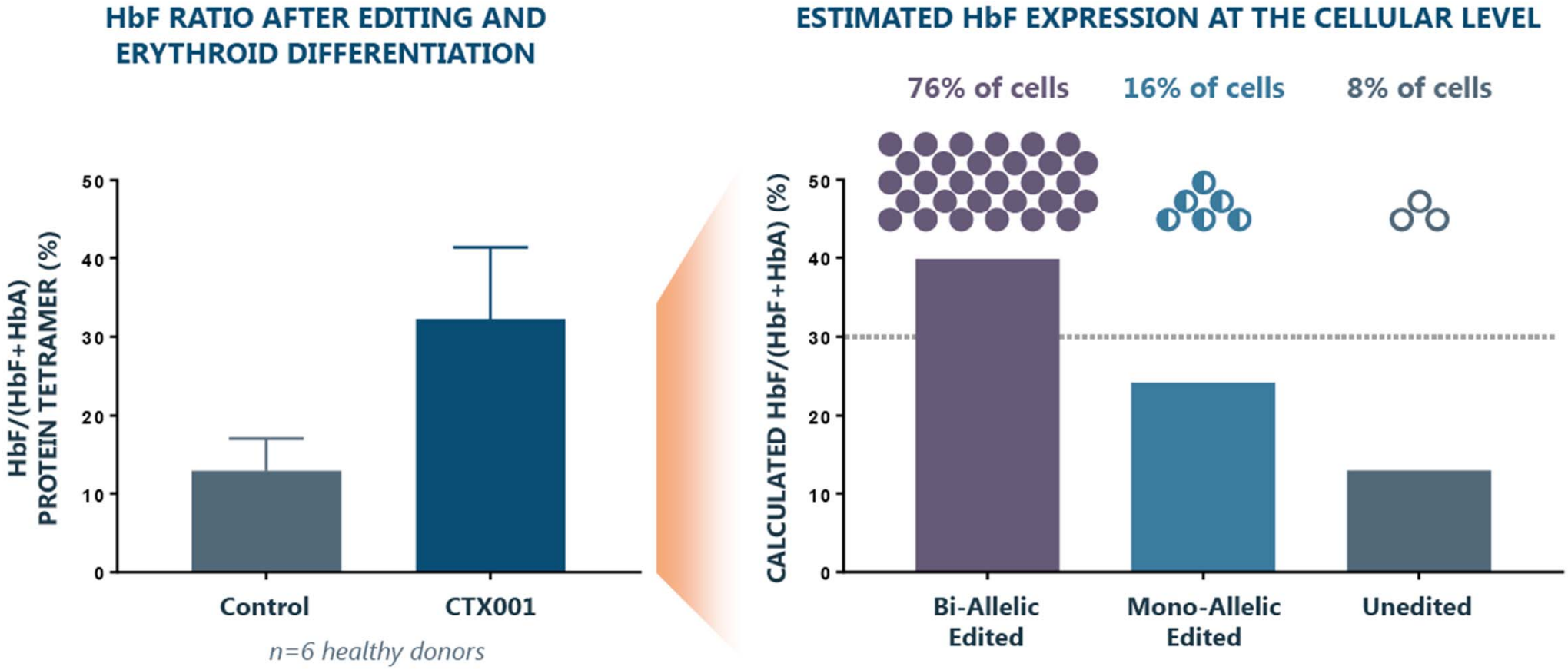
Current Treatment
Only helps certain patients

Life-Threatening
Complications and frequent hospitalizations; Reduced life expectancy

VERTEX | CRISPR THERAPEUTICS

Sickle Cell Disease and Beta Thalassemia

Gene Editing



- Phase 1/2 Studies Ongoing in Sickle Cell Disease and Beta Thalassemia -

- Enrollment Ongoing for Each Study -

VERTEX | CRISPR THERAPEUTICS

2019 and Beyond

Completing the Journey in CF

Advancing the Pipeline Beyond CF

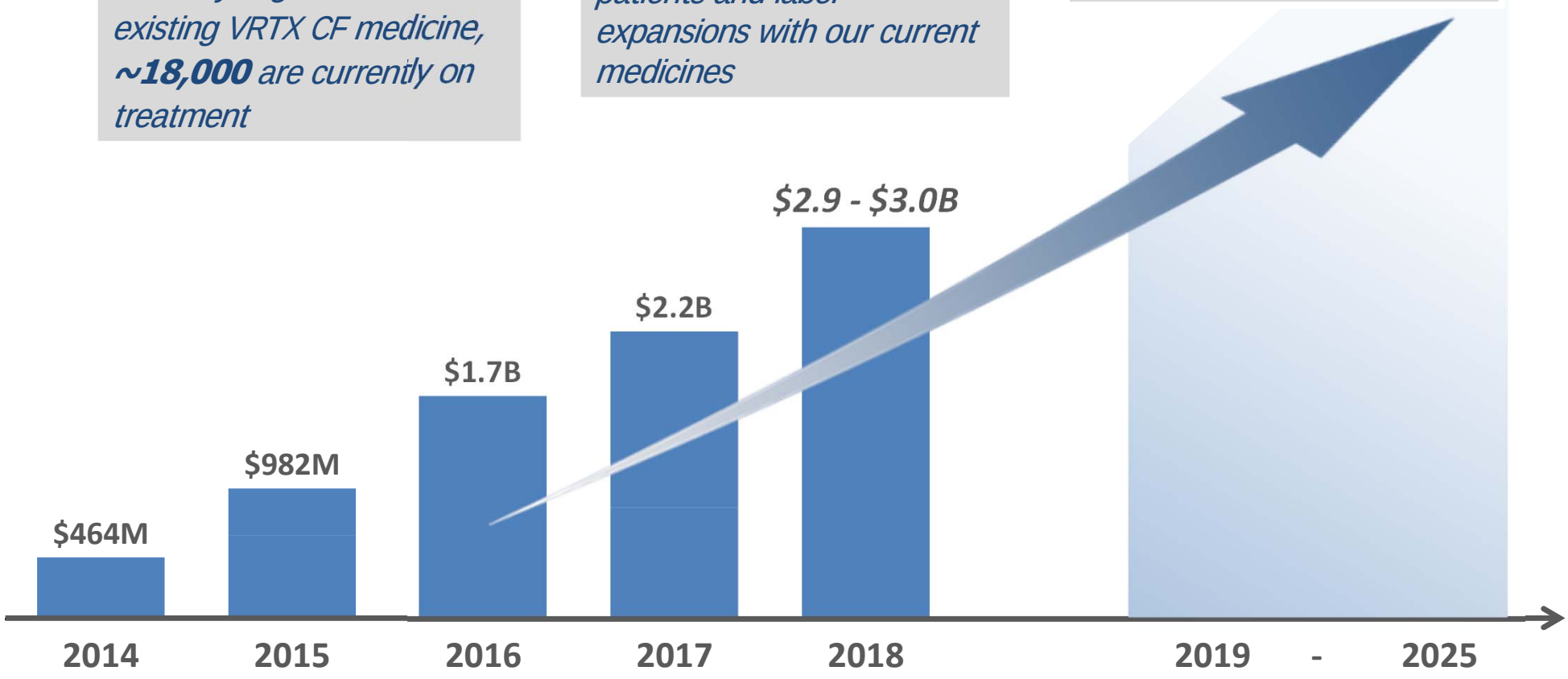
Revenue and Earnings Growth

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*

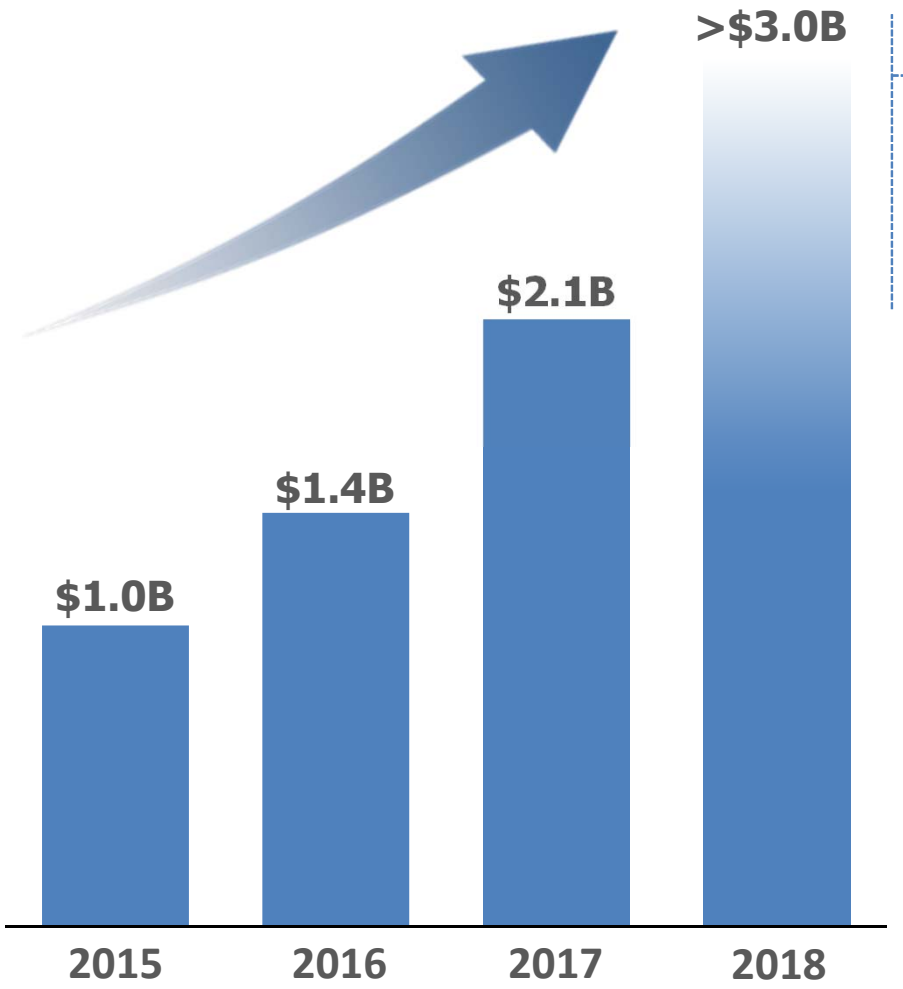
*With a triple combination regimen, VRTX has the potential to increase treatment from **~44,000** to **~68,000** patients worldwide*



GLOBAL CF PRODUCT REVENUES

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



Net Cash at Year-End

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

CRISPR THERAPEUTICS
GENOMICS PLC
arbor
FSGS
X-CHEM

VERTEX

• *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

	2018	2019
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	☐ Phase 3 data for VX-445 in patients ages 12+ ☐ **Submit NDA for a triple combination regimen no later than mid-2019** ☐ U.S. approval for SYMDEKO for children ages 6 through 11 ☐ Initiate POC study of additional next-generation corrector ☐ Phase 2 dose-ranging study of potential once-daily regimen VX-561
EXPAND PIPELINE BEYOND CF	☑ Advance one or more compounds from research into clinical development ☑ Initiate clinical development of CRISPR-Cas9 treatment in Beta Thalassemia & Sickle Cell Disease	☐ **Complete Phase 1 studies in at least two new diseases** ☐ **Bolster pipeline with internal and external assets** ☐ Advance one or more compounds from research into clinical development
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	☐ Continued CF product revenue growth ☐ **Continued uptake and reimbursement for ORKAMBI and SYMDEKO in additional countries outside the U.S.** ☐ Continued management of non-GAAP combined R&D and SG&A expenses ☐ **Continued expansion of non-GAAP operating margins and cash flow**

VERTEX

We Are Vertex

Transformative Medicines for People with Serious Diseases

VERTEX

J.P. Morgan Healthcare Conference

Jeffrey Leiden, M.D., Ph.D.

Chairman, President and CEO

VERTEX

THE SCIENCE *of* POSSIBILITY

January 7, 2019