VERTEX

THE SCIENCE *of* POSSIBILITY

J.P. MORGAN HEALTHCARE CONFERENCE

RESHMA KEWALRAMANI, M.D.

JANUARY 2022

SAFE HARBOR STATEMENT & NON-GAAP FINANCIAL MEASURES

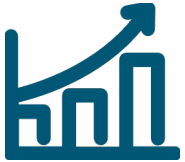
This presentation contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, including, without limitation, the information provided regarding future financial performance and operations, and statements regarding (i) the expectations, development plans, anticipated timelines for and potential benefits of the company's therapies and pipeline programs, including study designs, clinical site initiations, patient enrollment, data availability, anticipated regulatory filings, approvals, and timing thereof, (ii) expectations for the CTX001 program, including the potential of CTX001 to be a curative approach for patients with TDT and SCD, the expectation of regulatory filings in 2022, expectations for program approval and launch, and potential commercial opportunity, (iii) expectations for uptake of and expanded access to the company's medicines, including additional reimbursement agreements, label expansions and approvals in new markets, (iv) expectations for continued growth in the number of CF patients treated with our medicines, including reaching all CF patients who can benefit from TRIKAFTA/KAFTRIO, expansion of treatment options for the patients who do not benefit from CFTR modulators and anticipated size of patient populations, (v) our plans to treat additional CF patients with mRNA, including plans for a CFTR mRNA IND filing in 2022, (vi) expectations for our pain program, including for available data in the first quarter of 2022, (vii) beliefs about delivering treatments and potential cures for more patients in multiple new disease areas, including potential commercial opportunities in the disease areas in which we focus, (viii) expectations for our T1D program, including dosing additional patients with VX-880 and an IND submission for our T1D cells and device program in 2022, (ix) expectations for our next-in-class, once-daily triple regimen for CF patients, including our Phase 3 program expectations, enrollment plans and related economics, (x) plans to initiate and advance the VX-147 pivotal program in AMKD and potential commercial opportunity, (xi) our plans to advance small molecule AAT correctors and other new programs into the clinic, and (xii) 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 only 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 its future financial and operating performance may be incorrect (including because one or more of the company's assumptions underlying its expectations may not be realized), that the company may not be able to submit anticipated regulatory filings on expected timelines, or at all, that COVID-19 may have different or more significant impacts on the company's business or operations than the company currently expects, that data from preclinical testing or clinical trials, especially if based on a limited number of patients, may not be indicative of final results, that actual patient populations able to participate in our trials or eligible for our products may be smaller than we anticipated, that data from the company's development programs may not be available on expected timelines, or at all, and may not support registration or further development of its potential medicines due to safety, efficacy or other reasons, and other risks listed under Risk Factors in Vertex's annual report and subsequent filings filed with the Securities and Exchange Commission and available through the company's website at www.vrtx.com and on the SEC's website at www.sec.gov. You should not place undue reliance on these statements or the scientific 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 that the company believes is helpful to an understanding of its ongoing business. A reconciliation of the GAAP financial results to non-GAAP financial results is included in the appendix hereto.

POISED FOR CONTINUED SIGNIFICANT GROWTH BY EXTENDING OUR LEADERSHIP IN CYSTIC FIBROSIS AND TRANSFORMING MORE DISEASES

Transforming the lives of all CF patients with our current and future medicines, driving continued significant revenue growth

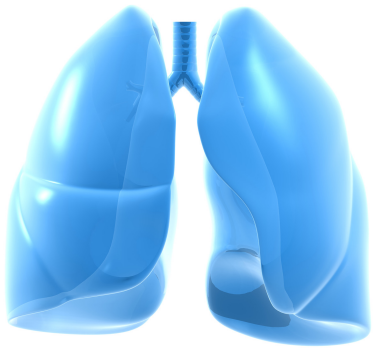
Pipeline delivering potential treatments and cures for more patients in multiple new disease areas, representing multibillion-dollar opportunities



Differentiated business model drives strong profitability and enables continued investment in internal and external innovation

IN 2021, WE MEANINGFULLY EXPANDED OUR LEADERSHIP IN CF

>40,000
patient-years of data



TREATING MORE PATIENTS

- Secured reimbursement for TRIKAFTA/KAFTRIO in 16 countries
- Launched TRIKAFTA for patients 6 to 11 years of age in the U.S.

REAL-WORLD DATA RAISING THE BAR

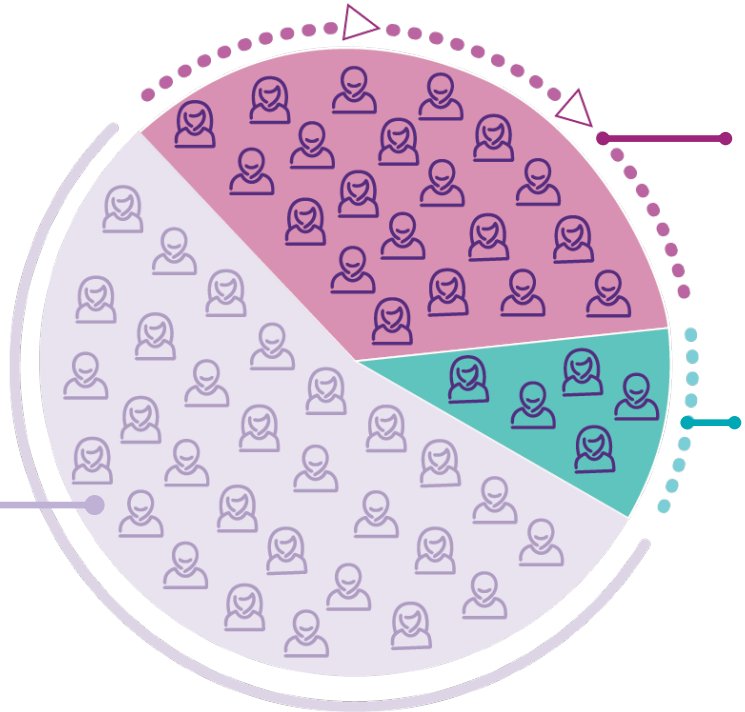
- Significant disease modification with dramatic reductions in complications and death

ADVANCING NEW THERAPIES

- VX-121/TEZ/VX-561 triple combo now in Phase 3
- CFTR mRNA IND filing planned for 2022

CONTINUED GROWTH AHEAD IN CF

83,000 patients with CF in U.S., Europe, Australia and Canada



Rapid uptake for our CF medicines in currently eligible patients

Growth Opportunities

1. **>25,000 patients** that are addressable with triple combination are still untreated
   - Continued uptake
   - New reimbursements
   - Label expansion to younger ages
2. **NEW:** potential to treat additional **5,000+** patients with mRNA; IND planned for 2022

VERTEX MEDICINES ARE TRANSFORMING THE LIVES OF CF PATIENTS

Real-world data from >16,000 U.S. patients treated with TRIKAFTA show:

87% ↓
Reduction in risk of lung transplant*

77% ↓
Fewer pulmonary exacerbations**

74% ↓
Reduction in risk of death*

In addition, TRIKAFTA 96-week follow-up data from pivotal trials showed no reduction in lung function

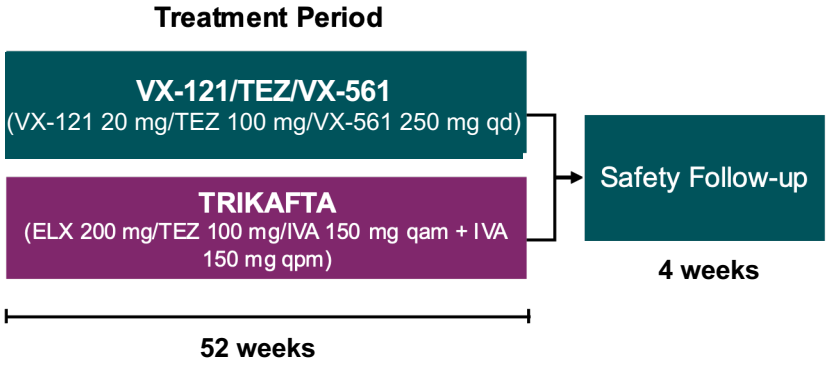
* Unadjusted estimate relative to historical 2019 U.S. Cystic Fibrosis Foundation registry data for patients older than 12 with at least one copy of F508del mutation
** Relative to 12-month period prior to TRIKAFTA treatment initiation
Data from observational post-authorization safety study on >16,000 TRIKAFTA-treated patients with mean of ~9 months of exposure, from U.S Cystic Fibrosis Foundation patient registry.

VX-121/TEZACAFTOR/VX-561 TRIPLE REGIMEN MAY FURTHER ENHANCE PATIENT BENEFIT

Two Phase 3 global, randomized, double-blind, active-controlled trials underway (N=950 total):

SKYLINE 102 STUDY

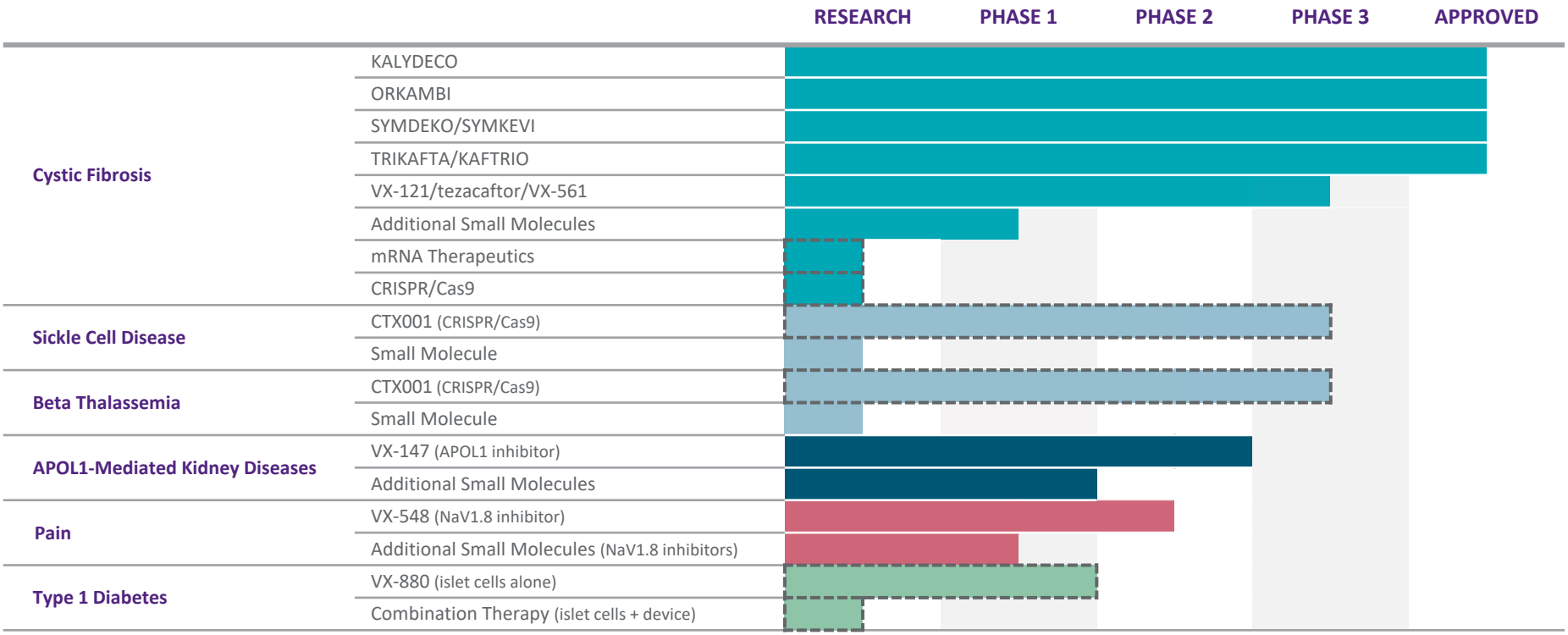
SKYLINE 103 STUDY



Next-in-Class, Once-Daily Triple Regimen

- Preclinical and Phase 2 clinical data for next-in-class triple demonstrate potential for superior efficacy over TRIKAFTA
- Plan to complete pivotal program enrollment by late 2022/early 2023
- Once-daily regimen
- Enhanced economics

VERTEX IS ADVANCING A BROAD AND DEEP CLINICAL PIPELINE ACROSS MULTIPLE MODALITIES



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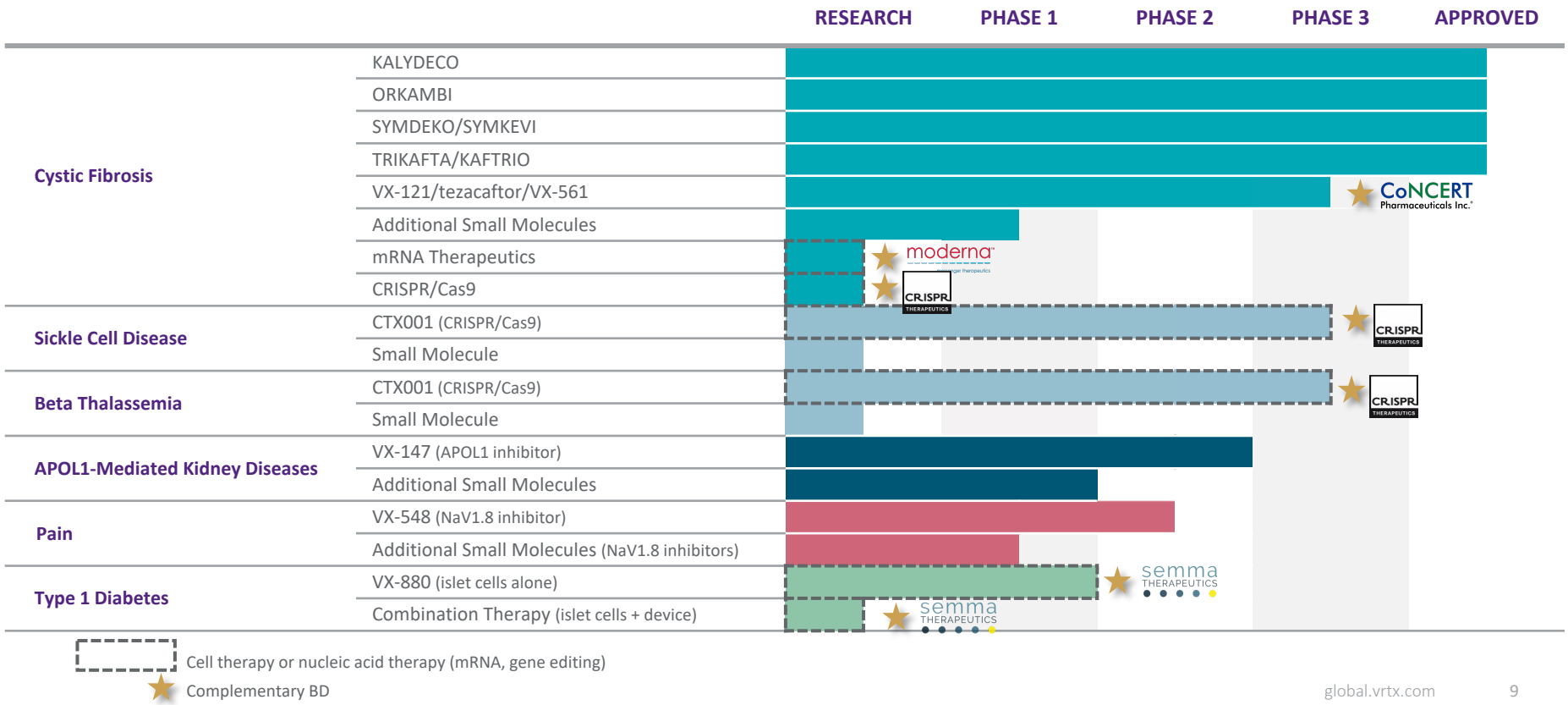


KEY PIPELINE ADVANCES IN 2021 CREATE HIGH-VALUE CATALYSTS IN 2022

Completed in 2021	Planned for 2022
Completed enrollment in pivotal studies of CTX001 and dosed >70 patients	Plan to file for regulatory approval by year-end 2022
First type 1 diabetes patients dosed with VX-880	• Dose more patients with VX-880 • File IND for cells+device approach in 2022
Proof-of-concept established for VX-147, small molecule for APOL1-mediated kidney disease	Advancing to pivotal development in Q1 2022
Initiation and rapid enrollment of two Phase 2 POC studies of VX-548 in acute pain	POC readouts in Q1 2022 could establish basis for advancing to pivotal development

SIGNIFICANT PROGRESS IN THE CTX001 PROGRAM

Potential to be the first approved genetic therapy for sickle cell disease

Strong physician and patient interest

- Phase 3 enrollment complete
- Studies oversubscribed
- >70 patients dosed to date

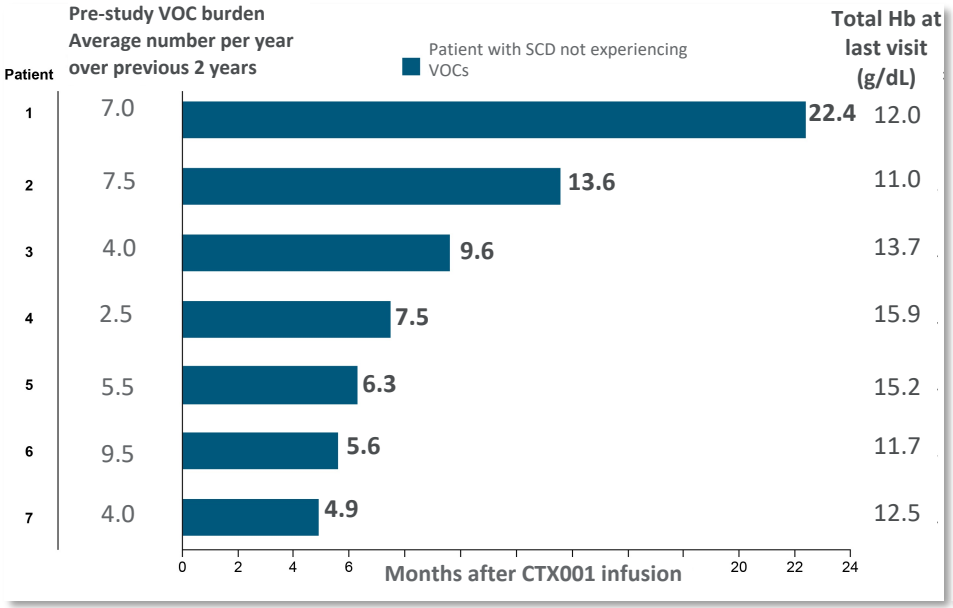
- Reached agreement with regulators on multiple elements of filing package
- Completing discussions on endpoints and duration of follow-up needed for BLA filing

- Launch preparedness underway
- Continue efforts towards commercial readiness for SCD and beta thal

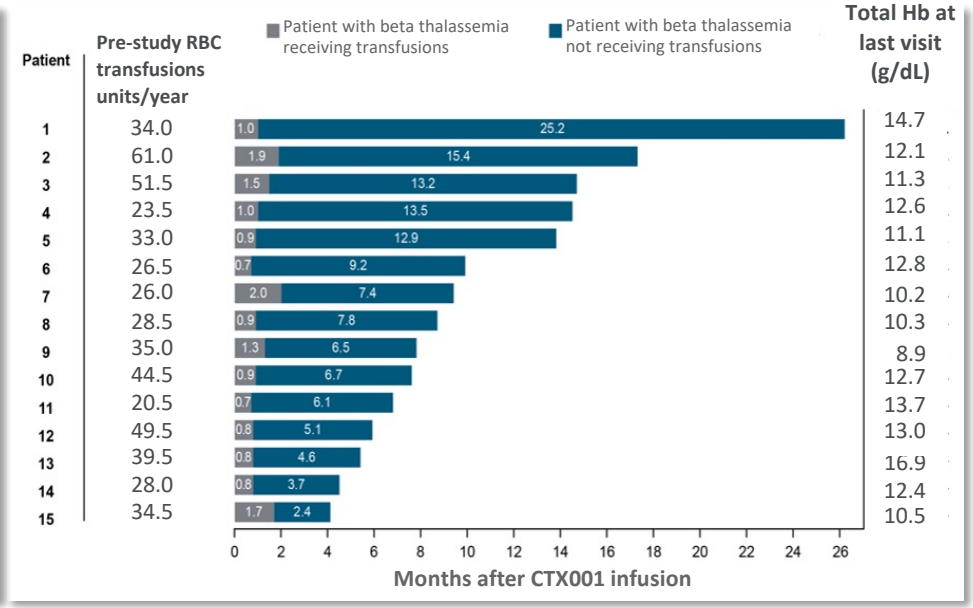
- Initial multibillion-dollar opportunity is ~32,000 patients with severe disease
- Potential to expand to ~170,000 patients across U.S. and EU

CTX001: A POTENTIALLY CURATIVE APPROACH IN SICKLE CELL DISEASE AND BETA THALASSEMIA

Sickle Cell Disease



Beta Thalassemia



Data presented at European Hematology Association Annual Meeting, June 2021

Plan to file BLA/MAA in Q4 2022

VX-880: STEM CELL-DERIVED, FULLY DIFFERENTIATED ISLETS FOR THE TREATMENT OF TYPE 1 DIABETES

1922: Leonard Thompson, first patient successfully treated with insulin


THE TORONTO DAILY STAR

TORONTO DOCTORS ON TRACK OF DIABETES CURE

RAILROAD UNIONS IN U.S. MAY JOIN IN MINERS' STRIKE

DIABETES SUFFERERS GIVEN MESSAGE OF HOPE

"DRY" LAWS HERE CAUSE HARDSHIP IN OLD FRANCE

RESERVES OF COAL ARE HIGH IN CITY, PRICE TO GO DOWN

CIVIL WAR STAGE NOT YET REACHED, BUT DANGER GREAT


LEONARD THOMPSON
First patient to receive insulin in Toronto.

2021: First patient dosed with fully differentiated, stem cell-derived islet cells

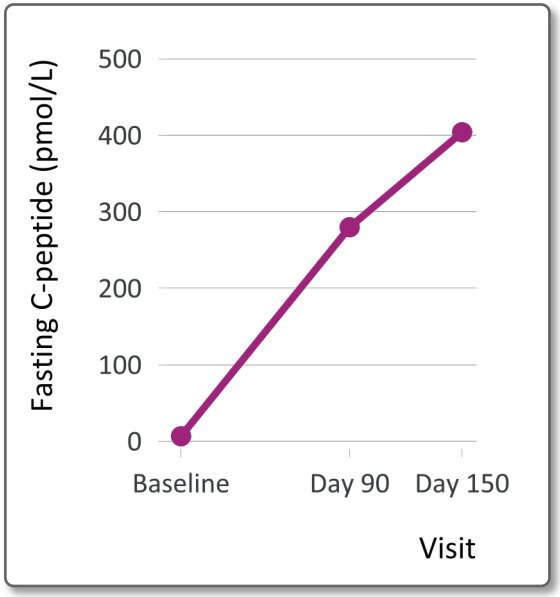
The New York Times

A Cure for Type 1 Diabetes? For One Man, It Seems to Have Worked.

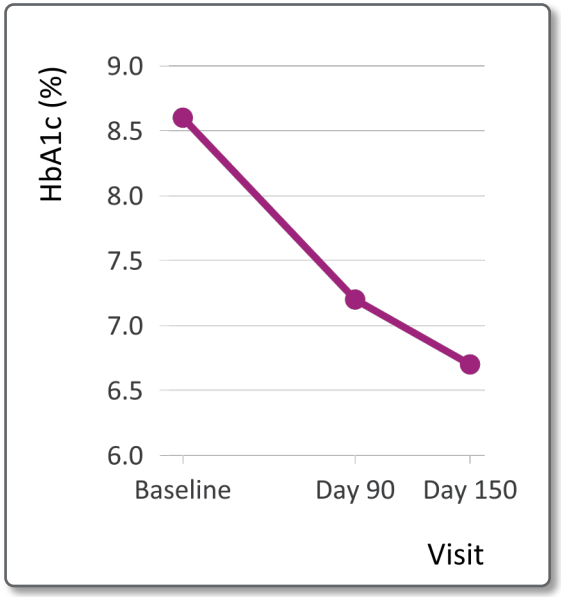
VX-880: POTENTIALLY TRANSFORMATIVE CELL THERAPY FOR TYPE 1 DIABETES

Day 150 data: 92% reduction in exogenous insulin use, simultaneous rapid improvement in glycemic control in 1st patient

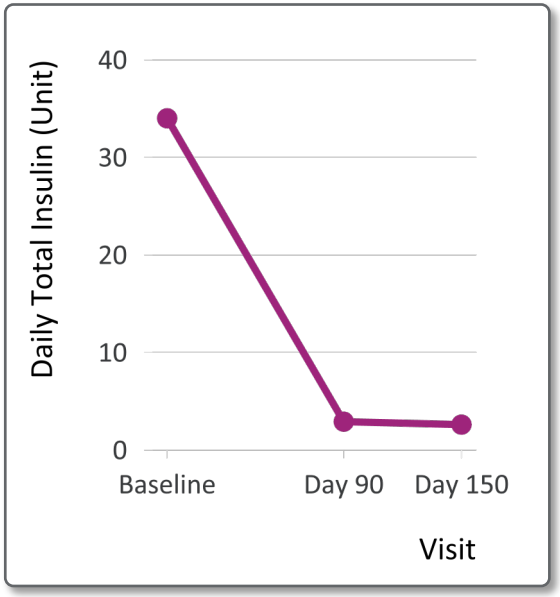
Fasting C-peptide increase to 404 pmol/L



HbA1c decline to 6.7%



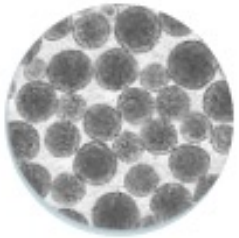
92% reduction in daily insulin use



VERTEX GOAL: PROVIDE CURATIVE TREATMENT TO ALL 2.6 MILLION PEOPLE LIVING WITH TYPE 1 DIABETES

TODAY

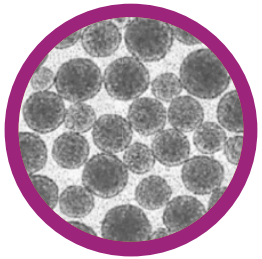
Stem cell-derived islets with standard immunosuppression



VX-880 Phase 1/2 underway

TOMORROW

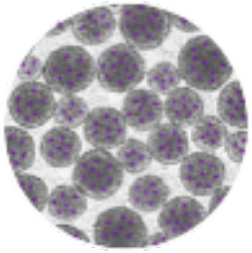
Stem cell-derived islets with encapsulation



IND expected to be filed in 2022

FUTURE

Stem cell-derived islets with hypoimmune gene editing

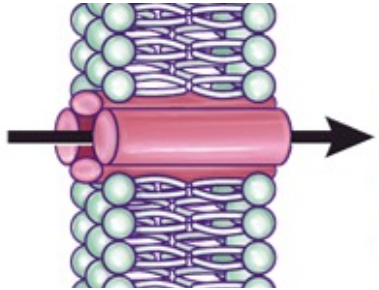


In preclinical development

Foundational advance: Fully differentiated, stem cell-derived islet cells that produce insulin

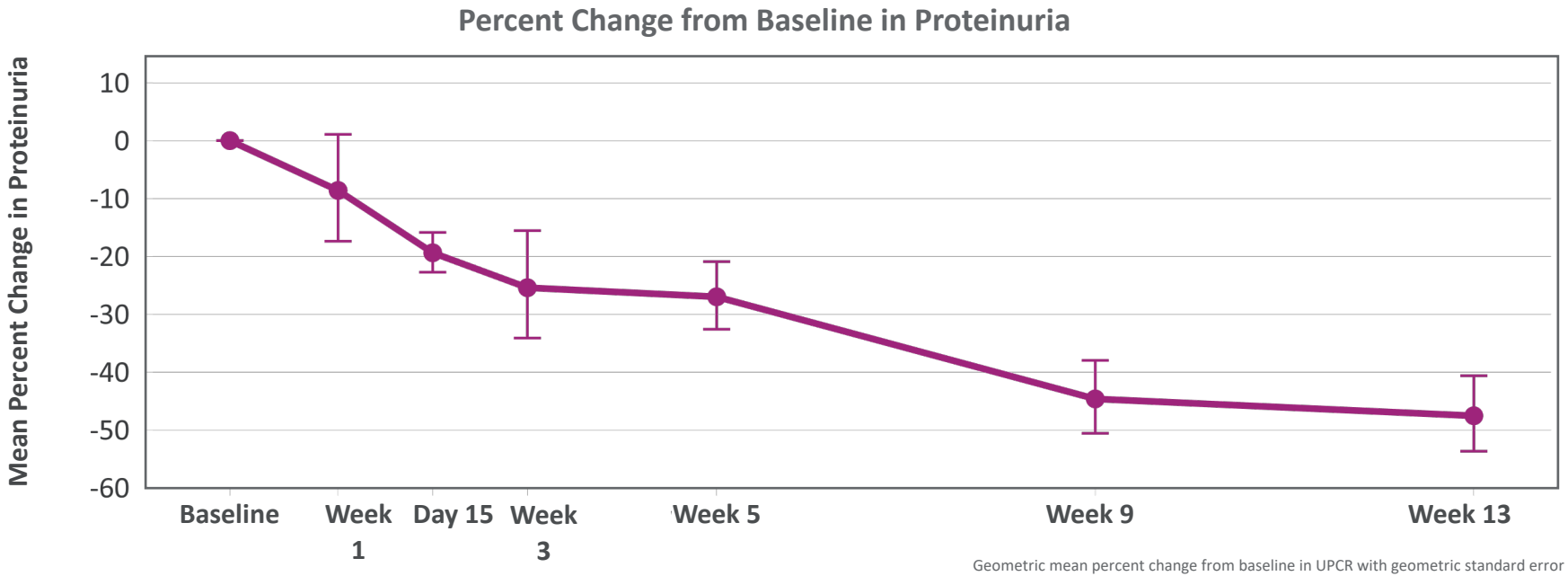
VX-147: PRECISION MEDICINE FOR APOL1-MEDIATED KIDNEY DISEASE

- There has been limited progress in the development of effective kidney disease medicines over the past 25 years
- The biggest barrier has been lack of insight into the underlying causal human biology of severe kidney disease
- VX-147 has the potential to become the first targeted therapy for APOL1-mediated kidney disease (AMKD), addressing a significant unmet need



VX-147: FIRST MEDICINE TARGETING APOL1-MEDIATED KIDNEY DISEASE

Phase 2 results in APOL1-mediated FSGS show 47.6% mean reduction in proteinuria, on top of standard-of-care

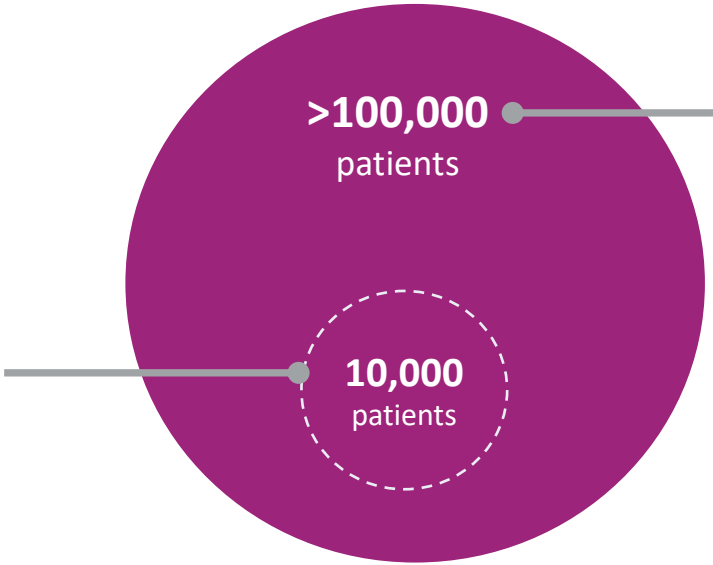


Geometric mean percent change from baseline in UPCR with geometric standard error

Plan to initiate VX-147 pivotal program in AMKD in Q1 2022

APOL1-MEDIATED KIDNEY DISEASE REPRESENTS A SIGNIFICANT OPPORTUNITY

APOL1-mediated kidney disease includes different clinical/histological presentations with the same genetic cause



APOL1-MEDIATED KIDNEY DISEASE

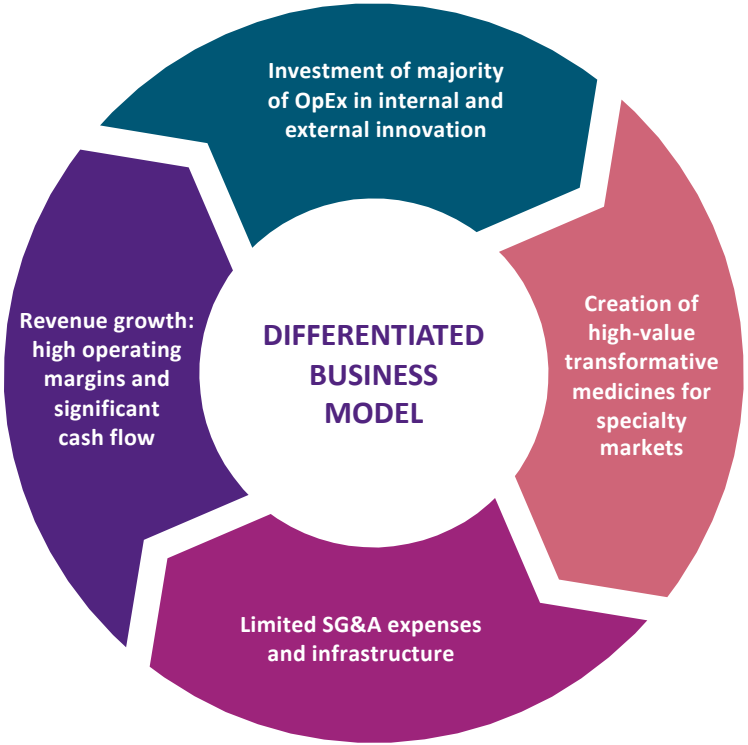
- **Broader** population
  - Includes APOL1-mediated FSGS
- Moderate to heavy proteinuria
- Clinically diagnosed
- Two APOL1 mutations

APOL1-MEDIATED FSGS

- **Narrower** population
- Heavy proteinuria
- Biopsy-diagnosed
- Two APOL1 mutations

OUR STRATEGY AND BUSINESS MODEL ARE DELIVERING

A BLUEPRINT FOR SERIAL INNOVATION



CORPORATE STRATEGY

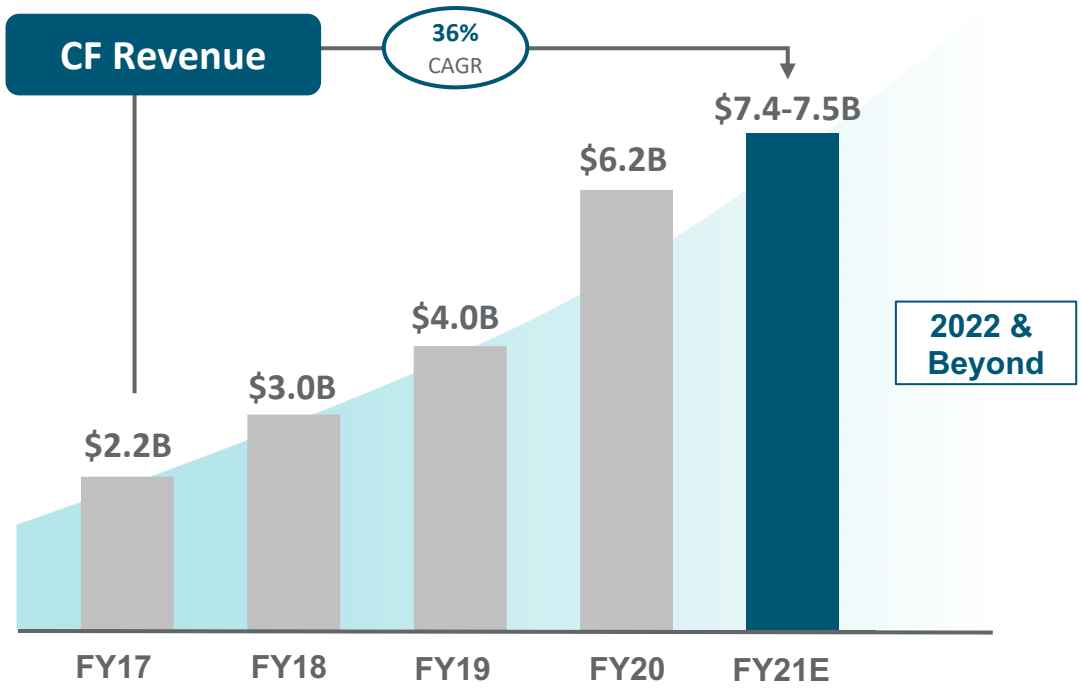
Vertex invests in scientific innovation to create transformative medicines for people with serious diseases with a focus on specialty markets

RESEARCH & DEVELOPMENT 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

STRONG TRACK RECORD OF REVENUE GROWTH, POISED FOR CONTINUED EXPANSION IN 2022 AND BEYOND



Future Revenue Growth Driven By:

Continued Growth in CF

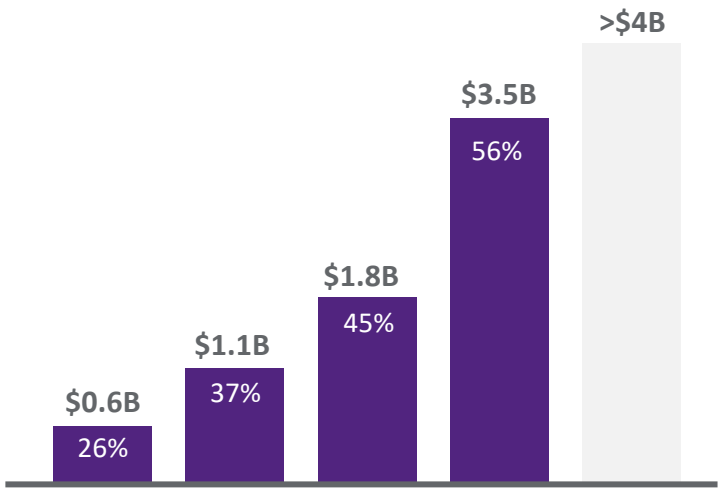
- Younger Age Groups
- New Reimbursements
- New Markets
- Expanded Addressable Patient Population

Commercialization in several new serious diseases, starting with sickle cell disease and beta thalassemia

Notes: FY19 CF Revenues are non-GAAP; see appendix for a reconciliation of FY19 CF Revenues; 2021 reflects the total CF revenue guidance updated on 11/2/2021; not meant as a reiteration of guidance; future revenue growth provided as a graphical representation and not intended as financial guidance; CAGR calculated based on midpoint of guidance range

BUSINESS MODEL SUSTAINS HIGH LEVELS OF PROFITABILITY, CASH FLOW AND SIGNIFICANT REINVESTMENT IN INNOVATION

Non-GAAP Operating Income and Non-GAAP Operating Margin (%)



Vertex Capital Deployment Priorities

Investment in Internal R&D

- Advancing our clinical and preclinical pipeline

Investment in External Innovation

- Approx. $3B invested and 14 new transactions since 2019
- External investments are represented in 40% of the clinical pipeline

Targeted Share Repurchases

- $2B in repurchases have reduced share count since 2019

Notes: See appendix for a reconciliation of FY17-FY20 GAAP Operating Income and Operating Margin to non-GAAP Operating Income and Operating Margin; FY21E Non-GAAP Operating Income reflects the midpoints of the total CF revenue and combined non-GAAP R&D & SG&A expense guidance ranges provided on 11/2/2021 and an estimate of approximately 13% for cost of revenues. Estimated 2021 GAAP Operating Income would be over $2.5B utilizing the same methodology. 2021 year-end cash and investments estimate based on approximately $7B of cash and investments as of 9/30/2021. Not intended as a reiteration of guidance.

KEY MILESTONES THAT WILL MARK OUR FORWARD PROGRESS

Continue to Innovate in Cystic Fibrosis

- Reach all CF patients who can benefit from TRIKAFTA/KAFTRIO
- Deliver therapies that drive ~90% of CF patients to carrier levels of CFTR function
  - Complete Phase 3 program for next-in-class VX-121/tez/VX-561 triple combination regimen
  - Continue to discover and develop innovative CFTR combination regimens
- Progress genetic therapies for the last ~10% of patients

Advance the Pipeline Beyond CF

- Secure approval & launch CTX001 a first-in-class gene editing approach for beta thal & SCD
- Advance VX-147 through pivotal development for APOL1-mediated kidney disease
- Progress novel NaV 1.8 inhibitors into pivotal development
- Advance cell therapies for type 1 Diabetes
- Move small molecule AAT correctors into the clinic and deliver PoC
- Advance new programs into the clinic (e.g., DMD, DM1, NaV1.7 for pain)
- Continue to invest in internal and external innovation

Deliver Strong Financial Performance

- Continued significant CF revenue growth through mid-decade
- Launch of new medicines to drive additional growth beyond CF
- Disciplined OpEx growth allowing continued high operating margins and cash flow

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APPENDIX

RECONCILIATION OF GAAP TO NON-GAAP FINANCIAL INFORMATION

	FY17	FY18	FY19	FY20	Q3'21 YTD
GAAP operating income	$123	$635	$1.20B	$2.86B	$1.90B
GAAP operating margin	*5%*	*21%*	*29%*	*46%*	*35%*
Stock compensation expense	291	325	360	430	323
Other adjustments	150	152	228	205	993
Non-GAAP operating income	564	1.11B	1.79B	3.49B	3.22B
Non-GAAP operating margin	*26%*	*37%*	*45%*	*56%*	*59%*

	FY19
GAAP total revenues	$4.16B
ORKAMBI adjustment	(156)
Non-GAAP total revenues	4.01B

Notes: All numbers in the above reconciliation table are in millions except where noted.