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THE SCIENCE *of* POSSIBILITY

# Phase 3 *EVOLVE & EXPAND* Studies of Tezacaftor/Ivacaftor Combination Show Statistically Significant Improvements in Lung Function and Other Measures in CF Patients

March 29, 2017

# Agenda

## Introduction

*Michael Partridge, VP Investor Relations*

## CF Strategy and Key Outcomes

*Jeff Leiden, M.D., Ph.D., Chairman, President and CEO*

## Phase 3 Data Discussion

*Jeff Chodakewitz, M.D., EVP and Chief Medical Officer*

## Q&A

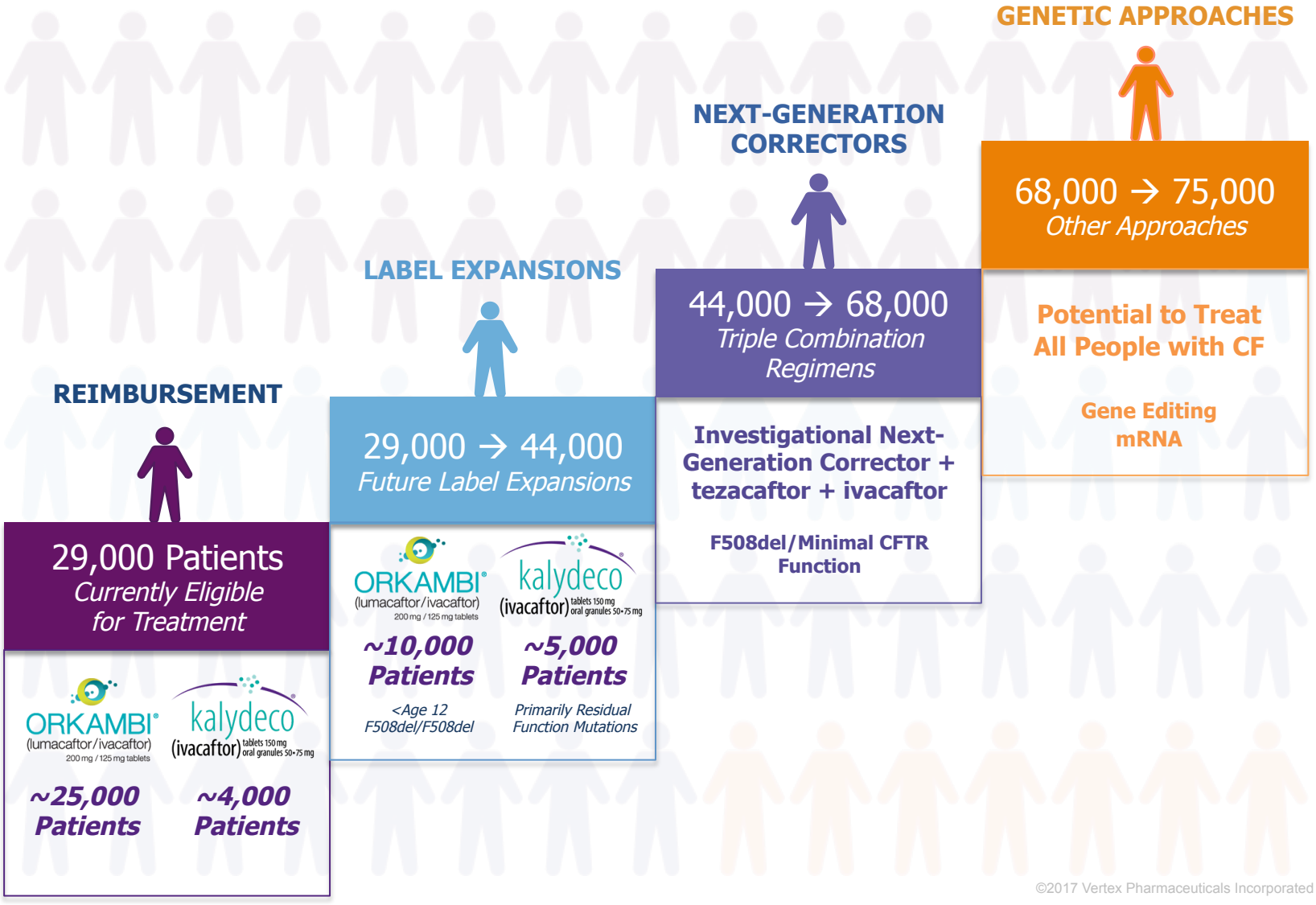
*Ian Smith, EVP, COO and CFO*

*Stuart Arbuckle, EVP and Chief Commercial Officer*

# Safe Harbor Statement

This presentation contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, including, without limitation, (i) information pertaining to tezacaftor in combination with ivacaftor, KALYDECO and ORKAMBI and the ongoing discovery, development and commercialization of Vertex's product candidates, and (ii) the timing of planned regulatory applications. 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, risks related to obtaining approval for tezacaftor in combination with ivacaftor, 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, and the risks and uncertainties listed in the Company's March 29, 2017 press release and under Risk Factors in the Company's 10-K and other filings with the SEC.

# Path to Treating All Patients



# Tezacaftor/Ivacaftor Combination:
## *Key Outcomes*

### Dual Combination Regimen

Potentially promising treatment option for two distinct patient groups:

- ✓ People with two copies of F508del mutation
- ✓ People with one residual function mutation and one F508del mutation

### Foundation for Triple Combination Regimen

Well-characterized two-drug combination for use as part of a future triple combination regimen when added to a next-generation corrector

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# *EVOLVE*

## Phase 3 Study of Tezacaftor/Ivacaftor Combination in People with F508del/F508del Mutations

*Jeff Chodakewitz, M.D.*
*EVP and Chief Medical Officer*

**Study Design and Baseline Characteristics**

**Primary Endpoint Results**

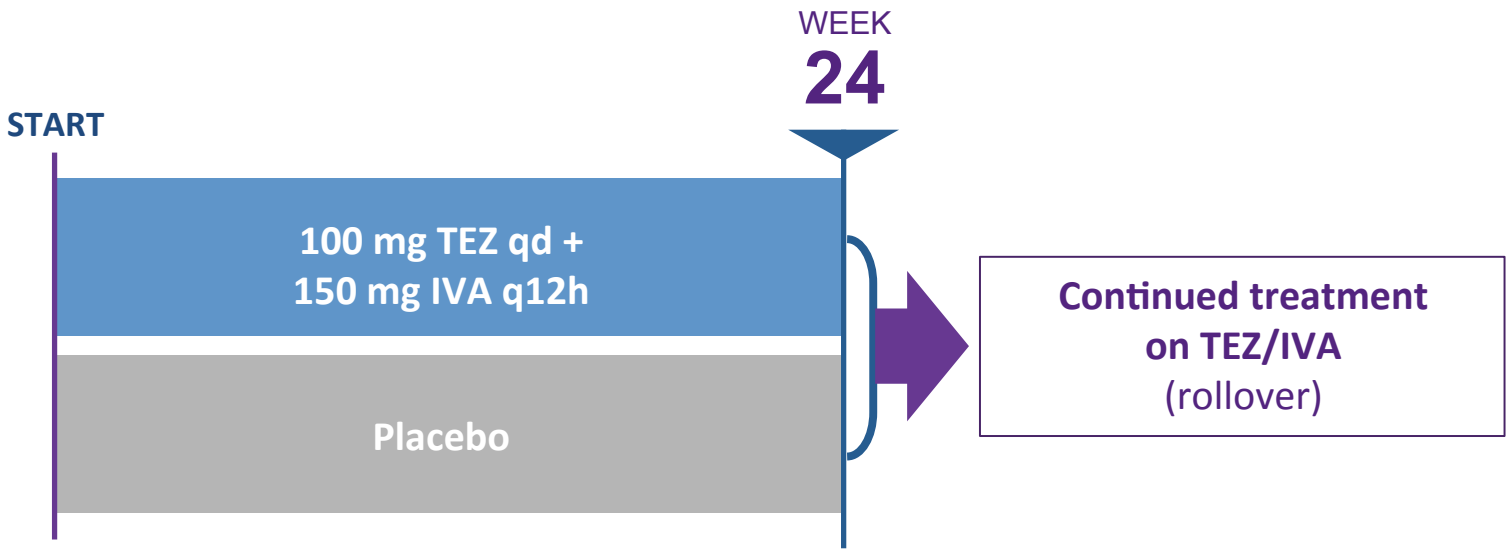
**Key Secondary Endpoints Results**

**Safety**

# Phase 3 Trial Design

EVOLVE

DESIGN & CHARACTERISTICS | PRIMARY ENDPOINT | SECONDARY ENDPOINTS | SAFETY




- Global Phase 3 randomized, double-blind, placebo-controlled study
- Enrolled more than 500 patients at more than 90 trial sites in North America and Europe
- Primary endpoint was mean absolute change from baseline in lung function in combination treatment compared to placebo through 24 weeks

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# Baseline Characteristics

EVOLVE



| Characteristics | Placebo n=256 | TEZ/IVA n=248 |
|---|---|---|
| **Sex** | | |
| Male | 131 (51.2) | 127 (51.2) |
| Female | 125 (48.8) | 121 (48.8) |
| **Age** | | |
| Mean (SD) | 25.7 (9.5) | 26.9 (11.2) |
| # of patients <18 (%) | 58 (22.7) | 58 (23.4) |
| # of patients ≥18 (%) | 198 (77.3) | 190 (76.6) |
| **Region** | | |
| North America (%) | 68 (26.6) | 59 (23.8) |
| Europe (%) | 188 (72.4) | 189 (76.2) |
| **% Predicted $FEV_1$ at Baseline** | | |
| Mean (SD) | 60.4 (15.7) | 59.6 (14.7) |
| # of patients <40 (%) | 24 (9.4) | 23 (9.3) |
| # of patients ≥40 to <=90 (%) | 225 (87.9) | 222 (89.5) |
| # of patients >90 (%) | 7 (2.7) | 2 (0.8) |

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# Efficacy Results:
## *Absolute Change in Lung Function*

EVOLVE

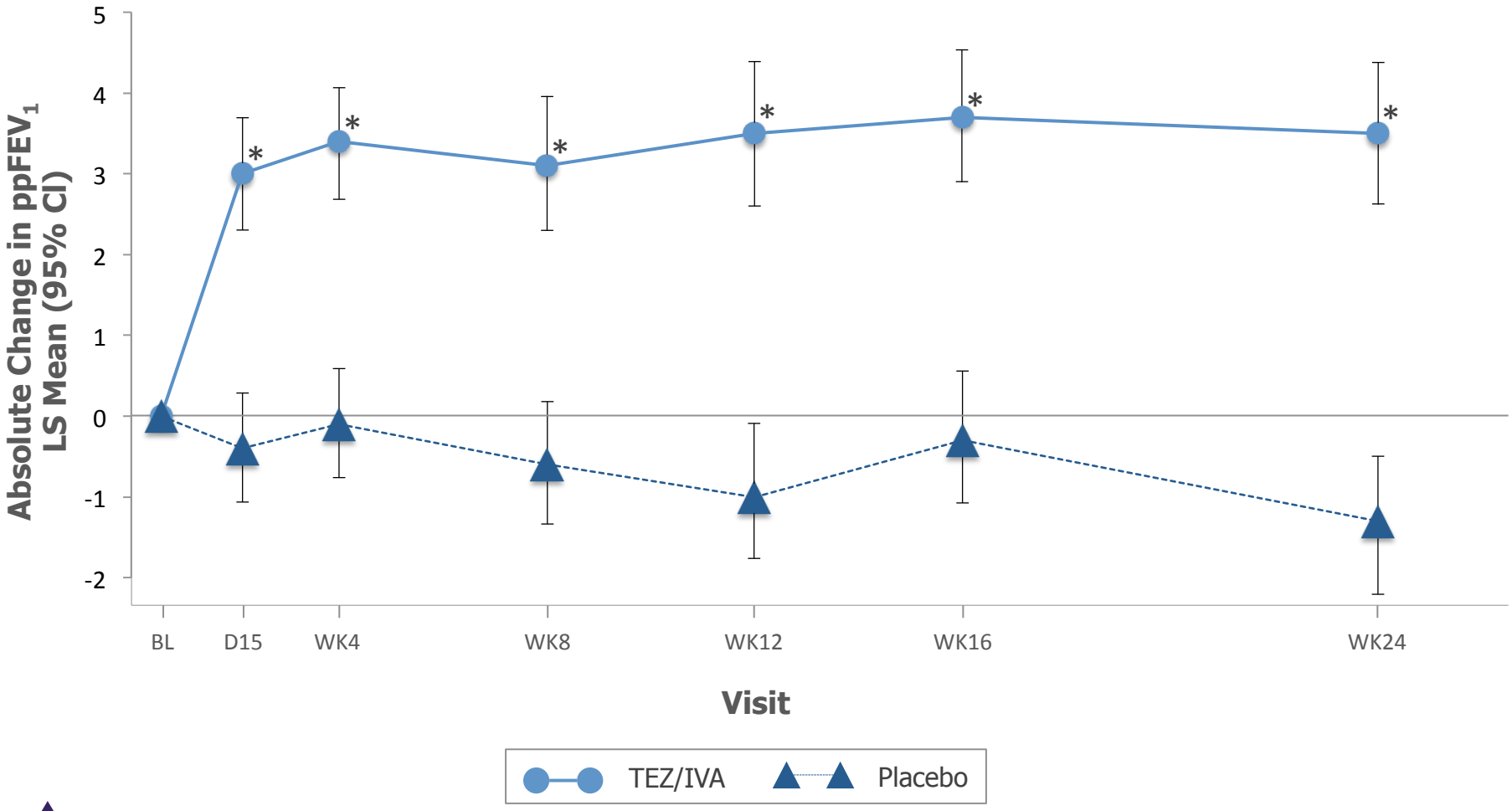
DESIGN & CHARACTERISTICS | **PRIMARY ENDPOINT** | SECONDARY ENDPOINTS | SAFETY

| | | Placebo n=256 | TEZ/IVA n=248 |
|---|---|---|---|
| *Mean absolute change in ppFEV$_1$ from baseline through week 24* | Treatment Difference | N/A | **+4.0** (p<0.0001) |
| | Within Group | -0.6 (p=0.0601) | +3.4 (p<0.0001) |

# Absolute Change in Lung Function Over Time

EVOLVE

DESIGN & CHARACTERISTICS | **PRIMARY ENDPOINT** | SECONDARY ENDPOINTS | SAFETY

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** p <0.0001 v. placebo and within group*

# Efficacy Results:
## *Key Secondary Endpoints*

EVOLVE



| Endpoint | | Placebo n=256 | TEZ/IVA n=248 |
|---|---|---|---|
| Relative $ppFEV_1$ through week 24 | Treatment Difference | N/A | +6.8 (p<0.0001^) |
| | Within Group | -0.5 (p=0.3823) | +6.3 (p<0.0001) |
| # of Pulmonary Exacerbations | Rate Ratio | N/A | 0.65 (p=0.0054^) |
| | # of Events (rate per 48 wks) | 122 (0.99) | 78 (0.64) |
| Change in BMI ($kg/m^2$) at week 24 | Treatment Difference | N/A | +0.06 (p=0.4127) |
| | Within Group | +0.12 (p=0.0134) | +0.18 (p=0.0004) |
| Change in CFQ-R through week 24 | Treatment Difference | N/A | +5.1 (p<0.0001) |
| | Within Group | -0.1 (p=0.8889) | +5.0 (p<0.0001) |

*^ Statistical significance was confirmed in the hierarchical testing procedure*

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# Frequency of Pulmonary Exacerbations Significantly Reduced

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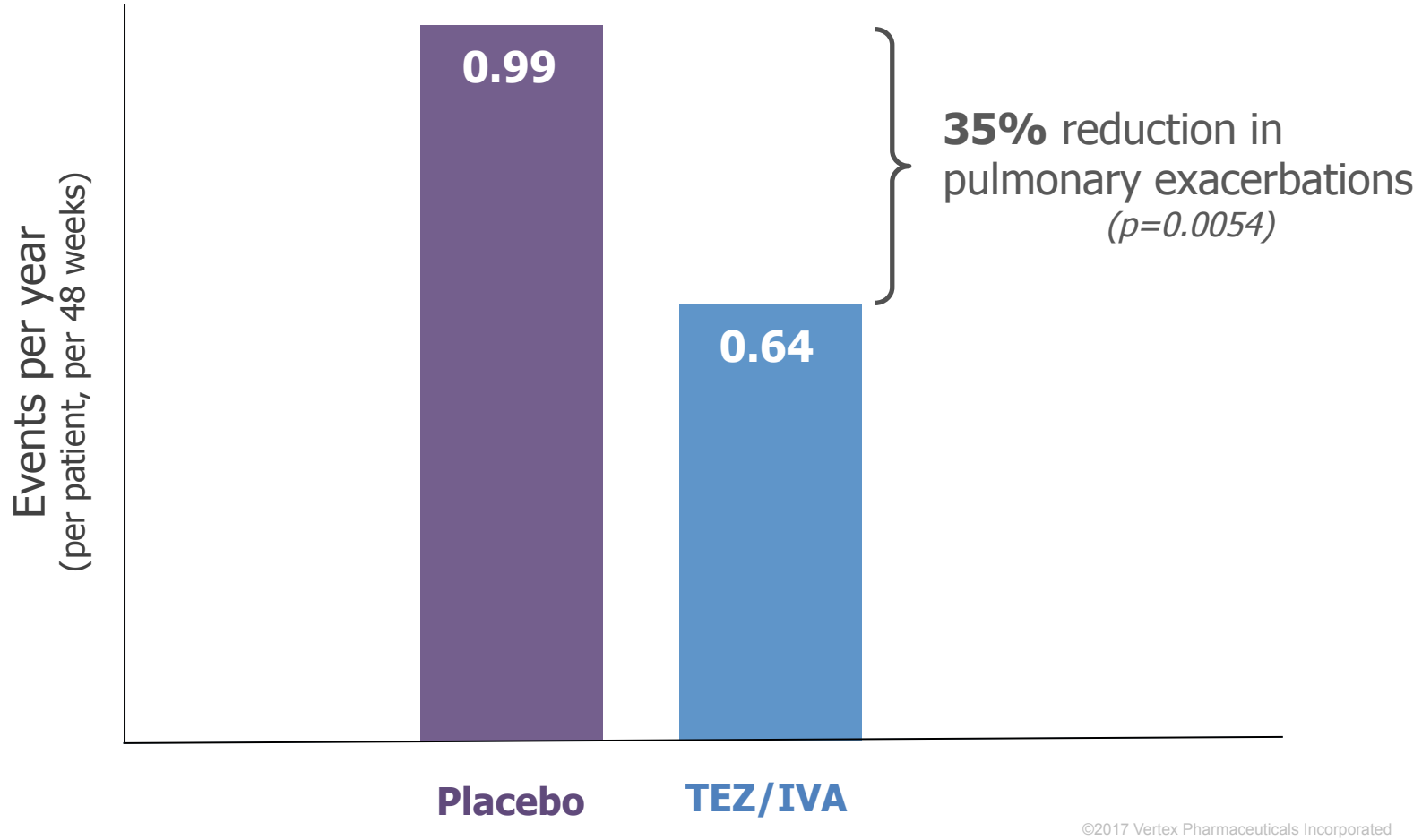

# Safety Summary

EVOLVE



- **Overall safety profile was favorable**
  - ✓ Rate of discontinuations due to adverse events was low and similar to placebo
  - ✓ Rates of adverse events and serious adverse events were similar to placebo
- **Rate of respiratory-related adverse events was similar to placebo**
- **97% of patients that completed treatment continued onto rollover study**

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# Safety Data

EVOLVE



| | Placebo n=258 (%) | TEZ/IVA n=251 (%) |
|---|---|---|
| Number of patients who experienced **any adverse event** | 245 (95.0) | 227 (90.4) |
| Number of patients who experienced **a serious adverse event** | 47 (18.2) | 31 (12.4) |
| Number of patients who **discontinued treatment due to adverse events** | 8 (3.1) | 7 (2.8) |
| **Most common adverse events:** | | |
| - Infective Pulmonary Exacerbation | 96 (37.2) | 75 (29.9) |
| - Cough | 84 (32.6) | 66 (26.3) |
| - Headache | 37 (14.3) | 44 (17.5) |
| - Nasopharyngitis | 39 (15.1) | 42 (16.7) |
| - Sputum Increased | 42 (16.3) | 36 (14.3) |
| Number of patients who experienced **any respiratory adverse event**: | 41 (15.9) | 33 (13.1) |
| Number of patients who experienced **selected respiratory adverse events:** | | |
| - Dyspnea | 18 (7.0) | 16 (6.4) |
| - Respiration Abnormal | 11 (4.3) | 11 (4.4) |
| - Bronchospasm | 2 (0.8) | 1 (0.4) |

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# *EXPAND*

## Phase 3 Study of Tezacaftor/Ivacaftor Combination and Ivacaftor Monotherapy in People with Residual Function/F508del Mutations

*Jeff Chodakewitz, M.D.*
*EVP and Chief Medical Officer*

**Study Design and Baseline Characteristics**

**Primary Endpoint Results**

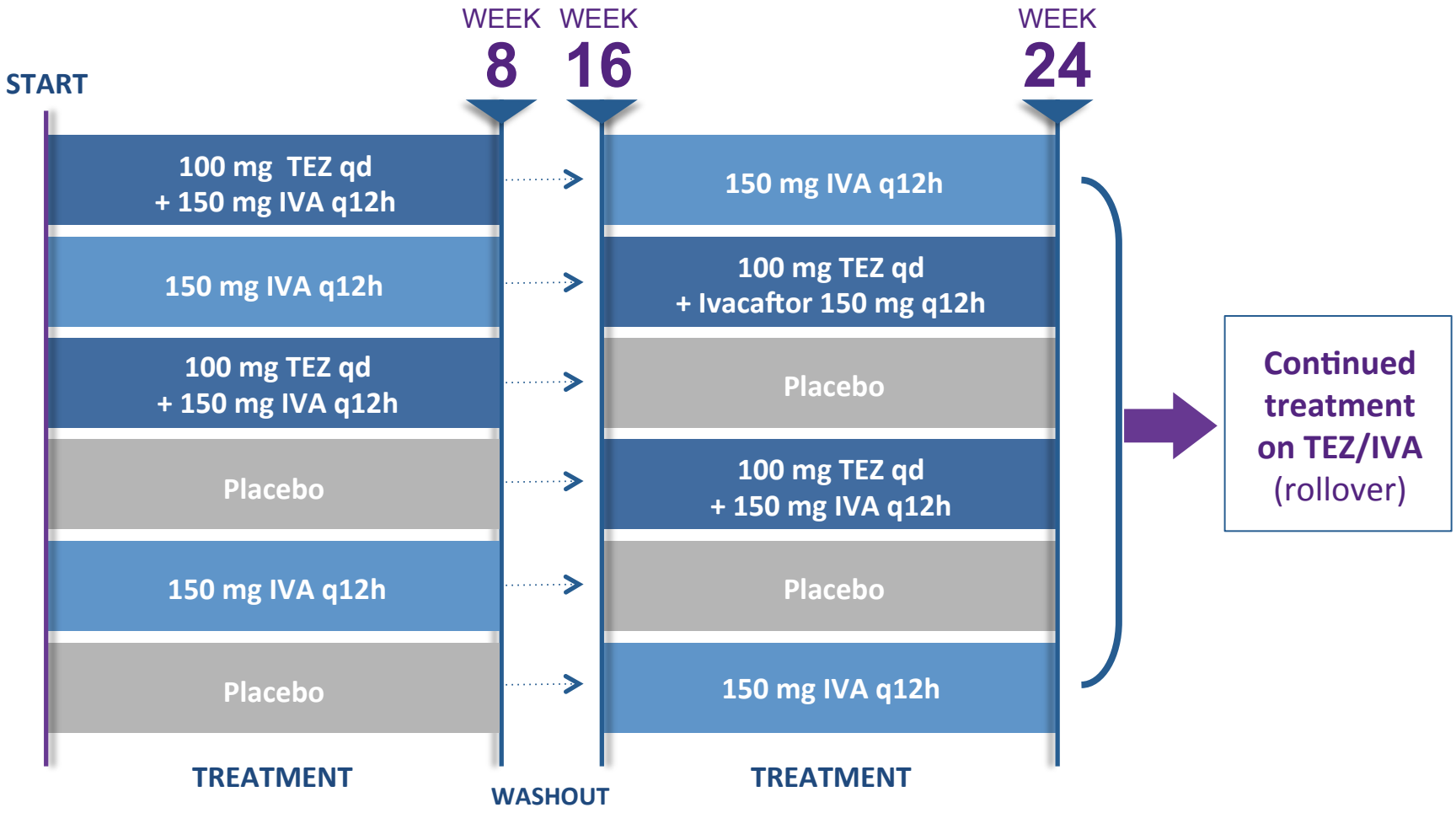
**Key Secondary Endpoint Results**

**Safety**

# Phase 3 Trial Design

**EXPAND**

**DESIGN & CHARACTERISTICS** | PRIMARY ENDPOINT | SECONDARY ENDPOINT | SAFETY



# Baseline Characteristics

EXPAND



| Characteristics | Placebo n=80 | IVA n=81 | TEZ/IVA n=83 |
|---|---|---|---|
| **Sex** | | | |
| Male | 34 (42.5) | 41 (50.6) | 35 (42.2) |
| Female | 46 (57.5) | 40 (49.4) | 48 (57.8) |
| **Age** | | | |
| Mean (SD) | 32.6 (13.9) | 36.3 (15.2) | 35.6 (13.5) |
| # of patients <18 (%) | 11 (13.8) | 12 (14.8) | 11 (13.3) |
| # of patients ≥18 (%) | 69 (86.3) | 69 (85.2) | 72 (86.7) |
| **Region** | | | |
| North America (%) | 39 (48.8) | 36 (44.4) | 45 (54.2) |
| Europe (%) | 41 (51.3) | 45 (55.6) | 38 (45.8) |
| **% Predicted $FEV_1$ at Baseline** | | | |
| Mean (SD) | 62.1 (14.0) | 62.8 (14.6) | 61.8 (14.9) |
| # of patients <40 (%) | 6 (7.5) | 8 (9.9) | 8 (9.6) |
| # of patients ≥40 to <=90 (%) | 73 (91.3) | 72 (88.9) | 73 (87.9) |
| # of patients >90 (%) | 1 (1.3) | 1 (1.2) | 2 (2.4) |

*n = Number of patients who received 8-week course of treatment based on randomization by first treatment. Almost all patients received two courses of treatment.*

# Primary Endpoint:
## *Absolute Change in Lung Function*

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### *Primary Endpoint*

| | | Placebo n=161 | Treatment Arm |
|---|---|---|---|
| **Tezacaftor + Ivacaftor** n=161 | Treatment Difference | N/A | **+6.8** (p<0.0001) |
| | Within Group | -0.3 (p=0.5035) | +6.5 (p<0.0001) |
| **Ivacaftor** n=156 | Treatment Difference | N/A | **+4.7** (p<0.0001) |
| | Within Group | -0.3 (p=0.5035) | +4.4 (p<0.0001) |

### *Pre-Specified Analysis*

| | | IVA n=156 | TEZ/IVA n=161 |
|---|---|---|---|
| **Tezacaftor + Ivacaftor vs. Ivacaftor** | Treatment Difference | N/A | +2.1 (p<0.0001) |
| | Within Group | +4.4 (p<0.0001) | +6.5 (p<0.0001) |

***Primary Endpoint*** *= mean absolute change in ppFEV1 from baseline to average of week 4 and week 8 measurements for the treatment groups (TEZ/IVA and IVA monotherapy) compared to placebo.*

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# Absolute Change in Lung Function Over Time

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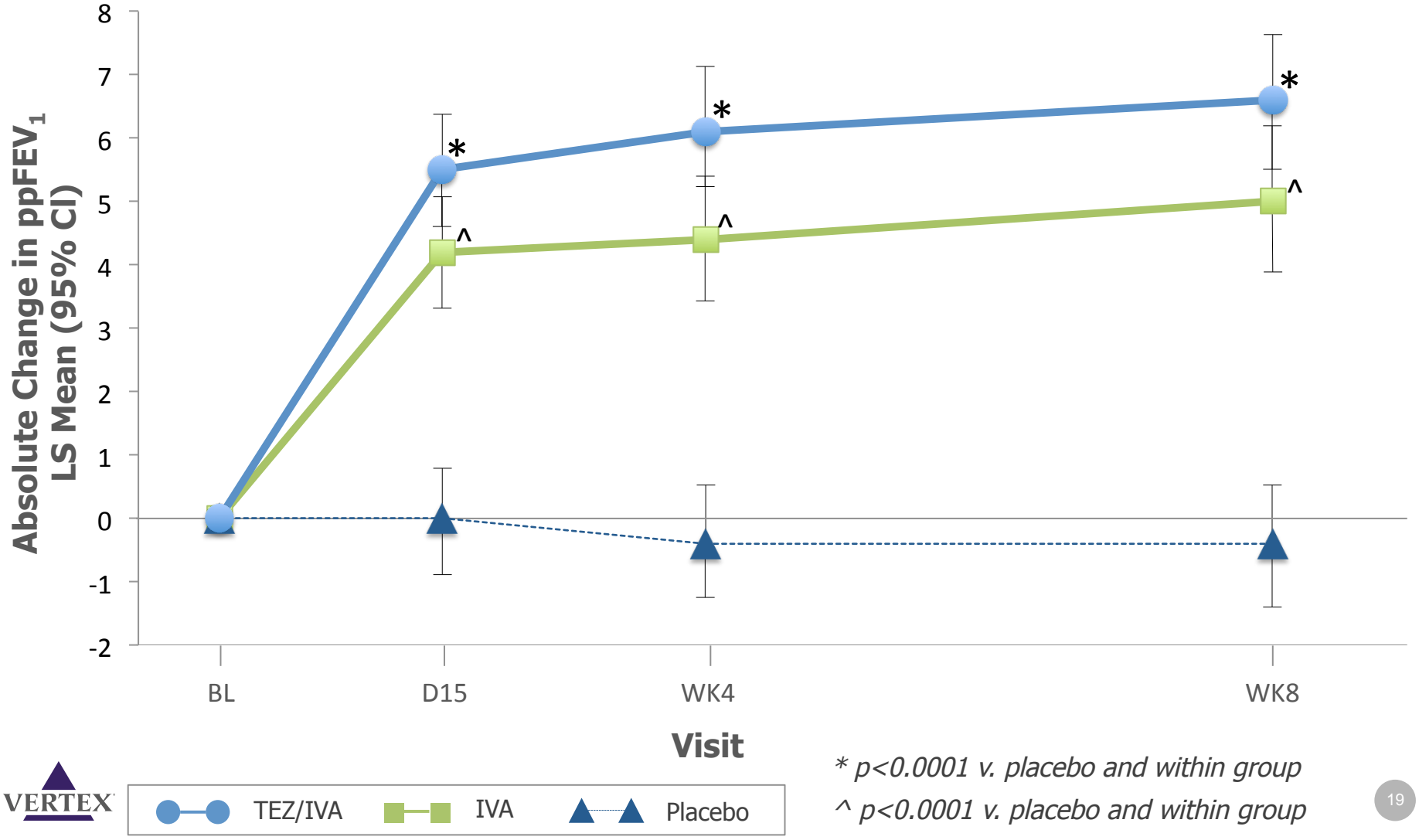
DESIGN & CHARACTERISTICS | **PRIMARY ENDPOINT** | SECONDARY ENDPOINT | SAFETY




** p<0.0001 v. placebo and within group*

*^ p<0.0001 v. placebo and within group*

# Secondary Endpoint:
## *Absolute Change in CFQ-R*

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| | | Placebo n=161 | Treatment Arm |
|---|---|---|---|
| **Tezacaftor + Ivacaftor** n=161 | Treatment Difference | N/A | **+11.1** (p<0.0001) |
| | Within Group | -1.0 (p=0.3265) | +10.1 (p<0.0001) |
| **Ivacaftor** n=156 | Treatment Difference | N/A | **+9.7** (p<0.0001) |
| | Within Group | -1.0 (p=0.3265) | +8.7 (p<0.0001) |

***Secondary Endpoint*** *= mean absolute change in CFQ-R from baseline to average of week 4 and week 8 measurements for the treatment groups (TEZ/IVA and IVA monotherapy) compared to placebo.*

# Safety Summary

EXPAND



- **Overall safety profile was favorable and similar to EVOLVE study**
  - ✓ Rate of discontinuations due to adverse events was low and similar to placebo
  - ✓ Rates of adverse events and serious adverse events were similar to placebo
- **Rate of respiratory-related adverse events was similar to placebo**
- **97% of patients that completed treatment continued onto rollover study**

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# EVOLVE and EXPAND Studies

| | Ph 3 EVOLVE (F508del/F508del) | Ph 3 EXPAND (Residual Function/ F508del) |
|---|---|---|
| Statistically significant and clinically meaningful improvements in lung function | ✓ | ✓ |
| Statistically significant improvements in multiple key secondary endpoints | ✓ | ✓ |
| Favorable safety profile | ✓ | ✓ |

**NDA and MAA submissions planned for Q3 2017**

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# Treating the Underlying Cause of CF

Phase 3 and long-term follow-up data provide significant evidence that any eligible CF patient should be **treated with a CFTR modulator**

Vertex remains committed to ensuring eligible patients gain **access to our medicines** as quickly as possible

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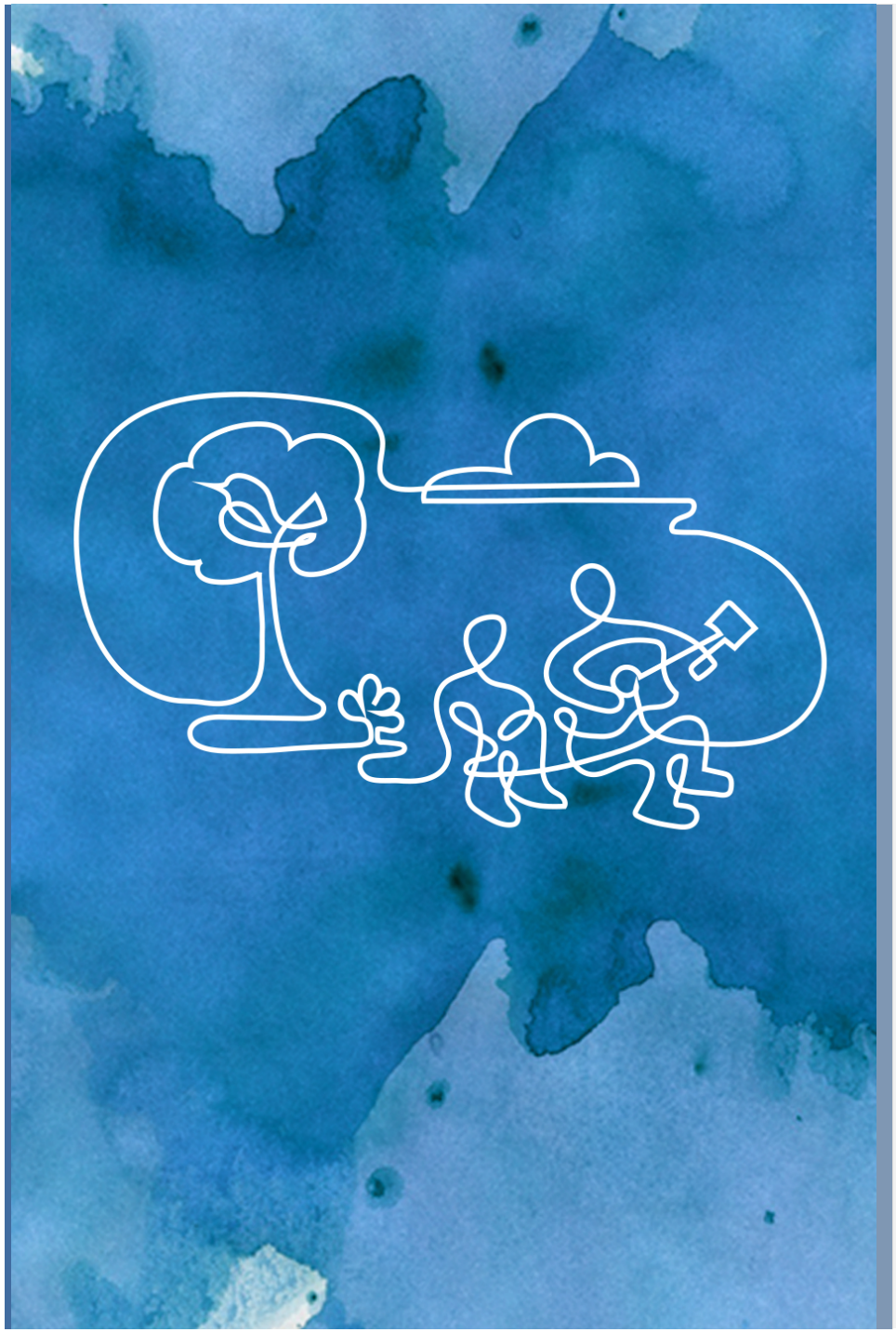

# *Thank You*

*…to the hundreds of patients who took part in our clinical trials, and the physicians, nurses, families and others who care for them.*

*…to our employees for their dedication to helping advance the treatment of CF.*

*…and to the CF community for their support and commitment to changing the course of CF.*