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THE SCIENCE *of* POSSIBILITY

# Phase 1 and 2 Data for Triple Combination Regimens Demonstrate Improvements in Lung Function and Other Measures in CF Patients

July 18, 2017

# Agenda

## Introduction

*Michael Partridge, VP Investor Relations*

## Advancing Vertex's CF Strategy

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

## Highlights of Data and Next Steps

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

## Q&A

*Ian Smith, EVP, COO and CFO*

# Safe Harbor Statement

This presentation contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, including (i) the path to treating all patients with CF and (ii) Vertex's plans to initiate pivotal development of one or more triple combination regimens in the first half of 2018. 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 a number of factors that could cause actual events or results to differ materially from those indicated by such forward-looking statements. Those risks and uncertainties include, among other things, (i) that Vertex could experience unforeseen delays in conducting its development programs relating to triple combination treatments and in submitting related regulatory filings, (ii) that the initial results set forth in this press release may differ from the final results from these ongoing studies, (iii) that regulatory authorities may not approve, or approve on a timely basis, triple combination treatments due to safety, efficacy or other reasons, and (iv) and other risks listed under Risk Factors in Vertex's annual report and quarterly reports filed with the Securities and Exchange Commission and available through the company's website at www.vrtx.com. Vertex disclaims any obligation to update the information contained in this presentation as new information becomes available.

# Path to Treating All Patients

**30,000 Patients**
*Currently Eligible for Treatment*

ORKAMBI® (lumacaftor/ivacaftor) 200 mg / 125 mg tablets

kalydeco® (ivacaftor) tablets 150 mg, oral granules 50+75 mg

**Tezacaftor/Ivacaftor**
***NDA Submitted & MAA Planned for Q317***
***(F508del/F508del Ages 12+)***

**30,000 → 44,000**
*Future Label Expansions & Investigational Tezacaftor/Ivacaftor Combination*

| | |
|---|---|
| ORKAMBI® (lumacaftor/ivacaftor) 200 mg / 125 mg tablets | *F508del/F508del <Age 12* |
| kalydeco® (ivacaftor) tablets 150 mg, oral granules 50+75 mg | *Residual Function & Ages 0-2* |
| **Tezacaftor/ Ivacaftor*** | *Residual Function/ F508del Ages 12+* |

**NDA Submitted & MAA Planned Q317*

**44,000 → 68,000**
*Triple Combination Regimens*

**Investigational Next-Generation Corrector + Tezacaftor / Ivacaftor**

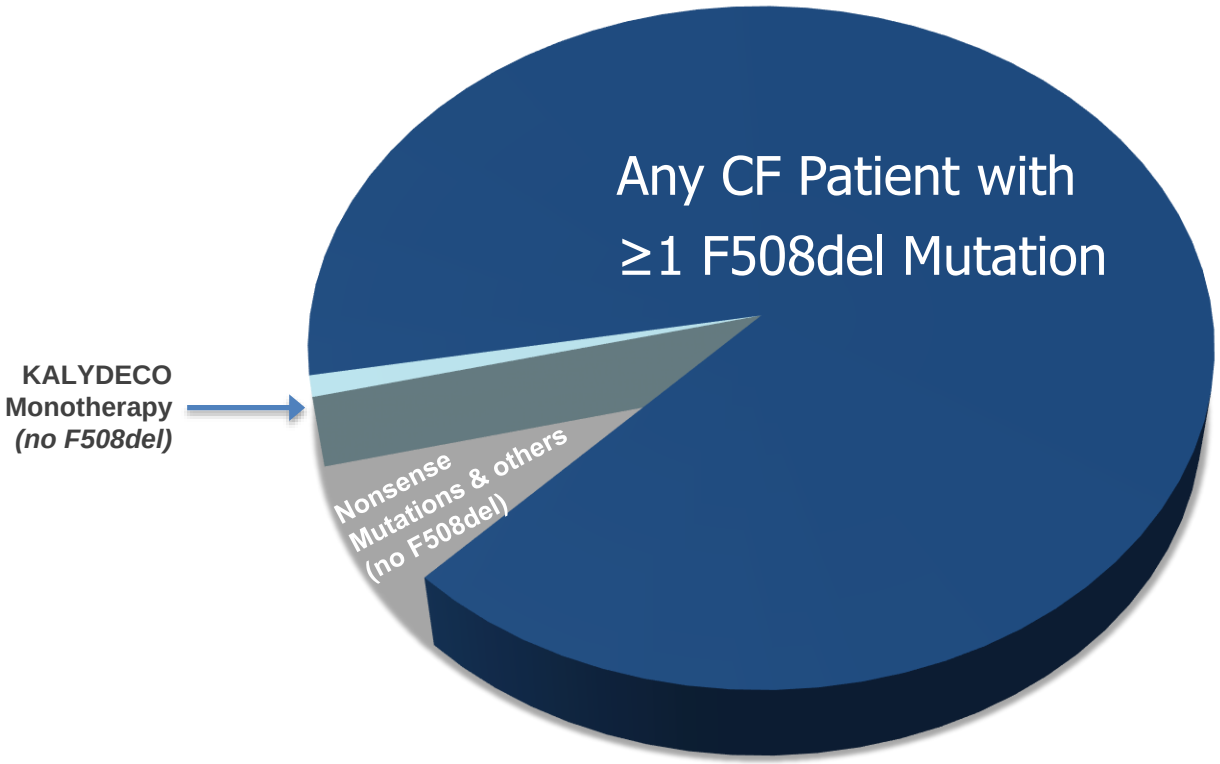
*F508del/Minimal CFTR Function*

**68,000 → 75,000**
*Other Future Approaches*

**Gene Editing**
**mRNA**

*Potential to treat all people with CF*

# Potential to Treat 90% of CF Patients with Next Generation Triple Combination Regimens




**GOAL:** Create Medicines that Fundamentally Alter the Progression of CF for All Patients

# Key Takeaways

**First Demonstration that Triple Combination Regimens Can Improve Lung Function and Other Clinical Measures in F508del/Min patients**

**Addition of a Next-Gen Corrector to Tez/Iva Can Provide Significant Additional Benefit in F508del Homozygous patients**

**Safety Profile Favorable to Date and Supports Further Development of Any One or More of These Regimens**

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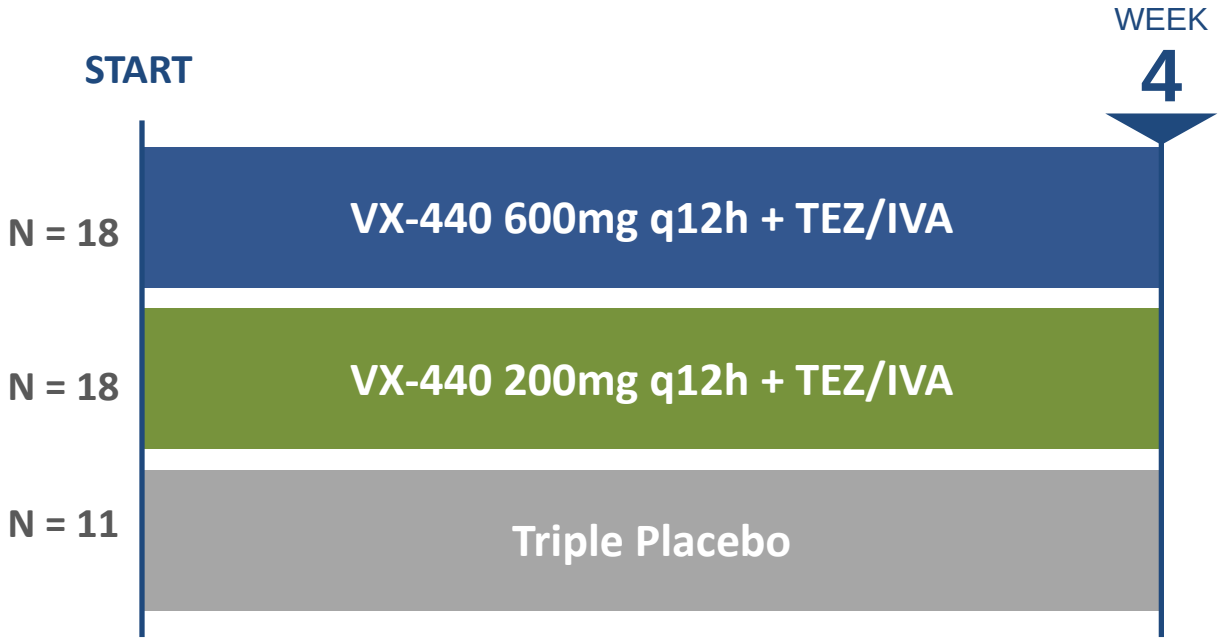
# VX-440

**Phase 2 Evaluation in Cystic Fibrosis Patients**

- F508del/Minimal function (n=47)
- F508del homozygous (n=26)

# VX-440 Dosing in CF Patients with F508del/minimal function mutations




- Primary Objectives: Safety, tolerability and efficacy as assessed by mean absolute change in $ppFEV_1$ from baseline
- Secondary Endpoints: Sweat chloride and CFQ-R
- Key eligibility criteria for these cohorts:
  - F508del/minimal function mutations
  - ≥18 years old
  - $ppFEV_1$, 40-90% inclusive
  - Excluded patients with G6PD Deficiency

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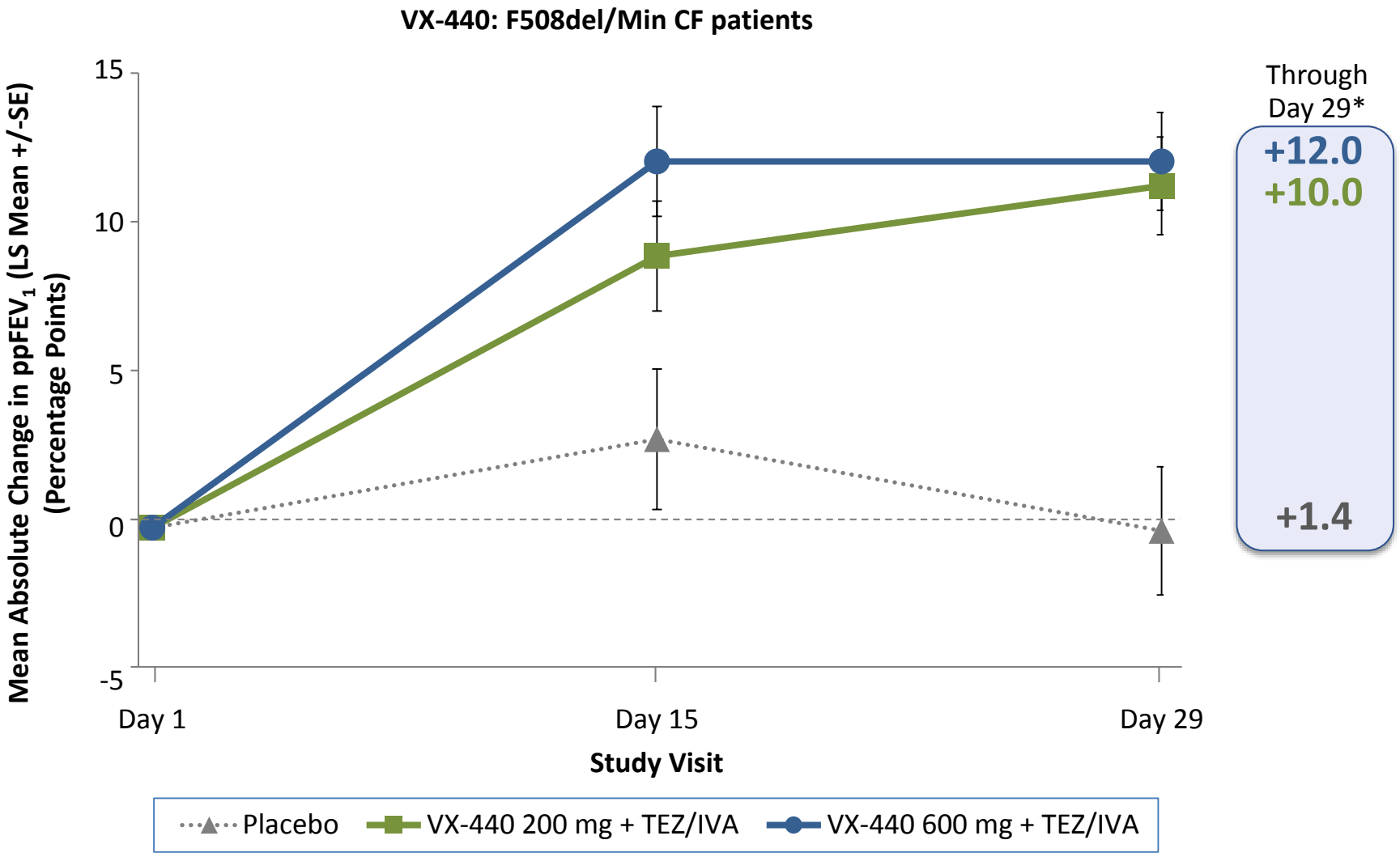
# VX-440: Safety Summary

**In Phase 2 studies in F508del/Min and F508del/F508del patients:**

- VX-440 in combination with tezacaftor and ivacaftor was generally well tolerated and the overall safety profile was favorable
- The majority of adverse events were mild or moderate
- The most common adverse events, regardless of treatment group, were infective pulmonary exacerbation, cough, sputum increased and diarrhea
- One patient treated with VX-440 600mg q12h had elevated liver enzymes >5x ULN and discontinued treatment. One patient treated with VX-440 600 mg q12h had elevated liver enzymes >8x ULN, which were observed on the final day of dosing. In both patients, the elevated liver enzymes returned to normal after treatment discontinuation or completion.

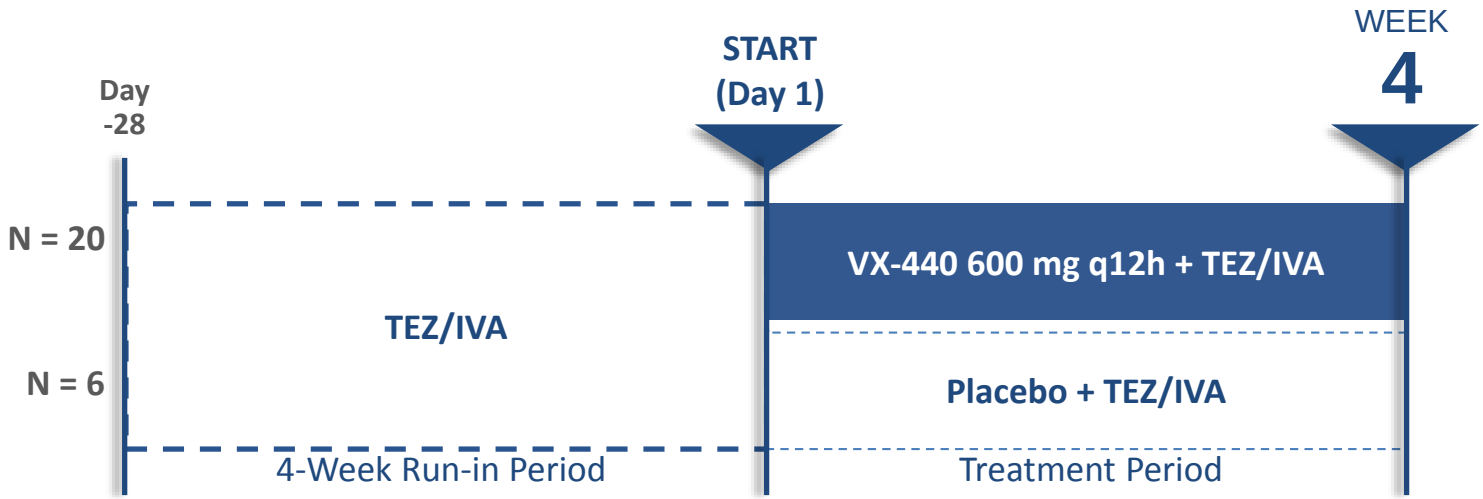
VERTEX

# Absolute Change in Lung Function Over Time




*Values expressed as "Through Day 29" are the average of Day 15 and Day 29 measures, the primary efficacy endpoint of the study

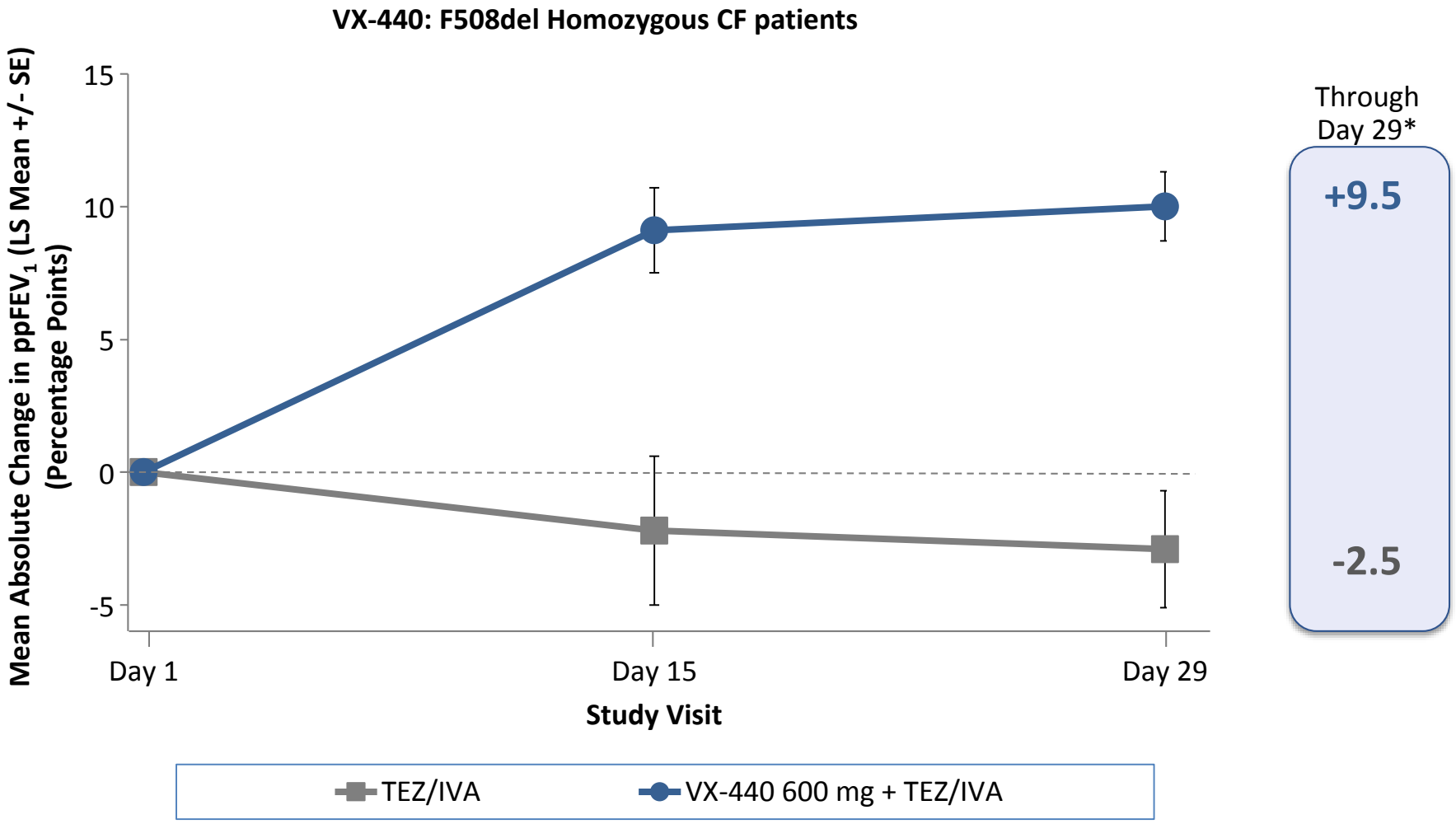
# VX-440 Dosing in CF Patients Homozygous for F508del, Following Run-in with TEZ/IVA




- Primary Objectives: Safety, tolerability and efficacy as assessed by mean absolute change in ppFEV$_1$ from baseline (post the 4-week TEZ/IVA run-in period)
- Secondary Endpoint: Sweat chloride (post the 4-week TEZ/IVA run-in period)
- Key eligibility criteria for these cohorts:
  - F508del/F508del homozygous mutations
  - ≥18 years old
  - ppFEV$_1$, 40-90% inclusive
  - Excluded patients with G6PD Deficiency

VERTEX

# Absolute Change in Lung Function Over Time

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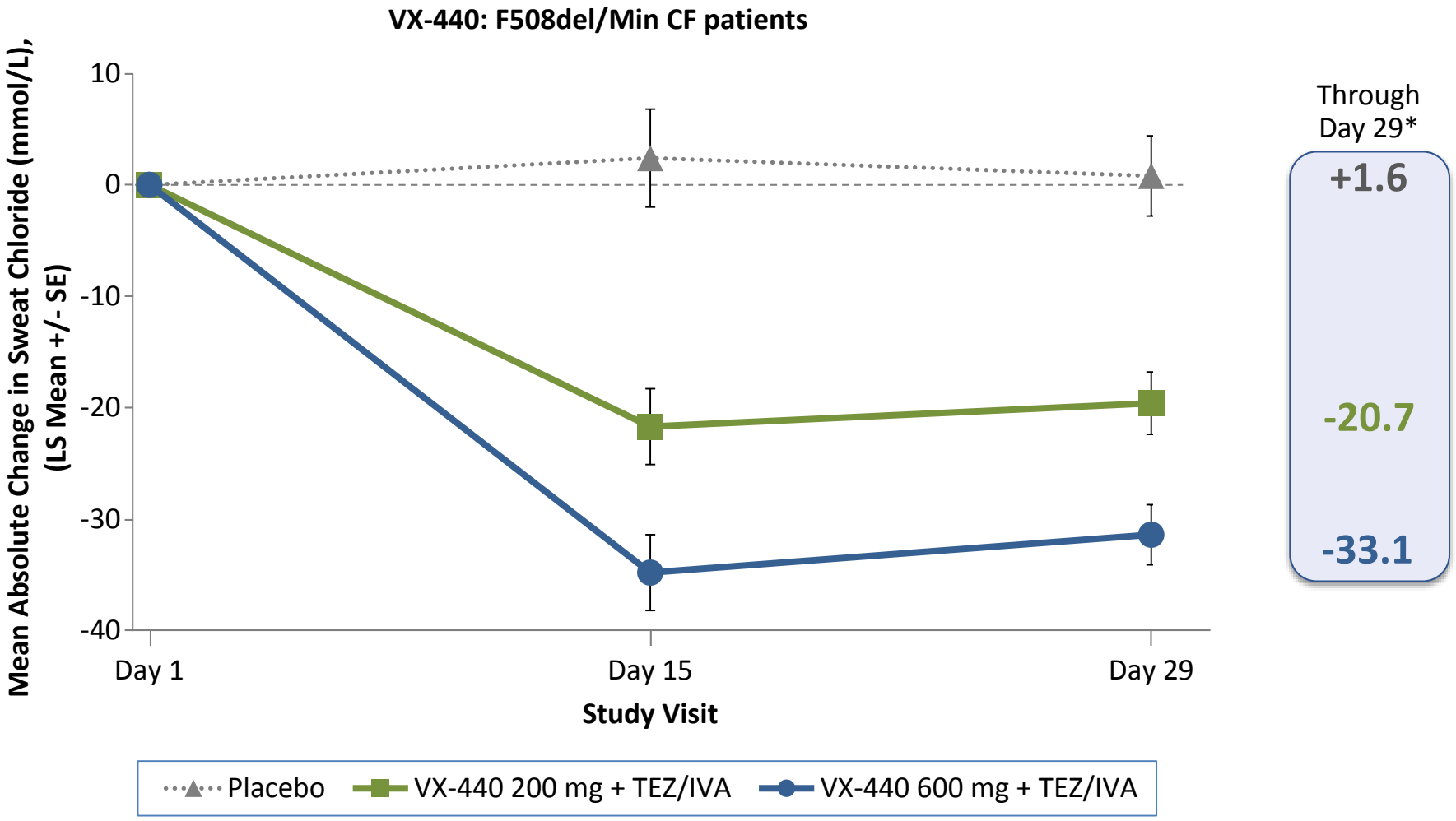
# Sweat Chloride Significantly Reduced

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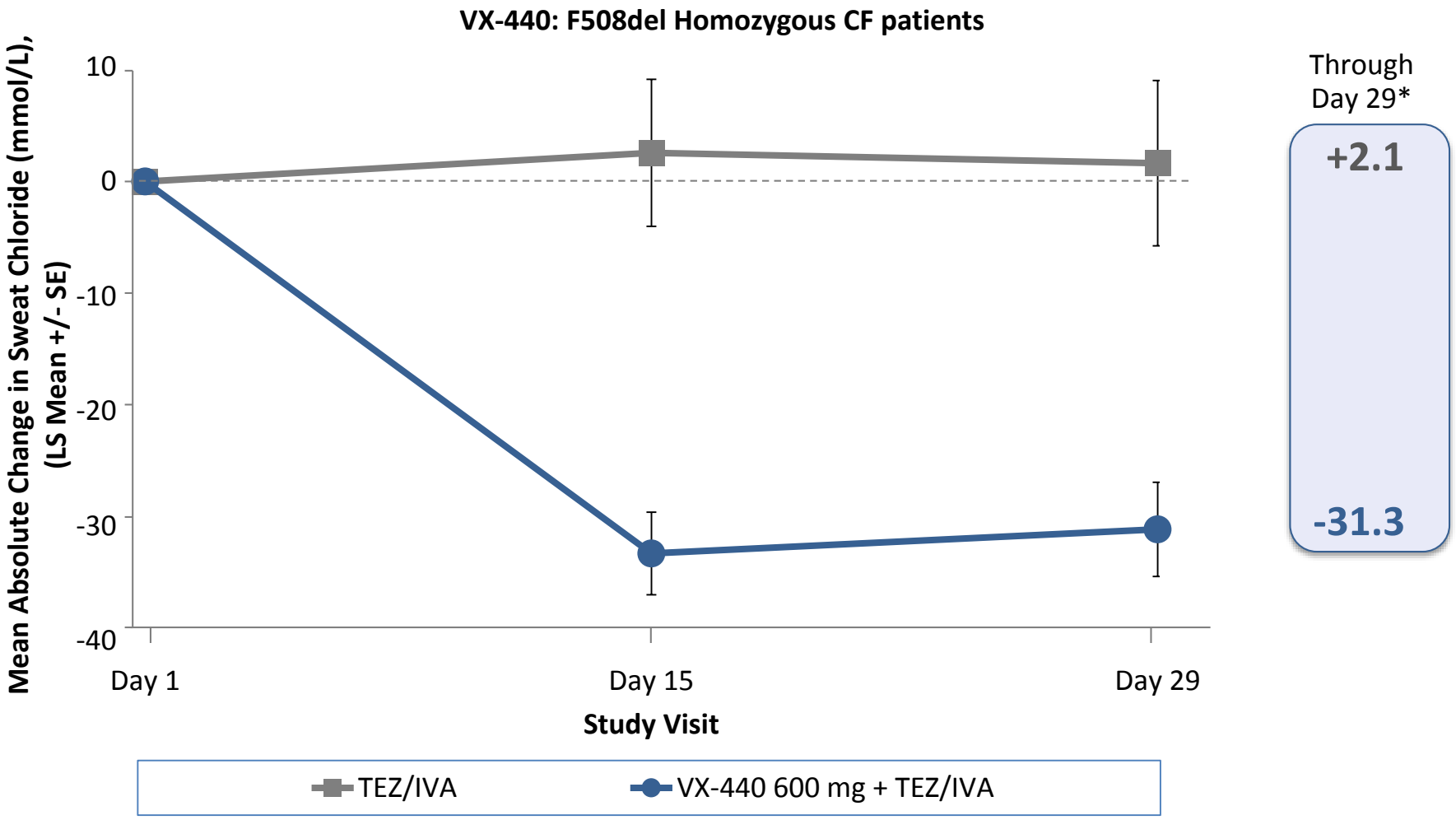



*Values expressed as "Through Day 29" are the average of Day 15 and Day 29 measures

# Significant Improvements in Respiratory Symptoms

**VX-440: F508del/Min CF patients**

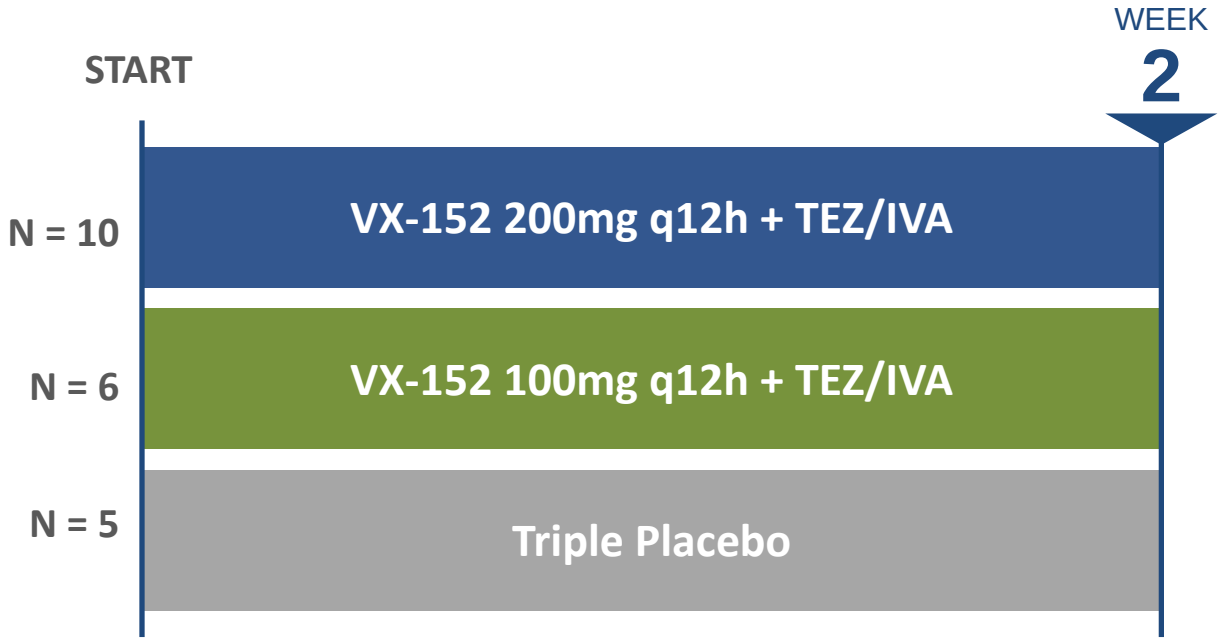
| Treatment Arm | Mean Absolute Change CFQ-R Respiratory Domain at Day 29 (LS Mean, points) |
|---|---|
| Triple Placebo | +2.2 |
| VX-440 200 mg + TEZ/IVA | +18.3 |
| VX-440 600 mg + TEZ/IVA | +20.7 |

# VX-152

**Initial Phase 2 Evaluation in Cystic Fibrosis Patients**

- F508del/minimal function (n=21)
- F508del homozygous (n=14)

# VX-152 Dosing in CF Patients with F508del/minimal function mutations



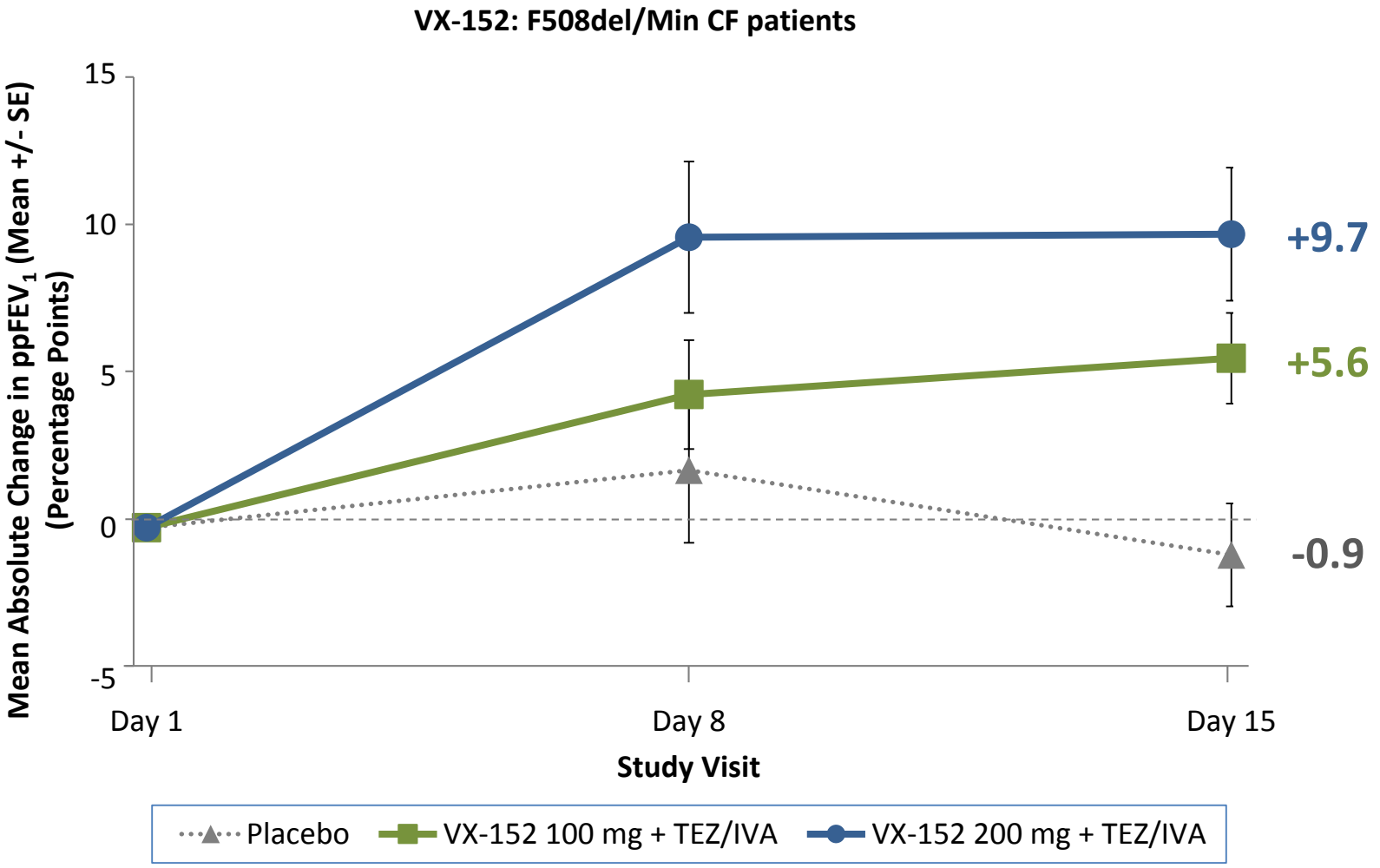

- Primary Objective: Safety and Tolerability
- Secondary Endpoints: Mean absolute change in $ppFEV_1$ from baseline and change in sweat chloride
- Key eligibility criteria for these cohorts:
  - F508del/minimal function mutations
  - ≥18 years old
  - $ppFEV_1$, 40-90% inclusive
  - Excluded patients with G6PD Deficiency

# VX-152: Safety Summary

**In Phase 2 studies in F508del/Min and F508del/F508del patients:**

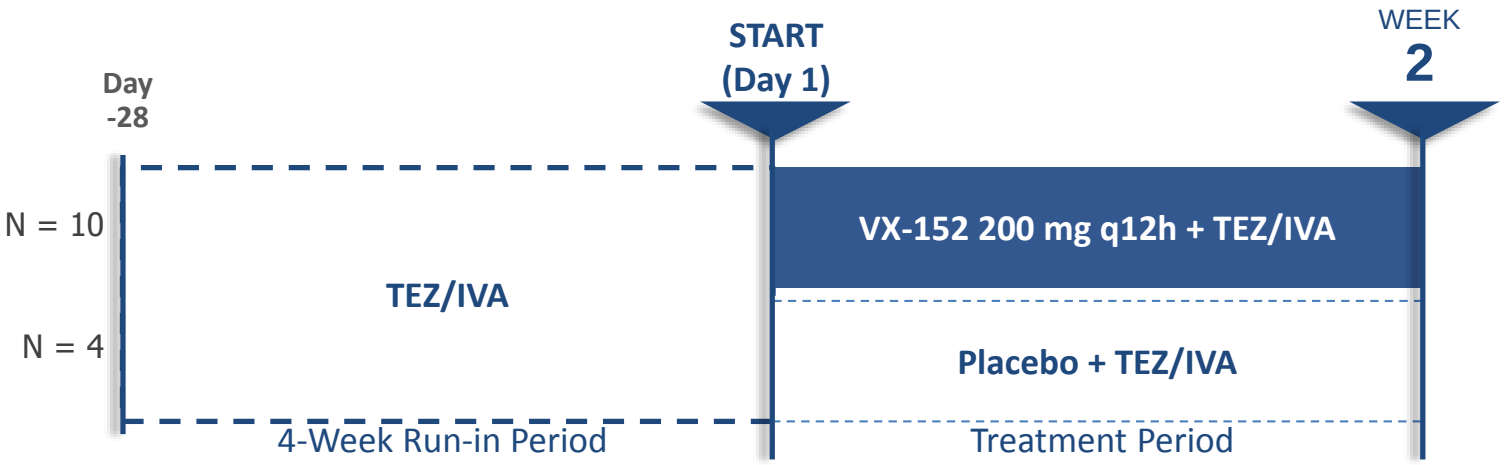
- VX-152 in combination with tezacaftor and ivacaftor was generally well tolerated and the overall safety profile was favorable
- The majority of adverse events were mild to moderate
- The most common adverse events, regardless of treatment group, were cough, sputum increased, infective pulmonary exacerbation, productive cough, diarrhea and fatigue
- There was one discontinuation due to pneumonia in a patient receiving VX-152 200mg q12h

# Absolute Change in Lung Function Over Time




Graph depicts observed data; an efficacy analysis using mixed effect models will be conducted following completion of an additional cohort of patients currently being treated in the study

# VX-152 Dosing in CF Patients Homozygous for F508del, Following Run-in with TEZ/IVA




- Primary Objective: Safety and tolerability
- Secondary Objectives: Mean absolute change in $ppFEV_1$ and change in sweat chloride from baseline (post 4-week TEZ/IVA run-in period)
- Key eligibility criteria for these cohorts:
  - F508del/F508del homozygous mutations
  - ≥18 years old
  - $ppFEV_1$, 40-90% inclusive
  - Excluded patients with G6PD Deficiency

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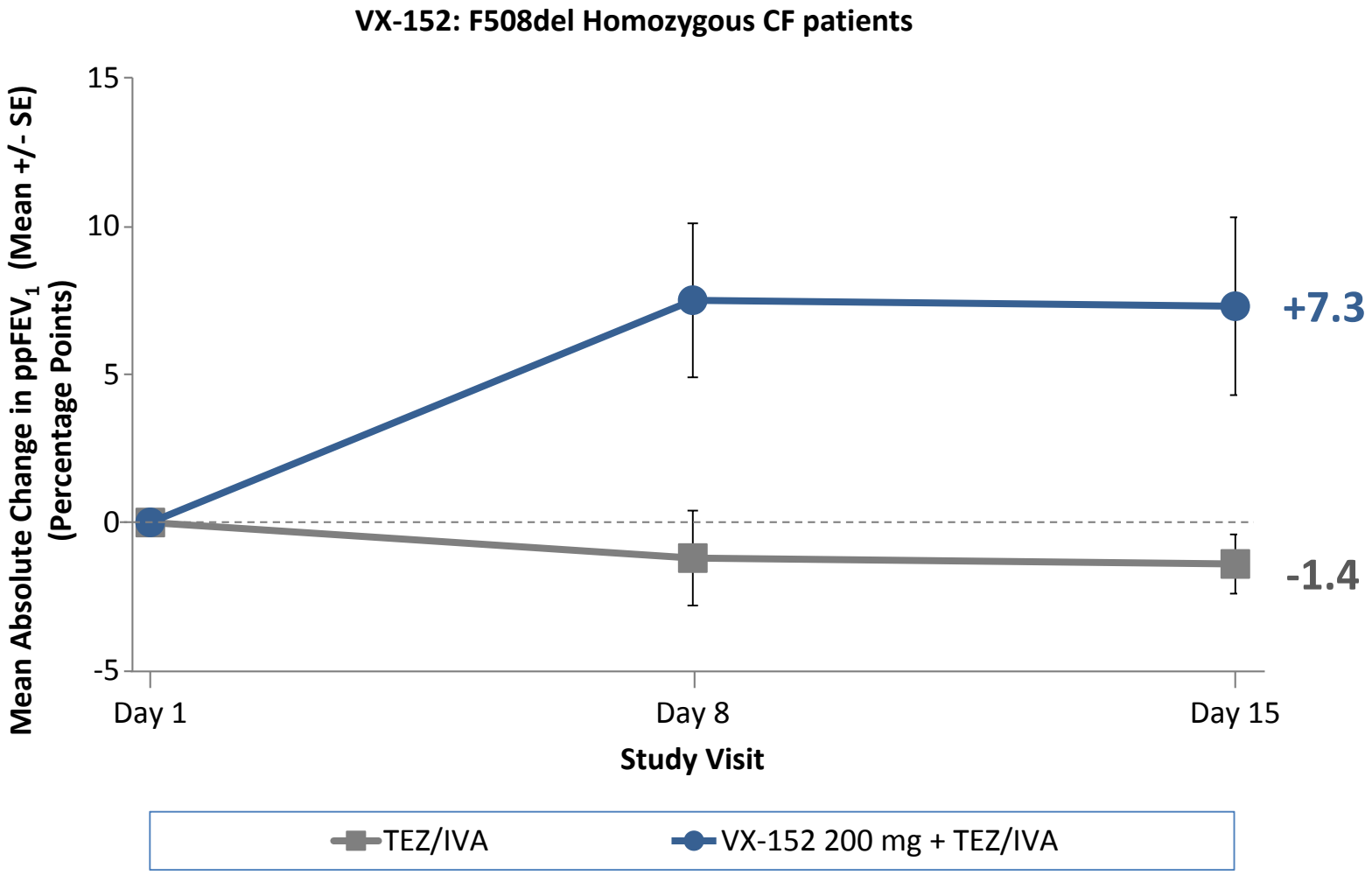
# Absolute Change in Lung Function Over Time

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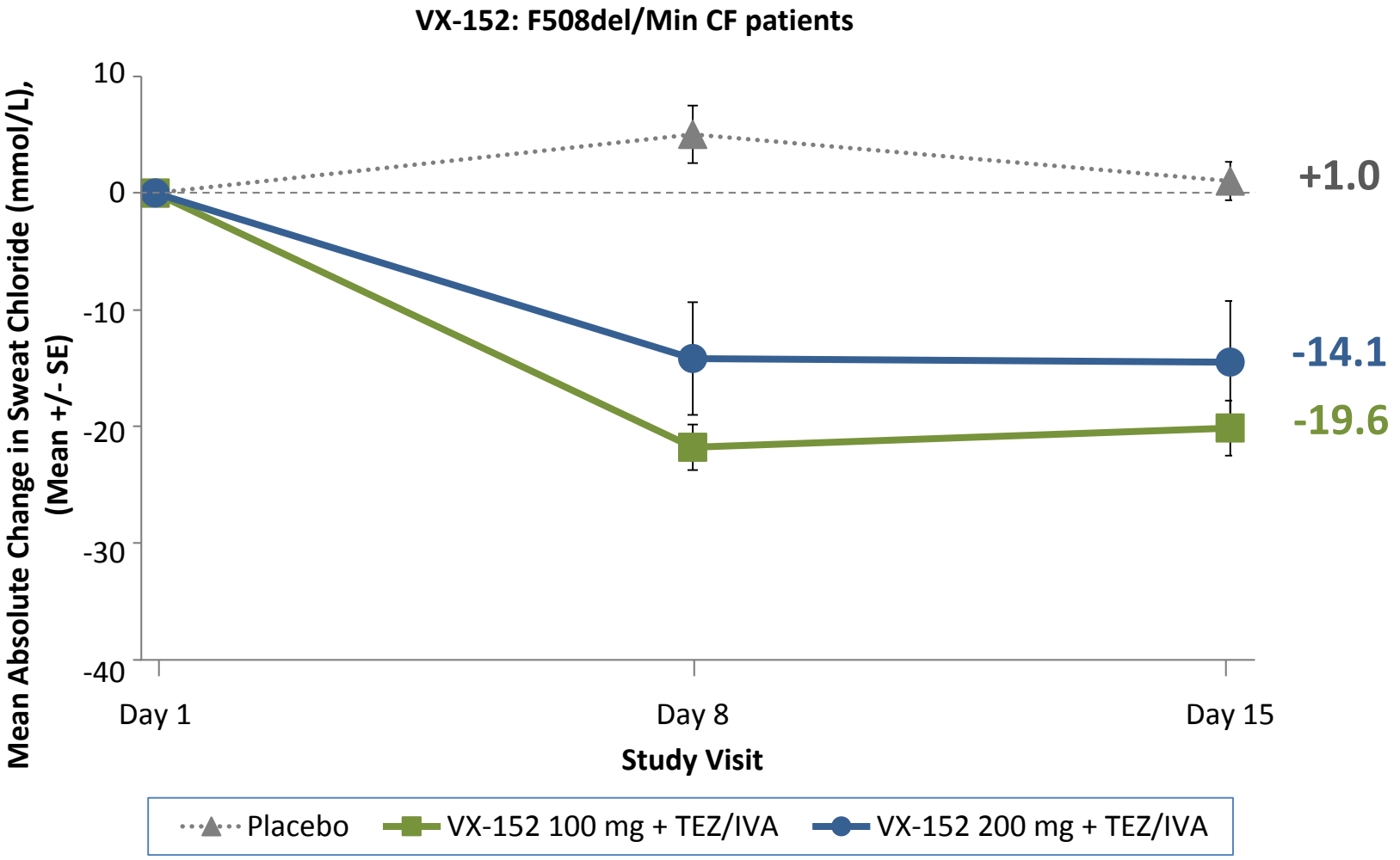
# Sweat Chloride Significantly Reduced

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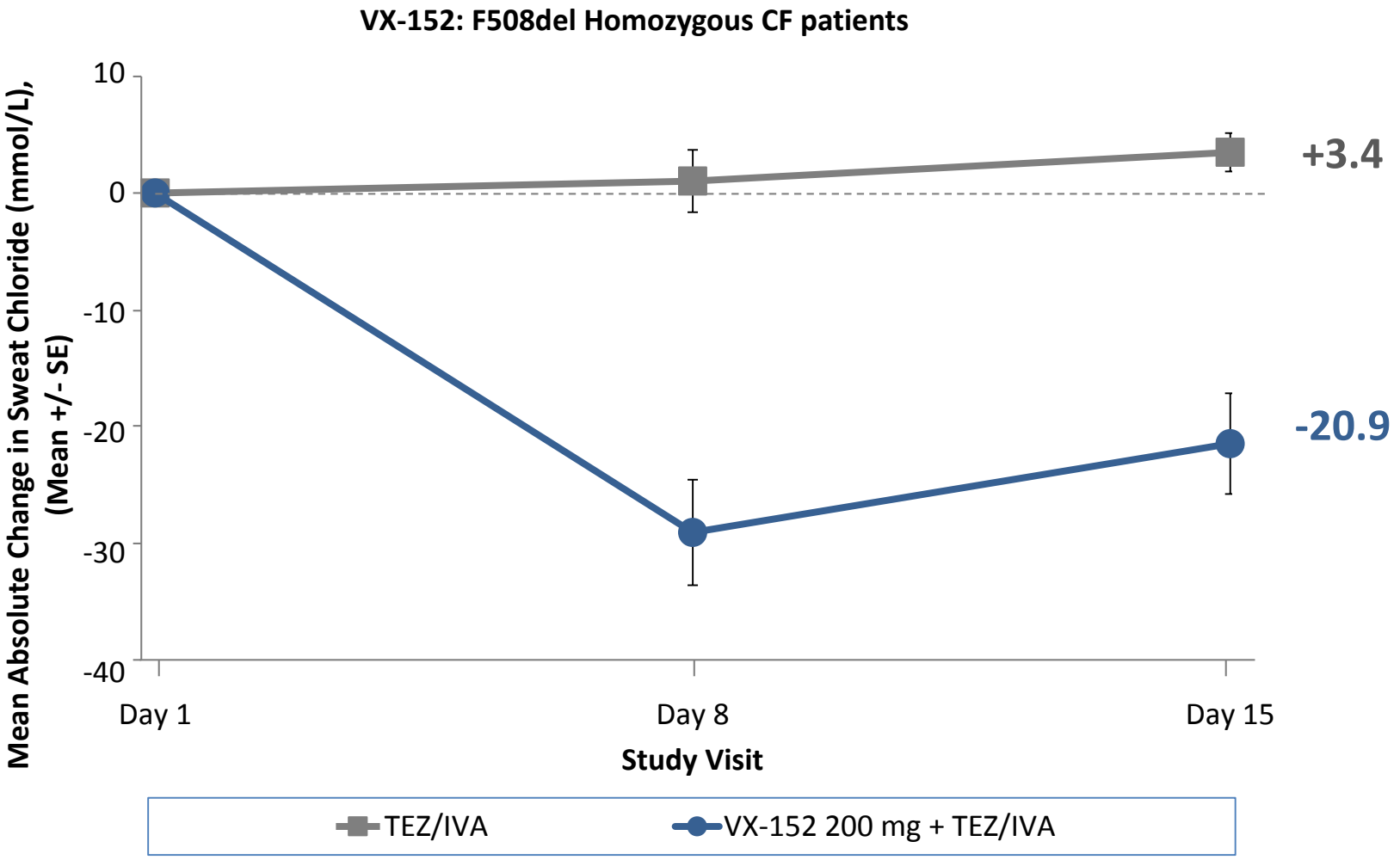
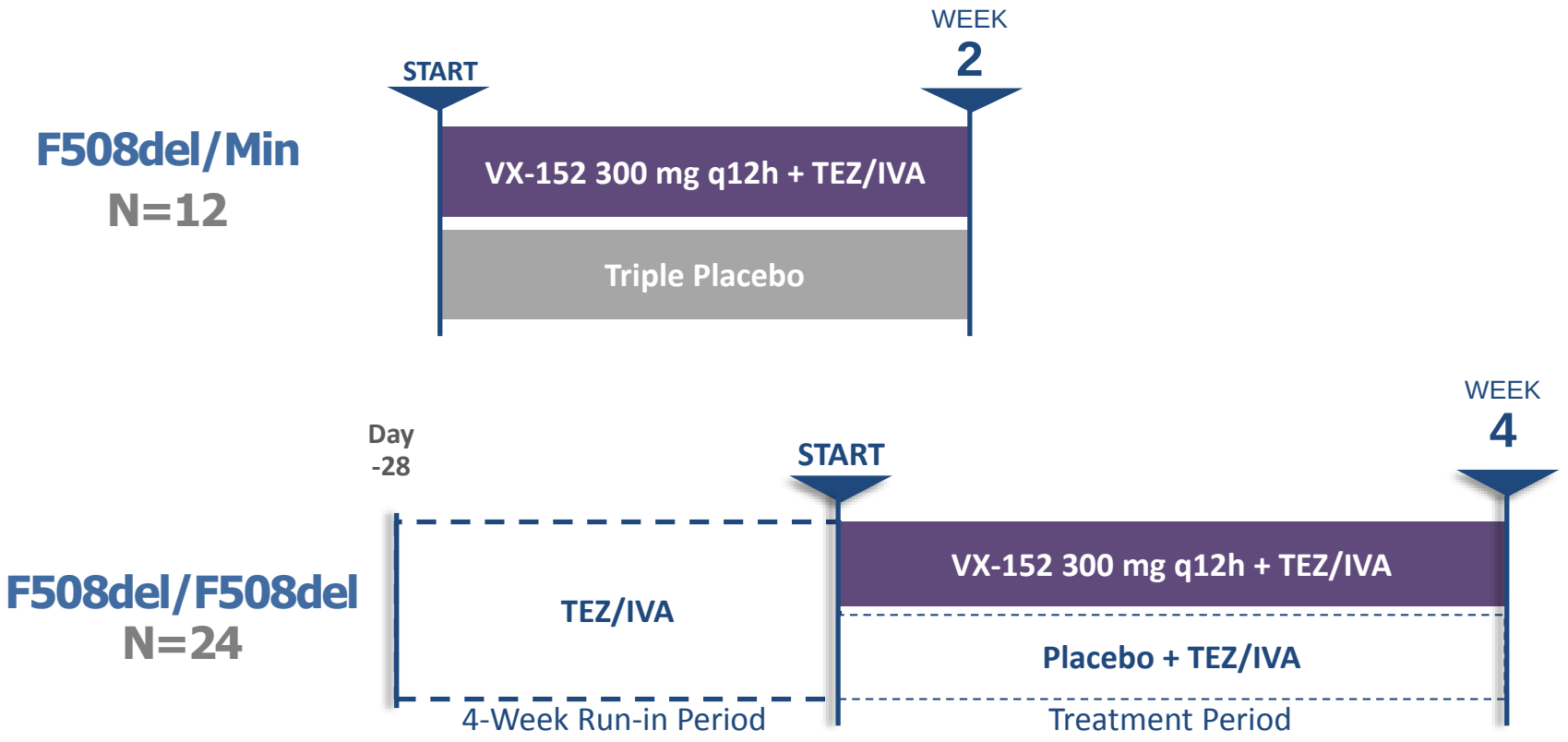



Graph depicts observed data; an efficacy analysis using mixed effect models will be conducted following completion of an additional cohort of patients currently being treated in the study

# Ongoing Evaluation of VX-152 300 mg q12h Dose




- Primary Objective: Safety and Tolerability
- Secondary Objectives: Mean absolute change in $ppFEV_1$ from baseline and change in sweat chloride

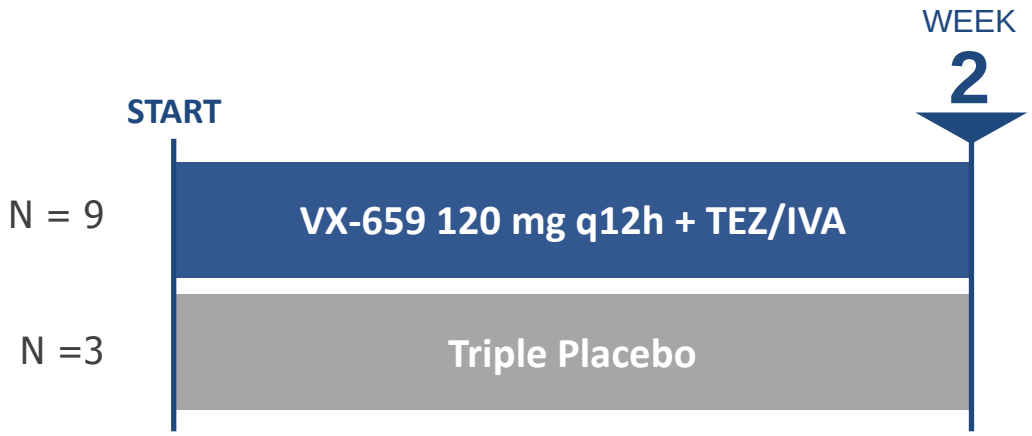
Key eligibility criteria: ≥18 years old; ppFEV1, 40-90% inclusive; excluded patients with G6PD Deficiency

# VX-659

**Initial Phase 1 Evaluation in a Cohort of Cystic Fibrosis Patients**

- F508del/minimal function (n=12)

# VX-659 Dosing in CF Patients with F508del/minimal function mutations in Phase 1




- Primary Objective: Safety and tolerability
- Other Endpoints: Change in sweat chloride, and mean absolute change in ppFEV$_1$ from baseline was evaluated as part of the safety analysis
- Key eligibility criteria for these cohorts:
  - F508del/minimal function mutations
  - ≥18 years old
  - ppFEV$_1$, 40-90% inclusive
  - Excluded patients with G6PD Deficiency

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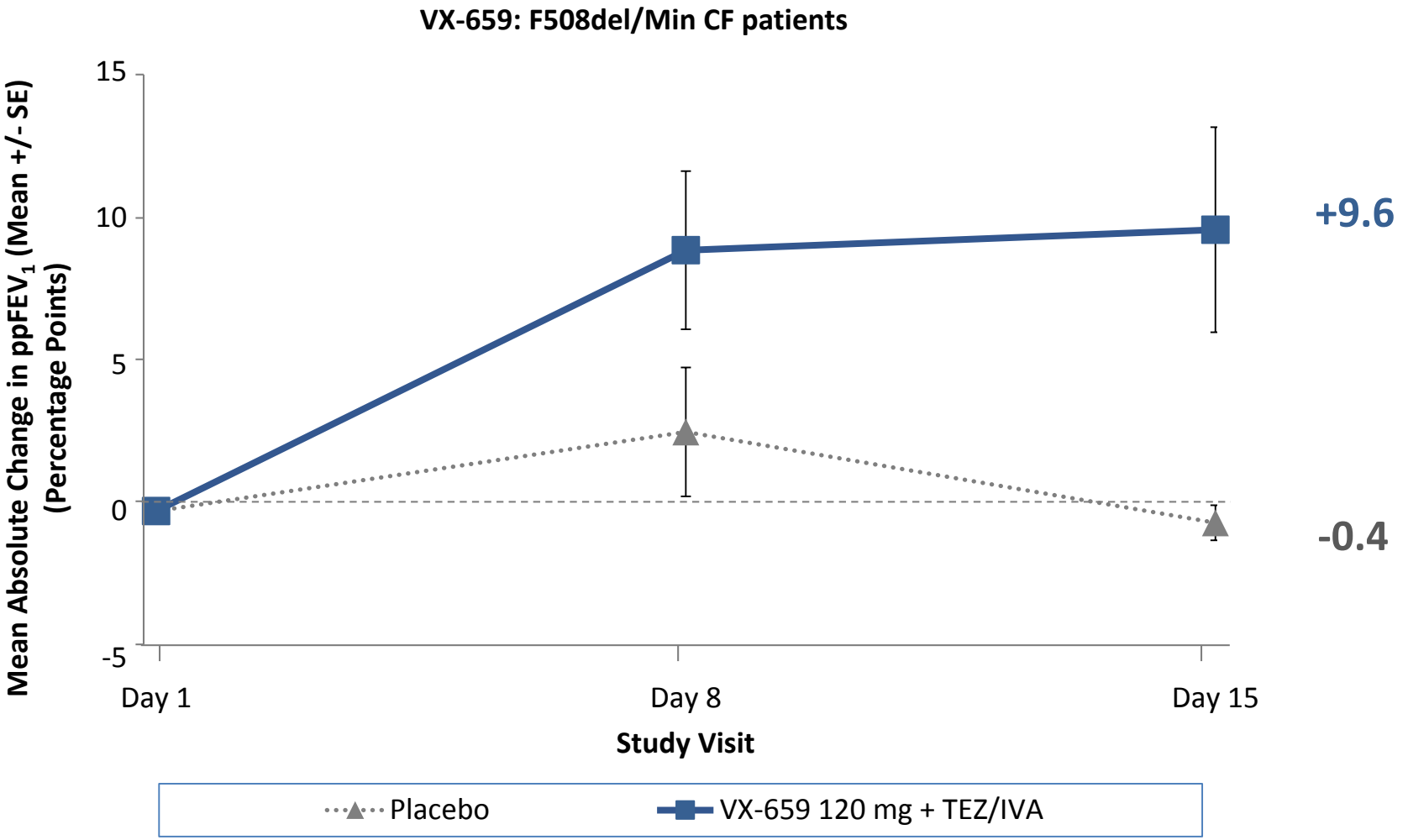
# VX-659 Safety Summary

**In this Phase 1 study in F508del/min patients:**

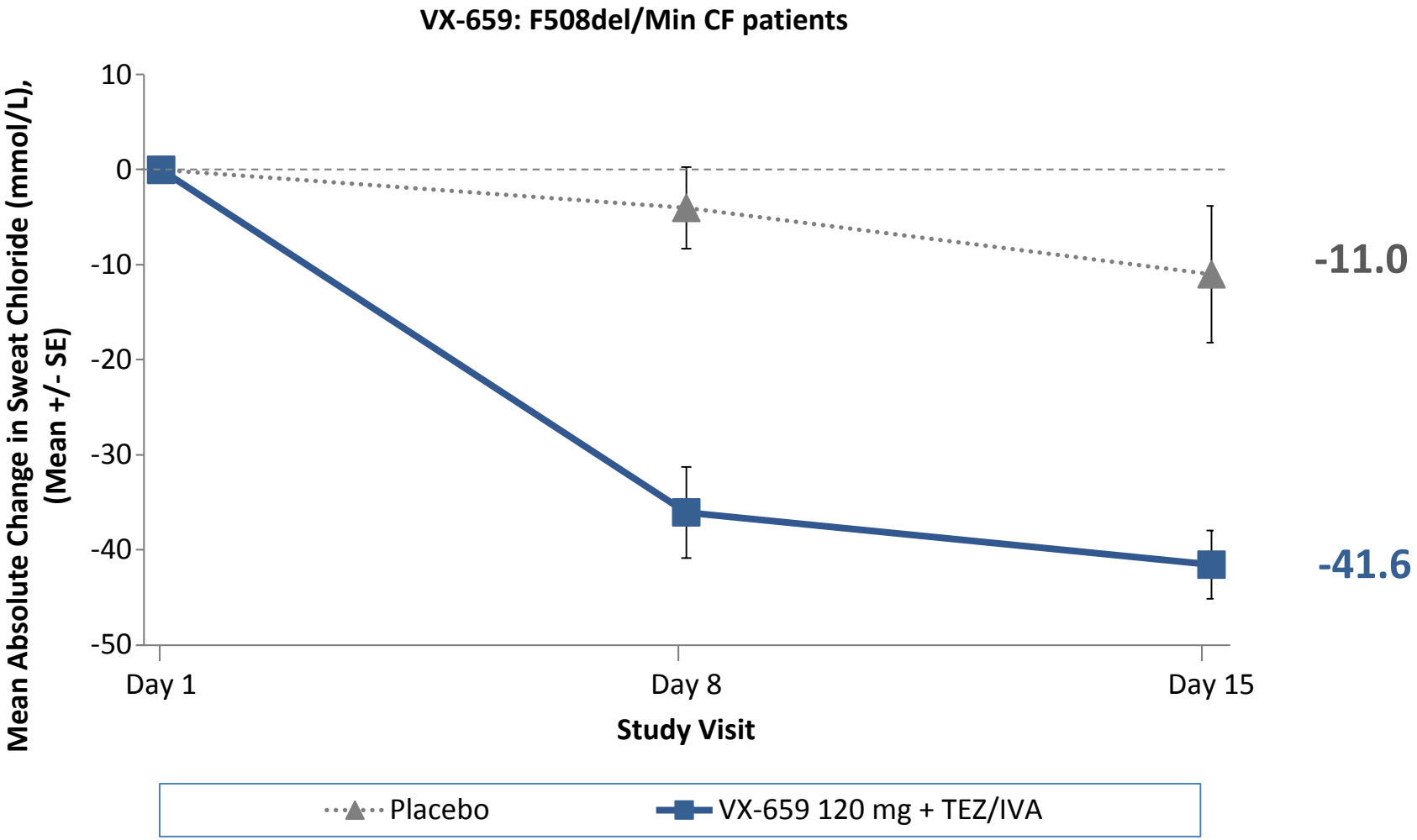
- VX-659 in combination with tezacaftor and ivacaftor was generally well tolerated and the overall safety profile was favorable
- The majority of adverse events were mild to moderate
- The most common adverse events, regardless of treatment group, were cough, infective pulmonary exacerbation and productive cough
- There were no discontinuations due to adverse events

# Absolute Change in Lung Function Over Time



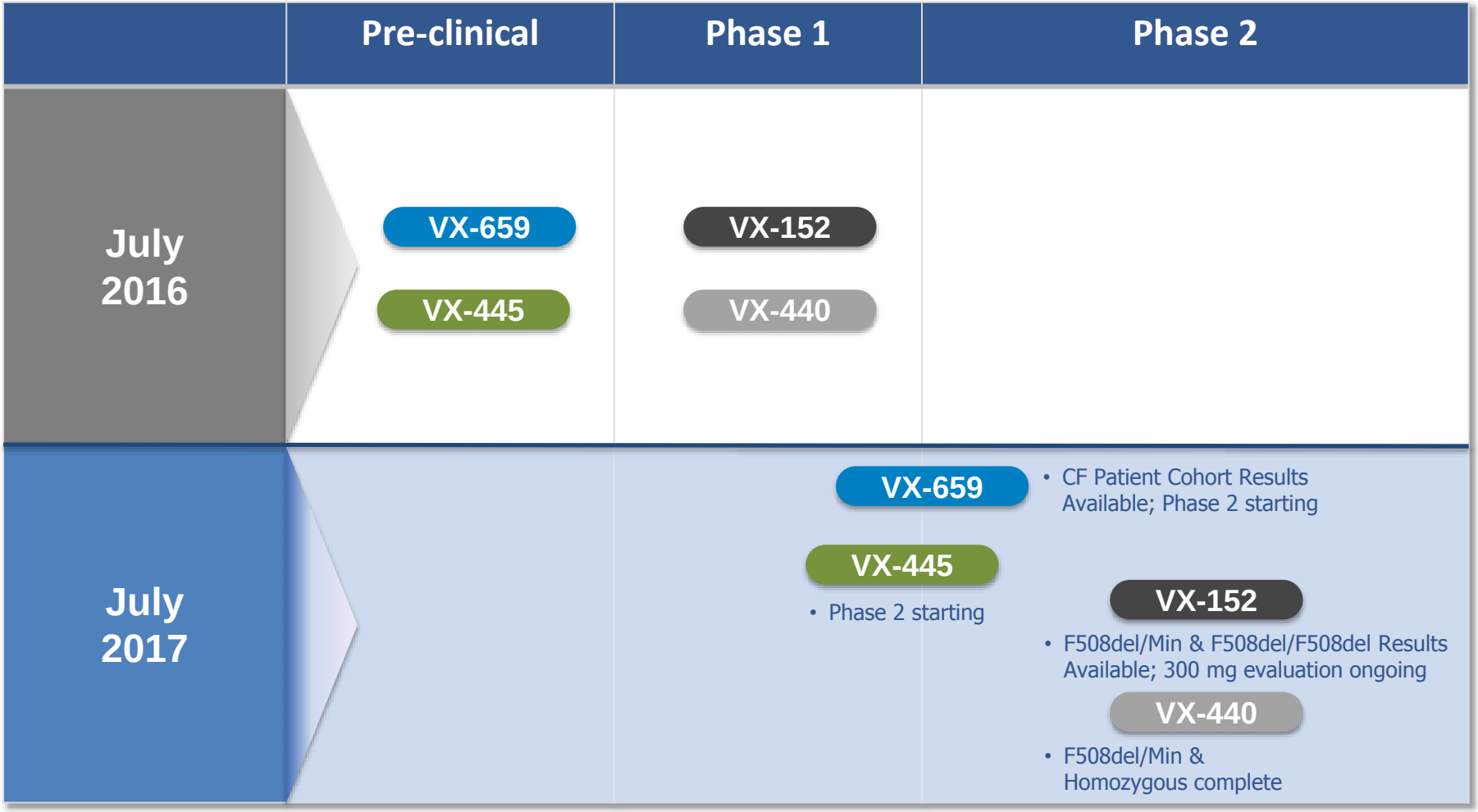

Graph depicts observed data

# Sweat Chloride Significantly Reduced




Graph depicts observed data

# Next-Gen Corrector Clinical Program has Progressed Rapidly



# Next Steps for Vertex Triple Combination CF Portfolio

The Phase 2 studies of VX-440 and VX-152 are ongoing, and Phase 2 development is underway for VX-659 and VX-445

Based on Phase 2 data for all four next generation correctors, planned discussions with regulatory agencies and input from CF experts, Vertex plans to initiate pivotal development of any one or more of these triple regimens in the first half of 2018

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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.*