

1 Long-Term Safety and Efficacy of Tezacaftor/Ivacaftor in People With
2 Cystic Fibrosis \geq 12 Years of Age Homozygous or Heterozygous for
3 *F508del-CFTR* From an Open-label Extension Study
4

5 Patrick A. Flume, MD^{1,a}; Reta Fischer Biner, MD²; Damian G. Downey, MD³; Cynthia Brown,
6 MD⁴; Manu Jain, MD^{5,a}; Rainald Fischer, MD^{6,a}; Kris De Boeck, MD^{7,a}; Gregory S. Sawicki,
7 MD⁸; Philip Chang, PhD⁹; Hildegard Paz-Diaz, MD⁹; Jaime L. Rubin, MPH⁹; Yoojung Yang,
8 PharmD⁹; Xingdi Hu, PhD⁹; David J. Pasta, MS¹⁰; Stefanie J. Millar, MS¹⁰; Daniel Campbell,
9 PhD⁹; Xin Wang, PhD¹¹; Neil Ahluwalia, MD⁹; Caroline A. Owen, MD⁹; Claire E. Wainwright,
10 MD^{12,a}; on behalf of the VX14-661-110 study group
11

12 ¹MUSC Health Cystic Fibrosis Center, Medical University of South Carolina, Charleston, SC

13 ²Quartier Bleu, Lindenhof Hospital, Bern, Switzerland

14 ³Centre for Experimental Medicine, Queen's University Belfast, Belfast, UK

15 ⁴Department of Pulmonary and Critical Care Medicine, Indiana University School of Medicine,
16 Indianapolis, IN

17 ⁵Feinberg School of Medicine, Northwestern University, Chicago, IL

18 ⁶Pneumologische Praxis München-Pasing, Munich, Germany

19 ⁷Pediatric Pulmonology, University Hospital of Leuven, Leuven, Belgium

20 ⁸Department of Pediatrics, Boston Children's Hospital, Harvard Medical School, Boston, MA

21 ⁹Vertex Pharmaceuticals Incorporated, Boston, MA

22 ¹⁰ICON Clinical Research Inc, North Wales, PA

23 ¹¹Formerly of Vertex Pharmaceuticals Incorporated, Boston, MA^b

24 ¹²Child Health Research Centre, University of Queensland, Brisbane, QLD, Australia

25 ^a Professor.

26 ^b Current affiliation: US Food and Drug Administration, Silver Spring, MD.

27

28 **Corresponding author:**

29 Patrick A. Flume, MD

30 Medical University of South Carolina

31 96 Jonathan Lucas Street, Room 816-CSB

32 Charleston, SC 29425

33 Email: flumepa@musc.edu

34 Phone: (843) 792-3167

35

36 **Target:** *The Lancet Respiratory Medicine*

37 **Number of words (limit: 3,500; includes manuscript text only):** 5,503

38 **Number of references (limit: 30):** 42

39 **Number of figures (no limit specified):** 4

40 **Number of tables (no limit specified):** 3

41 **Supplementary appendix:** List of investigators and sites, methods, 12 tables, and 2 figures

42

43 **ABSTRACT** (Limit: 250; currently: 393)

44 **Background:** Tezacaftor/ivacaftor is an approved CFTR modulator shown to be efficacious and
45 generally safe and well tolerated over 8 to 24 weeks in Phase 3 clinical studies in participants
46 ≥ 12 years of age with CF homozygous for the *F508del-CFTR* mutation (*F/F*; study 661-106) or
47 heterozygous for the *F508del-CFTR* mutation and a residual function mutation (*F/RF*; study
48 661-108). Longer-term (>24 weeks) safety and efficacy of tezacaftor/ivacaftor has not been
49 evaluated in clinical studies. Here, we present results of study 661-110, a 96-week open-label
50 extension study that evaluated long-term safety, tolerability, and efficacy of tezacaftor/ivacaftor
51 in participants ≥ 12 years of age homozygous or heterozygous for the *F508del-CFTR* mutation.

52 **Methods:** Participants were ≥ 12 years of age, had CF, were homozygous or heterozygous for
53 *F508del-CFTR*, and completed one of several studies of tezacaftor/ivacaftor. Participants
54 received tezacaftor 100 mg once daily and ivacaftor 150 mg once every 12 hours for up to 96
55 weeks. The primary endpoint of study 661-110 was safety and tolerability. Secondary endpoints
56 were changes in lung function, nutritional parameters, and respiratory symptom scores;
57 pulmonary exacerbations; and pharmacokinetic parameters. A post hoc analysis evaluated the rate
58 of lung function decline in *F/F* participants who received up to 120 weeks of tezacaftor/ivacaftor
59 in studies 661-106 (*F/F*) and/or 661-110 compared with a matched cohort of CFTR modulator–
60 untreated historical *F/F* controls from the Cystic Fibrosis Foundation Patient Registry.
61 (ClinicalTrials.gov identifier, NCT02565914)

62 **Findings:** This study was conducted from August 31, 2015, to May 31, 2019. The safety profile
63 of tezacaftor/ivacaftor in study 661-110 ($n=1042$) was consistent with CF manifestations and
64 with the safety profiles of the parent studies. Twenty-two participants (2.1%) had TEAEs leading
65 to discontinuation; 351 (33.7%) had serious TEAEs. *F/F* ($n=459$) and *F/RF* ($n=226$) participants

66 beginning tezacaftor/ivacaftor in study 661-110 had improvements in efficacy endpoints
67 consistent with parent studies; improvements in tezacaftor/ivacaftor groups observed in the
68 parent studies were generally maintained in study 661-110. The annualized rate of lung function
69 decline was 61·5% (95% CI, 35·8 to 86·1) lower in tezacaftor/ivacaftor–treated *F/F* participants
70 versus untreated matched historical controls.

71 **Interpretation:** Tezacaftor/ivacaftor was generally safe, well tolerated, and efficacious for up to
72 120 weeks. Rate of lung function decline was significantly reduced in *F/F* participants,
73 consistent with CF disease modification. Our results support the clinical benefit of long-term
74 tezacaftor/ivacaftor treatment for people ≥ 12 years of age with CF with *F/F* or *F/RF* genotypes.

75 **Funding:** Vertex Pharmaceuticals Incorporated.

76

77

78 **RESEARCH IN CONTEXT**

79 **Evidence before this study**

80 We searched PubMed on September 11, 2020, using the terms “ivacaftor” or “VX-770” and
81 “tezacaftor” or “VX-661”, with no restrictions on publication date or language. We retrieved
82 four relevant clinical trial publications: a Phase 3 trial of tezacaftor/ivacaftor (TEZ/IVA; up to 24
83 weeks) in participants ≥ 12 years of age with cystic fibrosis (CF) homozygous for the *F508del-*
84 *CFTR* mutation (study 661-106; *F/F* participants), a Phase 3 trial of TEZ/IVA (up to 12 weeks)
85 in participants ≥ 12 years of age with CF heterozygous for the *F508del-CFTR* mutation and a
86 minimal function mutation (study 661-107; *F/MF* participants), a Phase 3 trial of TEZ/IVA (up
87 to 8 weeks) in participants ≥ 12 years of age with CF heterozygous for the *F508del-CFTR*
88 mutation and a residual function mutation (study 661-108; *F/RF* participants), and a Phase 3b

89 trial of TEZ/IVA (up to 56 days) in participants ≥ 12 years of age with CF homozygous for the
90 *F508del-CFTR* mutation who discontinued lumacaftor/ivacaftor due to treatment-related
91 respiratory signs or symptoms (study 661-114; *F/F* participants). The clinical efficacy and safety
92 of TEZ/IVA in people ≥ 12 years of age with CF was established based on the results of Phase 3
93 trials 661-106 and 661-108.

94

95 **Added value of this study**

96 The safety and efficacy of longer-term (>24 weeks) TEZ/IVA treatment has not been previously
97 evaluated in clinical studies. Study 661-110 was a 96-week open-label extension study designed
98 to assess long-term safety, tolerability, and efficacy of TEZ/IVA in participants ≥ 12 years of age
99 homozygous or heterozygous for the *F508del-CFTR* mutation who completed one of several
100 pivotal parent studies of TEZ/IVA, including studies 661-106 (*F/F*) and 661-108 (*F/RF*). The
101 rate of lung function decline in TEZ/IVA-treated participants has not been previously evaluated.
102 A post hoc analysis was conducted to evaluate rate of lung function decline in *F/F* participants
103 who received up to 120 weeks of TEZ/IVA in studies 661-106 (*F/F*) and 661-110 compared with
104 a matched cohort of CF transmembrane conductance regulator (CFTR) modulator–untreated
105 historical *F/F* controls from the Cystic Fibrosis Foundation Patient Registry. We observed that
106 up to 120 weeks of TEZ/IVA treatment was generally safe and well tolerated, with a safety
107 profile consistent with that observed in the parent studies. The observed benefits of TEZ/IVA on
108 lung function, nutritional status, and pulmonary exacerbation rates were generally maintained for
109 up to 120 weeks of treatment. Post hoc analysis demonstrated that TEZ/IVA treatment was
110 associated with a significant reduction in lung function decline in *F/F* participants compared
111 with CFTR modulator–untreated historical *F/F* controls.

112

113 **Implications of all the available evidence**

114 Study 661-110 showed that TEZ/IVA was generally safe and well tolerated for up to 120 weeks,
115 with a safety profile consistent with that observed in the parent studies. Our results support the
116 clinical value of long-term TEZ/IVA treatment for people ≥ 12 years of age with CF with an *F/F*
117 or *F/RF* genotype. The rate of lung function decline was significantly reduced in *F/F* participants
118 taking TEZ/IVA, consistent with modification of the course of CF disease.

119

120 **INTRODUCTION**

121 Cystic fibrosis (CF) is a life-shortening, multisystem genetic disease affecting approximately
122 85,000 people worldwide.¹ CF is caused by mutations in the CF transmembrane conductance
123 regulator (*CFTR*) gene that reduce the quantity and/or function of the CFTR protein (an anion
124 channel) on epithelial cell surfaces.^{1,2} The *F508del-CFTR* mutation, the most common *CFTR*
125 mutation, severely impairs the processing and trafficking of the CFTR protein to the epithelial
126 cell surface and the function of the CFTR protein that reaches the cell surface.^{2,3} People with two
127 copies of the *F508del-CFTR* mutation (*F/F* genotype) develop severe multisystem disease with
128 progressive loss of lung function.^{4,5} Approximately 5% of people with CF (pwCF) have *CFTR*
129 mutations resulting in residual CFTR anion transport due to partially retained CFTR expression
130 and function on epithelial cell surfaces.^{4,6} However, pwCF possessing residual function (RF)
131 mutations still develop multisystem manifestations of CF and severe disease.^{4,7} RF mutations are
132 most commonly inherited with the *F508del-CFTR* mutation (*F/RF* genotype) on the other allele.⁸
133 Compared with pwCF who are homozygous for *F508del-CFTR* (*F/F*), those with *F/RF*
134 genotypes generally have slower disease progression and are more likely to be pancreatic
135 sufficient and have sweat chloride concentrations <90 mmol/L, indicative of partially preserved
136 CFTR activity.^{6,9-11} Nevertheless, pwCF with *F/RF* genotypes develop lung disease with
137 increasing age and die prematurely.⁷

138
139 Small-molecule CFTR modulator (CFTRm) therapies have been developed for pwCF that target
140 the underlying CFTR dysfunction.¹²⁻¹⁵ CFTR correctors (e.g., lumacaftor, tezacaftor, and
141 elxacaftor) bind to the protein product of the *F508del-CFTR* mutation to improve processing of
142 the mutant, misfolded protein and its trafficking to cell surfaces.¹³⁻¹⁵ CFTR potentiators (e.g.,

143 ivacaftor [IVA]) increase the open probability of the CFTR channels present on cell surfaces.¹²
144 The first two approved CFTRm therapies, IVA and lumacaftor/ivacaftor combination therapy
145 (LUM/IVA), were shown to modify the progression of CF disease in their indicated populations
146 compared with matched CFTRm-untreated controls in the US CF Foundation Patient Registry
147 (CFFPR).¹⁶⁻¹⁹ Both IVA and LUM/IVA treatments reduced lung function decline in their
148 indicated populations.¹⁶⁻¹⁹ In addition, IVA treatment was associated with reductions in
149 mortality, lung transplant, pulmonary exacerbation, and hospitalization rates and improvements
150 in nutritional status.^{16,17} Tezacaftor/ivacaftor combination therapy (TEZ/IVA) was shown to be
151 effective and generally safe and well tolerated in 24- or 8-week Phase 3 clinical studies
152 (EVOLVE or EXPAND, respectively) in participants ≥ 12 years of age with CF who have *F/F* or
153 *F/RF* genotypes, respectively.^{20,21} TEZ/IVA is approved to treat pwCF with TEZ/IVA-
154 responsive mutations who are ≥ 6 years of age in the United States and ≥ 12 years of age in other
155 regions.^{22,23} The safety and efficacy of longer-term (>24 weeks) TEZ/IVA use has not been
156 evaluated in clinical studies.

157
158 Here, we report the findings of a 96-week extension study (661-110; EXTEND) that assessed the
159 long-term safety and efficacy of TEZ/IVA treatment in participants ≥ 12 years of age with CF
160 homozygous or heterozygous for the *F508del-CFTR* mutation who completed a placebo (PBO)
161 and/or IVA-controlled parent study of TEZ/IVA. A post hoc analysis was also conducted to
162 evaluate the rate of lung function decline in *F/F* participants who received up to 120 weeks of
163 TEZ/IVA in studies 661-106 (*F/F*) and/or 661-110, compared with a matched cohort of CFTRm-
164 untreated historical *F/F* controls from the CFFPR. This analysis was not possible in the *F/RF*
165 cohort due to an insufficient sample size.

166

167 **METHODS**

168 **Study Design and Eligibility Criteria**

169 Study 661-110 (ClinicalTrials.gov identifier, NCT02565914) was a 96-week, Phase 3,
170 multicenter, open-label study (**Figure 1**) in participants ≥ 12 years of age with CF homozygous or
171 heterozygous for the *F508del-CFTR* mutation who completed one of several studies of
172 TEZ/IVA. Participants who completed study-drug treatment (TEZ/IVA, IVA alone, or PBO)
173 during the treatment period in parent studies 661-103 (NCT02070744; *F/F*), 661-106
174 (NCT02347657; *F/F*),²⁰ 661-107 (NCT02516410; *F/MF* [heterozygous for *F508del-CFTR* and a
175 minimal function *CFTR* mutation]),²⁴ 661-108 (NCT02392234; *F/RF*),²¹ 661-109
176 (NCT02412111; *F/gating* or *F/R117H* [heterozygous for *F508del-CFTR* and either a *CFTR*
177 gating or a *R117H-CFTR* mutation]), or 661-111 (NCT02508207; *F/F*) were eligible for study
178 661-110. Study 661-103 (*F/F*) was a Phase 2, randomized, PBO-controlled, 12-week study of the
179 safety, efficacy, pharmacokinetics, and pharmacodynamics of TEZ/IVA in participants ≥ 18 years
180 of age with CF. Study 661-106 (*F/F*) was a Phase 3, randomized, PBO-controlled, 24-week
181 study of the efficacy and safety of TEZ/IVA in participants ≥ 12 years of age with CF.²⁰ Study
182 661-107 (*F/MF*) was a Phase 3, randomized, PBO-controlled, 12-week study of the efficacy and
183 safety of TEZ/IVA in participants ≥ 12 years of age with CF.²⁴ Study 661-108 (*F/RF*) was a
184 Phase 3, randomized, PBO- and IVA-controlled, crossover study (2 8-week interventional
185 periods) of the efficacy and safety of TEZ/IVA in participants ≥ 12 years of age with CF.²¹ Study
186 661-109 (*F/gating* and *F/R117H*) was a Phase 3, randomized, IVA-controlled, 8-week study of
187 the efficacy and safety of TEZ/IVA in participants ≥ 12 years of age with CF. Study 661-111
188 (*F/F*) was a Phase 2, randomized, PBO-controlled, 29-day exploratory study of the effects of

189 TEZ/IVA on lung and extrapulmonary systems in participants ≥ 18 years of age with CF.
190 Efficacy in 661-110 was reported only in participants with an *F/F* or *F/RF* genotype who
191 enrolled from study 661-106 (*F/F*) or 661-108 (*F/RF*); eligible RF mutations for 661-108 (*F/RF*)
192 are reported in the **appendix (p 9)**. Participants from studies 661-107 (*F/MF*) and 661-109
193 (*F/gating* or *F/R117H*) were discontinued early from study 661-110 because these parent studies
194 did not meet their primary endpoint; accordingly, efficacy was not assessed in these participants
195 in 661-110. Efficacy endpoints were assessed in participants who transitioned from studies 661-
196 103 (*F/F*) and 661-111 (*F/F*); however, the sample sizes were small and results from these
197 participants are not reported here. Exclusion criteria included history of any comorbidity (e.g.,
198 cirrhosis with portal hypertension) that, in the opinion of the investigator, might confound the
199 results of the study or pose an additional risk in administering TEZ/IVA to participants. Full
200 eligibility criteria are reported in the **appendix (pp 10-11)**.

201

202 Participants received TEZ 100 mg once daily and IVA 150 mg every 12 hours for up to 96
203 weeks. Procedural methods on the transition to study 661-110, the timing of assessments, and
204 treatment compliance are reported in the **appendix (p 7)**.

205

206 **Objectives and Endpoints**

207 The primary objective of study 661-110 was to evaluate the long-term safety and tolerability of
208 TEZ/IVA in participants with CF homozygous or heterozygous for the *F508del-CFTR* mutation.
209 The primary endpoint was safety and tolerability based on adverse events (AEs), ophthalmologic
210 examinations (in participants < 18 years of age at the date of informed consent/assent in the

211 parent study), clinical laboratory values (serum chemistry, hematology, coagulation, lipids,
212 vitamins, and urinalysis), standard digital electrocardiograms, vital signs, and pulse oximetry.
213

214 The secondary objective was to evaluate the long-term efficacy of TEZ/IVA. Secondary
215 endpoints were absolute change from baseline in percent predicted forced expiratory volume in 1
216 second (ppFEV₁); relative change from baseline in ppFEV₁; number of pulmonary exacerbations
217 (PEX); absolute change from baseline in body mass index (BMI), BMI *z* score (in participants
218 <20 years of age), CF Questionnaire–Revised (CFQ-R) respiratory domain score, body weight,
219 body weight *z* score (in participants <20 years of age), and height *z* score (in participants <20
220 years of age); time to first PEX; and pharmacokinetics parameters of TEZ, M1-TEZ, IVA, and
221 M1-IVA.

222
223 A post hoc analysis of the rate of lung function decline was conducted on *F/F* participants treated
224 with TEZ/IVA for up to 120 weeks in studies 661-106 (*F/F*) and/or 661-110 and a propensity
225 score–matched cohort of CFTRm-untreated *F/F* historical controls ≥12 years of age using data
226 from the CFFPR from 2012 through 2014, prior to commercial availability of the first CFTRm
227 for *F/F* pwCF in the United States. To be eligible for the analysis, both TEZ/IVA–treated and
228 historical control participants had to have at least three consecutive lung function measurements
229 spanning ≥6 months.

230

231 **Statistical Analyses**

232 This study did not have a target sample size; a convenience sample was used (see the **appendix**
233 **p 7** for additional information). The Safety Set included all participants, regardless of their

234 genotype and from all 6 parent studies, who received at least one dose of study drug at any time
235 during the 96-week treatment period of study 661-110. The Full Analysis Set (FAS) included all
236 participants who received at least one dose of study drug at any time during the 96-week
237 treatment period of study 661-110 and had *F/F* or *F/RF* genotypes. There were two efficacy sets:
238 the 106/110 Efficacy Set (*F/F*) included all participants in the FAS who transitioned from study
239 661-106 (*F/F*), and the 108/110 Efficacy Set (*F/RF*) included all participants in the FAS who
240 transitioned from study 661-108 (*F/RF*). PEx were analyzed using the 106/110 PEx Analysis Set
241 (*F/F*) or the 108/110 PEx Analysis Set (*F/RF*), which included all participants receiving
242 TEZ/IVA in either studies 661-106 (*F/F*) or 661-108 (*F/RF*), respectively, and/or 661-110. For
243 the PEx analysis in participants transitioning from study 661-108 (*F/RF*), only PEx data from
244 period 2 of study 661-108 (*F/RF*) were pooled with PEx data from study 661-110 because there
245 was an 8-week TEZ/IVA washout between the two treatment periods in study 661-108 (*F/RF*).
246
247 Continuous variables were summarized using descriptive statistics: number of participants,
248 mean, SD, median, minimum, and maximum. Categorical variables were summarized using
249 counts and percentages. Continuous efficacy endpoints were analyzed using a mixed-effects
250 model for repeated measures. Wang and Hankinson (W-H) equations were used to calculate
251 ppFEV₁ for change-from-baseline analyses.^{25,26} The number of PEx was analyzed using a
252 negative binomial regression model, and time to first PEx was analyzed using the Kaplan-Meier
253 approach. Statistical comparisons of PEx rates in study 661-110 versus those in the parent
254 studies were not conducted because PEx events in the parent studies in participants receiving
255 TEZ/IVA treatment were pooled with the PEx events in participants in study 661-110 in the PEx
256 Analysis Sets.

257
258 In the 106/110 Efficacy Set (*F/F*), endpoints were assessed in two groups who transitioned to
259 study 661-110: participants randomized to PBO (PBO-TEZ/IVA) and those randomized to
260 TEZ/IVA (TEZ/IVA-TEZ/IVA) in study 661-106 (*F/F*). In the 108/110 Efficacy Set (*F/RF*),
261 endpoints were assessed in three groups who transitioned to study 661-110 based on the
262 treatment assignment from period 2 in the parent study: participants randomized to PBO (PBO-
263 TEZ/IVA), IVA (IVA-TEZ/IVA), and TEZ/IVA (TEZ/IVA-TEZ/IVA) in study 661-108 (*F/RF*).
264 In the 106/110 Efficacy Set (*F/F*), for participants who were randomized to the PBO group in
265 study 661-106 (*F/F*), baseline was defined as the most recent nonmissing measurement before
266 the first dose of study drug in study 661-110 because the study specified that a previous value
267 that is available (e.g., Screening) should be used if the Day 1 value was missing. For efficacy
268 analyses of endpoints in all other groups, baseline was defined as the most recent nonmissing
269 measurement before the first dose of study drug in the parent study. Results were not compared
270 between groups within study 661-110; data from groups in study 661-110 and data from parent
271 studies are displayed only to allow visual comparisons.

272
273 In the post hoc analysis of rate of lung function decline, TEZ/IVA–treated *F/F* participants were
274 matched with up to five eligible *F/F* historical controls in the CFFPR using the propensity score
275 method (**appendix pp 12-13**) previously described in similar analyses with IVA and
276 LUM/IVA.^{18,19} In this analysis, Global Lung (Function) Initiative (GLI) equations were used to
277 calculate ppFEV₁ to be consistent with the CFFPR.²⁷ W-H equations were used in a sensitivity
278 analysis. For TEZ/IVA–treated participants, the analysis excluded spirometry measurements in
279 the first 22 days after TEZ/IVA initiation in order to exclude acute lung function improvements

280 observed with TEZ/IVA initiation from the slope estimation. In a sensitivity analysis, to evaluate
281 potential selection bias in comparing a clinical trial population with a registry population, pwCF
282 in the registry who had a record of participating in any clinical trial were excluded from the
283 analysis. Further details about analysis methods, including additional sensitivity analyses, are
284 provided in the **appendix (pp 7-8)**.

285

286 SAS version 9.4 software (SAS Institute, Cary, NC, USA) was used for all statistical analyses.

287

288 **Ethical Considerations**

289 The study protocol was reviewed and approved by local institutional review boards or ethics
290 committees. Written informed consent (and assent, if applicable) was provided before screening.

291 This study was conducted in accordance with the Declaration of Helsinki, local applicable laws
292 and regulations, and current Good Clinical Practice Guidelines of the International Council for
293 Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.

294

295 **Role of the Funding Source**

296 The funder participated in the design of the protocol, conducted the statistical analysis, collected
297 the data, and was involved in the data interpretation. Medical writing, editorial support, and
298 coordination were provided by the funder. All authors had full access to the study data. All
299 authors contributed to data interpretation, conception, drafting, and/or revisions to the
300 manuscript, and all approved the final version that was submitted for publication.

301

302 **RESULTS**

303 **Disposition and Baseline Characteristics of Participants**

304 This study was conducted from August 31, 2015, to May 31, 2019. Of 1044 participants enrolled
305 in study 661-110, 1042 received at least one dose of study drug at any time during the 96-week
306 treatment period of study 661-110 and were included in the Safety Set (**Figure 1**); the Safety Set
307 included participants from all 6 parent studies (study 661-103, n=23; study 661-106, n=462;
308 study 661-107, n=159; study 661-108, n=227; study 661-109, n=138; study 661-111, n=33). Of
309 these 1042 participants, 253 participants (24.3%) who had enrolled in study 661-110 after
310 completing studies 661-107 (*F/MF*) or 661-109 (*F/gating* or *F/R117H*) were discontinued from
311 study 661-110 by the sponsor when these parent studies demonstrated that TEZ/IVA was not
312 efficacious in participants with these mutations versus the study comparator. Participants from
313 the 661-107 (*F/MF*) and 661-109 (*F/gating* or *F/R117H*) studies were included in the Safety Set
314 but not in the Efficacy Sets. Of the 789 remaining participants, 682 (86.4%) completed the 96-
315 week treatment regimen, 24 (3.0%) discontinued due to AEs, and 83 (10.5%) discontinued for
316 other reasons (**appendix p 14**). Among the 24 participants who discontinued TEZ/IVA due to
317 AEs, two participants discontinued TEZ/IVA due to AEs that occurred outside the treatment-
318 emergent period (from start of TEZ/IVA to 28 days after the last dose of TEZ/IVA, as defined in
319 the protocol and statistical analysis plan). Thus, there were 24 discontinuations due to AEs but
320 only 22 discontinuations due to treatment-emergent AEs (TEAEs). There were 741 participants
321 in the FAS, 459 in the 106/110 Efficacy Set (*F/F*), 226 in the 108/110 Efficacy Set (*F/RF*), 479
322 in the 106/110 PEx Analysis Set (*F/F*), and 233 in the 108/110 PEx Analysis Set (*F/RF*).
323 Demographics and baseline characteristics for the 106/110 (*F/F*) and 108/110 (*F/RF*) Efficacy
324 Sets are reported in **Table 1**. In the 106/110 (*F/F*) and 108/110 (*F/RF*) Efficacy Sets, the mean

325 (SD) age at screening was 26·1 (10·4) years and 35·1 (14·2) years, respectively, and the mean
326 (SD) baseline ppFEV₁ was 60·0 (15·1) and 62·2 (14·5), respectively.

327

328 **Primary Endpoint: Safety**

329 The mean (SD) TEZ/IVA exposure for participants in the Safety Set was 76·0 (31·8) weeks;
330 after excluding participants from parent studies 661-107 (*F/MF*) and 661-109 (*F/gating* or
331 *F/R117H*) who were discontinued from study 661-110, the mean (SD) exposure was 90·2 (18·2)
332 weeks. Of 1042 participants, 995 (95·5%) had at least one TEAE (**appendix p 15**). The most
333 frequent TEAEs ($\geq 10\%$ of participants) were infective PEx of CF, cough, nasopharyngitis,
334 sputum increased, hemoptysis, headache, pyrexia, oropharyngeal pain, upper respiratory tract
335 infection, abdominal pain, nausea, and diarrhea. Time-adjusted AE rates (number of AEs per 100
336 participant-years) for the most frequent TEAEs were generally comparable to or lower than the
337 time-adjusted rates for the TEZ/IVA group in study 661-106 (*F/F*) (**Table 2**). The majority of
338 participants had mild or moderate TEAEs that were deemed unlikely related or not related to
339 study drug. Ninety participants (8·6%) had TEAEs leading to treatment interruption, and 22
340 (2·1%) had TEAEs leading to treatment discontinuation. The most frequent TEAEs leading to
341 treatment discontinuation (occurring in at least two participants) were increased aspartate and
342 alanine aminotransferase (n=4 [0·4%] each), increased blood creatine phosphokinase (n=4
343 [0·4%]), and infective PEx of CF (n=2 [0·2%]).

344

345 Serious TEAEs (SAEs) were experienced by 351 participants (33·7%); the most frequently
346 reported SAEs (occurring in $\geq 1\%$ of participants) were infective PEx of CF (n=243 [23·3%]),
347 hemoptysis (n=25 [2·4%]), and distal intestinal obstruction syndrome (n=12 [1·2%]). No deaths

348 occurred during the treatment-emergent period. Two deaths occurred after the treatment-
349 emergent period: one due to influenza-related complications and the other due to esophageal
350 cancer. The investigators deemed the events leading to death as not related to the study drug.

351
352 Based on prior experience with CFTR modulators, elevated transaminases and respiratory events
353 and symptoms were predefined as AEs of interest in study 661-110.²⁸⁻³⁰ Sixty-four participants
354 (6·1%) had an AE of elevated transaminases, the majority of which were mild or moderate in
355 severity (**appendix p 16**). Five participants (0·5%) had SAEs of elevated transaminases, and five
356 (0·5%) had AEs of elevated transaminases that led to treatment discontinuation. Liver function
357 test results that met threshold criteria are summarized in the **appendix (p 17)**. A total of 181
358 participants (17·4%) had AEs of respiratory events and symptoms (**appendix p 18**). Most
359 treatment-emergent respiratory events were mild or moderate in severity, and none were serious
360 or led to treatment discontinuation.

361
362 No clinically meaningful trends were observed in serum chemistry, hematology, coagulation,
363 urinalysis, vital signs, physical examinations, ophthalmological examinations, standard
364 electrocardiograms, or pulse oximetry.

365

366 **Secondary Endpoints: Efficacy**

367 In the 106/110 (*F/F*) Efficacy Set, the least squares (LS) mean absolute change from baseline in
368 ppFEV₁ at week 96 was 2·1 percentage points (95% CI, 0·8 to 3·3) in the PBO-TEZ/IVA group
369 and 2·0 percentage points (95% CI, 0·7 to 3·2) in the TEZ/IVA-TEZ/IVA group (**appendix pp**
370 **19-20**). In the 108/110 (*F/RF*) Efficacy Set, the LS mean absolute change from baseline in

371 ppFEV₁ at week 96 was 4·1 percentage points (95% CI, 2·2 to 6·0) in the PBO-TEZ/IVA group,
372 6·7 percentage points (95% CI, 4·7 to 8·7) in the IVA-TEZ/IVA group, and 7·5 percentage
373 points (95% CI, 5·6 to 9·4) in the TEZ/IVA-TEZ/IVA group (**appendix pp 21-22**). In the
374 106/110 (*F/F*) and 108/110 (*F/RF*) Efficacy Sets, PBO-TEZ/IVA participants in study 661-110
375 had an increase in ppFEV₁ that was similar in magnitude to that observed in TEZ/IVA-treated
376 participants in their parent studies. Increases in ppFEV₁ observed in each efficacy set in study
377 661-110 were generally maintained for up to 120 weeks of TEZ/IVA treatment (**appendix pp**
378 **19-22; Figure 2A; Figure 3A**). In the 106/110 (*F/F*) and 108/110 (*F/RF*) Efficacy Sets, the
379 increases in relative change in ppFEV₁ from baseline (**appendix pp 19-22**) were similar to those
380 for absolute change from baseline in ppFEV₁.

381
382 In the 106/110 PEx Analysis Set (*F/F*), in the PBO-TEZ/IVA group, the estimated annualized
383 event rates for PEx, PEx requiring intravenous (IV) antibiotics, and PEx requiring hospitalization
384 were 0·68 (95% CI, 0·55 to 0·83), 0·34 (95% CI, 0·25 to 0·44), and 0·23 (95% CI, 0·16 to 0·32),
385 respectively (**appendix pp 19-20**). In the TEZ/IVA-TEZ/IVA group, the estimated annualized
386 event rates for PEx, PEx requiring IV antibiotics, and PEx requiring hospitalization were 0·76
387 (95% CI, 0·63 to 0·92), 0·36 (95% CI, 0·28 to 0·47), and 0·24 (95% CI, 0·18 to 0·32),
388 respectively.

389
390 In the 108/110 PEx Analysis Set (*F/RF*), in the PBO-TEZ/IVA group, the estimated annualized
391 event rates for PEx, PEx requiring IV antibiotics, and PEx requiring hospitalization were 0·44
392 (95% CI, 0·29 to 0·66), 0·09 (95% CI, 0·04 to 0·22), and 0·07 (95% CI, 0·03 to 0·18),
393 respectively (**appendix pp 21-22**). In the IVA-TEZ/IVA group, the estimated annualized event

394 rates for PEx, PEx requiring IV antibiotics, and PEx requiring hospitalization were 0·28 (95%
395 CI, 0·18 to 0·44), 0·09 (95% CI, 0·04 to 0·22), and 0·09 (95% CI, 0·04 to 0·22), respectively. In
396 the TEZ/IVA-TEZ/IVA group, the estimated annualized event rates for PEx, PEx requiring IV
397 antibiotics, and PEx requiring hospitalization were 0·22 (95% CI, 0·14 to 0·35), 0·05 (95% CI,
398 0·02 to 0·13), and 0·05 (95% CI, 0·02 to 0·13), respectively.

399

400 In the 106/110 (*F/F*) and 108/110 (*F/RF*) PEx Analysis Sets, the estimated PEx event rate per
401 year with TEZ/IVA treatment in study 661-110 was numerically lower than that in the PBO
402 group in the respective 661-106 (*F/F*) and 661-108 (*F/RF*) parent studies and comparable to that
403 in the TEZ/IVA group in these parent studies (**appendix pp 19-22; Figure 2B; Figure 3B**).

404 Improvements in rates of PEx requiring hospitalization and/or IV antibiotics followed a similar
405 pattern as the overall PEx rate in the 106/110 PEx Analysis Set (*F/F*). Rates of PEx requiring
406 hospitalization and rates of PEx requiring treatment with IV antibiotics were not evaluated in
407 study 661-108 (*F/RF*) (due to the short treatment period) but were low in all three groups that
408 transitioned from study 661-108 (*F/RF*) to study 661-110. Time to first PEx is shown in the
409 **appendix (p 24)**, and the event-free probabilities are shown in the **appendix (pp 19-22)**.

410

411 In the 106/110 (*F/F*) Efficacy Set, the LS mean absolute change from baseline in CFQ-R
412 respiratory domain score at week 96 was 1·7 (95% CI, -0·6 to 4·0) in the PBO-TEZ/IVA group
413 and 3·0 (95% CI, 0·7 to 5·3) in the TEZ/IVA-TEZ/IVA group (**appendix pp 19-20**). In the
414 108/110 (*F/RF*) Efficacy Set, the LS mean absolute change from baseline in CFQ-R respiratory
415 domain score at week 96 was 10·3 (95% CI, 7·0 to 13·6) in the PBO-TEZ/IVA group, 11·2
416 (95% CI, 7·7 to 14·7) in the IVA-TEZ/IVA group, and 13·8 (95% CI, 10·3 to 17·2) in the

417 TEZ/IVA-TEZ/IVA group (**appendix pp 21-22**). In the 106/110 (*F/F*) and 108/110 (*F/RF*)
418 Efficacy Sets, PBO-TEZ/IVA participants in study 661-110 had an improvement in CFQ-R
419 respiratory domain score that was similar in magnitude to the improvement in CFQ-R respiratory
420 domain score observed in TEZ/IVA-treated participants in their parent studies. The benefits in
421 CFQ-R respiratory domain score observed in each efficacy set in study 661-110 were generally
422 maintained for up to 120 weeks of treatment (**appendix pp 19-22; Figure 2C; Figure 3C**).

423
424 In the 106/110 (*F/F*) and 108/110 (*F/RF*) Efficacy Sets, increases in BMI and weight observed in
425 the parent studies were generally maintained in all treatment groups over 96 weeks in study 661-
426 110 (**appendix pp 19-22; Figure 2D; Figure 3D**). The mean *z* scores (BMI, weight, and height
427 in participants <20 years of age) remained stable and close to the mean values for the age-
428 matched general population during the 96 weeks in both efficacy sets (**appendix pp 19-22**).

429

430 **Secondary Endpoint: Pharmacokinetics**

431 The pharmacokinetics exposures to TEZ, IVA, and major metabolites were similar to those
432 observed in the parent studies (data not shown).

433

434 **Analysis of Rate of Lung Function Decline**

435 A total of 407 *F/F* participants receiving TEZ/IVA in study 661-106 (*F/F*) and/or study 661-110
436 were propensity score-matched to 1383 CFTRm-untreated *F/F* historical controls in the CFFPR
437 who met the inclusion criteria (on average, 3.4 controls per TEZ/IVA-treated participant)
438 (**appendix p 25**). The two groups were well matched across baseline characteristics based on
439 effect size differences of <0.20 and $P > 0.10$ (**appendix pp 12-13**); in both groups, mean age was

440 approximately 26 years, and baseline ppFEV₁ was approximately 59 (**Table 3**). The time frame
441 for this analysis was 2015 to 2019 for the *F/F* participants receiving TEZ/IVA and 2012 to 2014
442 for the historical controls. The annualized rate of ppFEV₁ decline was significantly lower for
443 TEZ/IVA-treated participants versus untreated matched-control participants: -0.80 (95% CI,
444 -1.31 to -0.30) in the TEZ/IVA group and -2.08 (95% CI, -2.34 to -1.82) in the CFFPR
445 historical control group (**Figure 4**). The mean difference (CFFPR control group versus TEZ/IVA
446 group) was -1.27 per year (95% CI, -1.84 to -0.71; *P*<0.001), which represents a 61.5%
447 relative reduction (95% CI, 35.8 to 86.1) in the annualized rate of decline in ppFEV₁. In the
448 sensitivity analysis excluding registry historical controls who had a record of participating in
449 clinical trials, the resulting difference in the annualized rate of lung function decline was -1.39
450 per year (95% CI, -1.96 to -0.82; *P*<0.001), representing a 61.7% relative reduction (95% CI,
451 38.0 to 84.2) (**appendix p 23**). Additional sensitivity analyses were conducted and yielded
452 consistent findings, with a range of relative reduction from 59.7% to 61.7%.

453

454 **DISCUSSION**

455 This study is the first to evaluate the long-term safety and efficacy of the dual CFTRm TEZ/IVA.
456 TEZ/IVA was found to be generally safe and well tolerated for up to 96 weeks in this open-label
457 extension study 661-110. With extended treatment in study 661-110, the AE profile of TEZ/IVA
458 remained consistent with prior PBO-controlled parent studies.^{20,21} Most pwCF had at least one
459 TEAE over 96 weeks in study 661-110; this finding is not surprising given the morbidity
460 associated with CF and is entirely consistent with prior experience in long-term extension studies
461 of other CFTR modulators.^{19,31} No increases in time-adjusted rates of TEAEs were observed
462 following up to 120 weeks of TEZ/IVA treatment, and the rate of discontinuations due to AEs

463 was low in study 661-110. The most common AEs were generally infectious, respiratory, or
464 gastrointestinal in nature and consistent with the manifestations of CF. In general, time-adjusted
465 rates of AEs were lower in participants in study 661-110 than in TEZ/IVA-treated participants in
466 feeder study 661-106 (*F/F*). This is a typical finding in other 96 week open-label extension
467 studies of other CFTR modulators.¹⁹ One possible explanation for this finding is that recurrent
468 AEs are less frequently captured over longer-term treatment. PwCF experience elevations in
469 transaminase levels due to underlying hepatic disease and treatment with concomitant
470 medications, including antibiotics³²⁻³⁴; the transaminase data in study 661-110 were generally
471 consistent with previous experience with TEZ/IVA and background transaminase elevations
472 occurring in pwCF.^{20,21} Consistent with the PBO-controlled parent studies, there was no evidence
473 of an increased incidence of respiratory TEAEs associated with extended TEZ/IVA
474 treatment.^{20,21}

475
476 CF is a severe progressive disease, and maintaining or improving lung function is an important
477 goal in the management of pwCF because loss of lung function is the major driver of increased
478 morbidity and mortality.⁵ TEZ/IVA use was associated with two important effects on CF lung
479 disease. First, participants with *F/F* and *F/RF* genotypes experienced an acute improvement in
480 lung function, which was observed by day 15 following initiation of TEZ/IVA in both the parent
481 studies and study 661-110 (for those who received PBO in the parent studies). Improvements in
482 ppFEV₁ observed in TEZ/IVA-treated participants with the *F/F* and *F/RF* genotypes were
483 generally maintained in study 661-110. Second, a 61·5% relative reduction in the rate of lung
484 function decline was demonstrated in participants with the *F/F* genotype compared with a cohort
485 of CFTRm-untreated historical controls from the CFFPR. Study 661-110 was not designed to

486 compare the magnitude of the effect of TEZ/IVA with that of other CFTRm on clinical outcome
487 assessments. However, these results are consistent with prior published studies showing that
488 CFTR modulation with IVA and LUM/IVA significantly reduced the long-term rate of lung
489 function decline in participants with the *G551D* mutation by 47·1% (data not shown) and with
490 the *F/F* genotype by 42%, respectively.^{18,19} It was not possible to examine the effect of TEZ/IVA
491 on the rate of lung function decline in participants with *F/RF* genotypes due to the limited
492 sample size of eligible participants in the registry. However, it is noteworthy that the benefits in
493 lung function observed in participants with *F/RF* genotypes were generally maintained for up to
494 104 weeks of treatment.

495
496 PEx are important events in the lives of pwCF and have been independently associated with
497 progressive lung function decline and an increased risk of mortality.³⁵⁻³⁷ The reductions in the
498 risk of PEx observed with TEZ/IVA treatment in studies 661-106 (*F/F*) and 661-108 (*F/RF*)
499 were generally maintained for up to 120 weeks of treatment in study 661-110, with an annualized
500 PEx rate similar to that observed in the parent studies. The reduction in the PEx rate with
501 extended TEZ/IVA treatment may have contributed to the slower rate of lung function decline in
502 *F/F* participants. Improvements in CFQ-R respiratory domain scores were generally maintained
503 in *F/F* and *F/RF* participants, indicating that TEZ/IVA reduced the respiratory symptom burden
504 during long-term treatment. Improving growth and nutritional parameters is an important goal in
505 the management of pwCF because they are important determinants of lung function and survival
506 in pwCF.^{38,39} Improvements in BMI that were observed in the parent studies were generally
507 maintained in study 661-110. In participants <20 years of age in study 661-110, growth

508 parameters were maintained close to those for the age-matched general population without CF
509 (as assessed by z scores).

510

511 The clinical benefit observed in study 661-110 was consistent with that observed in the parent
512 studies. Although study 661-110 was not a PBO-controlled study and lacked a long-term
513 comparator group, the results are interpretable because pwCF with F/F and F/RF genotypes who
514 are not treated with CFTRm have multisystem disease that progresses over time, including
515 relentless loss of lung function.^{4,7} The analysis of rate of lung function decline, which
516 demonstrated that TEZ/IVA was associated with slower lung function decline versus matched
517 historical controls not treated with CFTRm, was a post hoc analysis, and causality cannot be
518 definitively established. The analysis used a cohort of historical controls from the US CFFPR
519 between 2012 and 2014 to avoid the confounding effect of use of LUM/IVA in the F/F
520 population because this CFTRm was approved by the US Food and Drug Administration for this
521 population in 2015; the time frame for the F/F participants receiving TEZ/IVA in this study was
522 2015 to 2019. The use of a noncontemporaneous cohort has the potential to introduce a temporal
523 bias due to possible secular changes in lung function decline due to changes in clinical care.
524 However, to our knowledge, no major advances in background CF care management occurred
525 during this time. Nevertheless, because this analysis employed rigorous epidemiological and
526 statistical methods, including propensity score matching, to balance the risk factors of lung
527 function decline between groups, any bias introduced due to the use of noncontemporaneous
528 controls would likely be addressed. Although the ability to match participants was limited to the
529 variables collected in both the registry and the clinical study, the analysis accounted for the most
530 important variables that are known to influence lung function decline based on the published

531 literature. In evaluating a sensitivity analysis of the potential for selection bias in comparing a
532 clinical trial population with a registry population, we observed consistent results indicating that
533 no such bias exists in our analysis. The registry included data from participants in the United
534 States, whereas study 661-110 enrolled participants not only in the United States but also in
535 Canada, Europe, and Australia, where the characteristics of the pwCF may differ. It is not
536 possible, due to sample size limitations, to restrict the rate of decline in FEV₁ analysis to one
537 geographical region. Other limitations of this analysis are that the model that estimated the mean
538 annual rate of decline was based on ppFEV₁ measurements from variable observation periods
539 across participants included in the analysis. Also, the model assumed that the rate of decline in
540 ppFEV₁ was constant over the observation period for each participant.

541
542 A limitation of this study is its open-label design, which may be associated with potential biases
543 including biases in symptom reporting by study participants, evaluation of the severity and
544 relatedness of AEs to study drug by site investigators, and patient-reported outcomes, including
545 the CFQ-R respiratory domain score. Other limitations of our efficacy assessments include the
546 fact that participants with *F*/*RF* genotypes were evaluated as a group due to the rare prevalence
547 of these *RF* mutations. Due to small sample sizes, it is not possible to provide efficacy data for
548 TEZ/IVA on individual *F*/*RF* genotypes. However, the results indicate that TEZ/IVA treatment
549 led to improvements in efficacy endpoints over the longer term in pwCF with *F*/*RF* genotypes
550 who were included in study 661-110.

551
552 TEZ/IVA is the foundation of a triple-combination CFTRm therapy (elexacaftor
553 [ELX]/TEZ/IVA). A recent Phase 3 study confirmed that ELX/TEZ/IVA resulted in significant

554 and clinically meaningful improvements in ppFEV₁, sweat chloride concentrations, and CFQ-R
555 respiratory domain scores, and clinical meaningful improvements in nutritional parameters
556 compared with TEZ/IVA dual-combination therapy in participants ≥ 12 years of age with CF
557 with the *F/F* genotype.⁴⁰ ELX/TEZ/IVA combination therapy was recently approved in the
558 United States to treat pwCF ≥ 12 years of age with at least one copy of the *F508del-CFTR*
559 mutation,⁴¹ noting that its effect on long-term lung function decline has not yet been reported.
560

561 Study 661-110 showed that TEZ/IVA was generally safe and well tolerated for up to 120 weeks
562 and had a safety profile consistent with that observed in the parent studies. The multisystem
563 clinical benefits observed with TEZ/IVA in the parent studies in participants with *F/F* and *F/RF*
564 genotypes were generally maintained over 96 weeks and were also observed in participants who
565 transitioned from PBO to TEZ/IVA in study 661-110. The post hoc analysis of rate of lung
566 function decline demonstrated that TEZ/IVA was associated with a significantly slower lung
567 function decline among *F/F* participants vs CFTRm-untreated matched historical controls. Thus,
568 longer-term TEZ/IVA use was associated with sustained benefits, and the rate of lung function
569 decline was significantly reduced in *F/F* participants consistent with modification of the course
570 of CF disease. These results support the clinical benefit of long-term TEZ/IVA treatment for *F/F*
571 or *F/RF* pwCF ≥ 12 years of age.
572

573 **CONTRIBUTORS**

574 All authors contributed to data interpretation, conception, drafting, and/or revisions to the
575 manuscript, and all approved the final version that was submitted for publication. **CAO:** study
576 design, data collection, data analysis, and literature searches. **CB:** no additional contributions.
577 **CEW:** data collection. **DC:** data analysis. **DGD:** data collection. **DJP:** statistical analysis and
578 interpretation of analysis. **GSS:** study design. **HPD:** no additional contributions. **JLR:** study
579 design, analysis, and interpretation of the rate of lung function decline and development of the
580 manuscript. **KDB:** conceptualization and design of the report and figure layout. **MJ:** no
581 additional contributions. **NA:** data collection and data analysis. **PAF:** study design, data
582 collection, and data analysis. **PC:** data analysis. **RF:** data collection. **RFB:** data analysis. **SJM:**
583 analysis design and statistical analysis. **XH:** study design, data interpretation, and writing the
584 manuscript, all with a focus on the analysis of the rate of lung function decline. **XW:** data
585 analysis and figures. **YY:** study design, analysis, and interpretation of the rate of lung function
586 decline and development of the manuscript.

587

588 **DECLARATION OF INTERESTS**

589 All authors received nonfinancial support (assistance with manuscript preparation) from
590 ArticulateScience LLC, which received funding from Vertex Pharmaceuticals Incorporated.
591 Additional disclosures are as follows: **CAO, DC, HPD, JLR, NA, PC, XH,** and **YY** are
592 employees of Vertex Pharmaceuticals Incorporated and may own stock or stock options in
593 Vertex Pharmaceuticals Incorporated. **CB:** grants from Vertex Pharmaceuticals Incorporated
594 during the conduct of the study; grants from Cystic Fibrosis Foundation Therapeutics
595 Incorporated, Translate Bio, Concert Pharmaceuticals, Parlon Sciences, Nivalis Therapeutics,

596 Anthera Pharmaceuticals, and PTC Therapeutics outside of the submitted work. **CW:** Advisory
597 board for Vertex; editor for *Respirology* (associate editor) and *Thorax* (deputy editor); honoraria
598 from *BMJ*, DKBmed, Gilead, In Vivo Academy, Novartis, *Thorax*, University of Miami, and
599 Vertex; research grant from Novo Nordisk; study investigator for Boehringer Ingelheim and
600 Vertex; and travel expenses from Vertex. **DGD:** grants and personal fees from Vertex
601 Pharmaceuticals Incorporated, Proteostasis, and Chiesi outside the submitted work. **GSS:**
602 personal fees from and advisory board for Vertex Pharmaceuticals Incorporated during the
603 conduct of the study; grants from Vertex Pharmaceuticals Incorporated and personal fees from
604 Gilead Sciences outside the submitted work. **DJP** and **SJM** are employees of ICON Clinical
605 Research which was paid by Vertex Pharmaceuticals Incorporated for providing analytical
606 services on this project; ICON Clinical Research is paid by various pharmaceutical,
607 biotechnology, and device companies for providing clinical research services outside the
608 submitted work. **KDB:** consultancy from Boehringer, Protalix, Raptor, Novabiotics, Eloxx, and
609 Chiesi outside the submitted work; speaker fees from Teva outside the submitted work;
610 consultancy/PI in studies for Galapagos outside the submitted work; member of steering
611 committee/advisory board/PI in studies for Vertex Pharmaceuticals Incorporated outside the
612 submitted work. **MJ:** grants, personal fees, advisory board, and speaker's bureau from Vertex
613 Pharmaceuticals Incorporated outside the submitted work. **PAF:** grants and personal fees from
614 Vertex Pharmaceuticals Incorporated outside the submitted work. **RF:** grants for study conduct
615 from Vertex Pharmaceuticals Incorporated during the conduct of the study. **RFB** has nothing
616 further to disclose. **XW** was an employee of Vertex Pharmaceuticals Incorporated at the time the
617 study was conducted and may own stock or stock options in Vertex Pharmaceuticals
618 Incorporated.

619

620 **DATA SHARING STATEMENT**

621 Vertex is committed to advancing medical science and improving the health of people with
622 cystic fibrosis. This includes the responsible sharing of clinical trial data with qualified
623 researchers. Proposals for the use of these data will be reviewed by a scientific board. Approvals
624 are at the discretion of Vertex and will be dependent on the nature of the request, the merit of the
625 research proposed, and the intended use of the data. Please contact CTDS@vrtx.com if you
626 would like to submit a proposal or need more information.

627

628 **ACKNOWLEDGMENTS**

629 We thank the patients and their families for participating in this trial and the trial investigators
630 and coordinators for their contributions to the trial. A list of investigators and trial sites is
631 included in the appendix (pp 4-6). Editorial coordination and support were provided by Thomas
632 Pickette, PharmD, MBA, of Vertex Pharmaceuticals Incorporated; Thomas Pickette may own
633 stock or stock options in that company. Medical writing and editorial support were provided
634 under the direction of the authors by Christopher Edwards, PhD, and Karen Kaluza Smith, PhD,
635 CMPP. Christopher Edwards, PhD, and Karen Kaluza Smith, PhD, CMPP, are employees of
636 ArticulateScience LLC, which received funding from Vertex Pharmaceuticals Incorporated. This
637 study was supported by Vertex Pharmaceuticals Incorporated.

638

639 **REFERENCES**

- 640 1 De Boeck K, Amaral MD. Progress in therapies for cystic fibrosis. *Lancet Respir Med*
641 2016; **4**: 662–74.
- 642 2 Riordan JR, Rommens JM, Kerem B, et al. Identification of the cystic fibrosis gene:
643 cloning and characterization of complementary DNA. *Science* 1989; **245**: 1066–73.
- 644 3 Dalemans W, Barbry P, Champigny G, et al. Altered chloride ion channel kinetics
645 associated with the delta F508 cystic fibrosis mutation. *Nature* 1991; **354**: 526–8.
- 646 4 Salvatore D, Padoan R, Buzzetti R, et al. Patients with cystic fibrosis having a residual
647 function mutation: data from the Italian registry. *Pediatr Pulmonol* 2019; **54**: 150–7.
- 648 5 Elborn JS. Cystic fibrosis. *Lancet* 2016; **388**: 2519–31.
- 649 6 Castellani C, Cuppens H, Macek M Jr, et al. Consensus on the use and interpretation of
650 cystic fibrosis mutation analysis in clinical practice. *J Cyst Fibros* 2008; **7**: 179–96.
- 651 7 McKone EF, Goss CH, Aitken ML. CFTR genotype as a predictor of prognosis in cystic
652 fibrosis. *Chest* 2006; **130**: 1441–7.
- 653 8 Cystic Fibrosis Foundation. The clinical and functional translation of CFTR (CFTR2).
654 <https://www.cftr2.org/>. Accessed September 16, 2020.
- 655 9 McKone EF, Emerson SS, Edwards KL, Aitken ML. Effect of genotype on phenotype
656 and mortality in cystic fibrosis: a retrospective cohort study. *Lancet* 2003; **361**: 1671–6.
- 657 10 Comer DM, Ennis M, McDowell C, et al. Clinical phenotype of cystic fibrosis patients
658 with the G551D mutation. *QJM* 2009; **102**: 793–8.
- 659 11 Rodman DM, Polis JM, Heltshe SL, et al. Late diagnosis defines a unique population of
660 long-term survivors of cystic fibrosis. *Am J Respir Crit Care Med* 2005; **171**: 621–6.

661 12 Van Goor F, Hadida S, Grootenhuis PD, et al. Rescue of CF airway epithelial cell
662 function in vitro by a CFTR potentiator, VX-770. *Proc Natl Acad Sci U S A* 2009; **106**: 18825–
663 30.

664 13 Van Goor F, Grootenhuis P, Hadida S, et al. Nonclinical profile of the CFTR corrector
665 VX-661. *Pediatr Pulmonol* 2016; **51** [abstract 217].

666 14 Van Goor F, Hadida S, Grootenhuis PDJ, et al. Correction of the F508del-CFTR protein
667 processing defect in vitro by the investigational drug VX-809. *Proc Natl Acad Sci U S A* 2011;
668 **108**: 18843–8.

669 15 Keating D, Marigowda G, Burr L, et al. VX-445–tezacaftor–ivacaftor in patients with
670 cystic fibrosis and one or two Phe508del alleles. *N Engl J Med* 2018; **379**: 1612–20.

671 16 Bessonova L, Volkova N, Higgins M, et al. Data from the US and UK cystic fibrosis
672 registries support disease modification by CFTR modulation with ivacaftor. *Thorax* 2018; **73**:
673 731–40.

674 17 Volkova N, Moy K, Evans J, et al. Disease progression in patients with cystic fibrosis
675 treated with ivacaftor: Data from national US and UK registries. *J Cyst Fibros* 2020; **19**: 68–79.

676 18 Sawicki GS, McKone EF, Pasta DJ, et al. Sustained benefit from ivacaftor demonstrated
677 by combining clinical trial and cystic fibrosis patient registry data. *Am J Respir Crit Care Med*
678 2015; **192**: 836–42.

679 19 Konstan MW, McKone EF, Moss RB, et al. Assessment of safety and efficacy of long-
680 term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis
681 homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. *Lancet*
682 *Respir Med* 2017; **5**: 107–18.

683 20 Taylor-Cousar J, Munck A, McKone EF, et al. Tezacaftor–ivacaftor in patients with
684 cystic fibrosis homozygous for Phe508del. *N Engl J Med* 2017; **377**: 2013–23.

685 21 Rowe SM, Daines C, Ringshausen FC, et al. Tezacaftor-ivacaftor in residual-function
686 heterozygotes with cystic fibrosis. *N Engl J Med* 2017; **377**: 2024–35.

687 22 Symdeko (tezacaftor/ivacaftor) [package insert]. Boston, MA: Vertex Pharmaceuticals
688 Inc; 2019.

689 23 Symkevi (tezacaftor/ivacaftor) [summary of product characteristics]. Dublin, Ireland:
690 Vertex Pharmaceuticals (Ireland) Ltd; 2019.

691 24 Munck A, Kerem E, Ellemunter H, et al. Tezacaftor/ivacaftor in people with cystic
692 fibrosis heterozygous for minimal function CFTR mutations. *J Cyst Fibros* 2020 June 13 [Epub
693 ahead of print].

694 25 Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG Jr. Pulmonary function between 6
695 and 18 years of age. *Pediatr Pulmonol* 1993; **15**: 75–88.

696 26 Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of
697 the general U.S. population. *Am J Respir Crit Care Med* 1999; **159**: 179–87.

698 27 Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for
699 the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; **40**: 1324–43.

700 28 Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor-ivacaftor in patients with
701 cystic fibrosis homozygous for Phe508del CFTR. *N Engl J Med* 2015; **373**: 220–31.

702 29 Elborn JS, Ramsey BW, Boyle MP, et al. Efficacy and safety of lumacaftor/ivacaftor
703 combination therapy in patients with cystic fibrosis homozygous for Phe508del CFTR by
704 pulmonary function subgroup: a pooled analysis. *Lancet Respir Med* 2016; **4**: 617–26.

705 30 Kalydeco (ivacaftor) [package insert]. Boston, MA, United States: Vertex
706 Pharmaceuticals Inc; 2019.

707 31 McKone EF, Borowitz D, Drevinek P, et al. Long-term safety and efficacy of ivacaftor in
708 patients with cystic fibrosis who have the Gly551Asp-CFTR mutation: a phase 3, open-label
709 extension study (PERSIST). *Lancet Respir Med* 2014; **2**: 902–10.

710 32 Ledder O, Haller W, Couper RT, Lewindon P, Oliver M. Cystic fibrosis: an update for
711 clinicians. Part 2: hepatobiliary and pancreatic manifestations. *J Gastroenterol Hepatol* 2014; **29**:
712 1954–62.

713 33 Andrade RJ, Tulkens PM. Hepatic safety of antibiotics used in primary care. *J*
714 *Antimicrob Chemother* 2011; **66**: 1431–46.

715 34 Jong T, Geake J, Yerkovich S, Bell SC. Idiosyncratic reactions are the most common
716 cause of abnormal liver function tests in patients with cystic fibrosis. *Intern Med J* 2015; **45**:
717 395–401.

718 35 Waters V, Stanojevic S, Atenafu EG, et al. Effect of pulmonary exacerbations on long-
719 term lung function decline in cystic fibrosis. *Eur Respir J* 2012; **40**: 61–6.

720 36 de Boer K, Vandemheen KL, Tullis E, et al. Exacerbation frequency and clinical
721 outcomes in adult patients with cystic fibrosis. *Thorax* 2011; **66**: 680–5.

722 37 Konstan MW, Morgan WJ, Butler SM, et al. Risk factors for rate of decline in forced
723 expiratory volume in one second in children and adolescents with cystic fibrosis. *J Pediatr* 2007;
724 **151**: 134–9.e1.

725 38 Konstan MW, Butler SM, Wohl MEB, et al. Growth and nutritional indexes in early life
726 predict pulmonary function in cystic fibrosis. *J Pediatr* 2003; **142**: 624–30.

727 39 Sharma R, Florea VG, Bolger AP, et al. Wasting as an independent predictor of mortality
728 in patients with cystic fibrosis. *Thorax* 2001; **56**: 746–50.

729 40 Heijerman HGM, McKone EF, Downey DG, et al. Efficacy and safety of the elexacaftor
730 plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for
731 the F508del mutation: a double-blind, randomised, phase 3 trial. *Lancet* 2019; **394**: 1940–8.

732 41 Vertex Pharmaceuticals Incorporated. FDA approves TRIKAFTA
733 (elexacaftor/tezacaftor/ivacaftor and ivacaftor) to treat the underlying cause of cystic fibrosis in
734 people ages 12 and older who have at least one F508del mutation [press release]. 2019.

735 42 Austin PC. Assessing balance in measured baseline covariates when using many-to-one
736 matching on the propensity-score. *Pharmacoepidemiol Drug Saf* 2008; **17**: 1218–25.

737

738 TABLES

739 Table 1. Participant Demographics and Baseline Characteristics

	106/110 Efficacy Set (F/F) (n=459)	108/110 Efficacy Set (F/RF) (n=226)
Age at screening, mean (SD), years	26·1 (10·4)	35·1 (14·2)
Age ≥18 years at screening, n (%)	350 (76·3)	194 (85·8)
Female sex, n (%)	222 (48·4)	121 (53·5)
White race, n (%)	454 (98·9)	221 (97·8)
BMI, mean (SD), kg/m ²	21·00 (2·94)	24·21 (5·00)
ppFEV ₁ , mean (SD)	60·0 (15·1)	62·2 (14·5)
ppFEV ₁ category, n (%)		
<40%	42 (9·2)	20 (8·8)
≥40% to <70%	283 (61·7)	132 (58·4)
≥70% to ≤90%	125 (27·2)	70 (31·0)
>90%	8 (1·7)	4 (1·8)

740 BMI, body mass index; ppFEV₁, percent predicted forced expiratory volume in 1 second using

741 Wang and Hankinson equations.

742

743 **Table 2. Time-Adjusted TEAEs in ≥10% of Participants in the Study 661-106 (F/F) Safety Set's TEZ/IVA Group or in the**
744 **Study 661-110 (F/F and F/RF) Safety Set**

	Study 661-106 (F/F) Safety Set ^a (n=509)				Study 661-110 (F/F and F/RF) Safety Set (n=1042)	
	PBO (n=258)		TEZ/IVA (n=251)		TEZ/IVA (n=1042)	
	Participants, n (%)	Events Per 100 Participant- Years ^b	Participants, n (%)	Events Per 100 Participant- Years ^b	Participants, n (%)	Events Per 100 Participant- Years ^b
Any TEAE	245 (95.0)	1344.78	227 (90.4)	1086.15	995 (95.5)	661.47
Infective PEx of CF	96 (37.2)	126.02	75 (29.9)	92.25	549 (52.7)	91.11
Cough	84 (32.6)	101.34	66 (26.3)	75.97	374 (35.9)	46.31
Nasopharyngitis	39 (15.1)	48.47	42 (16.7)	48.84	227 (21.8)	24.18
Hemoptysis	35 (13.6)	41.42	26 (10.4)	30.75	179 (17.2)	23.72
Sputum increased	42 (16.3)	42.30	36 (14.3)	37.08	224 (21.5)	21.28
Headache	37 (14.3)	52.87	44 (17.5)	51.55	147 (14.1)	19.83
Pyrexia	32 (12.4)	33.49	28 (11.2)	35.27	136 (13.1)	14.16
Oropharyngeal pain	29 (11.2)	31.72	22 (8.8)	20.80	136 (13.1)	12.52
Upper respiratory tract infection	10 (3.9)	10.57	7 (2.8)	8.14	135 (13.0)	11.86
Abdominal pain	22 (8.5)	25.56	23 (9.2)	25.32	107 (10.3)	9.35
Nausea	18 (7.0)	18.51	23 (9.2)	23.51	107 (10.3)	9.29
Diarrhea	23 (8.9)	28.20	17 (6.8)	18.99	105 (10.1)	8.30

745 CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; F/F, homozygous for the *F508del-CFTR* mutation;

746 F/RF, heterozygous for the *F508del-CFTR* mutation and a residual function *CFTR* mutation; PBO, placebo; PEx, pulmonary

747 exacerbation; TEAE, treatment-emergent adverse event; TEZ/IVA, tezacaftor/ivacaftor combination therapy.

748 ^a The study 661-106 (F/F) Safety Set included all participants who received at least one dose of the study drug in study 661-106 (F/F).

749 ^b The number of events per 100 participant-years equaled the number of events/(total exposure in days/[365·25 × 100]).

750 **Table 3. Demographics and Baseline Characteristics of F/F Participants Included in the**
 751 **Post Hoc Analysis of Rate of ppFEV₁ Decline**

	TEZ/IVA-Treated Group (n=407)	CFFPR Matched- Control Group^a (n_w=407; n=1383)
Age at baseline, mean (SD), years	26·03 (10·35)	26·04 (5·57)
≥18 years of age at baseline, n (%)	310 (76·2)	310 (76·2)
Female sex, n (%)	191 (46·9)	182 (44·7)
CF-related diabetes prior to baseline, n (%)	72 (17·7)	75 (18·4)
BMI, mean (SD), kg/m ²	21·03 (2·97)	21·13 (1·66)
ppFEV ₁ , mean (SD)	58·95 (14·54)	59·43 (9·25)
<i>Pseudomonas</i> positive, n (%)	292 (71·7)	286 (70·4)
Dornase alfa, n (%)	293 (72·0)	307 (75·4)
Inhaled corticosteroid, n (%)	152 (37·3)	131 (32·1)

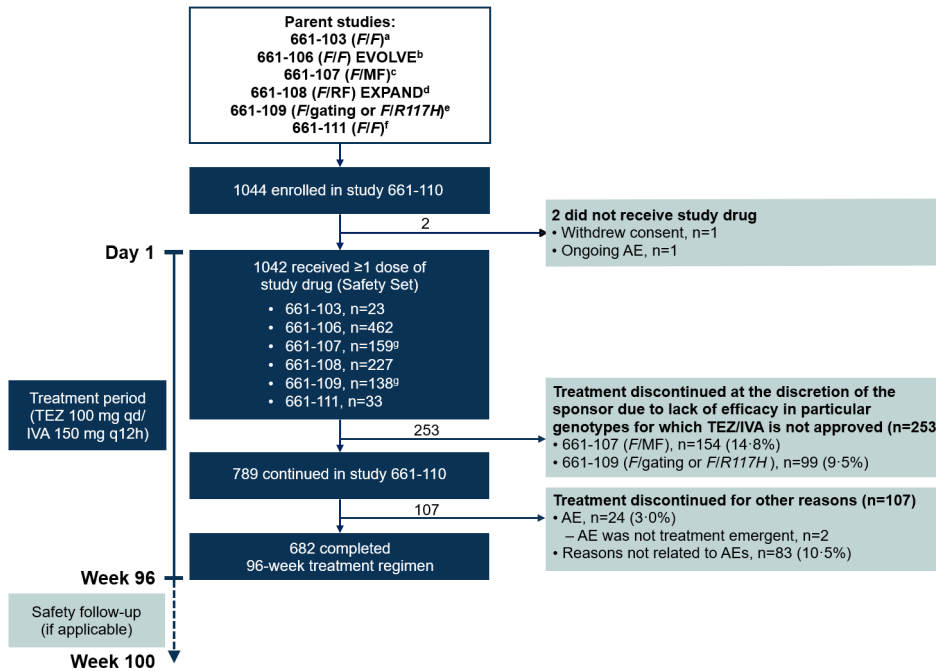
752 BMI, body mass index; CF, cystic fibrosis; CFFPR, CF Foundation Patient Registry; CFTR, CF
 753 transmembrane conductance regulator; F/F, homozygous for the *F508del-CFTR* mutation; GLI,
 754 Global Lung (Function) Initiative; ppFEV₁, percent predicted forced expiratory volume in 1
 755 second using GLI equations; TEZ/IVA, tezacaftor/ivacaftor combination therapy.
 756 ^a n_w represents the weighted sample size of the historical control group using the inverse of the
 757 number of controls in each matched set to account for one-to-many matching used in the
 758 analysis.⁴²

759

760 FIGURES

761

762 Figure 1. Study Design



763

764 AE, adverse event; CF, cystic fibrosis; CFTR, CF transmembrane conductance regulator; IVA,
 765 ivacaftor; F/F, homozygous for the *F508del-CFTR* mutation; F/gating, heterozygous for the
 766 *F508del-CFTR* mutation and a *CFTR* gating mutation; F/MF, heterozygous for the *F508del-*
 767 *CFTR* mutation and a minimal function *CFTR* mutation; F/R117H, heterozygous for the
 768 *F508del-CFTR* mutation and the *R117H-CFTR* mutation; F/RF, heterozygous for the *F508del-*
 769 *CFTR* mutation and a residual function *CFTR* mutation; PBO, placebo; qd, once daily; q12h,
 770 once every 12 hours; TEZ, tezacaftor; TEZ/IVA, tezacaftor/ivacaftor.

771 ^a Study 661-103 was a Phase 2, randomized, PBO-controlled, 12-week study of TEZ/IVA in
772 participants ≥ 18 years of age with CF with the *F/F* genotype.

773 ^b Study 661-106 was a Phase 3, randomized, PBO-controlled, 24-week study of TEZ/IVA in
774 participants ≥ 12 years of age with CF with the *F/F* genotype.²⁰

775 ^c Study 661-107 was a Phase 3, randomized, PBO-controlled, 12-week study of TEZ/IVA in
776 participants ≥ 12 years of age with CF with an *F/MF* genotype.²⁴

777 ^d Study 661-108 was a Phase 3, randomized, PBO- and IVA-controlled, crossover study of
778 TEZ/IVA (2 8-week interventional periods) in participants ≥ 12 years of age with CF with an
779 *F/RF* genotype.²¹

780 ^e Study 661-109 was a Phase 3, randomized, IVA-controlled, 8-week study of TEZ/IVA in
781 participants ≥ 12 years of age with CF with an *F/gating* or *F/R117H* genotype.

782 ^f Study 661-111 was a Phase 2, randomized, PBO-controlled, 29-day study of TEZ/IVA in
783 participants ≥ 18 years of age with CF with the *F/F* genotype.

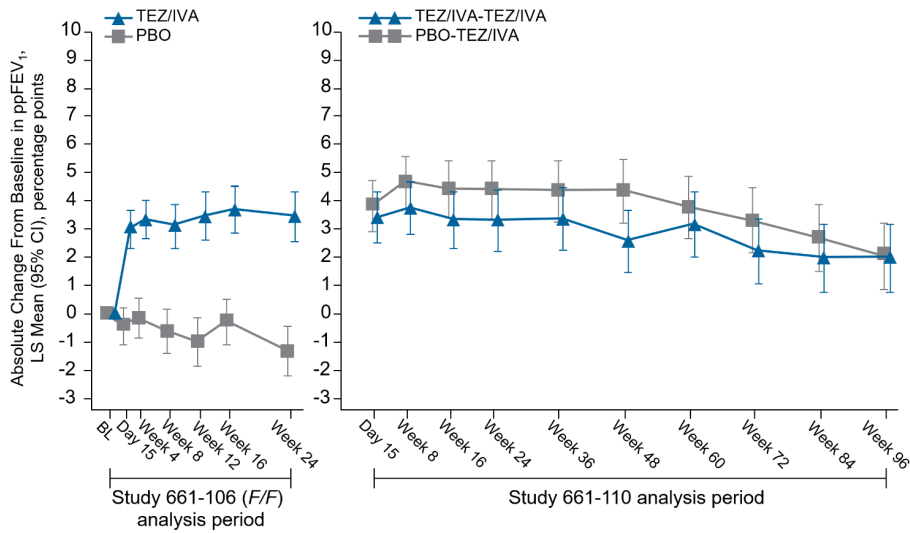
784 ^g Participants who had enrolled in study 661-110 after completing study 661-107 (*F/MF*) or 661-
785 109 (*F/gating* or *F/R117H*) were discontinued from study 661-110 by the sponsor when the
786 parent study demonstrated that TEZ/IVA was not efficacious in these participants versus the
787 study comparator.

788 Flume P, et al. Presented at the North American Cystic Fibrosis Conference 2019. Poster 853.
789 Reprinted with permission by the author.

790

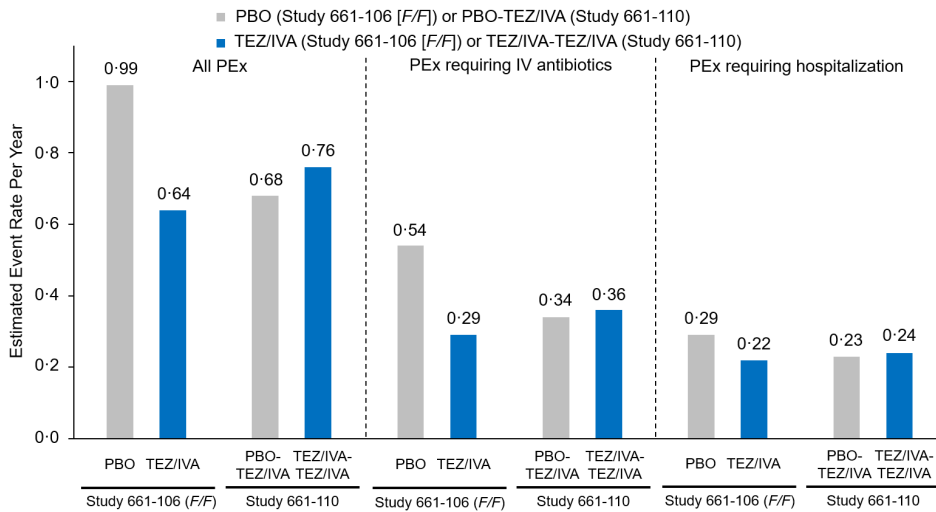
791 **Figure 2. 106/110 Efficacy Results (F/F)**

792 **A. Absolute Change From Baseline in ppFEV₁^a**



793

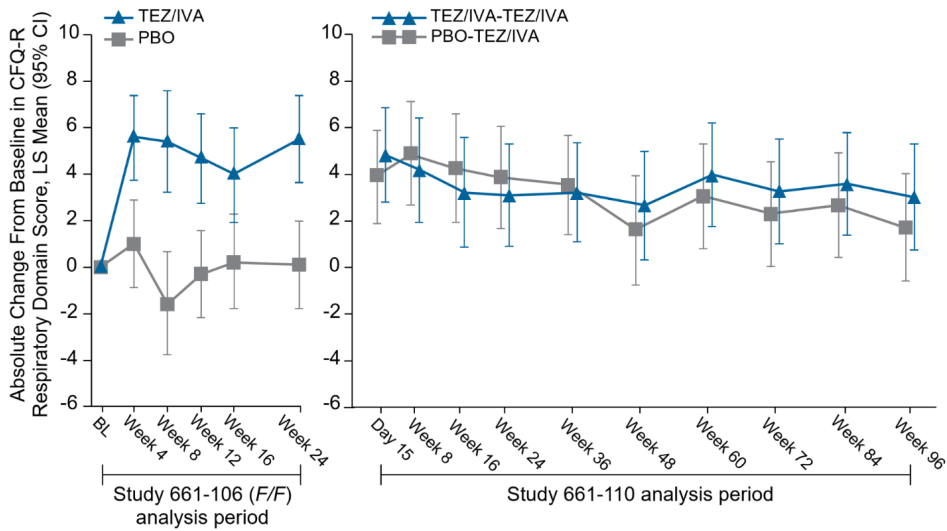
794 **B. PEx Rates in Study 661-106 (F/F) and Study 661-110^{b,c}**



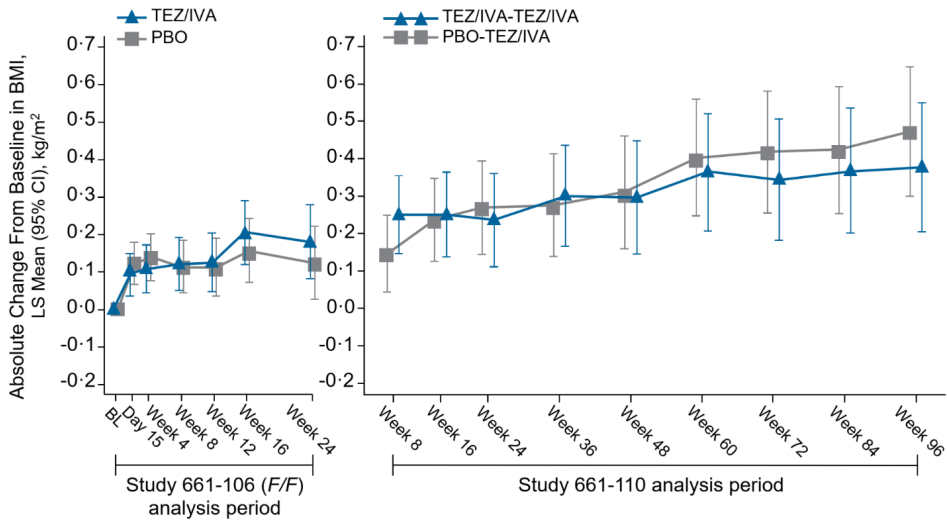
795

796

797 **C. Absolute Change From Baseline in CFQ-R Respiratory Domain Score^a**



799 **D. Absolute Change From Baseline in BMI^a**



801 BL, baseline; BMI, body mass index; CFQ-R, Cystic Fibrosis Questionnaire–Revised; CFTR,
 802 cystic fibrosis transmembrane conductance regulator; *F/F*, homozygous for the *F508del-CFTR*

803 mutation; IV, intravenous; LS, least squares; PBO, placebo; PEx, pulmonary exacerbation;
804 ppFEV₁, percent predicted forced expiratory volume in 1 second using Wang and Hankinson
805 equations; TEZ/IVA, tezacaftor/ivacaftor combination therapy.

806 ^a Analyses were conducted on the 106/110 Efficacy Set (*F/F*). Data from the PBO and TEZ/IVA
807 groups in the 661-106 (*F/F*) parent study are shown only for visual comparison. Statistical
808 comparisons were not performed between groups within study 661-110 or between this study
809 and the parent study.

810 ^b Analysis was conducted on the 106/110 PEx Analysis Set (*F/F*). The PEx event rates in the
811 PBO and TEZ/IVA groups of the 661-106 (*F/F*) parent study are shown only for visual
812 comparison. Statistical comparisons were not performed between groups within study 661-110 or
813 between this study and the parent study.

814 ^c Annualized PEx rate was calculated based on 48 weeks in a year.

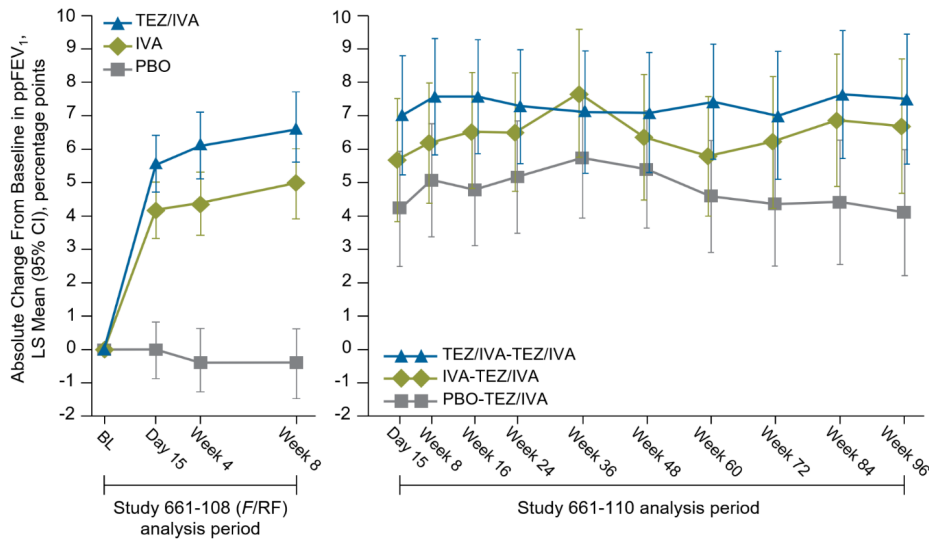
815 Panel A: Flume P, et al. Presented at the North American Cystic Fibrosis Conference 2019.

816 Poster 853. Reprinted with permission by the author.

817

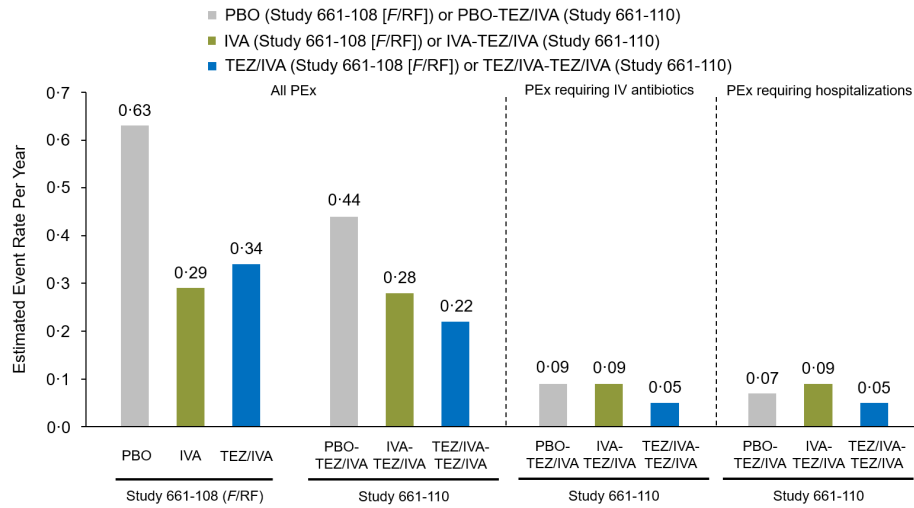
818 **Figure 3. 108/110 Efficacy Results (F/RF)**

819 **A. Absolute Change From Baseline in ppFEV₁^a**



820

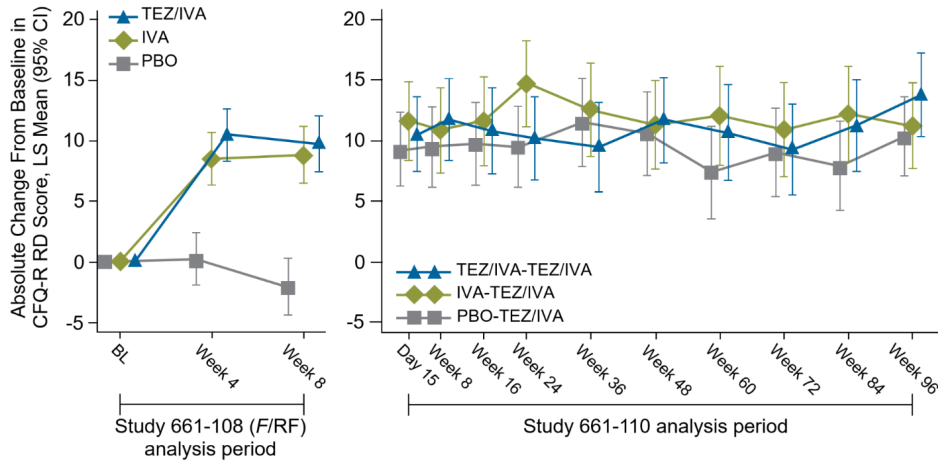
821 **B. PEx Rates in Study 661-108 (F/RF) and Study 661-110^{b,c}**



822

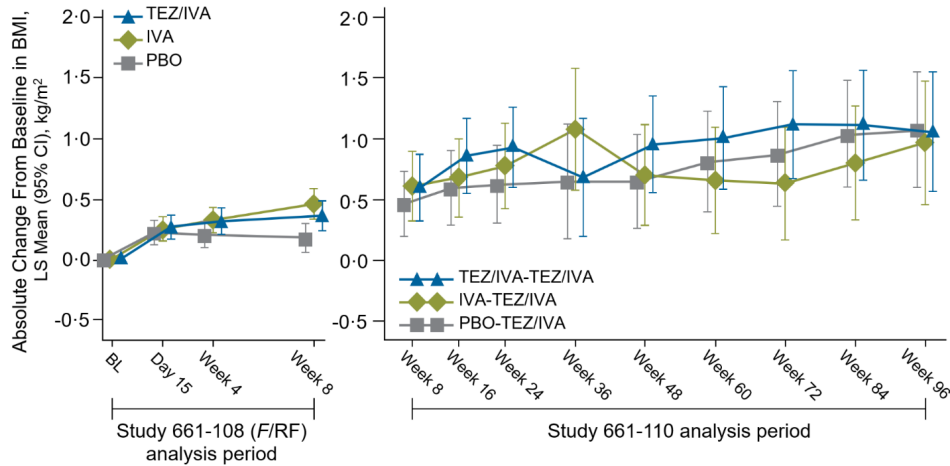
823

824 **C. Absolute Change From Baseline in CFQ-R Respiratory Domain Score^a**



825

826 **D. Absolute Change From Baseline in BMI^a**



827

828 BL, baseline; BMI, body mass index; CFQ-R, Cystic Fibrosis Questionnaire–Revised; CFTR,
 829 cystic fibrosis transmembrane conductance regulator; *F/RF*, heterozygous for the *F508del-CFTR*
 830 mutation and a residual function *CFTR* mutation; IV, intravenous; IVA, ivacaftor monotherapy;
 831 LS, least squares; PBO, placebo; PEx, pulmonary exacerbation; ppFEV₁, percent predicted

832 forced expiratory volume in 1 second using Wang and Hankinson equations; TEZ/IVA,
833 tezacaftor/ivacaftor combination therapy.

834 ^a Analyses were conducted on the 108/110 Efficacy Set (*F/RF*). Data from the PBO, IVA, and
835 TEZ/IVA groups in the 661-108 (*F/RF*) parent study are shown only for visual comparison.
836 Statistical comparisons were not performed between groups within study 661-110 or between
837 this study and the parent study.

838 ^b Analysis was conducted on the 108/110 PEx Analysis Set (*F/RF*). The PEx event rates in the
839 PBO, IVA and TEZ/IVA groups of the 661-108 (*F/RF*) parent study are shown only for visual
840 comparison. Statistical comparisons were not performed between groups within study 661-110 or
841 between this study and the parent study.

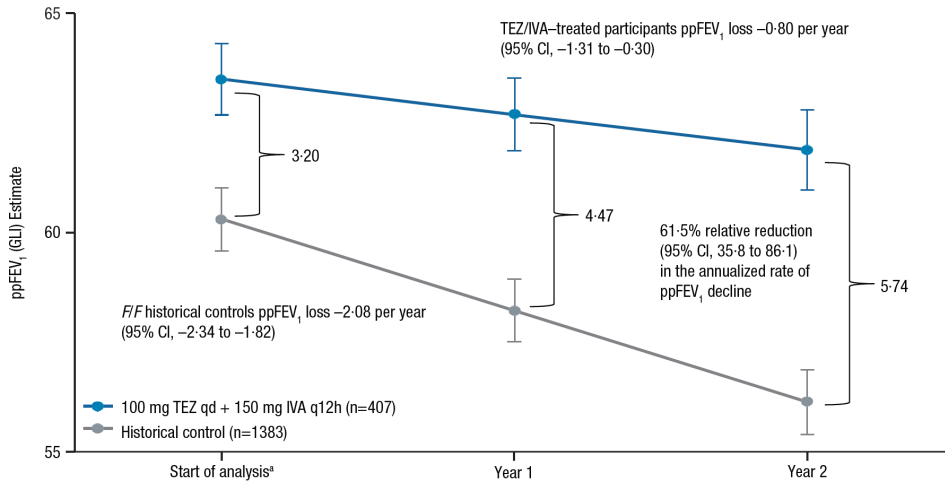
842 ^c Annualized PEx rate was calculated based on 48 weeks in a year.

843 Panel A: Flume P, et al. Presented at the North American Cystic Fibrosis Conference 2019.

844 Poster 853. Reprinted with permission by the author.

845

846 **Figure 4. Rate of ppFEV₁ Decline in Participants With the *F/F* Genotype**



847
 848 CF, cystic fibrosis; CFTR, CF transmembrane conductance regulator; *F/F*, homozygous for the
 849 *F508del-CFTR* mutation; GLI, Global Lung (Function) Initiative; LUM/IVA,
 850 lumacaftor/ivacaftor; ppFEV₁, percent predicted forced expiratory volume in 1 second using GLI
 851 equations; q12h, once every 12 hours; qd, once daily; TEZ/IVA, tezacaftor/ivacaftor
 852 combination therapy. The *F/F* historical controls were propensity-matched controls from the
 853 Cystic Fibrosis Foundation Patient Registry between 2012 and 2014 to avoid the confounding
 854 effect of use of LUM/IVA, a CFTR modulator that was approved by the US Food and Drug
 855 Administration for this population in 2015.

856 ^a Start of analysis was defined as 22 days after TEZ/IVA initiation to remove the acute lung
 857 function improvement with TEZ/IVA from the calculation of rate of ppFEV₁ decline.

858 Flume P, et al. Presented at the North American Cystic Fibrosis Conference 2019. Poster 853.

859 Reprinted with permission by the author.

860