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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Symkevi

Tezacaftor / Ivacaftor

Procedure no: EMEA/H/C/004682/P46/008.1

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AMP	adenosine monophosphate
AST	aspartate transaminase
ATC	anatomic class
BLQ	below the limit of quantification
BMI	body mass index
CF	cystic fibrosis
CFLD	cystic fibrosis liver disease
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	CF transmembrane conductance regulator protein
CFTR	CF transmembrane conductance regulator gene
CI	confidence interval
CK	creatine kinase
Cl	chloride ion
COVID-19	coronavirus disease
CPK	creatine phosphokinase
CRF	case report form
CSR	clinical study report
CV	coefficient of variation
CYP	cytochrome P450
DBP	diastolic blood pressure
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ERT	eResearch Technology, Inc
ES	Efficacy Set
ETT	Early Termination of Treatment
EU	European Union
F/F	homozygous for *F508del-CFTR*
F/gating	heterozygous for *F508del* and a *CFTR* mutation that results in a gating defect
F/MF	heterozygous for *F508del* and a *CFTR* mutation that results in minimal CFTR function (non-TEZ/IVA-responsive mutation)
F/R117H	heterozygous for *F508del* and *R117H*
F/RF	heterozygous for *F508del* and a *CFTR* mutation that results in residual function *F508del CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
FAS	Full Analysis Set
FDC	fixed-dose combination
FEF25%-75%	forced expiratory flow, midexpiratory phase
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HR	heart rate
IA	interim analysis
IA2	second interim analysis
ICF	informed consent form
ICH	International Council for Harmonization
IDMC	independent data monitoring committee
IEC	independent ethics committee
IP	investigational product
IPD	important protocol deviation
IRB	institutional review board
IV	intravenous
IVA	ivacaftor
IVA-TEZ/IVA	treatment group for Study 110 subjects randomized to IVA in parent study
LDCT	low-dose computed tomography

LFT	liver function test
LLN	lower limit of normal
LS	least squares
LT-SS	Long-term Safety Set MAA
MAA	marketing authorisation application
max	maximum value
MCID	minimally clinically important difference(s)
MedDRA	Medical Dictionary for Regulatory Activities
MF	minimal function
min	minimum value
MMRM	mixed-effects model for repeated measures
n	size of subsample
N	total sample size
N1	number of subjects with at least 1 non-missing measurement during the 110 TE Period
NBLQ	number of values that are below the limit of quantification
NE	not estimable
NOS	not otherwise specified
OE	ophthalmological examination
PBO	placebo
PBO-TEZ/IVA	treatment group for Study 110 subjects randomized to placebo in parent study
PC-SS	Phase 3-controlled Safety Set
PE	physical examination
PEx	pulmonary exacerbation
PK	pharmacokinetic, pharmacokinetics
ppFEV1	percent predicted forced expiratory volume in 1 second
PR	PR interval, segment
PT	Preferred Term
q12h	every 12 hours
qd	once daily
QRS	the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization
QT	QT interval
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericiai¦s formula
R117H	CFTR missense gene mutation that results in the replacement of an arginine residue at position 117 of CFTR with a histidine residue
REML	restricted maximum likelihood
RF	residual function
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SF-12	12-Item Short Form Health Survey
SI	SI units (International System of Units)
SOC	System Organ Class
SOP	standard operating procedure
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TEZ	tezacaftor
TEZ/IVA-TEZ/IVA	treatment group for Study 110 subjects randomized to TEZ/IVA in parent study
UK	United Kingdom
ULN	upper limit of normal
UN	unstructured
USA	United States of America
WHO-DD	World Health Organization Drug Dictionary

Table of contents

1. Introduction

On 15 May 2023, the MAH submitted the completed Study VX14-661-110, for Cystic Fibrosis patients 12 years of age and older, homozygous or heterozygous for the *F508del-CFTR* mutation, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Cystic fibrosis (CF) is an autosomal recessive genetic disease caused by decreased quantity and/or function of the CFTR protein due to mutations in the CFTR gene. CTFR is a channel that regulates the flow of chloride and other anions across epithelia in multiple organs and tissues, including the lungs, pancreas and other gastrointestinal organs, and sweat glands.

The most common disease-causing mutation is *F508del*: approximately 84.7% of people with CF in the US and 81.1% in Europe have at least one F508del allele. At present, there is no cure for CF. CFTR modulators (CFTRm; i.e., correctors and potentiators) represent a major advancement in the treatment of CF because they are systemic therapies that target the underlying cause of the disease and have been shown to improve CF survival by modifying the course of disease. Approved treatment regimens include ivacaftor (IVA) monotherapy (Kalydeco™), lumacaftor (LUM)/IVA dual combination therapy (Orkambi™), tezacaftor (TEZ)/IVA dual combination therapy (Symkevi™) and elexacaftor (ELX)/TEZ/IVA triple combination therapy (Kaftrio™).

In the EU, Symkevi is indicated as a combination regimen with ivacaftor tablets for the treatment of patients with cystic fibrosis (CF) aged 6 years and older who are homozygous for the *F508del* mutation or who are heterozygous for the *F508del* mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: *P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T*.

Table 1 Dosing recommendations for patients aged 6 years and older

Age	Morning (1 tablet)	Evening (1 tablet)
6 to < 12 years weighing < 30 kg	tezacaftor 50 mg/ivacaftor 75 mg	ivacaftor 75 mg
6 to < 12 years weighing ≥ 30 kg	tezacaftor 100 mg/ivacaftor 150 mg	ivacaftor 150 mg
≥ 12 years	tezacaftor 100 mg/ivacaftor 150 mg	ivacaftor 150 mg

Information on the pharmaceutical formulation used in the study

The following tablets were used in the study:

- TEZ/IVA 100-mg/150-mg fixed-dose combination (FDC) tablet
- IVA 150-mg tablet

2.2. Clinical aspects

Abbreviated study numbers: In this report, study numbers are abbreviated to the last 3 digits for TEZ studies:

Study VX14-661-110 is Study 110: A Phase 3, Open-label, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous or Heterozygous for the *F508del-CFTR* Mutation

Study VX13-661-103 is Study 103: A Phase 2, Randomized, Multicenter, Double-blind, Placebo-controlled Study to Evaluate Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of VX-661 in Combination With Ivacaftor for 12 Weeks in Subjects With CF, Homozygous for the *F508del-CFTR* Mutation With an Open-label Extension

Study VX14-661-106 is Study 106: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With CF, Homozygous for the *F508del-CFTR* Mutation

Study VX14-661-107 is Study 107: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With CF, Heterozygous for the *F508del-CFTR* Mutation and With a Second CFTR Mutation That Is Not Likely to Respond to VX-661 and/or Ivacaftor Therapy (*F508del*/NR)

Study VX14-661-108 is Study 108: A Phase 3, Randomized, Double-blind, Placebo-controlled, Crossover Study to Evaluate the Efficacy and Safety of Ivacaftor and VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With CF, Heterozygous for the *F508del-CFTR* Mutation, and a Second Allele With a CFTR Mutation Predicted to Have Residual Function

Study VX14-661-109 is Study 109: A Phase 3, Randomized, Double-blind, Ivacaftor-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With CF, Heterozygous for the *F508del-CFTR* Mutation and a Second CFTR Allele With a Gating Defect That Is Clinically Demonstrated to be Ivacaftor-responsive

Study VX14-661-111 is Study 111: A Phase 2, Randomized, Double-blind, Placebo-controlled, Parallel-group, Exploratory Study to Evaluate Effects of VX-661 in Combination With Ivacaftor on Lung and Extrapulmonary Systems in Subjects Aged 18 Years and Older With CF, Homozygous for the *F508del-CFTR* Mutation

Study VX15-661-112 is Study 112: A Phase 2, Randomized, Placebo-controlled, Double-blind, Study to Evaluate Effect of VX-661 in Combination With Ivacaftor on Chest Imaging Endpoints in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation

Study VX16-661-114 is Study 114: Phase 3b, Randomized, Double-blind, Placebo-controlled, Parallel Group Study to Assess the Safety, Efficacy, and Tolerability of Tezacaftor/Ivacaftor (TEZ/IVA) in an Orkambi-experienced Population Who Are Homozygous for the *F508del-CFTR* Mutation

2.2.1. Introduction

The MAH submitted a final report for:

Study VX14-661-110, a Phase 3, multicenter, open-label, 3-part rollover study in subjects with CF who are homozygous or heterozygous for the *F508del-CFTR* mutation and who participated in Studies VX13-661-103 (Study 103), VX14-661-106 (Study 106), VX14-661-107 (Study 107), VX14-661-108 (Study 108), VX14-661-109 (Study 109), VX14-661-111 (Study 111), VX15-661-112 (Study 112), VX16-661-114 (Study 114), or other Vertex studies investigating VX-661 in combination with ivacaftor.

During the MAA of Symkevi (EMA/CHMP/567306/2018), two interim analyses of Study VX14-661-110 were already submitted.

Study VX14-661-110 consists of three parts, Part A, Part B and Part C. The final results of Study VX14-661-110 Part A treatment Cohort were submitted in EMEA/H/C/004682/II/0016.

2.2.2. Clinical study

Study Title

Phase 3, Open-label, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous or Heterozygous for the *F508del-CFTR* Mutation

Description

Study VX14-661-110 (Study 110) was a Phase 3, open-label, rollover Study to evaluate the safety and efficacy of long-term treatment With VX-661 in combination with Ivacaftor in subjects aged 12 years and older with Cystic Fibrosis, homozygous or heterozygous for the *F508del-CFTR* mutation. Study 110 consisted of 3 parts (Figure 1).

Part A (treatment period of approximately 96 weeks) enrolled subjects who participated in parent Studies VX14-661-103 (Study 103), VX14-661-106 (Study 106), VX14-661-107 (Study 107), VX14-661-108 (Study 108), VX14-661-109 (Study 109), or VX14-661- 111 (Study 111). Study 110 Part A consisted of a Treatment Cohort (eligible subjects 12 years of age and older) and an Observational Cohort (eligible subjects <18 years of age).

Part B (treatment period of approximately 96 weeks) enrolled subjects who participated in parent Study VX14-661-112 (Study 112) or Study VX14-661-114 (Study 112) or subjects who completed study drug treatment in Part A and who met the eligibility criteria. Subjects who permanently discontinued study drug treatment or who withdrew consent during the parent study or in Part A were not eligible for enrolment in Part B.

Part C (treatment period of approximately 192 weeks) enrolled subjects who completed study drug treatment in Part B and who met all the eligibility criteria.

CHMP comments

The parent studies were conducted in patients with F/F, F/RF and F/MF genotype. The conclusions of the involved parent studies are shortly summarised:

Study 106 in CF patients with F/F genotype has led to the authorisation of Symkevi for these patients.

Study 108 in CF patients with F/RF genotype has led to the authorisation of Symkevi for CF patients with F/RF genotype that were included in the trial i.e. *P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272 26A→G, and 3849+10kbC→T*.

Study 107 in CF patients with F/MF genotype was terminated early. The results of Study 107 demonstrated that TEZ/IVA is not efficacious in patients who have the F/MF mutation.

The results of Study 109 showed that TEZ/IVA is as efficacious in patients who have the *F508del*/gating mutation as ivacaftor alone. These patients are not aimed for in the indication of TEZ/IVA.

The results of Study 112 in CF patients with F/F genotype showed a benefit in chest imaging endpoints, while the safety was similar to the safety found in the MAA.

The results of Study 114 in CF patients with F/F genotype indicated that on face value the observed respiratory adverse events of specific interest did not lead to a specific pattern or signal in the group treated with TEZ/IVA, although no confirmatory conclusion could be drawn.

Study 111 seems not to have been submitted previously. Awaiting further clarity, this is not further addressed at the moment.

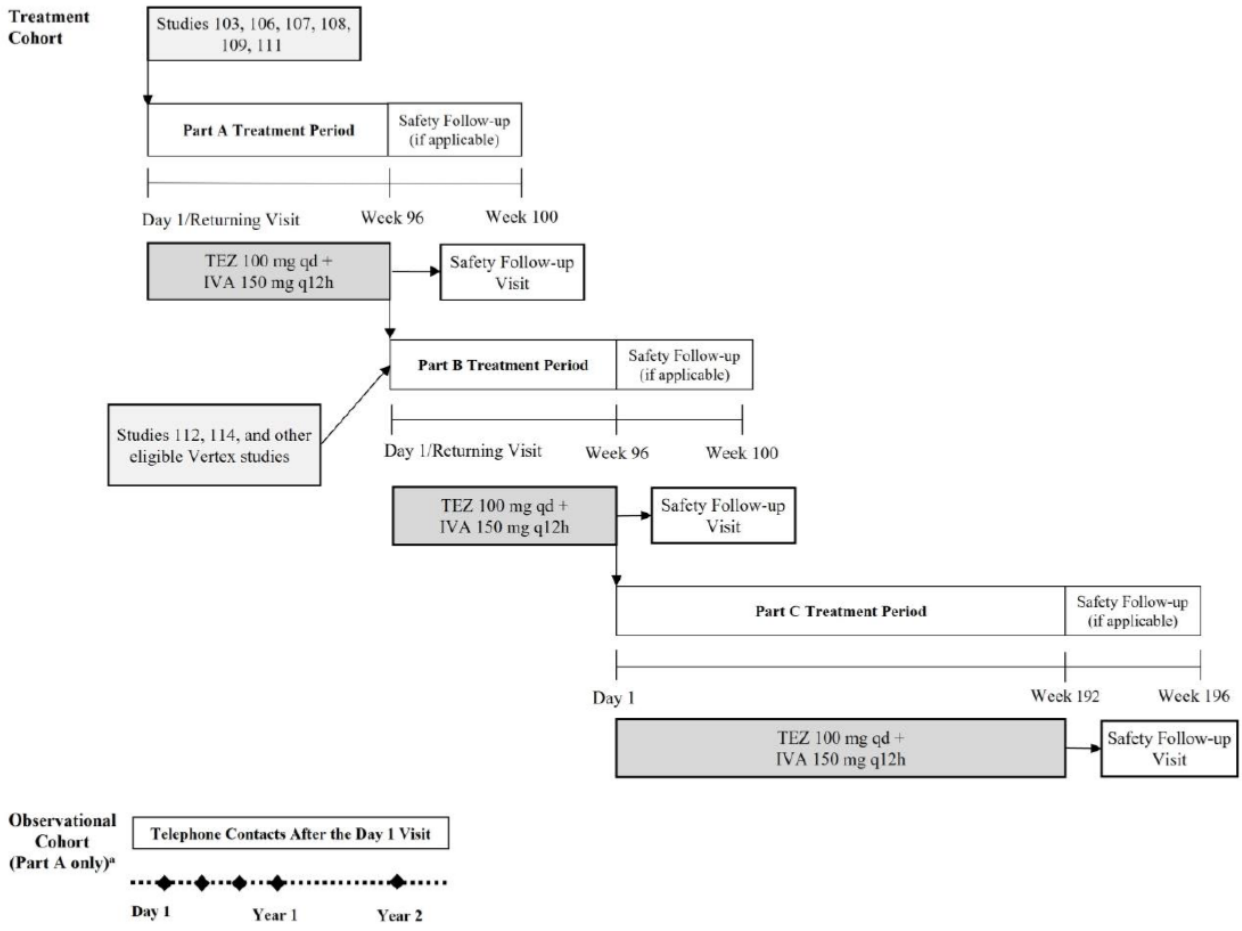
The Treatment Period of Study 110 was up to approximately 96 weeks each for **Part A** and **Part B**, and up to approximately 192 weeks for **Part C**. Subjects who received TEZ/IVA in the parent study and continued to receive this combination in Study 110 could have received treatment for up to approximately 8 years, providing further information on the safety and efficacy of long-term treatment with TEZ/IVA.

Part A consisted of two cohorts:

- Treatment cohort → subjects who completed study drug treatment (i.e., TEZ/IVA, IVA monotherapy, or placebo) during the Treatment Period in the parent study who met the eligibility criteria;
- Observational cohort → subjects <18 years of age who received at least 4 weeks of study drug in the parent study, who were not eligible for the Treatment Cohort or who elected not to enrol in the Treatment Cohort, and met eligibility criteria. These subjects did not receive study drug, but had regularly scheduled telephone calls for approximately 2 years after their last dose of study drug in the parent study to assess post-treatment safety of TEZ/IVA combination therapy.

The study period was from 31 August 2015 until 05 December 2022.

Figure 1 Study Design for VX14-661-110



Source: Adapted from Module 5.3.5.2/Study 110 CSR/Figure 9-1
IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor
Notes: All subjects received a TEZ 100-mg/IVA 150-mg FDC tablet qd in the morning and IVA 150-mg tablet qd in the evening.
[a] No subjects enrolled in the Observational Cohort of Study 110.

CHMP comments

In the parent studies, it was concluded that TEZ/IVA was generally safe and well tolerated. It was also demonstrated that clinical efficacy was greater than IVA alone in most studies, except for studies 107 and 109 in patients harbouring F/MF and F/gating genotypes, respectively.

The main focus for Study 110 was on assessment of safety. Although the subjects included in Study 110 had different genotypes and had different treatment backgrounds in this complex study, assessment of safety as one group is possible because the safety was generally similar through the clinical programme of Symkevi for the different genotypes. However, where necessary, safety reporting will be requested in events/patient years.

As actually no subjects were included in the Part A observational cohort, very limited description will be given in the AR. This cohort did not provide additional information.

Methods

Study participants

The study included male and female subjects 12 years of age or older who were homozygous or heterozygous for the *F508del-CFTR* mutation and completed study drug treatment during the Treatment Period in a parent study (Studies 103, 106, 107, 108, 109, 111, 112, or 114). The key eligibility criteria are shown in Table 2.

Table 2 Key eligibility criteria in Study 110

Inclusion Criteria	Exclusion Criteria
• Confirmed diagnosis of CF as determined by investigator • F/F or F/RF *CFTR* genotype • 12 years of age or older • Willingness to remain on stable CF medication (and supplement) through completion of study participation • Part A only: Completed study drug treatment in one of the following parent studies: Studies 103, 106, 107, 108, or 109 • Part A only: Completed study drug treatment *and* Safety Follow-up in Study 111 • Part B only: Did not withdraw consent from parent study or Study 110 Part A • Part B only: Completed study drug treatment in Study 110 Part A or parent study (Studies 112 or 114) • Part C only: Did not withdraw consent from Study 110 Part B	• History of any comorbidity that might confound the results of the study or pose an additional risk in administering study drug to the subject • History of drug intolerance in parent study or any part of Study 110 • Pregnant or nursing females • Participation in an investigational drug trial (other than a parent study) or use of a commercially available CFTR modulator • Part B only: Subjects who permanently discontinue study drug treatment during the parent study or Part A, including at the last visit of the Treatment Period • Part C only: Subjects who permanently discontinue study drug treatment during the parent study or Parts A or B, including at the last visit of the Treatment Period

Source: Study 110 Protocol Version 5.0/Section 9.1 and Section 9.2
CF: cystic fibrosis; CFTR: cystic fibrosis transmembrane conductance regulator; F/F: homozygous for *F508del*; F/RF: heterozygous for *F508del* and a residual function mutation; TEZ/IVA: tezacaftor/ivacaftor

Subjects who withdrew or were withdrawn during the study drug Treatment Period were not replaced.

CHMP comment

As a result of the different parent studies, the included population is heterogenous, with different genotypes (F/F, F/MF, F/RF, and F/gating) and different treatment backgrounds (TEZ/IVA, IVA or placebo) and different treatment periods (4-72 weeks) before entering the study.

Treatments

In **Part A**, all subjects of the Treatment Cohort received one FDC tablet of TEZ/IVA daily in the morning and one IVA tablet in the evening. Subjects in the Observational Cohort did not receive any treatment. In **Part B** and **C**, all subjects received one FDC tablet of TEZ/IVA daily in the morning and one IVA tablet in the evening.

For **Parts A** and **B**, TEZ/IVA administration was planned for 96 weeks with a Safety Follow-up Visit 28 days (± 7 days) after the last dose. For **Part C**, TEZ/IVA administration was planned for 192 weeks with a Safety Follow-up Visit 28 days (± 7 days) after the last dose.

CHMP comment

The used dosing is in line with the approved posology and TEZ/IVA treatment in the parent studies. The treatment periods of 96 weeks for Part A as well as for Part B and 192 weeks for Part C is sufficient to assess long-term safety and maintenance of efficacy.

Dose modification

Dose modification was not permitted during the study (except in the case of concomitant dosing with moderate or strong inhibitors of cytochrome P450 (CYP) 3A), but the investigator could have interrupted or stopped treatment.

Study Restrictions

Prohibited medications and certain foods were not allowed in this study while subjects were receiving study drug. This was only applicable for subjects in the Treatment Cohort (in Parts A, B, and C).

Prior and Concomitant Medications

Subjects were required to remain on a stable CF medication (and supplement) regimen through the Safety Follow-up Visit. Stable medication regimen was defined as the current medication regimen for CF that subjects had been following for at least 28 days before Day 1.

For Part A, information about bronchodilator use during the study was collected and documented. Subjects who were using a bronchodilator had their spirometry assessments performed according to the American Thoracic Society Guidelines; spirometry was measured pre-bronchodilator.

Objective(s)

Primary objective:
To evaluate the long-term safety and tolerability of TEZ/IVA in **Part A** in subjects with CF, homozygous or heterozygous for the *F508del-CFTR* mutation in the Treatment Cohort.

Secondary Objectives:
Part A: To evaluate the long-term efficacy of TEZ/IVA for subjects in the Treatment Cohort.

Part B: To evaluate the long-term safety, tolerability, and efficacy of TEZ/IVA

Part C: To evaluate the long-term safety and tolerability of TEZ/IVA

Observational Cohort (**Part A** only): To evaluate the post-treatment safety of TEZ in combination with IVA for subjects in the Observational Cohort.

Outcomes/endpoints

Primary endpoint:
Treatment Cohort: Safety and tolerability of long-term treatment of TEZ/IVA in **Part A** based on adverse events (AEs), ophthalmologic examinations (OE; subjects <18 years of age [age on the date of informed consent/assent in the parent study]), clinical laboratory values (serum chemistry, haematology, coagulation, lipids, vitamins, and urinalysis), standard 12-lead ECGs, vital signs, and pulse oximetry.

Secondary endpoints:

Part A Treatment Cohort:

- Efficacy: absolute change from baseline in percent predicted forced expiratory volume in 1 second (ppFEV1), relative change from baseline in ppFEV1, number of pulmonary exacerbations (PEx), absolute change from baseline in body mass index (BMI), absolute change from baseline in BMI z-score for subjects <20 years of age, absolute change from baseline in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score, absolute change from baseline in body weight, absolute change from baseline in body weight z-score for subjects <20 years of age, absolute change from baseline in height z-score for subjects <20 years of age, time-to-first PEx
- Pharmacokinetic (PK) parameters of TEZ, a TEZ metabolite (M1-TEZ), IVA, and an IVA metabolite (M1-IVA)

Part B Treatment Cohort:

- Safety: AEs, serum liver function tests (LFTs), and OEs (subjects <18 years of age [age on the date of informed consent/assent in the parent study])
- Efficacy: absolute change from baseline in ppFEV1, absolute change from baseline in BMI, absolute change from baseline in BMI z-score (for subjects <20 years of age), and number of PEx

Part C Treatment Cohort:

- Safety: AEs, serum LFTs, and OEs (subjects <18 years of age [age on the date of informed consent/assent in the parent study])

Other endpoints

Part A Treatment Cohort: quality of life (12-Item Short Form Survey [SF-12]) physical, mental, and utility component scores, rate of change in ppFEV1

Part B Treatment Cohort: absolute change in Total Brody/CF-CT scores and sub-scores from baseline using LDCT scans (only for subjects enrolling from Study VX15-661-112)

CHMP comment

The primary endpoint of long-term safety and tolerability of TEZ/IVA in Part A is considered appropriate for an open label extension (OLE) study, given the duration of 96 weeks. Efficacy is assessed in Part A and B. Efficacy endpoints are in line with commonly used efficacy endpoints in CF studies.

Sample size

Study 110 was a rollover study.

For **Part A**, approximately up to 1375 subjects were potentially eligible to be enrolled from the following parent studies: 40 subjects from Study 103, 490 subjects from Study 106, 300 subjects from Study 107, up to 300 subjects from Study 108, up to 200 subjects from Study 109, and 45 subjects from Study 111.

Up to approximately 500 subjects were potentially eligible to continue from Part A of Study 110 into Part B. An additional up to approximately 40 subjects from Study 112 and up to approximately 30 subjects from Study 114 were potentially eligible to enrol in **Part B**.

Up to 334 subjects were potentially eligible to continue from Part B of Study 110 into **Part C**.

CHMP comment

No formal sample size was set. Instead, sample size appears to be based on the numbers of the parent studies, which is acceptable for a roll-over study.

Randomisation and blinding (masking)

Randomisation was not required because all subjects received the same open-label active study drug in the Treatment Cohort.

Study 110 was an open-label study. However, subjects were not informed of their study-related spirometry results during the study regardless of whether the subject had prematurely discontinued treatment.

Study Variables Assessed

Pharmacokinetics

A single blood sample was collected within 60 minutes before dosing for the determination of the plasma concentrations of VX-661, M1-661, ivacaftor, and M1-ivacaftor on Day 1, Day 15, and at Weeks 8, 16, 24, 36, 48, 72, 84 and 96.

Samples were analyzed using a validated analytical method in compliance with Vertex or designee standard operating procedures (SOPs). A description of the assay and validation data were provided in separate reports (Reports M314 and P163).

CHMP comment

The bioanalytical reports, with reference to the validation report for PPD Method P1331, issued 25 June 2015, were provided.

Statistical Methods – Part A

Analysis sets

Part A data will be locked and analysed when this part is completed.

The following analysis sets were defined:

- **All Subjects Set (Part A)**: all subjects who have signed inform consent (enrolled) or have received at least 1 dose of study drug in Part A.
- **Full Analysis Set (FAS) (Part A)**: all enrolled subjects who have received at least 1 dose of study drug in Part A and have one of the following mutations: *F/F* or *F/RF*.
    - **106/110 Efficacy Set (ES)**: all the FAS subjects (F/F genotype) rolling over from Study 106.
    - **108/110 ES**: all the FAS subjects (F/RF genotype) rolling over from Study 108.
    - **106/110 PEx Analysis Set**: all subjects (F/F genotype) from Study 106 who received TEZ/IVA in Study 106 or Part A.
    - **108/110 PEx Analysis Set**: all subjects from Study 108 (F/RF genotype) who received TEZ/IVA in Study 108 or Part A.

– **Safety Set (Part A)**: all subjects who have received at least 1 dose of study drug in Part A irrespective of their genotype.

Efficacy analyses

No hypothesis testing was done for between-group comparisons.

Efficacy analyses were performed for the following periods in Part A:

- **110 Efficacy Analysis Period**: The time period from the first dose of study drug in Part A to the date of the last efficacy assessment in Part A

PEx Efficacy Analysis Period: Time period from the first dose of TEZ/IVA in the parent study (after the washout period, if applicable) or Part A to the date of last efficacy assessment in parent study or Part A

Efficacy analyses were only performed for subjects with F/F or F/RF genotype. Efficacy analyses were performed separately for each parent study as shown in Table 3.

Table 3 Summary of Efficacy Analyses - Part A

Parent Study	*CFTR* Genotype	Endpoints Analyzed	Study 110 Part A Baseline
103	F/F	Relative change in ppFEV$_1$; Absolute change in ppFEV$_1$, BMI, body weight, and CFQ-R respiratory domain score	All groups: Study 103 baseline
106	F/F	Relative change in ppFEV$_1$; Absolute change in ppFEV$_1$, BMI, BMI *z*-score,[a] height *z*-score,[a] body weight, body weight *z*-score,[a] and CFQ-R respiratory domain score; Number of PEx and time-to-first PEx	TEZ/IVA-TEZ/IVA group: Study 106 baseline PBO-TEZ/IVA group: Study 110 Part A baseline
108	F/RF	Relative change in ppFEV$_1$; Absolute change in ppFEV$_1$, BMI, BMI *z*-score,[a] height *z*-score,[a] body weight, body weight *z*-score,[a] and CFQ-R respiratory domain score; Number of PEx and time-to-first PEx	All groups: Study 108 baseline
111	F/F	Relative change in ppFEV$_1$; Absolute change in ppFEV$_1$, BMI, and body weight	All groups: Study 111 baseline

BMI: body mass index; CFQ-R: Cystic Fibrosis Questionnaire-Revised; F/F: homozygous for *F508del-CFTR*; F/RF: heterozygous for *F508del* and a *CFTR* mutation that results in residual function; IVA: ivacaftor; PBO: placebo; PEx: pulmonary exacerbation; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

[a] *Z*-scores were calculated for subjects <20 years of age at screening.

Mixed-effects Modelling of Repeated Measures (for 106/110 ES and 108/110 ES) Fixed effects (covariates) were: treatment, visit, treatment-by-visit interaction, parent study baseline. In 106/110 ES additionally: sex and age group at screening (<18, ≥18 years old), parent study baseline by-visit interaction. The model assumed an unstructured (UN) covariance structure to model the within-subject errors and used Kenward-Roger degrees of freedom and the restricted maximum likelihood (REML) method. Time points will be included up to the last timepoint that has approximately 70% of the number of subjects of the parent study. Data were assumed to be missing at random and missing data were not imputed, unless specified otherwise.

The number of subjects, least-squares (LS) means at scheduled visits within each treatment group, along with the corresponding SE and 95% CI were presented. The LS means (± 95% CI) for change from baseline at each visit were plotted by treatment group.

PEx Analysis

The number of PEx and PEx requiring intravenous (IV) antibiotics or hospitalisation were analysed for the 106/110 PEx Analysis Set and the 108/110 PEx Analysis Set using a negative binomial regression model with the logarithm of PEx analysis period duration as the offset. For the 106/110 PEx covariates were treatment, sex, age group at screening (<18, ≥18 years old), and parent study baseline ppFEV1 and for 108/110 ES: treatment (TEZ/IVA-TEZ/IVA, IVA-TEZ/IVA, and PBO-TEZ/IVA), residual function mutation (Class V non-canonical splice and Classes II to IV residual function), age group at screening (<18, ≥18 years old), and parent study baseline ppFEV1. PEx results were reported as the event rate, along with the 95% CI. Time-to-first PEx on TEZ/IVA during PEx Analysis Period was analysed and plotted by treatment group using the Kaplan-Meier approach.

Safety analyses

Results of safety assessments were summarized for the Safety Set using descriptive statistics; no formal hypothesis testing was performed. All safety analyses were based on the following Study 110 treatment-emergent (TE) periods and baseline measurements:

TE Period included the time from the first active dose of TEZ/IVA or IVA (in the parent study or Part A, but after the washout period, if applicable) to the Safety Follow-up Visit in Part A or 28 days after the last dose of study drug for subjects who did not have a Safety Follow-up Visit or who had their Safety Follow-up Visit more than 35 days after the last dose in Part A. For subjects who left Part A to participate in another qualified Vertex study before completing Part A and re-enrolled in Study 110, the TE Period excluded the time spent in the other study.

110 TE Period was defined as the time from the first dose of the study drug in Part A to the Safety Follow-up Visit in Part A or 28 days after the last dose of the study drug for subjects who did not have a Safety Follow-up Visit or who had their Safety Follow-up Visit more than 35 days after the last dose in Part A. For subjects who participated in another qualified Vertex study before completing Part A and re-enrolled in Study 110, the TE Period excluded the time spent in the other study.

Safety analysis baseline was defined as the last non-missing assessment prior to the first dose of active treatment (TEZ/IVA or IVA) from the parent study (after the washout period, where applicable) or Part A, whichever was earlier.

Summaries of treatment-emergent AEs (TEAEs) presented the number and percentages of subjects with AEs, as well as the number of events per 100 patient-years (number of events adjusted for the total duration of exposure).

Clinical laboratory results, ECGs, vital signs, and pulse oximetry data were summarized by the raw values and change from parent study baseline values at each visit. For subjects <18 years of age, abnormal OE results were listed.

Multiplicity control

No multiplicity adjustment were performed.

Interim analyses

Two interim analyses (IAs) were conducted:

1. IA1 (Study 110 Part A subjects only): The IA included the ongoing data as of the 06 March 2017 cut-off date from subjects who rolled over from the completed parent studies (Studies 103, 106, 107, and 108). Studies 109 and 111 were not unblinded at the time of the IA; therefore, subjects from these studies were not analysed in the IA. Safety analyses were performed by pooling subjects from all studies together, regardless of exposure duration to TEZ/IVA. Efficacy analyses were conducted only for subjects who rolled over from Study 106 (F/F population; homozygous for *F508del*) and Study 108 (F/RF population; F/RF: heterozygous for *F508del* and a *CFTR* mutation that results in residual function) and were done separately for these 2 populations. The results of this IA are reported in the Study 110 IA1 CSR (dated 02 June 2017). Details of the IA are described in a separate IA SAP (Version 2.0).
2. IA2: The second interim analysis (IA2) was performed to facilitate responses to regulatory questions based on a data cut-off that occurred on 14 November 2017. The scope of the IA2 included the following: (1) safety analyses for all the subjects enrolled in Study 110 who received ≥48 weeks of TEZ/IVA during the parent studies and/or Study 110 and (2) to update the efficacy analyses for all subjects enrolled in Study 110 from parent Studies 106 and 108. Analysis methods were documented in the IA2 SAP Version 1.0. In order to provide updated safety information beyond the planned safety analyses of IA2, an "IA2 Additional Safety SAP" was developed to document statistical analyses and data presentation for additional safety analyses based on the IA2 data cut-off.

CHMP comment

Statistical methods for Part A are acceptable.

As there was no hypothesis testing, type I error control is no issue (e.g., for interim analyses). This approach is acceptable for the aim of the study (estimation of long-term safety and efficacy).

Given the heterogeneity in parent studies (genotypes), the analyses by parent study are considered relevant.

For estimation of long-term efficacy effects, the model specifications including covariates (the mixed effects and negative binomial regression) are considered adequate. Including time points until the number of subjects of the parent study is lower than 70% guarantees some precision for the roll-over from largest parent studies (studies 106 and 108). In the context of drop-out/missing data, the interpretation of the mixed model repeated measures analysis for these studies is the effect as if the all subjects would have continued. This is considered relevant provided the reasons for drop-out/missing create no selection bias (to be discussed at the subject disposition).

According to the SAP, a subject in Part A could discontinue (e.g., at Day 50) Study 110 to enter another study of the Applicant and return to Study 110 (and study days of the subject would then commence at Day 51), if they finished the last study visit of other study and met the eligibility criteria of Study 110 again. This was allowed only once. Also, when TEZ/IVA became commercially available or not approved for their particular indication, subjects could be discontinued.

Patients with the F/MF (Study 107) and F/gating (Study 109) were not part of the FAS. This is considered acceptable, since both studies showed no clinical benefit of TEZ/IVA over IVA monotherapy and the combination is also not approved for patients with these genotypes. Considering the low

number of subjects who enrolled from Studies 103 and 111, the use of only descriptive summaries for these groups is also acceptable.

Statistical Methods – Part B

Analysis sets

The following analysis sets were defined:

- **All Subjects Set (Part B)**: all subjects who have signed informed consent (enrolled) or have received at least 1 dose of study drug in Part B of Study 110.
- **FAS (Part B)**: all enrolled subjects who have received at least 1 dose of study drug in Part B and have one of the following mutations: *F/F* or *F/RF*.
    - **F/F Mutation ES**: all subjects in the FAS who rolled over from studies 106, 111, 112 and 114 pooled together.
    - **F/RF Mutation ES**: all subjects in the FAS who rolled over from Study 108.
- **Safety Set (Part B)**: all subjects who received at least 1 dose of study drug in Study 110 Part B, regardless of subjects' parent study assignment or *CFTR* genotype.

Efficacy analyses

Efficacy Analyses were performed for the following period and baseline measurement:

- The **110 Part B Efficacy Analysis Period** began at the first dose of study drug in Part B and ended at the last efficacy assessment in Part B. For subjects who participated in another qualified Vertex study before completing Part B assessments and re-enrolled in Part B, the Efficacy Analysis Period excluded the time between the last dose before the discontinuation from Part B and the first dose after re-enrolment in Part B.

The **efficacy analysis baseline** for Part B was defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to the first dose of study drug in the parent studies for all subjects, except for subjects randomized to the placebo arm in Studies 106, 112, or 114.

- The efficacy analysis baseline for subjects randomized to the Study 106 placebo arm was defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to the first dose of study drug in Study 110 Part A.
- The efficacy analysis baseline for subjects randomized to either the Study 112 or 114 placebo arm was defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to the first dose of study drug in Study 110 Part B.

Efficacy analyses were performed by genotype, i.e., F/F or F/RF. Efficacy endpoints for Part B are presented using descriptive statistics for observed values and absolute changes from baseline.

Safety analyses

Results of safety assessments were summarized for the Safety Set using descriptive statistics; no formal hypothesis testing was performed. All safety analyses were based on the following Study 110 Part B TE Period and baseline measurement.

The **110 Part B TE Period** (or Safety Analysis Period) began at the first dose of study drug in Study 110 Part B and ended 28 days after the last dose of study drug in Part B, or at the date of Part B participation completion, whichever occurred first. For subjects who participated in another qualified

Vertex study before completing Part B and re-enrolled in Part B, the TE Period excluded the time spent in the other study.

The **safety analysis baseline** for Part B, unless otherwise specified, was defined as the last non-missing assessment prior to the first dose of active treatment (TEZ/IVA or IVA) from the parent study (after the washout period, where applicable) or Study 110 Parts A or B, whichever was earlier.

Summaries of TEAEs presented the total number of subjects and the percentage of subjects with AEs, as well as the event rate per 100 patient-years (number of events adjusted for the total duration of TE Period). Clinical laboratory results were summarized for each visit by raw values and change from parent study baseline values. For subjects <18 years of age, abnormal OE results were listed.

Multiplicity control

No multiplicity adjustment was performed.

Interim analyses

No interim analyses or data monitoring analyses were conducted.

CHMP comment

Statistical methods for Part B are acceptable. As the SAP elucidates, due to large number of drop-outs only descriptive summaries were provided instead of mixed model analyses.

Statistical Methods – Part C

Analysis sets

The following analysis sets were defined:

- **All Subjects Set (Part C)**: all subjects who have signed informed consent (enrolled) or have received at least 1 dose of study drug in Part C of Study 110.
- **Safety Set (Part C)**: all subjects who received at least 1 dose of study drug in Study 110 Part C.

Safety analyses

Results of safety assessments were summarized for the Safety Set using descriptive statistics; no formal hypothesis testing was performed. All safety analyses were based on the following Study 110 Part C Safety Analysis Period and baseline measurement.

The **110 Part C TE Period** (or Safety Analysis Period) began at the first dose of study drug in Part C and ended 28 days after the last dose of study drug in Part C, or at the date of Part C participation completion, whichever occurred first.

The **safety analysis baseline** for Part C, unless otherwise specified, was defined as the last non-missing assessment prior to the first dose of active treatment (TEZ/IVA or IVA) from the parent study (after the washout period, where applicable) or Study 110 Parts A or B, whichever was earlier.

Summaries of TEAEs presented the total number of subjects and the percentage of subjects with AEs, as well as the event rate per 100 patient-years (number of events adjusted for the total duration of study drug exposure). Clinical laboratory results were summarized for each visit by raw values and change from parent study baseline values. For subjects <18 years of age, abnormal OE results were listed.

Multiplicity control

No multiplicity adjustment was performed.

Interim analyses

No interim analyses or data monitoring analyses were conducted.

CHMP comment

Statistical methods for Part C are acceptable.

According to the SAP of Part C, patients could discontinue Part A or B for another study of the applicant and after finishing the study, re-enter in either Part A or B. Subjects leaving Part C were not allowed to re-enter in Part C. This re-entering in Part A or Part B did actually occur and could in principle introduce bias. However after comparing the data with and without these subjects, the observed impact is limited.

Results

Participant flow

For **Part A Treatment Cohort,** the number of subjects of from each of the parent studies is presented in Table 4.

Table 4 Number of Subjects from Each of the Parent Studies

Study ID	Number of patients (%)
Study 103	23 (2.2%)
Study 106	462 (44.3%)
Study 107	159 (15.3%)
Study 108	227 (21.8%)
Study 109	138 (13.2%)
Study 111	33 (3.2%)

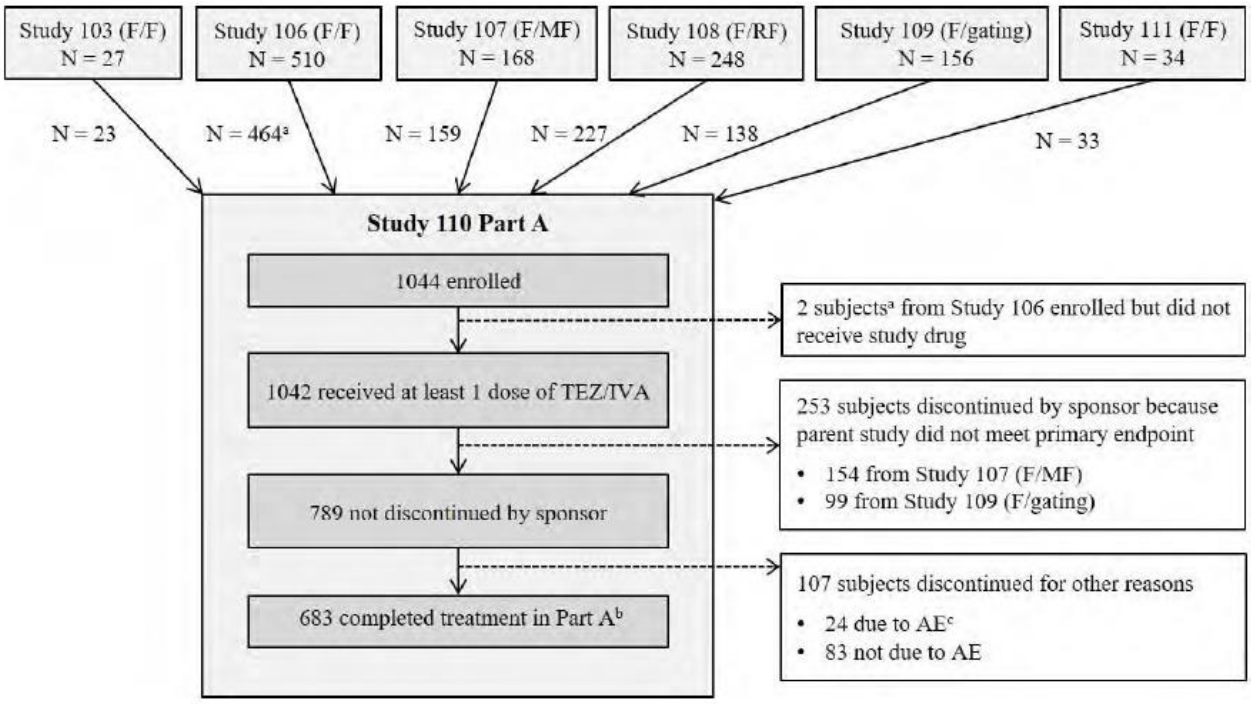
Of the 1042 subjects who received at least 1 dose of study drug in Part A (i.e., the Safety Set), 359 (34.5%) prematurely discontinued treatment. The majority of discontinuations (253 [24.3%] subjects) were due to study termination by sponsor because the parent study did not meet its primary endpoint (including Studies 107 and 109).

Of the 459 subjects in the 106/110 ES, 403 (87.8%) completed treatment and 55 (12.0%) subjects prematurely discontinued treatment, of which 13 (2.8%) subjects discontinued treatment due to an AE and 20 (4.4.%) because of subject refused further dosing not due to AE.

Of the 226 subjects in the 108/110 ES, 207 (91.6%) completed treatment and 19 (8.4%) subjects prematurely discontinued treatment, of which 6 (2.7%) subjects discontinued treatment due to an AE and 4 (1.8 %) because of subject refused further dosing not due to AE.

The participant flow is shown in Figure 2.

Figure 2 Study 110 Part A Subjects (Treatment Cohort)



Source: Table 14.1.1.1

AE: adverse event; F/F: homozygous for *F508del-CFTR*; F/gating: heterozygous for *F508del* and a *CFTR* mutation that results in a gating defect; F/MF: heterozygous for F508del and a CFTR mutation that results in minimal CFTR function (non-TEZ/IVA-responsive mutation); F/RF: heterozygous for *F508del* and a *CFTR* mutation that results in residual function; IVA: ivacaftor; MF: minimal function; N: total sample size; RF: residual function mutation; TE: treatment-emergent; TEZ: tezacaftor

Notes: Values (N) inside the parent study box indicate the All Subjects Set for the parent study. Values next to arrows indicate the number of subjects from each parent study who rolled over into Study 110.

[a] Two subjects enrolled in Study 110 but did not receive study drug (Listing 16.2.1).

[b] One subject who completed 96 weeks of treatment in Part A was not included in Table 14.1.1.1 under "completed treatment regimen" because no Study Completion Form was filled out for this subject.

[c] Of the 24 subjects who discontinued due to an AE, 2 subjects discontinued due to AEs that were not TE.

The subject disposition for the All Subjects Set is summarised in **Table 5**.

Table 5 Subject Disposition Part A (Treatment Cohort, All Subjects Set)

Disposition/Reason	Total n (%)
All Subjects Set	1044
Safety Set	1042
Full Analysis Set	741
Completed treatment regimen[a]	682 (65.5)[b]
Prematurely discontinued treatment	359 (34.5)
AE	24 (2.3)[c]
Subject refused further dosing (not due to AE)	28 (2.7)
Lost to follow-up	9 (0.9)
Death	0
Did not meet eligibility criteria	1 (0.1)[d]
Noncompliance with study drug	2 (0.2)
Other noncompliance	1 (0.1)
Physician decision	8 (0.8)
Requires prohibited medication	5 (0.5)
Pregnancy (self or partner)	6 (0.6)
Study terminated by sponsor	253 (24.3)
Commercial drug is available for subject	5 (0.5)
Other	17 (1.6)
Completed study[a]	951 (91.3)
Prematurely discontinued study[a]	91 (8.7)
AE	17 (1.6)
Withdrawal of consent (not due to an AE)	25 (2.4)
Lost to follow-up	12 (1.2)
Death (not treatment emergent)	1 (0.1)[e]
Other noncompliance	6 (0.6)
Physician decision	6 (0.6)
Study termination by sponsor	1 (0.1)
Commercial drug is available for subject	5 (0.5)
Other	18 (1.7)

Source: Table 14.1.1.1

AE: adverse event; IVA: ivacaftor; n: size of subsample; TE: treatment-emergent; TEZ: tezacaftor

Notes: The All Subjects Set was defined as all subjects who signed the inform consent (enrolled) or received at least 1 dose of study drug in Study 110 Part A. The Safety Set was defined as all subjects within the All Subjects Set who received at least 1 dose of study drug in Part A. Percentages were calculated relative to the number of subjects in the Safety Set. If a subject discontinued TEZ/IVA and IVA tablets for different reasons, the subject was counted for both reasons but counted only once in the total number of subjects who prematurely discontinued treatment.

[a] A subject could complete the study without completing treatment if they did not complete 96 weeks of TEZ/IVA treatment but completed the Safety Follow-up Visit. A subject could complete treatment without completing the study if they completed 96 weeks of treatment but did not complete the Safety Follow-up Visit.

[b] One subject who completed 96 weeks of treatment in Part A was not included under "completed treatment regimen" because no Study Completion Form was filled out for this subject.

[c] Of the 24 subjects who discontinued due to an AE, 2 subjects discontinued due to AEs that were not TE.

[d] This subject's discontinuation was incorrectly recorded. The subject did meet eligibility criteria for Part A but had a genotype that was not eligible for the parent study. Because this subject completed Study 108, the subject was eligible for Study 110 Part A.

[e] There were no TE deaths; however, 2 deaths occurred after the TE Period. One of these was captured in the database; the other occurred after the study site was locked in the database (Section 12.1.3.1.1).

The subject dispositions for Part A 106/110 ES and Part A 108/110 ES are summarised in Table 6 and Table 7, respectively.

Table 6 Subject Disposition for Part A (106/110 ES)

Disposition/Reason	Total N = 459 n (%)
Completed treatment regimen	403 (87.8)
Prematurely discontinued treatment in Part A[a]	55 (12.0)
AE	13 (2.8)
Subject refused further dosing (not due to an AE)	20 (4.4)
Lost to follow-up	3 (0.7)
Death	0
Did not meet eligibility criteria	0
Noncompliance with study drug	1 (0.2)
Other noncompliance	0
Physician decision	7 (1.5)
Requires prohibited medication	2 (0.4)
Pregnancy (self or partner)	3 (0.7)
Study termination by sponsor	0
Commercial drug is available for subject	0
Other	6 (1.3)

Source: Table 14.1.1.2

AE: adverse event; ES: Efficacy Set; F/F: homozygous for *F508del-CFTR*; FAS: full analysis set; IVA: ivacaftor; n: size of subsample; N: total sample size; TEZ: tezacaftor

Notes: Part A 106/110 ES was defined as subjects in the FAS who rolled over from Study 106. Two subjects who enrolled in Part A from Study 106 were not included in the 106/110 ES because they were discovered to not have the F/F genotype after enrolling in Part A. These 2 subjects were subsequently discontinued from Part A.

[a] If a subject discontinued TEZ/IVA and IVA tablets for different reasons, then the subject was counted for both reasons but counted only once in the total number of subjects who prematurely discontinued treatment.

Table 7 Subject Disposition for Part A (108/110 ES)

Disposition/Reason	Total N = 226 n (%)
Completed treatment regimen	207 (91.6)
Prematurely discontinued treatment in Part A[a]	19 (8.4)
AE	6 (2.7)
Subject refused further dosing (not due to an AE)	4 (1.8)
Lost to follow-up	1 (0.4)
Death	0
Did not meet eligibility criteria	0
Noncompliance with study drug	1 (0.4)
Other noncompliance	1 (0.4)
Physician decision	0
Requires prohibited medication	1 (0.4)
Pregnancy (self or partner)	2 (0.9)
Study termination by sponsor	0
Commercial drug is available for subject	3 (1.3)
Other	0

Source: Table 14.1.1.3

AE: adverse event; ES: Efficacy Set; F/RF: heterozygous for *F508del* and a *CFTR* mutation that results in residual function; FAS: full analysis set; IVA: ivacaftor; n: size of subsample; N: total sample size; TEZ: tezacaftor

Notes: Part A 108/110 ES was defined as subjects in the FAS who rolled over from Study 108. One subject who enrolled in Study 110 Part A from Study 108 was not included in the 108/110 ES because the subject was discovered to not have the F/RF genotype after enrolling in Part A. This subject was subsequently discontinued from Part A.

[a] If a subject discontinued TEZ/IVA and IVA tablets for different reasons, then the subject was counted for both reasons but counted only once in the total number of subjects who prematurely discontinued treatment.

Observational Cohort.

No subject enrolled in the Observational cohort in For **Part A**

Rapporteur's comment

For convenient and concise arrangement of the information for the EPAR, the applicant was requested to provide a table as is provided for part B, wherein the disposition of the subjects from Study 106 and Study 108 are displayed:

Disposition reason	F/F Mutation n (%)	F/RF Mutation n (%)	Total n (%)

Additional information revealed that there are only small differences in the reason for discontinuation between subjects with F/F mutation and subjects with F/RF mutations. The main reason in discontinuation was adverse event (2.8%) and 'refused further dosing not due to AE' (3.5%). 'Refused further dosing not due to AE' was higher in subjects with F/F mutation (4.4%). (see question 3 of the first RSI.)

Part B

The number of subjects in **Part B** of from each of the parent studies is presented in **Table 8**.

Table 8 Number of Subjects from Each of the Parent Studies

Study ID	Number of patients (%) with F/F mutation	Number of patients (%) with F/RF mutation	Total number of patients (%)
Study 106	260	-	260
Study 108	-	106	106
Study 109	-	-	10
Study 111	1		1
Study 112	39		39
Study 114	47		47

The participant flow is shown in

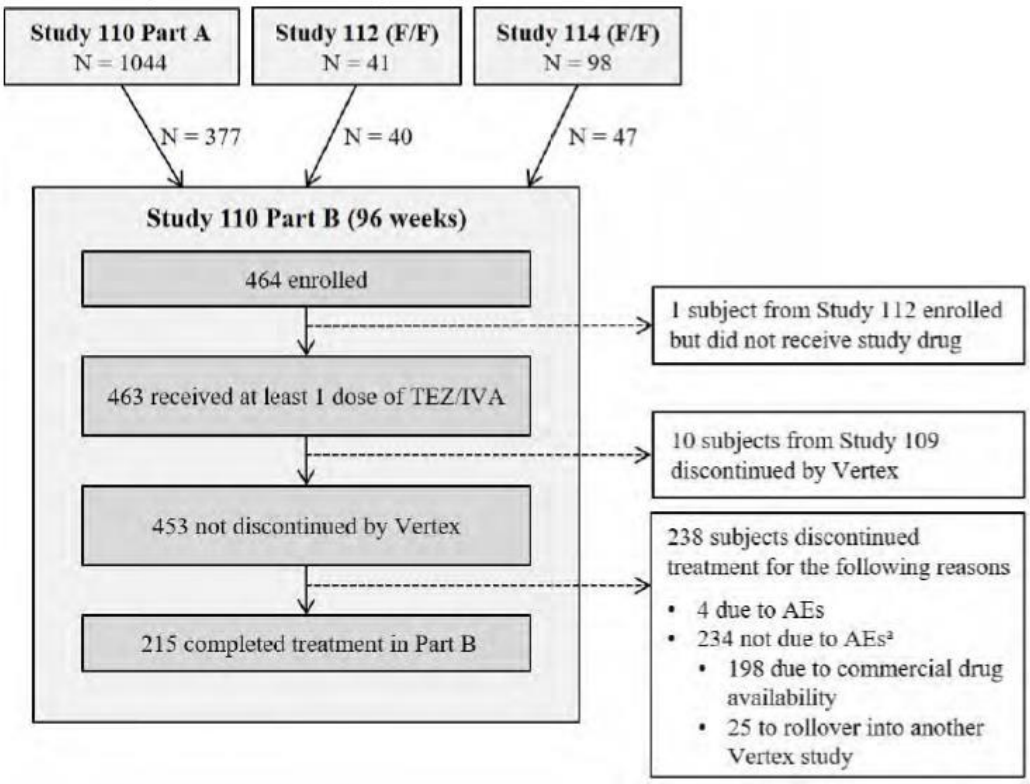
.

The subject disposition for the All Subjects Set is summarised in Table 9.

In total, 464 subjects were enrolled in Part B (All Subjects Set) and 215 subjects completed treatment. Most subjects who discontinued study drug treatment were discontinued due to commercial drug availability (198 subjects). Of the 26 subjects who discontinued Part B due to other reasons, 25 subjects rolled over into another Vertex study. Ten subjects from Study 109 were discontinued by Vertex because the parent study did not meet the primary endpoint. Four subjects discontinued due to AEs.

Of the 463 subjects in the Safety Set, 248 (53.6%) subjects discontinued treatment.

Figure 3 Study 110 Part B Subjects



Source: Table 14.1.1b and Listing 16.2.1b

AE: adverse event; F/F: homozygous for *F508del-CFTR*; IVA: ivacaftor; N: total sample size; TEZ: tezacaftor

Notes: Values (N) inside parent study box indicate the All Subjects Set for the parent study. Values next to arrows indicate the number of subjects from each parent study or Study 110 Part A who rolled over into Part B.

[a] Of the 234 subjects who discontinued treatment for reasons other than AEs, the reasons for discontinuation were as follows: 198 subjects due to commercial drug availability, 26 subjects due to other, 8 subjects due to subject refusing further dosing (not due to AE), 1 subject due to physician decision, and 1 subject due to partner pregnancy (Table 10-10).

Table 9 Subject Disposition Part B (All Subjects Set)

Disposition Reason	F/F Mutation n (%)	F/RF Mutation n (%)	Total[a] n (%)
All Subjects Set	348	106	464
Safety Set	347	106	463
Full Analysis Set	347	106	453
F/F Mutation Efficacy Set[b]	347	--	347
F/RF Mutation Efficacy Set[c]	--	106	106
Completed treatment	143 (41.2)	72 (67.9)	215 (46.4)
Discontinued treatment	204 (58.8)	34 (32.1)	248 (53.6)
Reason for discontinuation of treatment[d]			
Adverse event	4 (1.2)	0	4 (0.9)
Subject refused further dosing (not due to AE)	7 (2.0)	1 (0.9)	8 (1.7)
Lost to follow-up	0	0	0
Commercial drug is available for subject	177 (51.0)	21 (19.8)	198 (42.8)
Death	0	0	0
Did not meet eligibility criteria	0	0	0
Non-compliance with study drug	0	0	0
Other non-compliance	0	0	0
Physician decision	1 (0.3)	0	1 (0.2)
Requires prohibited medication	0	0	0
Pregnancy (self or partner)	1 (0.3)	0	1 (0.2)
Study terminated by sponsor	0	0	10 (2.2)
Other	14 (4.0)	12 (11.3)	26 (5.6)
Completed Part B of the Study	148 (42.7)	72 (67.9)	228 (49.2)
Discontinued from Part B of the Study	199 (57.3)	34 (32.1)	235 (50.8)
Reason for discontinuation			
Rolled over into another study	13 (3.7)	12 (11.3)	25 (5.4)
Adverse event	4 (1.2)	0	4 (0.9)
Withdrawal of consent (not due to AE)	5 (1.4)	1 (0.9)	6 (1.3)
Lost to follow-up	0	0	0
Commercial drug is available for subject	175 (50.4)	21 (19.8)	196 (42.3)
Death	0	0	0
Other non-compliance	0	0	0
Physician decision	1 (0.3)	0	1 (0.2)
Sponsor decision	0	0	2 (0.4)
Study terminated by sponsor	0	0	0
Other	1 (0.3)	0	1 (0.2)

Source: Table 14.1.1b

AE: adverse event; ES: Efficacy Set; F/F: homozygous for *F508del-CFTR*; F/RF: heterozygous for *F508del* and a *CFTR* mutation that results in residual function; n: size of subsample

Note: All Subjects Set was defined as all subjects who enrolled or received at least 1 dose of study drug in Study 110 Part B. The Safety Set was defined as all subjects who received at least 1 dose of study drug in Part B. The Full Analysis Set was defined as all subjects who received at least 1 dose of study drug in Part B and met the eligibility mutation criteria of F/F or F/RF. Percentages use the number of subjects in the Safety Set as denominator.

[a] Subjects from Study 109 counted in the total column only, as they were not F/F or F/RF mutation group.

[b] F/F Mutation ES includes subjects in the Full Analysis Set who rolled over to Study 110 Part B from Study 106, 111, 112, and 114.

[c] F/RF Mutation ES includes subjects in the Full Analysis Set who rolled over to Study 110 Part B from Study 108.

[d] If a subject discontinued treatment for multiple reasons, the subject is counted in each category but counted only once in the total number of subjects who discontinued treatment.

CHMP comment

A total of 464 subjects enrolled in part B;

Most subjects (n=377) were obtained from Part A, which regarded 36% of the original population of Part A; 40 subjects came from Study 112 (F/F genotype) and 47 subjects from Study 114 (F/F genotype). As a result, approximately 19% of the subjects was not previously included in the Part A of the study.

Part C

The number of subjects of from each of the parent studies is presented in Table 10.

Table 10 Number of Subjects from Each of the Parent Studies

Study ID	Number of patients (%) with F/F mutation	Number of patients (%) with F/RF mutation	Total number of patients (%)
Study 106	126	-	126
Study 108	-	69	69
Study 114	9		9

Of the All Subjects SET in Part B (N=464), 204 subjects were enrolled in Part C (All Subjects Set) and 2 subjects completed treatment. Most subjects who discontinued study drug treatment were discontinued due to commercial drug availability (175 subjects). Of the 13 subjects who discontinued study drug treatment in Part C due to other reasons, 2 subjects rolled over to other commercial drug and 11 subjects rolled over into another Vertex study. One subject discontinued due to AEs.

Of the 204 subjects in the Safety Set, 202 (99.0%) subjects discontinued treatment.

The subject disposition for the All Subjects Set is summarised in Table 11.

Table 11 Subject Disposition Part C (All Subjects Set)

Disposition/ Reason	F/F Mutation n (%)	F/RF Mutation n (%)	Total n (%)
All Subjects Set	135	69	204
Safety Set	135	69	204
Completed treatment	0	2 (2.9)	2 (1.0)
Discontinued treatment	135 (100.0)	67 (97.1)	202 (99.0)
Reason for discontinuation of treatment[a]			
Adverse event	1 (0.7)	0	1 (0.5)
Subject refused further dosing (not due to AE)	5 (3.7)	0	5 (2.5)
Lost to follow-up	0	0	0
Commercial drug is available for subject	116 (85.9)	59 (85.5)	175 (85.8)
Death	0	0	0
Did not meet eligibility criteria	0	0	0
Non-compliance with study drug	0	0	0
Other non-compliance	0	1 (1.4)	1 (0.5)
Physician decision	3 (2.2)	3 (4.3)	6 (2.9)
Requires prohibited medication	0	0	0
Pregnancy (self or partner)	0	1 (1.4)	1 (0.5)
Study terminated by sponsor	0	0	0
Other	10 (7.4)	3 (4.3)	13 (6.4)
Completed Part C of the study	4 (3.0)	3 (4.3)	7 (3.4)
Discontinued from Part C of the study	131 (97.0)	66 (95.7)	197 (96.6)
Reason for discontinuation			
Rolled over into another study	8 (5.9)	3 (4.3)	11 (5.4)
Adverse event	1 (0.7)	0	1 (0.5)
Withdrawal of consent (not due to AE)	4 (3.0)	0	4 (2.0)
Lost to follow-up	0	0	0
Commercial drug is available for subject	115 (85.2)	59 (85.5)	174 (85.3)
Death	0	0	0
Other non-compliance	1 (0.7)	1 (1.4)	2 (1.0)
Physician decision	2 (1.5)	3 (4.3)	5 (2.5)
Sponsor decision	0	0	0
Study terminated by sponsor	0	0	0
Other	0	0	0

Source: Table 14.1.1c

AE: adverse event; F/F: homozygous for *F508del-CFTR* mutation; F/RF: heterozygous for *F508del* and a *CFTR* mutation that results in residual function; n: size of subsample

Note: All Subjects Set was defined as all subjects who enrolled or received at least 1 dose of study drug in Part C. The Safety Set was defined as all subjects who received at least 1 dose of study drug in Part C. Percentages used the number of subjects in the Safety Set as the denominator.

[a] If a subject discontinued treatment for multiple reasons, the subject is counted in each category but counted only once in the total number of subjects who discontinued treatment.

CHMP comment

The number of treatment discontinuations was rather high (34.5% in Part A, 53.6% in Part B and 99% in Part C). However, this was mainly due to the study being terminated by the sponsor (Part A, Studies 107 and 109) and a commercial drug being available (Part B and C). Terminations due to AEs were low with a maximum of 2.3% in Part A. In Part A 106/110 ES, 12% discontinued treatment for possible informative reasons and in Part A 108/110 ES it was 7.1% (=8.4% -1.3%, Table 7).

Therefore, the impact of selection bias seems to be limited in these sets.

Recruitment

The study was conducted in North America, Europe, Israel, and Australia at 170 study sites during Part A, 87 sites during Part B, and 54 sites during Part C.

Study initiation: 31 August 2015 (date first eligible subject signed the informed consent form)

Study completion: 05 December 2022 (date last subject completed the last visit)

Conduct of study

The clinical study protocol was amended 4 times globally and in select regions. Major changes in study conduct are presented in **Table 12**.

Table 12 Summary of Study VX14-661-110 Protocol Amendments

Protocol Version	Date	Summary of Major Changes
Version 1.0	19 May 2015	Original version
Version 2.0	27 May 2016	Version for all countries except Sweden, the UK, and Germany. The protocol was amended to allow subjects to screen for other qualified Vertex studies of investigational CFTR modulators while participating in the Treatment Cohort of Study 110 and to provide the opportunity to re-enroll in the Treatment Cohort of Study 110 for eligible subjects who discontinued Study 110 to participate in another qualified Vertex study. In addition, the list of parent studies was revised to allow eligible subjects to enroll in the Treatment Cohort of Study 110 from other Vertex studies investigating TEZ in combination with IVA.
Version 3.0	25 May 2017	Protocol Version 2.0 was revised to add Part B to enroll subjects from eligible Vertex studies of TEZ in combination with IVA. A Data Monitoring Committee was added to Part A. LDCT scans were added as an additional endpoint for subjects enrolling from Study 112. Study restrictions were revised based on Phase 1 data. The statistical analysis plan for Part A was revised and the analysis plan for Part B was added.
Version 4.0	25 April 2019	Current version for all countries except US, Israel, Spain, Ireland, Sweden, the UK, and Germany. Protocol Version 3.0 was amended to revise the study design to add Part C.
Version 5.0	16 February 2021	Current version for all countries except US, Israel, Spain, Ireland, Sweden, the UK, and Germany. Protocol Version 4.0 was amended to extend the treatment duration of Part C to up to approximately 192 weeks.

IVA: ivacaftor; LDCT: low-dose computed tomography; TEZ: tezacaftor

Vertex implemented safety measures to provide subjects the opportunity to continue participation in this study while ensuring their safety by minimizing the risk to coronavirus disease (COVID-19) exposure through travel. Implemented measures included, among others, shipment of study drug from site to subject's home, telephone/video call for safety assessments, in home assessments, and use of local laboratories.

An important protocol deviation (IPD) was defined as a deviation that had the potential to affect the interpretation of study results (i.e., completeness, accuracy, and/or reliability of the study data) and/or to significantly affect a subject's rights, safety, or well-being.

- There were 78 IPDs (17 of which were received post-database lock) in **Part A**. Most IPDs were due to prohibited concomitant medication (27 IPDs) (mainly antifungals), study procedures and criteria (18 IPDs), or <80% study drug compliance (10 IPDs).

- There were 32 IPDs in **Part B**. Most important IPDs involved study procedures and criteria (18 IPDs) or were due to <80% drug compliance (6 IPDs).
- There were 8 IPDs in **Part C**: 3 IPDs due to study drug compliance and 5 related to study procedures and criteria.

CHMP comment

Protocol was amended mainly to include Part B (Version 3.0, 25 May 2017) and Part C (Version 4.0, 25 April 2019) in the study. Country-specific major amendments also mainly involved the inclusion of the changes from Versions 2.0 to 5.0. These changes, as well as those made due to the COVID-19 pandemic, are considered acceptable, as they are not expected to change the results of the different study parts, except that participants could participate in an Applicant's other study and return to study 110 per protocol Version 2.0. The interim period in the other study might have affected the subjects' health status. However, an analysis with and without these patients shows limited impact (response to OC 18).

In general, drug compliance was good, with only 1.0%, 1.3% and 0.5% of subjects having <80% drug compliance in the respective parts. These results are unlikely to affect study results.

Baseline data

Part A Treatment Cohort

The majority of subjects were White (98.9%) and not of Hispanic or Latino ethnicity (96.5%). A total of 237 (51.6%) subjects were male. The overall median age was 25.0 years (range: 12 to 64 years), with 109 (23.7%) subjects in the <18 years of age subgroup.

The following tables show subject demographics and baseline disease characteristics for the **Part A** Treatment Cohort (Table 13, Table 14).

Table 13 Subject Demographics for Part A

	F/F Mutation N = 459	F/RF Mutation N = 226	Total N = 685
Sex, n (%)			
Male	237 (51.6)	105 (46.5)	342 (49.9)
Female	222 (48.4)	121 (53.5)	343 (50.1)
Childbearing potential[1], n (%)			
Yes	191 (86.0)	97 (80.2)	288 (84.0)
No	31 (14.0)	24 (19.8)	55 (16.0)
Reason not of childbearing potential[2], n (%)			
Surgical Procedure	6 (19.4)	8 (33.3)	14 (25.5)
Postmenopausal	3 (9.7)	12 (50.0)	15 (27.3)
Premenarchal	21 (67.7)	4 (16.7)	25 (45.5)
Other	1 (3.2)	0	1 (1.8)
Age at screening[3] (years)			
n	459	226	685
Mean (SD)	26.1 (10.4)	35.1 (14.2)	29.0 (12.5)
Median	25.0	35.0	27.0
Min, max	12, 64	12, 72	12, 72
Age group at screening (years), n (%)			
<18	109 (23.7)	32 (14.2)	141 (20.6)
≥18	350 (76.3)	194 (85.8)	544 (79.4)
Ethnicity, n (%)			
Hispanic or Latino	8 (1.7)	7 (3.1)	15 (2.2)
Not Hispanic or Latino	443 (96.5)	218 (96.5)	661 (96.5)
Not collected per local regulations	8 (1.7)	1 (0.4)	9 (1.3)
Race, n (%)			
White	454 (98.9)	221 (97.8)	675 (98.5)
Black or African American	1 (0.2)	2 (0.9)	3 (0.4)
Asian	2 (0.4)	0	2 (0.3)
American Indian or Alaska Native	0	1 (0.4)	1 (0.1)
Native Hawaiian or other Pacific Islander	0	0	0
Not collected per local regulations	0	1 (0.4)	1 (0.1)
Other	2 (0.4)	1 (0.4)	3 (0.4)
Geographic region, n (%)			
North America	112 (24.4)	109 (48.2)	221 (32.3)
Europe	347 (75.6)	117 (51.8)	464 (67.7)

- 106/108-110A Analysis Set: all subjects, who rolled over from either parent study 106 or 108, and have received at least 1 dose of study drug in Study 110 Part A and meet the mutation eligibility criteria of F508del/F508del (F/F) or F508del/Residual function (F/RF).
- F/F Mutation Set consists of all subjects in 106/108-110A Analysis Set that were rolled over from study 106.
- F/RF Mutation Set consists of all subjects in 106/108-110A Analysis Set that were rolled over from study 108.
- [1]: Female n is the denominator.
- [2]: Female n with no childbearing potential is the denominator.
- [3]: Screening is the screening to the parent study.
- All demographic data, except sex, childbearing potential, reasons for not childbearing potential and regions are based on the data collected in the parent study.
- Total column is the sum of F/F Mutation and F/RF Mutation Efficacy Sets.
- Australia is included with Europe region.

Table 14 Baseline Disease Characteristics for Part A

	F/F Mutation N = 459	F/RF Mutation N = 226	Total N = 685
Weight (kg)			
n	459	226	685
Mean (SD)	58.4 (12.1)	69.6 (17.2)	62.1 (14.9)
Median	57.0	67.8	60.0
Min, max	29.0, 107.0	40.0, 156.9	29.0, 156.9
Weight z-score (subjects <20 years old at screening)			
n	145	39	184
Mean (SD)	-0.59 (0.95)	-0.01 (1.28)	-0.47 (1.05)
Median	-0.56	0.31	-0.41
Min, max	-3.32, 1.85	-2.63, 2.18	-3.32, 2.18
Height (cm)			
n	459	226	685
Mean (SD)	166.0 (10.0)	169.0 (9.5)	167.0 (10.0)
Median	166.0	169.0	167.0
Min, max	137.0, 193.0	146.0, 195.0	137.0, 195.0
Height z-score (subjects <20 years old at screening)			
n	145	39	184
Mean (SD)	-0.42 (0.95)	0.16 (0.86)	-0.30 (0.96)
Median	-0.46	0.12	-0.35
Min, max	-3.28, 1.63	-1.73, 2.11	-3.28, 2.11
BMI (kg/m^2)			
n	459	226	685
Mean (SD)	21.00 (2.94)	24.21 (5.00)	22.06 (4.04)
Median	20.72	23.49	21.45
Min, max	13.67, 32.24	15.19, 49.65	13.67, 49.65
BMI z-score (subjects <20 years old at screening)			
n	145	39	184
Mean (SD)	-0.50 (0.89)	-0.19 (1.39)	-0.44 (1.02)
Median	-0.52	0.05	-0.39
Min, max	-3.45, 1.87	-3.41, 2.23	-3.45, 2.23
$ppFEV_1$ (%)			
n	458	226	684
Mean (SD)	60.0 (15.1)	62.2 (14.5)	60.7 (14.9)
Median	59.3	61.4	60.4
Min, max	27.8, 96.2	34.6, 93.5	27.8, 96.2
$ppFEV_1$ (%)			
<40	42 (9.2)	20 (8.8)	62 (9.1)
≥40 to <70	283 (61.7)	132 (58.4)	415 (60.6)
≥70 to ≤90	125 (27.2)	70 (31.0)	195 (28.5)
>90	8 (1.7)	4 (1.8)	12 (1.8)
Missing	1 (0.2)	0	1 (0.1)
FEV_1 (L)			
n	458	226	684
Mean (SD)	2.12 (0.67)	2.21 (0.74)	2.15 (0.69)
Median	2.06	2.05	2.06
Min, max	0.76, 4.17	0.88, 4.72	0.76, 4.72

- 106/108-110A Analysis Set: all subjects, who rolled over from either parent study 106 or 108, and have received at least 1 dose of study drug in Study 110 Part A and meet the mutation eligibility criteria of F508del/F508del (F/F) or F508del/Residual function (F/RF).
- F/F Mutation Set consists of all subjects in 106/108-110A Analysis Set that were rolled over from study 106.
- F/RF Mutation Set consists of all subjects in 106/108-110A Analysis Set that were rolled over from study 108.
- Baseline is defined as baseline of the parent study.
- BMI: Body Mass Index = Weight/(Height*Height) (kg/m^2).
- Z-scores are calculated using US National Center for Health Statistics growth charts.
- Total column is the sum of F/F Mutation and F/RF Mutation Efficacy Sets.
- $ppFEV_1$ is derived using Hankinson and Wang standards.

CHMP comment

For convenient and concise arrangement of the information in the EPAR, the applicant was requested to provide a table for the demographics and for the baseline disease characteristics, respectively, for the subjects from Study 106 and Study 108 in one table as follows:

	F/F Mutation n (%)	F/RF Mutation n (%)	Total n (%)

The mean age in subjects with F/RF mutation was clearly higher than in subjects with F/F mutation. This difference may be explained with the difference in severity of the diseases between the 2 groups. The difference in nutritional parameters at baseline can be also explained with the difference in severity.

To be noted baseline is defined as baseline of the parent study. Therefore, baseline of Part B and Part C are quite similar to baseline of Part A with only small differences that can be contributed to the difference in numbers of subjects in the parts.

Part B:

Most subjects were White (F/F ES: 95.4%; F/RF ES: 99.1%) and not of Hispanic or Latino ethnicity. A total of 52.7% of F/F ES subjects were male and 48.1% of F/RF ES subjects were male. The median age among F/F ES subjects was 27.0 years (range: 12 to 64 years) and the median age among F/RF ES subjects was 35.5 years (range: 12 to 70 years).

Table 15 and **Table 16** show subject demographics and baseline disease characteristics respectively for **Part B**.

Table 15 Subject Demographics Part B (Full Analysis Set)

	F/F Mutation ES N = 347	F/RF Mutation ES N = 106	Total N = 453
Sex, n (%)			
Male	183 (52.7)	51 (48.1)	234 (51.7)
Female	164 (47.3)	55 (51.9)	219 (48.3)
Childbearing potential[a], n (%)			
Yes	155 (94.5)	45 (81.8)	200 (91.3)
No	9 (5.5)	10 (18.2)	19 (8.7)
Reason not of childbearing potential[b], n (%)			
Surgical Procedure	4 (44.4)	1 (10.0)	5 (26.3)
Postmenopausal	2 (22.2)	9 (90.0)	11 (57.9)
Premenarchal	2 (22.2)	0	2 (10.5)
Other	1 (11.1)	0	1 (5.3)
Age at screening[c] (years)			
n	347	106	453
Mean (SD)	27.7 (10.7)	35.1 (13.5)	29.4 (11.8)
Median	27.0	35.5	28.0
Min, max	12, 64	12, 70	12, 70
Age group at screening (years), n (%)			
<18	69 (19.9)	15 (14.2)	84 (18.5)
≥18	278 (80.1)	91 (85.8)	369 (81.5)
Ethnicity, n (%)			
Hispanic or Latino	3 (0.9)	3 (2.8)	6 (1.3)
Not Hispanic or Latino	324 (93.4)	102 (96.2)	426 (94.0)
Not collected per local regulations	20 (5.8)	1 (0.9)	21 (4.6)
Race, n (%)			
White	331 (95.4)	105 (99.1)	436 (96.2)
Black or African American	1 (0.3)	0	1 (0.2)
Asian	2 (0.6)	0	2 (0.4)
American Indian or Alaska Native	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Not collected per local regulations	12 (3.5)	1 (0.9)	13 (2.9)
Other	1 (0.3)	0	1 (0.2)
Geographic region, n (%)			
North America	18 (5.2)	8 (7.5)	26 (5.7)
Europe[d]	329 (94.8)	98 (92.5)	427 (94.3)

Source: Table 14.1.2b

ES: Efficacy Set; F/F: homozygous for *F508del-CFTR*; F/RF: heterozygous for *F508del* and a *CFTR* mutation that results in residual function; max: maximum value; min: minimum value; N: total sample size; n: size of subsample

Note: All demographic data, except sex, childbearing potential, reasons for not childbearing potential, and regions, are based on the data collected in the parent study. Total column is the sum of F/F Mutation ES and F/RF Mutation ES.

[a] Female n is the denominator.

[b] Female n with no childbearing potential is the denominator.

[c] Screening is the screening to the parent study.

[d] Australia is included with Europe region.

Table 16 Baseline Disease Characteristics for Part B (Full Analysis Set)

	F/F Mutation ES N = 347	F/RF Mutation ES N = 106	Total N = 453
Weight (kg)			
n	347	106	453
Mean (SD)	58.9 (11.9)	67.2 (15.4)	60.8 (13.2)
Median	58.0	66.0	59.0
Min, max	29.0, 95.0	40.0, 105.0	29.0, 105.0
Weight z-score (subjects <20 years old at screening)			
n	86	17	103
Mean (SD)	-0.54 (0.94)	-0.01 (1.38)	-0.45 (1.03)
Median	-0.40	0.77	-0.33
Min, max	-3.32, 2.19	-2.25, 2.18	-3.32, 2.19
Height (cm)			
n	347	106	453
Mean (SD)	167.1 (9.9)	169.4 (9.9)	167.6 (9.9)
Median	167.0	169.5	168.0
Min, max	135.0, 191.0	150.0, 195.0	135.0, 195.0
Height z-score (subjects <20 years old at screening)			
n	86	17	103
Mean (SD)	-0.31 (1.03)	0.29 (0.91)	-0.21 (1.03)
Median	-0.31	0.00	-0.20
Min, max	-2.80, 2.45	-1.04, 2.11	-2.80, 2.45
BMI[a] (kg/m^2)			
n	347	106	453
Mean (SD)	20.90 (2.79)	23.23 (4.09)	21.45 (3.29)
Median	20.66	22.79	20.86
Min, max	13.67, 32.24	15.19, 34.63	13.67, 34.63
BMI z-score (subjects <20 years old at screening)			
n	86	17	103
Mean (SD)	-0.51 (0.82)	-0.29 (1.56)	-0.48 (0.97)
Median	-0.54	0.14	-0.40
Min, max	-3.45, 1.64	-3.41, 2.23	-3.45, 2.23
$ppFEV_1$ (%)			
n	346	106	452
Mean (SD)	59.8 (18.8)	60.8 (14.2)	60.0 (17.8)
Median	58.1	60.2	58.4
Min, max	26.1, 128.0	35.1, 90.6	26.1, 128.0
$ppFEV_1$ (%)			
<40	50 (14.4)	10 (9.4)	60 (13.2)
≥40 to <70	190 (54.8)	66 (62.3)	256 (56.5)
≥70 to ≤90	84 (24.2)	29 (27.4)	113 (24.9)
>90	22 (6.3)	1 (0.9)	23 (5.1)
Missing	1 (0.3)	0	1 (0.2)
FEV_1 (L)			
n	346	106	452
Mean (SD)	2.13 (0.74)	2.20 (0.75)	2.15 (0.75)
Median	2.06	2.03	2.06
Min, max	0.65, 4.60	0.99, 4.36	0.65, 4.60

Source: Table 14.1.3b

BMI: body mass index; ES: Efficacy Set; FEV_1: forced expiratory volume in 1 second; F/F: homozygous for *F508del-CFTR*; F/RF: heterozygous for *F508del* and a *CFTR* mutation that results in residual function; max: maximum value; min: minimum value; N: total sample size; n: size of subsample; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; US: United States

Note: Baseline is defined as baseline of the parent study. Z-scores are calculated using US National Center for Health Statistics growth charts. Total column is the sum of F/F Mutation ES and F/RF Mutation ES.

[a] BMI: Body Mass Index = Weight/ (Height*Height) (kg/m^2).

Part C: Table 17 shows the subjects' demographics for **Part C**.

Most subjects were White (94.6%) and not of Hispanic or Latino ethnicity. A total of 56.4% of subjects were male, and the median age was 28.0 years (range: 12 to 70 years).

Table 17 Subject Demographics Part C (Safety Set)

Demographic	Total N = 204
Sex, n (%)	
Male	115 (56.4)
Female	89 (43.6)
Childbearing potential[a], n (%)	
Yes	76 (85.4)
No	13 (14.6)
Reason not of childbearing potential[b], n (%)	
Surgical Procedure	5 (38.5)
Postmenopausal	8 (61.5)
Premenarchal	0
Other	0
Age at screening[c] (years)	
n	204
Mean (SD)	29.6 (11.7)
Median	28.0
Min, max	12, 70
Age group at screening (years), n (%)	
<18	34 (16.7)
≥18	170 (83.3)
Ethnicity, n (%)	
Hispanic or Latino	5 (2.5)
Not Hispanic or Latino	184 (90.2)
Not collected per local regulations	15 (7.4)
Race, n (%)	
White	193 (94.6)
Black or African American	0
Asian	1 (0.5)
American Indian or Alaska Native	0
Native Hawaiian or other Pacific Islander	0
Not collected per local regulations	10 (4.9)
Other	0
Geographic region, n (%)	
North America	25 (12.3)
Europe	179 (87.7)

Source: Table 14.1.2c
max: maximum value; min: minimum value; N: total sample size; n: size of subsample
Note: All demographic data, except sex, childbearing potential, reasons for not childbearing potential, and regions, are based on the data collected in the parent study.
[a] Female n is the denominator.
[b] Female n with no childbearing potential is the denominator.
[c] Screening is the screening to the parent study.

CHMP comment

Overall, subject demographics resemble those of the different parent studies. The mean ages of the different analyses sets ranged between 26.1 and 35.1 years. Near 20% of the subjects was adolescent (23.7% in the 106/110 ES, 14.2% in the 108/110 ES, 19.9% in the F/F ES, 14.2% in the F/RF ES, and 16.7% in the Safety Set of Part C). As in the parent studies, most patients (>90%) were White.

Baseline disease characteristics differ somewhat between the analyses sets but are overall comparable to each other and to those of the parent studies. Subjects in the 106/110 ES and F/F mutation ES generally had a lower mean BMI and ppFEV1 values than patients from the 108/100 ES and F/RF mutation ES. These differences are not unexpected, given the fact that CF patients with an F/RF mutation, which are included in the 108/110 ES but not the 106/110 ES, generally have less severe disease.

Number analysed

For **Part A**, up to approximately 1375 subjects were potentially eligible to be enrolled. A total of 1044 subjects enrolled in Study 110 Part A and 1042 subjects received at least 1 dose of study drug. The final number of subjects per analysis set is summarised in **Table 18**.

Note that no patients were included in the observational cohort.

Table 18 Part A Analysis Populations

Disposition/Reason	Total n (%)
All Subjects Set	1044
Safety Set	1042
Full Analysis Set	741
106/110 Efficacy Set	459
108/110 Efficacy Set	226

For **Part B**, approximately 500 subjects were potentially eligible to continue from Part A and up to approximately 70 subjects from parent studies. A total of 464 subjects enrolled in Part B and 463 subjects received at least 1 dose of study drug. The final number of subjects per analysis set is summarised in Table 19.

Table 19 Part B Analysis Populations

Disposition Reason	F/F Mutation n (%)	F/RF Mutation n (%)	Total** n (%)
All Subjects Set	348	106	464
Safety Set	347	106	463
Full Analysis Set	347	106	453
F/F Mutation Efficacy Set	347	--	347
F/RF Mutation Efficacy Set	--	106	106

Approximately 334 subjects were eligible for **Part C**. A total of 204 subjects enrolled and all 204 subjects received at least 1 dose of study drug (Safety Set). Of these 204 subjects, 135 subjects had F/F mutation and 69 F/RF mutation.

CHMP comment

For each part of the study, most of the eligible subjects were enrolled. The final numbers of patients reached for each part were 1044, 464 and 204, respectively. As discussed before, the gradually lower number in Part B and Part C is explained by the number of treatment discontinuations mainly due to the study termination and availability of commercial drug.

Pharmacokinetics results

A summary of plasma concentrations of TEZ, M1-TEZ, IVA, and M1-IVA is presented in **Table 20**. Overall, the mean TEZ concentration based on pre-dose sampling at Week 24 was 2070 ng/ml, the mean M1-TEZ concentration was 4580 ng/ml, the mean IVA concentration was 892 ng/ml, and the mean M1-IVA concentration was 1740 ng/ml. These results were similar to those observed in the parent studies.

Table 20 Summary of plasma concentrations (ng/mL) of TEZ, M1-TEZ, IVA, and M1-IVA following administration of 100 mg TEZ qd/150 mg IVA q12h at Week 24

Analyte	N	Mean	CV%
TEZ	853	2070	67.1
M1-TEZ	853	4580	45.5
IVA	853	892	78.5
M1-IVA	853	1740	61.6

CHMP comment:

According to the protocol, predose sampling was conducted at various time points up to 96 weeks. Only summarized PK data for the 24 weeks time-point were provided. It is agreed that week 24 predose concentrations for TEZ, M1-TEZ, IVA, and M1-IVA are comparable to those obtained in the previously provided clinical studies.

In light of the trend of a reduced ppFEV1 in the 106/110 ES population (see efficacy part of this AR), Cmin over time figures were provided for the 106/110 ES population, as well as for the 108/110, 103/110 and 111/110 ES populations. The provided PK data indicate no clinically meaningful change in exposure over time. The 24 weeks time point PK data for the 106/110 ES population was comparable.

Efficacy results

Part A – 106/110 ES (F/F genotype)

For the efficacy analysis, the baseline was defined as the parent study baseline for all analysis groups except the PBO-TEZ/IVA group in the 106/110 ES, for which baseline was the Study 110 Part A baseline.

The treatment effects of TEZ/IVA, including effects on ppFEV1, PEx event rate, Cystic Fibrosis Questionnaire - Revised (CFQ-R) respiratory domain score, and body mass index (BMI) and weight, observed in the parent studies were generally maintained for up to 120 weeks of treatment (up to 24 weeks in the parent study and up to 96 additional weeks in Part A), demonstrating the sustained clinical benefit of CFTR modulation with TEZ/IVA in these patient populations.

In subjects previously naïve to TEZ/IVA, a similar magnitude of effect as that in the parent studies was observed after the initiation of TEZ/IVA treatment in this extension study, and these clinical benefits were generally sustained through 96 weeks of treatment.

Table 21 Summary of Spirometry, Nutritional Parameters, and CFQ-R Respiratory Domain Score MMRM Results at Week 96, 106/110 ES (F/F)

	PBO-TEZ/IVA (N = 231)	TEZ/IVA-TEZ/IVA[a] (N = 228)
Absolute Change from Baseline in $ppFEV_1$ (percentage points)		
n	187	194
LS mean (95% CI)	2.1 (0.8, 3.3)	2.0 (0.7, 3.2)
Relative Change from Baseline in $ppFEV_1$ (%)		
n	187	194
LS mean (95% CI)	4.3 (2.1, 6.5)	4.2 (2.0, 6.4)
Absolute Change From Baseline in CFQ-R Respiratory Domain Score (points)		
n	196	208
LS mean (95% CI)	1.7 (-0.6, 4.0)	3.0 (0.7, 5.3)
Absolute Change From Baseline in BMI (kg/m^2)		
n	195	208
LS mean (95% CI)	0.47 (0.30, 0.65)	0.38 (0.20, 0.55)
Absolute Change From Baseline in Weight (kg)		
n	195	208
LS mean (95% CI)	2.0 (1.4, 2.5)	2.1 (1.5, 2.6)
Absolute Change From Baseline in BMI z-score (Subjects <20 Years of Age at Screening)		
n	44	49
LS mean (95% CI)	0.10 (-0.04, 0.25)	-0.14 (-0.28, 0.00)
Absolute Change From Baseline in Weight z-score (Subjects <20 Years of Age at Screening)		
n	44	49
LS mean (95% CI)	0.07 (-0.06, 0.20)	-0.06 (-0.19, 0.07)
Absolute Change From Baseline in Height z-score (Subjects <20 Years of Age at Screening)		
n	42	49
LS mean (95% CI)	0.01 (-0.08, 0.11)	0.13 (0.04, 0.22)

Sources: Tables 14.2.1.2.1, 14.2.1.3.1, 14.2.2.2.1, 14.2.4.2.1, 14.2.3.2.1, 14.2.5.2.1, 14.2.6.2.1, and 14.2.7.2.1

BMI: body mass index; CFQ-R: Cystic Fibrosis Questionnaire–Revised; ES: Efficacy Set; F/F: homozygous for *F508del-CFTR*; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; PBO: placebo; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

[a] TEZ/IVA-TEZ/IVA treatment group corresponds to TEZ/IVA treatment group in source tables.

Table 22 Summary of Spirometry, Nutritional Parameters, and CFQ-R Respiratory Domain Score MMRM Results at Week 96, 108/110 ES (F/RF)

	PBO-TEZ/IVA (N = 80)	IVA-TEZ/IVA (N = 70)	TEZ/IVA-TEZ/IVA[a] (N = 76)
Absolute Change from Baseline in ppFEV$_1$ (percentage points)			
n	68	61	67
LS mean (95% CI)	4.1 (2.2, 6.0)	6.7 (4.7, 8.7)	7.5 (5.6, 9.4)
Relative Change from Baseline in ppFEV$_1$ (%)			
n	68	61	67
LS mean (95% CI)	7.9 (4.7, 11.1)	11.6 (8.2, 15.0)	13.0 (9.7, 16.2)
Absolute Change From Baseline in CFQ-R Respiratory Domain Score (points)			
n	74	65	68
LS mean (95% CI)	10.3 (7.0, 13.6)	11.2 (7.7, 14.7)	13.8 (10.3, 17.2)
Absolute Change From Baseline in BMI (kg/m^2)			
n	75	65	68
LS mean (95% CI)	1.07 (0.59, 1.55)	0.96 (0.45, 1.47)	1.05 (0.56, 1.55)
Absolute Change From Baseline in Weight (kg)			
n	75	65	68
LS mean (95% CI)	3.5 (1.9, 5.1)	3.5 (1.8, 5.2)	3.6 (2.0, 5.2)
Absolute Change From Baseline in BMI z-score (Subjects <20 Years of Age at Screening)			
n	13	7	10
LS mean (95% CI)	0.11 (-0.32, 0.54)	0.07 (-0.52, 0.65)	0.30 (-0.21, 0.80)
Absolute Change From Baseline in Weight z-score (Subjects <20 Years of Age at Screening)			
n	13	7	10
LS mean (95% CI)	0.15 (-0.25, 0.55)	0.09 (-0.45, 0.62)	0.43 (-0.04, 0.90)
Absolute Change From Baseline in Height z-score (Subjects <20 Years of Age at Screening)			
n	13	7	10
LS mean (95% CI)	-0.04 (-0.23, 0.15)	0.20 (-0.05, 0.45)	0.23 (0.00, 0.46)

Sources: Tables 14.2.1.2.2, 14.2.1.3.2, 14.2.2.2.2, 14.2.4.2.2, 14.2.3.2.2, 14.2.5.2.2, 14.2.6.2.2, and 14.2.7.2.2

BMI: body mass index; CFQ-R: Cystic Fibrosis Questionnaire–Revised; ES: Efficacy Set; F/RF: heterozygous for *F508del* and a *CFTR* mutation that results in residual function; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; PBO: placebo; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

[a] TEZ/IVA-TEZ/IVA treatment group corresponds to TEZ/IVA treatment group in source tables.

Table 23 Summary of Absolute Change from Baseline in Spirometry and Nutritional Parameter Scores at Week 96 for the F/F and F/RF Mutation Efficacy Sets Part B

	F/F Mutation ES (N = 347)	F/RF Mutation ES (N = 106)
ppFEV$_1$ (percentage points)		
Baseline		
n	345	105
Mean (SD)	58.9 (18.8)	60.8 (14.2)
Median (min, max)	57.3 (26.1, 128.0)	60.1 (35.1, 90.6)
Absolute Change from Baseline in ppFEV1 at Week 96		
n	132	49
Mean (SD)	1.7 (10.2)	8.3 (8.6)
Median (min, max)	1.5 (-46.0, 28.3)	8.8 (-12.9, 25.8)
BMI (kg/m^2)		
Baseline		
n	347	106
Mean (SD)	20.97 (2.71)	23.23 (4.09)
Median (min, max)	20.81 (13.67, 31.18)	22.79 (15.19, 34.63)
Absolute Change from Baseline in BMI at Week 96		
n	138	60
Mean (SD)	0.70 (1.45)	1.84 (2.21)
Median (min, max)	0.69 (-3.24, 6.42)	1.56 (-4.41, 9.21)
BMI z-score[a]		
Baseline		
n	68	14
Mean (SD)	-0.50 (0.86)	-0.17 (1.50)
Median (min, max)	-0.52 (-3.45, 1.64)	0.22 (-3.41, 2.23)
Absolute Change from Baseline in BMI z-score at Week 96		
n	21	6
Mean (SD)	-0.03 (0.71)	0.21 (0.46)
Median (min, max)	-0.08 (-1.49, 1.45)	0.23 (-0.56, 0.69)

Sources: Tables 14.2.1.1b, 14.2.1.2b, 14.2.2.1b, and 14.2.2.2b

BMI: body mass index; ES: Efficacy Set; F/F: homozygous for *F508del-CFTR* mutation; F/RF: heterozygous for *F508del* and a *CFTR* mutation that results in residual function; max: maximum value; min: minimum value; n: size of subsample; N: total sample size; ppFEV$_1$: percent predicted forced expiratory volume in 1 second

[a] For subjects <20 years of age at screening.

Absolute change in ppFEV1 from baseline

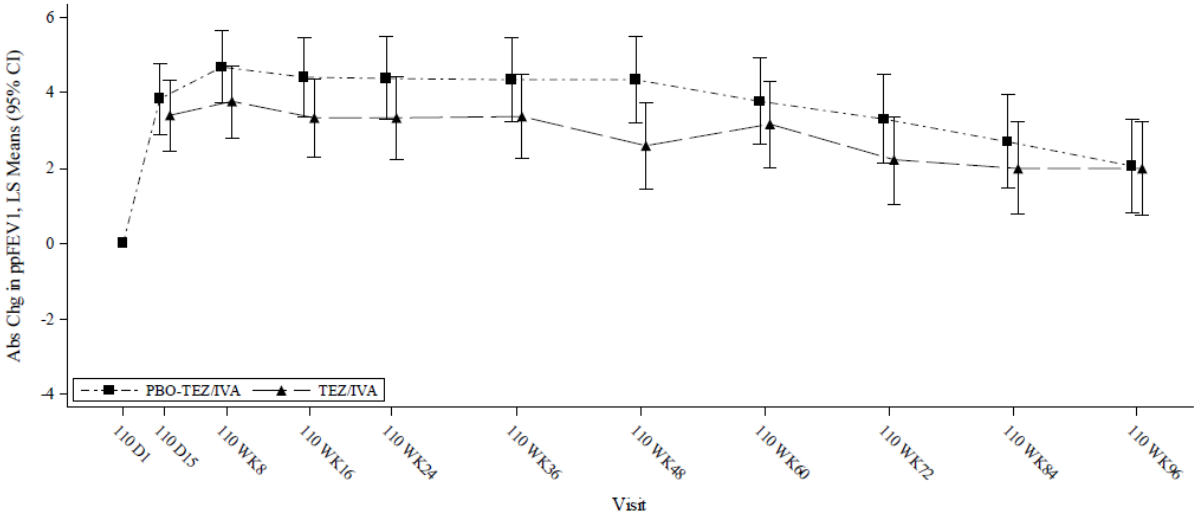
Part A – 106/110 ES (F/F genotype): Results from the MMRM analysis of the absolute change from baseline in ppFEV1 are shown in

Table 21 and Figure 4.

In Study 106, the LS mean absolute change from baseline in ppFEV1 through Week 24 was -0.6 percentage points (95% CI: -1.3, 0.0) in the placebo group and 3.4 percentage points (95% CI: 2.7, 4.0) in the TEZ/IVA group.

Subjects in the Study 106 placebo group who enrolled and initiated TEZ/IVA in Part A (PBO-TEZ/ IVA group) showed an increase in the LS mean absolute change from baseline in ppFEV1 as early as Day 15 of Part A, which was generally sustained at Week 96. (Table 21, Figure 4)

Figure 4 MMRM Analysis of Absolute Change from Baseline in Percent Predicted FEV1 (Percentage Points) at Each Visit - 110 Efficacy Analysis Period (106/110 Efficacy Set)



- Treatment group assignment is PBO-TEZ/IVA or TEZ/IVA for subjects randomized to Placebo or TEZ/IVA in Study 106 respectively.
- The following mixed model for repeated measures was used: sex, age at screening (<18 vs ≥18 years), parent study baseline ppFEV$_1$, treatment, Visit, treatment*visit, parent study baseline ppFEV$_1$*visit as fixed effects. Covariance Structure=UN, DF=Kenward-Roger. If the model fails to converge due to the UN covariance assumption, a CS covariance structure will be used.
- Covariance Structure=UN is used.
- Baseline is defined as the most recent non-missing measurement collected prior to the first dose of study drug in Study 106 for the subjects randomized to the active treatment arm in Study 106, and as the most recent non-missing measurement collected prior to the first dose of study drug in Study 110 for the subjects randomized to the placebo treatment arm in Study 106.
- Post-baseline visits in Study 106 are excluded in this model.
- Percent predicted FEV$_1$ is derived using Hankinson and Wang standards.

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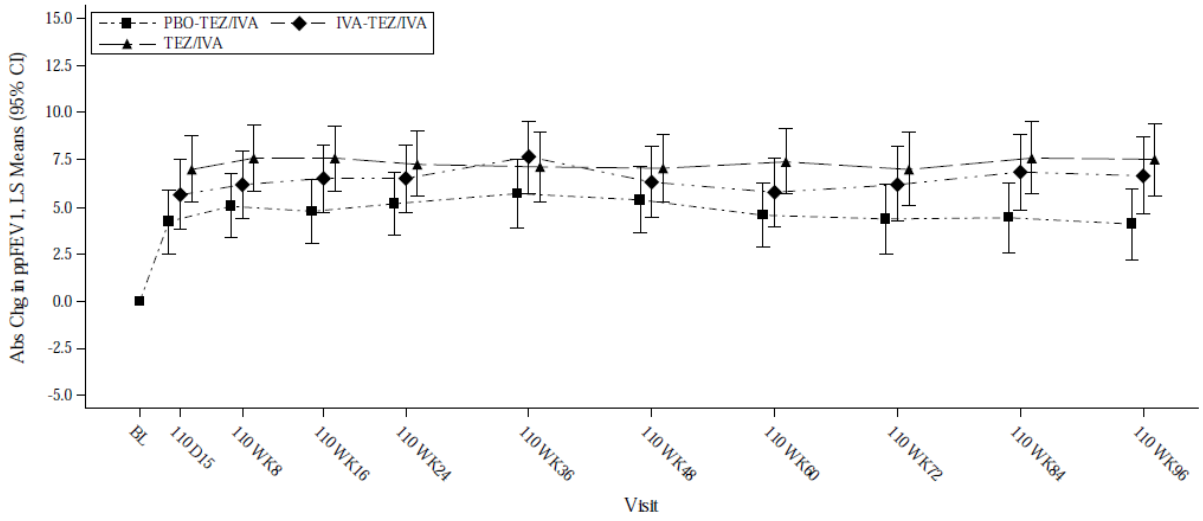
Part A – 108/110 ES (F/RF genotype): Results from the MMRM analysis of the absolute change from baseline in ppFEV1 are shown in Table 22 and Figure 5.

In Study 108, the LS mean absolute change in ppFEV1 from study baseline to the average of Week 4 and Week 8 was -0.3 percentage points (95% CI: -1.2, 0.6) in the placebo group, 4.4 percentage points (95% CI: 3.5, 5.3) in the IVA group, and 6.5 percentage points (95% CI: 5.6, 7.3) in the TEZ/IVA group. In Part A, there were additional numerical increases in both the IVA-TEZ/IVA and TEZ/IVA-TEZ/IVA groups at Week 96.

Subjects randomised to placebo treatment in Period 2 of Study 108 who enrolled and initiated TEZ/IVA in Part A (PBO-TEZ/IVA group) showed an increase in the LS mean absolute change from baseline in ppFEV1 as early as Day 15 of Part A, which was sustained at Week 96.

Figure 5 MMRM Analysis of Absolute change from Baseline in Percent Predicted FEV1 (Percentage Points) at Each Visit - 110 Efficacy Analysis Period (108/110 Efficacy Set)



- Treatment group assignment is PBO-TEZ/IVA, IVA-TEZ/IVA or TEZ/IVA for subjects randomized to Placebo, IVA or TEZ/IVA in Period 2 of Study 108 respectively.
- The following mixed model for repeated measures was used: treatment, visit, treatment*visit and parent study baseline ppFEV$_1$ as fixed effects. Covariance Structure=UN, DF=Kenward-Roger. If the model fails to converge due to the UN covariance assumption, a CS covariance structure will be used.
- Covariance Structure=UN is used.
- Baseline (BL) is defined as the most recent non-missing measurement collected prior to the first dose of study drug in Study 108.
- Post-baseline visits in Study 108 are excluded in this model.
- Percent predicted FEV$_1$ is derived using Hankinson and Wang standards.

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Part A – 103/110 and 111/110 ES: For subjects who rolled over from Study 103, the mean (SD) absolute change in ppFEV1 was 2.7 (10.0) percentage points (n=21) at Week 96.

For subjects who rolled over from Study 111, the mean (SD) absolute change in ppFEV1 at Week 96 was 4.1 (10.2) percentage points in the PBO-TEZ/IVA group (n=5) and 2.6 (6.6) percentage points in the TEZ/IVA-TEZ/IVA group (n=14).

The results for both efficacy sets were generally consistent with the 106/110 ES results in F/F subjects.

CHMP comment

Within the first 15 days, in the 106/110 subset of Part A (F/F genotype) the change in ppFEV1 increased for subjects who received placebo in the parent study to levels comparable of those that had already received TEZ/IVA. The effect of TEZ/IVA on ppFEV1 slightly decreased over 96 weeks, i.e., for PBO-TEZ/IVA a decrease from 3.8 (0.5)% to 2.1 (0.6)%, and for TEZ/IVA-TEZ/IVA from 3.4 (0.5)% to 2.0 (0.6)%.

In the 108/110 subset of Part A the change in ppFEV1 remained stable. However, while in the 106/110 ES, TEZ/IVA-TEZ/IVA and PBO-TEZ/IVA groups have after 120 weeks a similar increase in ppFEV1, in 108/110 ES population the difference is substantial i.e., PBO-TEZ/IVA 4.1%, IVA-TEZ/IVA 6.7 and TEZ/IVA-TEZ/IVA 7.5%. These numerical differences do not likely represent statistically or clinically meaningful differences between treatment groups because the 3 treatment groups had overlapping 95% confidence intervals (CI). The differences in observed point estimates could be due to individual subject variability, i.e., it is likely that the differences are due to subjects' characteristics rather than due to differences in the treatment. Overall, the results at week 96 show maintenance of treatment effect.

Furthermore, the effect of TEZ/IVA treatment on the absolute change in ppFEV1 is higher in the F/RF mutation group compared to the F/F mutation group, indicating that these patients may benefit more from TEZ/IVA treatment.

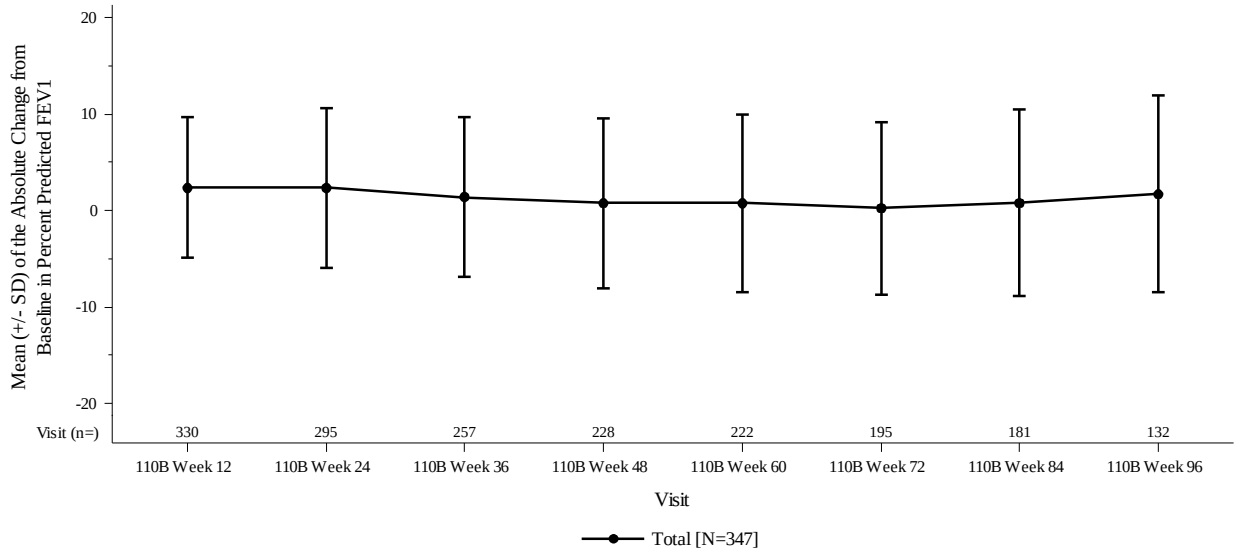
Part B

F/F Mutation Efficacy Set

Absolute change from baseline in ppFEV1 at selected visits is presented in

and Figure 6. The mean (SD) absolute change from study baseline to Week 96 was 1.7 (10.2) percentage points.

Figure 6 Mean Absolute Change from Baseline in Percent Predicted FEV_1(%) at Each Visit F/F Mutation Efficacy Set



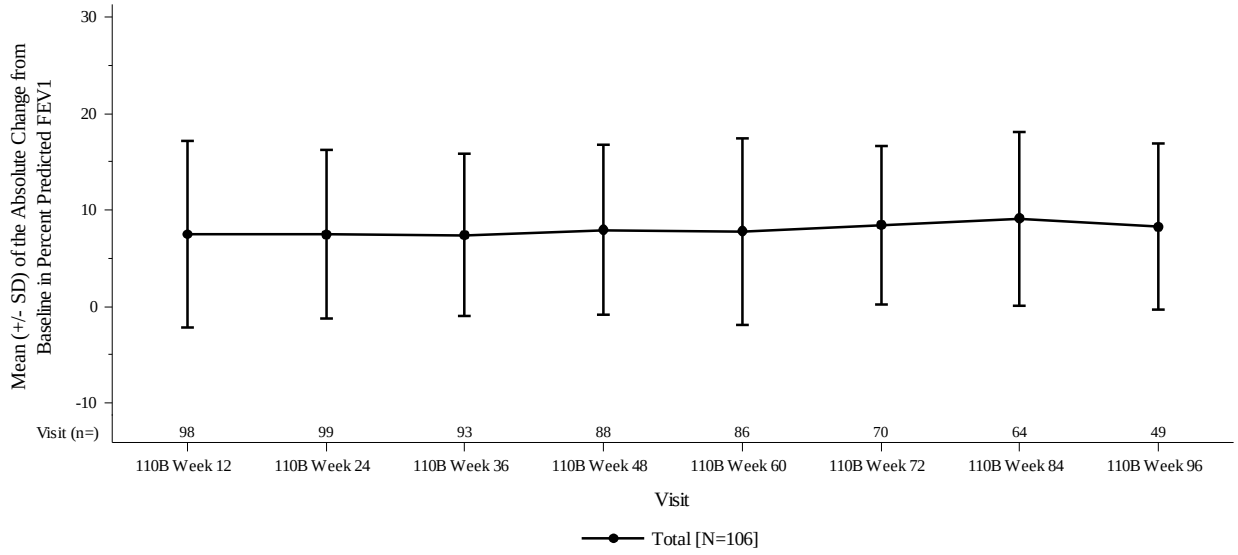
- Baseline for subjects randomized to TEZ/IVA group in parent studies 106, 112 and 114 is defined as the most recent non-missing measurement collected prior to the first dose of study drug in parent studies. Baseline for subjects randomized to Placebo group in parent studies 106, 112 and 114 is defined as the most recent non-missing measurement collected prior to the first dose of TEZ/IVA in Study 110 Part A for study 106 or Study 110 Part B for studies 112 and 114. Baseline for the subject rolled over from study 111 is defined as the baseline of the parent study.

F/RF Mutation Efficacy Set

Absolute change from baseline in ppFEV1 at selected visits is presented in Table 23 and

Figure 7. The mean (SD) absolute change from study baseline to Week 96 was 8.3 (8.6) percentage points.

Figure 7 Mean Absolute Change from Baseline in Percent Predicted FEV_1 (%) at Each Visit F/RF Mutation Efficacy Set



- Baseline is defined as the most recent non-missing measurement collected prior to the first dose of study drug in Study 108.

CHMP comments

Overall, these results provide evidence that clinically relevant improvements in ppFEV1 are sustained for at least 192 weeks, especially for the subjects with F/RF mutations.

For the subjects with F/F mutation, however, the increase from baseline is 1.7% only (note baseline is for TEZ/IVA group in parent Studies 106, 112, and 114 the most recent non-missing measurement collected prior to the first dose of study drug in parent studies). Baseline for subjects randomized to Placebo group in parent Studies 106, 112, and 114 is defined as the most recent non-missing measurement collected prior to the first dose of TEZ/IVA in Study 110 Part A for Study 106 or Study 110 Part B for Studies 112 and 114).

Overall after 192 weeks efficacy seems low, but the changes in ppFEV1 in Part B (i.e., a progressive decrease in treatment effect) are most likely attributable to the progressive nature of cystic fibrosis (CF) lung disease. Furthermore, although the results for all groups in Part B at week 96 are higher than at week 84 or 72, and other time points, there would be still an advantage over the natural history of CF at these timepoints.

Relative change in ppFEV1 from baseline

Part A – 106/110 ES (F/F): the LS mean (SD) relative change from baseline in ppFEV1 in PBO-TEZ/IVA patients was 7.2% (0.9%) at Day 15, 8.6% (1.0%) at Week 24, and 4.3% (1.1%) at Week 96. For TEZ/IVA-TEZ/IVA subjects values were 6.5% (0.9%) at Day 15, 6.1% (1.0%) at Week 24, and 4.2% (1.1%) at Week 96.

In Study 106, the LS mean relative change from baseline in ppFEV1 through Week 24 was -0.5% (95% CI: -1.7, 0.6) in the placebo group and 6.3% (95% CI: 5.1, 7.4) in the TEZ/IVA group.

Part A – 108/110 ES (F/RF): the LS mean (SD) relative change from baseline in ppFEV1 in PBO-TEZ/IVA patients was 8.0% (1.4%) at Day 15, 9.3% (1.4%) at Week 24, and 7.9% (1.6%) at Week 96. For IVA-TEZ/IVA subjects values were 10.3% (1.5%) at Day 15, 11.4% (1.5%) at Week 24, and 11.6% (1.7%) at Week 96. For TEZ/IVA-TEZ/IVA subjects values were 12.1% (1.5%) at Day 15, 12.6% (1.5%) at Week 24, and 13.0% (1.6%) at Week 96.

In Study 108, the LS mean relative change in ppFEV1 from study baseline to the average of Week 4 and Week 8 was -0.2% (95% CI: -1.7, 1.4) in the placebo group, 7.9% (95% CI: 6.4, 9.4) in the IVA group, and 11.2% (95% CI: 9.7, 12.7) in the TEZ/IVA group.

Part A – 103/110 and 111/110 ES (F/F and F/F): For subjects who rolled over from Study 103, the mean (SD) relative change in ppFEV1 was 6.4% (21.1%) at Week 96 (n=21).

For subjects who rolled over form Study 111, the mean (SD) relative change in ppFEV1 at Week 96 was 6.1% (14.4%) in the PBO-TEZ/IVA group (n=5) and 5.2% (11.5%) in the TEZ/IVA-TEZ/IVA group (n=14).

The results for both efficacy sets were generally consistent with the 106/110 ES results in F/F subjects.

CHMP comment

The results of relative change in ppFEV1 from baseline mirrors the results of absolute change in ppFEV1.

Number of Pulmonary Exacerbations

Part A - 106/110 PEx Analysis Set (F/F)

Modelled annualised events rates for PEx overall, those requiring hospitalisation, and those requiring IV antibiotics are shown for the PEx Analysis Period in **Table 24**. The PEx Analysis Period included all time that a given subject was on active treatment, which may have begun in either Study 106 or Part A.

During parent Study 106, the estimated PEx rate was 0.99 events per year in the placebo group and 0.64 events per year in the TEZ/IVA group. In study Part A, the overall exacerbation rate per year was 0.72.

Table 24 Number of Pulmonary Exacerbations in the PEx Analysis Period (106/110 PEx Analysis Set)

	Study 106/110		
Parameter	**PBO-TEZ/IVA N = 231**	**TEZ/IVA-TEZ/IVA[a] N = 248**	**Total N = 479**
Pulmonary exacerbations			
Number of subjects with events, n (%)	116 (50.2)	141 (56.9)	257 (53.7)
Total number of events	306	423	729
Observed event rate per year	0.71	0.75	0.73
Estimated event rate per year[b]	0.68	0.76	0.72
95% CI[b]	0.55, 0.83	0.63, 0.92	0.62, 0.84
Pulmonary exacerbations requiring hospitalization			
Number of subjects with events, n (%)	55 (23.8)	64 (25.8)	119 (24.8)
Total number of events	99	137	236
Observed event rate per year	0.23	0.24	0.24
Estimated event rate per year[b]	0.23	0.24	0.23
95% CI[b]	0.16, 0.32	0.18, 0.32	0.18, 0.30
Pulmonary exacerbations requiring IV antibiotics			
Number of subjects with events, n (%)	78 (33.8)	90 (36.3)	168 (35.1)
Total number of events	171	223	394
Observed event rate per year	0.40	0.40	0.40
Estimated event rate per year[b]	0.34	0.36	0.35
95% CI[b]	0.25, 0.44	0.28, 0.47	0.29, 0.43

Sources: Table 14.2.8.1.1, Table 14.2.8.3.1, and Table 14.2.8.4.1

IV: intravenous; IVA: ivacaftor; n: size of subsample; N: total sample size; PBO: placebo; PEx: pulmonary exacerbation; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

Notes: The observed event rate per year was the total number of events divided by the total duration of PEx Analysis Period (years).

[a] TEZ/IVA-TEZ/IVA treatment group corresponds to TEZ/IVA treatment group in source tables.

[b] Results were from a regression analysis for a negative binomial distribution with treatment, sex, age group at screening (<18 versus ≥18 years of age), and Study 106 baseline $ppFEV_1$ as covariates and with the logarithm of PEx Analysis Period as the offset. The same model was used for the Total column, except that treatment was removed from covariates.

Part A - 108/110 PEx Analysis Set (F/RF):

The results for the 108/110 PEx Analysis Set are shown in **Table 25**.

Table 25 Number of Pulmonary Exacerbations in the 110 PEx Analysis Period (108/110 PEx Analysis Set)

Parameter	Study 108/110			
	PBO-TEZ/IVA N = 81	IVA-TEZ/IVA N = 74	TEZ/IVA-TEZ/IVA[a] N = 78	Total N = 233
Pulmonary exacerbations				
Number of subjects with events, n (%)	40 (49.4)	36 (48.6)	28 (35.9)	104 (44.6)
Total number of events	89	51	46	186
Observed event rate per year	0.57	0.37	0.29	0.41
Estimated event rate per year[b]	0.44	0.28	0.22	0.31
95% CI[b]	0.29, 0.66	0.18, 0.44	0.14, 0.35	0.22, 0.44
Pulmonary exacerbations requiring hospitalization				
Number of subjects with events, n (%)	12 (14.8)	11 (14.9)	9 (11.5)	32 (13.7)
Total number of events	16	17	11	44
Observed event rate per year	0.10	0.12	0.07	0.10
Estimated event rate per year[b]	0.07	0.09	0.05	0.07
95% CI[b]	0.03, 0.18	0.04, 0.22	0.02, 0.13	0.03, 0.14
Pulmonary exacerbations requiring IV antibiotics				
Number of subjects with events, n (%)	14 (17.3)	13 (17.6)	12 (15.4)	39 (16.7)
Total number of events	30	21	16	67
Observed event rate per year	0.19	0.15	0.10	0.15
Estimated event rate per year[b]	0.09	0.09	0.05	0.08
95% CI[b]	0.04, 0.22	0.04, 0.22	0.02, 0.13	0.04, 0.16

Sources: Table 14.2.8.1.2, Table 14.2.8.3.2, and Table 14.2.8.4.2

IV: intravenous; IVA: ivacaftor; n: size of subsample; N: total sample size; PBO: placebo; PEx: pulmonary exacerbation; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; RF: residual function; TEZ: tezacaftor

Notes: The observed event rate per year was the total number of events divided by the total duration of PEx Analysis Period (years) number of years.

[a] TEZ/IVA-TEZ/IVA treatment group corresponds to TEZ/IVA treatment group in source tables.

[b] Results were from a regression analysis for a negative binomial distribution with treatment, type of RF mutation on the second *CFTR* allele, age at screening (<18 versus ≥18 years of age), and parent study baseline $ppFEV_1$ as covariates and with the logarithm of the PEx Analysis Period duration as the offset. The same model was used for the Total column, except that treatment was removed from covariates.

CHMP comment

The estimated event rate per year for PEx during Study 106 was 0.99 in the placebo group and 0.64 in the TEZ/IVA group. Unexpectedly, but in line with the first interim results, subjects who already received TEZ/IVA during Study 106 had higher estimated PEx event rate in Study 110 than those who received placebo first (0.68 vs 0.76). However, the estimated PEx event rate in PEx requiring hospitalisation and those requiring IV antibiotics are quite comparable between the groups.

In Study 108, the estimated PEx event rate per year was 0.63 in the placebo group, 0.29 in the IVA group, and 0.34 in the TEZ/IVA group. In the 108/110 subset of Part A, PEx event rates per year were higher for the PBO-TEZ/IVA group (0.44), than for the IVA-TEZ/IVA group (0.28) and the TEZ/IVA-TEZ/IVA group (0.22). These difference in observed rate is not reflected in the event rates of PEx

requiring hospitalisation and those requiring IV antibiotics, for which the estimated event rates are comparable.

A straight comparison is not possible as the reported Study 110 Part B PEx event rate per year is the observed event rate, not the estimated (event rate, which was reported for Study 110 Part A and Study 108. However, when comparing the observed rate per year, a small increase over time is observed. Nevertheless, the observed rate per year is still lower than the rate in the Study 108 placebo group (0.57 events/year). Although, it should be noted that Study 108 had only a duration of 8 weeks, which is very short to measure the exacerbations rate accurately because of the seasonal variability of exacerbations. The differences between the 3 groups could be due to the seasonal and natural variability in PEx events, low sample size, and status of the ongoing coronavirus-19 (COVID-19) pandemic. Moreover, the overlapping 95% CIs demonstrate that the rates are not statistically different.

Part B – F/F mutation ES: A total of 156 (45.0%) subjects had 386 events of PEx with an observed event rate of 0.77 events per year (**Table 26**). Of these, 77 subjects had 126 PEx events requiring hospitalisation (0.25 events per year) and 109 subjects had 228 PEx events requiring IV antibiotic therapy (0.46 events per year).

Table 26 Summary of Pulmonary Exacerbations During Efficacy Analysis Period in Part B

	F/F Mutation ES N = 347	F/RF Mutation ES N = 106
Total number of days (years) of the efficacy analysis period	167554 (498.67)	62132 (184.92)
Pulmonary exacerbations		
Number of subjects with events, n (%)	156 (45.0)	43 (40.6)
Total number of events	386	94
Observed event rate per year	0.77	0.51
Pulmonary exacerbations requiring hospitalization		
Number of subjects with events, n (%)	77 (22.2)	15 (14.2)
Total number of events	126	21
Observed event rate per year	0.25	0.11
Pulmonary exacerbations requiring IV antibiotic therapy		
Number of subjects with events, n (%)	109 (31.4)	18 (17.0)
Total number of events	228	37
Observed event rate per year	0.46	0.20
Pulmonary exacerbations requiring hospitalization or IV antibiotic therapy		
Number of subjects with events, n (%)	111 (32.0)	19 (17.9)
Total number of events	230	39
Observed event rate per year	0.46	0.21

Source: Table 14.2.3.1b (F/F Mutation ES) and Table 14.2.3.2b (F/RF Mutation ES)

ES: Efficacy Set; F/F: homozygous for *F508del-CFTR*; F/gating: heterozygous for *F508del* and a *CFTR* mutation that results in a gating defect; F/RF: heterozygous for *F508del* and a *CFTR* mutation that results in residual function; IV: intravenous; max: maximum value; min: minimum value; n: size of subsample; N: total sample size; PEx: pulmonary exacerbation

Note: Efficacy analysis period includes the time from the first dose date of study drug in Part B until the last study visit at which efficacy data are collected in Part B. For subjects who discontinued Part B to enroll in another qualified Vertex study, and later reenrolled in Part B, the analysis period excludes the time between the last dose before the discontinuation from Part B and the first dose after re-enrollment in Part B. Total duration of PEx Analysis Period (days) = sum total of (PEx Analysis Period end date - PEx Analysis Period start date + 1) across all the subjects. Total duration of PEx Analysis Period (years) = Total duration of PEx Analysis Period (days)/336. Observed event rate per year is the total number of events divided by total duration of PEx Analysis Period (years).

Part B – F/RF mutation ES: A total of 43 (40.6%) subjects had 94 events of PEx with an observed event rate of 0.51 events per year (**Table 27**). Of these, 15 subjects had 21 PEx events requiring hospitalisation (0.11 events per year) and 18 subjects had 37 PEx events requiring IV antibiotic therapy (0.20 events per year).

Table 27 Summary of Pulmonary Exacerbations During Efficacy Analysis Period in Part B

	F/F Mutation ES N = 347	F/RF Mutation ES N = 106
Total number of days (years) of the efficacy analysis period	167554 (498.67)	62132 (184.92)
Pulmonary exacerbations		
Number of subjects with events, n (%)	156 (45.0)	43 (40.6)
Total number of events	386	94
Observed event rate per year	0.77	0.51
Pulmonary exacerbations requiring hospitalization		
Number of subjects with events, n (%)	77 (22.2)	15 (14.2)
Total number of events	126	21
Observed event rate per year	0.25	0.11
Pulmonary exacerbations requiring IV antibiotic therapy		
Number of subjects with events, n (%)	109 (31.4)	18 (17.0)
Total number of events	228	37
Observed event rate per year	0.46	0.20
Pulmonary exacerbations requiring hospitalization or IV antibiotic therapy		
Number of subjects with events, n (%)	111 (32.0)	19 (17.9)
Total number of events	230	39
Observed event rate per year	0.46	0.21

Source: Table 14.2.3.1b (F/F Mutation ES) and Table 14.2.3.2b (F/RF Mutation ES)

ES: Efficacy Set; F/F: homozygous for *F508del-CFTR*; F/gating: heterozygous for *F508del* and a *CFTR* mutation that results in a gating defect; F/RF: heterozygous for *F508del* and a *CFTR* mutation that results in residual function; IV: intravenous; max: maximum value; min: minimum value; n: size of subsample; N: total sample size; PEx: pulmonary exacerbation

Note: Efficacy analysis period includes the time from the first dose date of study drug in Part B until the last study visit at which efficacy data are collected in Part B. For subjects who discontinued Part B to enroll in another qualified Vertex study, and later reenrolled in Part B, the analysis period excludes the time between the last dose before the discontinuation from Part B and the first dose after re-enrollment in Part B. Total duration of PEx Analysis Period (days) = sum total of (PEx Analysis Period end date - PEx Analysis Period start date + 1) across all the subjects. Total duration of PEx Analysis Period (years) = Total duration of PEx Analysis Period (days)/336. Observed event rate per year is the total number of events divided by total duration of PEx Analysis Period (years).

CHMP comment

In Part B, subjects with the F/RF mutation experienced less PEx than those with the F/F mutation (0.51 vs 0.77 events/year). Similar results were obtained for PEX requiring hospitalisation and those requiring IV antibiotic therapy. This can be explained by the difference in severity of the disease between the groups. Overall, these results show that PEx event rates in all groups over the course of this OLE study are lower compared with those in placebo groups of the parent studies.

For the F/RF group, a small increase over time was observed, when comparing the observed rate per year. However, in Part B, the observed rate per year is still lower than the rate in the Study 108 placebo group (0.57 events/year), despite the natural history. However, it should be noted that Study 108 had only a duration of 8 weeks, which is too measure exacerbations rate meaningfully. The differences between the 3 groups could be due to the natural variability in PEx events, low sample size, and status of the ongoing coronavirus-19 (COVID-19) pandemic. Furthermore, the population in Part B is different form the population in Part A due to the inclusion of subjects of other parent studies. Moreover, as said before, consistently with that TEZ/IVA therapy does not eliminate the decline in lung

function entirely, also an increase in the rate of PEx over time can be expected. Therefore, the differences are not considered of concern.

Time-to-First Pulmonary Exacerbation on TEZ/IVA Treatment

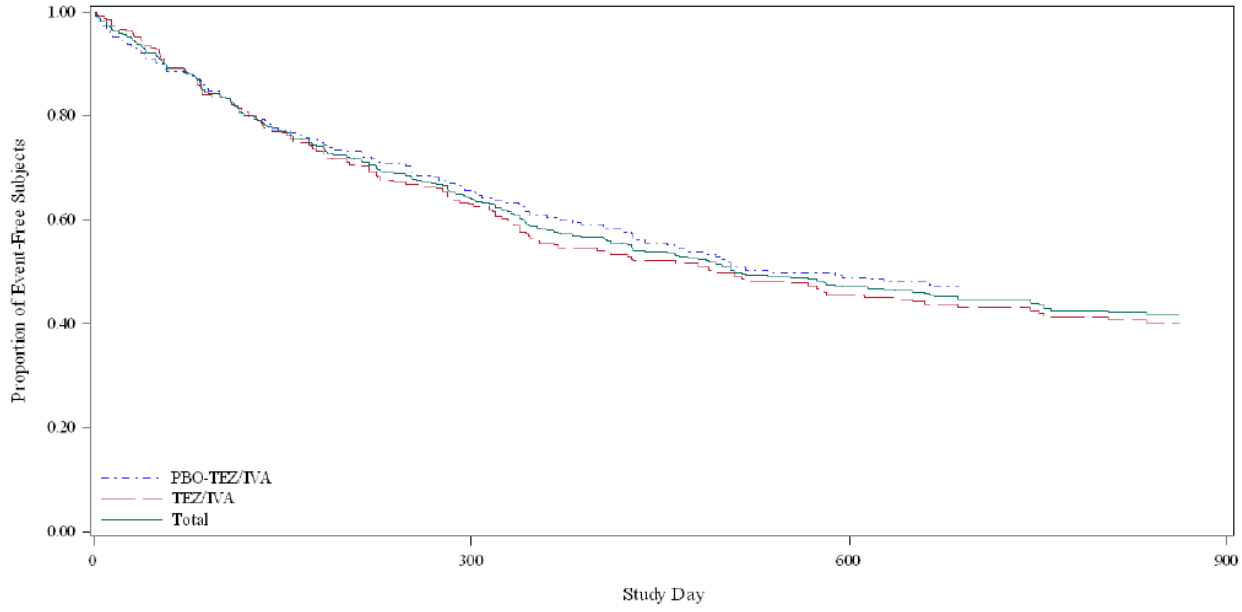
Part A - 106/110 PEx Analysis Set: The analysis of time-to-first PEx in the PEx Analysis Period is shown in Table 29, with the Kaplan-Meier analysis displayed in Figure 8. The PEx Analysis Period included all time that a given subject received active treatment, which may have begun in either Study 106 or Study 110 Part A.

Table 28 Time-to-First PEx on TEZ/IVA, PEx Analysis Period (106/110 PEx Analysis Set)

	PBO-TEZ/IVA (N = 231)	TEZ/IVA-TEZ/IVA[a] (N = 248)
Event-free time (weeks)		
50% of subjects (median)	76.6	70.6
Event-free probability, Kaplan-Meier estimate (95% CI)		
Event-free probability at Week 48	0.629 (0.562, 0.689)	0.591 (0.525, 0.650)
Event-free probability at Week 96	0.470 (0.402, 0.535)	0.438 (0.374, 0.501)

Source: Table 14.2.8.2.1
IVA: ivacaftor; N: total sample size; PBO: placebo; PEx: pulmonary exacerbation; TEZ: tezacaftor
Notes: Subjects without a PEx by the end of the PEx Analysis Period were censored at the end of the PEx Analysis Period.
[a] TEZ/IVA-TEZ/IVA treatment group corresponds to TEZ/IVA treatment group in source table.

Figure 8 Kaplan-Meier Plot for the Time-to-First Pulmonary Exacerbation on TEZ/IVA in the PEx Analysis Period (106/110 PEx Analysis Set)



Source: Figure 14.2.8.2.1
IVA: ivacaftor; PBO: placebo; PEx: pulmonary exacerbation; TEZ: tezacaftor
Note: TEZ/IVA in figure legend denotes TEZ/IVA-TEZ/IVA treatment group in Part A.

Part A - 108/110 PEx Analysis Set: The analysis of time-to-first PEx in the PEx Analysis Period is shown in Table 29, with the Kaplan-Meier analysis displayed in Figure 9. The PEx Analysis Period

included the consecutive time that a given subject was receiving TEZ/IVA, which may have begun in either Study 108 or Study 110 Part A.

Table 29 Time-to-First PEx on TEZ/IVA, PEx Analysis Period (108/110 PEx Analysis Set)

	PBO-TEZ/IVA (N = 81)	IVA-TEZ/IVA (N = 74)	TEZ/IVA-TEZ/IVA[a] (N = 78)
Event-free time (weeks)			
50% of subjects (median)	93.3	95.0	NE[b]
Event-free probability, Kaplan-Meier estimate (95% CI)			
Event-free probability at Week 48	0.676 (0.562, 0.766)	0.681 (0.560, 0.775)	0.763 (0.650, 0.844)
Event-free probability at Week 96	0.497 (0.383, 0.601)	0.493 (0.372, 0.603)	0.639 (0.519, 0.737)

Source: Table 14.2.8.2.2

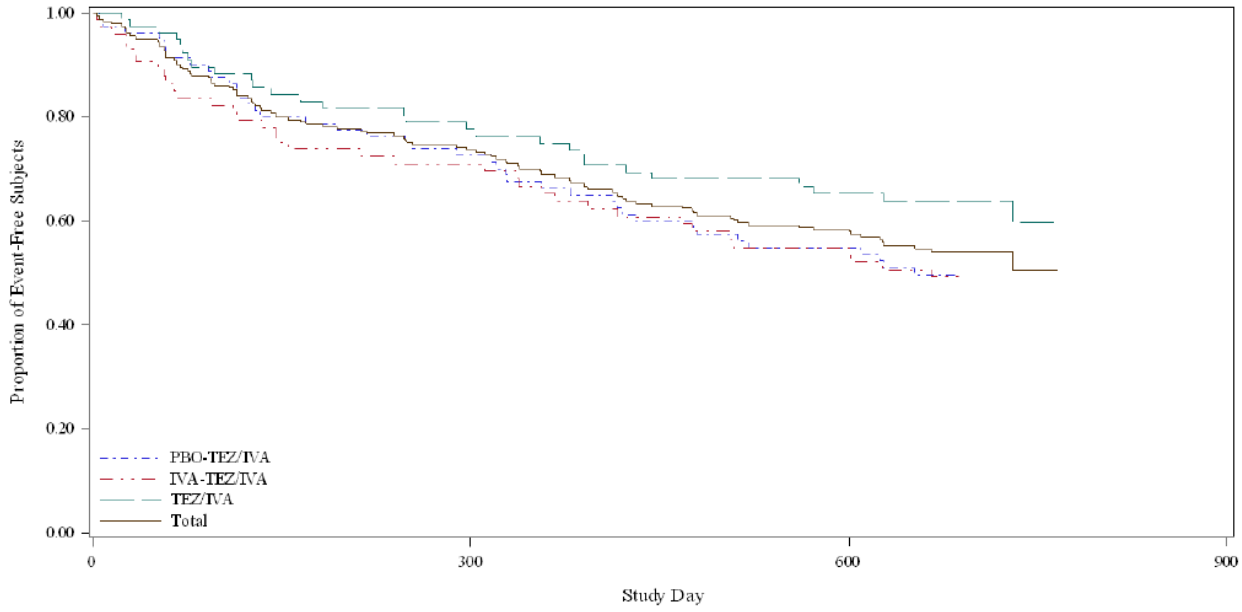
IVA: ivacaftor; N: total sample size; NE: not estimable; PBO: placebo; PEx: pulmonary exacerbation; TEZ: tezacaftor

Notes: Subjects without an exacerbation by the end of the PEx Analysis Period were censored at the end of the PEx Analysis Period.

[a] TEZ/IVA-TEZ/IVA treatment group corresponds to TEZ/IVA treatment group in source table.

[b] For the TEZ/IVA arm, the event-free probability at Week 96 was 0.639, so the estimated proportion of subjects who did not have PEx during TEZ/IVA treatment was greater than 50%. The median event-free time was thus beyond the 96-week duration of the study and was not estimated.

Figure 9 Kaplan-Meier Plot for the Time-to-First Pulmonary Exacerbation on TEZ/IVA in the PEx Analysis Period (108/110 PEx Analysis Set)



Source: Figure 14.2.8.2.2

IVA: ivacaftor; PBO: placebo; PEx: pulmonary exacerbation; TEZ: tezacaftor

Note: TEZ/IVA in figure legend denotes TEZ/IVA-TEZ/IVA treatment group in Part A.

CHMP comment

Event-free probability of PEx decreased for all subsets of Part A. There is some signal that this decrease was more in the PBO-TEZ/IVA and IVA-TEZ/IVA groups than in the TEZ/IVA-TEZ/IVA group at 96 weeks (In fact, the halfwidth of the 95%-CI is ~0.10 in each group, so the halfwidth of a 95%-CI for the difference between the groups is ~0.14, while the difference is ~0.15, so nominally this could

result in a p-value < 0.05). As no multiple testing procedure was specified, this does not mean 'statistically significant', but it can be regarded a signal compared to the expected natural variation.

Absolute Change in CFQ-R Respiratory Domain from Baseline

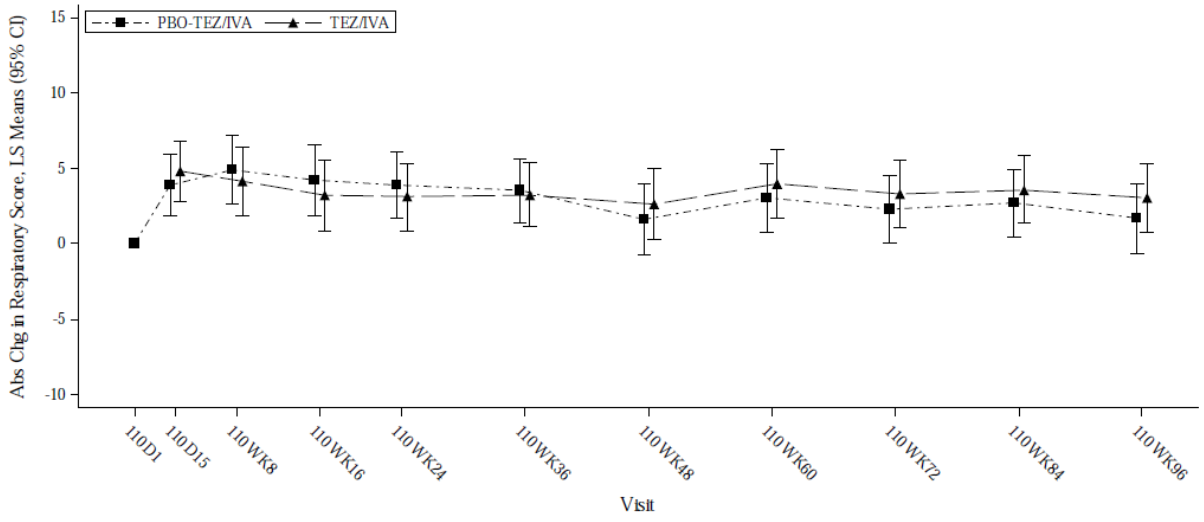
The pooled CFQ-R "Children Ages 12 and 13" and "Adolescents and Adults" versions were used for the analysis of CFQ-R respiratory domain score. The CFQ-R was only measured in Part A.

Part A - 106/110 Efficacy Set (F/F): Results from the MMRM analysis of the absolute change from baseline in CFQ-R respiratory domain score are shown in

Table **21** and Figure 10.

In Study 106, the LS mean absolute change from baseline in CFQ-R respiratory domain score through Week 24 was -0.1 points (95% CI: -1.6, 1.4) in the placebo group and 5.0 points (95% CI: 3.5, 6.5) in the TEZ/IVA group. For subjects in the Study 106 TEZ/IVA group who enrolled in Part A (TEZ/IVA-TEZ/IVA group), the LS mean absolute change from baseline in CFQ-R respiratory score was generally maintained from Day 15 of Part A to Week 96 (from 4.8 (1.0) to 3.0 (1.2)). Subjects in the Study 106 placebo group who enrolled and initiated TEZ/IVA in Part A (PBO-TEZ/IVA group) showed an increase in the LS mean absolute change from baseline in CFQ-R respiratory domain score as early as Day 15 of Part A (3.9 (1.0), which was generally maintained at Week 96 (1.7 (1.2)).

Figure 10 MMRM Analysis of Absolute Change from Baseline in CFQ-R Respiratory Domain Score (Pooled 'Children Ages 12 and 13' Version and 'Adolescents and Adults' Version) at Each Visit - 110 Efficacy Analysis Period (106/110 Efficacy Set)



- Treatment group assignment is PBO-TEZ/IVA or TEZ/IVA for subjects randomized to Placebo or TEZ/IVA in Study 106 respectively.
- The following mixed model for repeated measures was used: sex, age at screening (<18 vs ≥18 years), parent study baseline CFQ-R respiratory domain, treatment, visit, treatment*visit, parent study baseline CFQ-R respiratory domain *visit as fixed effects. Covariance Structure=UN, DF=Kenward-Roger. If the model fails to converge due to the UN covariance assumption, a CS covariance structure will be used.
- Covariance Structure=UN is used.
- Baseline is defined as the most recent non-missing measurement collected prior to the first dose of study drug in Study 106 for the subjects randomized to the active treatment arm in Study 106, and as the most recent non-missing measurement collected prior to the first dose of study drug in Study 110 for the subjects randomized to the placebo treatment arm in Study 106.
- Post-baseline visits in Study 106 are excluded in this model.

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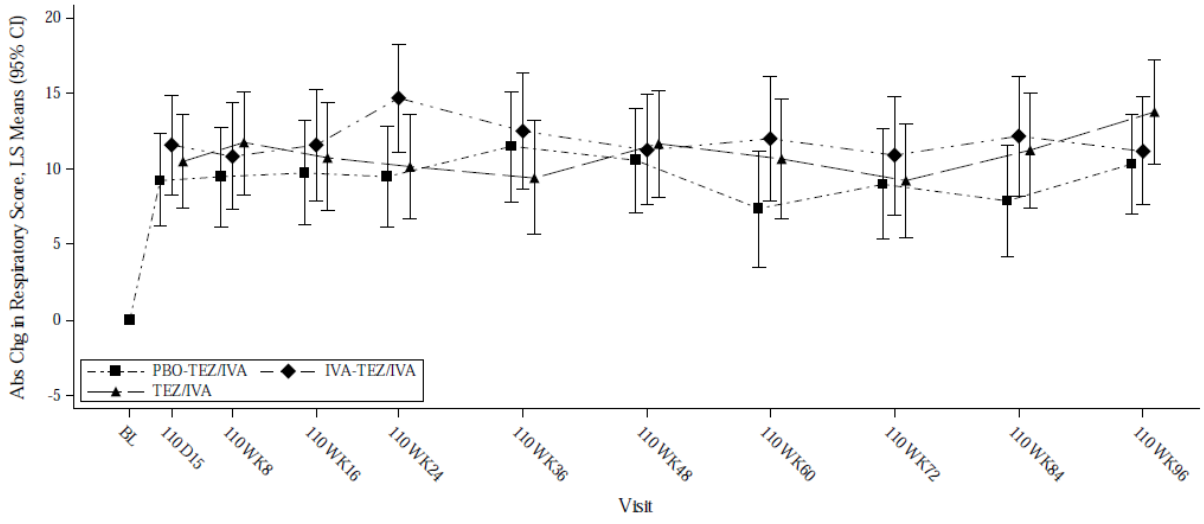
Part A - 108/110 Efficacy Set(F/RF): Results from the MMRM analysis of the absolute change from baseline in CFQ-R respiratory domain score are shown in

Table **22** and Figure 11.

In Study 108, the LS mean absolute change in CFQ-R respiratory domain score from study baseline to the average of Week 4 and Week 8 was -1.0 points (95% CI: -2.9, 1.0) in the placebo group, 8.7 points (95% CI: 6.8, 10.7) in the IVA group, and 10.1 points (95% CI: 8.2, 12.1) in the TEZ/IVA group.

In Part A, there were additional numerical increases in both the IVA-TEZ/IVA and TEZ/IVA-TEZ/IVA groups at Week 96. Subjects randomized to placebo treatment in Period 2 of Study 108 who enrolled and initiated TEZ/IVA in Part A (PBO-TEZ/IVA group) showed an increase in the LS mean (SE) absolute change from baseline in CFQ-R respiratory domain score as early as Day 15 of Part A (9.3 (1.5)). The effects were sustained at Week 96 in all groups: PBO-TEZ/IVA 10.3 (1.7) point, IVA-TEZ/IVA 11.2 (1.8) points, TEZ/IVA-TEZ/IVA 13.8 (1.7) points.

Figure 11 MMRM Analysis of Absolute Change from Baseline in CFQ-R Respiratory Domain Score (Pooled 'Children Ages 12 and 13' Version and 'Adolescents and Adults' Version) at Each Visit - 110 Efficacy Analysis Period (108/110 Efficacy Set)



- Treatment group assignment is PBO-TEZ/IVA, IVA-TEZ/IVA or TEZ/IVA for subjects randomized to Placebo, IVA or TEZ/IVA in Period 2 of Study 108 respectively.
- The following mixed model for repeated measures was used: treatment, visit, treatment*visit and parent study baseline CFQ-R respiratory domain as fixed effects. Covariance Structure=UN, DF=Kenward-Roger. If the model fails to converge due to the UN covariance assumption, a CS covariance structure will be used.
- Covariance Structure=UN is used.
- Baseline (BL) is defined as the most recent non-missing measurement collected prior to the first dose of study drug in Study 108.
- Post-baseline visits in Study 108 are excluded in this model.

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Part A - 103/110 Efficacy Set: At Week 96 in Part A, the mean (SD) absolute change in CFQ-R respiratory domain score was 8.6 (12.1) points (n = 22).

CHMP *comment*

Subjects who had received placebo treatment during the parent study obtained a mean absolute change in CFQ-R comparable to those who had received TEZ/IVA treatment during the first 15 days of Study 110.

The LS mean absolute changes from parent study baseline at Week 96 of Part A were 3.0 points (95% CI: 0.7, 5.3) and 1.7 points (95% CI: -06, 4.0) for the TEZ/IVA-TEZ/IVA group and PBO-TEZ/IVA group, respectively. As the minimum clinically important difference is 4.0 point, the subjects as a group did not meet this MCID. The proportion of subjects who met the MCID of the CFQ-R was 42.3%

for the placebo-TEZ/IVA group and 51.0% for TEZ/IVA-TEZ/IVA group. Given, the natural history of CF with a deterioration of QoL over time, the observed responder rates are considered relevant.

Absolute Change in BMI from Baseline

Part A - 106/110 Efficacy Set

The mean BMI increased during treatment with both TEZ/IVA (in Study 106 and Study 110 Part A) and placebo (in Study 106).

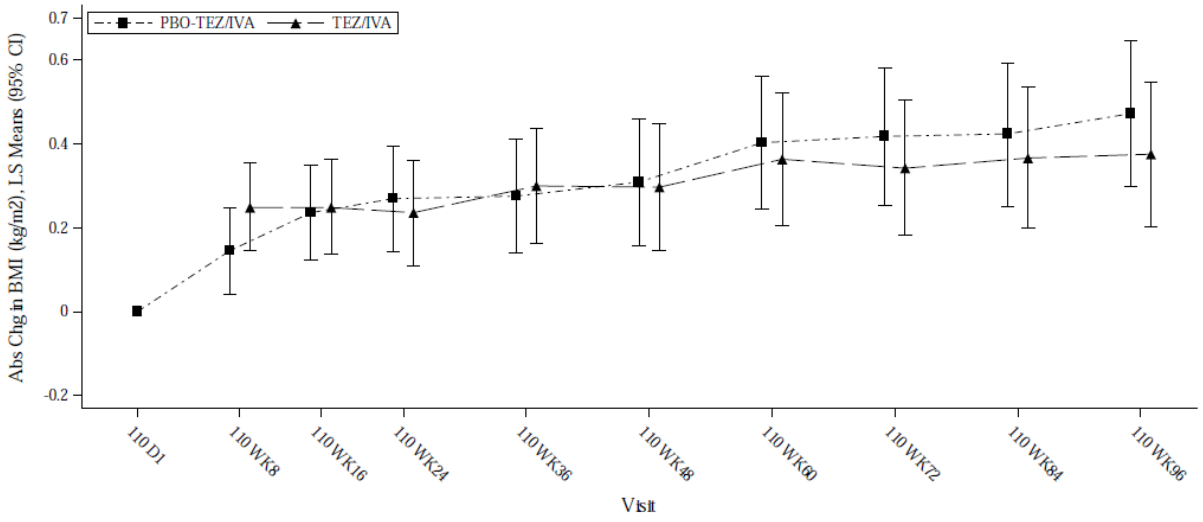
In Study 106, the LS mean absolute change from baseline in BMI at Week 24 was 0.18 kg/m2 (95% CI: 0.08, 0.28) in the TEZ/IVA group. There were also increases in the LS mean (SE) absolute change from baseline in BMI at Week 96 in Part A (0.38 (0.09) kg/m2)

In Study 106, the LS mean absolute change from baseline in BMI at Week 24 was 0.12 kg/m2 (95% CI: 0.03, 0.22) in the placebo group, and there were also increases in the LS mean (SE) absolute change from baseline in BMI at Week 96 in Part A (PBO-TEZ/IVA group (0.47 (0.09) kg/m2).

Results from the MMRM analysis of the absolute change from baseline in BMI are shown in

Table 21 and **Figure 12**.

Figure 12 MMRM Analysis of Absolute Change from Baseline in BMI (kg/m^2) at Each Visit - 110 Efficacy Analysis Period (106/110 Efficacy Set)



- Treatment group assignment is PBO-TEZ/IVA or TEZ/IVA for subjects randomized to Placebo or TEZ/IVA in Study 106 respectively.
- The following mixed model for repeated measures was used: sex, age at screening (<18 vs ≥18 years), parent study baseline BMI, treatment, visit, treatment*visit, parent study baseline BMI*visit as fixed effects. Covariance Structure=UN, DF=Kenward-Roger. If the model fails to converge due to the UN covariance assumption, a CS covariance structure will be used.
- Covariance Structure=UN is used.- Baseline is defined as the most recent non-missing measurement collected prior to the first dose of study drug in Study 106 for the subjects randomized to the active treatment arm in Study 106, and as the most recent non-missing measurement collected prior to the first dose of study drug in Study 110 for the subjects randomized to the placebo treatment arm in Study 106.
- Post-baseline visits in Study 106 are excluded in this model.

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Part A - 108/110 Efficacy Set

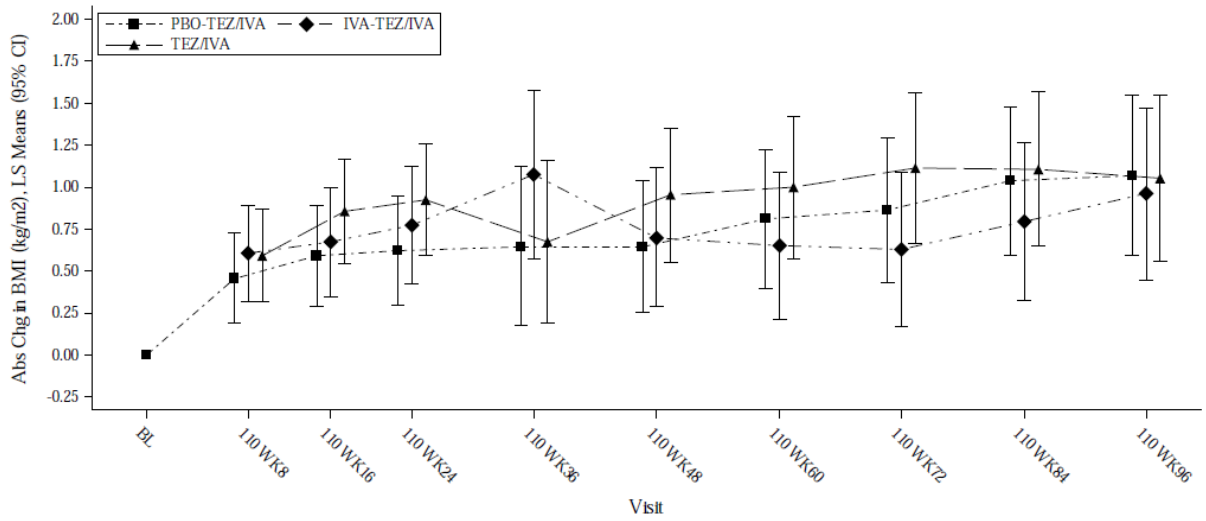
Results from the MMRM analysis of the absolute change from baseline in BMI are shown in **Table 22** and **Figure 13**.

The mean BMI increased in the TEZ/IVA group during Study 108: The mean (SD) absolute change at Week 8 was 0.34 (0.96) kg/m2 in the TEZ/IVA group. There were increases in the mean BMI in the TEZ/IVA-TEZ/IVA group at Week 96 in Part A (1.05 (0.25) kg/m^2).

The mean BMI increased in the placebo group during Study 108: The mean (SD) absolute change at Week 8 was 0.18 (0.81) kg/m2. There were also creases in the mean BMI in the PBO-TEZ/IVA group at Week 96 in Part A (during TEZ/IVA treatment) (1.07 (0.24) kg/m^2).

The mean BMI increased in the IVA group during Study 108: The mean (SD) absolute change at Week 8 was 0.47 (0.80) kg/m2. There were also increases in the mean BMI in the IVA-TEZ/IVA group at Week 96 in Part A (during TEZ/IVA treatment) (0.96 (0.26) kg/m^2).

Figure 13 MMRM Analysis of Absolute Change from Baseline in BMI (kg/m^2) at Each Visit - 110 Efficacy Analysis Period (108/110 Efficacy Set)



- Treatment group assignment is PBO-TEZ/IVA, IVA-TEZ/IVA or TEZ/IVA for subjects randomized to Placebo, IVA or TEZ/IVA in Period 2 of Study 108 respectively.
- The following mixed model for repeated measures was used: treatment, visit, treatment*visit and parent study baseline BMI as fixed effects. Covariance Structure=UN, DF=Kenward-Roger. If the model fails to converge due to the UN covariance assumption, a CS covariance structure will be used.
- Covariance Structure=UN is used.
- Baseline (BL) is defined as the most recent non-missing measurement collected prior to the first dose of study drug in Study 108.
- Post-baseline visits in Study 108 are excluded in this model.

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Part A - 103/110 Efficacy Set: At Week 96, the mean (SD) absolute change in BMI was 1.38 (1.73) kg/m2 (n = 22).

Part A - 111/110 Efficacy Set: At Week 96, the mean (SD) absolute change in BMI was 1.59 (2.08) kg/m^2 in the PBO-TEZ/IVA group (n = 5) and 0.26 (0.88) kg/m^2 in the TEZ/IVA-TEZ/IVA group (n = 14).

CHMP comment

An increase in mean BMI was obtained in all subsets over the course of Part A of the OLE study.

Part B

F/F Mutation Efficacy Set

Absolute change from baseline in BMI at selected visits is presented in Table 23.

The mean (SD) absolute change from study baseline to Week 96 was 0.70 (1.45) kg/m2.

F/RF Mutation Efficacy Set

Absolute change from baseline in BMI at selected visits is presented in Table 23.

The mean (SD) absolute change from study baseline to Week 96 was 1.84 (2.21) kg/m2.

CHMP comment

A further increase in mean BMI was obtained in all subsets over the course of part B of the OLE study.

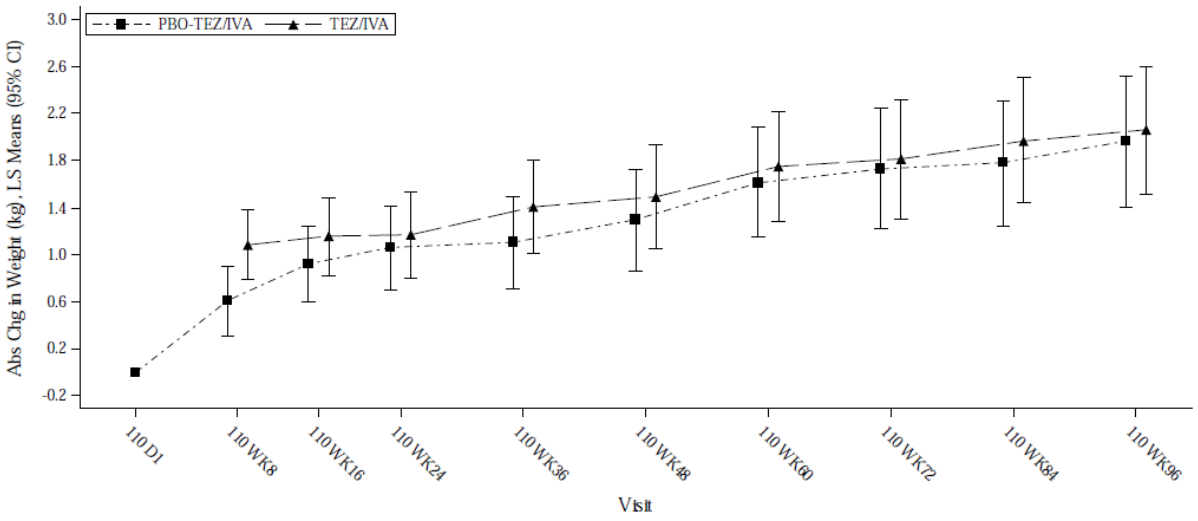
Absolute Change in Weight from Baseline

Part A - 106/110 Efficacy Set: Results from the MMRM analysis of the absolute change from baseline in body weight are shown in Table 21 and **Figure 14**.

In Study 106, the LS mean absolute change from baseline in body weight at Week 24 was 0.7 kg in the TEZ/IVA group, and there were also increases in the LS mean absolute change from baseline in body weight at Week 96 in Part A (TEZ/IVA-TEZ/IVA group) (2.1 (0.3) kg).

In Study 106, the LS mean absolute change from baseline in body weight at Week 24 was 0.6 kg in the placebo group, and there were also increases in the LS mean absolute change from baseline in body weight at Week 96 in Part A (PBO-TEZ/IVA group) (2.0 (0.3) kg).

Figure 14 MMRM Analysis of Absolute Change from Baseline in Weight (kg) at Each Visit - 110 Efficacy Analysis Period (106/110 Efficacy Set)



- Treatment group assignment is PBO-TEZ/IVA or TEZ/IVA for subjects randomized to Placebo or TEZ/IVA in Study 106 respectively.
- The following mixed model for repeated measures was used: sex, age at screening (<18 vs ≥18 years), parent study baseline weight, treatment, Visit, treatment*visit, parent study baseline weight*visit as fixed effects. Covariance Structure=UN, DF=Kenward-Roger. If the model fails to converge due to the UN covariance assumption, a CS covariance structure will be used.
- Covariance Structure=UN is used.
- Baseline is defined as the most recent non-missing measurement collected prior to the first dose of study drug in Study 106 for the subjects randomized to the active treatment arm in Study 106, and as the most recent non-missing measurement collected prior to the first dose of study drug in Study 110 for the subjects randomized to the placebo treatment arm in Study 106.
- Post-baseline visits in Study 106 are excluded in this model.

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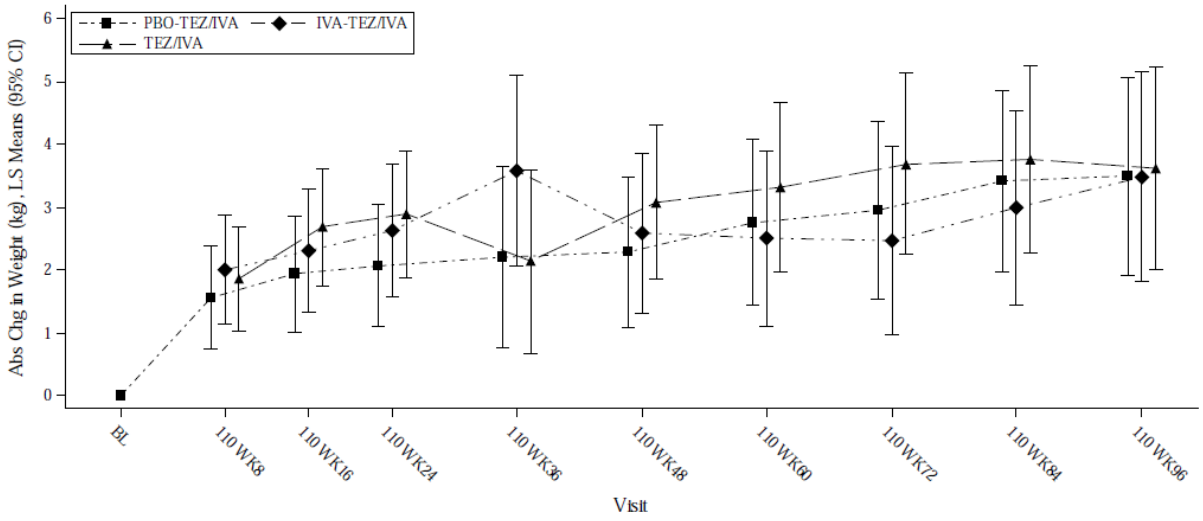
Part A - 108/110 Efficacy Set: Results from the MMRM analysis of the absolute change from baseline in body weight are shown in Table 22 and Figure 15.

Mean body weight increased in the TEZ/IVA group during Study 108: The mean (SD) absolute change at Week 8 was 1.0 (2.8) kg. There were also increases in body weight in the TEZ/IVA-TEZ/IVA group at Week 96 of Part A (3.6 (0.8) kg).

Mean body weight increased in the placebo group during Study 108: The mean (SD) absolute change at Week 8 was 0.6 (2.4) kg. There were also increases in body weight in the PBO-TEZ/IVA group at Week 96 in Part A (during TEZ/IVA treatment) (3.5 (0.8) kg).

Mean body weight increased in the IVA group during Study 108: The mean (SD) absolute change at Week 8 was 1.4 (2.4) kg. There were additional increases in body weight in the IVA-TEZ/IVA group at Week 96 in Part A (during TEZ/IVA treatment) (3.5 (0.8) kg).

Figure 15 MMRM Analysis of Absolute Change from Baseline in Weight (kg) at Each Visit - 110 Efficacy Analysis Period (108/110 Efficacy Set)



- Treatment group assignment is PBO-TEZ/IVA, IVA-TEZ/IVA or TEZ/IVA for subjects randomized to Placebo, IVA or TEZ/IVA in Period 2 of Study 108 respectively.
- The following mixed model for repeated measures was used: treatment, visit, treatment*visit and parent study baseline weight as fixed effects. Covariance Structure=UN, DF=Kenward-Roger. If the model fails to converge due to the UN covariance assumption, a CS covariance structure will be used.
- Covariance Structure=UN is used.
- Baseline (BL) is defined as the most recent non-missing measurement collected prior to the first dose of study drug in Study 108.
- Post-baseline visits in Study 108 are excluded in this model.

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Part A - 103/110 Efficacy Set: At Week 96, the mean (SD) absolute change in weight from baseline was 4.0 (5.0) kg (n = 22).

Part A - 111/110 Efficacy Set: At Week 96, the mean (SD) absolute change in weight from baseline was 4.2 (5.7) kg in the PBO-TEZ/IVA group (n = 5) and 0.6 (2.6) kg in the TEZ/IVA-TEZ/IVA group (n = 14).

CHMP comment

In line with results for BMI, a similar increase in body weight was seen in all subsets.

Absolute Change from Baseline in BMI Z-score, Weight Z-score, and Height Z-score

Part A - 106/110 Efficacy Set: The results from the MMRM analysis of the absolute change from baseline in BMI z-score, weight z-score, and height z-score at Week 96 for subjects <20 years of age at screening are shown in

Table **21** and **Table 30** and plotted by visit in Figure 16, Figure 17 and Figure 18 respectively.

Table 30 Summary of MMRM Analysis of Absolute Changes From Baseline at Week 96 in BMI Z-score, Weight Z-score, and Height Z-score, 106/110 ES, Subjects <20 Years of Age at Screening

	PBO-TEZ/IVA (N= 231)	TEZ/IVA-TEZ/IVA[a] (N = 228)
BMI *z*-score		
n	44	49
LS mean (95% CI)	0.10 (-0.04, 0.25)	-0.14 (-0.28, 0.00)
Weight *z*-score		
n	44	49
LS mean (95% CI)	0.07 (-0.06, 0.20)	-0.06 (-0.19, 0.07)
Height *z*-score		
n	42	49
LS mean (95% CI)	0.01 (-0.08, 0.11)	0.13 (0.04, 0.22)

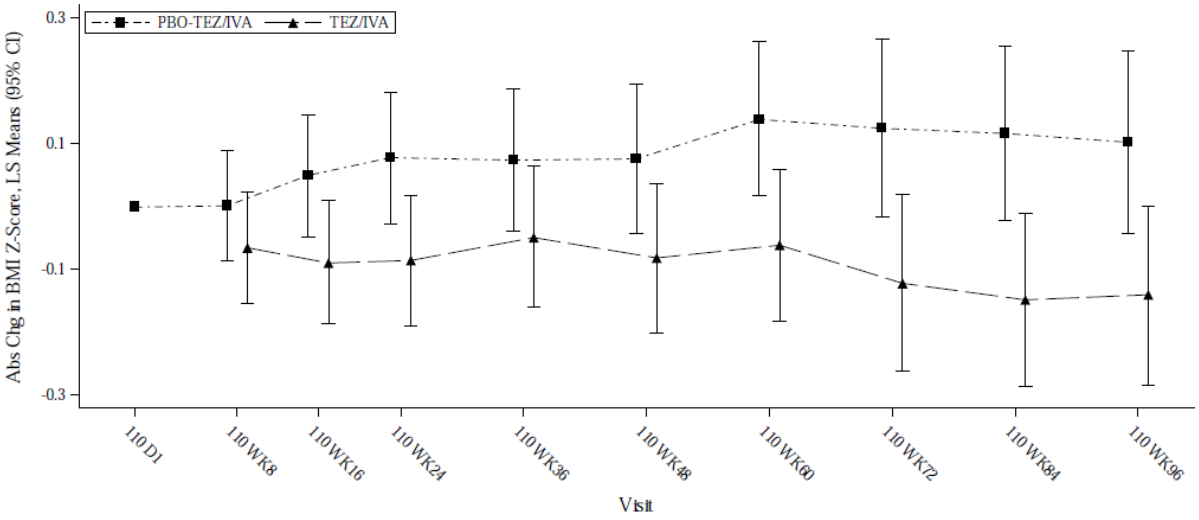
Sources: Table 14.2.3.2.1, Table 14.2.5.2.1, and Table 14.2.6.2.1

BMI: body mass index; ES: Efficacy Set; IVA: ivacaftor; LS mean: least squares mean; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; PBO: placebo; TEZ: tezacaftor

Notes: The following MMRM was used: sex, age at screening (<18 versus ≥18 years of age), parent study baseline *z*-score, treatment, visit, treatment × visit, and parent study baseline *z*-score × visit as fixed effects. An unstructured covariance structure was used to model the within-subject errors. A Kenward-Roger approximation was used for the denominator degrees of freedom. Summaries included z-score records at post-baseline visits up through 240 months of age (or 240.5 months of age for BMI z-scores).

[a] TEZ/IVA-TEZ/IVA treatment group corresponds to TEZ/IVA treatment group in source tables.

Figure 16 MMRM Analysis of Absolute Change from Baseline in BMI Z-Score at Each Visit - 110 Efficacy Analysis Period (106/110 Efficacy Set)



- Treatment group assignment is PBO-TEZ/IVA or TEZ/IVA for subjects randomized to Placebo or TEZ/IVA in Study 106 respectively.
- The following mixed model for repeated measures was used: sex, age at screening (<18 vs ≥18 years), parent study baseline BMI Z-score, treatment, Visit, treatment*visit, parent study baseline BMI Z-score *visit as fixed effects. Covariance Structure=UN, DF=Kenward-Roger. If the model fails to converge due to the UN covariance assumption, a CS covariance structure will be used.
- Covariance Structure=UN is used.- Baseline is defined as the most recent non-missing measurement collected prior to the first dose of study drug in Study 106 for the subjects randomized to the active treatment arm in Study 106, and as the most recent non-missing measurement collected prior to the first dose of study drug in Study 110 for the subjects randomized to the placebo treatment arm in Study 106.
- Post-baseline visits in Study 106 are excluded in this model.
- This summary includes z-score records at post-baseline visits up through 20 years (240.5 months) of age

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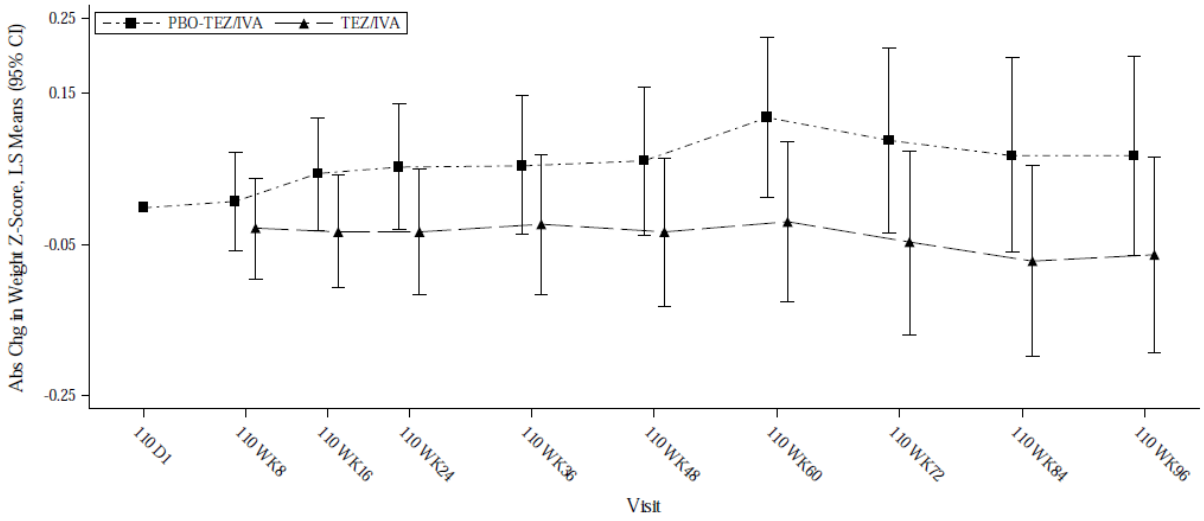
Figure 17 MMRM Analysis of Absolute Change from Baseline in Weight Z-Score at Each Visit - 110 Efficacy Analysis Period (106/110 Efficacy Set)



- Treatment group assignment is PBO-TEZ/IVA or TEZ/IVA for subjects randomized to Placebo or TEZ/IVA in Study 106 respectively.
- The following mixed model for repeated measures was used: sex, age at screening (<18 vs ≥18 years), parent study baseline weight Z-score, treatment, Visit, treatment*visit, parent baseline weight Z-score *visit as fixed effects. Covariance Structure=UN, DF=Kenward-Roger. If the model fails to converge due to the UN covariance assumption, a CS covariance structure will be used.
- Covariance Structure=UN is used.
- Baseline is defined as the most recent non-missing measurement collected prior to the first dose of study drug in Study 106 for the subjects randomized to the active treatment arm in Study 106, and as the most recent non-missing measurement collected prior to the first dose of study drug in Study 110 for the subjects randomized to the placebo treatment arm in Study 106.
- Post-baseline visits in Study 106 are excluded in this model.
- This summary includes z-score records at post-baseline visits up through 20 years (240 months) of age.

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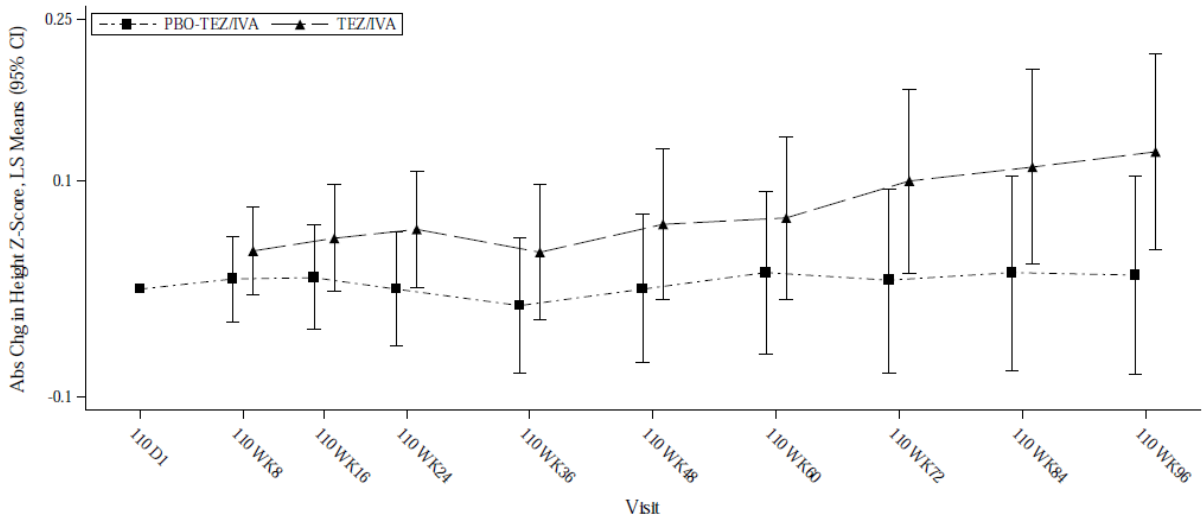
Figure 18 MMRM Analysis of Absolute Change from Baseline in Height Z-Score at Each Visit - 110 Efficacy Analysis Period (106/110 Efficacy Set)



- Treatment group assignment is PBO-TEZ/IVA or TEZ/IVA for subjects randomized to Placebo or TEZ/IVA in Study 106 respectively.
- The following mixed model for repeated measures was used: sex, age at screening (<18 vs ≥18 years), parent study baseline height Z-score, treatment, Visit, treatment*visit, parent baseline height Z-score *visit as fixed effects. Covariance Structure=UN, DF=Kenward-Roger. If the model fails to converge due to the UN covariance assumption, a CS covariance structure will be used.
- Covariance Structure=UN is used.
- Baseline is defined as the most recent non-missing measurement collected prior to the first dose of study drug in Study 106 for the subjects randomized to the active treatment arm in Study 106, and as the most recent non-missing measurement collected prior to the first dose of study drug in Study 110 for the subjects randomized to the placebo treatment arm in Study 106.
- Post-baseline visits in Study 106 are excluded in this model.
- This summary includes z-score records at post-baseline visits up through 20 years (240 months) of age.

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Part A - 108/110 Efficacy Set: The results from the MMRM analysis of the absolute change from baseline in BMI z-score, weight z-score, and height z-score at Week 96 for subjects <20 years of age at screening are shown in **Table 22** and **Table 31** and plotted by visit in **Figure 19**, **Figure 20** and **Figure 21**.

Table 31 Summary of MMRM Analysis of Absolute Changes From Baseline at Week 96 in BMI Z-score, Weight Z-score, and Height Z-score, 108/110 ES, Subjects <20 Years of Age at Screening

	PBO-TEZ/IVA (N = 80)	IVA-TEZ/IVA (N = 70)	TEZ/IVA-TEZ/IVA[a] (N = 76)
BMI *z*-score			
n	13	7	10
LS mean (95% CI)	0.11 (-0.32, 0.54)	0.07 (-0.52, 0.65)	0.30 (-0.21, 0.80)
Weight *z*-score			
n	13	7	10
LS mean (95% CI)	0.15 (-0.25, 0.55)	0.09 (-0.45, 0.62)	0.43 (-0.04, 0.90)
Height *z*-score			
n	13	7	10
LS mean (95% CI)	-0.04 (-0.23, 0.15)	0.20 (-0.05, 0.45)	0.23 (0.00, 0.46)

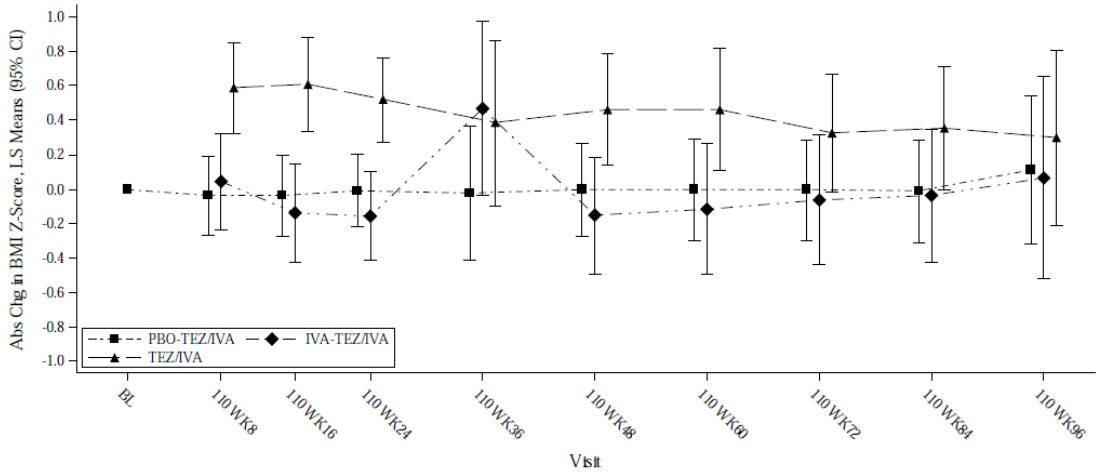
Sources: Table 14.2.3.2.2, Table 14.2.5.2.2, and Table 14.2.6.2.2

BMI: body mass index; ES: Efficacy Set; IVA: ivacaftor; LS mean: least squares mean; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; PBO: placebo; TEZ: tezacaftor

Notes: The following MMRM was used: treatment, visit, treatment × visit, and parent study baseline *z*-score as fixed effects. An unstructured covariance structure was used to model the within-subject errors. A Kenward-Roger approximation was used for the denominator degrees of freedom. Summaries included *z*-score records at post-baseline visits up through 240 months of age (or 240.5 months of age for BMI *z*-scores).

[a] TEZ/IVA-TEZ/IVA treatment group corresponds to TEZ/IVA treatment group in source tables.

Figure 19 MMRM Analysis of Absolute Change from Baseline in BMI Z-Score at Each Visit - 110 Efficacy Analysis Period (108/110 Efficacy Set)



- Treatment group assignment is PBO-TEZ/IVA, IVA-TEZ/IVA or TEZ/IVA for subjects randomized to Placebo, IVA or TEZ/IVA in Period 2 of Study 108 respectively.
- The following mixed model for repeated measures was used: treatment, visit, treatment*visit and parent study baseline BMI Z-score as fixed effects. Covariance Structure=UN, DF=Kenward-Roger. If the model fails to converge due to the UN covariance assumption, a CS covariance structure will be used.
- Covariance Structure=UN is used.
- Baseline (BL) is defined as the most recent non-missing measurement collected prior to the first dose of study drug in Study 108.
- Post-baseline visits in Study 108 are excluded in this model.
- This summary includes z-score records at post-baseline visits up through 20 years (240.5 months) of age.

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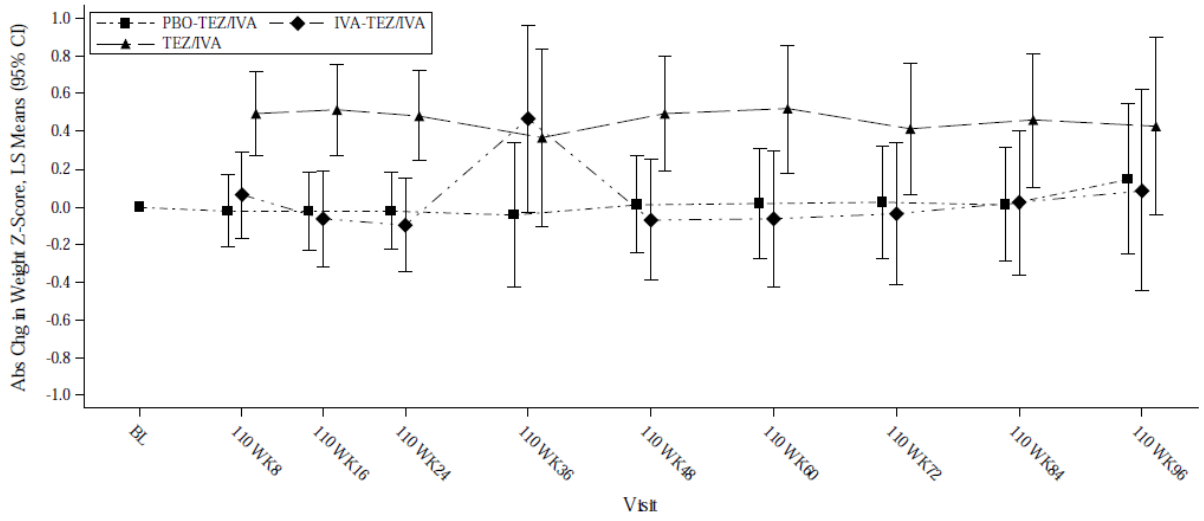
Figure 20 MMRM Analysis of Absolute Change from Baseline in Weight Z-Score at Each Visit - 110 Efficacy Analysis Period (108/110 Efficacy Set)



- Treatment group assignment is PBO-TEZ/IVA, IVA-TEZ/IVA or TEZ/IVA for subjects randomized to Placebo, IVA or TEZ/IVA in Period 2 of Study 108 respectively.
- The following mixed model for repeated measures was used: treatment, visit, treatment*visit and parent study baseline weight Z-score as fixed effects. Covariance Structure=UN, DF=Kenward-Roger. If the model fails to converge due to the UN covariance assumption, a CS covariance structure will be used.
- Covariance Structure=UN is used.
- Baseline (BL) is defined as the most recent non-missing measurement collected prior to the first dose of study drug in Study 108.
- Post-baseline visits in Study 108 are excluded in this model.
- This summary includes z-score records at post-baseline visits up through 20 years (240 months) of age.

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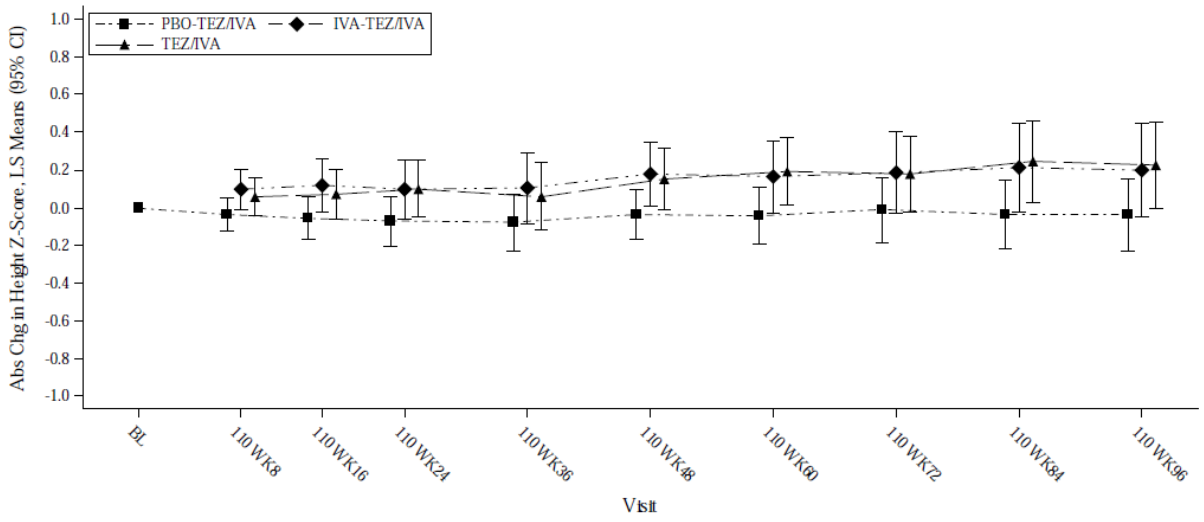
Figure 21 MMRM Analysis of Absolute Change from Baseline in Height Z-Score at Each Visit - 110 Efficacy Analysis Period (108/110 Efficacy Set)



- Treatment group assignment is PBO-TEZ/IVA, IVA-TEZ/IVA or TEZ/IVA for subjects randomized to Placebo, IVA or TEZ/IVA in Period 2 of Study 108 respectively.
- The following mixed model for repeated measures was used: treatment, visit, treatment*visit and parent study baseline height Z-score as fixed effects. Covariance Structure=UN, DF=Kenward-Roger. If the model fails to converge due to the UN covariance assumption, a CS covariance structure will be used.
- Covariance Structure=UN is used.
- Baseline (BL) is defined as the most recent non-missing measurement collected prior to the first dose of study drug in Study 108.
- Post-baseline visits in Study 108 are excluded in this model.
- This summary includes z-score records at post-baseline visits up through 20 years (240 months) of age.

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CHMP comment

In the 106/110 ES the mean absolute change in BMI z-score drops compared to baseline with -0.14 at Week 96 in the TEZ/IVA group, whereas the Weight z-score drops by -0.06. However, as weigh-z score drops while height-z score increased (0.13), the drop in BMI-z score is explained. However, the drop in weight-z score is in line with other results that after a longer treatment with TEZ-IVA the befits seem to decrease. In the PBO-TEZ/IVA group, an overall increase is seen in all three parameters.

In the 108/110 ES, changes in BMI, weight and height z-scores are relatively stable during Part A of the study.

Part B – F/F and F/RF mutation ES:

Absolute change from baseline at selected visits for BMI z-score for subjects <20 years of age at screening is presented in Table 23.

The mean (SD) absolute change from study baseline to Week 96 was -0.03 (0.71).

F/RF Mutation Efficacy Set

Absolute change from baseline at selected visits for BMI z-score for subjects <20 years of age at screening is presented in Table 23.

The mean (SD) absolute change from study baseline to Week 96 was 0.21 (0.46).

CHMP comments

The mean BMI z-score for F/F subjects remains relatively stable over the course of Part B, whereas the mean BMI z-score for F/RF subjects slightly increases.

Absolute change in Brody/CF-CT scores from baseline using LDCT scans (Part B)

With the exception of the hyperinflation subscore, the absolute mean change in Brody CF-CT total score and subscores for subjects who rolled over to Study 110 Part B were numerically higher than the scores reported for subjects enrolled in the TEZ/IVA or placebo groups in Study 112. For example, the mean (SD) total Brody CT-CF Score (SD) at baseline was 41.15 (29.56) and 58.53 (27.53) at Week 72 (mean (SD) absolute change of 17.38 (20.24)); in Study 112 these scores were 38.29 (22.91) for the TEZ/IVA group and 43.68 (33.96) for the placebo group.

Safety results

The primary aim of Study 110 was to evaluate the long-term safety and tolerability.

Safety population

The following safety populations were defined:

- **Part A - Safety Set**: all subjects who have received at least 1 dose of study drug in Part A irrespective of their genotype.
- **Part B - Safety Set**: all subjects who received at least 1 dose of study drug in Study 110 Part B.

- **Part C - Safety Set**: all subjects who received at least 1 dose of study drug in Study 110 Part C.

CHMP comments

In addition, Safety sets In the original MAA were defined as follows:

- Phase 3-controlled Safety Set (PC-SS): safety data derived from pooled analyses of Studies 106, 107 and 108. This set included 496 patients (in the TEZ/IVA group) with a mean treatment duration of 16.2 weeks.
- Long-term Safety Set (LT-SS): safety data derived from all patients with ≥48 weeks of TEZ/IVA exposure during the parent study and/or Study 110. This set included 326 patients with a mean exposure of 69.0 weeks.

These sets will be used to compare the safety observed currently.

Exposure

The Safety Set of **Part A** consisted of 1042 subjects. The mean exposure to TEZ/IVA was 76.0 weeks (range: 0.1 to 99.3 weeks) (Table 32). Excluding subjects from Studies 107 and 109, the mean exposure was 90.2 weeks (range: 0.1 to 99.3 weeks).

All data in **Table 32** refer to TEZ/IVA exposure only during the rollover study and not during the parent study.

Table 32 Summary of Exposure for Part A (Safety Set)

Category	Total N = 1042 n (%)
Total exposure (patient years)[a]	1518.0
Exposure duration (weeks)[b]	
n	1042
Mean (SD)	76.0 (31.8)
Median	95.9
Min, max	0.1, 99.3
Exposure duration by interval (weeks), n (%)	
>0 to ≤2	2 (0.2)
>2 to ≤8	9 (0.9)
>8 to ≤16	55 (5.3)
>16 to ≤24	101 (9.7)
>24 to ≤36	58 (5.6)
>36 to ≤48	28 (2.7)
>48 to ≤60	25 (2.4)
>60 to ≤72	21 (2.0)
>72 to ≤84	22 (2.1)
>84 to ≤96	421 (40.4)
>96	300 (28.8)

Source: Table 14.1.5
max: maximum value; min: minimum value; n: size of subsample; N: total sample size

[a] Patient years = sum (all subjects' duration of study drug exposure (days)/365.25).

[b] Duration of study drug exposure (weeks) = (last dose date - first dose date + 1)/7, regardless of any interruption between the first and last dose, excluding time spent in another qualified Vertex study.

The safety set of **Part B** consisted of 463 subjects, including 347 with an F/F mutation and 106 with an F/RF mutation. The mean exposure of all subjects to TEZ/IVA was 71.0 weeks (range: 0.1 to 98.1 weeks) (**Table 33**).

Table 33 Summary of Exposure for Part B (Safety Set)

	Total N = 463
Exposure duration (weeks)[a]	
n	463
Mean (SD)	71.0 (31.6)
Median	86.4
Min, max	0.1, 98.1
Exposure duration category (weeks), n (%)	
>0 to ≤12	31 (6.7)
>12 to ≤24	39 (8.4)
>24 to ≤36	41 (8.9)
>36 to ≤48	17 (3.7)
>48 to ≤60	17 (3.7)
>60 to ≤72	16 (3.5)
>72 to ≤84	56 (12.1)
>84 to ≤96	168 (36.3)
>96	78 (16.8)

Source: Table 14.1.5b

Max: maximum value; min: minimum value; n: size of subsample; N: total sample size

[a] Duration of study drug exposure (weeks) = (last dose date in Part B - first dose date in Part B + 1) / 7, regardless of any study drug interruption, excluding the time between the last dose before the discontinuation from Part B and the first dose after re-enrollment in Part B.

The safety set of **Part C** consisted of 204 subjects. The mean exposure of all subjects to TEZ/IVA was 71.0 weeks (range: 2.3 to 152.6 weeks) (**Table 34**).

Table 34 Summary of Exposure for Part C (Safety Set)

Category	Total N = 204
Exposure duration (weeks)	
n	204
Mean (SD)	71.0 (32.8)
Median	73.1
Min, max	2.3, 152.6
Exposure duration category (weeks), n (%)	
>0 to ≤12	12 (5.9)
>12 to ≤24	13 (6.4)
>24 to ≤36	15 (7.4)
>36 to ≤48	9 (4.4)
>48 to ≤60	12 (5.9)
>60 to ≤72	30 (14.7)
>72 to ≤84	37 (18.1)
>84 to ≤96	42 (20.6)
>96 to ≤108	13 (6.4)
>108 to ≤120	12 (5.9)
>120 to ≤132	4 (2.0)
>132 to ≤144	3 (1.5)
>144 to ≤156	2 (1.0)
>156 to ≤168	0
>168 to ≤180	0
>180 to ≤192	0
>192	0

Source: Table 14.1.5c
max: maximum value; min: minimum value; n: size of subsample; N: total sample size
Note: Duration of study drug exposure (weeks) = (last dose date in Part C – first dose date in Part C + 1) / 7, regardless of any study drug interruption.

CHMP comment

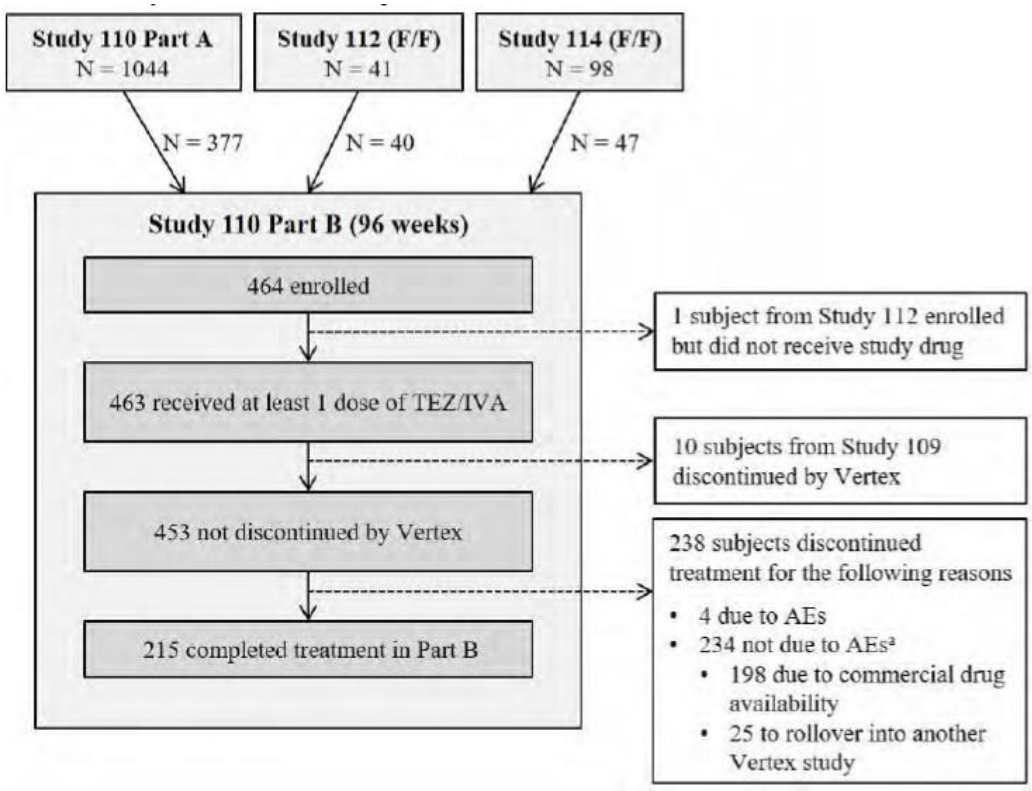
Due to the design (Subjects from Study 112 and Study 114 were included only in part B and C) and the early discontinuation of the subjects from Study 107 and Study 109, subjects had a different exposure. Therefore, the presentation of the different parts instead of pooling them together is agreed.

In **Part A**, the mean exposure to TEZ/IVA was 90.2 weeks excluding subjects from Studies 107 and 109, indicating that the compliance in Part A was high.

In **Part B**, the mean exposure of all subjects to TEZ/IVA was 71.0 weeks, lower than in Part A, that was caused by the high number of discontinuations (248 subjects) mainly because of commercial drug availability (198 subjects). (Figure 22)

Figure 22

*Figure **3 Study 110 Part B Subjects***



Source: Table 14.1.1b and Listing 16.2.1b

AE: adverse event; F/F: homozygous for *F508del-CFTR*; IVA: ivacaftor; N: total sample size; TEZ: tezacaftor

Notes: Values (N) inside parent study box indicate the All Subjects Set for the parent study. Values next to arrows indicate the number of subjects from each parent study or Study 110 Part A who rolled over into Part B.

[a] Of the 234 subjects who discontinued treatment for reasons other than AEs, the reasons for discontinuation were as follows: 198 subjects due to commercial drug availability, 26 subjects due to other, 8 subjects due to subject refusing further dosing (not due to AE), 1 subject due to physician decision, and 1 subject due to partner pregnancy (Table 10-10).

CHMP comment

In **Part C,** the mean exposure of all subjects to TEZ/IVA was 71.0 weeks (range: 2.3 to 152.6 weeks), indicating that no subjects finalised study treatment. The number of discontinuations (202 subjects), mainly because of commercial drug availability (175 subjects), was high again.

Adverse events

Table 35 summarises the percentage of subjects with AEs in **Part A**.

In Study 110 **Part A**, 995 (95.5%) subjects had at least 1 AE and 270 (25.9%) subjects had at least 1 AE that was considered (possibly) related to study drug. The majority of subjects had AEs that were mild or moderate in severity, whereas 191 (18.3%) had severe AEs, and 3 (0.3%) had life-threatening AEs.

A total of 351 (33.7%) subjects had at least 1 Serious AE (SAE) and 24 (2.3%) subjects had SAEs considered (possibly) related to study drug. There were no AEs that led to death.

Overall, 22 (2.1%) subjects had AEs leading to treatment discontinuation and 90 (8.6%) subjects had AEs leading to treatment interruption.

Exposure-adjusted AE and SAE rates were generally comparable to, or lower than, the exposure-adjusted rates for the TEZ/IVA group in parent Study 106 (F/F genotype).

Table 35 Overview of AEs for Part A (Safety Set)

Category	Total N = 1042 n (%)
Total exposure in 100 patient years (events/100 patient years[a])	15.18
Number of AEs (total)	10041
Subjects with any AEs	995 (95.5)
Subjects with AEs by strongest relationship	
Related	25 (2.4)
Possibly related	245 (23.5)
Unlikely related	286 (27.4)
Not related	439 (42.1)
Subjects with related AEs[b]	270 (25.9)
Subjects with AEs by maximum severity	
Mild	249 (23.9)
Moderate	552 (53.0)
Severe	191 (18.3)
Life-threatening	3 (0.3)
Subjects with Grade 3/4 AEs	194 (18.6)
Subjects with SAEs	351 (33.7)
Subjects with related SAEs[b]	24 (2.3)
Subjects with AEs leading to treatment discontinuation	22 (2.1)[c]
Subjects with AEs leading to treatment interruption	90 (8.6)
Subjects with AEs leading to death	0[d]

Source: Table 14.3.1.1
AE: adverse event; n: size of subsample; N: total sample size; SAE: serious adverse event; TE: treatment-emergent
Notes: When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percentage of subjects, a subject with multiple events within a category was counted only once in that category.
[a] Events/100 patient years: number of events per 100 patient years = number of events/(total exposure in days/(365.25 × 100)).
[b] Related AEs and related SAEs includes related, possibly related, and missing categories.
[c] In total, 24 subjects discontinued due to an AE (Table 10-1); 2 of these subjects discontinued due to AEs that were not TE.
[d] There were no TE deaths; however, 2 deaths occurred after the TE Period. Only 1 death was captured in the database; the other occurred after the study site was locked in the database (Section 12.1.3.1.1).

Table 36 summarizes the percentage of subjects with AEs in **Part B**.

In **Part B**, 427 (92.2%) subjects had at least 1 AE and 46 (9.9%) subjects had at least 1 AE that was considered (possibly) related to study drug. The majority of subjects had AEs that were mild or moderate in severity, whereas 62 (13.4%) had severe AEs. There were no life-threatening AEs.

A total of 136 (29.4%) subjects had at least 1 SAE and 4 (0.9%) subjects had SAEs considered (possibly) related to study drug. There were no AEs that led to death.

Four (0.9%) subjects had AEs leading to treatment discontinuation and 17 (3.7%) subjects had AEs leading to treatment interruption.

Table 36 Overview of AEs for Part B (Safety Set)

	Total N = 463 n (%)
Total exposure in 100 patient-years (events/100 patient years[a])	6.34
Number of AEs (Total)	3363
Subjects with any AEs	427 (92.2)
Subjects with AEs by strongest relationship[b]	
Not related	267 (57.7)
Unlikely related	114 (24.6)
Possibly related	36 (7.8)
Related	10 (2.2)
Subjects with AEs by maximum severity	
Mild	129 (27.9)
Moderate	236 (51.0)
Severe	62 (13.4)
Life-Threatening	0
Subjects with AE leading to treatment discontinuation	4 (0.9)
Subjects with AE leading to treatment interruption	17 (3.7)
Subjects with grade 3/4 AEs[c]	62 (13.4)
Subjects with related AEs[d]	46 (9.9)
Subjects with serious AEs	136 (29.4)
Subjects with related serious AEs[d]	4 (0.9)
Subjects with AE leading to death	0

Source: Table 14.3.1.1.1b

AE: adverse event; n: size of subsample; N: total sample size; TE: treatment-emergent

Note: When summarizing number of events, a subject with multiple events within a category is counted multiple times in that category. When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category. For the event rate all distinct events are counted. Exposure-adjusted number of events column uses all events in the corresponding category, regardless of the strongest relationship or maximum severity. If subjects only have one event which has missing severity, then the subject is summarized in the "Missing" category.

[a] Event Rate per 100 patient-years: number of events per 100 patient years = number of events/(total duration of TE Period in days/(365.25 × 100)).

[b] An AE with relationship missing is counted as Related.

[c] Subjects with grade 3/4 AEs include the 'Severe' and 'Life-Threatening' categories.

[d] When summarizing number of subjects with related AEs and related serious AEs, AEs with relationship of related, possibly related, and missing are counted.

Table 37 summarises the percentage of subjects with AEs in **Part C**.

In **Part C**, 168 (82.4%) subjects had at least 1 AE and 7 (3.4%) subjects had at least 1 AE that was considered (possibly) related to study drug. The majority of subjects had AEs that were mild or moderate in severity, whereas 24 (11.8%) had severe AEs. Two (1.0%) subjects had life-threatening AEs (one renal impairment and one pneumonia).

There were 44 (21.6%) subjects with at least 1 SAE, but no SAE was considered (possibly) related to study drug. There were no AEs that led to death.

One (0.5%) subjects had AE leading to treatment discontinuation and 2 (1.0%) subjects had AEs leading to treatment interruption.

Table 37 Overview of AEs for Part C (Safety Set)

	Total N = 204 n (%)
Number of AEs (Total)	1246
Subjects with any AEs	168 (82.4)
Subjects with AEs by strongest relationship[a]	
Not related	136 (66.7)
Unlikely related	25 (12.3)
Possibly related	5 (2.5)
Related	2 (1.0)
Subjects with AEs by maximum severity	
Mild	47 (23.0)
Moderate	95 (46.6)
Severe	24 (11.8)
Life-threatening	2 (1.0)
Subjects with AE leading to treatment discontinuation	1 (0.5)
Subjects with AE leading to treatment interruption	2 (1.0)
Subjects with Grade 3/4 AEs[b]	26 (12.7)
Subjects with related AEs[c]	7 (3.4)
Subjects with serious AEs	44 (21.6)
Subjects with related serious AEs[c]	0
Subjects with AE leading to death	0

Source: Table 14.3.1.1.1c

AE: adverse event; n: size of subsample; N: total sample size; TE: treatment-emergent

Note: When summarizing number of events, a subject with multiple events within a category is counted multiple times in that category. When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category. If subjects only have one event which has missing severity, then the subject is summarized in the "Missing" category.

[a] An AE with relationship missing is counted as Related.

[b] Subjects with Grade 3/4 AEs include the 'Severe' and 'Life-threatening' categories.

[c] When summarizing number of subjects with related AEs and related serious AEs, AEs with relationship of related, possibly related, and missing are counted.

CHMP comment

The number of subjects with AEs (including Grade 3/4 AEs, SAEs and related SAEs) decreased with each part of the study, i.e., most AEs were seen in Part A, which is likely a result of more patients discontinuing the study in Parts B and C.

In general, frequencies in Part A are higher compared with those in the parent studies. However, most parent studies were of short duration. In the MAA AEs up to 95.1% of the subjects were observed in the LT-SS, which is comparable to the 95.5% in Part A. Likewise, in the LT-SS, 27.9% had related AEs, 29.1% an SAE and 1.8% a related SAE. Frequencies in the Part A Safety Set were slightly higher, but overall comparable (25.9%, 33.7%, and 2.3%, respectively).

Common Adverse Events

Table 38 shows all AEs that occurred in at least 10% of subjects in **Part A**, summarised by SOC and PT. Most common AEs (occurring in ≥15%) were infective pulmonary exacerbation of CF (52.7%), cough (35.9%), nasopharyngitis (21.8%), sputum increased (21.5%), and haemoptysis (17.2%).

Table 38 AEs Occurring in At Least 10% of Subjects Overall by PT Summarised by SOC and PT in Part A (Safety Set)

System Organ Class Preferred Term	Total N = 1042 n (%)
Any AEs	995 (95.5)
Infections and infestations	845 (81.1)
Infective pulmonary exacerbation of CF	549 (52.7)
Nasopharyngitis	227 (21.8)
Upper respiratory tract infection	135 (13.0)
Respiratory, thoracic and mediastinal disorders	682 (65.5)
Cough	374 (35.9)
Sputum increased	224 (21.5)
Haemoptysis	179 (17.2)
Oropharyngeal pain	136 (13.1)
Gastrointestinal disorders	441 (42.3)
Abdominal pain	107 (10.3)
Nausea	107 (10.3)
Diarrhoea	105 (10.1)
General disorders and administration site conditions	298 (28.6)
Pyrexia	136 (13.1)
Nervous system disorders	260 (25.0)
Headache	147 (14.1)

Source: Table 14.3.1.2

AE: adverse event; CF: cystic fibrosis; MedDRA: Medical Dictionary for Regulatory Activities; n: size of subsample; N: total sample size; PT: Preferred Term; SOC: System Organ Class

Notes: AEs were coded using MedDRA Version 22.0. A subject with multiple events within a category was counted only once in that category.

AEs that occurred in at least 5% of subjects in **Part B** are shown in Table 39. Most common AEs (occurring in ≥15%) were infective pulmonary exacerbation of CF (51.6%), cough (24.2%), and nasopharyngitis (19.0%).

Table 39 AEs Occurring in At Least 5% of Subjects Overall by PT Summarized by SOC and PT in Part B (Safety Set)

System Organ Class Preferred Term	Total N = 463 n (%)
Subjects with any AEs	427 (92.2)
Infections and Infestations	372 (80.3)
Infective pulmonary exacerbation of CF	239 (51.6)
Nasopharyngitis	88 (19.0)
Upper respiratory tract infection	43 (9.3)
Rhinitis	28 (6.0)
Influenza	27 (5.8)
Respiratory, thoracic and mediastinal disorders	247 (53.3)
Cough	112 (24.2)
Haemoptysis	68 (14.7)
Sputum increased	46 (9.9)
Oropharyngeal pain	39 (8.4)
Dyspnoea	30 (6.5)
Gastrointestinal disorders	143 (30.9)
Abdominal pain	35 (7.6)
Diarrhoea	27 (5.8)
Abdominal pain upper	26 (5.6)
Constipation	26 (5.6)
General disorders and administration site conditions	101 (21.8)
Pyrexia	40 (8.6)
Fatigue	23 (5.0)
Investigations	99 (21.4)
Bacterial test positive	28 (6.0)
Musculoskeletal and connective tissue disorders	90 (19.4)
Arthralgia	29 (6.3)
Back pain	23 (5.0)
Nervous system disorders	72 (15.6)
Headache	47 (10.2)

Source: Table 14.3.1.1.2b

AE: adverse event; CF: cystic fibrosis; MedDRA: Medical Dictionary for Regulatory Activities; n: size of subsample; N: total sample size; PT: Preferred Term; SOC: System Organ Class

Note: AEs were coded using MedDRA Version 23.1. A subject with multiple events within a category was counted only once in that category. Table is sorted in descending order of frequency by SOC, and by PT within each SOC.

AEs that occurred in at least 5% of subjects in **Part C** are shown in Table 40. Only infective pulmonary exacerbation of CF occurred in ≥15% of subjects (45.1%).

Table 40 Summary of AEs Occurring in ≥5% of Subjects Overall by PT in Part C (Safety Set)

System Organ Class Preferred Term	Total N = 204 n (%)
Subjects with any AEs	**168 (82.4)**
Infections and infestations	133 (65.2)
Infective PEx of CF	92 (45.1)
COVID-19	19 (9.3)
Nasopharyngitis	13 (6.4)
Upper respiratory tract infection	12 (5.9)
Respiratory, thoracic and mediastinal disorders	86 (42.2)
Cough	29 (14.2)
Haemoptysis	26 (12.7)
Sputum increased	13 (6.4)
Musculoskeletal and connective tissue disorders	43 (21.1)
Back pain	11 (5.4)
General disorders and administration site conditions	42 (20.6)
Pyrexia	20 (9.8)
Investigations	32 (15.7)
Bacterial test positive	11 (5.4)
Nervous system disorders	28 (13.7)
Headache	20 (9.8)
Immune system disorders	26 (12.7)
Immunisation reaction	15 (7.4)

Source: Table 14.3.1.1.2c

AE: adverse event; CF: cystic fibrosis; COVID-19: coronavirus disease; MedDRA: Medical Dictionary for Regulatory Activities; n: size of subsample; N: total sample size; PEx: pulmonary exacerbation; PT: Preferred Term; SOC: System Organ Class

Note: AEs were coded using MedDRA Version 25.1. A subject with multiple events within a category (any, SOC, or PT) was counted only once in that category. Table is sorted in descending order of frequency by SOC, and by PT within each SOC.

CHMP comment

AEs occurring in ≥5% (Part B and Part C) or 10% of subjects (Part A) are in line with known AEs of TEZ/IVA, common manifestations of CF disease, or common illnesses in CF subjects 12 years of age and older. The frequencies are generally somewhat lower in Part B and Part C compared with Part A. For a fair comparison, events/100 patient years are helpful. A requested table presenting the PC-SS, safety set Part A, safety set Part B and safety set Part C in one table for AEs occurring in ≥5 % of subjects demonstrated that the incidences of the TAES are generally comparable between the safety sets. No new safety signals could be detected.

Furthermore, the number of immunisation reactions in Part C are remarkably high (7.4%), but these were all considered not related or unlikely related to study drug. Out of the 15 subjects with immunisation reactions, 13 can be contributed to vaccination COVID-19 vaccine and 1 to pneumococcal vaccine and 1 to an unspecified vaccine. The described terms of the immunisation reaction are in line with described AEs of the vaccine.

Severity of Adverse Events

In **Part A**, the majority of subjects had AEs that were mild (23.9%) or moderate (53.0%) in severity, whereas 191 (18.3%) had severe AEs, and 3 (0.3%) had life-threatening AEs. Two life-threatening AEs were suicide attempts and 1 subjects had 1 AE each of urine amphetamine positive, hyperglycaemia, hypokalaemia, hypomagnesemia, and toxic encephalopathy, which were all considered not related to study drug.

A total of 194 (18.6%) subjects had any Grade 3/4 AEs. The most common Grade 3/4 AEs by PT were infective Pex of CF (8.5%), creatine phosphokinase (CPK) increased (1.1%), and AST increased (1.0%). No other Grade 3/4 AEs occurred in ≥1% of subjects.

The majority of subjects in **Part B** had AEs that were mild (27.9%) or moderate (51.0%) in severity; 62 (13.4%) subjects had severe AEs. There were no life-threatening AEs.

A total of 62 (13.4%) subjects had any Grade 3/4 AEs. The most common Grade 3/4 AE by PT was infective Pex of CF (9.3%). No other Grade 3/4 AEs occurred in ≥1% of subjects.

The majority of AEs in **Part C** were mild (23.0%) or moderate (46.6%) in severity; 24 (11.8%) subjects had severe AEs and there were two (1.0%) with life-threatening AEs (both were also considered SAEs).

A total of 26 (12.7%) subjects had any Grade 3/4 AEs. The most common Grade 3/4 AEs by PT (occurring in ≥1% subjects) were infective Pex of CF (4.9%), haemoptysis (2.9%), and depression (1.0%).

CHMP comments

The Grade 3/4 AEs are presented in separate, extensive tables.

A few Grade 3/4 AEs were higher in the safety sets of Study 110 compared to the PC-SS. These concern pneumonia, haemoptysis, anaphylactic reaction, anxiety, depression, suicide attempt and deep vein thrombosis. Haemoptysis is a common symptom in CF. An overview of the safety data of pneumonia did not indicate a clear relationship between pneumonia and the use of TEZ/IVA. The anaphylactic reactions were due to insect bite (bee) and walnuts respectively. Both cases were not related to the treatment. Both cases of deep vein thrombosis were considered by the investigator as not related. Both resolved completely and the dose was not changed.

No further action is required.

Relationship of Adverse Events

Overall, 270 (25.9%) subjects of **Part A** had AEs considered by the investigator to be related or possibly related to study drug.

The most common related and/or possibly related AEs (occurring in ≥1% of subjects total) were blood CPK increased (4.4%), cough (3.4%), AST increased (3.1%), ALT increased (2.8%), sputum increased (2.7%), infective PEx of CF (2.5%), GGT increased (1.5%), abdominal pain (1.5%), headache (1.4%), diarrhoea (1.3%), haemoptysis (1.2%), constipation (1.2%), fatigue (1.2%), and respiration abnormal (1.0%).

In **Part B**, 46 (9.9%) subjects had AEs considered (possibly) related, with headache (1.3%) and infective PEx of CF (1.1%) being the most common (occurring in ≥1% of subjects total).

In **Part C**, 7 (3.4%) subjects had AEs considered (possibly) related. All AEs considered related and/or possibly related occurred in 1 (0.5%) subject each; these were drop attacks, headache, distal intestinal obstruction syndrome (DIOS), infective PEx of CF, depression, rhinorrhoea, and acne.

CHMP comments

At a glance, it appears that the frequency of related AEs decreases during the course of Study 110. Overall, there are no new related TEAEs with occurrence in ≥2% subjects in Study 110 compared to PC-SS. In general, the related TEAEs with occurrence in ≥2% subjects have a lower incidence in Study 110 compared to PC-SS. No further action is required.

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

In **Part A**, there were no deaths during the TE period. However, there were 2 deaths after treatment. One was due to intensive care unit acquired weakness, followed by influenza, acute respiratory failure, acute kidney injury, and shock. The other one was due to oesophageal carcinoma. Both were considered unrelated to study drug.

There were 351 (33.7%) subjects who had at least 1 SAE are presented in **Table 41**. Related SAEs occurred in 24 of these 351 subjects, of which infective PEx of CF (0.5%), blood CPK increased (0.4%), ALT increased (0.3%), and AST increased (0.3%) occurred in >1 subject.

Table 41 SAEs Occurring in At Least 1% of Subjects Overall by SOC and PT for Part A, (Safety Set)

System Organ Class Preferred Term	Total N = 1042 n (%)
Subjects with any SAEs, n (%)	351 (33.7)
Infections and infestations	269 (25.8)
Infective PEx of CF	243 (23.3)
Gastrointestinal disorders	44 (4.2)
Distal intestinal obstruction syndrome	12 (1.2)
Respiratory, thoracic and mediastinal disorders	35 (3.4)
Haemoptysis	25 (2.4)

Source: Table 14.3.2.2
AE: adverse event; CF: cystic fibrosis; MedDRA: Medical Dictionary for Regulatory Activities; n: size of subsample; N: total sample size; PEx: pulmonary exacerbation; PT: preferred term; SAE: serious adverse event; SOC: system organ class
Notes: AEs were coded using MedDRA Version 22.0. A subject with multiple events within a category was counted only once in that category.

There were no deaths in **Part B**. Overall, 136 (29.4%) subjects had SAEs. SAEs that occurred in >1% of subjects were Infective PEx of CF (103 subjects [22.2%]) and haemoptysis (10 subjects [2.2%]). Of these SAEs, four were considered related. Only urticaria occurred in more than one subject (2 subjects [0.4%]).

Table 42 SAEs Occurring in >1% of Subjects Overall by PT Summarized by SOC and PT for Part B, Safety Set

System Organ Class Preferred Term	Total N = 463 n (%)
Subjects with any SAEs	136 (29.4)
Infections and infestations	111 (24.0)
Infective PEx of CF	103 (22.2)
Respiratory, thoracic and mediastinal disorders	15 (3.2)
Haemoptysis	10 (2.2)

Source: Table 14.3.2.1.1b
AE: adverse event; CF: cystic fibrosis; MedDRA: Medical Dictionary for Regulatory Activities; n: size of subsample; N: total sample size; PEx: pulmonary exacerbation; PT: preferred term; SAE: serious adverse event; SOC: system organ class
Note: AEs were coded using MedDRA Version 23.1. A subject with multiple events within a category (Any, SOC, or PT) was counted only once in that category.

There were also no deaths in **Part C**. However, 44 (21.6%) subjects had SAEs. SAEs that occurred in >1% of subjects were infective PEx of CF (13.7%), haemoptysis (2.9%), and drug hypersensitivity (1.5%). The majority of SAEs had an outcome of recovered/resolved and were not considered related to study drug.

Table 43 SAEs Occurring in >1% of Subjects Overall by PT Summarized by SOC and PT (Part C), Safety Set

System Organ Class Preferred Term	Total N = 204 n (%)
Subjects with any SAEs	**44 (21.6)**
Infections and infestations	33 (16.2)
Infective PEx of CF	28 (13.7)
Respiratory, thoracic and mediastinal disorders	6 (2.9)
Haemoptysis	6 (2.9)
Immune system disorders	3 (1.5)
Drug hypersensitivity	3 (1.5)

Source: Table 14.3.2.1.1c
AE: adverse event; CF: cystic fibrosis; MedDRA: Medical Dictionary for Regulatory Activities; n: size of subsample; N: total sample size; PEx: pulmonary exacerbation; PT: preferred term; SAE: serious adverse event; SOC: system organ class
Note: AEs were coded using MedDRA Version 25.1. A subject with multiple events within a category (any, SOC, or PT) was counted only once in that category. Table is sorted in descending order of frequency by SOC, and by PT within each SOC.

CHMP comment

In general, the SAEs in Study 110 are comparable to what is known from the MAA and post-marketing experience with Symkevi. Of the SAE, most of the events are infective PEx of CF, a common disease-related event in CF population.

Further, it is agreed that the two life-threatening AEs /deaths that occurred after treatment are unlikely related to TEZ/IVA treatment.

Adverse Events of Special Interest

Elevated Transaminase Events

In **Part A**, 64 subjects (6.1%) had at least 1 elevated transaminase event. AST increased occurred in 55 (5.3%) subjects, ALT increased in 48 (4.6%) subjects, and hypertransaminasaemia in one (0.1%) subject. The majority of events were mild or moderate in severity, whereas 12 events (1.2%) were severe. Elevated transaminases led to treatment discontinuation in 5 subjects (0.5%) and to treatment interruption in 15 subjects (1.4%).

In addition to the elevated transaminase AEs, there were 2 primary hepatic SAEs that occurred in subjects who also had AEs of elevated transaminases. One was a post-treatment SAE of hepatic necrosis with asymptomatic elevated ALT and AST; the other one an SAE of toxic hepatitis and asymptomatic elevated ALT and AST.

The narratives of the these 2 subjects are briefly presented:

- Subject 108-802-004 (post-treatment SAE of hepatic necrosis) was a 23-year-old female with a history of cystic fibrosis liver disease (CFLD). At approximately Week 36, the subject experienced asymptomatic elevated ALT and AST (both ~5 × ULN) and bilirubin <1.2 × ULN. Study drug was withdrawn, and 2 months later the LFTs peaked with ALT and AST ~8 × ULN and bilirubin <1.2 × ULN. The reported SAEs of LFT increased and hepatic necrosis were both considered post-treatment events because they occurred more than 30 days after study drug discontinuation. The subject remained asymptomatic and the LFTs gradually returned to baseline values.
- Subject 106-813-002 (SAE of toxic hepatitis) was a 25-year-old female with a history of CFLD and elevated liver enzymes. The subject was taking concomitant ursodiol and sertraline, and on Week 48, following a flu-like illness treated with acetaminophen and multiple antibiotics, the subject had asymptomatic elevation of ALT up to 4 × ULN and AST up to 5 × ULN. Study drug was discontinued. The subject remained asymptomatic and the LFTs gradually returned to baseline values.

The exposure-adjusted AE rate for the SOC of hepatobiliary disorders was comparable to the exposure-adjusted rate for the TEZ/IVA group in parent Study 106

A total of 11 (2.4%) of subjects in **Part B** had AEs of elevated transaminases: 9 (1.9%) subjects with ALT increased, 7 (1.5%) subjects with AST increased and one (0.2%) with hypertransaminasaemia. Of these, only one (0.2%) subject had an AE of ALT increased that was considered serious. One (0.2%) subject had an AE of hypertransaminasaemia that led to treatment interruption.

One (0.5%) subject in **Part C** had AEs of elevated transaminases, which were both ALT increased and AST increased. Both were SAEs, considered moderate in severity, and resulted in treatment interruption.

CHMP comment

The incidence of elevated transaminase events is comparable to the incidence in the LT-SS data set of the MAA (6.7%). Overall, the incidence is low and most events were mild or moderate in severity.

The narratives of the 2 primary hepatic SAEs indicate that the post-treatment SAE of hepatic necrosis is unlikely related to Symkevi and that for the SAE of toxic hepatitis multiple factors are present.

In an overview of all AEs of liver rated events, the incidence was low, and was dominated by ALT increased, AST increased and bilirubin increased. Other liver events were extremely rare and, according to the MAH, none were life-threatening or fatal.

Liver disease is a comorbidity of CF. Warnings concerning elevated transaminase and hepatic injury are already included in the SmPC as well as recommendations for liver functions testing.

Respiratory Symptoms and Events

In **Part A**, 181 (17.4%) subjects had any AE of respiratory events, including 142 (13.6%) subjects who had AEs associated with respiratory symptoms. Only one event (0.1%) was severe. The most common AEs associated with respiratory events were dyspnoea (99 subjects [9.5%]), respiration abnormal (46 subjects [4.4%]), and wheezing (36 subjects [3.5%]). No respiratory event or symptom was serious or led to treatment discontinuation.

Respiratory symptoms and events were not assessed in **Part B** and **C**.

CHMP comment

Respiratory events are common in CF. The incidence of respiratory events is comparable to that of the PC-SS data set (11.3%). Moreover, most events were mild or moderate in severity and there were no treatment discontinuations due to respiratory events. No further action is required.

Subgroups

In Part A, AE incidences were also analysed per subgroup: age at screening (<18 and ≥18 years of age) and ppFEV1 severity at baseline (<40, ≥40 to <70, and ≥70%).

- Age (<18 Years of Age and ≥18 Years of Age at Screening)
  Subjects with any AEs included 805 (94.9%) in the ≥18 years of age subgroup and 190 (97.9%) in the <18 years of age subgroup. Subjects with at least 1 SAE included 281 (33.1%) in the ≥18 years of age subgroup and 70 (36.1%) in the <18 years of age subgroup. SAEs are summarized by SOC and PT by age subgroup in Table 14.3.2.8.3.

  Overall, the AEs were similar in subjects <18 years of age and ≥18 years of age. By PT, the most common AEs (≥30%) in both subgroups were infective PEx of CF and cough. The most common SAE was infective PEx of CF in both age subgroups. Overall, no clinically meaningful differences were seen across the age subgroups.

- Baseline ppFEV1 Severity (<40, ≥40 to <70, and ≥70 Percentage Points)
  The overall incidence of AEs was higher in subjects with lower ppFEV1 at baseline. In particular, there was an increased incidence of infective PEx of CF in the subgroup with the greatest impairment in lung function (ppFEV1 <40 percentage points). Infective PEx of CF was also the most common SAE in each ppFEV1 subgroup.

CHMP comments

The SAEs are presented in extensive tables.

The adhoc tables 16.1 and 16.2, with the SAEs with occurrence in ≥3 subjects with parent study baseline age <18 years and ≥18 years, respectively did not reveal important differences between the

two age groups, although in subjects ≥18 years also additional SAEs. This is most likely because of the higher number of subjects ≥18 years in the study.

The adhoc tables 16.3, 16.4 and 16.5, the SAEs with occurrence in ≥3 subjects with parent study baseline ppFEV1 <40%, ppFEV1 ≥40% and <70% and ppFEV1 ≥70%, respectively also did not reveal important differences between groups.

The observed SAEs are generally in line with known AEs of TEZ/IVA, common manifestations of CF disease, or common illnesses in CF subjects 6 years of age and older, or are under review of the PRAC (anxiety). Event rates in the 110A Safety Set are generally lower than the event rates in the PC-SS. Therefore, no new changes in the SmPC regarding these findings are considered necessary. (See question 16).

Study Drug Discontinuation

Overall, 22 (2.1%) subjects in **Part A** had AEs that led to treatment discontinuation. Additionally, 2 subjects discontinued due to AEs that were not TE. AEs leading to treatment discontinuation in ≥ 2 subjects were ALT increased in 4 (0.4%) subjects, AST increased in 4 (0.4%) subjects, blood CPK increased in 4 (0.4%) subjects, and infective PEx of CF in 2 (0.2%) subjects. The 4 subjects who discontinued treatment due to an AE of ALT increased were the same 4 subjects who discontinued treatment due to an AE of AST increased. In addition to these subjects, another subject discontinued treatment due to an AE of hypertransaminasemia due to elevations in both AST and ALT.

Table 44 AEs Occurring in ≥2 Subjects Leading to Treatment Discontinuation by SOC and PT for Part A, Safety Set

	Total N = 1042 n (%)
Subjects with AEs leading to treatment discontinuation	22 (2.1)[a]
Investigations	7 (0.7)
ALT increased	4 (0.4)[b]
AST increased	4 (0.4)[b]
Blood CPK increased	4 (0.4)
Infections and infestations	3 (0.3)
Infective pulmonary exacerbation of CF	2 (0.2)

Source: Table 14.3.2.6.1

AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; CF: cystic fibrosis; CPK: creatine phosphokinase; MedDRA: Medical Dictionary for Regulatory Activities; n: size of subsample; N: total sample size; PT: Preferred Term; SOC: System Organ Class

Notes: AEs were coded using MedDRA Version 22.0. Table is sorted in descending order of the Total column by SOC and in descending order of the Total column by PT within each SOC. A subject with multiple events within a category was counted only once in that category.

[a] In total, 24 subjects discontinued due to an AE (Table 10-1); 2 of these subjects discontinued due to AEs that were not TE.

[b] There were 2 subjects that discontinued due to overlapping AEs of ALT increased and AST increased, these AEs were also considered by the investigator to be related SAEs (possibly related to study drug).

In **Part B**, 4 (0.9%) subjects had AEs that led to treatment discontinuation. Negative thoughts, suicidal ideation, obstructive pancreatitis, and urticaria each occurred in one subject.

Only one (0.5%) subject in **Part C** had an AE that led to treatment discontinuation. This AE of renal impairment was also considered an SAE.

Adverse Events That Led to Interruption of Study Drug

In **Part A**, 90 (8.6%) subjects had any AE that led to treatment interruption. AEs leading to treatment interruption occurring in ≥1% of subjects were infective PEx of CF in 18 (1.7%) subjects, AST increased in 15 (1.4%) subjects, and ALT increased in 12 (1.2%) subjects. Of note, there were several overlapping AEs leading to treatment interruption (e.g., all of the subjects who interrupted due to ALT increased also interrupted due to AST increased).

A total of 17 (3.7%) subjects in **Part B** had AEs leading to treatment interruption. Intestinal obstruction was reported for 2 (0.4%) subjects, all other AEs were reported by 1 subject each.

Two (1.0%) subjects in **Part C** had AEs leading to treatment interruption; these were ALT and AST increased and encephalopathy (one subject each).

CHMP comment

The number of subjects who had AEs leading to drug interruption and treatment discontinuation in Part A is slightly higher compared to the LT-SS (8.6% vs 6.7% and 2.1% vs 0.3%). AEs leading to treatment interruption/discontinuation were mainly known AEs of TEZ/IVA, i.e. ALT increased and AST increased. Overall, frequencies are considered acceptable and in line with the known safety of Symkevi.

Noticeably, one subject discontinued due to negative thoughts and another subject due to suicidal ideation in part B. Negative thoughts and suicidal ideation are important and serious AEs. The occurrence of negative thoughts, suicidal ideation and suicide has been recently discussed in PSUSA procedure EMEA/H/C/PSUSA/00010730/202302. As an outcome of this procedure the PRAC Rapporteur recommended an update of section 4.4 and 4.8 to include information on depression (including suicidal ideation and suicide attempt). As the product information will be updated as part of EMEA/H/C/PSUSA/00010730/202302, this issue is not further pursued within this procedure.

Clinical Laboratory Evaluation

Not all examinations were performed in **Part B** and **C**.

Chemistry

Liver function tests (LFTs)

There were 6 (0.6%) subjects who had ALT or AST elevations >3 × ULN and total bilirubin elevations >2 × ULN (at any time in the study, i.e., both concurrent or not concurrent). Four (0.4%) subjects did not have a transaminase elevation (ALT or AST >3 × ULN) concurrent with a new bilirubin elevation. Two (0.2%) subjects had ALT or AST elevations >3 × ULN concurrent with total bilirubin elevations >2 × ULN; however, both subjects had bilirubin elevations >2 × ULN prior to initiation of TEZ/IVA in Part A (either in parent Study 106 or at baseline in Part A)

Table 45 Threshold Analysis of LFTs Results During Part A TE Period, Safety Set

Parameter Threshold Analysis Criteria n/N1 (%)	Total N = 1042
ALT (U/L)	
>ULN to ≤3 × ULN	258/1041 (24.8)
>3 to ≤5 × ULN	24/1041 (2.3)
>5 to ≤8 × ULN	9/1041 (0.9)
>8 to ≤20 × ULN	6/1041 (0.6)
>20 × ULN	0/1041
AST (U/L)	
>ULN to ≤3 × ULN	305/1041 (29.3)
>3 to ≤5 × ULN	29/1041 (2.8)
>5 to ≤8 × ULN	13/1041 (1.2)
>8 to ≤20 × ULN	9/1041 (0.9)
>20 × ULN	1/1041 (0.1)
ALT or AST	
(ALT >ULN and ALT ≤3 × ULN) or (AST >ULN and AST ≤3 × ULN)	366/1041 (35.2)
(ALT >3 × ULN and ALT ≤5 × ULN) or (AST >3 × ULN and AST ≤5 × ULN)	35/1041 (3.4)
(ALT >5 × ULN and ALT ≤8 × ULN) or (AST >5 × ULN and AST ≤8 × ULN)	15/1041 (1.4)
(ALT >8 × ULN and ALT ≤20 × ULN) or (AST >8 × ULN and AST ≤20 × ULN)	12/1041 (1.2)
ALT >20 × ULN or AST >20 × ULN	1/1041 (0.1)
ALP (U/L)	
>ULN to ≤1.5 × ULN	181/1041 (17.4)
>1.5 to ≤2.5 × ULN	54/1041 (5.2)
>2.5 to ≤5 × ULN	14/1041 (1.3)
>5 to ≤20 × ULN	0/1041
>20 × ULN	0/1041
Total bilirubin (µmol/L)	
>ULN to ≤1.5 × ULN	89/1041 (8.5)
>1.5 to ≤2 × ULN	35/1041 (3.4)
>2 to ≤3 × ULN	20/1041 (1.9)
>3 to ≤10 × ULN	3/1041 (0.3)
>10 × ULN	0/1041
ALT and total bilirubin[a]	
ALT >3 × ULN and total bilirubin >2 × ULN	4/1041 (0.4)
AST and total bilirubin[a]	
AST >3 × ULN and total bilirubin >2 × ULN	5/1041 (0.5)
ALT or AST and total bilirubin[a]	
AST or AST >3 × ULN and total bilirubin >2 × ULN	6/1041 (0.6)
Concurrent	2/1041 (0.2)[b]
Concurrent with new bilirubin elevation	0/1041

Source: Table 14.3.4.2.2

ALP: alkaline phosphatase; ALT: alanine transaminase; AST: aspartate transaminase; LFT: liver function test; n: size of subsample; N: total sample size; N1: number of subjects with at least 1 non-missing measurement during the Part A TE Period; TE: treatment-emergent; ULN: upper limit of normal

Notes: For n, a subject was counted only once in the worst category of all post-baseline assessments during the 110 TE Period. Criteria involving 2 LFT parameters could be determined by assessments at different visits in the overall 110 TE Period.

[a] Concurrent or not concurrent transaminase and bilirubin elevation in the same subject.

[b] These 2 subjects had bilirubin elevations >2 × ULN prior to initiation of TEZ/IVA in Part A (either in parent Study 106 or at baseline in Study 110 Part A) (Listing 16.2.8.1.6, Study 106 CSR/Listing 16.2.8.1.5).

In **Part B**, no clinically important trends were observed. A total of 2 subjects had ALT or AST elevations >8 × ULN, and no subjects had ALT or AST values >20 × ULN. There were no subjects who had ALT or AST elevations >3 × ULN and total bilirubin elevations >2 × ULN (at any time in the study, i.e., both concurrent or not concurrent)

Table 46 Threshold Analysis of LFTs Results During Part B TE Period, Safety Set

Parameter Threshold Criteria n/N1 (%)	Total N = 463
ALT (U/L)	
>ULN to ≤3 × ULN	73/461 (15.8)
>3 to ≤5 × ULN	3/461 (0.7)
>5 to ≤8 × ULN	2/461 (0.4)
>8 to ≤20 × ULN	0/461
>20 × ULN	0/461
AST (U/L)	
>ULN to ≤3 × ULN	105/461 (22.8)
>3 to ≤5 × ULN	4/461 (0.9)
>5 to ≤8 × ULN	0/461
>8 to ≤20 × ULN	2/461 (0.4)
>20 × ULN	0/461
ALT or AST	
(ALT >ULN and ALT ≤3 × ULN) or (AST >ULN and AST ≤3 × ULN)	127/461 (27.5)
(ALT >3 × ULN and ALT ≤5 × ULN) or (AST >3 × ULN and AST ≤5 × ULN)	6/461 (1.3)
(ALT >5 × ULN and ALT ≤8 × ULN) or (AST >5 × ULN and AST ≤8 × ULN)	1/461 (0.2)
(ALT >8 × ULN and ALT ≤20 × ULN) or (AST >8 × ULN and AST ≤20 × ULN)	2/461 (0.4)
ALT >20 × ULN or AST >20 × ULN	0/461
Total bilirubin (µmol/L)	
>ULN to ≤1.5 × ULN	40/461 (8.7)
>1.5 to ≤2 × ULN	14/461 (3.0)
>2 to ≤3 × ULN	8/461 (1.7)
>3 to ≤10 × ULN	1/461 (0.2)
>10 × ULN	0/461
Direct bilirubin (µmol/L)	
>ULN to ≤1.5 × ULN	41/460 (8.9)
>1.5 to ≤2 × ULN	4/460 (0.9)
>2 to ≤3 × ULN	0/460
>3 to ≤10 × ULN	0/460
>10 × ULN	0/460
ALT and total bilirubin	
ALT >3 × ULN and total bilirubin >2 × ULN	0/461
AST and total bilirubin	
AST >3 × ULN and total bilirubin >2 × ULN	0/461
(ALT or AST) and total bilirubin	
(ALT >3 × ULN or AST >3 × ULN) and total bilirubin >2 × ULN	0/461

Source: Table 14.3.4.2b

ALT: alanine transaminase; AST: aspartate transaminase; LFT: liver function test; N: total sample size; n: number of subjects meeting the threshold criteria; N1: number of subjects with at least 1 non-missing measurement during the Part B TE Period; TE: treatment-emergent; ULN: upper limit of normal

In **Part C**, no clinically important trends were observed. No subjects had ALT or AST elevations >8 × ULN. No subjects had ALT or AST elevations >3 × ULN and total bilirubin elevations >2 × ULN (at any time in the study, i.e., both concurrent or not concurrent).

Table 47 Threshold Analysis of LFTs During Part C TE Period, Safety Set

Parameter Threshold Criteria n1/N1 (%)	Total N = 204
ALT (U/L)	
>ULN to ≤3 × ULN	10/193 (5.2)
>3 to ≤5 × ULN	1/193 (0.5)
>5 to ≤8 × ULN	0/193
>8 to ≤20 × ULN	0/193
>20 × ULN	0/193
AST (U/L)	
>ULN to ≤3 × ULN	25/193 (13.0)
>3 to ≤5 × ULN	3/193 (1.6)
>5 to ≤8 × ULN	0/193
>8 to ≤20 × ULN	0/193
>20 × ULN	0/193
ALT or AST	
(ALT >ULN and ALT ≤3 × ULN) or (AST >ULN and AST ≤3 × ULN)	26/193 (13.5)
(ALT >3 × ULN and ALT ≤5 × ULN) or (AST >3 × ULN and AST ≤5 × ULN)	3/193 (1.6)
(ALT >5 × ULN and ALT ≤8 × ULN) or (AST >5 × ULN and AST ≤8 × ULN)	0/193
(ALT >8 × ULN and ALT ≤20 × ULN) or (AST >8 × ULN and AST ≤20 × ULN)	0/193
ALT >20 × ULN or AST >20 × ULN	0/193
Total bilirubin (µmol/L)	
>ULN to ≤1.5 × ULN	13/193 (6.7)
>1.5 to ≤2 × ULN	6/193 (3.1)
>2 to ≤3 × ULN	2/193 (1.0)
>3 to ≤10 × ULN	0/193
>10 × ULN	0/193
Direct bilirubin (µmol/L)	
>ULN to ≤1.5 × ULN	17/193 (8.8)
>1.5 to ≤2 × ULN	1/193 (0.5)
>2 to ≤3 × ULN	0/193
>3 to ≤10 × ULN	0/193
>10 × ULN	0/193
ALT and total bilirubin	
ALT >3 × ULN and total bilirubin >2 × ULN	0/193
AST and total bilirubin	
AST >3 × ULN and total bilirubin >2 × ULN	0/193
(ALT or AST) and total bilirubin	
(ALT >3 × ULN or AST >3 × ULN) and total bilirubin >2 × ULN	0/193

Source: Table 14.3.4.2c

ALP: alkaline phosphatase; ALT: alanine transaminase; AST: aspartate transaminase; LFT: liver function test; N: total sample size; n1: number of subjects meeting the threshold criteria; N1: number of subjects with at least 1 non-missing measurement during the Part C TE Period; TE: treatment-emergent; ULN: upper limit of normal

CHMP comment

Elevated transaminase and hepatic injury are addressed in the SmPC: "Liver function decompensation, including liver failure leading to transplantation and death has been reported in CF patients with pre-

existing cirrhosis and portal hypertension whilst receiving treatment with other CFTR modulator regimens." And "Elevated transaminases are common in patients with CF and have been observed in some patients treated with Symkevi in combination with ivacaftor, as well as with ivacaftor monotherapy." Recommendations are given for liver functions tests and interruption or discontinuation in the event of significant elevations of liver function.

The observed results in the study parts are generally in line with the known numbers except in Part A 2 (0.2%) subjects had ALT or AST elevations >3 × ULN concurrent with total bilirubin elevations >2 × ULN, while none in the PS-SS.

As the issue is sufficiently addressed, no further action is necessary.

Creatine Kinase

In Part A, 83 (8.0%) subjects had an AE of blood CPK increased and 1 (0.1%) subject had an AE of rhabdomyolysis. Exposure adjusted AE rates for CK events were lower than the exposure adjusted rates for the TEZ/IVA group in parent Study 106. The majority of the AEs of CK elevations were mild or moderate in severity, non-serious, and did not lead to study drug interruption or discontinuation.

There were 8 (0.8%) subjects who had an SAE of blood CPK increased (7 subjects) or rhabdomyolysis (1 subject). Of these 8 subjects, 4 subjects had plausible alternative aetiology of strenuous exercise, and 2 subjects had a medical history of elevated CK including the 1 subject with rhabdomyolysis who had a history of rhabdomyolysis. Of the remaining 2 subjects, 1 subject had laboratory parameters suggestive of underlying rheumatologic disease and 1 subject had asymptomatic CK increase where the study drug was not resumed due to study discontinuation.

Other Serum Chemistry

There were no clinically meaningful trends in mean values of other non-LFT chemistry parameters (vitamin levels, lipid panel, and other serum chemistry).

Among AEs associated with clinical chemistry findings, those that were SAEs included blood CPK increased in 7 (0.7%) subjects and blood creatinine increased in 1 (0.1%) subject. The only events that led to TEZ/IVA treatment discontinuation were 1 nonserious AE each of blood CPK increased and blood lactate dehydrogenase increased and 3 SAEs of blood CPK increased

No clinically meaningful trends in other clinical chemistry parameters or associated AEs were observed.

Haematology (Part A only)

There were no trends observed in haematology parameters. Among the AEs associated with haematology, 1 event each of anaemia, bone marrow failure, and lymphadenitis were SAEs, and none led to TEZ/IVA treatment discontinuation.

Coagulation (Part A only)

There were no trends in coagulation parameter values or associated AEs. There was 1 SAE of deep vein thrombosis. None of the AEs associated with coagulation led to treatment discontinuation.

Urinalysis (Part A only)

Only 1 AE of urine amphetamine positive was serious. None of the AEs associated with urinalysis results led to treatment discontinuation.

Vital signs (Part A only)

No trends in vital signs data or associated AEs were observed. There was 1 SAE of pyrexia. No AE led to treatment discontinuation.

Pulse oximetry (Part A only)

No clinically meaningful trends in pulse oximetry results or associated AEs were observed. AEs related to pulse oximetry were infrequent, not serious and did not lead to treatment discontinuation.

ECG (Part A only)

A total of 9/1042 (0.9%) subjects had QTcF >450 msec (male) or >470 msec (female), and no subject had a QTcF ≥500 msec. None of the AEs associated with ECG findings were serious or led to treatment discontinuation. No clinically important trends in ECG parameter data or associated AEs were observed.

Ophthalmologic Examinations

In **Part A,** 10 subjects <18 years of age had TE cataracts detected (none had an AE of cataract). Of these, six were newly identified, but none were considered clinically significant. In addition, 5 adult subjects had an AE of cataract. All of the AEs were mild or moderate in severity and nonserious.

In Part B, The OE data for subjects <18 years of age who had cataracts any time on or after Part B Day 1 are provided for all subjects in Listing 16.2.8.1.4b. One new AE of cataract was reported in Part B, that was mild in severity and resolved without dose adjustment.

There were no new AEs of cataracts reported in **Part C**.

Pregnancy

Nine subjects became pregnant during **Part A** and discontinued study drug per protocol. Of these subjects, 4 had pregnancy outcomes pending at the time of this report, 2 had elective terminations, and 3 delivered healthy babies.

No subjects became pregnant during **Part B**. One subject was withdrawn from study treatment by the medical monitor due to the subject's partner becoming pregnant.

One subject became pregnant during **Part C**. One subject had elevated β-hCG levels of 6.88 at the Part C Early Termination visit. However, this elevation was not indicative of pregnancy as the subject was postmenopausal.

2.2.3. Discussion on clinical aspects

This current paediatric worksharing Art 46 concerns the final study results of Study VX14-661-110 Part A, Part B and Part C.

Symkevi (TEZ/IVA) is approved in a combination regimen with ivacaftor tablets for the treatment of patients with cystic fibrosis (CF) aged 6 years and older who are homozygous for the *F508del* mutation or who are heterozygous for the *F508del* mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T.

Currently the final results of VX14-661-110 Part A, Part B and Part C are submitted in which subjects have been treated for 96 weeks and 192 weeks, respectively.

The used dosing is in line with the approved posology of Symkevi.

Design and conduct of clinical study

The primary objective of Study 110 is to evaluate the long-term safety and tolerability of TEZ/IVA in **Part A** in subjects with CF, homozygous or heterozygous for the *F508del-CFTR* mutation in the Treatment Cohort. Efficacy outcome measures were included as secondary outcomes.

This study had a single arm, open label design. The study design was complex as the study was a roll over study and included patients from a total of the 6 parent studies in Part A and 8 parent studies in Part B. The study was conducted in heterogenous groups of CF patients, homozygotic (F/F) and heterozygotic for *F508del CTFR* (F/RF, F/MF, F/G). The study consisted of consecutive 3 Parts (A, B, C).

As a result of the design, the included patient population is not consistent over all parts of the study. Not all patients that were included in Part A rolled over to Part B and/or Part C; while study Part B also allowed the enrolment of patients from 2 additional studies.

In **Part A** (treatment period of approximately 96 weeks) the main analyses of PK and efficacy were based on subjects who rolled over from parent Study 106 (106/110 ES; F/F population) and parent study 108 (108/110 ES F/RF population). The safety analyses were based on all subjects who have received at least 1 dose of study drug in Part A irrespective of their genotype and includes subjects of all parent studies. In **Part B** (treatment period of approximately 96 weeks) the efficacy analyses were conducted based on CFTR genotype, i.e., either F/F or F/RF genotype. The safety analyses were based on all subjects who received at least 1 dose of study drug in Study 110 Part B, regardless of subjects' parent study assignment or *CFTR* genotype. In **Part C** (treatment period of approximately 192 weeks), no PK or efficacy analyses were performed. The safety analyses were based on all subjects who received at least 1 dose of study drug in Study 110 Part C.

The rules for concomitant stable CF medication, restriction of CYP3A inducers and dosing modification of CYP3A inhibitors were all acceptable. Subjects remained on a stable CF medication that the subject had been following for at least 28 days before Day 1. Co-administration of TEZ and IVA with moderate and strong CYP3A inducers was restricted in this study. Dosing modification recommendations for subjects taking concomitant CYP3A inhibitors were applied in line with the approved SmPC.

Outcome measures

Determination of the plasma concentrations of TEZ, M1-TEZ, IVA, and M1-IVA, is relevant for measuring the level of exposure of the subject and consequently the relation with efficacy.

Multiple outcomes were included. As efficacy was a secondary objective, no primary endpoint is included. The main secondary outcomes are ppFEV1, CFQ-R, BMI, height, weight, BMI-z, height-z, weight-z and pulmonary exacerbations.

Pulmonary function tests (ppFEV1) are considered important to measure an effect on one of the most important affected organs in CF. CFQ-R measures the quality of life and changes in BMI, height, weight inform over the nutritional status. Thus all parameters inform about a different aspect of CF and are considered important for measuring the efficacy of a CF modulator. Unfortunately, sweat chloride was not included as an important pharmacodynamic parameter for measuring the effect of a modulator on the underlying pathology.

Safety measures are adverse events (AEs), ophthalmologic examinations (OE; subjects <18 years of age, clinical laboratory values (serum chemistry, haematology, coagulation, lipids, vitamins, and urinalysis), standard 12-lead ECGs, vital signs, and pulse oximetry in **Part A**, in **Part B and C** the measures were AEs, serum LFTs, and OEs.

Statistics

Given the heterogeneity in parent studies in terms of genotype (and design), the analyses by study (or genotype) are most adequate.

It is considered sensible that modelling of long-term outcomes was only applied to the roll-over data from the largest studies, i.e., Study 106 and 108 (because the other studies had much less data and long-term outcomes were only described). The model specification was adequate in terms of correlation structure and chosen covariates and their interactions. The impact of missing data is somewhat mitigated a priori by the Applicant's requirement that time points are only included up to the point that missing data exceeds 30% of the patients.

Because of the differences in design of parent studies, the total treatment period for the subjects vary. Additionally, subjects were allowed to leave Part A or B (e.g., at day 50) to participate in another study of the Applicant and after completing that other study, were allowed to re-enrol in Study 110 (Part A or B) while their follow-up time was combined (e.g., after re-enrolment, follow-up starting at Day 51).

Discontinuation of follow-up in the roll-over study may create selection bias, but study discontinuation seemed to be low and mostly due to uninformative reasons (study drug becoming commercially available). The number of subjects with ppFEV1 value at week 96 dropped to 83% (106/110 ES) or 87% (108/110 ES) in Part A. Thus, given relatively limited possible informative drop-out, in combination with the relatively large longterm effects, the impact of possible bias seems limited.

Changes in conduct

Generally, the protocol amendments were acceptable, except the change that participants could participate in an Applicant's other study and return to Study 110 per protocol Version 2.0. The interim period in the other study might have affected the subject's health status. This did occur (3.5% from parent Study 106, 17.4% from parent Study 103, 30.3% from parent Study 111), however, an analysis with and without these patients showed that the impact of this is limited.

Results

Pharmacokinetics

Predose plasma levels at Week 24 for TEZ, M1-TEZ, IVA, and M1-IVA were comparable to those obtained in the previously provided clinical studies. Since PK samples in Study 110 were only collected at the Part A, Week 24 Visit, it not possible to assess PK trends over time in Study 110 in relation to the trend in ppFEV1 (see Efficacy part of this AR). However, provided Cmin data for the other Studies 103, 106, 108 and 111 indicate no clinically meaningful change in exposure over time. Week 24 PK exposures of TEZ, IVA, M1-TEZ, and M1-IVA observed in Study 110 were similar to those observed in the parent studies. Therefore, it is not expected that the observed decrease in ppFEV1 over time is caused by changes in exposure.

Bioanalytical and validation reports were provided.

Efficacy

In Part A, the majority of subjects were White (98.9%) and not of Hispanic or Latino ethnicity (96.5%). A total of 237 (51.6%) subjects were male. The overall median age was 25.0 years (range: 12 to 64 years), with 109 (23.7%) subjects in the <18 years of age subgroup.

The mean age in subjects with F/RF mutation (35.1 years) was clearly higher than in subjects with F/F mutation (26.1 years). This difference may be explained with the difference in severity of the diseases

between the 2 groups, i.e., symptoms are milder and e.g., lung function is longer preserved, with generally a longer survival. The difference in nutritional parameters at baseline can be also explained with the difference in severity.

The baseline of the demographics and disease characteristics is defined as baseline of the parent study in all parts. Therefore, the baseline demographics and characteristics of Part B and Part C are quite similar to baseline of Part A with only small differences that can be contributed to the difference in numbers of subjects in the parts.

- ppFEV1

In Part A, for subjects who received TEZ/IVA in Studies 106 (F/F) and 108 (F/RF), improvements in ppFEV1, were generally maintained throughout the 96 weeks of treatment. Somewhat lower results were observed in Part B, particularly for the F/F population.

For the F/F population in Part A, the LS mean absolute changes from parent study baseline at Week 96 was 2.0 % (95% CI: 0.7, 3.2) and 2.1 % (95% CI: 0.8, 3.3) for the TEZ/IVA-TEZ/IVA group and PBO-TEZ/IVA group, respectively. In Part B, the mean (SD) absolute change from baseline at Week 96 in ppFEV1 was 1.7 (10.2) %. However, these results are difficult to interpret because of the different parent studies. The included population is heterogenous, with different treatment backgrounds (TEZ/IVA, IVA or placebo) and different treatment periods (4-72 weeks) before entering the study. Nevertheless, the data still show an improvement over baseline lung function, while based on historical data, a lung function decline would be expected.

In Part B, for the subjects with F/F mutation, the increase from baseline is 1.7% only. Nevertheless, the data still show an improvement over baseline lung function, while based on historical data, a lung function decline would be expected.

For the F/RF population in Part A, the LS mean absolute changes from parent study baseline at Week 96 was 7.5 percentage points (95% CI: 5.6, 9.4), 6.7 percentage points (95% CI: 4.7, 8.7) and 4.1 percentage points (95% CI: 2.2, 6.0) for the TEZ/IVA-TEZ/IVA group, IVA-TEZ/IVA and PBO-TEZ/IVA group, respectively. In Part B, the mean (SD) absolute change from study baseline to Week 96 was 8.3 (8.6) percentage points.

These numerical differences in observed point estimates could be due to individual subject variability, i.e., it is likely that the differences are due to subjects' characteristics rather than due to differences in the treatment. Overall, the results at Week 96 show maintenance of treatment effect. Because of overlapping 95% confidence intervals of the 3 groups, these differences are not considered statistically meaningful differences. Overall, the increase in ppFEV1 is clinically relevant in all groups of the investigated subjects with F/RF mutations.

- CFQ-R respiratory domain

The CFQ-R respiratory domain was only measured in Part A.

Over time, the improvements over baseline in the CFQ-R RD decreased in both populations but at the end of the 96-week period still improvements were observed.

For the F/F population, the LS mean absolute changes from parent study baseline at Week 96 of Part A were 3.0 points (95% CI: 0.7, 5.3) and 1.7 points (95% CI: -0.6, 4.0) for the TEZ/IVA-TEZ/IVA group and PBO-TEZ/IVA group, respectively. As the minimum clinically important difference is 4.0 point, the subjects as a group did not meet this MCID. The proportion of subjects who met the MCID of the CFQ-R was 42.3% for the placebo-TEZ/IVA group and 51.0% for TEZ/IVA-TEZ/IVA group. Given, the natural history of CF with increases in symptoms over time, the observed responder rates are considered relevant.

For the F/RF population, larger improvement were shown i.e., the LS mean absolute changes from parent study baseline at Week 96 was 13.8 points (95% CI: 10.3, 17.2), 11.2 points (95% CI: 7.7, 14.7) and 10.3 points (95% CI: 7.0, 13.6) for the TEZ/IVA-TEZ/IVA group, IVA-TEZ/IVA and PBO-TEZ/IVA group, respectively.

- Nutritional status

Improvements in nutritional status (BMI and weight) were observed in both the F/F and R/F populations in Part A, which appear to be further improving in Part B of the study.

For subjects <20 years of age at screening the nutritional status was measured through BMI z-score, weight z-score, and height z-score. In the F/F population (106/110 ES) the mean BMI z-score, weight z-score, and height z-score dropped compared to baseline. However, as the height-z score increased, the drop in BMI-z score is explained. The drop in weight-z score is in line with other results that after a longer treatment with TEZ-IVA benefits seem to decrease. In the PBO-TEZ/IVA group, an overall increase is seen in all three parameters.

In the 108/110 ES, changes in BMI, weight and height z-scores are relatively stable in all groups during Part A of the study and are maintained in in Part B. Thus, overall an increase in nutritional parameters in the younger population (< 20 years) is seen except for the F/F subject in the TEZ/IVA-TEZ/IVA group.

- Pulmonary exacerbations

In Part A, in the F/F population, the annualized estimated PEx rates (events/year) were 0.76 in the TEZ/IVA-TEZ/IVA group and 0.68 in the PBO-TEZ/IVA group in Study 110 Part A compared with 0.99 in the placebo group in Study 106. The annualized estimated PEx rates were higher than 0.64 events per year in the TEZ/IVA group. Thus, although there is still a relevant improvement compared to placebo group in Study 106, the benefit seems to be somewhat less, as seen before. (overarching OC). Pulmonary exacerbations requiring hospitalisation and Pulmonary exacerbations requiring IV antibiotics were comparable between groups and similar to the corresponding event rates for subjects who received TEZ/IVA in Study 106. In Part B, the observed event rate was 0.77 events per year, rather similar to Part A. The estimated exacerbation-free probability at Week 96 of Part A was quite similar across both groups.

In the F/RF population, annualized estimated PEx rates (events/year) were low, with 0.22 in the TEZ/IVA-TEZ/IVA group, 0.28 in the IVA-TEZ/IVA group, and 0.44 in in the PBO-TEZ/IVA group in Study 110 Part A compared with 0.63 in the placebo group in Study 108. Because of the short duration of Study 108, no comparison can be made with this parent study. In Part B, the observed event rate was 0.51 events per year, somewhat higher than in Part A. However, a direct comparison is not possible as the reported Study 110 Part B PEx event rate per year is the observed event rate, not the estimated event rate, as in Study 110 Part A and Study 108. The differences between the 3 groups could be due to the natural variability in PEx events, low sample size, and status of the ongoing coronavirus-19 (COVID-19) pandemic. Moreover, the overlapping 95% CIs demonstrate that the rates are not statistically different.

In general, similar to the progressive decline in ppFEV1, an increase in the rate of PEx over time in an be expected based on the natural history of CF. Nevertheless, the small decreases of the effect on the exacerbation parameters are acceptable and can be contributed to the modifying effect of the natural history.

Safety

In Part A, 1042 subjects received at least 1 dose of TEZ/IVA. The mean exposure was 76.0 weeks and excluding subjects from Studies 107 and 109, 90.2 weeks. The median duration was 95.9 weeks indicating that most of the subjects remained on treatment.
In Part B, 463 subjects received at least 1 dose of TEZ/IVA. The mean exposure of all subjects to TEZ/IVA was 71.0 weeks, lower than the 92 weeks duration of the study. This was caused by the high number of treatment discontinuations (248 subjects) mainly because of commercial drug availability (198 subjects).
In Part C, the mean exposure was 71.0 weeks (range: 2.3 to 152.6 weeks), indicative that no subjects finalised study treatment. The number of discontinuations (202 subjects), mainly because of commercial drug availability (175 subjects), was high again.

Similar to previous studies, nearly all patients experience an adverse event i.e., i.e. 995 (95.5%) subjects, 427 (92.2%) subjects and 168 (82.4%) subjects in Part A, Part B and Part C respectively.

Most had AEs that were mild (23.9%, 27.9%, and 23.0% respectively) or moderate (53.0%, 51.0% and 46.6%, respectively) in severity. A total of 191 (18.3%), 62 (13.4%) and 24 (11.8%) subjects had severe AEs in Part A, Part B and Part C, respectively. In Part A, a total of 3 (0.3%) subjects had life-threatening AEs, considered not related to study drug. In Part B and Part C no subjects had life-threatening AEs.

- Common adverse evens

The most common AE in all 3 parts was infective PEx of CF, i.e. (52.7%), (51.6%), and (45.1%), in Part A, Part B and Part C, respectively. Infective PEx is common symptom of CF and commonly observed in subjects with and without modulator treatment. Other reported AEs ≥ 10% of subjects in all three parts are cough and haemoptysis adverse event that can be attributed to CF or to the treatment. The incidences of the TAES are generally comparable between the safety sets.

- Related adverse events

Overall, there are no new related TEAEs in Study 110 compared to the Phase 3-controlled Safety Set (PC-SS). In general, the related TEAEs with occurrence in ≥2% subjects have a lower incidence in Study 110 compared to PC-SS. No new drug related adverse events were identified.

- Deaths

There were no deaths in any part of the study.

- Serious adverse events

In **Part A**, 351 (33.7%) subjects had at least 1 SAE. SAEs occurring in at least 1 subject are infective PEx of CF, distal intestinal obstruction disorder syndrome and haemoptysis.
Related SAEs occurred in 24 (2.3%) of these 351 subjects, of which infective PEx of CF (0.5%), blood CPK increased (0.4%), ALT increased (0.3%), and AST increased (0.3%) occurred in >1 subject. These SAE are known AEs of TEZ/IVA and are addressed in the SmPC.

In P**art B**, 136 (29.4%) subjects had SAEs. SAEs that occurred in >1% of subjects were Infective PEx of CF (103 subjects [22.2%]) and haemoptysis (10 subjects [2.2%]). Of these SAEs, four were considered related. Only urticaria occurred in more than one subject (2 subjects [0.4%]).

In P**art C**, 44 (21.6%) subjects had at least 1 SAE. SAEs that occurred in >1% of subjects were infective PEx of CF (13.7%), haemoptysis (2.9%), and drug hypersensitivity (1.5%). The majority of SAEs had an outcome of recovered/resolved and were not considered related to study drug. One (0.5%) subject had an SAE of renal impairment that led to treatment discontinuation.

A few Grade 3/4 AEs were higher in the safety sets of Study 110 compared to the PC-SS. These concern pneumonia, haemoptysis, anaphylactic reaction, anxiety, depression, suicide attempt and deep vein thrombosis. Most of these events were not related to treatment or were already addressed in the SmPC. No changes to the PI or RMP are necessary based on these cases.

- Discontinuations

In Part A, 22 (2.1%) subjects had AEs that led to treatment discontinuation. The most common AEs that led to treatment discontinuation (occurring in >1 subject) were ALT increased in 4 (0.4%) subjects, AST increased in 4 (0.4%) subjects, blood CPK increased in 4 (0.4%) subjects, and infective PEx of CF in 2 (0.2%) subjects.
In Part B, 4 (0.9%) subjects had AEs that led to treatment discontinuation. These events included negative thoughts, suicidal ideation, obstructive pancreatitis, and urticaria (each event occurred in 1 subject). The issue of depression, including suicidal ideation and suicide attempt, has been already recently discussed by the PRAC (EMEA/H/C/PSUSA/00010730/202302). As an outcome an update of section 4.4 and 4.8 to include information on depression (including suicidal ideation and suicide attempt) is recommended. Therefore, this issue is not further pursued within this procedure.
In Part C, only 1 subject discontinued because of renal impairment.

- Treatment interruptions

The adverse events that led to treatment interruptions were generally comparable to previous studies and between the different parts of the study.
AE that led to treatment interruption were in 90 (8.6%), 17 (3.7%) and 2 (1.0%) of the subjects in Part A, Part B and Part C, respectively. In Part A, AEs leading to treatment interruption occurring in ≥1% of subjects were infective PEx of CF, AST increased, and ALT increased.
A total of 17 (3.7%) subjects in **Part B** had AEs leading to treatment interruption. Intestinal obstruction was reported for 2 (0.4%) subjects, all other AEs were reported by 1 subject each.
Two (1.0%) subjects in **Part C** had AEs leading to treatment interruption; these were ALT and AST increased and encephalopathy (one subject each). These AEs do not require further action.

Overall. the AEs leading and reported frequencies to treatment interruption are in line with the known safety profile of Symkevi.

- Elevated transaminases (AESI)

Elevated transaminases occur frequently in CF, but can also be related to treatment

In P**art A**, 64 (6.1%) subjects had AEs related to elevated transaminases. ALT increased occurred in 55 (5.3%) subjects, ALT increased in 48 (4.6%) subjects, and hypertransaminasaemia in one (0.1%) subject. A total of 12 events (1.2%) were severe. Five (0.5%) subjects had TE transaminase elevations that resulted in treatment discontinuation (including 4 subjects with 2 AEs each of ALT and AST increased and 1 subject with an AE of hypertransaminasemia due to elevations in both AST and ALT) and 15 (1.4%) subjects had TE transaminase elevations that led to treatment interruption.
The incidence of subjects with ALT or AST >3, >5, and >8 x ULN during the Study 110 TE Period was 6.1%, 2.7%, and 1.3%, respectively. No subject had a transaminase elevation (ALT or AST >3 x ULN) concurrent with a new bilirubin elevation >2 x ULN.

The 2 primary SAE elevated transaminases were unlikely related to treatment.

In **Part B**, 11 (2.4%) of subjects had AEs of elevated transaminases: 9 (1.9%) subjects with ALT increased, 7 (1.5%) subjects with AST increased and one (0.2%) with hypertransaminasaemia. Of

these, only one (0.2%) subject had an AE of ALT increased that was considered serious. One (0.2%) subject had an AE of hypertransaminasaemia that led to treatment interruption.
One (0.5%) subject in **Part C** had AEs of elevated transaminases, which were ALT increased and AST increased. Both were SAEs, considered moderate in severity, and resulted in treatment interruption.

In both Part B and Part C, the incidences of subjects with ALT or AST >3, >5, and >8 x ULN was low, and no subject had a transaminase elevation (ALT or AST >3 × ULN) concurrent with a total bilirubin elevation >2 x ULN.

In an overview of all AEs of liver rated events, liver events were rare, and none were life-threatening or fatal. Warnings concerning elevated transaminase and hepatic injury are already included in the SmPC as well as recommendations for liver functions testing.

- AEs associated with respiratory events (AESI)

In **Part A**, 181 (17.4%) subjects had AEs associated with respiratory events, including 142 (13.6%) subjects who had AEs associated with respiratory symptoms. Only 1 event was severe. The most common AEs (in >2% of subjects) associated with respiratory events were dyspnoea, respiratory abnormal, and wheezing commonly present symptoms in CF.
Respiratory symptoms and events were not assessed in **Part B** and **C**.

- Subgroups

In Part A, AE incidences were also analysed per subgroup: age at screening (<18 and ≥18 years of age) and ppFEV1 severity at baseline (<40, ≥40 to <70, and ≥70 percentage points).

Age (<18 Years of Age and ≥18 Years of Age at Screening)
Subjects with any AEs included 805 (94.9%) in the ≥18 years of age subgroup and 190 (97.9%) in the <18 years of age subgroup. Overall, no clinically meaningful differences were seen across the age subgroups.

Baseline ppFEV1 Severity (<40, ≥40 to <70, and ≥70 Percentage Points)
The overall incidence of AEs was higher in subjects with lower ppFEV1 at baseline. In particular, there was an increased incidence of infective PEx of CF in the subgroup with the greatest impairment in lung function (ppFEV1 <40 percentage points).

Additional submitted tables with the SAEs in the subgroups did not reveal important differences between the two groups. The observed SAEs are generally in line with known AEs of TEZ/IVA, common manifestations of CF disease, or common illnesses in CF subjects 6 years of age and older, or are under review of the PRAC (anxiety). Event rates in the Study 110A Safety Set are generally lower than the event rates in the PC-SS.

As result of the currently available data of Part B and Part C, the SmPC should be updated for section 5.1.

Conclusions

The results of the long term Study 110 Part A and Part B indicate that efficacy is maintained for the subject with **F/RF** mutations (108/110 ES).

For the subjects with **F/F** mutations (106/110 ES), the benefit appears, less clear, as smaller effects over time compared to baseline are seen. However, this is a long term study with a duration of 24, 92 and 92 weeks treatment respectively in a progressive disease that shows deterioration over time. Therefore, it is not unexpected that the effect over time decreases. Nevertheless, as still an improvement over baseline is shown, the efficacy is maintained.

Overall, TEZ/IVA was generally safe and well tolerated in the 3 part of the study. Unlike the parent studies, this long term study also detected the signal of related psychiatric events. SmPC section 5.1 was updated to reflect final long term efficacy results of Study 110.

3. CHMP overall conclusion and recommendation

☒ **Fulfilled:**

4. Request for supplementary information P008

Based on the data submitted, the MAH should address the following questions as part of this procedure:

Pharmacokinetics

1. Summarized PK data for all timepoints should be provided. Further, in light of the trend of a reduced ppFEV1 in the 106/110 ES population (see efficacy part of this AR), Cmin over time figures should be provided for the 106/110 ES population, as well as for the 108/110, 103/110 and 111/110 ES populations.
2. The bioanalytical and validation reports for the bioanalytical assays used in this submission should be provided.

Clinical

3. For convenient and concise arrangement of the EPAR, the applicant is requested to provide a table as is provided for Part B, wherein the disposition of the subjects from Study 106 and Study 108 are displayed:

Disposition Reason	F/F Mutation n (%)	F/RF Mutation n (%)	Total[a] n (%)

4. For convenient and concise arrangement of the information in the EPAR, the applicant is requested to provide a table for the demographics and for the baseline disease characteristics, respectively, for the subjects from Study 106 and Study 108 in 1 table:

	F/F Mutation n (%)	F/RF Mutation n (%)	Total n (%)

5. Change in ppFEV1: while in the 106/110 ES ,TEZ/IVA-TEZ-IVA and PBO-TEZ/IVA groups have after 120 weeks a similar increase in ppFEV1, in 108/110 ES population important differences are observed i.e., PBO-TEZ/IVA 4.1%, IVA-TEZ/IVA 6.7% and TEZ/IVA-TEZ/IVA 7.5%. The

applicant is requested to discuss the results of the 108/110 ES population whether there is an explanation for the observed difference.

6. Part B, change in ppFEV1: The results are difficult to interpret because of the different durations of treatment with TEZ/IVA, but overall efficacy seems low after 192 weeks. The applicant is requested for an in depth discussion, that includes also the results per subset (Study 106 TEZ/IVA-TEZ/IVA, PBO-TEZ/IVA, Study 112 and Study 114).

7. For the subjects with F/F mutations (106/110 ES), the efficacy results in Part A and Part B are becoming less than in the parent Study 106, especially for patients who received TEZ/IVA already in the parent study. This occurs for most of the efficacy parameters. However, as this a long term study with a duration of 24, 92 and 92 weeks treatment respectively, the natural disease course of these patients may confound the observed effects. this observation. This applicant is requested to discuss this overall picture of the results.

8. Part B PEx: For the F/RF group, the estimated event rate per year for PEx is higher than in the parent Study 108 and in Part A of Study 110. The applicant is requested to discuss.

9. Part A CFQ-R: The LS mean absolute changes from parent study baseline at Week 96 of Part A were 3.0 points (95% CI: 0.7, 5.3) and 1.7 points (95% CI: -0.6, 4.0) for the TEZ/IVA-TEZ/IVA group and PBO-TEZ/IVA group, respectively. As the minimum clinically important difference is 4.0 point, the subjects as a group did not meet this MCID. Please provide responder analyses of the % of subjects meeting the MCID.

Safety

10. The immunisation reactions in Part C are remarkably high (7.4%), but these were all considered not related or unlikely related to study drug. The applicant is asked to clarify the high number of immunisation reactions.

11. For a fair comparison of the AEs, events/100 patient years are requested for the PC-SS, safety set Part A, safety set Part B and safety set Part C in one table for AEs occurring in ≥ 5% of subjects.

12. The Grade 3/4 AEs are presented in separate, extensive tables. To allow for the assessment of these events, the events/100 patient years of the grade 3/4 are requested for the PC-SS, safety set Part A, safety set Part B and safety set Part C in one table for Grade 3/4 AEs occurring in ≥ 2 subjects.

13. The related AEs are presented in separate, extensive tables. To allow for the assessment of these events, the events/100 patient years of the related AE are requested for the PC-SS, safety set Part A, safety set Part B and safety set Part C in one table for related AEs occurring in ≥2% of the subjects.

14. The applicant is requested to discuss all the reported observations of negative thoughts, suicidal ideation and suicide in the PC-SS, safety set Part A, safety set Part B and safety set Part C.

15. The applicant is requested to discuss all the reported event of hepatotoxicity during the clinical programme i.e., events in all the parent studies and Study 110.

16. The SAEs in the subgroups are presented in extensive tables. To allow for the assessment of these events, the number (%) of the SAE are requested for the PC-SS and safety set Part A in one table for SAEs occurring in ≥ 3 subjects in any group.

17. The number of subjects with cataract in part B is not clearly provided, as only reference is made to an extensive table. The applicant is requested to provide the number of subjects with cataract, including a short description.

Statistical

18. The Applicant is requested to clarify how many patients left Study 110 for another Vertex study and re-entered later in the Study 110 and the rationale behind allowing this. In case this occurred, the impact and possible bias should be discussed (including a sensitivity analysis which omits these subjects). Also, it should be confirmed whether the trajectories were 'glued together' (e.g. if a subject left at Day 50 and re-entered, the study day in Study 110 for that subject would start at Day 51).

The timetable is a 30 day response timetable with clock stop.

MAH responses to Request for supplementary information P008

PHARMACOKINETICS

Question 1

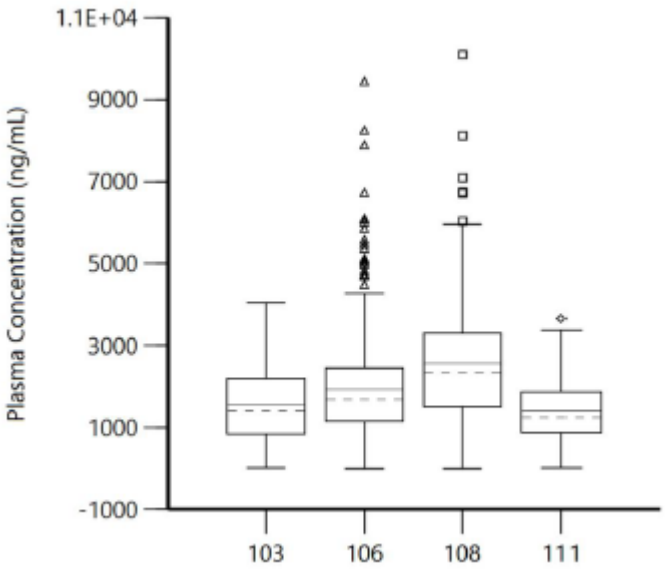
Summarized PK data for all timepoints should *be provided. Further, in light of the trend of a reduced ppFEV1 in the 106/110 ES population (see efficacy part of this AR), Cmin over time figures should be provided for the 106/110 ES population, as well as for the 108/110, 103/110 and 111/110 ES populations.*

Summary of the MAH's response

Vertex clarifies that pharmacokinetics (PK) samples were only collected at the Part A, Week 24 Visit, so it is not possible to assess PK trends over time in Study 110 in relation to the trend in percent predicted forced expiratory volume in 1 second (ppFEV1) (Question 6). These PK data are summarized in Study 110 CSR/Table 11-1, Figure 11-1, and Figure 11-2.

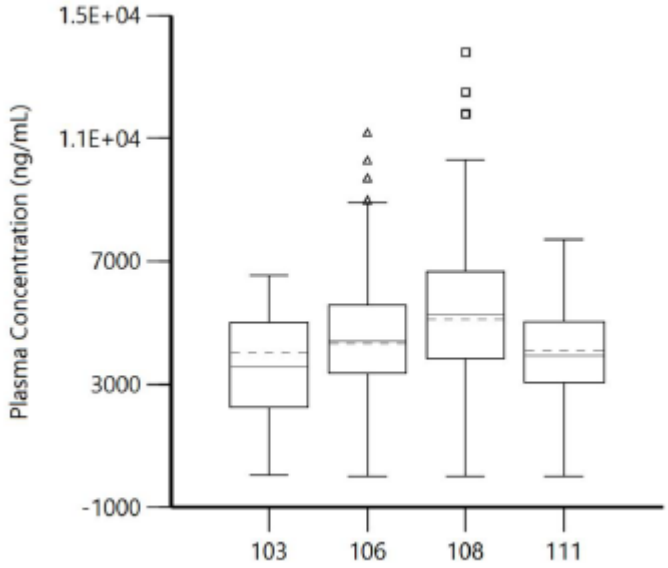
As requested, box plots of Cmin values at Week 24 are stratified by Efficacy Set (ES) (103/110, 106/110, 108/110, and 111/110) for tezacaftor (TEZ) (**Figure 23**), M1-TEZ (**Figure 24**), ivacaftor (IVA) (Figure 25), and M1-IVA (Figure 26).

Figure 23 Box Plot of Plasma Concentrations of TEZ Following Administration of 100 mg TEZ qd/150 mg IVA q12h by Efficacy Set



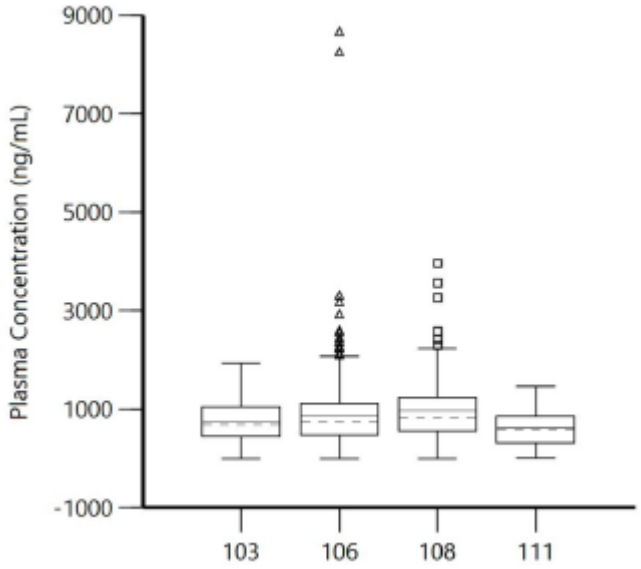
IQR: interquartile range; IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor
Notes: Dashed line represents median; solid line represents arithmetic mean; the box represents 25th and 75th percentiles; whiskers represent the lowest and highest value still within 1.5 of the IQR. Data values outside of the 1.5 × IQR are shown as individual points.

Figure 24 Box Plot of Plasma Concentrations of M1-TEZ Following Administration of 100 mg TEZ qd/150 mg IVA q12h by Efficacy Set



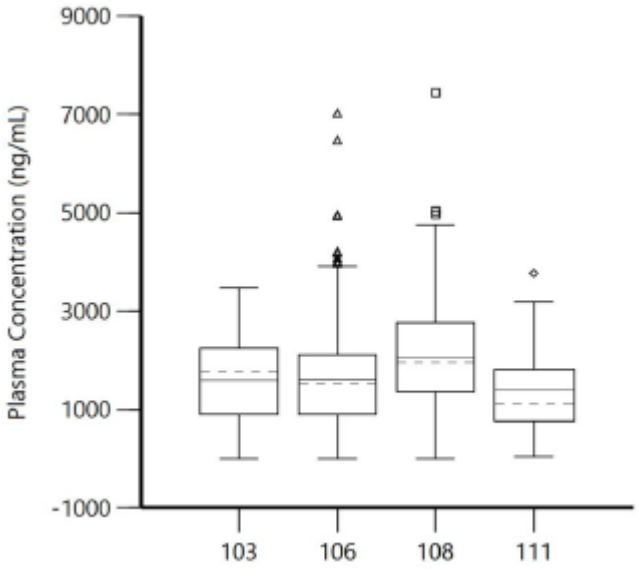
IQR: interquartile range; IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor; M1-TEZ: metabolite of tezacaftor
Notes: Dashed line represents median; solid line represents arithmetic mean; the box represents 25th and 75th percentiles; whiskers represent the lowest and highest value still within 1.5 of the IQR. Data values outside of the 1.5 × IQR are shown as individual points.

***Figure 25** Box Plot of Plasma Concentrations of IVA Following Administration of 100 mg TEZ qd/150 mg IVA q12h by Efficacy Set*



IQR: interquartile range; IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor
Notes: Dashed line represents median; solid line represents arithmetic mean; the box represents 25th and 75th percentiles; whiskers represent the lowest and highest value still within 1.5 of the IQR. Data values outside of the 1.5 × IQR are shown as individual points.

***Figure 26** Figure 4 Box Plot of Plasma Concentrations of M1-IVA Following Administration of 100 mg TEZ qd/150 mg IVA q12h by Efficacy Set*



IQR: interquartile range; IVA: ivacaftor; M1-IVA: metabolite of ivacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor
Notes: Dashed line represents median; solid line represents arithmetic mean; the box represents 25th and 75th percentiles; whiskers represent the lowest and highest value still within 1.5 of the IQR. Data values outside of the 1.5 × IQR are shown as individual points.

A summary of Cmin values at Week 24 of TEZ, M1-TEZ, IVA, and M1-IVA is presented in Table 1. A summary of Cmin values at steady-state of TEZ, M1-TEZ, IVA, and M1-IVA from the parent study is presented in Table 2. The mean concentrations for all analytes were similar between Efficacy Set (ES)

populations in Study 110. In addition, the Week 24 PK exposures of TEZ, IVA, M1-TEZ, and M1-IVA observed in Study 110 were similar to those observed in the parent studies, and consistent with the established PK profile for TEZ/IVA, suggesting that there was no clinically meaningful change in exposure over time across ES populations.

Table 48 Summary of Plasma Concentrations (ng/ml) of TEZ, M1-TEZ, IVA and M1-IVA Following Administration of 100 mg TEZ qd/150 mg IVA q12h at Week 24 by Efficacy Set

	103/110 (N = 23)	106/110 (N = 439)	108/110 (N = 223)	111/110 (N = 31)
Analyte	**Mean (CV%)**			
TEZ	1550 (69.6)	1930 (67.0)	2550 (61.7)	1400 (57.8)
M1-TEZ	3560 (54.2)	4400 (42.5)	5270 (45.4)	3920 (43.1)
IVA	745 (63.6)	880 (85.8)	973 (64.5)	631 (58.8)
M1-IVA	1600 (60.7)	1610 (61.3)	2050 (55.3)	1390 (64.1)

Source: Study 110 CSR/Appendix 16.2.5.2.1
CV: coefficient of variation; IVA: ivacaftor; M1-IVA: metabolite of ivacaftor; N: total sample size; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor; M1-TEZ: metabolite of tezacaftor

Table 49 Summary of Plasma Concentrations (ng/ml) of TEZ, M1-TEZ, IVA and M1-IVA at Steady-State Following Administration of 100 mg TEZ qd/150 mg IVA q12h from Parent Study

	103 (N = 15) Week 12 predose	106 (N = 233) Week 16 predose	108 (N = 161[a]) Week 8 predose	111 (N = 27) Day 29 predose
Analyte	**Mean (CV%)**			
TEZ	1750 (56.7)	1890 (60.9)	2370 (56.0)	1630 (46.2)
M1-TEZ	4030 (48.2)	4730 (36.5)	5230 (37.1)	4720 (25.7)
IVA	605 (57.4)	815 (70.2)	909 (58.3)	636 (49.8)
M1-IVA	1210 (57.7)	1590 (60.3)	2010 (52.4)	1540 (57.2)

Source: Study 110 CSR/Appendix 16.2.5.2.1
CV: coefficient of variation; IVA: ivacaftor; M1-IVA: metabolite of ivacaftor; N: total sample size; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor; M1-TEZ: metabolite of tezacaftor
[a] N = 157 for IVA and N = 159 for M1-IVA

Assessment of the MAH's response

Since PK samples in Study 110 were only collected at the Part A, Week 24 Visit, it not possible to assess PK trends over time in Study 110 in relation to the trend in ppFEV1. However, provided C_{min} data for the other studies 103, 106, 108 and 111 indicate no clinically meaningful change in exposure over time. Week 24 PK exposures of TEZ, IVA, M1-TEZ, and M1-IVA observed in Study 110 were similar to those observed in the parent studies. Therefore, it is not expected that the observed decrease in ppFEV1 over time is caused by changes in exposure.

As indicated in Question 6, it is accepted that the changes in ppFEV1 in Part B (i.e. a progressive decrease in treatment effect) are most likely attributable to the progressive nature of cystic fibrosis (CF) lung disease.

Conclusion

Issue resolved

Question 2

The bioanalytical and validation reports for the bioanalytical assays used in this submission should be provided.

Summary of the MAH's response

Vertex response

The requested reports are provided with these responses.

- Report M314
- Report P163

Assessment of the MAH's response

The bioanalytical reports, with reference to the validation report for PPD Method P1331, issued 25 June 2015, were provided.

Conclusion

Issue resolved.

CLINICAL

Question 3

For convenient and concise arrangement of the EPAR, the applicant is requested to provide a table as is provided for part B, wherein the disposition of the subjects from study 106 and study 108 are displayed:

Disposition Reason	F/F Mutation n (%)	F/RF Mutation n (%)	Total[a] n (%)

Summary of the MAH's response

The requested disposition tables are provided with these responses for Study 110 Part A (Ad hoc Ad hoc **Table**), Part B (Ad hoc Table 3.2), and Part C (Ad hoc Table 3.3).

Ad hoc Table 3.1 Disposition in 110A for F/F from 106 and F/RF from 108 106/108-110A Safety Set

Disposition/Reason	F/F Mutation n (%)	F/RF Mutation n (%)	Total n (%)
106/108-110A Safety Set	459	226	685**
106/108-110A Analysis Set	459	226	685
F/F Mutation Efficacy Set	459	--	459
F/RF Mutation Efficacy Set	--	226	226
Completed treatment	403 (87.8)	207 (91.6)	610 (89.1)
Discontinued treatment	55 (12.0)	19 (8.4)	74 (10.8)
Reason for discontinuation of treatment*			
Adverse event	13 (2.8)	6 (2.7)	19 (2.8)
Subject refused further dosing (not due to AE)	20 (4.4)	4 (1.8)	24 (3.5)
Lost to follow-up	3 (0.7)	1 (0.4)	4 (0.6)
Commercial drug is available for subject	0	3 (1.3)	3 (0.4)
Death	0	0	0
Did not meet eligibility criteria	0	0	0
Non-compliance with study drug	1 (0.2)	1 (0.4)	2 (0.3)
Other non-compliance	0	1 (0.4)	1 (0.1)
Physician decision	7 (1.5)	0	7 (1.0)
Requires prohibited medication	2 (0.4)	1 (0.4)	3 (0.4)
Pregnancy (self or partner)	3 (0.7)	2 (0.9)	5 (0.7)
Study terminated by sponsor	0	0	0
Other	6 (1.3)	0	6 (0.9)

Completed Part A of the Study	412 (89.8)	211 (93.4)	623 (90.9)
Discontinued from Part A of the Study	47 (10.2)	15 (6.6)	62 (9.1)
Reason for discontinuation			
Rolled over into another study	0	0	0
Adverse event	10 (2.2)	4 (1.8)	14 (2.0)
Withdrawal of consent (not due to AE)	18 (3.9)	3 (1.3)	21 (3.1)
Lost to follow-up	5 (1.1)	1 (0.4)	6 (0.9)
Commercial drug is available for subject	0	3 (1.3)	3 (0.4)
Death	0	0	0
Other non-compliance	2 (0.4)	2 (0.9)	4 (0.6)
Physician decision	3 (0.7)	2 (0.9)	5 (0.7)
Sponsor decision	0	0	0
Study terminated by sponsor	0	0	0
Other	9 (2.0)	0	9 (1.3)
Subjects from each parent study**			
Parent Study 106	459	--	459
Parent Study 108	--	226	226

- 106/108-110B Safety Set: all subjects who rolled over from either parent study 106 or 108 and completed study 110 Part A, and have received at least 1 dose of study drug in Study 110 Part B.
- 106/108-110B Analysis Set: all subjects, who rolled over from either parent study 106 or 108 and completed study 110 Part A, have received at least 1 dose of study drug in Study 110 Part B.
- F/F Mutation Efficacy Set includes subjects in the 106/108-110B Analysis Set who rolled over to Study 110 Part B originally from Study 106.
- F/RF Mutation Efficacy Set includes subjects in the 106/108-110B Analysis Set who rolled over to Study 110 Part B originally from Study 108.
- Percentages use the number of subjects in the Safety set as denominator.
- * If a subject discontinued treatment for multiple reasons, the subject is counted in each category but counted only once in the total number of subjects who discontinued treatment.
- Total column is the sum of F/F Mutation and F/RF Mutation Efficacy Sets.

Assessment of the MAH's response

The MAH provided the requested table (i.e. requested for Part A). For **Part B and Part C,** the tables were already presented (Table 9, Table 11). Therefore, Ad hoc Table 3.2 and Ad hoc Table 3.3. are not presented.

In Part A, there are only small differences in the reason for discontinuation. The main reason in discontinuation was adverse event (2.8%) and 'refused further dosing not due to AE' (3.5%). 'Refused further dosing not due to AE' was higher in subjects with F/F mutation (4.4%).

Conclusion

Issue resolved.

Question 4

For convenient and concise arrangement of the information in the EPAR, the applicant is requested to provide a table for the demographics and for the baseline disease characteristics, respectively, for the subjects from study 106 and study 108 in 1 table:

	F/F Mutation n (%)	F/RF Mutation n (%)	Total n (%)

Summary of the MAH's response

Ad hoc Table 4.1 Demographics 106/108-110A Analysis Set

	F/F Mutation N = 459	F/RF Mutation N = 226	Total N = 685
Sex, n (%)			
Male	237 (51.6)	105 (46.5)	342 (49.9)
Female	222 (48.4)	121 (53.5)	343 (50.1)
Childbearing potential[1], n (%)			
Yes	191 (86.0)	97 (80.2)	288 (84.0)
No	31 (14.0)	24 (19.8)	55 (16.0)
Reason not of childbearing potential[2], n (%)			
Surgical Procedure	6 (19.4)	8 (33.3)	14 (25.5)
Postmenopausal	3 (9.7)	12 (50.0)	15 (27.3)
Premenarchal	21 (67.7)	4 (16.7)	25 (45.5)
Other	1 (3.2)	0	1 (1.8)
Age at screening[3] (years)			
n	459	226	685
Mean (SD)	26.1 (10.4)	35.1 (14.2)	29.0 (12.5)
Median	25.0	35.0	27.0
Min, max	12, 64	12, 72	12, 72
Age group at screening (years), n (%)			
<18	109 (23.7)	32 (14.2)	141 (20.6)
≥18	350 (76.3)	194 (85.8)	544 (79.4)
Ethnicity, n (%)			
Hispanic or Latino	8 (1.7)	7 (3.1)	15 (2.2)
Not Hispanic or Latino	443 (96.5)	218 (96.5)	661 (96.5)
Not collected per local regulations	8 (1.7)	1 (0.4)	9 (1.3)
Race, n (%)			
White	454 (98.9)	221 (97.8)	675 (98.5)
Black or African American	1 (0.2)	2 (0.9)	3 (0.4)
Asian	2 (0.4)	0	2 (0.3)
American Indian or Alaska Native	0	1 (0.4)	1 (0.1)
Native Hawaiian or other Pacific Islander	0	0	0
Not collected per local regulations	0	1 (0.4)	1 (0.1)
Other	2 (0.4)	1 (0.4)	3 (0.4)
Geographic region, n (%)			
North America	112 (24.4)	109 (48.2)	221 (32.3)
Europe	347 (75.6)	117 (51.8)	464 (67.7)

- 106/108-110A Analysis Set: all subjects, who rolled over from either parent study 106 or 108, and have received at least 1 dose of study drug in Study 110 Part A and meet the mutation eligibility criteria of F508del/F508del (F/F) or F508del/Residual function (F/RF).
- F/F Mutation Set consists of all subjects in 106/108-110A Analysis Set that were rolled over from study 106.
- F/RF Mutation Set consists of all subjects in 106/108-110A Analysis Set that were rolled over from study 108.
- [1]: Female n is the denominator.
- [2]: Female n with no childbearing potential is the denominator.
- [3]: Screening is the screening to the parent study.
- All demographic data, except sex, childbearing potential, reasons for not childbearing potential and regions are based on the data collected in the parent study.
- Total column is the sum of F/F Mutation and F/RF Mutation Efficacy Sets.
- Australia is included with Europe region.

Ad hoc Table 4.4 Baseline Characteristics 106/108-110A Analysis Set

	F/F Mutation N = 459	F/RF Mutation N = 226	Total N = 685
Weight (kg)			
n	459	226	685
Mean (SD)	58.4 (12.1)	69.6 (17.2)	62.1 (14.9)
Median	57.0	67.8	60.0
Min, max	29.0, 107.0	40.0, 156.9	29.0, 156.9
Weight z-score (subjects <20 years old at screening)			
n	145	39	184
Mean (SD)	-0.59 (0.95)	-0.01 (1.28)	-0.47 (1.05)
Median	-0.56	0.31	-0.41
Min, max	-3.32, 1.85	-2.63, 2.18	-3.32, 2.18
Height (cm)			
n	459	226	685
Mean (SD)	166.0 (10.0)	169.0 (9.5)	167.0 (10.0)
Median	166.0	169.0	167.0
Min, max	137.0, 193.0	146.0, 195.0	137.0, 195.0
Height z-score (subjects <20 years old at screening)			
n	145	39	184
Mean (SD)	-0.42 (0.95)	0.16 (0.86)	-0.30 (0.96)
Median	-0.46	0.12	-0.35
Min, max	-3.28, 1.63	-1.73, 2.11	-3.28, 2.11
BMI (kg/m^2)			
n	459	226	685
Mean (SD)	21.00 (2.94)	24.21 (5.00)	22.06 (4.04)
Median	20.72	23.49	21.45
Min, max	13.67, 32.24	15.19, 49.65	13.67, 49.65
BMI z-score (subjects <20 years old at screening)			
n	145	39	184
Mean (SD)	-0.50 (0.89)	-0.19 (1.39)	-0.44 (1.02)
Median	-0.52	0.05	-0.39
Min, max	-3.45, 1.87	-3.41, 2.23	-3.45, 2.23
$ppFEV_1$ (%)			
n	458	226	684
Mean (SD)	60.0 (15.1)	62.2 (14.5)	60.7 (14.9)
Median	59.3	61.4	60.4
Min, max	27.8, 96.2	34.6, 93.5	27.8, 96.2
$ppFEV_1$ (%)			
<40	42 (9.2)	20 (8.8)	62 (9.1)
≥40 to <70	283 (61.7)	132 (58.4)	415 (60.6)
≥70 to ≤90	125 (27.2)	70 (31.0)	195 (28.5)
>90	8 (1.7)	4 (1.8)	12 (1.8)
Missing	1 (0.2)	0	1 (0.1)
FEV_1 (L)			
n	458	226	684
Mean (SD)	2.12 (0.67)	2.21 (0.74)	2.15 (0.69)
Median	2.06	2.05	2.06
Min, max	0.76, 4.17	0.88, 4.72	0.76, 4.72

- 106/108-110A Analysis Set: all subjects, who rolled over from either parent study 106 or 108, and have received at least 1 dose of study drug in Study 110 Part A and meet the mutation eligibility criteria of F508del/F508del (F/F) or F508del/Residual function (F/RF).
- F/F Mutation Set consists of all subjects in 106/108-110A Analysis Set that were rolled over from study 106.
- F/RF Mutation Set consists of all subjects in 106/108-110A Analysis Set that were rolled over from study 108.
- Baseline is defined as baseline of the parent study.
- BMI: Body Mass Index = Weight/(Height*Height) (kg/m^2).
- Z-scores are calculated using US National Center for Health Statistics growth charts.
- Total column is the sum of F/F Mutation and F/RF Mutation Efficacy Sets.
- $ppFEV_1$ is derived using Hankinson and Wang standards.

Ad hoc Table 4.6 Baseline Characteristics 106/108-110C Subjects Set

	F/F Mutation N = 126	F/RF Mutation N = 69	Total N = 195
Weight (kg)			
n	126	69	195
Mean (SD)	57.8 (11.8)	66.0 (14.6)	60.7 (13.4)
Median	58.0	66.0	59.0
Min, max	31.0, 91.0	40.0, 99.0	31.0, 99.0
Weight z-score (subjects <20 years old at screening)			
n	30	14	44
Mean (SD)	-1.01 (0.87)	0.07 (1.47)	-0.66 (1.19)
Median	-0.87	0.77	-0.79
Min, max	-3.32, 0.42	-2.25, 2.18	-3.32, 2.18
Height (cm)			
n	126	69	195
Mean (SD)	165.7 (10.2)	168.7 (9.6)	166.8 (10.1)
Median	166.0	170.0	167.0
Min, max	142.0, 189.0	150.0, 188.0	142.0, 189.0
Height z-score (subjects <20 years old at screening)			
n	30	14	44
Mean (SD)	-0.86 (0.93)	0.38 (0.89)	-0.47 (1.08)
Median	-0.64	0.14	-0.45
Min, max	-2.80, 1.16	-0.76, 2.11	-2.80, 2.11
BMI (kg/m^2)			
n	126	69	195
Mean (SD)	20.89 (2.81)	23.06 (4.20)	21.66 (3.52)
Median	20.66	22.57	20.94
Min, max	14.74, 32.24	15.19, 34.63	14.74, 34.63
BMI z-score (subjects <20 years old at screening)			
n	30	14	44
Mean (SD)	-0.72 (0.78)	-0.28 (1.71)	-0.58 (1.15)
Median	-0.62	0.22	-0.55
Min, max	-2.74, 0.79	-3.41, 2.23	-3.41, 2.23
$ppFEV_1$ (%)			
n	126	69	195
Mean (SD)	59.8 (15.2)	61.8 (14.1)	60.5 (14.8)
Median	57.2	60.6	58.7
Min, max	35.4, 91.3	35.1, 90.6	35.1, 91.3
$ppFEV_1$ (%)			
<40	9 (7.1)	6 (8.7)	15 (7.7)
≥40 to <70	80 (63.5)	42 (60.9)	122 (62.6)
≥70 to ≤90	36 (28.6)	20 (29.0)	56 (28.7)
>90	1 (0.8)	1 (1.4)	2 (1.0)
FEV_1 (L)			
n	126	69	195
Mean (SD)	2.13 (0.69)	2.22 (0.73)	2.17 (0.70)
Median	2.09	2.15	2.10
Min, max	1.08, 4.00	1.01, 3.79	1.01, 4.00

- 106/108-110C Subjects Set: all subjects, who rolled over from either parent study 106 or parent study 108 and completed study 110 Part B, enrolled or have received at least 1 dose of study drug in Study 110 Part C.
- F/F Mutation Set consists of all subjects in 106/108-110C Analysis Set that were originally rolled over from study 106.
- F/RF Mutation Set consists of all subjects in 106/108-110C Analysis Set that were originally rolled over from study 108.
- Baseline is defined as baseline of the parent study.
- BMI: Body Mass Index = Weight/(Height*Height) (kg/m^2).
- Z-scores are calculated using US National Center for Health Statistics growth charts.
- Total column is the sum of F/F Mutation and F/RF Mutation Efficacy Sets.
- $ppFEV_1$ is derived using Hankinson and Wang standards.

Assessment of the MAH's response

The MAH provided the requested table (i.e. requested for part A). For **Part B and Part C**, the tables were already presented (Table 15, Table 16, Table 17) except for the baseline characteristics of Part C. Therefore, the submitted Ad hoc Table 4.2, Table 4.3, and Table 4.5 are not presented.

In **Part A**, the mean age in subjects with F/RF mutation was clearly higher (35.1 years) than in subjects with F/F mutation (26.1 years). This difference may be explained with the difference in severity of the diseases between the 2 groups, i.e., sign and symptoms are milder and e.g. lung function is longer preserved, leading to a longer survival. The difference in nutritional parameters at baseline can be also explained with the difference in severity.

To be noted baseline is defined as baseline of the parent study. Therefore baseline of Part B and Part C are quite similar to baseline of Part A with only small differences that can be contributed to the difference in numbers of subjects in the parts.

Conclusion

Issue resolved.

Question 5

Change in ppFEV1: while in the 106/110 ES ,TEZ/IVA-TEZ-IVA and PBO-TEZ/IVA groups have after 120 weeks a similar increase in ppFEV1, in 108/110 ES population important differences are observed i.e., PBO-TEZ/IVA 4.1%, IVA-TEZ/IVA 6.7% and TEZ/IVA-TEZ/IVA 7.5%. The applicant is requested to discuss the results of the 108/110 ES population whether there is an explanation for the observed difference.

Summary of the MAH's response

Vertex clarifies that the timepoint referenced in Question 5 corresponds to the Week 96 Visit of Study 110 Part A.

Vertex considers that numerical differences in the mixed-effects model for repeated measures (MMRM) analysis of absolute change from baseline in ppFEV1 at Study 110 Part A Week 96 do not represent a statistically or clinically meaningful differences between treatment groups for the 108/110 ES. The 3 treatment groups had overlapping 95% confidence intervals (CI) for the MMRM analysis of absolute change from baseline in ppFEV1 (PBO-TEZ/IVA: 2.2, 6.0; IVA-TEZ/IVA: 4.7, 8.7; TEZ/IVA-TEZ/IVA: 5.6, 9.4); therefore these results are unable to be considered statistically different (Study 110 CSR/Table 11-4; Figure 5). Numerical differences in the LS mean change in ppFEV1 between treatment groups are judged not to be of clinical significance, with a well-maintained effect across time (Figure 5). The differences in observed point estimates are considered to be due to the sample size and individual subject variability; ppFEV1 is comparable across 108/110 ES groups.

Table 50 MMRM Analysis of Absolute Change From Baseline in ppFEV1 (Percentage Points) at Selected Visits during Study 110 Efficacy Analysis Period,108/110 ES

	PBO-TEZ/IVA N = 80	IVA-TEZ/IVA N = 70	TEZ/IVA-TEZ/IVA[a] N = 76
Baseline[b]			
n	80	70	76
Mean (SD)	62.2 (14.7)	62.0 (14.1)	62.4 (14.8)
Absolute change at Part A Day 15			
n	80	69	73
LS mean (SE)	4.2 (0.9)	5.7 (0.9)	7.0 (0.9)
95% CI	(2.5, 5.9)	(3.8, 7.5)	(5.2, 8.8)
Absolute change at Part A Week 24			
n	73	65	72
LS mean (SE)	5.2 (0.8)	6.5 (0.9)	7.3 (0.9)
95% CI	(3.5, 6.8)	(4.7, 8.3)	(5.6, 9.0)
Absolute change at Part A Week 48			
n	75	68	73
LS mean (SE)	5.4 (0.9)	6.3 (1.0)	7.1 (0.9)
95% CI	(3.6, 7.2)	(4.5, 8.2)	(5.3, 8.9)
Absolute change at Part A Week 72			
n	69	66	66
LS mean (SE)	4.3 (0.9)	6.2 (1.0)	7.0 (1.0)
95% CI	(2.5, 6.2)	(4.2, 8.2)	(5.1, 8.9)
Absolute change at Part A Week 96			
n	68	61	67
LS mean (SE)	4.1 (1.0)	6.7 (1.0)	7.5 (1.0)
95% CI	(2.2, 6.0)	(4.7, 8.7)	(5.6, 9.4)

Source: Table 14.2.1.2.2

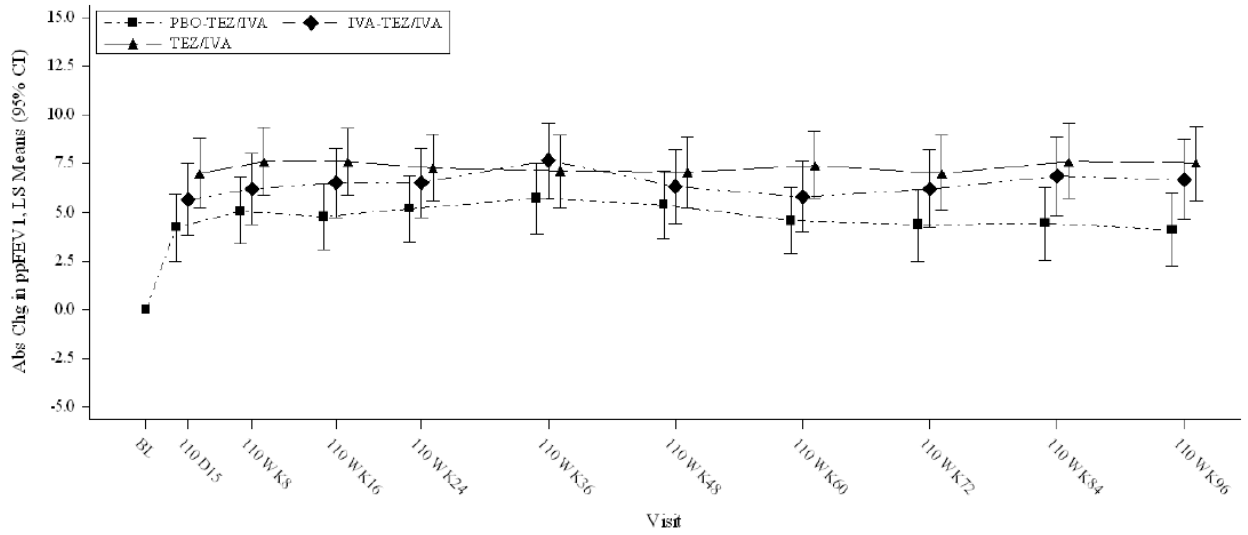
ES: Efficacy Set; IVA: ivacaftor; LS mean: least squares mean; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; PBO: placebo; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

Notes: The following MMRM was used: treatment, visit, treatment × visit, and parent study baseline $ppFEV_1$ as fixed effects. An unstructured covariance structure was used to model the within-subject errors, and the denominator degrees of freedom were based on the method proposed by Kenward-Roger.

[a] TEZ/IVA-TEZ/IVA treatment group corresponds to TEZ/IVA treatment group in source table.

[b] The efficacy analysis baseline was defined as the parent study baseline.

Figure 27 MMRM Analysis of Absolute Change from Baseline in Percent Predicted FEV1 (Percentage Points) at Each Visit - 110 Efficacy Analysis Period 108/110 Efficacy Set



Source: Study 110 CSR/Figure 14.2.1.2.2

BL: baseline; D: day; IVA: ivacaftor; LS: least squares mean; MMRM: mixed-effects model for repeated measures; PBO: placebo; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor; WK: week

Notes: Treatment group assignment are PBO-TEZ/IVA, IVA-TEZ/IVA or TEZ/IVA for subjects randomized to Placebo, IVA or TEZ/IVA in Period 2 of Study 108 respectively. The following mixed model for repeated measures was used: treatment, visit, treatment*visit and parent study baseline $ppFEV_1$ as fixed effects. Covariance Structure = UN, DF = Kenward-Roger. If the model failed to converge due to the UN covariance assumption, a CS covariance structure was used. Covariance Structure = UN is used. Post-baseline visits in Study 108 are excluded in this model. Baseline is defined as the most recent non-missing measurement collected prior to the first dose of study drug in Study 108. Percent predicted FEV_1 is derived using Hankinson and Wang standards.

Assessment of the MAH's response

The MAH considers that the numerical differences in the MMRM analysis of absolute change from baseline in ppFEV1 do not represent a statistically or clinically meaningful differences between treatment groups for the 108/110 ES. The reasoning of the MAH is accepted i.e., the 3 treatment groups had overlapping 95% confidence intervals (CI) and therefore these results are unable to be considered statistically different. It is acknowledged that the differences in observed point estimates could be due to individual subject variability. It is indeed likely that the differences are due to subjects characteristics than rather due to differences in the treatment. Overall, the results at week 96 show maintenance of treatment effect.

Conclusion

Issue resolved.

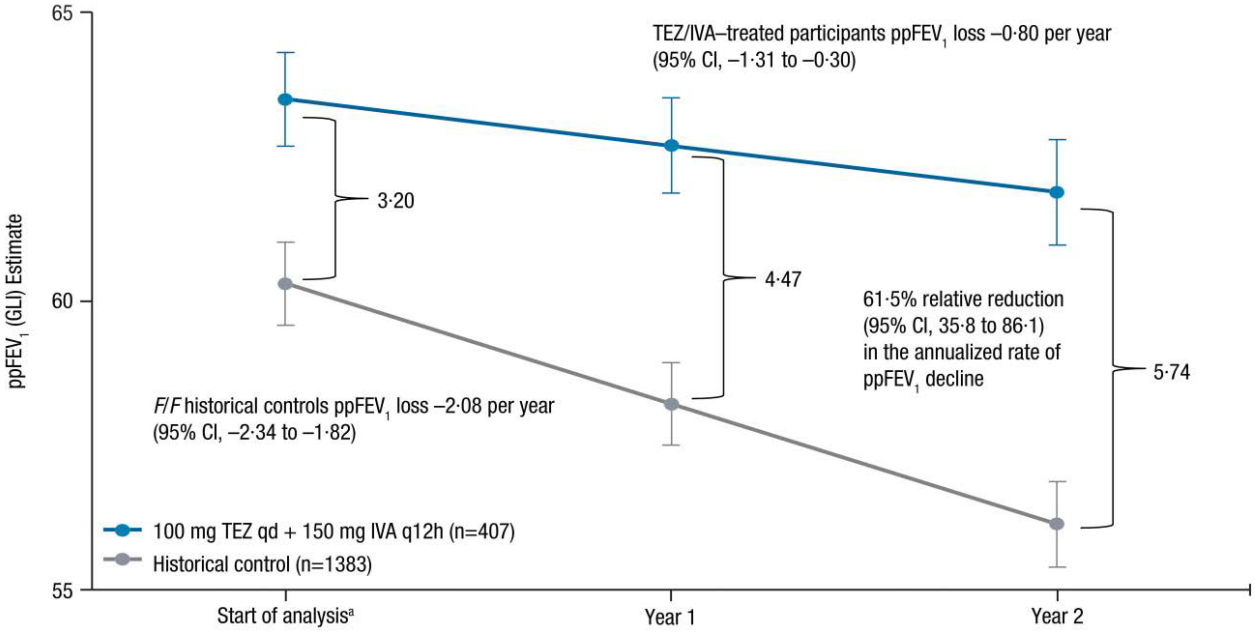
Question 6

Part B, change in ppFEV1: The results are difficult to interpret because of the different durations of treatment with TEZ/IVA, but overall efficacy seems low after 192 weeks. The applicant is requested for an in depth discussion, that includes also the results per subset (Study 106 TEZ/IVA-TEZ/IVA, PBO-TEZ/IVA, study 112 and study 114).

Summary of the MAH's response

Vertex acknowledges the Assessor's observation that the overall efficacy (as measured by absolute change from baseline in ppFEV1) for the F/F population declines slightly over 192 weeks (Study 110 Part B Week 96). Vertex considers that these changes in ppFEV1 in Part B are small and attributable to the progressive nature of cystic fibrosis (CF) lung disease. The natural history of CF in older adolescents and adults is marked by a progressive decline in lung function of approximately 1 to 3 percentage points per year.[1] TEZ/IVA therapy does not eliminate the decline in lung function entirely, but TEZ/IVA markedly slows the rate of decline (Figure 28).[2] In addition, it should be noted that people with CF with F/F genotypes generally have more severe disease than people with residual function (RF) genotypes (i.e., F/RF).

Figure 28 Rate of ppFEV1 Decline in Study 110 Part A Participants With the F/F Genotype



Source: Flume et al.[2] Figure S3

IVA: ivacaftorTEZ: tezacaftor

CI: confidence interval; CF: cystic fibrosis; F/F: homozygous for the *F508del-CFTR* mutation; GLI: Global Lung (Function) Initiative; LUM/IVA: lumacaftor/ivacaftor; $ppFEV_1$, percent predicted forced expiratory volume in 1 second using GLI equations; q12h: once every 12 hours; qd: once daily; TEZ/IVA, tezacaftor/ivacaftor combination therapy.

Notes: The F/F historical controls were propensity-matched controls from the CF Foundation Patient Registry between 2012 and 2014 to avoid the confounding effect of use of LUM/IVA, a CFTR modulator that was approved by the US Food and Drug Administration for this population in 2015.

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

Importantly, the ppFEV1 after approximately 4 years of TEZ/IVA treatment remain increased compared to baseline for both the 106/110 ES (F/F) and 108/110 ES (F/RF), as shown in Table 51. Therefore, the results after approximately 4 years of TEZ/IVA treatment are consistent with a positive treatment effect against the expected background of progressive decline (which is expected to be more severe in people with CF with F/F genotypes as compared to those with F/RF genotypes).

Table 51 Summary of Mean (SD) Absolute Change From Baseline in ppFEV1 at Selected Study Visits (percentage points)

	Mean (SD) Absolute Change From Baseline	
Study Visit	**106/110 (F/F) ES**	**108/110 (F/RF) ES**
Part A, Week 96	2.2 (8.9)	6.5 (8.4)
Part B, Week 96 (Week 192 of Study 110)	1.7 (10.2)	8.3 (8.6)

Sources: Study 110 Part A CSR/Table 14.2.1.1.1, Study 110 Part A CSR/Table 14.2.1.1.2, Study 110 CSR/Table 11-19

CSR: clinical study report; ES: Efficacy Set; F: *F508del*; ES: Efficacy Set; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; RF: residual function;

As requested, the results at each Study 110 Part B study visit by parent study and treatment group for Study 106 TEZ/IVA-TEZ/IVA, PBO-TEZ/IVA, Study 112 and Study 114 are provided in Ad hoc Table 6.1, and below for Week 96 (Table 52). The results of these analyses should be interpreted with caution due to differences in cohort attrition, small sample size for each population, and high variability, as reflected in the overlapping 95% CIs.

Table 52 Absolute Change from Baseline in ppFEV1 at Week 96 in Study 110 Part B, 106/112/114-110B Analysis Set

		106-110B			
	Statistic	**PBO-TEZ/IVA N = 127**	**TEZ/IVA-TEZ/IVA N = 133**	**112-110B N = 39**	**114-110B N = 47**
Absolute Change at Study 110B Week 96	n	57	61	8	6
	Mean (SD)	3.1 (9.9)	-0.1 (11.1)	3.7 (5.0)	4.8 (5.1)
	95% CI[a]	(0.5, 5.6)	(-2.9, 2.7)	(0.2, 7.1)	(0.7, 8.8)
	Median	3.8	0.9	3.1	3.8
	Min, max	-19.6, 28.3	-46.0, 20.4	-1.9, 10.0	-0.5, 11.2

Source: Ad hoc Table 6.1

IVA: ivacaftor; PBO: placebo; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

Notes: 106/112/114-110B Analysis Set consists of all subjects, who originally rolled over from either parent study 106, 112 or 114, and have received at least 1 dose of study drug in Study 110 Part B. The same definition of baseline was used as in the SAP for Study 110 Part B. Baseline for subjects randomized to TEZ/IVA group in the parent studies 106, 112 and 114 is defined as the most recent non-missing measurement collected prior to the first dose of study drug in parent studies. Baseline for subjects randomized to placebo group in parent studies 106, 112 and 114 is defined as the most recent non-missing measurement collected prior to the first dose of TEZ/IVA in Study 110 Part A for Study 106 or Study 110 Part B for Studies 112 and 114. $ppFEV_1$ is derived using Hankinson and Wang standards.

[a] 95% CI is calculated with the Normal approximation.

Ad hoc Table 6.1 Summary of ppFEV1 and Absolute Change from Baseline at Each Visit in 110 Part B 106/112/114-110B Analysis Set

		106-110B			
	Statistic	PBO-TEZ/IVA N = 127	TEZ/IVA-TEZ/IVA N = 133	112-110B N = 39	114-110B N = 47
Baseline	n	126	132	39	47
	Mean (SD)	56.8 (14.7)	58.3 (14.7)	88.1 (15.3)	42.0 (14.2)
	95% CI*	(54.2, 59.3)	(55.7, 60.8)	(83.3, 92.9)	(37.9, 46.0)
	Median	56.3	56.6	88.5	36.2
	Min, max	31.2, 94.1	35.4, 89.9	64.7, 128.0	26.1, 84.1
110B Week 12	n	122	128	37	43
	Mean (SD)	59.3 (15.2)	60.4 (16.6)	89.2 (14.1)	44.1 (13.2)
	95% CI*	(56.6, 62.0)	(57.5, 63.3)	(84.7, 93.8)	(40.2, 48.1)
	Median	58.2	58.6	91.3	40.9
	Min, max	31.2, 101.1	28.6, 105.7	65.3, 115.0	25.4, 84.7
Absolute Change at Study 110B Week 12	n	122	127	37	43
	Mean (SD)	2.9 (7.2)	1.9 (8.2)	1.5 (5.6)	2.8 (5.7)
	95% CI*	(1.6, 4.2)	(0.5, 3.4)	(-0.3, 3.3)	(1.1, 4.5)
	Median	3.3	2.7	1.6	1.5
	Min, max	-20.0, 21.9	-26.2, 20.5	-13.0, 12.2	-8.7, 20.3
110B Week 24	n	102	113	39	40
	Mean (SD)	60.6 (15.7)	60.6 (17.6)	89.9 (14.7)	43.7 (15.1)
	95% CI*	(57.6, 63.7)	(57.4, 63.9)	(85.3, 94.5)	(39.0, 48.4)
	Median	61.8	61.7	91.8	38.5
	Min, max	31.5, 100.5	22.9, 103.9	62.7, 118.1	24.5, 92.3
Absolute Change at Study 110B Week 24	n	102	113	39	40
	Mean (SD)	3.7 (8.5)	1.4 (9.3)	1.8 (6.4)	1.8 (5.5)
	95% CI*	(2.1, 5.4)	(-0.3, 3.2)	(-0.2, 3.8)	(0.1, 3.5)
	Median	3.9	2.1	1.4	1.0
	Min, max	-19.2, 39.9	-32.1, 28.3	-10.4, 23.0	-10.4, 14.8
110B Week 36	n	91	104	37	24
	Mean (SD)	59.7 (16.4)	58.7 (17.1)	88.0 (16.3)	44.7 (14.0)
	95% CI*	(56.3, 63.1)	(55.4, 62.0)	(82.8, 93.3)	(39.1, 50.3)
	Median	62.6	56.5	88.0	39.5
	Min, max	29.0, 100.4	24.4, 106.2	41.2, 120.4	27.4, 85.5
Absolute Change at Study 110B Week 36	n	91	104	37	24
	Mean (SD)	3.2 (8.0)	-0.3 (8.7)	0.7 (8.3)	3.2 (5.9)
	95% CI*	(1.6, 4.9)	(-2.0, 1.3)	(-2.0, 3.3)	(0.8, 5.6)
	Median	2.8	0.3	0.4	1.7
	Min, max	-12.9, 30.8	-36.9, 22.0	-24.5, 26.7	-8.3, 14.5
110B Week 48	n	83	97	37	11
	Mean (SD)	59.8 (17.0)	58.5 (16.6)	87.2 (15.3)	41.9 (11.3)
	95% CI*	(56.1, 63.5)	(55.2, 61.8)	(82.2, 92.1)	(35.2, 48.5)
	Median	61.1	57.1	89.4	41.7
	Min, max	29.0, 102.7	27.3, 103.4	49.9, 119.3	26.3, 59.4
Absolute Change at Study 110B Week 48	n	83	97	37	11
	Mean (SD)	2.8 (8.7)	-0.2 (9.4)	-0.9 (7.3)	-0.3 (6.6)
	95% CI*	(0.9, 4.7)	(-2.1, 1.7)	(-3.3, 1.4)	(-4.2, 3.6)
	Median	2.5	0.1	-0.7	-1.2
	Min, max	-15.8, 26.9	-42.9, 19.2	-15.9, 10.6	-15.0, 8.3
110B Week 60	n	82	93	37	10
	Mean (SD)	59.5 (16.3)	58.7 (16.7)	88.6 (14.5)	41.3 (10.3)
	95% CI*	(55.9, 63.0)	(55.3, 62.1)	(83.9, 93.2)	(35.0, 47.7)
	Median	60.9	55.4	89.5	41.1
	Min, max	26.1, 98.4	22.1, 104.9	45.9, 118.8	25.7, 57.8
Absolute Change at Study 110B Week 60	n	82	93	37	10
	Mean (SD)	2.3 (9.3)	-0.3 (9.6)	0.5 (7.8)	-1.4 (8.5)
	95% CI*	(0.3, 4.3)	(-2.2, 1.7)	(-2.0, 3.0)	(-6.7, 3.8)
	Median	2.5	0.2	2.3	-1.3
	Min, max	-26.8, 31.6	-37.5, 19.5	-21.1, 15.5	-16.6, 13.2

110B Week 72	n	73	76	36	10
	Mean (SD)	59.8 (16.3)	58.4 (17.3)	87.3 (13.8)	44.8 (12.3)
	95% CI*	(56.0, 63.5)	(54.5, 62.3)	(82.8, 91.8)	(37.2, 52.4)
	Median	60.3	54.7	90.2	42.7
	Min, max	30.2, 96.8	23.5, 106.0	57.9, 112.9	26.9, 71.6
Absolute Change at Study 110B Week 72	n	73	76	36	10
	Mean (SD)	1.9 (8.6)	-0.9 (9.8)	-0.9 (7.8)	1.5 (6.5)
	95% CI*	(0.0, 3.9)	(-3.2, 1.3)	(-3.5, 1.6)	(-2.5, 5.5)
	Median	2.3	0.2	-0.9	0.1
	Min, max	-22.7, 25.3	-46.0, 20.2	-17.8, 12.0	-11.0, 10.9
110B Week 84	n	60	76	36	9
	Mean (SD)	59.8 (16.6)	58.7 (17.1)	88.7 (15.4)	49.2 (15.6)
	95% CI*	(55.6, 64.0)	(54.8, 62.5)	(83.6, 93.7)	(39.0, 59.4)
	Median	60.6	54.2	91.3	46.1
	Min, max	32.3, 102.0	22.0, 105.7	53.5, 121.0	33.6, 84.2
Absolute Change at Study 110B Week 84	n	60	76	36	9
	Mean (SD)	2.2 (10.4)	-0.5 (10.2)	0.1 (7.2)	5.4 (6.7)
	95% CI*	(-0.5, 4.8)	(-2.8, 1.8)	(-2.3, 2.4)	(1.0, 9.7)
	Median	2.6	0.0	0.9	7.1
	Min, max	-28.7, 30.0	-37.8, 19.9	-15.6, 10.7	-5.5, 16.0
110B Week 96	n	57	61	8	6
	Mean (SD)	59.9 (15.6)	59.8 (16.7)	88.8 (18.5)	46.1 (19.3)
	95% CI*	(55.9, 64.0)	(55.6, 64.0)	(76.0, 101.6)	(30.7, 61.6)
	Median	58.9	57.6	90.5	38.7
	Min, max	30.6, 98.9	34.2, 105.7	64.0, 120.5	34.5, 84.6
Absolute Change at Study 110B Week 96	n	57	61	8	6
	Mean (SD)	3.1 (9.9)	-0.1 (11.1)	3.7 (5.0)	4.8 (5.1)
	95% CI*	(0.5, 5.6)	(-2.9, 2.7)	(0.2, 7.1)	(0.7, 8.8)
	Median	3.8	0.9	3.1	3.8
	Min, max	-19.6, 28.3	-46.0, 20.4	-1.9, 10.0	-0.5, 11.2

- 106/112/114-110B Analysis Set consists of all subjects, who originally rolled over from either parent study 106, 112 or 114, and have received at least 1 dose of study drug in Study 110 Part B.
- The same definition of baseline was used as in the SAP for Study 110 Part B. Baseline for subjects randomized to TEZ/IVA group in the parent studies 106, 112 and 114 is defined as the most recent non-missing measurement collected prior to the first dose of study drug in parent studies. Baseline for subjects randomized to placebo group in parent studies 106, 112 and 114 is defined as the most recent non-missing measurement collected prior to the first dose of TEZ/IVA in Study 110 Part A for Study 106 or Study 110 Part B for Studies 112 and 114.
- $ppFEV_1$ is derived using Hankinson and Wang standards.
- *: 95% CI is calculated with the Normal approximation.

Assessment of the MAH's response

The explanation of the MAH is generally agreed. It is accepted that the changes in ppFEV1 in Part B (i.e. a progressive decrease in treatment effect) are most likely attributable to the progressive nature of cystic fibrosis (CF) lung disease. This is depicted in Figure 7, that shows the progressive decline in lung function of the natural history of CF in older adolescents and adults with the progressive decline in lung function when treated with TEZ/IVA.

Furthermore, the mean (SD) absolute change from study baseline to Week 96 was 1.7 (10.2)% for the subjects with F/F mutation in **Part B**. The results for the treatment group for Study 106, Study 112 and Study 114 demonstrated substantial differences between the groups, which can be explained that within the group of subjects with F/F mutation variability exists in response to treatment with TEZ/IVA.

It is also noted that overall the results for all groups at week 96 are remarkably higher than at Week 84 or 72, and other time points. This difference could be due to the small sample size of the remaining subjects. Nevertheless, there would be still an advantage over the natural history of CF.

Conclusion

Issue resolved

Question 7

For the subjects with F/F mutations (106/110 ES), the efficacy results in Part A and part B are becoming less than in the parent study 106, especially for patients who received TEZ/IVA already in the parent study. This occurs for most of the efficacy parameters.

However, as this a long term study with a duration of 24, 92 and 92 weeks treatment respectively, the natural disease course of these patients may confound the observed effects. This applicant is requested to discuss this overall picture of the results.

Summary of the MAH's response

Vertex acknowledges the Assessor's observation that the overall efficacy for the F/F population declines slightly after 192 weeks; however, this decline is considered expected given the progressive nature of CF disease and the impact of TEZ/IVA in reducing the rate of decline.[2] Overall, the small decline in efficacy outcomes is lower that what would be expected in the absence of TEZ/IVA therapy.

Please see response to Question 6 for further discussion.

Assessment of the MAH's response

The MAH has already discussed the observed decline of FEV1 over time under treatment with Symkevi in question 6. It is accepted that under treatment with TEZ/IVA therapy there is still a decline in lung function entirely, but improvements from baseline are still present

The MAH did not discuss the other parameters. However as discussed for subjects with F/RF mutations in Question 8, it is accepted that similar to the progressive decline in ppFEV1, also an increase in the rate of PEx over time and impact on the quality of life can be expected. The small decreases in the parameters are acceptable and can be contributed to the modifying effect of the natural history.

Conclusion

Issue not further pursued; the issue is sufficiently addressed.

Question 8

Part B PEx: For the F/RF group, the estimated event rate per year for PEx is higher than in the parent study 108 and in Part A of study 110. The applicant is requested to discuss.

Summary of the MAH's response

As noted in the responses to Questions 6 and 7, CF is a disease that is associated with progressive lung function decline that leads to premature death. Pulmonary exacerbations (PEx) are discrete events that occur throughout the life of a patient with CF and are characterized by worsening respiratory symptoms that often require treatment with antibiotics and/or hospitalization. PEx are associated with a more rapid rate of decline in lung function[3-5] and have a negative impact on survival.[6,7] Similar to the progressive decline in ppFEV1, people with CF also experience an increase in the rate of PEx over time.[8] Any improvement in lung function or a reduction in the natural decline of lung function is impactful for patients and their quality of life.

Vertex clarifies that the reported Study 110 Part B PEx event rate per year is the observed event rate, not the estimated (i.e., modelled) event rate, which was reported for Study 110 Part A and Study 108. For comparison, observed PEx rates with 95% CI are provided for TEZ/IVA groups for Study 108 and Study 110 Parts A and B in Table 53. Comparisons between Study 108 and Study 110 Parts A and B should be interpreted with caution given the differences in disease progression, sample size, and status of the ongoing coronavirus-19 (COVID-19) pandemic; however, the overlapping 95% CIs demonstrate that the rates are not statistically different. The numerical differences in event rates between Study 108 and Study 110 (Parts A and B) are consistent with the progressive nature of CF disease and natural variability in PEx events, as reflected in the overlapping 95% CIs. In addition, the observed PEx

event rate for the Study 108 placebo group (0.65 events/year) was notably higher than the rate for all TEZ/IVA treatment groups.

The totality of the PEx data does not suggest that long-term TEZ/IVA treatment leads to an increased rate of PEx, but rather suggests a treatment benefit over a longer period of time in the context of the natural history of a progressive disease.

Table 53 Summary of PEx during the PEx Analysis Period for Study 108, 110 Part A and Part B, PEx Analysis Set

	Study		
	108 N = 161	**108-110 Part A N = 233**	**108-110 Part B N = 106**
Total number of days (years) of the PEx analysis period	10378 (30.89)	152340 (453.39)	62132 (184.92)
Number of subjects with events, n (%)	11 (6.8)	104 (44.6)	43 (40.6)
Total number of events	11	186	94
Observed event rate per year	0.36	0.41	0.51
95% CI[a]	0.18, 0.64	0.35, 0.47	0.41, 0.62

Source: Ad hoc Table 8.1

CI: confidence interval; F: *F508del*; IVA: ivacaftor; PEx: pulmonary exacerbation; RF: residual function; TEZ: tezacaftor

Notes: PEx: new or changed antibiotic therapy, associated with signs and symptoms of a pulmonary infection, as defined in the Clinical Study Protocol. Total number of days = sum of the individual duration (actual number of days) of the PEx analysis period across all subjects. Total number of years = total number of days / 336; for analysis purposes, 1 year is defined as 48 weeks or 336 days. 108 PEx Analysis Set consists of subjects in Study 108 who received at least one dose of TEZ/IVA in either Treatment Period 1 or Treatment Period 2. 108-110A PEx analysis Set: defined as in the original SAP which consists of all randomized subjects from Study 108 who received TEZ/IVA during either Study 108 Period 2 or during Study 110. Subjects who received TEZ/IVA in Study 108 Period 1 and did not enroll in the treatment cohort of Study 110 will also be included. 108-110B PEx analysis Set: defined as in the original SAP which consists of all subjects in F/RF Mutation Efficacy group in Study 110 Part B. Observed Event rate per year is calculated as the total number of events divided by total number of years.

[a] Exact Poisson CI

Assessment of the MAH's response

For the F/RF group, a small increase over time was observed. When comparing the observed rate per year. However, in Part B, the observed rate per year is still lower than the rate in the Study 108 placebo group (0.65 events/year), despite the natural history. However, it should be noted that Study 108 had only a duration of 8 weeks, which is very short to measure exacerbations rate meaningfully. The differences between the 3 groups could be due to the natural variability in PEx events, low sample size, and status of the ongoing coronavirus-19 (COVID-19) pandemic. Furthermore, the populations in Part B is different form the population in Part A due to the inclusion of subjects of other parent studies. Moreover, as said before, consistently with that TEZ/IVA therapy does not eliminate the decline in lung function entirely, also an increase in the rate of PEx over time can be expected. Therefore, the differences are not considered of concern.

Conclusion

Issue resolved

Question 9

Part A CFQ-R: The LS mean absolute changes from parent study baseline at Week 96 of Part A were 3.0 points (95% CI: 0.7, 5.3) and 1.7 points (95% CI: -06, 4.0) for the TEZ/IVA-TEZ/IVA group and PBO-TEZ/IVA group, respectively. As the minimum clinically important difference is 4.0 point, the subjects as a group did not meet this MCID. Please provide responder analyses of the % of subjects meeting the MCID.

Summary of the MAH's response

Responder analyses for the percentage of subjects meeting the minimal clinically important difference (MCID) for the 106/110A Analysis Set for Week 96 are presented in **Table 54** and at all study visits in Ad hoc Table 9.1. The percentage of subjects meeting the MCID was generally consistent across the 96 weeks of TEZ/IVA treatment in Study 110 Part A, and similar between parent study treatment groups.

Table 54 Proportion of Subjects with CFQ-R RD Score Change From Baseline >4 Points at Week 96, 106/110A Analysis Set

	106-110A	
Visit	PBO-TEZ/IVA N = 231 n/N1 (%)	TEZ/IVA-TEZ/IVA N = 228 n/N1 (%)
Study 110A Week 96	83/196 (42.3)	106/208 (51.0)

Source: Ad hoc Table 9.1

CFQ-R RD: cystic fibrosis questionnaire-revised respiratory domain; IVA: ivacaftor; PBO: placebo; TEZ: tezacaftor

Notes: 106/108-110A Analysis Set: all subjects, who rolled over from either parent study 106 or 108, and have received at least 1 dose of study drug in Study 110 Part A and meet the mutation eligibility criteria of F/F. Baseline for TEZ/IVA group in 106 and both groups in 108 is defined as the most recent non-missing measurement collected prior to the first dose of study drug in the corresponding parent study. Baseline for PBO-TEZ/IVA group in 106 is defined as the most recent non-missing measurement collected prior to the first dose of study drug in Study 110 Part A. N: number of subjects in the corresponding arm, PBO-TEZ/IVA, TEZ/IVA, or IVA-TEZ/IVA. N1: number of subjects with non-missing CFQ-R change from baseline at the given visit. n (%): number of subjects at a given visit with CFQ-R change from baseline >4 at the given visit; percentage is n/N1.

Ad hoc Table 9.1 Proportion of Subjects with CFQ-R Respiratory Domain Score Change from Baseline > 4 at Each Visit 106-110A Analysis Set

	106-110A	
	PBO-TEZ/IVA N = 231 n/N1 (%)	TEZ/IVA-TEZ/IVA N = 228 n/N1 (%)
Absolute Change at Study 110A Day 15	114/230 (49.6)	115/226 (50.9)
Absolute Change at Study 110A Week 8	117/229 (51.1)	120/226 (53.1)
Absolute Change at Study 110A Week 16	119/226 (52.7)	112/225 (49.8)
Absolute Change at Study 110A Week 24	116/221 (52.5)	108/222 (48.6)
Absolute Change at Study 110A Week 36	103/216 (47.7)	110/222 (49.5)
Absolute Change at Study 110A Week 48	95/216 (44.0)	112/218 (51.4)
Absolute Change at Study 110A Week 60	94/208 (45.2)	118/217 (54.4)
Absolute Change at Study 110A Week 72	100/207 (48.3)	102/214 (47.7)
Absolute Change at Study 110A Week 84	89/199 (44.7)	102/210 (48.6)
Absolute Change at Study 110A Week 96	83/196 (42.3)	106/208 (51.0)

- 106-110A Analysis Set: all subjects, who rolled over from parent study 106, and have received at least 1 dose of study drug in Study 110 Part A and meet the mutation eligibility criteria of F508del/F508del (F/F).
- Baseline for TEZ/IVA group in 106 is defined as the most recent non-missing measurement collected prior to the first dose of study drug in the parent study. Baseline for PBO-TEZ/IVA group in 106 is defined as the most recent non-missing measurement collected prior to the first dose of study drug in Study 110 Part A.
- N: number of subjects in the corresponding arm, PBO-TEZ/IVA, TEZ/IVA, or IVA-TEZ/IVA.
- N1: number of subjects with non-missing CFQ-R change from baseline at the given visit
- n (%): number of subjects at a given visit with CFQ-R change from baseline > 4 at the given visit; percentage is n/N1

Assessment of the MAH's response

The proportion of subjects who met the MCID of the CFQ-R was 42.3% for the placebo-TEZ/IVA group and 51.0% for TEZ/IVA-TEZ/IVA group. Given, the natural history of CF with a deterioration of QoL over time, the observed responder rates are considered relevant.

Conclusion

Issue resolved

SAFETY

Question 10

The immunisation reactions in Part C are remarkably high (7.4%), but these were all considered not related or unlikely related to study drug. The applicant is asked to clarify the high number of immunisation reactions.

Summary of the MAH's response

There were 24 adverse events (AEs) of immunization reaction reported in 15 subjects. Thirteen subjects had immunization reactions to the COVID-19 vaccine and 1 subject had a reaction to the pneumococcal vaccine. One of the subjects with a reaction to the COVID-19 vaccine also had immunization reactions (swollen lymph nodes, arm ache) due to an unspecified vaccine. The reported terms for the reactions to the COVID-19 vaccine included symptoms such as fatigue, body ache, headache, and fever, which are commonly reported events following COVID-19 vaccination.[9] None of the AEs of immunization reaction were considered possibly related or related to TEZ/IVA.

Study 110 Part C was conducted during the spring and summer of 2021, when COVID-19 vaccines first became available. The availability of COVID-19 vaccines at this time likely explains the high number of immunization reaction AEs in the study, at a time when many people were being vaccinated as soon as doses became available.

Assessment of the MAH's response

Out of the 15 subjects with Immunisation reactions, 13 can be contributed to vaccination COVID-19 vaccine can be contributed to vaccination COVID-19 vaccine and 1 to pneumococcal vaccine and 1 to an unspecified vaccine. The described terms of the immunization reaction are in line with described AEs of the AEs.

Conclusion

Issue resolved

Question 11

For a fair comparison of the AEs, events/100 patient years are requested for the PC-SS, safety set Part, safety set Part B and safety set Part C in one table for AEs occurring in ≥ 5% of subjects.

Summary of the MAH's response

As requested, events per 100 patients for AEs occurring in ≥5% of subjects are presented by System Organ Class and preferred term (PT) for the Phase 3-controlled Safety Set (PC-SS), and Study 110

Safety Sets for Parts A, B, and C in Ad hoc Table 11.1, and by PT in Ad hoc Table 11.2. No safety concerns were identified from review of the requested tables.

Ad hoc Table 11.1 TEAEs with Occurrence in ≥5% subjects in Any Part of Study 110 Part A, B and C and PC-SS by System Organ Class and Preferred Term Safety Set in Study 110 Part A, B and C, and Phase 3-controlled Safety Set

	PC-SS									
	Placebo N = 505		TEZ/IVA N = 496		110A Safety Set N = 1042		110B Safety Set N = 463		110C Safety Set N = 204	
System Organ Class Preferred Term	n (%)	Event/100 Patient years	n (%)	Event/100 Patient years	n (%)	Event/100 Patient years	n (%)	Event/100 Patient years	n (%)	Event/100 Patient years
Total exposure in 100 patient years	--	2.03	--	2.00	--	15.57	--	6.34	--	2.80
Infections and infestations	235 (46.5)	175.06	205 (41.3)	147.56	778 (74.7)	147.10	335 (72.4)	156.86	118 (57.8)	112.81
Infective pulmonary exacerbation of cystic fibrosis	153 (30.3)	101.79	117 (23.6)	76.53	549 (52.7)	88.84	239 (51.6)	107.20	92 (45.1)	84.61
Nasopharyngitis	49 (9.7)	32.45	57 (11.5)	35.01	227 (21.8)	23.57	88 (19.0)	20.97	13 (6.4)	6.07
Influenza	14 (2.8)	7.38	15 (3.0)	8.00	69 (6.6)	4.75	27 (5.8)	4.41	2 (1.0)	0.71
Upper respiratory tract infection	20 (4.0)	11.31	15 (3.0)	9.00	135 (13.0)	11.56	43 (9.3)	11.19	12 (5.9)	8.21
Rhinitis	17 (3.4)	8.85	14 (2.8)	7.00	55 (5.3)	4.95	28 (6.0)	5.52	5 (2.5)	2.86
Viral upper respiratory tract infection	17 (3.4)	8.85	12 (2.4)	6.50	69 (6.6)	5.91	15 (3.2)	3.31	1 (0.5)	0.36
Sinusitis	9 (1.8)	4.43	11 (2.2)	5.50	80 (7.7)	7.52	20 (4.3)	4.10	7 (3.4)	2.86
COVID-19	0	0.00	0	0.00	0	0.00	1 (0.2)	0.16	19 (9.3)	7.14
Respiratory, thoracic and mediastinal disorders	243 (48.1)	252.26	204 (41.1)	209.59	622 (59.7)	131.11	208 (44.9)	82.13	67 (32.8)	58.19
Cough	141 (27.9)	89.50	108 (21.8)	65.53	374 (35.9)	45.16	112 (24.2)	30.43	29 (14.2)	17.14
Sputum increased	65 (12.9)	37.37	57 (11.5)	32.01	224 (21.5)	20.75	46 (9.9)	10.09	13 (6.4)	6.43
Haemoptysis	56 (11.1)	35.40	48 (9.7)	33.01	179 (17.2)	23.13	68 (14.7)	18.92	26 (12.7)	21.42
Oropharyngeal pain	44 (8.7)	25.08	36 (7.3)	18.51	136 (13.1)	12.20	39 (8.4)	8.67	9 (4.4)	6.43
Dyspnoea	36 (7.1)	20.65	30 (6.0)	17.01	99 (9.5)	7.97	30 (6.5)	5.99	9 (4.4)	3.93
Nasal congestion	28 (5.5)	15.74	24 (4.8)	13.51	77 (7.4)	6.42	7 (1.5)	1.10	2 (1.0)	0.71
Productive cough	15 (3.0)	11.80	19 (3.8)	11.00	56 (5.4)	6.36	15 (3.2)	3.47	3 (1.5)	1.07
Rhinorrhoea	19 (3.8)	10.33	19 (3.8)	9.50	55 (5.3)	4.88	16 (3.5)	3.15	1 (0.5)	0.36
Sinus congestion	11 (2.2)	6.39	17 (3.4)	9.50	53 (5.1)	4.24	2 (0.4)	0.32	2 (1.0)	0.71
Gastrointestinal disorders	110 (21.8)	97.36	104 (21.0)	81.03	341 (32.7)	42.07	102 (22.0)	27.75	32 (15.7)	16.78
Nausea	34 (6.7)	18.69	38 (7.7)	21.51	107 (10.3)	9.06	21 (4.5)	4.26	9 (4.4)	4.28
Diarrhoea	34 (6.7)	21.64	31 (6.3)	17.51	105 (10.1)	8.09	27 (5.8)	4.73	5 (2.5)	1.78
Abdominal pain	34 (6.7)	21.14	29 (5.8)	18.01	107 (10.3)	9.12	35 (7.6)	7.25	7 (3.4)	3.21
Vomiting	21 (4.2)	11.80	18 (3.6)	9.00	82 (7.9)	6.87	12 (2.6)	2.52	7 (3.4)	3.21
Constipation	24 (4.8)	11.80	15 (3.0)	7.50	76 (7.3)	5.65	26 (5.6)	4.41	8 (3.9)	3.57
Abdominal pain upper	21 (4.2)	12.29	13 (2.6)	7.50	44 (4.2)	3.28	26 (5.6)	4.57	2 (1.0)	0.71
General disorders and administration site conditions	91 (18.0)	54.58	72 (14.5)	47.52	217 (20.8)	21.90	58 (12.5)	13.08	27 (13.2)	13.21
Pyrexia	49 (9.7)	27.54	41 (8.3)	26.51	136 (13.1)	13.81	40 (8.6)	9.14	20 (9.8)	10.71
Fatigue	51 (10.1)	27.05	38 (7.7)	21.01	101 (9.7)	8.09	23 (5.0)	3.94	7 (3.4)	2.50
Nervous system disorders	57 (11.3)	42.78	68 (13.7)	44.02	147 (14.1)	19.34	47 (10.2)	23.17	20 (9.8)	39.27
Headache	57 (11.3)	42.78	68 (13.7)	44.02	147 (14.1)	19.34	47 (10.2)	23.17	20 (9.8)	39.27
Investigations	56 (11.1)	36.39	37 (7.5)	23.51	204 (19.6)	19.53	43 (9.3)	9.77	14 (6.9)	5.35
Blood creatine phosphokinase increased	17 (3.4)	10.33	19 (3.8)	10.50	83 (8.0)	6.23	3 (0.6)	0.47	0	0.00
Aspartate aminotransferase increased	15 (3.0)	7.87	12 (2.4)	6.00	55 (5.3)	4.18	7 (1.5)	1.26	1 (0.5)	0.36
Bacterial test positive	20 (4.0)	11.31	9 (1.8)	6.00	49 (4.7)	4.50	28 (6.0)	6.78	11 (5.4)	3.93
Pulmonary function test decreased	10 (2.0)	6.88	2 (0.4)	1.00	55 (5.3)	4.63	8 (1.7)	1.26	3 (1.5)	1.07
Musculoskeletal and connective tissue disorders	20 (4.0)	12.29	18 (3.6)	10.50	112 (10.7)	9.19	49 (10.6)	9.77	20 (9.8)	12.14
Back pain	8 (1.6)	3.93	11 (2.2)	6.50	57 (5.5)	4.18	23 (5.0)	3.78	11 (5.4)	7.14
Arthralgia	14 (2.8)	8.36	7 (1.4)	4.00	62 (6.0)	5.01	29 (6.3)	5.99	9 (4.4)	5.00
Immune system disorders	0	0.00	0	0.00	0	0.00	0	0.00	15 (7.4)	8.57
Immunisation reaction	0	0.00	0	0.00	0	0.00	0	0.00	15 (7.4)	8.57

- The same MedDRA versions were used as in the original CSR for each study/part.
- TEAE: Treatment-emergent adverse event.
- PC-SS (Phase 3-controlled Safety Set): consists of the combined safety sets of the Phase 3 placebo-controlled studies, Study 106, Study 107, and Study 108.
- Only TEAEs with occurrence in ≥5% subjects of at least one of the corresponding safety sets are included.
- n: number of subjects in each AE category from each of the safety sets in study 110 Part A, B, C and PC-SS; Events/100 patient years: number of events per 100 patient years = number of events/(total exposure in days/(365.25 * 100)).
- When summarizing number of events, a subject with multiple events within a category is counted multiple times in that category.
- When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category.
- System organ class and preferred terms are sorted in the descending order of n (%) in PC-SS TEZ/IVA.
- Data are summarized at each study Treatment-emergent Period. The treatment-emergent period for each study is defined in the individual study SAP.

Ad hoc Table 11.2 TEAEs with Occurrence in ≥5% Subjects in Any Part of Study 110 Part A, B and C and PC-SS by Preferred Term Safety Set in Study 110 Part A, B and C, and Phase 3-controlled Safety Set

	PC-SS									
	Placebo N = 505		TEZ/IVA N = 496		110A Safety Set N = 1042		110B Safety Set N = 463		110C Safety Set N = 204	
Preferred Term	n (%)	Event/100 Patient years	n (%)	Event/100 Patient years	n (%)	Event/100 Patient years	n (%)	Event/100 Patient years	n (%)	Event/100 Patient years
Total exposure in 100 patient years	--	2.03	--	2.00	--	15.57	--	6.34	--	2.80
Infective pulmonary exacerbation of cystic fibrosis	153 (30.3)	101.79	117 (23.6)	76.53	549 (52.7)	88.84	239 (51.6)	107.20	92 (45.1)	84.61
Cough	141 (27.9)	89.50	108 (21.8)	65.53	374 (35.9)	45.16	112 (24.2)	30.43	29 (14.2)	17.14
Headache	57 (11.3)	42.78	68 (13.7)	44.02	147 (14.1)	19.34	47 (10.2)	23.17	20 (9.8)	39.27
Nasopharyngitis	49 (9.7)	32.45	57 (11.5)	35.01	227 (21.8)	23.57	88 (19.0)	20.97	13 (6.4)	6.07
Sputum increased	65 (12.9)	37.37	57 (11.5)	32.01	224 (21.5)	20.75	46 (9.9)	10.09	13 (6.4)	6.43
Haemoptysis	56 (11.1)	35.40	48 (9.7)	33.01	179 (17.2)	23.13	68 (14.7)	18.92	26 (12.7)	21.42
Pyrexia	49 (9.7)	27.54	41 (8.3)	26.51	136 (13.1)	13.81	40 (8.6)	9.14	20 (9.8)	10.71
Fatigue	51 (10.1)	27.05	38 (7.7)	21.01	101 (9.7)	8.09	23 (5.0)	3.94	7 (3.4)	2.50
Nausea	34 (6.7)	18.69	38 (7.7)	21.51	107 (10.3)	9.06	21 (4.5)	4.26	9 (4.4)	4.28
Oropharyngeal pain	44 (8.7)	25.08	36 (7.3)	18.51	136 (13.1)	12.20	39 (8.4)	8.67	9 (4.4)	6.43
Diarrhoea	34 (6.7)	21.64	31 (6.3)	17.51	105 (10.1)	8.09	27 (5.8)	4.73	5 (2.5)	1.78
Dyspnoea	36 (7.1)	20.65	30 (6.0)	17.01	99 (9.5)	7.97	30 (6.5)	5.99	9 (4.4)	3.93
Abdominal pain	34 (6.7)	21.14	29 (5.8)	18.01	107 (10.3)	9.12	35 (7.6)	7.25	7 (3.4)	3.21
Nasal congestion	28 (5.5)	15.74	24 (4.8)	13.51	77 (7.4)	6.42	7 (1.5)	1.10	2 (1.0)	0.71
Blood creatine phosphokinase increased	17 (3.4)	10.33	19 (3.8)	10.50	83 (8.0)	6.23	3 (0.6)	0.47	0	0.00
Productive cough	15 (3.0)	11.80	19 (3.8)	11.00	56 (5.4)	6.36	15 (3.2)	3.47	3 (1.5)	1.07
Rhinorrhoea	19 (3.8)	10.33	19 (3.8)	9.50	55 (5.3)	4.88	16 (3.5)	3.15	1 (0.5)	0.36
Vomiting	21 (4.2)	11.80	18 (3.6)	9.00	82 (7.9)	6.87	12 (2.6)	2.52	7 (3.4)	3.21
Sinus congestion	11 (2.2)	6.39	17 (3.4)	9.50	53 (5.1)	4.24	2 (0.4)	0.32	2 (1.0)	0.71
Constipation	24 (4.8)	11.80	15 (3.0)	7.50	76 (7.3)	5.65	26 (5.6)	4.41	8 (3.9)	3.57
Influenza	14 (2.8)	7.38	15 (3.0)	8.00	69 (6.6)	4.75	27 (5.8)	4.41	2 (1.0)	0.71
Upper respiratory tract infection	20 (4.0)	11.31	15 (3.0)	9.00	135 (13.0)	11.56	43 (9.3)	11.19	12 (5.9)	8.21
Rhinitis	17 (3.4)	8.85	14 (2.8)	7.00	55 (5.3)	4.95	28 (6.0)	5.52	5 (2.5)	2.86
Abdominal pain upper	21 (4.2)	12.29	13 (2.6)	7.50	44 (4.2)	3.28	26 (5.6)	4.57	2 (1.0)	0.71
Aspartate aminotransferase increased	15 (3.0)	7.87	12 (2.4)	6.00	55 (5.3)	4.18	7 (1.5)	1.26	1 (0.5)	0.36
Viral upper respiratory tract infection	17 (3.4)	8.85	12 (2.4)	6.50	69 (6.6)	5.91	15 (3.2)	3.31	1 (0.5)	0.36
Back pain	8 (1.6)	3.93	11 (2.2)	6.50	57 (5.5)	4.18	23 (5.0)	3.78	11 (5.4)	7.14
Sinusitis	9 (1.8)	4.43	11 (2.2)	5.50	80 (7.7)	7.52	20 (4.3)	4.10	7 (3.4)	2.86
Bacterial test positive	20 (4.0)	11.31	9 (1.8)	6.00	49 (4.7)	4.50	28 (6.0)	6.78	11 (5.4)	3.93
Arthralgia	14 (2.8)	8.36	7 (1.4)	4.00	62 (6.0)	5.01	29 (6.3)	5.99	9 (4.4)	5.00
Pulmonary function test decreased	10 (2.0)	6.88	2 (0.4)	1.00	55 (5.3)	4.63	8 (1.7)	1.26	3 (1.5)	1.07
COVID-19	0	0.00	0	0.00	0	0.00	1 (0.2)	0.16	19 (9.3)	7.14
Immunisation reaction	0	0.00	0	0.00	0	0.00	0	0.00	15 (7.4)	8.57

- The same MedDRA versions were used as in the original CSR for each study/part.
- TEAE: Treatment-emergent adverse event.
- PC-SS (Phase 3-controlled Safety Set): consists of the combined safety sets of the Phase 3 placebo-controlled studies, Study 106, Study 107, and Study 108.
- Only TEAEs with occurrence in ≥5% subjects in at least one the corresponding safety sets are included.
- n: number of subjects in each AE category from each of the safety sets in study 110 Part A, B, C and PC-SS; Events/100 patient years: number of events per 100 patient years = number of events/(total exposure in days/(365.25 * 100)).
- When summarizing number of events, a subject with multiple events within a category is counted multiple times in that category.
- When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category.
- System organ class and preferred terms are sorted in the descending order of n (%) in PC-SS TEZ/IVA.
- Data are summarized at each study Treatment-emergent Period. The treatment-emergent period for each study is defined in the individual study SAP.

Assessment of the MAH's response

The incidences of the TAES are generally comparable between the safety sets.

The most frequent AEs were generally consistent with common manifestations of CF disease, with common illnesses in CF subjects 12 years of age and older or already known AEs of Kaftrio.

Based on these new tables, no new safety signals are detected.

Conclusion

Issue resolved

Question 12

The Grade 3/4 AEs are presented in separate, extensive tables. To allow for the assessment of these events, the events/100 patient years of the grade 3/4 are requested for the PC-SS,

safety set Part, safety set Part B and safety set Part C in one table for Grade 3/4 AEs occurring in ≥ 2 subjects.

Summary of the MAH's response

As requested, events per 100 patient-years for Grade 3/4 AEs occurring in ≥2 subjects are presented for the PC-SS, and Study 110 Safety Sets for Parts A, B, and C in Ad hoc Table 12.1.

No safety concerns were identified from review of the requested table.

Ad hoc Table 12.1 Grade 3/4 TEAEs with Occurrence in ≥2 Subjects in Any Part of Study 110 Part A, B and C and PC-SS by System Organ Class and Preferred Term Safety Set in Study 110 Part A, B and C, and Phase 3-controlled Safety Set

	PC-SS									
	Placebo N = 505		TEZ/IVA N = 496		110A Safety Set N = 1042		110B Safety Set N = 463		110C Safety Set N = 204	
System Organ Class Preferred Term	n (%)	Event/100 Patient years	n (%)	Event/100 Patient years	n (%)	Event/100 Patient years	n (%)	Event/100 Patient years	n (%)	Event/100 Patient years
Total exposure in 100 patient years	--	2.03	--	2.00	--	15.57	--	6.34	--	2.80
Infections and infestations	19 (3.8)	11.31	19 (3.8)	10.00	107 (10.3)	9.31	44 (9.5)	10.40	11 (5.4)	6.07
Infective pulmonary exacerbation of cystic fibrosis	19 (3.8)	10.33	18 (3.6)	9.00	89 (8.5)	7.84	43 (9.3)	9.93	10 (4.9)	5.35
Pneumonia	1 (0.2)	0.49	2 (0.4)	1.00	3 (0.3)	0.19	2 (0.4)	0.32	1 (0.5)	0.71
Appendicitis	0	0.00	0	0.00	4 (0.4)	0.26	0	0.00	0	0.00
Gastroenteritis	0	0.00	0	0.00	5 (0.5)	0.32	0	0.00	0	0.00
Influenza	1 (0.2)	0.49	0	0.00	7 (0.7)	0.45	1 (0.2)	0.16	0	0.00
Lung infection	0	0.00	0	0.00	2 (0.2)	0.26	0	0.00	0	0.00
Respiratory, thoracic and mediastinal disorders	5 (1.0)	2.46	4 (0.8)	2.00	11 (1.1)	0.84	4 (0.9)	1.58	6 (2.9)	3.57
Haemoptysis	5 (1.0)	2.46	4 (0.8)	2.00	7 (0.7)	0.58	3 (0.6)	0.63	6 (2.9)	3.57
Cough	0	0.00	0	0.00	2 (0.2)	0.13	0	0.00	0	0.00
Pneumothorax spontaneous	0	0.00	0	0.00	2 (0.2)	0.13	2 (0.4)	0.95	0	0.00
Gastrointestinal disorders	2 (0.4)	0.98	3 (0.6)	1.50	15 (1.4)	1.09	6 (1.3)	1.42	2 (1.0)	1.07
Distal intestinal obstruction syndrome	1 (0.2)	0.49	2 (0.4)	1.00	7 (0.7)	0.51	1 (0.2)	0.16	1 (0.5)	0.36
Abdominal pain	1 (0.2)	0.49	1 (0.2)	0.50	2 (0.2)	0.13	0	0.00	0	0.00
Constipation	0	0.00	0	0.00	2 (0.2)	0.13	2 (0.4)	0.32	1 (0.5)	0.71
Gastrointestinal pain	0	0.00	0	0.00	0	0.00	2 (0.4)	0.47	0	0.00
Intestinal obstruction	0	0.00	0	0.00	2 (0.2)	0.19	2 (0.4)	0.32	0	0.00
Nausea	0	0.00	0	0.00	2 (0.2)	0.13	1 (0.2)	0.16	0	0.00
Investigations	3 (0.6)	3.44	2 (0.4)	1.00	21 (2.0)	1.93	1 (0.2)	0.32	0	0.00
Alanine aminotransferase increased	1 (0.2)	0.49	1 (0.2)	0.50	9 (0.9)	0.58	1 (0.2)	0.16	0	0.00
Blood creatine phosphokinase increased	2 (0.4)	1.48	1 (0.2)	0.50	11 (1.1)	0.71	0	0.00	0	0.00
Aspartate aminotransferase increased	2 (0.4)	1.48	0	0.00	10 (1.0)	0.64	1 (0.2)	0.16	0	0.00
Nervous system disorders	1 (0.2)	1.48	1 (0.2)	0.50	6 (0.6)	0.39	0	0.00	0	0.00
Headache	1 (0.2)	1.48	1 (0.2)	0.50	4 (0.4)	0.26	0	0.00	0	0.00
Syncope	0	0.00	0	0.00	2 (0.2)	0.13	0	0.00	0	0.00
General disorders and administration site conditions	2 (0.4)	0.98	0	0.00	0	0.00	1 (0.2)	0.16	0	0.00
Fatigue	2 (0.4)	0.98	0	0.00	0	0.00	1 (0.2)	0.16	0	0.00
Immune system disorders	0	0.00	0	0.00	2 (0.2)	0.13	0	0.00	1 (0.5)	0.36
Anaphylactic reaction	0	0.00	0	0.00	2 (0.2)	0.13	0	0.00	1 (0.5)	0.36
Injury, poisoning and procedural complications	0	0.00	0	0.00	4 (0.4)	0.32	0	0.00	0	0.00
Ligament rupture	0	0.00	0	0.00	2 (0.2)	0.19	0	0.00	0	0.00
Rib fracture	0	0.00	0	0.00	2 (0.2)	0.13	0	0.00	0	0.00

Musculoskeletal and connective tissue disorders	0	0.00	0	0.00	2 (0.2)	0.13	0	0.00	0	0.00
Back pain	0	0.00	0	0.00	2 (0.2)	0.13	0	0.00	0	0.00
Psychiatric disorders	0	0.00	0	0.00	7 (0.7)	0.58	1 (0.2)	0.32	2 (1.0)	0.71
Anxiety	0	0.00	0	0.00	4 (0.4)	0.26	0	0.00	0	0.00
Depression	0	0.00	0	0.00	2 (0.2)	0.13	1 (0.2)	0.16	2 (1.0)	0.71
Suicide attempt	0	0.00	0	0.00	3 (0.3)	0.19	1 (0.2)	0.16	0	0.00
Renal and urinary disorders	0	0.00	0	0.00	5 (0.5)	0.45	0	0.00	0	0.00
Nephrolithiasis	0	0.00	0	0.00	5 (0.5)	0.45	0	0.00	0	0.00
Vascular disorders	0	0.00	0	0.00	2 (0.2)	0.13	0	0.00	0	0.00
Deep vein thrombosis	0	0.00	0	0.00	2 (0.2)	0.13	0	0.00	0	0.00

- The same MedDRA versions were used as in the original CSR for each study/part.
- TEAE: Treatment-emergent adverse event.
- PC-SS (Phase 3-controlled Safety Set): consists of the combined safety sets of the Phase 3 placebo-controlled studies, Study 106, Study 107, and Study 108.
- Only TEAEs with occurrence in ≥2 subjects in at least one the corresponding safety sets are included.
- n: number of subjects in each AE category from each of the safety sets in study 110 Part A, B, C and PC-SS; Events/100 patient years: number of events per 100 patient years = number of events/(total exposure in days/(365.25 * 100)).
- When summarizing number of events, a subject with multiple events within a category is counted multiple times in that category.
- When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category.
- System organ class and preferred terms are sorted in the descending order of n (%) in PC-SS TEZ/IVA.
- Data are summarized at each study Treatment-emergent Period. The treatment-emergent period for each study is defined in the individual study SAP.

Assessment of the MAH's response

A few Grade 3/4 AEs were higher in the safety sets of Study 110 compared to the PC-SS. These concern pneumonia, haemoptysis, anaphylactic reaction, anxiety, depression, suicide attempt and deep vein thrombosis.

Haemoptysis is a common symptom in CF. Although pneumonia is less common in CF, an overview of the safety data of pneumonia does not indicate a clear relationship between pneumonia and the use of TEZ/IVA. No further action is required for pneumonia.

	TEAE pneumonia		Related TEAE pneumonia	
	n (%)	Events/100 patient years		
PC-SS Placebo	5 (1.0)		1 (0.2)	
PC-SS TEZ/IVA	3 (0.6)		0	
Study 110 Part A	13 (1.2)	0.86	1 (0.1)	0.07
Study 110 Part B	7 (1.5)	1.42	0	0
Study 110 Part C	1 (0.5)	0.71	0	0

The anaphylactic reactions were due to insect bite (bee) and walnuts respectively. Both cases were not related to the treatment.

Both cases of deep vein thrombosis were considered by the investigator as not related. Both resolved completely and in cases the dose was not changed.

All 4 cases of anxiety were considered as not or unlikely be related to study drug. In 3 cases the dose was not changed, in the last case study drug was withdrawn. None of the cases was recovered. Based on the investigators conclusions on the relationship, no relationship can be concluded. The other psychiatric events will be discussed in question 14.

No further action is required.

Conclusion

Issue resolved

Question 13

The related AEs are presented in separate, extensive tables. To allow for the assessment of these events, the events/100 patient years of the related AE are requested for the PC-SS, safety set Part, safety set Part B and safety set Part C in one table for related AEs occurring in ≥2% of the subjects.

Summary of the MAH's response

Events per 100 patient-years for related AEs occurring in ≥2% of subjects are presented for the PC-SS, and Study 110 Safety Sets for Parts A, B, and C in Ad hoc Table 13.1. No safety concerns were identified from review of the requested table.

Ad hoc Table 13.1 Related TEAEs with occurrence in ≥2% subjects in Study 110 Part A, B and C and PC-SS by System Organ Class and Preferred Term Safety Set in Study 110 Part A, B and C, and Phase 3-controlled Safety Set

	PC-SS									
	Placebo N = 505		TEZ/IVA N = 496		110A Safety Set N = 1042		110B Safety Set N = 463		110C Safety Set N = 204	
System Organ Class Preferred Term	n (%)	Event/100 Patient years	n (%)	Event/100 Patient years	n (%)	Event/100 Patient years	n (%)	Event/100 Patient years	n (%)	Event/100 Patient years
Total exposure in 100 patient years	--	2.03	--	2.00	--	15.57	--	6.34	--	2.80
Investigations	20 (4.0)	18.69	22 (4.4)	15.51	71 (6.8)	8.48	4 (0.9)	1.10	0	0.00
Blood creatine phosphokinase increased	11 (2.2)	7.38	13 (2.6)	7.50	46 (4.4)	3.47	0	0.00	0	0.00
Alanine aminotransferase increased	10 (2.0)	5.41	9 (1.8)	4.50	29 (2.8)	2.38	4 (0.9)	0.63	0	0.00
Aspartate aminotransferase increased	11 (2.2)	5.90	7 (1.4)	3.50	32 (3.1)	2.63	3 (0.6)	0.47	0	0.00
Respiratory, thoracic and mediastinal disorders	23 (4.6)	15.74	20 (4.0)	11.00	47 (4.5)	4.50	2 (0.4)	0.32	0	0.00
Sputum increased	12 (2.4)	6.39	12 (2.4)	6.50	28 (2.7)	1.80	1 (0.2)	0.16	0	0.00
Cough	17 (3.4)	9.34	9 (1.8)	4.50	35 (3.4)	2.70	1 (0.2)	0.16	0	0.00
Nervous system disorders	13 (2.6)	6.88	12 (2.4)	6.00	15 (1.4)	0.96	6 (1.3)	0.95	1 (0.5)	0.36
Headache	13 (2.6)	6.88	12 (2.4)	6.00	15 (1.4)	0.96	6 (1.3)	0.95	1 (0.5)	0.36
Gastrointestinal disorders	5 (1.0)	2.95	10 (2.0)	5.50	9 (0.9)	0.64	1 (0.2)	0.16	0	0.00
Nausea	5 (1.0)	2.95	10 (2.0)	5.50	9 (0.9)	0.64	1 (0.2)	0.16	0	0.00
General disorders and administration site conditions	15 (3.0)	7.87	9 (1.8)	5.00	13 (1.2)	0.84	2 (0.4)	0.32	0	0.00
Fatigue	15 (3.0)	7.87	9 (1.8)	5.00	13 (1.2)	0.84	2 (0.4)	0.32	0	0.00
Infections and infestations	12 (2.4)	7.87	4 (0.8)	3.00	26 (2.5)	3.08	5 (1.1)	1.58	1 (0.5)	0.36
Infective pulmonary exacerbation of cystic fibrosis	12 (2.4)	7.87	4 (0.8)	3.00	26 (2.5)	3.08	5 (1.1)	1.58	1 (0.5)	0.36

- The same MedDRA versions were used as in the original CSR for each study/part.
- TEAE: Treatment-emergent adverse event.
- PC-SS (Phase 3-controlled Safety Set): consists of the combined safety sets of the Phase 3 placebo-controlled studies, Study 106, Study 107, and Study 108.
- Only TEAEs with occurrence in ≥2% subjects in at least one the corresponding safety sets are included.
- n: number of subjects in each AE category from each of the safety sets in study 110 Part A, B, C and PC-SS; Events/100 patient years: number of events per 100 patient years = number of events/(total exposure in days/(365.25 * 100)).
- When summarizing number of events, a subject with multiple events within a category is counted multiple times in that category.
- When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category.
- System organ class and preferred terms are sorted in the descending order of n (%) in PC-SS TEZ/IVA.
- Data are summarized at each study Treatment-emergent Period.

Assessment of the MAH's response

Overall, there are no new related TEAEs with occurrence in ≥2% subjects in Study 110 compared to PC-SS. In general, the related TEAEs with occurrence in ≥2% subjects have a lower incidence in Study 110 compared to PC-SS.

No further action is required.

Conclusion

Issue resolved.

Question 14

The applicant is requested to discuss all the reported observations of negative thoughts, suicidal ideation and suicide in the PC-SS, safety set Part A, safety set Part B and safety set part C.

Summary of the MAH's response

The incidence of negative thoughts, suicidal ideation, suicide attempt, and completed suicide was low across the TEZ/IVA development program. There were no events of negative thoughts, suicidal ideation, suicide attempt, or completed suicide in the PC-SS (**Table 55**).

Table 55 TEAEs of Negative Thoughts and Suicide-related Events in Study 110 Part A, B and C and PC-SS; Safety Set in Study 110 Part A, B and C, and PC-SS

	PC-SS									
	Placebo N=505		TEZ/IVA N=496		110A Safety Set N=1042		110B Safety Set N=463		110C Safety Set N=204	
Preferred Term	n (%)	Event/100 PY	n (%)	Event/100 PY	n (%)	Event/100 PY	n (%)	Event/100 PY	n (%)	Event/100 PY
Total exposure in 100 PY	--	**2.03**	--	**2.00**	--	**15.57**	--	**6.34**	--	**2.80**
Negative thoughts	0	0.00	0	0.00	1 (0.1)	0.06	1 (0.2)	0.16	0	0.00
Suicidal ideation	0	0.00	0	0.00	1 (0.1)	0.06	1 (0.2)	0.47	0	0.00
Suicide attempt	0	0.00	0	0.00	3 (0.3)	0.19	1 (0.2)	0.16	0	0.00
Completed suicide	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

Source: Ad hoc Table 14.1

IVA: ivacaftor; n: size of subsample; PC-SS: Phase 3-controlled Safety Set; PY: patient-years; TEAE: treatment-emergent adverse event; TEZ: tezacaftor

Notes: When summarizing number of events, a subject with multiple events within a category is counted multiple times in that category. n: number of subjects in each AE category from each of the safety sets in study 110 Part A, B, C and PC-SS; Events/100 patient years: number of events per 100 patient years = number of events/(total exposure in days/(365.25 * 100)). When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category. Data are summarized for each study's Treatment-emergent Period.

In Study 110, including the Safety Sets for Parts A, B, and C, there were 2 AEs of negative thoughts (Table 7). Both events were non-serious. There were 4 serious adverse events (SAEs) of suicide attempt and 3 SAEs and 1 nonserious AE of suicidal ideation reported in 2 subjects.

There were no events of completed suicide (Table 55). Four of the 8 suicide-related events resolved without change to study drug dosing, suggesting they were not related to study drug with alternative suspected aetiologies (pre-existing depression, anxiety, or suicidal ideation, or significant psychosocial stressors). A brief description of the remaining 4 events, which occurred in 2 subjects, is provided below, including Vertex's assessment of these events (**Table 56**). Both subjects had significant psychiatric medical history and psychosocial stressors, which were identified as the likely aetiology by the investigator. Both subjects had events with onset latency >1 month after started TEZ/IVA, which is inconsistent with drug-induced depression per DSM-5 criteria.[10] Upon detailed case review, the data do not suggest an association between TEZ/IVA and negative thoughts, suicidal ideation, or suicide attempt. The benefit/risk profile of TEZ/IVA remains unchanged.

Table 56 TEZ/IVA Clinical Trial Cases With Event Resolution After Interruption or Discontinuation

Trial/ Sex/Age	PT/ Case (if serious)/ Seriousness	Onset latency	Relevant MHx/ CM	Description	Vertex Assessment
661-110/ M/43	Suicide attempt/ 2018-003663/ Serious (LT, H)	>2.5 years	Depression/ Not relevant	20 May 2016 initiated TEZ/IVA. 24 May 2018, psychiatric hospitalization after suicide attempt which was attributed to severe underlying depression and not related to TEZ/IVA. Study drug interrupted for 6 days, started on new psychotropic medications. Study drug was restarted 29 May 2018 and subject discharged 01 June 2018, with resolution of the AE.	Unlikely related to TEZ/IVA given substantial mental health history and long latency >2 years, which is inconsistent with drug-induced depression. In addition, subject was able to restart drug without recurrence.
661-110/ M/15	Suicidal ideation/ 2018-005117/ Serious (LT, H)	5 weeks	Suicidal ideation for 2 years per subject's psychiatrist/ Not relevant	13 June 2018 initiated TEZ/IVA. 19 Jul 2018, hospitalized for PEx and suicidal ideation, after family found subject intoxicated with pre-meditated self-harm. Investigator assessed the event as due to pre-existing mental health disease, not related to study drug. Study drug interrupted and suicidal ideation downgraded to a non-serious event after ~ 1week, but low mood persisted.	Unlikely related to TEZ/IVA given substantial long-standing symptoms before starting study drug. Initial event latency >1 month; event onset latency after TEZ/IVA restart ~2 months. Several psychosocial stressors were identified, and symptoms continued for >1 month after stopping study drug, which is inconsistent with drug-induced depression.
	Suicidal ideation/ Not applicable/ Non-serious	Not applicable (TEZ/IVA interrupted)		03 Oct 2018, previous SAE downgraded to non-serious AE, which was considered resolved on 11 Dec 2018. Study drug restarted on the same day.	
	Suicidal ideation/ 2019-001290/ Serious (MS, H)	8 months		8 Feb 2019 hospitalized with suicidal ideation, after several weeks of erratic behavior. Study drug discontinued and subject terminated from study. 06 Mar 2019 hospitalized for intense ongoing suicidal ideation, suspected etiologies included death in the family, academic stressors, and chronic illness.	

Sources: CIOMS; Study 110 CSR/Listing 16.2.7.1b

AE: adverse event; CM: concomitant medications; H: hospitalized; IVA: ivacaftor; LT: life-threatening; M: male; MHx: medical history; MS: medically significant; PEx: pulmonary exacerbation; PT: preferred term; SAE: serious AE; TEZ: tezacaftor

Assessment of the MAH's response

The provide description of the 4 events, which occurred in 2 subjects, indicated that both subjects had a psychiatric medical history and psychosocial stressors.

The issue of the occurrence of negative thoughts, suicidal ideation and suicide has been recently discussed in PSUSA procedure EMEA/H/C/PSUSA/00010730/202302. As an outcome of this procedure the PRAC Rapporteur recommended an update of section 4.4 and 4.8 to include information on depression (including suicidal ideation and suicide attempt). As the product information will be updated as part of EMEA/H/C/PSUSA/00010730/202302, this issue is not further pursued within this procedure.

Conclusion

Issue resolved

Question 15

The applicant is requested to discuss all the reported event of hepatotoxicity during the clinical programme i.e., events in all the parent studies and study 110.

Summary of the MAH's response

The clinical database was searched for any PTs related to hepatoxicity by including all terms included in the following standard MedDRA queries (SMQ) [narrow]:

- Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions
- Liver-related investigations, signs and symptoms
- Hepatitis, non-infectious
- Cholestasis and jaundice of hepatic origin.

Overall, the rate of liver-related events was low. The majority of events were laboratory abnormalities, especially alanine aminotransferase (ALT) increased and aspartate aminotransferase (AST) increased (**Table 57**, **Table 58**, and Table 59). Laboratory abnormalities of increased transaminases are a known adverse drug reaction (ADR) for TEZ/IVA. Other liver events were extremely rare in the TEZ/IVA clinical program, and none were life-threatening or fatal. Liver disease is a well-documented comorbidity of CF and the low rate of incidence of these events in the population of subjects enrolled in the TEZ/IVA clinical program does not suggest an association between TEZ/IVA and hepatotoxicity events other than the already identified ADRs.

Table 57 Hepatotoxicity TEAEs Incidence in Parent Studies of Study 110; Safety Set in Parent Studies of Study 110

Preferred Term	Safety Set 103 n (%)	Safety Set 106 n (%)	Safety Set 107 n (%)	Safety Set 108 n (%)	Safety Set 109 n (%)	Safety Set 111 n (%)	Safety Set 112 n (%)	Safety Set 114 n (%)
ALT increased	4 (10.3)	21 (4.1)	4 (2.4)	8 (3.3)	4 (2.6)	1 (2.9)	1 (2.4)	1 (1.0)
AST increased	4 (10.3)	19 (3.7)	3 (1.8)	9 (3.7)	2 (1.3)	1 (2.9)	2 (4.9)	1 (1.0)
Blood bilirubin unconjugated increased	1 (2.6)	0	0	0	0	0	0	0
GGT increased	1 (2.6)	6 (1.2)	2 (1.2)	2 (0.8)	3 (1.9)	1 (2.9)	1 (2.4)	1 (1.0)
Bilirubin conjugated increased	0	0	0	2 (0.8)	1 (0.6)	0	0	0
Blood bilirubin increased	0	3 (0.6)	0	2 (0.8)	2 (1.3)	0	1 (2.4)	1 (1.0)
Hepatic cirrhosis	0	0	0	0	0	0	1 (2.4)	0
Hepatic fibrosis	0	1 (0.2)	0	0	0	0	0	0
Hepatic lesion	0	1 (0.2)	0	0	0	0	0	0
Hepatomegaly	0	1 (0.2)	0	0	0	0	0	0
Hypertransaminasaemia	0	1 (0.2)	0	0	0	0	0	0
Transaminases increased	0	0	0	0	0	0	1 (2.4)	0
Ultrasound liver abnormal	0	0	0	0	0	0	1 (2.4)	0

Source: Ad hoc Table 15.3

ALT: alanine amino transferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; TEAE: treatment-emergent adverse event

Notes: The same MedDRA versions were used as in the original CSR for each study/part. Only selected hepatotoxic TEAEs are included. When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category. Preferred terms are sorted in the descending order of n (%) in 103 safety set. Data are summarized for each study's Treatment-emergent Period.

Table 58 Hepatotoxicity TEAEs Exposure Adjusted Rates in Parent Studies of Study 110 by Preferred Term; Safety Set in Parent Studies of Study 110

	Events/100 patient years							
Preferred Term	Safety Set 103	Safety Set 106	Safety Set 107	Safety Set 108	Safety Set 109	Safety Set 111	Safety Set 112	Safety Set 114
Total exposure in 100 patient years	0.35	2.29	0.51	0.94	0.37	0.05	0.56	0.18
ALT increased	11.58	9.17	9.72	10.63	10.84	19.21	1.79	5.43
AST increased	11.58	8.74	5.83	11.70	5.42	19.21	3.57	5.43
Blood bilirubin unconjugated increased	5.79	0.00	0.00	0.00	0.00	0.00	0.00	0.00
GGT increased	2.89	2.62	3.89	2.13	8.13	19.21	1.79	5.43
Bilirubin conjugated increased	0.00	0.00	0.00	2.13	2.71	0.00	0.00	0.00
Blood bilirubin increased	0.00	1.75	0.00	2.13	5.42	0.00	1.79	5.43
Hepatic cirrhosis	0.00	0.00	0.00	0.00	0.00	0.00	1.79	0.00
Hepatic fibrosis	0.00	0.44	0.00	0.00	0.00	0.00	0.00	0.00
Hepatic lesion	0.00	0.44	0.00	0.00	0.00	0.00	0.00	0.00
Hepatomegaly	0.00	0.44	0.00	0.00	0.00	0.00	0.00	0.00
Hypertransaminasaemia	0.00	0.44	0.00	0.00	0.00	0.00	0.00	0.00
Transaminases increased	0.00	0.00	0.00	0.00	0.00	0.00	1.79	0.00
Ultrasound liver abnormal	0.00	0.00	0.00	0.00	0.00	0.00	1.79	0.00

Source: Ad hoc Table 15.4

ALT: alanine amino transferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; TEAE: treatment-emergent adverse event

Notes: The same MedDRA versions were used as in the original CSR for each study/part. Only selected hepatotoxic TEAEs are included. When summarizing number of events, a subject with multiple events within a category is counted multiple times in that category. Preferred terms are sorted in the descending order of adjusted event rate in 103 safety set. Data are summarized for each study's Treatment-emergent Period. Events/100 patient years: number of events per 100 patient years = number of events/(total exposure in days/(365.25 * 100).

Table 59 Hepatotoxicity TEAEs in Study 110 Part A, B and C; Safety Set in Study 110 Part A, B and C

	110A Safety Set N = 1042		110B Safety Set N = 463		110C Safety Set N = 204	
Preferred Term	n (%)	Event/100 PY	n (%)	Event/100 PY	n (%)	Event/100 PY
Total exposure in 100 PY	--	15.57	--	6.34	--	2.80
AST increased	55 (5.3)	4.18	7 (1.5)	1.26	1 (0.5)	0.36
ALT aminotransferase increased	48 (4.6)	3.66	9 (1.9)	1.58	1 (0.5)	0.36
GGT increased	25 (2.4)	1.61	2 (0.4)	0.32	0	0.00
Blood bilirubin increased	10 (1.0)	0.71	4 (0.9)	0.63	0	0.00
Bilirubin conjugated increased	4 (0.4)	0.26	2 (0.4)	0.32	0	0.00
Hepatic steatosis	2 (0.2)	0.13	1 (0.2)	0.16	1 (0.5)	0.36
Hepatomegaly	2 (0.2)	0.13	0	0.00	0	0.00
Blood bilirubin unconjugated increased	1 (0.1)	0.06	0	0.00	0	0.00
Hepatic mass	1 (0.1)	0.06	0	0.00	0	0.00
Hepatitis toxic	1 (0.1)	0.06	0	0.00	0	0.00
Hypertransaminasaemia	1 (0.1)	0.06	1 (0.2)	0.16	0	0.00
Ultrasound liver abnormal	1 (0.1)	0.06	0	0.00	0	0.00
Ammonia increased	0	0.00	1 (0.2)	0.16	0	0.00
Biliary cirrhosis	0	0.00	1 (0.2)	0.16	0	0.00
Hepatic cirrhosis	0	0.00	1 (0.2)	0.16	0	0.00
Hepatic cytolysis	0	0.00	0	0.00	1 (0.5)	0.71
Hepatic lesion	0	0.00	1 (0.2)	0.16	0	0.00
Liver disorder	0	0.00	0	0.00	1 (0.5)	0.36
Oesophageal varices haemorrhage	0	0.00	1 (0.2)	0.47	0	0.00
Portal hypertension	0	0.00	2 (0.4)	0.32	0	0.00

Source: Ad hoc Table 15.2

ALT: alanine amino transferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; PY: patient years; TEAE: treatment-emergent adverse event

Notes: The same MedDRA versions were used as in the original CSR for each study/part. Only selected hepatotoxicity TEAEs are included. n: number of subjects in each AE category from each of the safety sets in study 110 Part A, B and C; Events/100 patient years: number of events per 100 patient years = number of events / (total exposure in days/(365.25 * 100)). When summarizing number of events, a subject with multiple events within a category is counted multiple times in that category. When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category. Preferred terms are sorted in the descending order of n (%) in 110A. Data are summarized for each study Treatment-emergent Period.

Assessment of the MAH's response

Overall, the rate of liver-related events was low, dominated by the laboratory abnormalities, especially ALT increased, AST increased and bilirubin increased. Laboratory abnormalities of increased transaminases and bilirubin are a known adverse drug reaction (ADR) for TEZ/IVA. Other liver events were rare and, according to the MAH, none were life-threatening or fatal.

Liver disease is a comorbidity of CF. Warnings concerning elevated transaminase and hepatic injury are already included in the SmPC as well as recommendations for liver functions testing.

No further action is required

Conclusion

Issue resolved

Question 16

The SAEs in the subgroups are presented in extensive tables. To allow for the assessment of these events, the number (%) of the SAE are requested for the PC-SS and safety set Part in one table for SAEs occurring in ≥ 3 subjects in any group.

Summary of the MAH's response

Table 60 (Ad hoc) Serious TEAEs with occurrence in ≥3 subjects with parent study baseline age <18 years Safety Subset in study 110 Part A and Phase 3-controlled Safety Set

	PC-SS (<18 years at baseline)				110A Safety Set (<18 years at parent study baseline) N = 194	
	Placebo N = 101		TEZ/IVA N = 98			
Preferred Term	n (%)	Event/100 Patient years	n (%)	Event/100 Patient years	n (%)	Event /100 Patient years
Total exposure in 100 patient years	--	0.40	--	0.40	--	2.87
Infective pulmonary exacerbation of cystic fibrosis	12 (11.9)	32.16	9 (9.2)	32.58	48 (24.7)	30.33
Distal intestinal obstruction syndrome	0	0.00	1 (1.0)	2.51	6 (3.1)	3.14
Appendicitis	0	0.00	0	0.00	3 (1.5)	1.05
Pulmonary function test decreased	3 (3.0)	7.42	0	0.00	1 (0.5)	0.35

- The same MedDRA versions were used as in the original CSR for each study/part.
- TEAE: Treatment-emergent adverse event.
- PC-SS (Phase 3-controlled Safety Set): consists of the combined safety sets of the Phase 3 placebo-controlled studies, Study 106, Study 107, and Study 108.
- Only TEAEs with occurrence in ≥3 subjects in at least one of the corresponding safety sets are included.
- n: number of subjects in each of the safety sets in study 110 Part A and PC-SS; Events/100 patient years: number of events per 100 patient years = number of events/(total duration of TE period in days/(365.25 * 100)).
- When summarizing number of events, a subject with multiple events within a category is counted multiple times in that category.
- When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category.
- Preferred terms are sorted in the descending order of n (%) in PC-SS TEZ/IVA.
- Data are summarized at each study Treatment-emergent Period.

Table 61 (Ad hoc) Serious TEAEs with occurrence in in ≥3 subjects with parent study baseline age ≥18 years Safety Set in study 110 Part A and Phase 3-controlled Safety Set

	PC-SS (≥18 years at baseline)				110A Safety Set (≥18 years at parent study baseline) N = 848	
	Placebo N = 404		TEZ/IVA N = 398			
Preferred Term	n (%)	Event/100 Patient years	n (%)	Event/100 Patient years	n (%)	Event/100 Patient years
Total exposure in 100 patient years	--	1.63	--	1.60	--	12.70
Infective pulmonary exacerbation of cystic fibrosis	40 (9.9)	27.62	24 (6.0)	16.25	195 (23.0)	25.12
Haemoptysis	5 (1.2)	3.68	5 (1.3)	3.75	23 (2.7)	2.20
Distal intestinal obstruction syndrome	0	0.00	2 (0.5)	1.25	6 (0.7)	0.63
Blood creatine phosphokinase increased	0	0.00	1 (0.3)	0.62	6 (0.7)	0.47
Influenza	2 (0.5)	1.23	1 (0.3)	0.62	5 (0.6)	0.39
Pneumonia	3 (0.7)	1.84	1 (0.3)	0.62	5 (0.6)	0.39
Abdominal pain	2 (0.5)	1.23	0	0.00	5 (0.6)	0.39
Anxiety	0	0.00	0	0.00	5 (0.6)	0.39
Aspartate aminotransferase increased	0	0.00	0	0.00	3 (0.4)	0.24
Constipation	2 (0.5)	1.23	0	0.00	7 (0.8)	0.55
Infective exacerbation of bronchiectasis	0	0.00	0	0.00	4 (0.5)	0.47
Intestinal obstruction	0	0.00	0	0.00	4 (0.5)	0.39
Nephrolithiasis	0	0.00	0	0.00	4 (0.5)	0.31

- The same MedDRA versions were used as in the original CSR for each study/part.
- TEAE: Treatment-emergent adverse event.
- PC-SS (Phase 3-controlled Safety Set): consists of the combined safety sets of the Phase 3 placebo-controlled studies, Study 106, Study 107, and Study 108.
- Only TEAEs with occurrence in ≥3 subjects in at least one of the corresponding safety sets are included.
- n: number of subjects in each of the safety sets in study 110 Part A and PC-SS; Events/100 patient years: number of events per 100 patient years = number of events/(total duration of TE period in days/(365.25 * 100)).
- When summarizing number of events, a subject with multiple events within a category is counted multiple times in that category.
- When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category.
- Preferred terms are sorted in the descending order of n (%) in PC-SS TEZ/IVA.
- Data are summarized at each study Treatment-emergent Period.

Table 62 (Ad hoc) Serious TEAEs with occurrence in ≥3 subjects with parent study baseline ppFEV1<40 Safety Set in study 110 Part A and Phase 3-controlled Safety Set

	PC-SS (baseline ppFEV1<40)				110A Safety Set (parent study baseline ppFEV1<40) N = 86	
	Placebo N = 43		TEZ/IVA N = 49			
Preferred Term	n (%)	Event/100 Patient years	n (%)	Event/100 Patient years	n (%)	Event/100 Patient years
Total exposure in 100 patient years	--	0.18	--	0.20	--	1.28
Infective pulmonary exacerbation of cystic fibrosis	11 (25.6)	66.46	10 (20.4)	60.63	34 (39.5)	57.03
Haemoptysis	0	0.00	2 (4.1)	10.11	3 (3.5)	2.34

- The same MedDRA versions were used as in the original CSR for each study/part.
- TEAE: Treatment-emergent adverse event.
- PC-SS (Phase 3-controlled Safety Set): consists of the combined safety sets of the Phase 3 placebo-controlled studies, Study 106, Study 107, and Study 108.
- Only TEAEs with occurrence in ≥3 subjects in at least one of the corresponding safety sets are included.
- n: number of subjects in each of the safety sets in study 110 Part A and PC-SS; Events/100 patient years: number of events per 100 patient years = number of events/(total duration of TE period in days/(365.25 * 100)).
- When summarizing number of events, a subject with multiple events within a category is counted multiple times in that category.
- When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category.
- Preferred terms are sorted in the descending order of n (%) in PC-SS TEZ/IVA.
- Data are summarized at each study Treatment-emergent Period.

Table 63 (Ad hoc) Serious TEAEs with occurrence in ≥3 subjects with parent study baseline ppFEV1 ≥40 and <70 Safety Set in study 110 Part A and Phase 3-controlled Safety Set

	PC-SS (baseline ppFEV1 ≥40 and <70)				110A Safety Set (parent study baseline ppFEV1 ≥40 and <70)	
	Placebo N = 310		TEZ/IVA N = 304		N = 646	
Preferred Term	n (%)	Event/100 Patient years	n (%)	Event/100 Patient years	n (%)	Event/100 Patient years
Total exposure in 100 patient years	--	1.23	--	1.23	--	9.47
Infective pulmonary exacerbation of cystic fibrosis	31 (10.0)	28.38	17 (5.6)	17.04	162 (25.1)	27.45
Distal intestinal obstruction syndrome	0	0.00	3 (1.0)	2.43	8 (1.2)	1.06
Haemoptysis	5 (1.6)	4.87	3 (1.0)	3.24	18 (2.8)	2.32
Blood creatine phosphokinase increased	0	0.00	1 (0.3)	0.81	4 (0.6)	0.42
Influenza	2 (0.6)	1.62	1 (0.3)	0.81	3 (0.5)	0.32
Pneumonia	2 (0.6)	1.62	1 (0.3)	0.81	3 (0.5)	0.32
Appendicitis	0	0.00	0	0.00	3 (0.5)	0.32
Aspartate aminotransferase increased	0	0.00	0	0.00	3 (0.5)	0.32
Constipation	1 (0.3)	0.81	0	0.00	6 (0.9)	0.63
Forced expiratory volume decreased	0	0.00	0	0.00	3 (0.5)	0.32
Intestinal obstruction	0	0.00	0	0.00	3 (0.5)	0.42

- The same MedDRA versions were used as in the original CSR for each study/part.
- TEAE: Treatment-emergent adverse event.
- PC-SS (Phase 3-controlled Safety Set): consists of the combined safety sets of the Phase 3 placebo-controlled studies, Study 106, Study 107, and Study 108.
- Only TEAEs with occurrence in ≥3 subjects in at least one of the corresponding safety sets are included.
- n: number of subjects in each of the safety sets in study 110 Part A and PC-SS; Events/100 patient years: number of events per 100 patient years = number of events/(total duration of TE period in days/(365.25 * 100)).
- When summarizing number of events, a subject with multiple events within a category is counted multiple times in that category.
- When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category.
- Preferred terms are sorted in the descending order of n (%) in PC-SS TEZ/IVA.
- Data are summarized at each study Treatment-emergent Period.

Table 64 (Ad hoc) Serious TEAEs with occurrence in ≥3 subjects with parent study baseline ppFEV1 ≥70 Safety Set in study 110 Part A and Phase 3-controlled Safety Set

	PC-SS (baseline ppFEV1 ≥70)					
	Placebo N = 152		TEZ/IVA N = 142		110A Safety Set (parent study baseline ppFEV1 ≥70) N = 308	
Preferred Term	n (%)	Event/100 Patient years	n (%)	Event/100 Patient years	n (%)	Event/100 Patient years
Total exposure in 100 patient years	--	0.62	--	0.56	--	4.78
Infective pulmonary exacerbation of cystic fibrosis	10 (6.6)	17.75	6 (4.2)	10.64	47 (15.3)	15.28
Pneumonia	0	0.00	1 (0.7)	1.77	3 (1.0)	0.63
Abdominal pain	1 (0.7)	1.61	0	0.00	5 (1.6)	1.05
Distal intestinal obstruction syndrome	0	0.00	0	0.00	4 (1.3)	1.46
Haemoptysis	1 (0.7)	1.61	0	0.00	4 (1.3)	1.46
Influenza	0	0.00	0	0.00	3 (1.0)	0.63

- The same MedDRA versions were used as in the original CSR for each study/part.
- TEAE: Treatment-emergent adverse event.
- PC-SS (Phase 3-controlled Safety Set): consists of the combined safety sets of the Phase 3 placebo-controlled studies, Study 106, Study 107, and Study 108.
- Only TEAEs with occurrence in ≥3 subjects in at least one of the corresponding safety sets are included.
- n: number of subjects in each of the safety sets in study 110 Part A and PC-SS; Events/100 patient years: number of events per 100 patient years = number of events/(total duration of TE period in days/(365.25 * 100)).
- When summarizing number of events, a subject with multiple events within a category is counted multiple times in that category.
- When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category.
- Preferred terms are sorted in the descending order of n (%) in PC-SS TEZ/IVA.
- Data are summarized at each study Treatment-emergent Period.

Assessment of the MAH's response

In adhoc table 16.1 and adhoc table 16.2, the SAEs with occurrence in ≥3 subjects with parent study baseline age <18 years and ≥18 years are presented, respectively. Generally, the same SAEs are observed, i.e. the SAE that occur in subjects <18 years also occur in subjects ≥18 years. However, in subjects ≥18 years also additional SAEs e,g. nephrolithiasis, were observed, but this might be explained by the higher number of subjects ≥18 years in the study. The observed SAEs are generally in line with known AEs of TEZ/IVA, common manifestations of CF disease, or common illnesses in CF subjects 6 years of age and older, or are under review of the PRAC (anxiety). Event rates in the 110A Safety Set are generally lower than the event rates in the PC-SS. Therefore, no new changes in the SmPC regarding these findings are considered necessary.

In adhoc table 16.3, adhoc table 16.4 and adhoc table 16.5, the SAEs with occurrence in ≥3 subjects with parent study baseline ppFEV1 <40%, ppFEV1 ≥40% and <70% and ppFEV1 ≥70% are presented, respectively. Again, the same SAEs are observed in the 3 groups, i.e. the SAE that occur in subjects with ppFEV1 <40% also occur in subjects with ppFEV1 ≥40%. However, in subjects with ppFEV1 < 70% and ≥40% also additional SAEs were observed, that is most likely due to higher number of subjects in the other groups. The observed SAEs are generally in line with known AEs of TEZ/IVA, common manifestations of CF disease, or common illnesses in CF subjects 6 years of age and older, or are under review of the PRAC (anxiety). Event rates in the 110A Safety Set are generally lower than the event rates in the PC-SS. Therefore, no new changes in the SmPC regarding these findings are considered necessary.

Conclusion

Issue resolved.

Question 17

The number of subjects with cataract in part B is not clearly provided, as only reference is made to an extensive table. The applicant is requested to provide the number of subjects with cataract, including a short description.

Summary of the MAH's response

Per study protocol, only subjects <18 years of age when they signed the informed consent form (ICF) in the parent study were required to have ophthalmological examinations (OEs) (at time points specified in the schedule of assessments).

Four of the 84 subjects <18 years of age in the Full Analysis Set had cataract findings in their OE in Part B. Only 1 of these was considered by the investigator as an AE. In addition, two of the subjects with cataract findings had no cataracts detected upon follow-up OE.

Six subjects had a lens opacity not associated with cataract identified by OE. None of these lens opacities was considered by the investigator as an AE.

In the Safety Set including subjects of all ages, a total of 4 subjects had cataract-related AEs (PTs of cataract, cataract subcapsular, cataract cortical, and cataract nuclear). Three of these 4 subjects did not have OEs as a study assessment per protocol because they were ≥18 years of age. All of the AEs were mild or moderate in severity and did not lead to change in study drug dosing.

In the safety set including subjects of all ages, a total of 3 additional subjects had an opacity related AE (PTs of lenticular opacities or eye opacity). All of the AEs were mild in severity and did not lead to change in study drug dosing.

Assessment of the MAH's response

The MAH provided the requested number of subjects with cataract. According to this, for the subjects < 18 years, only 1 of 4 findings of cataract in 84 subjects was considered an AE.

However, when checking the listings, more subjects with the AE cataracts were found.

In Part A, 7 subjects are found with AE cataract with IDs: 106-110-002/F/20/W, 106-160-003/M/12/W, 106-208-004/M/38/W, 106-506-013/M/13/W, 106-805-008/F/51/W, 108-015-002/F/39/W, 108-045-005/F/49/W (Listing 16.2.7.1)

In Part B, only 1 new subject was found with AE cataract, ID 114-320-005/M/47/W (Listing 16.2.7.1b)

In Part C, no new subjects with AE cataract were found, 106-208-004/M/38/W, 106-805-008/F/51/W (Listing 16.2.7.1c)

Thus, there seems a difference between the number of cataracts in the response of the MAH and the number of subjects with an AE cataracts in the listings (Listing 16.2.7.1, Listing 16.2.7.1b, Listing 16.2.7.1c). This needs to be explained.

Conclusion

Issue not resolved. The MAH is requested to explain the discrepancy between the number of subjects with an AE in the response and the listings. (OC)

STATISTICAL

Question 18

The Applicant is requested to clarify how many patients left study 110 for another Vertex study and re-entered later in the study 110 and the rationale behind allowing this. In case this occurred, the impact and possible bias should be discussed (including a sensitivity analysis which omits these subjects). Also, it should be confirmed whether the trajectories were 'glued together' (e.g. if a subject left at day 50 and re-entered, the study day in study 110 for that subject would start at day 51).

Summary of the MAH's response

In total, 30 subjects with F/F genotypes from parent Studies 103, 106, and 111 left Study 110 and enrolled in another Vertex study, and then returned to Study 110 (Ad hoc Table 18.1); no Study 110 subjects from parent Study 108 (F/RF genotypes) left and returned. The rationale for allowing this was to help facilitate enrolment of the elexacaftor/TEZ/IVA pivotal study (Study 445-103), which was concurrently enrolling a similar population of subjects with CF.

Table 65 (Ad hoc) Disposition for subjects who departed 110 and returned to 110 before end of study Sensitivity Efficacy Set in Study 110

	Study			
	103 N = 4	106 N = 16	111 N = 10	Total N = 30
Number of subjects who departed 110 Part A and returned later to 110 Part A, n1	4	16	10	30
Genotype, n2 (%[1])				
F/F	4 (100.0)	16 (100.0)	10 (100.0)	30 (100.0)
F/RF	0	0	0	0
Number of subjects who departed 110 Part B and returned later to 110 Part B, n3	0	0	0	0

- 103-110A(or B) Sensitivity Efficacy Set in Study 110 A (or B) consists of only subjects in the efficacy set of 110 Part A (or B) who were originally from Study 103, did not depart to join another Vertex study and later returned to Study 110 A (or B).
- 106-110A (or B) Sensitivity Efficacy Set in Study 110 Part A (or B) consists of only subjects in the efficacy set of 110 Part A (or B) who were originally from Study 106, didn't depart to join another Vertex study and later returned to Study 110 A (or B).
- 111-110A (or B) Sensitivity Efficacy Set in Study 110 Part A (or B) consists of only subjects in the efficacy set of 110 Part A (or B) who were originally from Study 111, did not depart to join another Vertex study and later returned to Study 110 A (or B).
- [1]: Number of subjects who departed 110 Part A and returned later to 110 Part A n1 is the denominator.

Study 110 re-entry was permitted to provide the option of continued treatment with TEZ/IVA in regions where commercially available product was not yet available. The primary objective of Study 110 was to assess the long-term safety and tolerability of TEZ/IVA; the protocol re-entry provision did not impact this objective.

It is challenging to quantify the potential bias of this provision because subjects who were doing less well in Study 110 may have been more likely to transition out of the study, whereas subjects who left Study 110 and did less well in another clinical study may have been more likely to return to Study 110. Therefore, the ability to assess bias is not based solely on outcomes within Study 110. The requested sensitivity analyses of ppFEV1 at each study visit excluding F/F subjects from each applicable parent study (Study 103, 106, and 111) who departed and returned to Study 110 are provided in the following tables. The results of these analyses are generally consistent with the full ES analyses for ppFEV1 for Part A (Study 110 CSR/Table 14.2.1.1.1).

Vertex confirms that subjects who left Study 110 to enroll in another qualified Vertex study and then re-enrolled in Study 110 resumed treatment with TEZ/IVA at the next study day after their previous treatment discontinuation in Study 110, i.e., the trajectories were 'glued together'.

Table 66 (Ad hoc) Summary of ppFEV1 excluding subjects departed and returned to Study 110 before end of study, 106/110A Sensitivity Efficacy Set in Study 110 Part A

Visit	Statistic	PBO-TEZ/IVA N = 223	TEZ/IVA N = 220	Total N = 443
Baseline	n	223	218	441
	Mean (SD)	59.2 (15.7)	59.4 (14.5)	59.3 (15.1)
	Median	58.2	58.5	58.3
	Min, max	31.2, 107.4	30.3, 91.1	30.3, 107.4
Study 110A Week 96	n	180	189	369
	Mean (SD)	60.4 (16.2)	62.2 (16.0)	61.3 (16.1)
	Median	60.6	61.2	61.1
	Min, max	24.9, 99.0	33.5, 106.9	24.9, 106.9
Absolute Change at Study 110A Week 96	n	180	188	368
	Mean (SD)	1.9 (8.4)	2.2 (9.4)	2.1 (8.9)
	Median	2.3	2.6	2.4
	Min, max	-31.3, 26.1	-28.8, 36.3	-31.3, 36.3
Relative Change at Study 110A Week 96	n	180	188	368
	Mean (SD)	3.9 (15.0)	4.5 (16.2)	4.2 (15.6)
	Median	4.2	4.2	4.2
	Min, max	-38.6, 58.1	-43.3, 71.3	-43.3, 71.3

- 106/110A Sensitivity Efficacy Set in Study 110 Part A consists of only subjects in the efficacy set of 110 Part A who were originally from Study 106, didn't depart to join another Vertex study and later returned to Study 110.
- Treatment group assignment is PBO-TEZ/IVA or TEZ/IVA for subjects randomized to Placebo or TEZ/IVA in Study 106 respectively.
- The same definition of baseline was used as in the SAP for Study 110 Part A. Baseline for subjects randomized to TEZ/IVA group in the parent study 106 is defined as the most recent non-missing measurement collected prior to the first dose of study drug in Study 106. Baseline for subjects randomized to placebo group in the parent study 106 is defined as the most recent non-missing measurement collected prior to the first dose of study drug in Study 110 Part A.
- $ppFEV_1$ is derived using Hankinson and Wang standards.

Table 67 (Ad hoc) Summary of ppFEV1 excluding subjects departed and returned to Study 110 before end of study, 103/110A Sensitivity Efficacy Set in Study 110 Part A

Visit	Statistic	Total N = 19
Baseline	n	19
	Mean (SD)	53.7 (15.5)
	Median	50.1
	Min, max	36.5, 93.7
Study 110A Week 96	n	17
	Mean (SD)	57.3 (17.7)
	Median	54.4
	Min, max	28.6, 98.0
Absolute Change at Study 110A Week 96	n	17
	Mean (SD)	4.5 (9.8)
	Median	4.5
	Min, max	-11.9, 22.9
Relative Change at Study 110A Week 96	n	17
	Mean (SD)	9.8 (21.7)
	Median	8.1
	Min, max	-29.4, 44.8

- 103/110A Sensitivity Efficacy Set in Study 110 consists of only subjects in the efficacy set of 110 Part A who were originally from Study 103, did not depart to join another Vertex study and later returned to Study 110.
- The same definition of baseline was used as in the SAP for Study 110 Part A. Baseline is defined as the most recent non-missing measurement collected prior to the first dose of study drug in Study 103.
- $ppFEV_1$ is derived using Hankinson and Wang standards.

Table 68 (Ad hoc) Summary of ppFEV1 excluding subjects departed and returned to Study 110 before end of study, 111/110A Sensitivity Efficacy Set in Study 110 Part A

Visit	Statistic	PBO-TEZ/IVA N = 5	TEZ/IVA N = 18	Total N = 23
Baseline	n	5	18	23
	Mean (SD)	66.6 (7.0)	65.1 (14.4)	65.5 (13.1)
	Median	68.0	68.9	68.6
	Min, max	55.8, 73.5	37.0, 95.7	37.0, 95.7
Study 110A Week 96	n	4	11	15
	Mean (SD)	69.2 (16.2)	71.3 (9.1)	70.8 (10.8)
	Median	64.0	70.3	69.2
	Min, max	56.1, 92.8	59.0, 89.6	56.1, 92.8
Absolute Change at Study 110A Week 96	n	4	11	15
	Mean (SD)	4.3 (11.8)	1.5 (7.1)	2.2 (8.2)
	Median	1.2	0.7	0.7
	Min, max	-6.4, 21.2	-10.2, 16.0	-10.2, 21.2
Relative Change at Study 110A Week 96	n	4	11	15
	Mean (SD)	6.0 (16.6)	3.2 (12.1)	3.9 (12.9)
	Median	1.9	1.0	1.0
	Min, max	-9.4, 29.6	-14.8, 33.0	-14.8, 33.0

- 111/110A Sensitivity Efficacy Set in Study 110 Part A consists of only subjects in the efficacy set of 110 Part A who were originally from Study 111, did not depart to join another Vertex study and later returned to Study 110.
- Treatment group assignment is PBO-TEZ/IVA or TEZ/IVA for subjects randomized to Placebo or TEZ/IVA in Study 111 respectively.
- The same definition of baseline was used as in the SAP for Study 110 Part A. Baseline is defined as the most recent non-missing measurement collected prior to the first dose of study drug in Study 111.
- $ppFEV_1$ is derived using Hankinson and Wang standards.

Assessment of the MAH's response

The numbers of leave-and-return subjects were:

study	Number left and returned	% left and returned	PpFEV1: Maximal difference in mean (maximal difference in SD)
106	16 (of 459)	3.5%	0.5 (0.5)
103	4 (of 23)	17.4%	3.4 (1.4)
111	10 (of 33)	30.3%	4.2 (3)

* across the visits between original data and data without the patients that left and returned in terms of absolute and relative difference

Especially data from parent Studies 103 and 111 had a non-negligible percentage of patients that left and returned. This had in Study 103 and 111 more impact on visit's mean (visit's SD) than in Study 106, but still outcomes at visits were rather comparable when comparing the visits' mean and SD between the original descriptive statistics and that after removing the patients that left and returned. The impact in parent Study 106 (the bulk of the data) was limited, so the overall there seems little impact of the patients that left and returned on the original analysis.

In the MMRM for Study 106 (too few patients for an MMRM in Study 103 and 111), the difference in least-square means was limited: maximal 0.2 for the absolute (change in) ppFEV1 and 0.5 for the relative (change in) ppFEV1. As parent Study 106 is the bulk of data in Study 110, the influence of patients that left and returned on the original analysis seems not much.

Conclusion

Issue resolved.

REFERENCES

1 Liou TG, Elkin EP, Pasta DJ, Jacobs JR, Konstan MW, Morgan WJ, et al. Year-to-year changes in lung function in individuals with cystic fibrosis. J Cyst Fibros. 2010;9(4):250-56.

2 Flume PA, Biner RF, Downey DG, Brown C, Jain M, Fischer R, et al. Long-term safety and efficacy of tezacaftor-ivacaftor in individuals with cystic fibrosis aged 12 years or older who are homozygous or heterozygous for Phe508del CFTR (EXTEND): an open label extension study. Lancet Respir Med. 2021;S2213-2600(20)30510-5. doi:10.1016/S2213-2600(20)30510-5:Epub ahead of print.

3 Collaco JM, Green DM, Cutting GR, Naughton KM, Mogayzel PJ, Jr. Location and duration of treatment of cystic fibrosis respiratory exacerbations do not affect outcomes.Am J Respir Crit Care Med. 2010;182(9):1137-43.

4 Konstan MW, Morgan WJ, Butler SM, Pasta DJ, Craib ML, Silva SJ, et al. Risk factors for rate of decline in forced expiratory volume in one second in children and adolescents with cystic fibrosis. J Pedia. 2007;151(2):134-39.e1.

5 Waters V, Stanojevic S, Atenafu EG, Lu A, Yau Y, Tullis E, et al. Effect of pulmonary exacerbations on long-term lung function decline in cystic fibrosis. Eur Respir J. 2011;40(1):61-66.

6 de Boer K, Vandemheen KL, Tullis E, Doucette S, Fergusson D, Freitag A, et al. Exacerbation frequency and clinical outcomes in adult patients with cystic fibrosis. Thorax. 2011;66(8):680-5.

7 Liou TG. Predictive 5-year survivorship model of cystic fibrosis. Am J Epidemiol. 2001;153(4):345-52.

8 Rabin HR, Butler SM, Wohl MEB, Geller DE, Colin AA, Schidlow DV, et al. Pulmonary exacerbations in cystic fibrosis. Pediatr Pulmonol. 2004;37(5):400-06.

9 Remmel A. COVID vaccines and safety: what the research says. Nature. 2021;590(7847):538-40.

10 American Psychiatric Association. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Arlington, VA: American Psychiatric Association; 2013.

5. 2nd Request for supplementary information P008.1

1. The number of subjects with cataract in part B is not clear, as there is discrepancy between the response of the MAH and the relevant listings. The MAH is requested to explain the discrepancy between the response and the listings. A complete list of the subjects with an AE of cataracts needs to be provided.
2. The MAH is requested to include the proposed changes to section 5.1. of the SmPC.

MAH responses to 2nd Request for supplementary information P008.1

CLINICAL

Question 1

The number of subjects with cataract in part B is not clear, as there is discrepancy between the response of the MAH and the relevant listings. The MAH is requested to explain the discrepancy between the response and the listings. A complete list of the subjects with an AE of cataracts needs to be provided.

Summary of the MAH's response

To clarify, in the first request for supplementary information (RSI) Vertex interpreted the question as referring only to Part B of the study, therefore the response described only events that occurred in Part B. In this second RSI we understand that the Rapporteur is referring to the number of subjects with reported adverse events (AEs) of cataract throughout Study 110. Please see below; three separate tables are provided with this response and include listings of all subjects with AE of cataract in Part A, Part B and Part C of Study 110. <note Rapporteur: the three listings are summarised in the assessment below, please refer to the response document of the MAH for the tables.>

Assessment of the MAH's response

The MAH clarified that in the previous response only events that occurred in Part B were described. In the current response the MAH presented complete listings of all subjects with an AE of cataract throughout Study 110. In Part A, 7 patients reported 9 AEs of cataract. Of these 9 AEs, 6 were mild in severity and 3 moderate. In Part B, 4 patients reported 5 events (4 mild, 1 moderate). One event was newly reported in Part B. This AE was mild in severity and resolved without dose adjustment. Three out of 4 patients had continuing events that had been reported during Part A also. In Part C, no new events were reported. Two patients reported 2 continuing AEs of cataract, that were also reported in Part A and B listings. Throughout Study 110, the drug was withdrawn in 1 patient and interrupted in 1 other patient. With all other events the dose was not changed. Cases of non-congenital lens opacities/cataracts without impact on vision have previously been reported in paediatric patients treated with ivacaftor and ivacaftor-containing regimens. Baseline and follow-up ophthalmological examinations are already recommended in paediatric patients initiating Symkevi treatment in combination with ivacaftor. As such, no additional risk minimisation is considered warranted for Symkevi.

Conclusion

Issue resolved.

Question 2

The MAH is requested to include the proposed changes to section 5.1. of the SmPC.

Summary of the MAH's response

Vertex accepts EMA's recommendation with slight changes to remove "the design was complex" as this statement is not commonly used in the label and doesn't provide additional beneficial information to the provider. The last statement "Generally similar results are observed in part B and part C" has also been modified to accurately represent the studies.

Assessment of the MAH's response

The MAH has included the proposed changes as requested, except for 2 small changes as clarified above. This is agreed.

Conclusion

Issue resolved.