Amsterdam, 26 June 2019
EMA/CHMP/401041/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Symkevi/Kalydeco

International non-proprietary name: TEZACAFTOR/ IVACAFTOR

Procedure no.: EMEA/H/C/004682/P46/005 + EMEA/H/C/002494/P46/026

Marketing authorisation holder (MAH): Vertex Pharmaceuticals (Ireland) Limited

Note

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

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LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transaminase
ATS	American Thoracic Society
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	CF transmembrane conductance regulator gene
CI	confidence interval
CYP	cytochrome P450
DBP	diastolic blood pressure
EAP	expanded access program
ERS	European Respiratory Society
ETT	Early Termination of Treatment
EU	European Union
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
FDA	Food and Drug Administration
FDC	fixed-dose combination
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
G551D	CFTR missense gene mutation that results in the replacement of a glycine residue at position 551 of CFTR with an aspartic acid residue
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
ICF	informed consent form
ICH	International Council for Harmonization
IDMC	independent data monitoring committee
IEC	independent ethics committee
IPD	important protocol deviation
IRB	institutional review board
IVA	ivacaftor

IWRS	interactive web response system
LFT	liver function test
LLN	lower limit of normal
LUM	lumacaftor
Max	maximum value
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum value
N	size of subsample
N	total sample size
PAP	pulmonary arterial pressure
PE	physical examination
PEx	pulmonary exacerbation
PI	principal investigator
PM	evening
PN	Preferred Name
ppFEV1	percent predicted forced expiratory volume in 1 second
PT	Preferred Term
q12h	every 12 hours
qd	once daily
QT	QT interval
RAESIs	respiratory adverse events of special interest
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
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
ULN	upper limit of normal

US	United States
USA	United States of America
VX-661	tezacaftor
VX-770	ivacaftor
WHO-DD	World Health Organization-Drug Dictionary

Definitions of Terms

Abbreviated study numbers: In the body of the text, study numbers are abbreviated to the last 3 digits for tezacaftor/ivacaftor studies (e.g., Study VX11-661-114 is Study 114)

1. Introduction

On 06 February 2019, the MAH submitted a completed paediatric study Study VX16-661-114 for Symkevi (tezacaftor/ivacaftor) 100 mg/150 mg film coated tablets in a combination regimen with ivacaftor 150 mg tablets, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Study VX16-661-114 involved the use of two authorised medicinal products held by Vertex Pharmaceuticals (Ireland) Limited:

- Symkevi (tezacaftor/ivacaftor) 100 mg/150 mg film coated tablets.

- Kalydeco (ivacaftor) 150 mg film-coated tablets

The same Article 46 submission has therefore been submitted in parallel for Kalydeco.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Study VX16-661-114 is a 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. In the EU, TEZ/IVA is approved as a combination regimen of Symkevi® with IVA 150-mg tablets (Kalydeco®) for the treatment of patients with CF 12 years of age and older who are homozygous for the *F508del-CFTR* mutation or who are heterozygous for the *F508del-CFTR* mutation and have 1 of the following mutations in the *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*.

Vertex initiated a postmarketing study on respiratory safety (Study 114) in CF subjects 12 years of age and older, homozygous for the *F508del-CFTR* mutation. Respiratory safety was evaluated based on the incidence of respiratory adverse events of special interest (RAESIs), which include 7 Preferred Terms (PTs) predefined to explore selected adverse events (AEs) within the respiratory system. These terms are the same as those summarized in the Orkambi SmPC as "respiratory adverse reactions."
In addition, conventional CF endpoints were evaluated to assess the safety and efficacy of TEZ/IVA in CF subjects homozygous for the *F508del-CFTR* mutation and who discontinued treatment with Orkambi due to respiratory symptoms considered related to treatment. Evaluation of AEs, clinical parameters (laboratory assessments, vital signs, physical examinations, and pulse oximetry), and post-dose spirometry provided further measures of safety. Spirometry and the Cystic Fibrosis Questionnaire-Revised (CFQ-R) were used to assess efficacy.

Orkambi (LUM/IVA) was registered before Symkevi in CF subjects homozygous for the *F508del-CFTR* mutation. In LUM/IVA, there was a decline in percent predicted forced expiratory volume in 1 second (ppFEV1) observed within 4 hours of LUM/IVA dosing in Phase 1 studies with healthy subjects. Post-dose spirometry was not assessed in Phase 3 studies with LUM/IVA, but the incidence of respiratory symptoms (i.e., chest discomfort, dyspnea, and respiration abnormal) was 22.0% in subjects who received the commercialized dose of the LUM/IVA and 13.8% in subjects who received placebo. Post-marketing data for Orkambi suggested that patients discontinued treatment due to respiratory events.

Study VX16-661-114, is a stand-alone study. A line listing is not provided as Study VX16-661-114 is not part of a development program for Symkevi or Kalydeco.

2.2. Information on the pharmaceutical formulation used in the study<ies>

No new paediatric formulation was evaluated in Study 114. The test product was the same as the commercially approved product, Symkevi, for patients 12 years of age and older (TEZ 100-mg/IVA 150-mg fixed-dose combination tablets). The test product was administered to study subjects orally at a dose of TEZ 100-mg once daily (qd)/IVA 150-mg every 12 hours (q12h), which is also the commercially approved dose of Symkevi.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

VX16-661-114: 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.

2.3.2. Clinical study

VX16-661-114: 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.

Dates of Study:

Study initiation: 24 May 2017 (date first eligible subject signed the informed consent form)

Study completion: 09 August 2018 (date last subject completed the last visit)

Description

This was a Phase 3b, randomized, double-blind, placebo-controlled, parallel group, multicenter study in CF subjects 12 years of age and older who are homozygous for *F508del* and who discontinued Orkambi due to respiratory symptoms considered related to treatment. This study was designed to evaluate the safety and efficacy of TEZ/IVA.

At the time this study initiated, Orkambi was the only modulator therapy approved for CF subjects homozygous for F508del. Tezacaftor, an experimental CFTR corrector, in combination with IVA, was being evaluated in several Phase 3 studies in CF subjects who are either homozygous for *F508del* or heterozygous for *F508del* with other CFTR mutations. Since subjects entering this study were not taking corrector/potentiator therapy, the use of placebo in this study was deemed ethical and necessary to adequately assess the benefit of TEZ/IVA treatment.

Methods

Objective(s)

Primary

To evaluate the respiratory safety of TEZ/IVA in subjects with cystic fibrosis (CF) homozygous for F508del who discontinued treatment with Orkambi® due to respiratory symptoms considered related to treatment.

Secondary

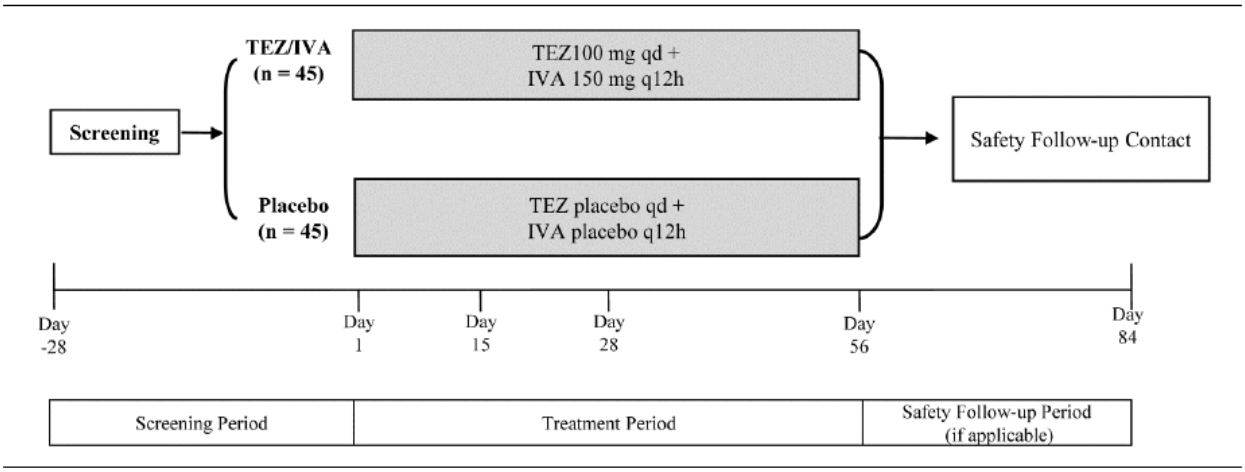
- To evaluate the efficacy of TEZ/IVA in subjects with CF homozygous for the F508del-CFTR mutation and who discontinued treatment with Orkambi due to respiratory symptoms considered related to treatment.
- To evaluate patient-reported outcomes after treatment with TEZ/IVA in subjects with CF homozygous for the *F508del-CFTR* mutation and who discontinued treatment with Orkambi due to respiratory symptoms considered related to treatment.

Study design

Study 114 was a Phase 3b, randomized, double-blind, placebo-controlled, parallel-group, multicenter study in Orkambi-experienced CF subjects 12 years of age and older homozygous for the *F508del-CFTR* mutation.

This study included the following: Screening Period (Day -28 through Day -1), Treatment Period (Day 1 through Day 56) and Safety Follow-up Contact (Day 56 through Day 84, if applicable). (Figure 1)

Figure 1 Schematic of the Study Design



IVA: ivacaftor; n: number of subjects planned; qd: once daily; q12h: every 12 hours; TEZ: tezacaftor
Note: Clinical visits were on Days -28, 1, 15, 28, and 56. A telephone contact on Day 3 collected AEs. The Safety Follow-up was a clinic visit or telephone call.

Study population /Sample size

This study was conducted at 37 sites in the United States, Germany, and France.

Ninety-eight subjects were randomized and 97 subjects received at least 1 dose of study drug.

Key inclusion criteria

Table 1 summarizes the key inclusion criteria.

Table 1 Key Inclusion Criteria and Enrolment of CF Subjects in Study 114

Enrollment Criteria	Study 114
CFTR mutation on both alleles	Homozygous for the *F508del-CFTR* mutation
Age	12 years of age or older
$ppFEV_1$	At least 25% and not greater than 90% of predicted at the Screening Visit, calculated using the following standards: • Wang et al.[1] (for female subjects 12 to 15 years of age [inclusive] and male subjects 12 to 17 years of age [inclusive]) • Hankinson et al.[2] (for female subjects 16 years of age and older and male subjects 18 years of age and older)
Prior discontinuation of Orkambi	Discontinuation of Orkambi therapy within approximately 12 weeks from the first dose of Orkambi with at least 1 respiratory sign or symptom considered related to therapy, including but not limited to the following: chest discomfort, dyspnea, respiration abnormal, asthma, bronchial hyperreactivity, bronchospasm, wheezing, or an asymptomatic reduction in relative change in $ppFEV_1$ of >12% within 2 weeks after Orkambi initiation.

Source: VX16-661-114 CSR/Section 9.3.1
CF: cystic fibrosis; $ppFEV_1$: percent predicted forced expiratory volume in 1 second

- resolution or stabilization of qualifying event(s) >28 days prior to Screening.

Key exclusion criteria

1. History of any comorbidity that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject. For example:

• Respiratory

o Massive haemoptysis within the last 12 months

o Any of the following within the past 12 months and not associated with an acute, resolved event:

☐ Six-minute walk test distance <400 m

☐ Resting arterial blood gas on room air showing PaCO2 >50 mm Hg or PaO2 <55 mm Hg

- ☐ Systolic pulmonary arterial pressure (PAP) >35 mm Hg on echocardiography or a mean PAP >25 mm Hg measured by right heart catheterization, in the absence of a hypoxemic exacerbation or with an alternate aetiology to explain the findings.

• Non-respiratory: history of cirrhosis with portal hypertension, history of and/or risk factors for ventricular arrhythmia (e.g., long QT interval syndrome, hypokalaemia, heart failure, left ventricular hypertrophy, bradycardia, myocardial infarction, cardiomyopathy, morbid obesity, acute neurologic events [subarachnoid haemorrhage, intracranial haemorrhage, cerebrovascular accident, and intracranial trauma], autonomic neuropathy, and significant anaemia).

2. Recent rapid or progressive deterioration in respiratory status

3. Receiving continuous oxygen at >2 L/minute or on face-mask ventilation

4. Any of the following abnormal laboratory values at Screening:

- Abnormal liver function defined as any 2 or more of the following:

- ≥ 3 × upper limit of normal (ULN) aspartate transaminase (AST), ≥ 3 × ULN alanine transaminase (ALT), ≥ 3 × ULN gamma-glutamyl transpeptidase, ≥ 3 × ULN alkaline phosphatase (ALP), or ≥ 2 × ULN total bilirubin.

- Abnormal liver function defined as any increase of ≥ 5 × ULN AST or ALT.
- Abnormal renal function defined as glomerular filtration rate ≤ 50 mL/minute/1.73 m2 (calculated by the Modification of Diet in Renal Disease Study Equation) for subjects ≥18 years of age and ≤45 mL/minute/1.73 m2 (calculated by the Counahan-Barratt equation) for subjects aged 12 to 17 years (inclusive).

5. Child-Pugh Class B or C hepatic impairment

6. An acute upper or lower respiratory infection, PEx, or change in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1 (first dose of study drug)

7. Documentation of colonization with organisms associated with a more rapid decline in pulmonary status (e.g., Burkholderia cenocepacia, Burkholderia dolosa, and Mycobacterium abscessus)

8. History of lung transplantation since most recent initiation of Orkambi

9. History of alcohol or drug abuse in the past year as deemed by the investigator, including but not limited to cannabis, cocaine, and opiates

10. Participation in an investigational drug study or use of a CFTR modulator (including Orkambi) within 28 days or 5 terminal half-lives before screening of the previous investigational study drug or CFTR modulator, whichever is longer

- Ongoing participation in a non-interventional study (including observational studies and studies requiring assessments without administration of study drug) were permitted.

11. Use of restricted medications or foods within the specified window before the first dose of study drug, or an anticipated need or use of restricted medication or foods after the first dose of study drug,

12. Pregnant or nursing females: Females of child-bearing potential were required to have a negative pregnancy test at Screening and Day 1

Removal/Replacement of Subjects

Subjects could have withdrawn from the study at any time at their own request.

A subject will be withdrawn from study drug treatment for any of the following reasons:

- A female subject or a female partner of a male subject has a confirmed pregnancy.
- Treatment unblinding by the investigator.
- Development of a life-threatening AE or a serious AE (SAE) that places him/her at immediate risk, and discontinuation of study drug treatment and withdrawal from the study are deemed necessary.
- Following randomization, the screening CFTR genotype results does not confirm study eligibility. The subject will undergo ETT and/or Safety Follow-up Contact and will then be discontinued from the study. After discontinuation of study drug treatment, the subject will not undergo any further assessments other than those performed at the ETT and/or Safety Follow-up Contact.

A subject may be withdrawn from study drug treatment after a discussion between the investigator and the medical monitor for any of the following reasons:

- Development of a medical condition that requires prolonged concomitant therapy with a prohibited medication or prolonged interruption of the study drug.
- Noncompliance with study requirements.
- An increase in liver function
- Development of a cataract or lens opacity.

Rapporteurs' comments

The inclusion criteria are compliant with the indication. The inclusion criterion 'discontinuation of Orkambi within approximately 12 weeks due to a respiratory sign or symptom related to Orkambi' complies with the objective of this study. Therefore, the inclusion criteria are justified.

The exclusion criteria are similar to the initial studies performed for Symkevi, and are acceptable.

Prior and Concomitant Medications

• Subjects remained on a stable medication (including supplements and inhaled antibiotics) regimen for their CF from 28 days before Day 1 through the Safety Follow-up Contact. A 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.

• There were no restrictions on the concomitant use of corticosteroids.

• 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 guidelines.

Rapporteurs' comments

Definition of prior and concomitant medication is acceptable.

Additional Dietary Restrictions/Prohibited Medications

Prohibited medications and certain foods were not allowed in this study (Screening Period through the Safety Follow-up Contact:

- moderate and strong CYP3A inhibitors (except ciprofloxacin),

- moderate and strong CYP3A inducers ,

- certain fruits and fruit juices (Grapefruit, grapefruit juice, Seville oranges, marmalade).

Commercially available CFTR modulators (e.g., Kalydeco, Orkambi, or others) were not allowed within 28 days or 5 terminal half-lives before screening, whichever was longer through the Safety Follow-up Contact.

Rapporteurs' comments

Additional dietary restrictions and prohibited medication are in line with the recommendations for Symkevi.

Treatments

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION

• 100-mg TEZ/150-mg IVA, film-coated fixed-dose combination (FDC) tablet

• 150-mg IVA, film-coated tablet

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION

• 0-mg TEZ/0-mg IVA, placebo film-coated tablet

• 0-mg IVA, placebo film-coated tablet

Study drugs were administered orally.

Study Drug Interruption

Study drug administration was interrupted immediately (prior to confirmatory testing), and the medical monitor was notified, if any of the following criteria was met and confirmed with repeat testing:

• ALT or AST >8 × ULN

• ALT or AST >5 × ULN for more than 2 weeks

• ALT or AST >3 × ULN in association with total bilirubin >2 × ULN and/or clinical jaundice

A thorough investigation of potential causes was conducted, and the subject was followed closely for clinical progression.

Outcomes/endpoints

CRITERIA FOR EVALUATION

Endpoints

The primary safety endpoint was the incidence of RAESIs while subjects were on treatment.

The key secondary efficacy endpoint was the absolute change from baseline in ppFEV1 to the average of Day 28 and Day 56.

Efficacy Assessments

Spirometry and Cystic Fibrosis Questionnaire-Revised (CFQ-R).

Safety Assessments

- Respiratory adverse events of special interest (RAESIs), adverse events (AEs),
- clinical laboratory assessments (i.e., haematology, serum chemistry, coagulation studies, and urinalysis),
- vital signs, physical examinations (PEs),
- pulse oximetry, and post-dose spirometry.

Timing of assessments

Table **2** shows the timing of the assessments.

Table 2 Study VX16-661-114: Treatment Period, ETT, and Safety Follow-up Contact Assessments

Event/Assessment[a]	Day 1	Day 3 Telephone Contact[b]	Day 15 (± 3 Days)	Day 28 (± 5 Days)	Day 56 (± 5 Days)	Early Termination of Treatment[c]	Safety Follow-up Contact 28(±7) Days After Last Dose of Study Drug[d]
Inclusion and exclusion criteria review	X		X	X	X		
Randomization[e]	X						
Clinic visit	X		X	X	X	X	
CFQ-R[f]	X		X	X	X	X	
Spirometry[g]	X		X	X	X	X	
Height (<18 years old only)	X		X	X	X	X	
Vital signs[h]	X		X	X	X	X	
Pulse oximetry[h]	X		X	X	X	X	
Physical examination[i]	X					X	
Pregnancy test	urine		urine	urine	serum	serum	
Safety labs[j]	X		X		X	X	
Snack or meal at site[k]	X		X	X	X		
Study drug dosing[l]	X		X	X	X		
Study drug count	X		X	X	X	X	
Concomitant medications	X		X	X	X	X	X
Concomitant treatment and procedures review	X		X	X	X	X	X
AEs and SAEs	Continuous from signing of the ICF and assent (where applicable) through the Safety Follow-up Contact[m]						

AE: adverse event; CFQ-R: Cystic Fibrosis Questionnaire-Revised; ETT: Early Termination of Treatment; ICF: informed consent form; PE: physical exam; IWRS: interactive web response system; SAE: serious adverse event

a All assessments were performed before dosing unless noted otherwise.

b On Day 3, there was a telephone contact to collect AEs.

c If the subject prematurely discontinued study drug treatment, an ETT Visit was scheduled as soon as possible after the decision to terminate study treatment. Subjects who prematurely discontinued study drug treatment were also required to complete the Safety Follow-up Contact, approximately 28 (± 7) days after their last dose of study drug. If the ETT Visit occurred 3 weeks or later following the last dose of study drug, then the ETT Visit replaced the Safety Follow-up Contact, and a separate Safety Follow-up Contact was not required.

d Telephone contact was acceptable. A clinic visit was required at the discretion of the investigator.

e Randomization occurred after all inclusion and exclusion criteria were met and before the first dose of study drug. Randomization was done through IWRS. Randomization occurred on Day -1.

f The CFQ-R was completed as the first assessment at each visit.

g Pre-dose spirometry was performed before dosing and prebronchodilator at all visits. Post-dose spirometry was performed at 2 hours (± 30 minutes) and 4 hours (± 30 minutes) after dosing on Day 1 only.

h Vital signs (pulse rate, blood pressure, and respiration rate) and pulse oximetry were collected after the subject had been at rest in the seated or supine position for at least 5 minutes. Vital signs and pulse oximetry were collected pre-dose at all visits.

i In addition to the complete PEs indicated, symptom-targeted PEs occurred at any time during the study if triggered by AEs or if deemed necessary by the investigator.

j Includes serum chemistry, hematology, coagulation and urinalysis.

k Fat-containing food such as a "standard CF" high-fat, high-calorie meal or snack was provided at the site to subjects after all pre-dose assessments occurred.

l On days of scheduled visits, the morning dose of study drug was administered at the site after pre-dose assessments had been completed.

m For enrolled subjects who did not have a Safety Follow-up Contact, AEs and SAEs were collected through the earliest of either 28 days after the last dose of study drug, or the ETT Visit (if that visit was 3 weeks or later following the last dose of study drug).

Method of assessment efficacy and safety parameters

Definition of RAESI

• Asthma

• Bronchial hyperreactivity

• Bronchospasm

• Wheezing

• Chest discomfort

• Dyspnea

• Respiration abnormal

Spirometry

Spirometry was performed according to the ATS/ERS guidelines.

Pre-bronchodilator spirometry was defined as spirometry testing performed for subjects who had

• withheld their short-acting bronchodilators for more than 4 hours before the spirometry assessment;

• withheld their twice-daily, long-acting bronchodilator for more than 12 hours before the spirometry assessment;

• withheld their once-daily, long-acting bronchodilator for more than 24 hours before the spirometry assessment.

The parameters, FEV1 (L), Forced vital capacity (FVC) (L), FEV1/FVC (ratio), Forced expiratory flow 25% to 75% (L/s) were normalized using the standards of Wang et al. (for female subjects aged 12 to 15 years [inclusive] and male subjects aged 12 to 17 years [inclusive]) or Hankinson et al. (for female subjects aged 16 years and older and male subjects aged 18 years and older):

Post-dose spirometry assessment was performed 2 hours (± 30 minutes) and 4 hours (± 30 minutes) after dosing on Day 1.

In the event that a subject forgets to withhold bronchodilator(s), spirometry should be performed according to the following:

- If a subject's Day 1 spirometry is performed prebronchodilator, but on a subsequent visit the subject does not withhold bronchodilator, a postbronchodilator spirometry will be obtained for that visit only, and the visit will not be rescheduled.
- If a subject does not withhold his/her dose of bronchodilator on Day 1, spirometry at that visit and at all subsequent visits (according to the schedule of assessments detailed in Table 3-2) should be performed postbronchodilator.
- Each spirometry assessment will be recorded in the source documents as pre- or postbronchodilator.

Rapporteurs' comments

Spirometry is performed according to ATS/ERS criteria.

Cystic Fibrosis Questionnaire-Revised

Subjects completed the CFQ-R in their native language before the start of any other assessments. Subjects who were <14 years of age at Day 1 completed the CFQ-R child version themselves, and their

parents/caregivers completed the CFQ-R Parent version, at all visits, regardless of whether the subject subsequently turned 14 years of age during the study. Subjects 14 years of age and older at Day 1 completed the adolescent/adult version of the questionnaire themselves at all visits.

Rapporteurs' comments

Different CFQ-R for the age groups is according to standard practice.

Pulse Oximetry

Arterial oxygen saturation by pulse oximetry was assessed following at least a 5-minute rest (seated or supine).

Ophthalmologic Examination

Subjects <18 years of age who did not have an ophthalmological examination prior to starting Orkambi underwent an ophthalmologic examination if they had not had an ophthalmologic examination within 6 months before the Screening Period. Additional ophthalmologic examinations were conducted at the discretion of the investigator.

Statistical Methods

Sample size calculation

Sample size calculation was based on the key secondary endpoint of absolute change in ppFEV1 to the average of the Day 28 and Day 56 measurements.

A Bayesian approach was used to assess the treatment effect on the change in ppFEV1. The study was considered successful if the posterior probability that the treatment difference between TEZ/IVA and placebo was greater than 0 was at least 80%, using a non-informative prior distribution. Assuming a 3.0 percentage points mean treatment difference between TEZ/IVA and placebo and a SD of 6.0 percentage points, with 45 TEZ/IVA subjects and 45 placebo subjects, the Bayesian power to achieve the posterior probability criterion was at least 90% (92.6%). After adjusting for an assumed dropout rate of 5%, a total sample size of 90 subjects was needed.

The above assumptions were based on the results of Study VX14-661-106 (beyond that of the reported primary output) in which the mean within-group absolute change from baseline to 8 weeks for TEZ/IVA was 3.0 percentage points for subjects with a baseline ppFEV1 <40%. This subgroup best approximates the population that was expected to enrol in Study VX16-661-114.

The SD of the primary endpoint in Study VX14-661-106 was ~5% based on 6 post-baseline observations. Given that this study averaged only 2 post-baseline observations, it was reasonable to expect the SD to be slightly higher, and, therefore, the SD for this study was set at 6.0%.

Subjects were stratified by age at the Screening Visit (<18 versus ≥18 years old), sex (male versus female), and percent predicted forced expiratory volume in 1 second (ppFEV1) severity determined during the Screening Visit (<40% versus ≥40% predicted), and then randomized (1:1) to 1 of the following 2 treatment groups:

• Tezacaftor/Ivacaftor: TEZ/IVA 100/150 mg tablet once each morning + IVA 150 mg tablet once each evening

• Placebo: placebo regimen with visually matched tablets

Rapporteurs' comments

Regarding the sample size, the MAH choose a Bayesian 'success' criterion for the trial instead of a frequentist one. Theoretically this could have led to a smaller trial than for a more usual frequentist comparison. However, if the Applicant had chosen to obtain 90% power for detecting statistical significance at the 0.05 level when the underlying assumptions are the same (a difference of 3 percent points with a standard deviation of 6 percent points), then 15 subjects per group would have been needed. Thus, the method did not lead to a smaller trial.

However, the Applicant did not specify what kind of non-informative prior was used. Therefore the results of the Bayesian analysis will be compared to that of a frequentist one in the assessment later on.

On the choice of the criterion itself, the criterion means that the 60%-credible interval of the mean is above 0 (assuming that the credible interval is symmetric which is considered reasonable given the normalizing influence of taking the average of the week 28 and 56 measurement and taking the change from baseline). Here the credible interval is the Bayesian counter part of the frequentist confidence interval. This reformulation also makes clear that the choice of this criterion is somewhat arbitrary, because the 60% is not justified, and there is no particular argument in favour or against this choice.

Analysis Sets

The following analysis sets were defined: All Subjects Set, Randomized Set, Full Analysis Set (FAS), and Safety Set.

The All Subjects Set was defined as all subjects who had been randomized or had received at least 1 dose of study drug. This analysis set was used in subject listings and the disposition summary table, unless otherwise specified.

The Randomized Set was defined as all subjects who had been randomized.

The Full Analysis Set (FAS) was defined as all randomized subjects who carried the intended CFTR allele mutation and had received at least 1 dose of study drug.

The Safety Set was defined as all subjects who received at least 1 dose of study drug.

Statistical Analyses

Continuous variables were summarized using the following descriptive summary statistics: the number of subjects (n), mean, standard deviation (SD), median, minimum value (Min), and maximum value (Max).

Categorical variables were summarized using counts and percentages.

Baseline Value, unless otherwise specified, was defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to or on the first dose of study drug.

Change (absolute change) from baseline was calculated as Post-baseline value - Baseline value.

Relative change from baseline was calculated and expressed in percentage as 100 × (Post-baseline value - Baseline value) / Baseline value.

Treatment-emergent (TE) Period was defined in the following way:

- For subjects who completed the Safety Follow-up Contact, the TE period included the time from the first dose of the study drug to the Safety Follow-up Contact.

- For subjects who discontinued and had an ETT Visit but no Safety Follow-up Contact, the TE period included the time from the first dose of the study drug until the ETT visit.
- For subjects who withdrew consent, the TE period included the time from the first dose of the study drug until withdrawal.
- For subjects who enrolled in Study VX14-661-110 (EU only) or in the EAP (US only), the TE period in this study (Study 114) included the time from the first dose of study drug in Study 114 until the earlier of last study participation day OR until 28 days after the last dose of the study drug in Study 114.
- For all other subjects, including those who did not have a Safety Follow-up Contact, the TE period included the time from the first dose of the study drug until the earlier of last study participation day OR until 28 days after the last dose of the study drug.

Unscheduled Visits: Unscheduled visit measurements were included in the following:

1. Derivations of measurements at scheduled visits per specified visit windowing rules below;
2. Derivations of baseline/last on-treatment measurements;
3. Derivations of the Max/Min on-treatment values and Max/Min changes from baseline values for safety analyses;
4. Data listings where appropriate.

Visit Windowing Rules: The windows were applied based on the rules included in Appendix 16.1.9/SAP Version 1.0/Section 7.1.

Incomplete/Missing data were not be imputed, unless otherwise specified.

Outliers: No formal statistical analyses were performed to detect or remedy the presence of statistical outliers, unless otherwise specified.

Primary Safety Endpoint

Respiratory safety of TEZ/IVA was the primary objective of this study and was assessed in terms of incidence, including the following respiratory adverse events of special interest (RAESIs) while subjects were on treatment: Chest discomfort , Dyspnea (shortness of breath), Respiration abnormal (chest tightness), Asthma, bronchial hyperreactivity, bronchospasm, wheezing

Respiratory adverse events of special interest were also summarized by PT for the following treatment intervals:

• 0 to 1 Week: [Day 1, Day 7]

• >1 to 4 Weeks: [Day 8, Day 28]

• >4 to 8 Weeks: [Day 29, Day 56]

• >8 Weeks: [Day 57, end of TE period]

Data Monitoring

An independent data monitoring committee (IDMC), as defined in a separate document (IDMC Charter), was formed before study initiation. The IDMC conducted regular planned safety reviews of study data as outlined in the IDMC Charter and IDMC Analysis Plan. The first IDMC analysis was performed when approximately 50% of subjects completed their Day 56 visit.

Important Protocol Deviations

Important protocol deviations (IPDs) were a subset of protocol deviations that may have significantly impacted the completeness, accuracy, and/or reliability of the study data or that may have significantly affected a subject's rights, safety, or well-being. Important protocol deviation rules were developed and finalized before database lock.

Important protocol deviations (from the clinical database or from the site deviation log) were summarized descriptively based on the FAS and presented by treatment. Additionally, IPDs were provided as a subject data listing.

Changes in Conduct of Study

The Study 114 protocol was amended 2 times, and there were US- and French-specific versions. The major changes in each protocol version are summarized below.

Protocol History	
Version and Date of Protocol	**Comments**
Version 1.0, 22 December 2016	Original version
Version 2.1 US, 19 April 2017	Version for US. The protocol was amended to revise sample size, and the time from Orkambi initiation to discontinuation was changed from <8 weeks to within approximately 12 weeks. Additional safety measures were added, and subjects who complete the Day 56 Visit were given the opportunity to receive tezacaftor/ivacaftor (TEZ/IVA) through the Expanded Access Program.
Version 2.2 FR, 19 April 2017	Version for FR. Changes were similar to Version 2.1 US, except subjects who completed the Day 56 Visit were given the opportunity to enroll in a long-term, open-label safety study of TEZ/IVA.
Version 3.1 US, 09 June 2017	Final version for US. The protocol was amended to include additional postdose spirometry time points on Day 1, and restrictions on concomitant use of corticosteroids were removed. Timing of pulse oximetry and vital sign assessments at all visits as well as timing of study drug administration on days with no scheduled clinic visits were clarified.
Version 3.2 FR, 09 June 2017	Final version for FR. Changes were similar to Version 3.1 US

Results

Recruitment/ Number analysed

Ninety-eight subjects were randomized: 47 subjects in the placebo group and 51 subjects in the TEZ/IVA group. One subject in the TEZ/IVA group was judged not clinically stable by the principal investigator (PI) at the Day 1 visit and did not receive any study drug.

Of the 97 subjects who received at least 1 dose of study drug (Full Analysis Set [FAS]), 93 (95.9%) completed dosing. The number of subjects who prematurely discontinued study drug treatment due to any reason was low and similar in both treatment groups (TEZ/IVA: 2 subjects [4.0%]; placebo: 2 subjects [4.3%]). (Table 3)

Table 3 Subject Disposition, All Subjects Set

Disposition/Reason, n (%)	Placebo N = 47	TEZ/IVA N = 51	Total N = 98
All Subjects Set[a]	47	51	98
Randomized Set[b]	47	51	98
Safety Set[c]	47	50	97
FAS[d]	47	50	97
Completed treatment regimen	45 (95.7)	48 (96.0)	93 (95.9)
Prematurely discontinued treatment (any tablet)[e]	2 (4.3)	2 (4.0)	4 (4.1)
Reason for discontinuation from treatment			
AE	1 (2.1)	2 (4.0)	3 (3.1)
Subject refused further dosing (not due to AE)	1 (2.1)	0	1 (1.0)
Completed study	46 (97.9)	48 (96.0)	94 (96.9)
Prematurely discontinued the study	1 (2.1)	2 (4.0)	3 (3.1)
Reason for discontinuation from study			
AE	0	1 (2.0)	1 (1.0)
Withdrawal of consent (not due to AE)	0	0	0
Lost to follow-up	0	0	0
Death	0	1 (2.0)	1 (1.0)
Other non-compliance	0	0	0
Physician decision	0	0	0
Study terminated by sponsor	0	0	0
Other	1 (2.1)[f]	0	1 (1.0)

Source: Table 14.1.1

AE: adverse event; FAS: Full Analysis Set; FDC: fixed-dose combination; IVA: ivacaftor; n: size of subsample; N: total sample size; TEZ: tezacaftor

Notes: Percentages are based on the Safety Set. Number of subjects who completed study includes those who completed the safety follow-up contact (US subjects) or those who completed treatment and rolled over to the extension (EU subjects).

[a] The All Subjects Set was defined as all subjects who were randomized or received at least 1 dose of the study drug.

[b] The Randomized Set was defined as all subjects who were randomized.

[c] The Safety Set was defined as all subjects who received at least 1 dose of the study drug.

[d] The FAS was defined as all randomized subjects who carried the intended *CFTR* allele mutation and received at least 1 dose of study drug.

[e] Any tablet refers to FDC TEZ/IVA tablet or IVA mono tablet.

[f] Subject chose to withdraw from the study to take prescribed commercialized drug.

Rapporteurs' comments

Discontinuation is low (4.1%) and is comparable in both arms. In the placebo arm in total 2 patients discontinued treatment of which one patient discontinued because of an AE. In TEZ/IVA arm two patient discontinued treatment, both patients because of an AE. (for details see further in the safety section).

Baseline data

Demographics and Other Baseline Characteristics

Demographic parameters were similar between the TEZ/IVA and placebo groups. The majority of subjects were White (86.6%) and not Hispanic or Latino (83.5%); 62.9% of subjects were female. The overall mean age was 33.8 years (range: 15 to 59 years).

Table 4 Subject Demographics, Full Analysis Set

Demographics	Placebo N = 47	TEZ/IVA N = 50	Total N = 97
Sex, n (%)			
Male	17 (36.2)	19 (38.0)	36 (37.1)
Female	30 (63.8)	31 (62.0)	61 (62.9)
Childbearing potential, n (%)			
Yes	26 (86.7)	26 (83.9)	52 (85.2)
No	4 (13.3)	5 (16.1)	9 (14.8)
Age at baseline (years)			
Mean (SD)	33.3 (10.0)	34.3 (8.7)	33.8 (9.3)
SE	1.5	1.2	0.9
Median	31.0	34.5	34.0
Min, Max	15, 59	18, 50	15, 59
Ethnicity, n (%)			
Hispanic or Latino	3 (6.4)	1 (2.0)	4 (4.1)
Not Hispanic or Latino	40 (85.1)	41 (82.0)	81 (83.5)
Not Collected per Local Regulation	4 (8.5)	8 (16.0)	12 (12.4)
Race, n (%)			
White	42 (89.4)	42 (84.0)	84 (86.6)
Black or African American	1 (2.1)	0	1 (1.0)
Asian	0	0	0
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Not Collected per Local Regulations	4 (8.5)	8 (16.0)	12 (12.4)
Other	0	0	0
Country, n (%)			
USA	24 (51.1)	24 (48.0)	48 (49.5)
France	4 (8.5)	8 (16.0)	12 (12.4)
Germany	19 (40.4)	18 (36.0)	37 (38.1)

Source: Table 14.1.3
FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; TEZ: tezacaftor
Notes: Percentage of subjects who are of childbearing potential is based on the total number of female subjects. All other percentages are calculated relative to the number of subjects in the FAS.

Characteristics such as age, height, spirometry measures, and use of prior medications were similar across treatment groups at baseline.

The highest proportion of subjects had a baseline ppFEV1 value <40 (49.5%). The mean (SD) ppFEV1 was 44.6 (16.1) in the TEZ/IVA group and 48.0 (18.1) in the placebo group.

Before the first dose of study drug, the majority of subjects used any bronchodilator (99.0%), dornase alfa (73.2%), and any inhaled antibiotic (67.0%).

Table 5 Baseline Characteristics, Full Analysis Set

Demographics	Placebo N = 47	TEZ/IVA N = 50	Total N = 97
Age at screening			
<18	1 (2.1)	0	1 (1.0)
≥18	46 (97.9)	50 (100.0)	96 (99.0)
Height at baseline (cm) (subjects <18 years old only)			
n	1	0	1
Mean (SD)			
SE			
Median			
Min, Max			
Percent predicted FEV_1 (%) category at baseline, n (%)			
<40	21 (44.7)	27 (54.0)	48 (49.5)
≥40 to <70	17 (36.2)	19 (38.0)	36 (37.1)
≥70	9 (19.1)	4 (8.0)	13 (13.4)
FEV_1 at baseline (L)			
n	47	50	97
Mean (SD)	1.65 (0.66)	1.56 (0.61)	1.60 (0.63)
SE	0.10	0.09	0.06
Median	1.46	1.40	1.44
Min, Max	0.81, 3.38	0.65, 3.16	0.65, 3.38
Percent predicted FEV_1 (%) at baseline			
n	47	50	97
Mean (SD)	48.0 (18.1)	44.6 (16.1)	46.3 (17.1)
SE	2.6	2.3	1.7
Median	43.0	38.1	40.3
Min, Max	26.0, 86.0	22.6, 82.3	22.6, 86.0
Use of dornase alfa[a], n (%)			
Yes	34 (72.3)	37 (74.0)	71 (73.2)
No	13 (27.7)	13 (26.0)	26 (26.8)
Use of inhaled antibiotic[a], n (%)			
Yes	30 (63.8)	35 (70.0)	65 (67.0)
No	17 (36.2)	15 (30.0)	32 (33.0)
Use of azithromycin[a] n (%)			
Yes	24 (51.1)	27 (54.0)	51 (52.6)
No	23 (48.9)	23 (46.0)	46 (47.4)
Use of any bronchodilator (inhaled or oral)[a], n (%)			
Yes	47 (100.0)	49 (98.0)	96 (99.0)
No	0	1 (2.0)	1 (1.0)
Use of inhaled bronchodilator[a], n (%)			
Yes	46 (97.9)	48 (96.0)	94 (96.9)
No	1 (2.1)	2 (4.0)	3 (3.1)
Use of inhaled hypertonic saline[a], n (%)			
Yes	30 (63.8)	24 (48.0)	54 (55.7)
No	17 (36.2)	26 (52.0)	43 (44.3)
Use of inhaled corticosteroids[a], n (%)			
Yes	33 (70.2)	21 (42.0)	54 (55.7)
No	14 (29.8)	29 (58.0)	43 (44.3)

Source: Table 14.1.4

CFQ-R: Cystic Fibrosis Questionnaire-Revised; FEV_1: forced expiratory volume in 1 second; IVA: ivacaftor; n: size of subsample; N: total sample size; TEZ: tezacaftor

Notes: Baseline is defined as the most recent non-missing measurement before the first dose of study drug. Baseline CFQ-R respiratory domain scores are described in Table 14.2.2.

[a] Included medications started before the first dose of study drug.

Rapporteurs' comments

There is a small imbalance for ppFEV1. More patients in the placebo group had a ppFEV1 ≥ 70% (9 versus 4 for placebo and TEZ/IVA respectively) and less patients have ppFEV1 < 40% (21 versus 27 for placebo and TEZ/IVA respectively). Therefore, overall patients in the TEZ/IVA group had overall more severe CF.

Furthermore, there is an imbalance in use of inhaled corticosteroids (ICS); more patients in the placebo group used ICS (70.2% and 42% for placebo and TEZ/IVA, respectively). This could be an indication for concomitant asthma.

Medical history

The most common medical history conditions (incidence ≥15% of subjects by PT in the FAS) are summarized in

Table 6 Medical History With an Incidence of At Least 15% of Subjects in Any Treatment Group by Preferred Term, Full Analysis Set

Preferred Term, n (%)	Placebo N = 47	TEZ/IVA N = 50	Total N = 97
Subjects with any medical history	47 (100.0)	50 (100.0)	97 (100.0)
Pancreatic failure	46 (97.9)	48 (96.0)	94 (96.9)
Cystic fibrosis lung	42 (89.4)	47 (94.0)	89 (91.8)
Gastrooesophageal reflux disease	19 (40.4)	21 (42.0)	40 (41.2)
Cystic fibrosis related diabetes	24 (51.1)	19 (38.0)	43 (44.3)
Chronic sinusitis	17 (36.2)	18 (36.0)	35 (36.1)
Nasal polyps	3 (6.4)	13 (26.0)	16 (16.5)
Constipation	8 (17.0)	12 (24.0)	20 (20.6)
Bronchiectasis	15 (31.9)	12 (24.0)	27 (27.8)
Drug hypersensitivity	9 (19.1)	12 (24.0)	21 (21.6)
Seasonal allergy	5 (10.6)	10 (20.0)	15 (15.5)
Vitamin D deficiency	8 (17.0)	10 (20.0)	18 (18.6)
Lung infection pseudomonal	6 (12.8)	9 (18.0)	15 (15.5)
Rhinitis allergic	8 (17.0)	9 (18.0)	17 (17.5)
Central venous catheterisation	8 (17.0)	9 (18.0)	17 (17.5)
Osteopenia	7 (14.9)	9 (18.0)	16 (16.5)
Asthma	15 (31.9)	8 (16.0)	23 (23.7)
Anxiety	9 (19.1)	8 (16.0)	17 (17.5)
Bacterial disease carrier	14 (29.8)	7 (14.0)	21 (21.6)
Depression	12 (25.5)	7 (14.0)	19 (19.6)
Appendectomy	8 (17.0)	5 (10.0)	13 (13.4)

Source: Table 14.1.5
IVA: ivacaftor; n: size of subsample; N: total sample size; PT: Preferred Term; TEZ: tezacaftor
Notes: A subject with multiple conditions within a category (PT) is counted only once within that category. Table is sorted in descending order of frequency in the TEZ/IVA column.

Rapporteurs' comments

More patients in the placebo group had asthma (31.9% and 16% for placebo and TEZ/IVA, respectively). As asthma is one of the RAESI, this imbalance can be a confounder. Moreover, asthma symptoms overlap with CF symptoms; this imbalance can also be a confounder for these overlap symptoms.

Prior Medications

The most common prior medications (used by ≥ 30% of subjects in any treatment group) were dornase alfa (TEZ/IVA: 74.0%; placebo: 72.3%), sodium chloride (TEZ/IVA: 68.0%; placebo: 70.2%), pancreatin (TEZ/IVA: 60.0%; placebo: 68.1%), salbutamol (TEZ/IVA: 56.0%; placebo: 55.3%), azithromycin (TEZ/IVA: 54%; placebo: 51.1%), colecalciferol (TEZ/IVA: 42.0%; placebo: 42.6%), tobramycin (TEZ/IVA: 34.0%; placebo: 31.9%), salbutamol sulfate (TEZ/IVA: 32.0%; placebo: 27.7%), aztreonam lysine (TEZ/IVA: 30.0%; placebo: 21.3%), ursodeoxycholic acid (TEZ/IVA: 26.0%; placebo: 36.2%), and fluticasone propionate; salmeterol xinafoate (TEZ/IVA: 20.0%; placebo: 38.3%).

Concomitant Medications

All subjects used medication concomitantly with the study drug. The most common concomitant medications (used by ≥30% of subjects overall in the FAS) during the study period were for CF management and included dornase alfa (74.2%), sodium chloride (71.1%), pancreatin (63.9%), salbutamol (58.8%), azithromycin (51.5%), colecalciferol (44.3%), tobramycin (37.1%), aztreonam lysine (30.9%), salbutamol sulfate (30.9%), and ursodeoxycholic acid (30.9%).

Concomitant medications used by ≥15% of subjects are summarized in Table 7.

Table 7 Concomitant Medications Received by At Least 15% of Subjects Overall by Preferred Name, Full Analysis Set

Preferred Name, n%	Placebo N = 47	TEZ/IVA N = 50	Total N =97
Subjects with any concomitant medication	47 (100.0)	50 (100.0)	97 (100.0)
Dornase alfa	35 (74.5)	37 (74.0)	72 (74.2)
Sodium chloride	34 (72.3)	35 (70.0)	69 (71.1)
Pancreatin	32 (68.1)	30 (60.0)	62 (63.9)
Salbutamol	27 (57.4)	30 (60.0)	57 (58.8)
Azithromycin	22 (46.8)	28 (56.0)	50 (51.5)
Colecalciferol	21 (44.7)	22 (44.0)	43 (44.3)
Tobramycin	17 (36.2)	19 (38.0)	36 (37.1)
Aztreonam lysine	13 (27.7)	17 (34.0)	30 (30.9)
Salbutamol sulfate	13 (27.7)	17 (34.0)	30 (30.9)
Colecalciferol; Menadiol; Retinol; Palmitate; Tocopheryl acetate	13 (27.7)	13 (26.0)	26 (26.8)
Pancrelipase	12 (25.5)	13 (26.0)	25 (25.8)
Ursodeoxycholic acid	17 (36.2)	13 (26.0)	30 (30.9)
Omeprazole	10 (21.3)	12 (24.0)	22 (22.7)
Retinol	7 (14.9)	12 (24.0)	19 (19.6)
Ibuprofen	9 (19.1)	11 (22.0)	20 (20.6)
Ipratropium bromide	5 (10.6)	11 (22.0)	16 (16.5)
Paracetamol	4 (8.5)	11 (22.0)	15 (15.5)
Colistimethate sodium	8 (17.0)	10 (20.0)	18 (18.6)
Fluticasone Propionate	8 (17.0)	10 (20.0)	18 (18.6)
Fluticasone propionate; Salmeterol xinafoate	18 (38.3)	10 (20.0)	28 (28.9)
Ciprofloxacin	8 (17.0)	9 (18.0)	17 (17.5)
Insulin lispro	14 (29.8)	9 (18.0)	23 (23.7)
Vitamins NOS	8 (17.0)	9 (18.0)	17 (17.5)
Insulin glargine	14 (29.8)	7 (14.0)	21 (21.6)
Tiotropium bromide	12 (25.5)	7 (14.0)	19 (19.6)

Source: Table 14.1.7.1
IVA: ivacaftor; n: size of subsample; N: total sample size; NOS: not otherwise specified; PN: Preferred Name; TE: treatment-emergent; TEZ: tezacaftor; WHO-DD: World Health Organization-Drug Dictionary
Notes: Medications were coded using WHO-DD, Version March 2018, format B3. Preferred Names are sorted in descending order of frequency based on the TEZ/IVA column. A subject with multiple medications within a category was counted only once within that category.

Rapporteurs' comments

Concomitant medications were balanced except for specific asthma medication. Asthma medication was higher in the placebo group in line with the imbalance of the asthma between the two treatment groups.

Measurements of Treatment Compliance

The majority of subjects in both treatment groups had ≥ 80% study drug compliance (resulting in a mean compliance of 99.9% in the TEZ/IVA group and 99.6% in the placebo group based on study drug exposure). One subject in the TEZ/IVA group and 2 subjects in the placebo group had <80% drug compliance.

Protocol Deviations

An 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.

Important protocol deviation involving inclusion/exclusion criteria

Three (3.1%) subjects (1 in the TEZ/IVA group and 2 in the placebo group) were enrolled despite violation of inclusion and exclusion criteria; no safety issues were identified for these subjects:

• One subject (TEZ/IVA group) was randomized to TEZ/IVA study drug and dosed on Day 1 before reporting a change in therapy, the initiation of ciprofloxacin due to recent microbiology results positive for Pseudomonas. The Vertex medical monitor provided permission for this subject to continue in the study. The subject completed the study.

• One subject (placebo group) was on a restricted medication (CYP3A inhibitor, itraconazole) for the duration of the study. The subject completed the study.

• One subject (placebo group) had a PEx after screening and prior to randomization to placebo study drug. The Vertex medical monitor provided permission for this subject to continue in the study. The subject completed the study.

Important protocol deviation involving study drug compliance and missed or incorrect doses

Three (3.1%) subjects (1 in the TEZ/IVA group and 2 in the placebo group) had <80% compliance with study drug. It is not likely that these IPDs impacted the ability to interpret the overall study results, given their limited number and magnitude:

• One subject (TEZ/IVA group) had 77% study drug compliance during the Treatment Period and was assessed as overall noncompliant to TEZ/IVA administration

• One subject (placebo group) had a 73.7% study drug compliance based on FDC and mono tablets taken

• One subject (placebo group) had 78% study drug compliance between the Day 28 and Day 56 visits; subject could not recall which dates and/or doses were missed

Two (2.1%) subjects (1 in the TEZ/IVA group and 1 in the placebo group) missed doses. The subject in the TEZ/IVA group returned buffer packages during the Day 15 visit and ran out of study drug 5 days before the Day 56 visit. In total, the subject missed 5 doses of TEZ/IVA and 7 doses of IVA although a total of 56 days of treatment had taken place. The subject in the placebo group returned buffer packages during the Day 15 visit and therefore ran out of study drug 3 days before the Day 56 visit. In total, the subject missed 3 doses of placebo although a total of 56 days of treatment had already taken place.

One subject in the TEZ/IVA group inadvertently received an incorrect dosage kit (placebo). The subject took 2 doses from the incorrect kit before a new kit was provided.

Other IPDs

One subject in the placebo group had no spirometry completed on the Day 28 visit as the spirometry machine did not work.

One subject in the TEZ/IVA group did not sign the ICF before study assessments at the rescreening visit. The ICF was signed on Day 1 of the Treatment Period.

There were no safety laboratory hematology results for 1 subject in the TEZ/IVA group due to specimen hemolysis.

One subject in the placebo group took rescue medication (Albuterol) less than 4 hours prior to the spirometry tests on Days 14, 32, and 57.

Rapporteurs' comments

The MAH did not define a population without major protocol deviations, as per protocol set (PPS).

In this study, safety is the primary objective. For safety, it is important to analyse the full set and results of the safety set/FAS is most relevant.

For efficacy, a PPS would be of interest for efficacy. However, efficacy is a secondary objective. Therefore it is considered acceptable that no efficacy analyses are performed on a PPS.

EFFICACY RESULTS

Rapporteurs' comments

Efficacy was the secondary objective.

All efficacy analyses were based on the FAS, which included 97 subjects who were randomized and received at least 1 dose of study drug (50 subjects received TEZ/IVA and 47 subjects received placebo).

Primary analysis: the actual Bayesian posterior probability

The primary analysis of the key secondary efficacy variable, the actual Bayesian posterior probability calculated for a > 0 treatment effect difference in absolute change from baseline in ppFEV1 to the average of the Day 28 and Day 56 measurements, was met (Table 8). The probability for a >0 treatment effect difference in mean ppFEV1 change between TEZ/IVA and placebo was 0.9991 (posterior mean difference: 2.7; 95% Credible Interval: 1.0, 4.4).

Table 8 Bayesian Posterior Summaries of Absolute Change in ppFEV1 From Baseline to the Average of Day 28 and Day 56 (Percentage Points)

	Placebo N = 47	TEZ/IVA N = 50
Baseline		
n	47	50
Mean (SD)	48.0 (18.1)	44.6 (16.1)
Average absolute change at Day 28 and Day 56		
N	46	50
Mean (SD)	-0.6 (3.4)	2.2 (4.8)
Mean diff (TEZ/IVA vs placebo), 95% credible interval	-	2.7 (1.0, 4.4)
Bayesian posterior probability for mean diff >0	-	0.9991

Source: Table 14.2.1.1

diff: difference; IVA: ivacaftor; n: size of subsample; N: total sample size; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

Note: Baseline is defined as the most recent non-missing measurement before the first dose of study drug.

Rapporteurs' comments

From Table 9 it can be calculated (t-test on changes from baseline to average of day 28 and 56) that the 95%-CI is from 1.09199 to 4.50801; that the 0.99943 of the CI lies above 0. Therefore, the results from the Bayesian analysis are close to a frequentist analysis, which addresses the question whether the prior (claimed to be non-informative) is sufficiently non-informative. As this is the case, the analysis can be trusted upon. This is also confirmed by the Applicant's own frequentist analysis (below).

Secondary Analysis: Absolute Change in ppFEV1 From Baseline to the Average of the Day 28 and Day 56 Measurements

The mean treatment difference between the TEZ/IVA and placebo groups from baseline to the average of the Day 28 and Day 56 measurements was 2.7 percentage points (95% CI: 1.0, 4.4). The mean treatment difference between the TEZ/IVA and placebo groups in the absolute change from baseline in ppFEV1 was 2.0 percentage points (CI: 0.4, 3.6) at Day 15, 2.2 percentage points (CI: 0.3, 4.1) at Day 28, and 3.5 percentage points (CI: 1.8, 5.1) at Day 56.

The within-group difference in mean absolute change in ppFEV1 from baseline to the average of the Day 28 and Day 56 measurements was 2.2 percentage points (SD: 4.8) in the TEZ/IVA group and -0.6 percentage points (SD: 3.4) in the placebo group.

Table 9 Summary Statistics for Absolute Change in ppFEV1 From Baseline at Average of Day 28 and Day 56(Percentage Points), FAS

Visit	Placebo N = 47	TEZ/IVA N = 50
Absolute change at average of Day 28 and Day 56		
n	46	50
Mean (SD)	-0.6 (3.4)	2.2 (4.8)
SE	0.5	0.7
Median	-0.8	1.5
Min, Max	-7.5, 7.6	-17.2, 13.2
Mean diff, 95% CI	-	2.7 (1.0, 4.4)

Source: Table 14.2.1.2

diff: difference; FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

Notes: Baseline is defined as the most recent non-missing measurement before the first dose of study drug. Mean diff is the difference (TEZ/IVA versus Placebo) in raw means. CI is based on the pooled sample variance.

Rapporteurs' comments

The mean treatment difference between the TEZ/IVA and placebo groups from baseline to the average of the Day 28 and Day 56 measurements was 2.7 percentage points (95% CI: 1.0, 4.4), being lower than the marketing application (MA) study VX16-661-106 in which a difference of 4.0 (3.1, 4.8) had been observed.

Summary statistics of the within-group difference in mean absolute change in ppFEV1 is 2.2% for the TEZ/IVA group, being lower compared to the MA study while the difference in placebo was comparable to the decrease in ppFEV1 (-0.6%) at 24 weeks in the placebo group.

The MAH provided the absolute difference from baseline to Day 56 which allowed for a more direct comparison with the MA study VX16-661-106. The mean difference of 3.5 pp (95 CI: 1.8, 5.1) is more similar to that found in study 106 (4.0; 95% CI: 3.1; 4.8). The difference from baseline to Day 56 is based on 48 and 44 subjects in the TEZ/IVA and placebo groups respectively. Even though it is difficult to follow what has been done and how calculations have been performed (as it appears that for the calculation of the average at day 28 and day 56, values obtained at unscheduled visits may have been used), no further issues are raised in this respect.

An MMRM analysis was requested for ppFEV1 for the absolute difference from baseline to Day 56. No MMRM analysis was provided. Although the justications of the MAH can be questioned, it is considered that the MMRM will not mean fully give more information and can therefore be omitted.

In this study VX16-661-114, patients with lower ppFEV1 (FEV1>25%) were allowed to participate compared to the MA study (FEV1>40%). However, some patients were included in study 106 with a ppFEV<40%. In study 106, the treatment effects are comparable among the subgroups of baseline ppFEV1 ≥70% (3.7 [95% CI, 2.2, 5.2]), ≥40% to <70% (4.2 [95% CI, 3.1, 5.2]), and <40% (3.5 [95% CI, 1.0, 6.1]).

Overall, we consider that the effects seen in study 114 might be numerically lower, but these differences cannot be considered statistically significant or clinically relevant.

Secondary Analysis: Relative change in ppFEV1

The mean treatment difference between the TEZ/IVA and placebo groups from baseline to the average of the Day 28 and Day 56 measurements was 6.7% (95% CI: 2.5, 10.9). The mean treatment difference between the TEZ/IVA and placebo groups in the relative change from baseline in ppFEV1 was 4.9% (CI: 1.2, 8.6) at Day 15, 5.7% (CI: 1.0, 10.4) at Day 28 and 8.3% (CI: 4.4, 12.2) at Day 56.

Rapporteurs' comments

The difference between the two groups in relative change in ppFEV1 was 6.7% confirming the treatment favour of TEZ/IVA.

Secondary Analysis: Absolute Change in CFQ-R Respiratory Domain Score From Baseline to the Average of the Day 28 and Day 56 Measurements

The CFQ-R is a validated instrument; the respiratory domain assesses subject reported changes in respiratory-related quality of life. The pooled CFQ-R "Children Ages 12 and 13" Version and "Adolescents and Adults" Version were used for the analysis.

The absolute change in CFQ-R respiratory domain score between the TEZ/IVA and placebo groups from baseline to the average of the Day 28 and Day 56 measurements was 1.1 points (95% CI: -4.9, 7.0). The within group difference from baseline to the average of the Day 28 and Day 56 measurements was 5.7 points (SD: 14.2) for the TEZ/IVA group and 4.7 points (SD: 15.4) for the placebo group.

Summary statistics for the analysis of the change from baseline in the respiratory domain of the CFQ-R are shown in Table 10.

Table 10 Summary Statistics for Absolute Change in CFQ-R Respiratory Domain Score From Baseline (Points), Full Analysis Set

Visit	Placebo N = 47	TEZ/IVA N = 50
Absolute change at average of Day 28 and Day 56		
n	47	50
Mean (SD)	4.7 (15.4)	5.7 (14.2)
SE	2.2	2.0
Median	5.6	5.6
Min, Max	-41.7, 33.3	-36.1, 33.3
Mean diff, 95% CI	-	1.1 (-4.9, 7.0)

Source: Table 14.2.2
CFQ-R: Cystic Fibrosis Questionnaire-Revised; diff: difference; IVA: ivacaftor; n: size of subsample; N: total sample size; TEZ: tezacaftor
Notes: Baseline is defined as the most recent measurement before the first dose of study drug. Mean diff is the difference (TEZ/IVA versus placebo) in raw means. CI is based on the pooled sample variance.

Rapporteurs' comments

The mean difference is 1.1 points in CFQ-R after 8 weeks compared to the MA study 5.1, however, this difference was observed after 24 weeks.

SAFETY RESULTS

Rapporteurs' comments

Safety was the primary objective of the study.

Extent of Exposure

Ninety-seven subjects received at least 1 dose of study drug during the TE Period. The mean exposure was 7.7 weeks in the TEZ/IVA group and 7.9 weeks in the placebo group. The majority of subjects received >4 weeks and ≤8 weeks of treatment (60.0% subjects in the TEZ/IVA group and 53.2% subjects in the placebo group). Table 11 provides summary statistics for study drug exposure.

Table 11 Summary of Exposure, Full Analysis Set

	Placebo N = 47	TEZ/IVA N = 50	Total N = 97
Total exposure (patient weeks)	371.3	386.1	757.4
Exposure duration (weeks)			
n	47	50	97
Mean (SD)	7.9 (1.1)	7.7 (0.9)	7.8 (1.0)
SE	0.2	0.1	0.1
Median	8.0	7.9	8.0
Min, Max	1.6, 9.0	2.4, 9.1	1.6, 9.1
Exposure duration category (weeks) n (%)			
>0 and ≤1	0	0	0
>1 and ≤4	1 (2.1)	1 (2.0)	2 (2.1)
>4 and ≤8	25 (53.2)	30 (60.0)	55 (56.7)
>8	21 (44.7)	19 (38.0)	40 (41.2)

Source: Table 14.1.8
IVA: ivacaftor; n: size of subsample; N: total sample size; TEZ: tezacaftor
Note: Duration of study drug exposure (days) = (last dose date – first dose date) + 1, regardless of any study drug interruption.

Rapporteurs' comments

A total of 40 patients had an exposure duration of > 8 weeks. According to the design the treatment Period (Day 1 through Day 56) is 8 weeks. Patients that had an exposure duration > 8 weeks, did pass this 8 week treatment duration due to a plus or minus 5-day window for the Day 56 Visit

Primary Safety Endpoint

Respiratory Adverse Events of Special Interest

The RAESIs are a group of 7 PTs pre-defined to explore select AEs within the respiratory system. The RAESIs were defined as AEs with any of the following PTs:

- Asthma
- Bronchial hyperreactivity
- Bronchospasm
- Wheezing
- Chest discomfort
- Dyspnea
- Respiration abnormal

Seventeen (17.5%) subjects had at least 1 RAESI: 7 (14.0%) subjects in the TEZ/IVA group and 10 (21.3%) subjects in the placebo group. In most subjects who had RAESIs, in both treatment groups, the events were considered either mild or moderate in severity; no severe or life-threatening RAESIs occurred. No subjects interrupted or discontinued treatment due to an RAESI, and there were no RAESIs that were considered serious or led to death.

The most common RAESI (incidence ≥10% of subjects in any treatment group) was dyspnea (TEZ/IVA: 5 [10.0%] subjects; placebo: 5 [10.6%] subjects).

Most RAESIs were considered unlikely related or not related to study drug. Five subjects (5.2%) had RAESIs which were considered possibly related (1 in TEZ/IVA; 4 in placebo). No RAESIs were considered related to study drug.

The greatest incidence of RAESIs were during >0 to ≤1 week (TEZ/IVA: 6.0%; placebo: 10.6%) and >1 to ≤4 weeks (TEZ/IVA: 4.0%; placebo: 12.8%).

Table 12 Overview of Treatment-emergent RAESIs, Safety Set

	Placebo N = 47	TEZ/IVA N = 50	Total N = 97
Subjects with any events, n (%)	10 (21.3)	7 (14.0)	17 (17.5)
Chest discomfort	1 (2.1)	0	1 (1.0)
Dyspnoea	5 (10.6)	5 (10.0)	10 (10.3)
Respiration abnormal	1 (2.1)	3 (6.0)	4 (4.1)
Asthma	1 (2.1)	0	1 (1.0)
Bronchial hyperreactivity	0	0	0
Bronchospasm	2 (4.3)	0	2 (2.1)
Wheezing	2 (4.3)	0	2 (2.1)
Subjects with any events by maximum severity, n (%)	10 (21.3)	7 (14.0)	17 (17.5)
Mild	6 (12.8)	4 (8.0)	10 (10.3)
Moderate	4 (8.5)	3 (6.0)	7 (7.2)
Severe	0	0	0
Life-threatening	0	0	0
Subjects with any events by relationship, n (%)			
Not related	3 (6.4)	4 (8.0)	7 (7.2)
Unlikely related	3 (6.4)	2 (4.0)	5 (5.2)
Possibly related	4 (8.5)	1 (2.0)	5 (5.2)
Related	0	0	0
Subjects with events leading to treatment discontinuation, n (%)	0	0	0
Subjects with serious events, n (%)	0	0	0
Subjects with related serious events[a], n (%)	0	0	0
Subjects with events leading to death, n (%)	0	0	0
Duration of events (days)[b]			
Number of events	12	8	20
Number of events with duration	6	6	12

Mean (SD)	11.3 (9.7)	15.7 (16.4)	13.5 (13.1)
SE	4.0	6.7	3.8
Median	8.5	8.0	8.5
Min, Max	2, 29	3, 45	2, 45
By onset time interval[c]			
Subjects with any events, n (%)	10 (21.3)	7 (14.0)	17 (17.5)
>0 to ≤1 week (Day 1, Day 7)	5 (10.6)	3 (6.0)	8 (8.2)
>1 to ≤4 weeks (Day 8, Day 28)	6 (12.8)	2 (4.0)	8 (8.2)
>4 to ≤8 weeks (Day 29, Day 56)	0	1 (2.0)	1 (1.0)
>8 weeks (Day 57, end of TE period)	0	1 (2.0)	1 (1.0)

Source: Table 14.3.1.1
IVA: ivacaftor; n: size of subsample; N: total sample size; RAESI: respiratory adverse event; TEZ: tezacaftor
Notes: RAESIs were coded using MedDRA version 21.0. All percentages were calculated relative to the number of subjects in the Safety Set. A subject with multiple events within a category was counted only once in that category.
[a] Related serious events = Study drug regimen-related serious events, which includes related, possibly related, and missing categories.
[b] The duration was only calculated for the events with complete start and end dates.
[c] The onset time was calculated as RAESI start date – first dose date (+1 if RAESI started on or after first dose date of study drug).

Rapporteurs' comments

A total of 17 patients (17.5%) had a respiratory adverse event of specific interest. The number of patients is low, and it will be difficult to draw a robust conclusion. Overall, more patients in the placebo group experienced a RAESI. However, more patients in the placebo group were diagnosed with asthma. Asthma symptoms overlap with CF symptoms. An imbalance in asthma can act as a confounder for these overlap symptoms. Therefore, the most equal distribution of the events could have been confounded by this imbalance in asthma. However, for most of the RAES none of the patients in the TEZ/IVA had an event. Only respiration abnormal was experience more frequently in the TEZ/IVA group. The most common RAESI dyspnoea was balanced (TEZ/IVA: 5 [10.0%] subjects; placebo: 5 [10.6%] subjects). However, dyspnoea is symptom in CF as well as in asthma.

Most RAESIs were considered unlikely related or not related to study drug with no significant differences between the two groups.

Most events started within the first 4 weeks.

In conclusion, on face value the observed RAESIs do not lead to a specific pattern or signal in the group treated with TEZ/IVA, although it should be emphasized that the interpretation of the safety data is based on the limited number of patients and any statistical substantiation is lacking.

Adverse events

Seventy-six (78.4%) subjects had at least 1 AE, including 37 (74.0%) subjects in the TEZ/IVA group and 39 (83.0%) subjects in the placebo group.

The majority of subjects had AEs that were considered either mild (37.1%) or moderate (35.1%) in severity; 5.2% of subjects had severe AEs. One life-threatening AE occurred in the TEZ/IVA group.

Fourteen (14.4%) subjects had an SAE, including 5 (10.0%) subjects in the TEZ/IVA group and 9 (19.1%) subjects in the placebo group. No SAEs were considered related to study drug in the TEZ/IVA group, and only 1 (2.1%) was considered related in the placebo group. There was 1 AE that led to death in the TEZ/IVA group.

Adverse events that led to treatment discontinuation occurred in 2 (4.0%) subjects in the TEZ/IVA group (1 subject had malaise, and 1 subject had sepsis) and 1 (2.1%) subject in the placebo group (pleuritic pain). Adverse events that led to treatment interruption occurred in 1 (2.0%) subject in the TEZ/IVA group (gastrointestinal) and 1 (2.1%) subject in the placebo group.

The majority of subjects had AEs that were considered not related or unlikely related. Twenty-six (26.8%) subjects had at least 1 AE considered possibly related or related to study drug, including 10 (20.0%) subjects in the TEZ/IVA group and 16 (34.0%) subjects in the placebo group. Table 13 summarizes the percentage of subjects with AEs.

Table 13 Overview of Adverse Events, Safety Set

Parameter	Placebo N = 47 n (%)	TEZ/IVA N = 50 n (%)	Total N = 97 n (%)
Number of AEs (total)	155	124	279
Subjects with any AEs	39 (83.0)	37 (74.0)	76 (78.4)
Subjects with AEs by strongest relationship			
Not related	17 (36.2)	18 (36.0)	35 (36.1)
Unlikely related	6 (12.8)	9 (18.0)	15 (15.5)
Possibly related	15 (31.9)	10 (20.0)	25 (25.8)
Related	1 (2.1)	0	1 (1.0)
Subjects with related AEs	16 (34.0)	10 (20.0)	26 (26.8)
Subjects with AEs by maximum severity			
Mild	20 (42.6)	16 (32.0)	36 (37.1)
Moderate	16 (34.0)	18 (36.0)	34 (35.1)
Severe	3 (6.4)	2 (4.0)	5 (5.2)
Life-threatening	0	1 (2.0)	1 (1.0)
Subjects with grade 3/4 AEs	3 (6.4)	3 (6.0)	6 (6.2)
Subjects with AEs leading to treatment discontinuation	1 (2.1)	2 (4.0)	3 (3.1)
Subjects with AEs leading to treatment interruption	1 (2.1)	1 (2.0)	2 (2.1)
Subjects with SAEs	9 (19.1)	5 (10.0)	14 (14.4)
Subjects with related SAEs	1 (2.1)	0	1 (1.0)
Subjects with AEs leading to death	0	1 (2.0)	1 (1.0)

Source: Table 14.3.1.4.1
AE: adverse event; IVA: ivacaftor; n: size of subsample; N: total sample size; PT: Preferred Term; SAE: serious AE; TEZ: tezacaftor
Notes: AEs were coded using MedDRA Version 21.0. When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and % of subjects, a subject with multiple events within a category was counted only once in that category. An AE with relationship missing was counted as related.

Rapporteurs' comments

Overall, the frequency of AEs, SAE, and TEAE were comparable between the placebo and TEZ/IVA groups. Moreover, compared to the initial MA studies, the pattern of AEs appeared to be similar. No new safety signal for TEZ/IVA became apparent.

Analysis of Common Adverse Events

The most common AEs by PT (incidence ≥10% of subjects overall) were infective PEx of CF (20.6%), cough (17.5%), headache (13.4%), and dyspnoea (10.3%).

Adverse events that occurred in ≥ 5% of subjects by PT in any treatment group were more common in the placebo group than in the TEZ/IVA group except the following: nasopharyngitis (TEZ/IVA: 12.0%

[6 subjects]; placebo: 0%), cough (TEZ/IVA: 18.0% [9 subjects]; placebo: 17.0% [8 subjects]), haemoptysis (TEZ/IVA: 6.0% [3 subjects]; placebo: 4.3% [2 subjects]), respiration abnormal (TEZ/IVA: 6.0% [3 subjects]; placebo: 2.1% [1 subject]), constipation (TEZ/IVA: 10.0% [5 subjects]; placebo: 0%), nausea (TEZ/IVA: 8.0% [4 subjects]; placebo: 4.3% [2 subjects]), and bacterial test positive (TEZ/IVA: 6.0% [3 subjects]; placebo: 0%). (

Table **14**)

Table 14 Adverse Events With an Incidence of At Least 5% of Subjects in Any Treatment Group by System Organ Class and Preferred Term, Safety Set

System Organ Class[a] Preferred Term, n (%)	Placebo N = 47	TEZ/IVA N = 50	Total N = 97
Any adverse event	39 (83.0)	37 (74.0)	76 (78.4)
Infections and infestations	20 (42.6)	21 (42.0)	41 (42.3)
Infective pulmonary exacerbation of cystic fibrosis	13 (27.7)	7 (14.0)	20 (20.6)
Nasopharyngitis	0	6 (12.0)	6 (6.2)
Respiratory, thoracic, and mediastinal disorders	17 (36.2)	20 (40.0)	37 (38.1)
Cough	8 (17.0)	9 (18.0)	17 (17.5)
Dyspnoea	5 (10.6)	5 (10.0)	10 (10.3)
Haemoptysis	2 (4.3)	3 (6.0)	5 (5.2)
Respiration abnormal	1 (2.1)	3 (6.0)	4 (4.1)
Oropharyngeal pain	3 (6.4)	2 (4.0)	5 (5.2)
Sputum increased	5 (10.6)	2 (4.0)	7 (7.2)
Gastrointestinal disorders	11 (23.4)	15 (30.0)	26 (26.8)
Constipation	0	5 (10.0)	5 (5.2)
Abdominal pain upper	5 (10.6)	4 (8.0)	9 (9.3)
Nausea	2 (4.3)	4 (8.0)	6 (6.2)
Diarrhea	3 (6.4)	1 (2.0)	4 (4.1)
Nervous system disorders	9 (19.1)	6 (12.0)	15 (15.5)
Headache	7 (14.9)	6 (12.0)	13 (13.4)
General disorders and administration site conditions	7 (14.9)	5 (10.0)	12 (12.4)
Fatigue	4 (8.5)	2 (4.0)	6 (6.2)
Investigations	6 (12.8)	4 (8.0)	10 (10.3)
Bacterial test positive	0	3 (6.0)	3 (3.1)
Metabolism and nutrition disorders	5 (10.6)	2 (4.0)	7 (7.2)
Decreased appetite	3 (6.4)	1 (2.0)	4 (4.1)

Source: Table 14.3.1.5
IVA: ivacaftor; n: size of subsample; N: total sample size; TEZ: tezacaftor
Note: AEs were coded using MedDRA Version 21.0.
[a] Preferred terms were provided only for adverse events that occurred in ≥5% of subjects in any treatment group. A subject with multiple events within a System Organ Class or Preferred Term was counted only once within the System Organ Class or Preferred Term.

Rapporteurs' comments

Overall, the frequency of specific AEs was comparable between the placebo and TEZ/IVA groups.

Severity of Adverse Events

The majority of subjects had AEs that were considered mild (37.1%) or moderate (35.1%) in severity. The 1 subject who had a life-threatening AE was in the TEZ/IVA group. This event was also an SAE.

Table 15 Incidence and Severity of Adverse Events, Safety Set

Severity, n (%)	Placebo N = 47	TEZ/IVA N = 50	Total N = 97
Mild	20 (42.6)	16 (32.0)	36 (37.1)
Moderate	16 (34.0)	18 (36.0)	34 (35.1)
Severe	3 (6.4)	2 (4.0)	5 (5.2)
Life-threatening	0	1 (2.0)	1 (1.0)

Source: Table 14.3.1.9
IVA: ivacaftor; n: size of subsample; N: total sample size; PT: Preferred Term; SOC: System Organ Class; TEZ: tezacaftor
Note: AEs were coded using MedDRA Version 21.0. A subject with multiple events within a category (Any, SOC, or PT) is counted with the maximum severity in that category. Table is sorted in descending order of TEZ/IVA column.

Table 16 summarizes all Grade 3/4 (i.e., severe and life-threatening) AEs. No Grade 3/4 AE by PT occurred in more than 1 subject in either treatment group.

Table 16 Grade 3/4 Adverse Events by Preferred Term, Safety Set

Preferred Term, n (%)	Placebo N = 47	TEZ/IVA N =50	Total N = 97
Number of subjects with any Grade 3 or higher AE	3 (6.4)	3 (6.0)	6 (6.2)
Infective pulmonary exacerbation of cystic fibrosis	1 (2.1)	1 (2.0)	2 (2.1)
Sepsis	0	1 (2.0)	1 (1.0)
Constipation	0	1 (2.0)	1 (1.0)
Multiple organ dysfunction syndrome	0	1 (2.0)	1 (1.0)
Muscle spasms	0	1 (2.0)	1 (1.0)
Depression	0	1 (2.0)	1 (1.0)
Hypotension	0	1 (2.0)	1 (1.0)
Pericardial effusion	1 (2.1)	0	1 (1.0)
Pleuritic pain	1 (2.1)	0	1 (1.0)

Source: Table 14.3.1.7
AE: adverse event; IVA: ivacaftor; n: size of subsample; N: total sample size; PT: Preferred Term; SOC: System Organ Class; TEZ: tezacaftor
Notes: Adverse events are coded from MedDRA, Version 21.0. A subject with multiple events within a category (Any, SOC, or PT) is counted only once in that category. AEs are sorted by PT in descending order of the TEZ/IVA treatment group. Grade 3 or higher includes severe and life-threatening.

Rapporteurs' comments

One patient experienced a life-threatening AE. This patient was treated with TEZ/IVA. However, numbers of patients and events are low. Moreover, the event was considered unrelated to the medication. Therefore, no conclusions can be drawn based on these numbers.

Relationship of Adverse Events

The majority of AEs were considered not related or unlikely related to study drug. Twenty-six (26.8%) subjects had AEs considered possibly related or related to study drug; including 10 (20.0%) subjects in the TEZ/IVA group and 16 (34.0%) subjects in the placebo group.

Table 17 Incidence and Relationship to Study Drug of Adverse Events, Safety Set

Relationship, n (%)	Placebo N = 47	TEZ/IVA N = 50	Total N = 97
Subjects with any AEs	39 (83.0)	37 (74.0)	76 (78.4)
Not related	17 (36.2)	18 (36.0)	35 (36.1)
Unlikely related	6 (12.8)	9 (18.0)	15 (15.5)
Possibly related	15 (31.9)	10 (20.0)	25 (25.8)
Related	1 (2.1)	0	1 (1.0)

Source: Table 14.3.1.8

AE: adverse event; IVA: ivacaftor; n: size of subsample; N: total sample size; TEZ: tezacaftor

Notes: Adverse events are coded from MedDRA, Version 21.0. A subject with multiple study drug relationships for the same adverse event was only counted under the adverse event with the maximum relationship (in order of increasing relatedness to study drug from not related to related study drug categories). An AE with relationship missing is counted as related.

Overall, the most common related and/or possibly related AEs (incidence ≥2 subjects total) were abdominal pain upper (5 subjects), cough (5 subjects), headache (3 subjects), diarrhoea (2 subjects), nausea (2 subjects), increased viscosity of bronchial secretion (2 subjects), and dyspnoea (2 subjects). The incidence of these AEs was generally similar between treatment groups.

The AEs related to treatment that were more frequently present in TEZ/IVA group were:

- abdominal pain upper 4 (8.0) versus 1 (2.1)
- Constipation 1 (2.0) versus 0
- Distal intestinal obstruction syndrome 1 (2.0) versus 0
- Flatulence 1 (2.0) versus 0
- Respiration abnormal 1 (2.0) versus 0
- Headache 2 (4.0) versus 1 (2.1)
- Pyrexia 1 (2.0) versus 0

Rapporteurs' comments

Overall, there were more treatment related AEs in the TEZ/IVA group compared to the placebo group. These concerned possibly related AE (15(31.9%) versus 10 (20%)). These could be mainly found in the SOC Gastrointestinal disorders. Overall, these types of adverse events were already detected in the MA studies.

Adverse Events Associated With Elevated Transaminases

No subjects in the TEZ/IVA group and 1 (2.1%) subject in the placebo group had at least 1 AE associated with elevated transaminases. The events were mild in severity and did not lead to treatment discontinuation, treatment interruption, or death.

Deaths

There was 1 death in the study. One subject, who received TEZ 100 mg/IVA 150 mg, died as a result of life-threatening SAEs on Day 46 of the study, following influenza viral infection. The subject received study drug from Days 1 to Day 29 and discontinued from study drug. The SAEs with a fatal outcome

were assessed by the investigator as not related to study drug. A narrative for this event was provided.

Rapporteurs' comments

One patient experienced a life-threatening AE resulting in the death of this patient. This patient was treated with TEZ/IVA. The investigator considered the AEs and death to be unrelated to study drug.

This is accepted as this death seems to be cause by an influenza viral infection

Other Serious Adverse Events

The percentage of subjects who had at least 1 SAE was lower in the TEZ/IVA group (5 subjects, 10.0%) than in the placebo group (9 subjects, 19.1%). By PT, the most common SAE overall was infective PEx of CF, which occurred in 3 (6.0%) subjects in the TEZ/IVA group and 7 (14.9%) subjects in the placebo group. All other SAEs occurred in 1 subject in 1 of the treatment groups by PT. The majority of SAEs had an outcome of recovered/resolved.

Only 1 subject had an SAE (pleuritic pain) that was considered by the investigator to be related or possibly related to study drug (in the placebo group), which resolved with.

Table 18 Serious Adverse Events by System Organ Class and Preferred Term, Safety Set

System Organ Class Preferred Term, n (%)	Placebo N = 47	TEZ/IVA N = 50	Total N = 97
Subjects with any SAE	9 (19.1)	5 (10.0)	14 (14.4)
Infections and infestations	8 (17.0)	4 (8.0)	12 (12.4)
Infective pulmonary exacerbation of CF	7 (14.9)	3 (6.0)	10 (10.3)
Sepsis	0	1 (2.0)	1 (1.0)
Lower respiratory tract infection	1 (2.1)	0	1 (1.0)
Gastrointestinal disorders	0	1 (2.0)	1 (1.0)
Constipation	0	1 (2.0)	1 (1.0)
General disorders and administration site conditions	0	1 (2.0)	1 (1.0)
Multiple organ dysfunction syndrome	0	1 (2.0)	1 (1.0)
Psychiatric disorders	0	1 (2.0)	1 (1.0)
Suicidal ideation	0	1 (2.0)	1 (1.0)
Cardiac disorders	1 (2.1)	0	1 (1.0)
Pericardial effusion	1 (2.1)	0	1 (1.0)
Musculoskeletal and connective tissue disorders	1 (2.1)	0	1 (1.0)
Musculoskeletal chest pain	1 (2.1)	0	1 (1.0)
Respiratory, thoracic, and mediastinal disorders	1 (2.1)	0	1 (1.0)
Pleuritic pain	1 (2.1)	0	1 (1.0)

Source: Table 14.3.1.10

CF: cystic fibrosis; IVA: ivacaftor; n: size of subsample; N: total sample size; PT: Preferred Term; SAE: serious adverse event; SOC: System Organ Class; TEZ: tezacaftor

Notes: Serious adverse events are coded from MedDRA, Version 21.0. A subject with multiple events within an SOC or PT was counted only once within the SOC or PT. Table is sorted in descending order of TEZ/IVA column by SOC, and by PT within each SOC.

Rapporteurs' comments

Overall, the frequency of SAEs was higher in the placebo group compared to the TEZ/IVA group. Events that were higher in the TEZ/IVA group could be mainly found in the SOC Gastrointestinal

disorders. Overall, numbers of patients and events are low. Therefore, no conclusions can be drawn based on these numbers.

Adverse Events That Led to Discontinuation of Study Drug or That Led to Interruption of Study Drug

Three (3.1%) subjects had AEs that led to treatment discontinuation: 2 (4.0%) subjects in the TEZ/IVA group (Malaise, Multiple organ dysfunction syndrome/ Sepsis) and 1 (2.1%) subject in the placebo group (Pleuritic pain). All AEs that led to treatment discontinuation occurred in 1 subject each. None of the AEs that led to treatment discontinuation were RAESIs.

Two (2.1%) subjects had AEs that led to treatment interruption: 1 (2.0%) subject in the TEZ/IVA group (GI symptoms) and 1 (2.1%) subject in the placebo group.

Rapporteurs' comments

Overall, the frequency of AEs that led to treatment discontinuation/treatment interruption was comparable between the placebo and TEZ/IVA groups. Due to low number, no specific conclusions can be drawn.

Liver Function Test

The mean values for LFT parameters were generally within normal ranges in both treatment groups at all visits during the TE Period. No clinically meaningful trends were observed.

No subjects in either the placebo or TEZ/IVA groups had AST or ALT elevations >3 × ULN in association with bilirubin >2 × ULN.

Adverse events associated with elevated transaminases were assessed as mild in severity and did not lead to treatment interruption, treatment discontinuation, or death.

Rapporteurs' comments

There were no important finding in liver functions tests.

Other Serum Chemistry

For other clinical chemistry parameters no clinically meaningful trends were observed.

Overall, no clinically meaningful trends attributable to TEZ/IVA were observed. All AEs related to other chemistry findings occurred at an incidence of 1 (1.0%) subject in either treatment group, including 1 subject in the TEZ/IVA group with blood creatine phosphokinase increased; 1 subject in the placebo group with blood glucose increased, 1 subject in the placebo group with blood bilirubin increased; and 1 subject in the placebo group with blood Liver parameters increased.

All AEs related to other chemistry findings were mild and did not lead to treatment interruption or discontinuation. Two of the AEs related to other chemistry findings in the placebo group (liver parameters increased) were considered possibly related to study drug and were ongoing at the end of the study.

Haematology

No clinically meaningful trends in mean haematology parameter values and changes from baseline were observed. No clinically meaningful trends attributable to treatment with TEZ/IVA were observed.

One AE related to haematology findings, reticulocyte count increased, occurred in 1 (2.1%) subject in the placebo group. The AE was considered mild, unlikely related to study group, and did not lead to treatment interruption or discontinuation.

Coagulation

No clinically meaningful trends in mean coagulation parameter values and changes from baseline were observed.

All AEs related to coagulation occurred at an incidence of 1 (1.0%) subject, and all occurred in subjects in the placebo group. Two AEs occurred concurrently in 1 (2.1%) subject in the placebo group and included coagulation parameters. One additional AE related to coagulation, activated partial thromboplastin time prolonged, occurred in 1 subject in the placebo group. The AEs were all considered mild and did not lead to treatment interruption or discontinuation. Two of the AEs on coagulation parameters were considered possibly related to study drug.

Urinalysis

All AEs related to urinalysis occurred at an incidence of 1 (1.0%) subject in either treatment group, including 1 subject in the placebo group with urine calcium increased (considered not related to study drug) and 1 subject in the placebo group with crystal urine present (considered unlikely related to study drug). Both AEs were not serious and did not lead to changes in treatment.

Vital Signs

Overall, there were no major differences in vital signs between treatment groups, and no clinically meaningful trends were observed over time. Overall, there were no clinically meaningful trends attributable to treatment with TEZ/IVA, with the percentage of subjects meeting any given criterion being generally similar across treatment groups.

Adverse events related to vital signs findings included hypotension in 1 (2.0%) subject in the TEZ/IVA group; blood pressure decreased, pericardial effusion, and tachycardia in 1 (2.1%) subject each in the placebo group. One event, pericardial effusion, was considered an SAE. Among these events, none led to treatment interruption or discontinuation. One AE, blood pressure decreased in the placebo group, was considered by the investigator to be possibly related to study drug.

Rapporteurs' comments

There were no important findings in chemistry, haematology coagulation, urinalysis and vital signs.

Pulse Oximetry

Mean pulse oximetry results and changes from baseline were similar across treatment groups and showed no clinically meaningful trends over time.

No clinically meaningful trends attributable to treatment with TEZ/IVA were observed in the shift analysis of pulse oximetry results. Of the 57 subjects who had a normal (oxygen saturation >95%) or missing baseline oxygenation value, 21 subjects had a shift to low (oxygen saturation ≤ 95%) during the TE Period: 9/50 (18.0%) subjects in the TEZ/IVA group and 12/47 (25.5%) subjects in the placebo group.

There were no AEs related to pulse oximetry findings.

Post-dose Spirometry

The mean absolute changes in ppFEV1 from pre-dose to post-dose on Day 1 were -0.6 percentage points in the TEZ/IVA group at 2 hours post-dose and 0.3 percentage points in the placebo group; -0.8 percentage points in the TEZ/IVA group at 4 hours post-dose and 0 percentage points in the placebo group. Threshold analysis of ppFEV1 from pre-dose to post-dose revealed that no subjects in either treatment group had a post-dose decline ≥ 10 percentage points 2 hours post-dose. One subject in the TEZ/IVA group had a post-dose decline of ≥10 percentage points 4 hours post-dose.

One subject, a, had a ppFEV1 decline of 21.3 percentage points at 4 hours post-dose on Day 1. Other spirometric parameters showed a drop in FVC, an increased FEV1/FVC ratio, and a flow-volume loop consistent with a poor inspiratory effort. On the same day, the subject had a mild AE of respiratory chest tightness (PT: respiration abnormal), which had resolved by Day 6 without having required treatment. No other complaints or AEs were reported. The subject completed the study with a positive response (ppFEV1, CFQ-R) to study drug (TEZ/IVA).

Table 19 Mean Change From Pre-dose to Post-dose ppFEV1 on Day 1, Safety Set

Statistic	Placebo N = 47	TEZ/IVA N = 50	Total N = 97
Day 1 (Predose)			
n	47	48	95
Mean (SD)	48.0 (18.1)	45.1 (16.2)	46.5 (17.2)
Median	43.0	39.1	41.3
Min, Max	26.0, 86.0	22.6, 82.3	22.6, 86.0
Absolute change from predose to 2 hours postdose			
n	43	45	88
Mean (SD)	0.3 (1.9)	-0.6 (2.1)	-0.2 (2.1)
Median	0.2	-0.4	0.0
Min, Max	-4.3, 7.0	-4.9, 3.9	-4.9, 7.0
Absolute decline from Day 1 (predose) at Day 1 (2 hours postdose)			
n	43	45	88
≥10 percentage points	0	0	0
≥15 percentage points	0	0	0
≥20 percentage points	0	0	0
Absolute change from predose to 4 hours postdose			
n	43	45	88
Mean (SD)	0.0 (1.9)	-0.8 (4.3)	-0.4 (3.3)
Median	0.0	-0.5	-0.1
Min, Max	-6.8, 4.4	-21.3, 7.0	-21.3, 7.0
Absolute decline from Day 1 (predose) at Day 1 (4 hours postdose)			
n	43	45	88
≥10 percentage points	0	1 (2.2)[a]	1(1.1)
≥15 percentage points	0	1 (2.2)[a]	1 (1.1)
≥20 percentage points	0	1 (2.2)[a]	1 (1.1)

Sources: Table 14.3.5.5 and Table 14.3.5.6

IVA: ivacaftor; n: size of subsample; N: total sample size; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

Notes: For predose, n is the number of subjects who had non-missing assessment at the predose on Day 1. For postdose, n is the number of subjects who had non-missing assessment at the predose on Day 1 and at least 1 corresponding non-missing postdose assessment at the postdose time point.

[a] Subject with a postdose decline ≥20 percentage points is listed in all applicable categories.

Rapporteurs' comments

The mean absolute changes in ppFEV1 from pre-dose to post-dose on Day 1 were -0.6 percentage points in the TEZ/IVA group at 2 hours post-dose and 0.3 percentage points in the placebo group and at 4 hours post-dose -0.8 percentage points in the TEZ/IVA group at 4 hours post-dose and 0 percentage points in the placebo group. These differences are not clinically relevant.

There was 1 patient with a post-dose decrease of ppFEV1 of >20%. It is agreed with the Company that this is probably because of a poor effort. On top of this patient, 3 patients had a decrease between 5-10% in ppFEV1 in TEZ/IVA group and 1 patient in placebo group.

In conclusion, post dose decrease in ppFEV1 was minimal.

2.3.3. Discussion on clinical aspects

This study was a Phase 3b, randomized, double-blind, placebo-controlled, parallel-group, multicenter study in CF subjects 12 years of age and older who are homozygous for the F508del-CFTR mutation who discontinued treatment with Orkambi due to respiratory symptoms considered related to treatment. The study was designed to further evaluate the safety and tolerability of TEZ/IVA. Efficacy was evaluated as a secondary objective. The treatment period was 56 days.

Study population

Of the 97 subjects who received at least 1 dose of study drug (Full Analysis Set [FAS]), 93 (95.9%) completed dosing. All efficacy analyses were based on the FAS: 50 subjects received TEZ/IVA and 47 subjects received placebo). Only one adolescent was included, who was randomised to placebo. The number of subjects who prematurely discontinued study drug treatment due to any reason was low in both treatment groups (TEZ/IVA: 2 [4.0%] subjects; placebo: 2 [4.3%] subjects).

Overall the population was balanced for most demographics and characteristics, prior and concomitant medication. There was a small imbalance for ppFEV1 resulting that patients in the TEZ/IVA group had overall more severe CF. Furthermore, more patients in the placebo group had asthma (31.9% and 16% for placebo and TEZ/IVA, respectively). As asthma is one of the RAESI, this imbalance can be a confounder. Moreover, asthma symptoms overlap with CF symptoms; this imbalance can also be a confounder for these overlap symptoms.

The sample size calculation was based, on the Bayesian 'success' criterion approach, targeting an efficacy parameter.

Efficacy

The primary analysis of the key secondary efficacy variable, the actual Bayesian posterior probability calculated for a >0 treatment effect difference in absolute change from baseline in ppFEV1 to the average of the Day 28 and Day 56 measurements, was met. The probability for a >0 treatment effect difference in mean ppFEV1 change between TEZ/IVA and placebo was 0.9991 (posterior mean difference: 2.7; 95% Credible Interval: (1.0, 4.4) in line with the frequentist analysis).
The mean treatment difference between the TEZ/IVA and placebo groups from baseline to the average of the Day 28 and Day 56 measurements was 2.7 percentage points (95% CI: 1.0, 4.4), which was lower than in the marketing application (MA) study VX16-661-106 (difference of 4.0 (3.1, 4.8).
Summary statistics of the within-group difference in mean absolute change in ppFEV1 is 2.2% for the TEZ/IVA group, being lower compared to the MA study while the difference in placebo was comparable to the decrease in ppFEV1 (-0.6%) at 24 weeks in the placebo group. In this study VX16-661-114,

patients with lower ppFEV1 (FEV1>25%) were allowed to participate compared to the MA study (FEV1>40%).However, some patients were included in study 106 with a ppFEV<40%. In study 106, the treatment effects are comparable among the subgroups of baseline ppFEV1 ≥70% (3.7 [95% CI, 2.2, 5.2]), ≥40% to <70% (4.2 [95% CI, 3.1, 5.2]), and <40% (3.5 [95% CI, 1.0, 6.1]). Overall, we consider that the effects seen in study 114 might be numerically lower, but these differences cannot be considered statistically significant or clinically relevant.

The mean treatment difference between the TEZ/IVA and placebo groups in absolute change from baseline in CFQ-R respiratory domain score to the average of Day 28 and Day 56 was 1.1 points (95% CI: -4.9, 7.0).

As only one adolescent was included, who was randomised to placebo, results on the paediatric population are not available.

Safety

Ninety-seven subjects received at least 1 dose of study drug during the TE Period. The mean exposure was 7.7 weeks in the TEZ/IVA group and 7.9 weeks in the placebo group. A total of 40 patients had an exposure duration of > 8 weeks. According to the design the treatment Period (Day 1 through Day 56) is 8 weeks. ~~P~~atients that had an exposure duration > 8 weeks, did pass this 8 week treatment duration due to a plus or minus 5-day window for the Day 56 Visit~~.~~

The primary safety endpoint was incidence of RAESI. RAESI were: asthma, bronchial hyperreactivity, bronchospasm, wheezing, chest discomfort, dyspnoea, respiration abnormal.
Seventeen (17.5%) subjects had at least 1 RAESI: 7 (14.0%) subjects in the TEZ/IVA group and 10 (21.3%) subjects in the placebo group. All RAESIs were mild or moderate in severity and there were no severe or life-threatening RAESIs. No RAESIs were serious or led to treatment discontinuation in either treatment group. The most common RAESI by PT (incidence ≥10% subjects in any treatment group) was dyspnoea, with similar incidence between the 2 treatment groups. However, more patients in the placebo group were diagnosed with asthma. Asthma symptoms overlap with CF symptoms. Therefore, the most equal distribution of the events could have been confounded by this imbalance in asthma. However, for most of the RAES none of the patients in the TEZ/IVA had an event. Only respiration abnormal was experience more frequently in the TEZ/IVA group (3 patients). The most common RAESI dyspnoea was balanced (TEZ/IVA: 5 [10.0%] subjects; placebo: 5 [10.6%] subjects). However, no conclusion can be drawn because dyspnoea is symptom in CF as well as in asthma. Moreover, the number of patients is low.

Most RAESIs were considered unlikely related or not related to study drug. Five subjects (5.2%) had RAESIs which were considered possibly related (1 in TEZ/IVA; 4 in placebo). No RAESIs were considered related to study drug. However, the sample size calculation was based on the efficacy and endpoint and not to detect differences in the RAESIs. Therefore it is questionable whether differences could be detected. Overall, more patients in the placebo group experienced a RAESI. More patients in the placebo group were diagnosed with asthma. Asthma symptoms overlap with CF symptoms; this imbalance can also be a confounder for these overlap symptoms. The most equal distribution of the events could have been confounded by this imbalance in asthma. However, for most of the RAES none of the patients in the TEZ/IVA had an event. Only respiration abnormal was experience more frequently in the TEZ/IVA group. The most common RAESI dyspnoea was balanced (TEZ/IVA: 5 [10.0%] subjects; placebo: 5 [10.6%] subjects). However, dyspnoea is symptom in CF as well as in asthma.

Most RAESIs were considered unlikely related or not related to study drug with no significant differences between the two groups.

Seventy-six (78.4%) subjects had at least 1 AE, with 37 (74.0%) subjects in the TEZ/IVA group and 39 (83.0%) subjects in the placebo group. The majority of subjects had AEs that were considered either mild (37.1%) or moderate (35.1%) in severity. One subject in the TEZ/IVA group had life-threatening AEs concerning sepsis that led to death. The events with a fatal outcome were considered by the investigator to not be related to TEZ/IVA. The majority of subjects had AEs that were considered not related or unlikely related to study drugs. Twenty-six (26.8%) subjects had AEs that were considered possibly related or related to study drugs, including 10 (20.0%) subjects in the TEZ/IVA group, and 16 (34.0%) in the placebo group.

Consistent with expected CF clinical manifestations, the most common AEs by PT (incidence ≥10% of subjects overall) were infective PEx of CF (20.6%), cough (17.5%), headache (13.4%), dyspnoea (10.3%).

Fourteen (14.4%) subjects had at least 1 SAE. The number of subjects with at least 1 SAE was 5 (10.0%) subjects in the TEZ/IVA group and 9 (19.1%) subjects in the placebo group. No SAEs were considered related to study drug in the TEZ/IVA group, and only 1 SAE was considered possibly related in the placebo group (2.1%).

No clinically meaningful trend was identified for LFT results.

The mean absolute changes in ppFEV1 from pre-dose to post-dose on Day 1 were -0.6 percentage points in the TEZ/IVA group and 0.3 percentage points in the placebo group at 2 hours post-dose and -0.8 percentage points in the TEZ/IVA group and 0 percentage points in the placebo group at 4 hours post-dose. No subject in either treatment group had a post-dose decline ≥10 percentage points 2 hours post-dose. One subject in the TEZ/IVA group had a post-dose decline ≥20 percentage points 4 hours post-dose most likely related to a poor effort.

Overall, TEZ/IVA was generally safe and well tolerated for up to 56 days of treatment in patients who discontinued Orkambi due to treatment-related respiratory symptoms. No new safety concerns were identified. In conclusion, based on the limited number of patients, the observed RAESIs do not lead to a specific pattern or a safety signal. No conclusion can be drawn because the number of patients is low, and the groups are not equally balanced for an important concomitant disease asthma.

3. Rapporteur's overall conclusion and recommendation

The primary safety endpoint was the incidence of RAESIs while subjects were on treatment. In this small study tezacaftor/ivacaftor did not result numerically in an increased rate of RAESIs compared to placebo in subjects who discontinued Orkambi due to treatment-related respiratory symptoms. Overall, a slightly higher number of patients in the placebo group experienced a RAESI. Most events started within the first 4 weeks. For most of the RAES none of the patients in the TEZ/IVA had an event. Only respiration abnormal was experience more frequently in the TEZ/IVA group. However, more patients in the placebo group were diagnosed with asthma. As asthma symptoms overlap with CF symptoms, the more or less similar distribution in events could have been confounded by this imbalance in asthma. Dyspnoea is symptom in CF as well as in asthma. Descriptively, the most common RAESI dyspnoea was balanced (TEZ/IVA: 5 [10.0%] subjects; placebo: 5 [10.6%] subjects). The AEs were mostly expected manifestations of CF disease; no new safety concerns were identified. The incidence of treatment discontinuation due to AEs was low and similar in both treatment group.

In conclusion, on face value the observed RAESIs do not lead to a specific pattern or signal in the group treated with TEZ/IVA, although no confirmatory conclusion could be drawn. The interpretation of the safety data is based on the limited number of patients, imbalances in asthma were observed in

favour of the TEZ/IVA group and any statistical pre-assumption/substantiation of the safety objective is lacking.

For the key secondary efficacy endpoint of absolute change from baseline in ppFEV1 to the average of Day 28 and Day 56, the mean treatment difference for TEZ/IVA compared to placebo was 2.7 percentage points (95% CI: 1.0, 4.4~~).~~

For the secondary efficacy endpoint of absolute change from baseline in CFQ-R respiratory domain score to the average of Day 28 and Day 56, the mean treatment difference for TEZ/IVA compared to placebo was 1.1 points (95% CI: -4.9, 7.0).

As only one adolescent was included, and who was randomised to placebo, results on the paediatric population are not available.

☒ **Fulfilled:**

No regulatory action required.

4. Additional clarification requested

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

1. The sample size calculation was based, following a Bayesian 'success' criterion approach, on an efficacy parameter. It is therefore questioned whether the sample size was large enough to detect any clinically relevant differences in the RAESIs, the predefined primary objective of this study. The MAH is requested to discuss.
2. Summary statistics are provided for the absolute change in ppFEV1 from baseline to the average of the Day 28 and Day 56 values. The MAH is requested to provide the absolute change from baseline to Day 56 for comparative purposes. In addition, a MMRM analysis of the absolute change from baseline though Day 56 in pppFEV1 vs. the placebo group and the corresponding treatment difference together with a discussion of the results is requested.
3. The mean treatment difference between the TEZ/IVA and placebo groups from baseline to the average of the Day 28 and Day 56 measurements was 2.7 percentage points (95% CI: 1.0, 4.4), which was lower than in the marketing application (MA) study VX16-661-106 (difference of 4.0 (3.1, 4.8) and also lower than in subjects enrolled in study 106 with ppFEV1 below 40 pp. In the current study VX16-661-114, patients FEV1 < 40% were allowed to participate. In total, 48 (49.5%) of the patients had ppFEV1 < 40%. The MAH is requested to provide a subanalysis comparing patients with FEV1 ≥ 40% and patients with FEV1 < 40%. In addition, a discussion is requested for the comparison of the results with the results of study 106.
4. Ninety-seven subjects received at least 1 dose of study drug during the TE Period. A total of 40 patients had an exposure duration of > 8 weeks. According to the design the treatment Period (Day 1 through Day 56) is 8 weeks. It is not understood how/why these patients had an exposure duration > 8 weeks. The Company is requested for an explanation.

MAH responses to Request for supplementary information

Question 1:
The sample size calculation was based, following a Bayesian 'success' criterion approach, on an efficacy parameter. It is therefore questioned whether the sample size was large enough to detect any clinically relevant differences in the RAESIs, the predefined primary objective of this study. The MAH is requested to discuss.

Response MAH:

The primary objective of Study 114 was to evaluate the respiratory safety of tezacaftor/ivacaftor (TEZ/IVA) in subjects with cystic fibrosis (CF) homozygous for F508del and who discontinued treatment with Orkambi due to respiratory symptoms considered related to Orkambi. Study 114 was not designed to detect a statistically significant difference in the incidence of respiratory adverse events of special interest (RAESI) between the TEZ/IVA and placebo groups. However, the sample size was considered large enough to identify any association in RAESIs and treatment (TEZ/IVA or placebo). In addition, as typical for interpretation of safety data, the assessment and conclusions are based on the totality of the data.

In Study 114, the incidence of RAESIs in the TEZ/IVA group (14.0%) was comparable to that in the placebo group (21.3%). In addition, the incidence of RAESIs in the TEZ/IVA group from Study 114 (14.0%) was comparable to that observed in the TEZ/IVA group from Study 106, a larger pivotal Phase 3 study: 13.1% in the TEZ/IVA group (n = 251) compared to 15.9% in the placebo group (n = 258). These data demonstrate that TEZ/IVA is not associated with an increased risk of RAESIs. Moreover, in contrast to respiratory events associated with Orkambi, there were no RAESIs in Study 114 that were serious adverse events (SAEs) or that led to interruption or discontinuation of TEZ/IVA.

Assessment

It is acknowledged that the safety and identification of any association in RAESIs and treatment is typically assessed on the totality of data. However, the MAH did NOT provide arguments for their statement that "the sample size was considered large enough to identify any association in RAESIs and treatment (TEZ/IVA or placebo)". It can be said that with 47-50 patients events with a prevalence of 3% of more can be detected (i.e. if the true prevalence of an RAESI is >3% then there is 78% chance that one would see it in at least 1 patient. However, even taking this into account, it can still be questioned whether the sample size of study 114 is large enough to detect a clinically relevant difference in this trial, Although the incidence of RAESIs is indeed considered numerically comparable to the larger 106 study. , the current study 114 is not specifically powered with clinically acceptable pre-specified safety margins. Therefore, we consider that no robust conclusion can be drawn from study 114 on this matter **Issue unresolved, but not further pursued.**

Question 2
Summary statistics are provided for the absolute change in ppFEV1 from baseline to the average of the Day 28 and Day 56 values. The MAH is requested to provide the absolute change from baseline to Day 56 for comparative purposes. In addition, a MMRM analysis of the absolute change from baseline though Day 56 in pppFEV1 vs. the placebo group and the corresponding treatment difference together with a discussion of the results is requested.

Response MAH:

As requested, the absolute change in percent predicted forced expiratory volume in 1 second (ppFEV1) from baseline to Day 56 in Study 114 is provided in Table 1. The results are consistent with the pre-

specified analysis of the absolute change in ppFEV1 from baseline to the average of Day 28 and Day 56 (Table 1).

In Study 114, the pre-specified analysis for ppFEV1 in the statistical analysis plan (SAP) was descriptive summary statistics along with 95% CI. Because of the low dropout rate (2 subjects in the TEZ/IVA group and 2 subjects in the placebo group) in this study, the results from an MMRM analysis, i.e., the estimated treatment difference and its 95% CI, will be similar to the results shown in Table 1. Therefore, a mixed-effects model for repeated measures (MMRM) analysis of the absolute change from baseline through Day 56 in ppFEV1 was not performed.

Table 1 Summary Statistics for $ppFEV_1$ Change From Baseline

Visit	Statistic	TEZ/IVA N = 50	Placebo N = 47
Absolute Change at Day 56	n	48	44
	Mean (SD)	2.4 (4.4)	-1.1 (3.5)
	Mean Difference, 95% CI	3.5 (1.8, 5.1)	-
Key Secondary Endpoint: **Absolute Change at Average of Day 28 and Day 56**	n	50	46
	Mean (SD)	2.2 (4.8)	-0.6 (3.4)
	Mean Difference, 95% CI	2.7 (1.0, 4.4)	-

IVA: ivacaftor; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor
Note: Mean difference (TEZ/IVA versus placebo) is in raw means. The CI is based on the pooled sample variance.

Assessment

Regarding the change from baseline to Day 56 in ppFEV1, the mean difference of 3.5 pp (95 CI: 1.8, 5.1) is more similar to that found in study 106 (4.0; 95% CI: 3.1; 4.8). The difference from baseline to Day 56 is based on 48 and 44 subjects in the TEZ/IVA and placebo groups respectively. What the Applicant does not provide in their answer is the study ID of subjects for whom ppFEV1 values were not available and at which visits data were lacking. A simple comparison of the number of subjects available for each of the analyses above shows that at day 56, ppFEV1 was not available for 2 subjects in the TEZ/IVA group while apparently values for these subjects were available at day 28. Similarly, for the placebo group at day 56 data were not available for 2 subjects while apparently these data were available at day 28. A subject in the placebo group is not counted in any of the analyses as the subject prematurely discontinued the study. Even though it is difficult to follow what has been done and how calculations have been performed (as it appears that for the calculation of the average at day 28 and day 56, values obtained at unscheduled visits may have been used), no further issues are raised in this respect.

The MMRM analysis has not been performed and this is justified because the dropout rate is low (2 subjects in each group). While this may be acceptable what would have been useful (as previously said) is that the Applicant had identified the subjects for whom data are not available and the exact visits when data on ppFEV1 are missing. Furthermore, even in the context of no missing data, the MMRM analysis would use not only the baseline and day 56 data, but also the measurements at day 15 and 28. In particular the correlation between the repeated measurements would increase precision and therefore lead to a more precise estimate (smaller 95%-CI) of the difference. Therefore, the MAH's argument of low drop-out seems irrelevant. What can be argued, however, is that the difference between both arms has already a 95%-CI above 0. Thus, the MMRM analysis will only make the 95%-

CI smaller and despite it may change the point estimate (center of the 95%-CI) and thus the location somewhat, it is likely that the 95%-CI will still be above 0. Therefore, it is considered that the MMRM will not mean fully give more information and can therefore be omitted.

No further questions are raised on any of the issues above as the regulatory impact is expected to be low with no changes requested for the SmPC based on study 114 which is primarily a safety study although (Bayesian) sample size estimation uses an efficacy variable (please refer to Question 1).

Question 3

The mean treatment difference between the TEZ/IVA and placebo groups from baseline to the average of the Day 28 and Day 56 measurements was 2.7 percentage points (95% CI: 1.0, 4.4), which was lower than in the marketing application (MA) study VX16-661-106 (difference of 4.0 (3.1, 4.8) and also lower than in subjects enrolled in study 106 with ppFEV1 below 40 pp. In the current study VX16-661-114, patients FEV1 < 40% were allowed to participate. In total, 48 (49.5%) of the patients had ppFEV1 < 40%. The MAH is requested to provide a subanalysis comparing patients with FEV1 ≥ 40% and patients with FEV1 < 40%. In addition, a discussion is requested for the comparison of the results with the results of study 106.

Response MAH:

Vertex acknowledges that the observed treatment effect of 2.7 in Study 114 is numerically lower than that observed in the pivotal Phase 3 Study 106, which is 4.0. Despite this lower value, the treatment effect seen in Study 114 was statistically significant. The 95% CI of the treatment effect in Study 114 (1.1 to 4.4) substantially overlapped with that seen in Study 106 (3.1 to 4.8), indicating that there is no statistical reason to believe that the overall treatment effect between Studies 114 and 106 would be different. Similarly, as the 95% CI of the treatment effect in Study 114 (1.1 to 4.4) also overlapped substantially with that of the Study 106 subgroup of baseline ppFEV1 below 40% (1.0, 6.1), the 2 treatment effects from respective studies are not statistically different. More important, in Study 106, the treatment effects are comparable among the subgroups of baseline ppFEV1 ≥70% (3.7 [95% CI, 2.2, 5.2]), ≥40% to <70% (4.2 [95% CI, 3.1, 5.2]), and <40% (3.5 [95% CI, 1.0, 6.1]). Therefore, these results from Studies 106 and 114 collectively support the conclusion that all subjects will benefit from TEZ/IVA treatment regardless of the baseline ppFEV1.

Assessment

This question was asked to see whether the more severely affected population (with ppFEV1 <40%) perceived less benefit of TEZ/IVA, and could be the reason for the numerically lower effect as seen in study 114. The MAH did not provide the requested data on the patients with FEV1 ≥40% and patients with FEV1 <40%, but did provide a discussion on the comparison of the data with pivotal study 106.

Overall, taking also the analysis provided in question 2 into account, we consider that the effects seen in study 114 might be numerically lower, but that these differences cannot be considered statistically significant or clinically relevant.

Issue resolved

Question 4

Ninety-seven subjects received at least 1 dose of study drug during the TE Period. A total of 40 patients had an exposure duration of > 8 weeks. According to the design the treatment

Period (Day 1 through Day 56) is 8 weeks. It is not understood how/why these patients had an exposure duration > 8 weeks. The Company is requested for an explanation.

Response MAH:

In Study 114, the exposure duration is defined as the date of last dose of study drug minus the date of the first dose plus 1 day. There was a plus or minus 5-day window for the Day 56 Visit. Therefore, exposure exceeded 8 weeks (56 days) for subjects who completed the actual Day 56 Visit between 1 and 5 days after 56 days in the Treatment Period (Day 57 to Day 61).

Assessment

The MAH sufficiently explained the exposure duration of > 8 weeks in some of the patients.

Issue resolved