26 July 2018
EMA/CHMP/567306/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Symkevi

International non-proprietary name: tezacaftor / ivacaftor

Procedure No. EMEA/H/C/004682/0000

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
ANCOVA	analysis of covariance
ATC	anatomic class
ATS	American Thoracic Society
BMI	body mass index
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	CF transmembrane conductance regulator protein
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human use
CI	confidence interval
Cl	chloride ion
CM	Continuous Manufacturing corresponding to position 508 of the wild-type gene
CPK	creatine phosphokinase
CPP	Critical process parameter
CPV	Continuous Process Verification
CQA	Critical Quality Attribute
CTFR	cystic fibrosis transmembrane conductance regulator gene
CTFR	CF transmembrane conductance regulator protein
C_{trough}	concentration at the end of the dosage interval
CYP	cytochrome P450
CYP3A	cytochrome P450 3A
DMR	Desired Manufacturing Range
DNA	deoxyribonucleic acid
DoE	Design of experiments
EC	European Commission
ECG	electrocardiogram
eCRF	electronic case report form
EG	Extragranular
ERS	European Respiratory Society
EU	European Union
F/F	F508del/F508del mutation
F/G551D	F508del/G551D mutation
F/MF	F508del/minimal function mutation
F/NR	F508del and another allele not likely to responsive to tezacaftor/ivacaftor
F/RF	F508del/residual function mutation
F*508del*	CFTR gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type gene
F508del-CFTR	CFTR gene mutation with an in-frame deletion of a phenylalanine

	codon corresponding to position 508 of the wild-type protein
F508del-CFTR	CFTR protein with a deletion of phenylalanine corresponding to position 508 of the wild-type protein forced expiratory volume in 1 second
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
FE-1	fecal elastase-1
FEF25-75%	forced midexpiratory flow rate
FEV_1	forced expiratory volume in 1 second
FRT	Fischer rat thyroid
FT-IR	Fourrier Transform Infrared Spectroscopy
FVC	forced vital capacity
GC	Gas Chromatography
GC-MS	Gas chromatography mass spectrometry
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GPS	Global Patient Safety
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IG	Intragranular
IPC	In-process control
IPD	important protocol deviations
IR	Infrared
IRT	immunoreactive trypsinogen
IV	intravenous
IVA	ivacaftor
KF	Karl Fischer titration
LC-MS/MS	liquid chromatography–mass spectrometry/mass spectrometry
LDPE	Low Density Polyethylene
LFT	liver function test
LIW	Loss In Weight
LS	least squares
LUM	lumacaftor
LUM/IVA	lumacaftor/ivacaftor
LUM/IVA	lumacaftoe/ivacaftor
M1-IVA	M1-ivacaftor
M1-TEZ	M1-tezacaftor
Max	maximum value
MCID	minimum clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MF	minimal function
Min	minimum value
MMRM	mixed-effects model for repeated measures

n	size of subsample
N	total sample size
NA	not applicable
NIR	Near Infrared Spectroscopy
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NOR	Normal Operating Range
OLE	open-label extension
P	probability
PAMPC	Post-Approval Change Management Protocol
PAR	Proven Acceptable Range
PAT	Process Analytical Technology
PBO	placebo
PCTFE	Polychlorotrifluoroethylene
PD	pharmacodynamics
PDE	Permitted Daily Exposure
PE/PEx	pulmonary exacerbation
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetics
PN	preferred name
pp	percent predicted
ppFEV1	percent predicted forced expiratory volume in 1 second
PT	Preferred Term
PVC	Polyvinyl chloride
q12h	every 12 hours
QbD	Quality by design
qd	daily
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's formula
QTPP	Quality target product profile
RF	residual function
RH	Relative Humidity
RMP	Rik Management Plan
RTRT	Real Time Release Testing
SAE	serious adverse event
SD	standard deviation
SDD	Spray Dried Dispersion
SE	standard error
SmPC	Summary of Product Characteristics
SOC	standard of care
SOP	standard operating procedures

TAMC	Total Aerobic Microbial Count
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TEZ	tezacaftor
TEZ/IVA	tezacaftor 100 mg qd/ivacaftor 150 mg q12h
TRU	Tablet Relaxation Unit
TYMC	Total Combined Yeasts/Moulds Count
ULN	upper limit of normal
US	United States
UV	Ultraviolet
VX-661	tezacaftor
VX-770	ivacaftor

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Vertex Pharmaceuticals (Europe) Ltd. submitted on 25 July 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Symkevi, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 13 October 2016.

Symkevi, was designated as an orphan medicinal product EU/3/17/1828 on 27 February 2017 in the following condition: treatment of Cystic Fibrosis (CF).

The applicant applied for the following indication:

Symkevi is indicated in a combination regimen with Kalydeco (ivacaftor 150 mg tablet) for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the *F508del* mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that is responsive to tezacaftor/ivacaftor based on *in vitro* and/or clinical evidence (see section 5.1).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0193/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0193/2017 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Symkevi as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: ema.europa.eu/Find medicine/Human medicines/European public assessment reports.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No

847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Applicant's request for consideration

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14(9) of Regulation (EC) No 726/2004. On 18 May 2017, the CHMP did not recommend to grant the accelerated assessment procedure.

New active Substance status

The applicant requested the active substance tezacaftor contained in the above fixed dose combination medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union. Ivacaftor was considered to be a known active substance.

Protocol assistance

The applicant received Protocol assistance from the CHMP:

Scientific advice	date	Area
EMEA/H/SA/2814/1/2014/III	23 October 2014	the scientific advice pertained to non-clinical and clinical aspects
EMEA/H/SA/2814/1/FU/1/2014/PA/II	22 January 2015	the scientific advice pertained to clinical aspects
EMEA/H/SA/2814/2/2016/I	15 December 2016	the scientific advice pertained to quality aspects

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Nithyanandan Nagercoil

The application was received by the EMA on	25 July 2017
The procedure started on	17 August 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	3 November 2017
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	8 November 2017

The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	17 November 2017
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 December 2017
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 January 2018
The following GMP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product: – A GMP inspection at one site responsible for manufacture of the finished product in the USA between 16 and 20 October 2017. The outcome of the inspection carried out was issued on	2 February 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	28 February 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	8 March 2018
The CHMP agreed on a first list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	22 March 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	27 April 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	17 May 2018
The CHMP agreed on a second list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	31 May 2018
The applicant submitted the responses to the CHMP second List of Outstanding Issues on	5 June 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the second List of Outstanding Issues to all CHMP members on	15 June 2018
The CHMP agreed on a third list of outstanding issues in writing to be sent to the applicant on	28 June 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	3 July 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the third List of Outstanding Issues to all CHMP members on	11 July 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Symkevi on	26 July 2018
The CHMP adopted a report on similarity of Symkevi with Bronchitol, Cayston, Tobi Podhaler and Kalydeco (Appendix 1) on	26 July 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Cystic Fibrosis (CF) is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality, and at present, there is no cure. Cystic fibrosis is caused by mutations in the CFTR gene that result in absent or deficient function of the CFTR protein at the cell surface. The CFTR protein is an epithelial chloride channel responsible for aiding in the regulation of salt and water absorption and secretion. The failure to regulate chloride transport in these organs results in the multisystem pathology associated with CF. In patients with CF, loss of chloride transport due to defects in the CFTR protein result in the accumulation of thick, sticky mucus in the bronchi of the lungs, loss of exocrine pancreatic function, impaired intestinal absorption, reproductive dysfunction, and elevated sweat chloride concentration. Lung disease is the primary cause of morbidity and mortality in people with CF.

2.1.2. Epidemiology

CF affects approximately 30,000 individuals in the United States (US) and 32,000 in the EU. The incidence and prevalence of CF varies between racial groups; CF is considerably more common in the Caucasian populations of North America and Europe than in Asian and African populations.

2.1.3. Aetiology and pathogenesis

The CFTR protein is an epithelial chloride ion (CL^-) channel located in the epithelia of multiple organs, including lungs, pancreas, intestinal tract, liver, and vas deferens, that is responsible for aiding in the regulation of salt and water absorption and secretion. More than 1900 mutations in the CFTR gene have been identified. These can be classified according to the mechanisms by which they disrupt CFTR function. Stop codon mutations (class I) result in a truncated non-functional CFTR, class II mutations consist of aberrantly folded CFTR protein that is degraded by the cell quality control system, while class III mutations lead to defective regulation of the CFTR protein and, consequently, the absence of CFTR function. These three classes usually lead to a classic CF phenotype with pancreatic insufficiency. CFTR mutations that lead to defective chloride conductance are grouped together in class IV. Class V mutations interfere with normal transcription, thereby reducing the amount of otherwise normal CFTR. These latter two classes are mostly associated with a milder expression of the disease.

The most prevalent mutation is an in-frame deletion in the CFTR gene resulting in a loss of phenylalanine at position 508 in the CFTR protein (F508del-CFTR) and it is a Class II mutation: it prevents most of the CFTR protein from reaching the cell surface, resulting in little-to-no chloride transport. The decrease in the amount of F508del-CFTR at the cell surface is due to a defect in the processing and trafficking of the F508del-CFTR protein. The very small amount of F508del-CFTR protein that reaches the cell surface also has defective channel gating and a decreased stability at the cell surface. Patients who are homozygous with F508del-CFTR defects have little or no CFTR protein at the cell surface and hence suffer from a severe form of CF disease.

CF-causing mutations can be divided into 2 groups based on the extent of loss of chloride transport caused by the mutation. A complete or near complete loss of CFTR chloride transport is referred to as "minimal function" of CFTR. A less complete loss of CFTR-mediated chloride transport is referred to as "residual function" of CFTR.

2.1.4. Clinical presentation, diagnosis

The median predicted survival for CF patients in the United States was 39.3 years (95% CI, 37.3-41.4) according to the Cystic Fibrosis Foundation 2014 Registry Report. The classic or typical form of cystic fibrosis (CF) is diagnosed if a patient demonstrates clinical disease in one or more organ systems and has elevated sweat chloride (≥60 mmol/L). Most of these patients have disease manifestations in multiple organ systems (pancreas, upper and lower respiratory tract, and male reproductive tract). However, patients may demonstrate mild or atypical symptoms. About 2 percent of patients fulfil diagnostic criteria for CF but have a normal or intermediate sweat chloride result, indicating that there is a wide spectrum of severity in CF.

2.1.5. Management

CF medications range from CFTR modulators and enzyme supplements, to mucolytics, antibiotics, and vitamins. Current treatment guidelines recommend CFTR modulator and non-modulator medications concomitantly administered to maintain and improve lung function, reduce the risk of infections and exacerbations, and improve quality of life. As stated before, cystic fibrosis is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that affect the production of the CFTR protein. Drugs that target the underlying defect in the cystic fibrosis transmembrane conductance regulator (CFTR) protein are called CFTR modulators. CFTR modulators are small molecules that target specific defects caused by mutations in the CFTR gene and thus treat the underlying cause of the disease. CFTR modulators are not intended as a replacement for or an alternative to any of the current non-modulator therapies, but rather provide added benefit. The goal of therapy is to maintain and restore respiratory function.

There are two main types of modulators, potentiators and correctors. Potentiators recover the function of the CFTR protein at the apical surface of epithelial cells that is disrupted in class III and IV genetic mutations, while correctors improve intracellular processing of the CFTR protein, increasing surface expression, in class II mutations. A third type is production correctors or read-through agents, which promote transcription of CFTR in class I mutations. Potentiators help chloride flow through the CFTR protein channel at the cell surface. The CFTR protein is shaped like a tunnel that can be closed by a gate. Potentiators hold the gate open so chloride can flow through. By holding the gate on the CFTR protein open, potentiators allow more chloride to flow through and reduce the symptoms of CF. However, there is an inter-dependence between channel gating and cellular processing given that each depend on CFTR protein folding, thus a sharp distinction between potentiators and correctors is somewhat artificial.

Kalydeco (ivacaftor, IVA) and Orkambi (lumacaftor/ivacaftor, LUM/IVA) are the only CFTR modulators approved for CF patients with specific mutations. Ivacaftor (in Kalydeco as mono-component and in Orkambi as part of a fixed dose combination) is a potentiator, the active substance lumacaftor is a corrector (present in the fixed dose combination Orkambi). Clinical efficacy of ivacaftor monotherapy has been established in Class III mutations that cause defects in channel gating as well as in the Class III/IV mutation R117H. Clinical efficacy of the combination of lumacaftor and ivacaftor has been established in patients homozygous for the F508del mutation in the CFTR gene. However, some

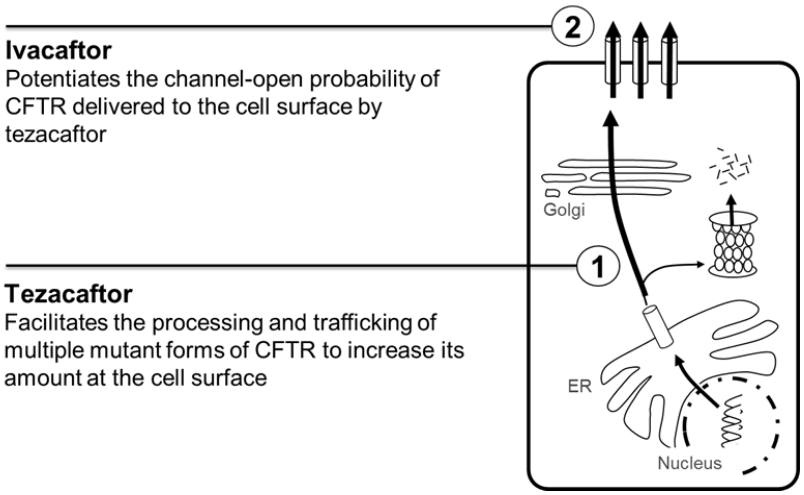
patients are not able to tolerate treatment with LUM/IVA due to respiratory events related to off-target effects of the lumacaftor component. In addition, lumacaftor is a strong CYP3A inducer and some patients may not take it because of the DDI. Currently, no corrector-potentiator therapy is available in patients who have the F508del mutation and a residual function mutation in the CFTR gene. The combination TEZ/IVA could be of interest for CF patients who have the F508del mutation and a mutation in CFTR gene that is responsive to TEZ/IVA and also may be an alternative for CF patients who are homozygous for F508del and cannot tolerate LUM/IVA.

About the product

Symkevi belongs to the pharmacotherapeutic group of '**Other respiratory system products'**; ATC code: R07AX31.

Symkevi is a fixed dose combination containing two substances, tezacaftor and ivacaftor, that work by improving activity of CFTR in the lungs, which is necessary to produce thin, normal mucus. Tezacaftor is a CFTR corrector that facilitates the cellular processing and trafficking of normal or multiple mutant forms of CFTR (including F508del-CFTR) to increase the amount of functional CFTR protein delivered to the cell surface, resulting in increased chloride transport. Ivacaftor is a CFTR potentiator that potentiates the channel-open probability (or gating) of CFTR at the cell surface to increase chloride transport. For ivacaftor to function, CFTR protein must be present at the cell surface. Ivacaftor can potentiate the CFTR protein delivered to the cell surface by tezacaftor, leading to a further enhancement of chloride transport than either agent alone. The combined effect of tezacaftor and ivacaftor is increased quantity and function of CFTR at the cell surface, resulting in increases in chloride transport, airway surface liquid height, and ciliary beat frequency, see **Figure 1** below.

Figure 1 Mechanisms of Action of Tezacaftor and Ivacaftor



The initially claimed indication was:

Symkevi is indicated in a combination regimen with Kalydeco (ivacaftor 150 mg tablet) for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro and/or clinical evidence (see section 5.1).

TEZ/IVA combination therapy is proposed to be dosed orally each day in 2 tablets as follows:

- Morning dose: 1 fixed-dose combination (FDC) tablet containing 100 mg TEZ and 150 mg IVA, supplied as a yellow, film-coated tablet.
- Evening dose: 1 tablet containing 150 mg IVA, supplied as a blue, film-coated tablet.

Type of Application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the fact that due the designs of performed studies, patient populations included, uncertainties aroused whether the claimed unmet medical need would be addressed by TEZ/IVA. Furthermore, the proposed combination of TEZ/IVA was not considered to be of major public health interest for patients with CF aged 12 years and older who have the F508del mutation and a residual function mutation in the CFTR gene, or for patients with CF aged 12 years and older who are homozygous for the F508del mutation in the CFTR gene, who are not able to take Orkambi due to concomitant medications or those who may not be able to tolerate Orkambi, nor is it considered a major therapeutic innovation.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as fixed-dose combination (FDC) film-coated tablets containing 100 mg of tezacaftor and 150 mg of ivacaftor as active substances.

Ivacaftor is currently approved in the EU as a single-entity film-coated tablet: product 'Kalydeco' (EMEA/H/C/002494 Centralised Procedure), and also in a fixed dose combination film-coated tablet: product 'Orkambi' (EMEA/H/C/003954) with active substances Lumacaftor and Ivacaftor.

Other ingredients are:

Tablet core: hypromellose acetate succinate, sodium laurilsulfate (E487), hypromellose (E464), microcrystalline cellulose (E460(i)), croscarmellose sodium (E468), magnesium stearate (E470b)

Tablet film coat: hypromellose (E464), hydroxypropyl cellulose (E463), titanium dioxide (E171), talc (E553b), iron oxide yellow (E172).

The product is available in blisters consisting of PCTFE (polychlorotrifluoroethylene)/PVC (polyvinyl chloride) with a paper-backed aluminum foil lidding as described in section 6.5 of the SmPC.

2.2.2. Active Substance

Ivacaftor

General information

The chemical-pharmaceutical documentation provided for ivacaftor in this marketing authorisation dossier is the same as provided and accepted for Kalydeco and Orkambi dossiers.

The chemical name of ivacaftor is: *N*-(2,4-di-tert-butyl-5-hydroxyphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide or *N*-(2,4-di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide.

The compound has the following molecular structure:

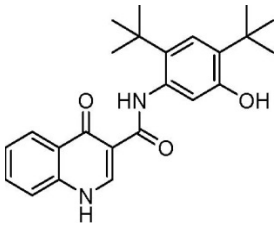


Figure 2 ivacaftor structure

Molecular formula: $C_{24}H_{28}N_2O_3$ Molecular weight: 392.49 g·mol^{-1}

Ivacaftor has a non-chiral molecular structure.

The structure of ivacaftor has been confirmed by elemental analysis, ^{1}H-, ^{13}C- and two dimensional NMR spectroscopy, UV-Visible spectroscopy, mass spectrometry, and crystallographic analysis.

The active substance is a white to off-white crystalline slightly hygroscopic solid which is practically insoluble in water and buffers with pH 1.0-7.0, slightly soluble in ethanol, methanol and acetone and soluble in 2-methyl tetrahydrofuran.

Multiple polymorphic forms have been identified for ivacaftor. The active substance produced by the proposed manufacturing process consists of a mixture of two major crystalline neat polymorphic forms, Form B and Form C. The control of the final isolation and drying conditions ensures that mixtures of the neat crystalline forms B and C are consistently produced. Nevertheless, the polymorphic form of ivacaftor during the synthesis of the active substance is not a CQA since during the manufacture of the drug product, ivacaftor is fully dissolved in a spray-drying solvent system to provide an amorphous intermediate, which is then converted to the final drug product. Therefore ivacaftor's physical form is only a CQA for ivacaftor SDD (spray dried dispersion) and the final tablets, since it is critical to maintain the amorphous form to ensure bioavailability.

Manufacture, characterisation and process controls

A Quality by Design (QbD) approach was also used for the development of ivacaftor. The manufacturing process consists of four main steps using commercially available well defined starting materials with acceptable specifications.

The starting materials were agreed during the assessment of the approved Kalydeco dossier. The synthetic routes for the starting materials have been described in detail and all potential related impurities or degradation products have been described and characterized. There are different suppliers for each starting material. However, the same synthetic route is used by the different suppliers of the same starting material. Description of the manufacturing process of the active substance including the in-process controls is adequate.

A QbD approach has also been used in product and process development of ivacaftor. For the active substance synthesis, a combination of multivariate analyses and range-finding studies was used to define a design space for each step (namely, coupling, methanololysis, form conversion/crystallization and drying). All parameters with a potential impact on CQAs of the active substance were identified and thoroughly investigated. The applicant has proposed a combination of proven acceptable ranges (PARs) and design spaces for the manufacturing process of the active substance.

Although the design spaces were developed at small laboratory scales, a design space verification protocol providing demonstration of the risk of scale dependence of the parameters which define each design space was submitted. For the first three design spaces (coupling, methanolys, and ivacaftor form conversion/crystallization), the assessment concluded that there is low risk of scale dependence and, therefore, the ranges defined at laboratory scale are applicable to commercial scale. This is supported by confirmatory experiments, and scale up/down calculations conducted at pilot scale at the higher risk points in the design space. For the design space of drying of ivacaftor drug substance, the engineering-based assessment determined that there is a higher risk of scale dependence than for the other three design spaces. Drying data were collected from the commercial scale and multiple confirmatory experiments, supported by appropriate engineering modelling, and scale up/down calculations were conducted. The robustness of the process has been confirmed with the manufacture of fifteen large-scale batches of ivacaftor drug substance, which have consistently met the acceptance criteria for all drug substance CQAs. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design spaces.
Ivacaftor drug substance is packaged inside a low density polyethylene (LDPE) bag and secured with an appropriate closure (twist tie or equivalent). The bag is then placed inside a second LDPE bag and secured appropriately; the closed LDPE bags are placed into a secondary container suitable for storage and shipping. The LDPE is compliant with the Directive 2002/72/EC and the European Pharmacopoeia Monograph 3.1.3 “Polyolefins”.

Specification

The active substance specification includes tests for includes tests for appearance (visual inspection), identification (FTIR), assay (HPLC), organic impurities (HPLC), acetamide (GC-MS), inorganic impurities-sulphated ash (Ph. Eur.), and residual solvents (GC).

A detailed study on the potential, theoretical and observed organic impurities has been presented. Impurity limits in the specification are justified and found safe. The limit proposed for acetamide (hydrolysis by-product of the process solvent acetonitrile) in the active substance has been established according to the Guideline on the Limits of Genotoxic Impurities. Limits for polymorphic form and particle size are not included; this is not necessary considering that the active substance is completely dissolved as part of the finished product manufacturing process.

The limits set for specification parameters are acceptable and in line with batch results, stability studies and CHMP guidelines. Analytical methods used are sufficiently described and fully validated in line with the CHMP requirements.

All batch results (including those of the batches used in the clinical studies) are in compliance with the proposed specification.

Stability

The stability data are the same as approved to date. Stability data on three pilot scale batches of active substance from the proposed manufacturers stored in the intended commercial package for 60 months under long term conditions at 30 °C / 65% RH and for up to 6 months under accelerated conditions at 40 °C / 75% RH according to the ICH guidelines were provided.

The following parameters were tested: appearance, assay, related substances, water content, physical form, microbial limits and water activity. The analytical methods used were the same as for release, with the addition of XRPD for physical form determination, and were stability indicating.

No trends in the assay or water content data were observed through 60months of storage at 30 °C / 65% RH. Although a statistically significant trend was observed for these parameters on samples stored at 40 °C / 75% RH through 6 months, all results remained well within the commercial specification acceptance limit. The XRPD stability data show that ivacaftor remains crystalline at all test points under all storage conditions. In addition, data presented show no increase on water activity levels and no change in microbial content after storage for 12 months at 30 °C /6 5% RH. Thus, all tested parameters remained within the commercial specification acceptance limits.

Ivacaftor active substance was also subjected to stress conditions including exposure to heat and heat combined with humidity for up to 21 days, treatment under acidic, basic, neutral and oxidative conditions for up to 14 days, exposure to pH 4 and pH 7 for up to 7 days and exposure to light conforming to ICH Q1B option 2 requirements. Ivacaftor was found to be the least stable under basic conditions and when in solution exposed to light. No degradation was observed when ivacaftor was exposed to the other stress conditions. Analysis of the stressed samples confirmed that the commercial HPLC method for assay and organic impurities determination in ivacaftor active substance is stability indicating.

In addition, photostability testing following the ICH guideline Q1B was performed on one batch. The data, showing no changes in the fully exposed test sample and the covered control, confirm that ivacaftor drug substance is photostable and therefore does not require light protective packaging.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 30 months in the proposed container closure system, which is the one authorised in Kalydeco and Orkambi.

Tezacaftor

General information

The chemical name of tezacaftor is: 1-(2,2-difluoro-2*H*-1,3-benzodioxol-5-yl)-N-{1-[(2*R*)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1Hindol-5-yl}cyclopropane-1-carboxamide corresponding to the molecular formula $C_{26}H_{27}N_2F_3O_6$. It has a molecular weight of 520.50 g/mol and the following molecular structure:

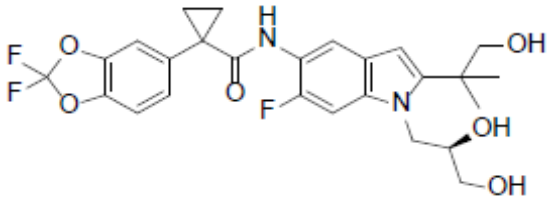


Figure 3 tezacaftor structure

Tezacaftor exhibits stereoisomerism due to the presence of one chiral centre. The active substance is the *R*-isomer. The chirality of the active substance is assured by chiral control of the starting materials. The downstream chemistry does not promote racemization of the stereocenter. This was supported by spiking and stability studies.

The chemical structure of tezacaftor was elucidated by a combination of elemental analysis, ^{1}H, ^{13}C, and two-dimensional NMR spectroscopy, UV/Vis, IR and Raman spectroscopy, high resolution mass spectrometry and crystallographic analysis.

Tezacaftor is a non-hygroscopic white to off-white crystalline solid. The substance is practically insoluble in aqueous solvents tested at pH = 1.0-9.0 and more soluble in organic solvents. It is practically insoluble in fasted state simulated intestinal fluid, and very slightly soluble in fed state simulated intestinal fluid at room temperature and 37°C. Because of its poor solubility in water, a SDD, where the active substance is in an amorphous form to provide sufficient oral bioavailability was developed (see finished product section).

Physical characterization of tezacaftor was conducted by X-ray powder diffraction, differential scanning calorimetry, thermal gravimetric analysis and dynamic vapour sorption. The physical form of tezacaftor active substance manufactured by the proposed commercial process has been confirmed. To understand the polymorph landscape of tezacaftor, a comprehensive polymorph screening was conducted.

During the manufacture of the SDD, tezacaftor is completely dissolved in methanol process solvent, therefore polymorphic form and particle size are not CQAs.

Manufacture, characterisation and process controls

The commercial manufacturing process for the synthesis of tezacaftor involves seven steps from commercially available well-defined starting materials with acceptable specifications and three crystallizations. The selected starting materials in the synthesis are approvable, in view of ICH Q11 and its Q&A, and the CHMP guideline on chemistry of the active substance (EMA/454576/2016); sufficient justification and discussion for the choice of these compounds is provided. The names and addresses of the starting material manufacturers/suppliers are laid down in the dossier. This also holds regarding the synthesis routes of the starting materials applied by the manufacturers/suppliers. Two active substances manufacturers which use the same route of synthesis are proposed.

Following an enhanced QbD quality approach, the tezacaftor active substance manufacturing process was risk assessed to determine which process parameters had the potential to have the greatest impact on tezacaftor CQAs. On this basis critical and non-critical parameters have been defined to describe the manufacturing process and process controls. Design spaces have been established for several process steps, based on Designs of experiments (DoE) studies performed.

The DoE studies to support the design spaces were based on full factorial and fractional factorial designs with resolutions at mainly levels IV, based on the risk assessments as done for Orkambi development. The resulting design spaces are considered acceptable.

Design space verification was completed for each unit operation in line with EMA “Questions and Answers on Design Space Verification” (EMA/603905/2013). This design space verification and lifecycle management were based on a risk assessment of potential scale dependent phenomena for each step along with the control strategy demonstrated during development studies. As a result, none of the design spaces were categorized as high risk but as medium scale-up risk. Thus, well-established chemical engineering science and scale-up principles (e.g. heat transfer, solids suspension, liquid blending) and correlations were used to examine potentially scale-dependent phenomena and confirm that they do not impact process performance, and that the design spaces developed at laboratory scale apply to (are verified for) commercial scale. The consistency of commercial scale batches (15 batches) with lab scale predictions provided further support for the design space scale verification conclusions.

Adequate in-process controls (IPCs) are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The tezacaftor active substance control strategy comprises the starting materials, reagents and solvents specifications, the active substance synthesis design spaces, IPCs and active substance specification. The impurities's data and justifications (including purge and fate studies) support the control strategy; absence of carry-over of impurities through the synthesis has sufficiently been demonstrated and the control strategy is in line with the guidelines (e.g. ICH Q3A, Q3C, M7, Q11).

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Detailed information regarding the manufacturing process development of tezacaftor active substance has been presented. The proposed commercial manufacturing process uses the same bond making and breaking steps as the initial process. Further development work led to improvement of steps. The changes made during development are considered minor and are not expected to impact on the quality of the active substance.

The active substance is packaged inside a LPDE bag and secured with an appropriate closure (twist tie or equivalent). The bag is then placed inside a second LDPE bag and secured appropriately; the closed LDPE bags are placed into a secondary container suitable for storage and shipping which complies with the European Guideline on Plastic Immediate Packaging Materials (CPMP/QWP/4359/03). The LDPE resin used to manufacture the bags is suitable to be in contact with food and complies with the requirements of Commission Regulation (EU) No 10/2011 and the Ph.Eur. Monograph 3.1.3 “Polyolefines”.

Specification

Tezacaftor specification includes tests and limits for appearance, identification (IR), assay (HPLC), organic impurities (HPLC), inorganic impurities: palladium (Ph. Eur.) and residue on ignition/ sulphated ash (Ph. Eur.) and, residual solvents (GC).

The active substance specification is based on the active substance CQAs. The CQA identified are appearance, identification, assay, organic impurities, chiral purity, inorganic impurities, residual solvents, palladium and copper. A justification for the absence of control of chiral purity, copper, heavy metals, residual trimethylamine, water content, physical form, particle size and microbial count has been provided and is considered acceptable.

Specifically, the absence for a control of chiral purity has been justified on the basis that tezacaftor contains a single chiral center, which is a secondary carbinol, its origin and stability. Therefore, the control of chiral purity of tezacaftor active substance is established according to ICH Q6A (decision tree #5) by applying limits in the relevant starting material as supported by development studies. The carry over studies and design spaces studies showed that the stereo-chemical enantiomers, if formed, do not carry through the synthesis and that the limit established at starting material level is adequate. This justification is acceptable.

Elemental impurities are controlled in line with ICH Q3D.

Water content is not a CQA of tezacaftor because the crystalline active substance is non-hygroscopic (< 0.2% w/w water uptake up to 80% RH at 25°C), and water does not affect active substance stability or finished product manufacture.

With regards to active substance polymorphism, physical form has been monitored during all development and stability studies. To date, there has been no change in the tezacaftor polymorphic form. In addition, the active substance fully dissolves in organic solvents at the beginning of the spray-drying process. Form A is freely soluble at the maximum solids load in the spray drying solvent system (80% dichloromethane / 20% methanol). For this reason, polymorphic form is not a CQA of the tezacaftor active substance and it is not included in its specification.

Likewise, particle size of tezacaftor is not a CQA because the active substance is completely dissolved in the spray drying solvent system (80% dichloromethane/ 20% methanol) as the first step of the SDD manufacture.

Tezacaftor has not been shown to be bactericidal or bacteriostatic. However, the active substance manufacturing process follows classic chemical synthesis which is hostile to microorganisms. In addition, the microbial limits and water activity test results from 3 representative active substance lots presented show very low bioburden, absence of specified microorganisms using validated compendial microbial limits methods, and water activities less than 0.6 (consistent with the fact that the drug substance has low hygroscopicity and indicating the material is not likely to support microbial growth). The primary stability showed that water activity levels remain below the threshold for microbial growth promotion (0.6), and no change in microbial content after storage for 12 months at 25°C/60% RH in the intended container closure system. These combined data indicate that tezacaftor active substance possesses very low risk of microbial contamination and microbial testing of commercial lots is not necessary.

The tests and limits in the specifications are considered appropriate for controlling the quality of this active substance.

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

All batch results (including those of the batches used in the clinical studies) are in compliance with the proposed specification.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standard used for assay and impurities testing has been presented.

Batch analysis data on 21 pilot or commercial scale batches of the active substance used for non-clinical studies, clinical studies, and formal stability studies, or intended for future clinical or commercial use have been provided. The results are within the proposed specifications and consistent from batch to batch.

Stability

Stability data from three commercial scale batches of active substance from one of the proposed manufacturers stored in the intended commercial package for up to 18 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: appearance, assay, organic impurities, chiral purity (HPLC), water content (KF titration), physical form (XRPD), microbial limits (USP <61> and <62>), specified microorganisms (*E. coli*) and water activity (USP <1112>). All results met the acceptance criteria for the attributes evaluated and no trends were observed. Water activity levels remained below the threshold for microbial growth promotion (0.6), and no change in microbial content after storage for 12 months at 25°C/60% RH in the intended container closure system was observed. The stability data show that tezacaftor active substance is stable when packaged in the intended container closure system under all storage conditions.

Photostability testing following the ICH guideline Q1B option 2 was performed on one batch. Samples were tested for appearance, assay, organic impurities and chiral purity. The data, showing no changes in the fully exposed test sample and the covered control, confirm that tezacaftor active substance is photostable and does not require light protective packaging.

Results on stress studies including heat (80°C), heat/humidity (80°C/75%RH), treatment under acidic (0.2N HCl, ambient), basic (0.2N NaOH, ambient), and oxidative (0.02% H_2O_2, ambient) conditions for up to 14 days, and exposure to UV and visible light (solid and solution) were also provide on one batch. Tezacaftor was found to be the least stable under the oxidative condition and when exposed to light stress conditions in solution. Results from the primary stability studies demonstrate that none of the degradation products observed under these stress conditions are found at or above the reporting threshold when the active substance is packaged and stored according to label requirements. No degradation was observed when tezacaftor was exposed to the other stress conditions listed above. All tezacaftor samples from this study were tested for spectral peak purity. The tezacaftor peak was found to be spectrally pure in all stressed samples demonstrating that the commercial HPLC method for assay and organic impurities determination of tezacaftor drug substance is stability indicating.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 24 months when stored in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is a yellow immediate-release film coated tablet for oral administration. The tablet is a FDC of the active ingredients tezacaftor (100 mg) and ivacaftor (150 mg). As indicated above,

both tezacaftor and ivacaftor active substances are provided as SDD intermediates. The applicant declared that ivacaftor SDD used in this Symkevi submission is identical to the one used and approved for Kalydeco.

Specifically, ivacaftor active substance was approved in 2012 (Kalydeco Centralised Procedure) and in 2015 as a FDC tablet (Orkambi Centralised Procedure). It is a stable crystalline material of high purity with well characterized physical and chemical properties. While crystalline ivacaftor is chemically and physically stable, it practically insoluble in aqueous media and has low bioavailability. Various approaches to obtain materials with better aqueous solubility were explored Given the acceptable chemical and physical stability of the neat amorphous form (), combined with its significantly improved dissolution rate and bioavailability the amorphous form was selected as the most appropriate active substance form for development. Theactive substance is spray driedto make an amorphous SDD prior to manufacturing the final tablet. As mentioned above, this is the same approach used in the approved Kalydeco and Orkambi products.

Ivacaftor is compatible with the processing solvents and excipients used in the SDD as confirmed by stability studies.

Binary excipient compatibility studies were conducted with development ivacaftor SDD formulations mixed with common tableting excipients. These studies were conducted under open dish conditions at 40°C/75%RH and showed no changes to the physical or chemical stability of ivacaftor with any of the excipients tested. In addition, no physical or chemical stability changes have been noted with any finished product lot on stability.

Tezacaftor active substance is the new active substance (NAS) component of the proposed FDC tablets. It is provided as a crystalline solid which is practically insoluble in water and buffer solutions from pH 1.0 to pH 9.0. The amorphous form of tezacaftor was selected as the most appropriate physical form for development due to increased solubility as compared to a crystalline form. The active substance is spray dried to produce an amorphous SDD drug product intermediate. Tezacaftor SDD is packaged inside a LDPE bag/liner which is placed inside a second LDPE bag/liner. The closed LDPE bag/liners are then sealed in a foil laminated bag with desiccant.

The tablet core excipients are hypromellose acetate succinate (HPMCAS) (physical stabilizer), sodium lauryl sulfate (E487) (wetting agent), purified water, hypromellose (HPMC) (E464) (physical stabilizer), microcrystalline cellulose (E460(i)) (filler), croscarmellose sodium (E468) (disintegrant) and magnesium stearate (E470b) (lubricant). The tablet film coat excipients are hypromellose (E464), hydroxypropyl cellulose (E463), titanium dioxide (E171) talc (E553b) and iron oxide yellow (E172).

There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards, except iron oxide yellow which complies with EU Regulation 231/2012. The specifications of the excipients were carefully discussed and justified in view of the continuous manufacturing process of the tablets involving PAT methods. In this regard, a risk assessment was performed to determine the potential for excipients to impact the CQA of the product in the context of the specific manufacturing process for the tablets. The risk was determined to be low for all excipients used in the formulation. As a result, the Ph. Eur. specifications were deemed sufficient, with except for one of the excipients, where an additional test was added to further characterize the material properties. Furthermore, multiple lots of each excipient have been used throughout development and clinical manufacture with no impact observed on the processability or product quality due to lot-to-lot variation. In addition, the design and operation of the loss in weight (LIW) feeders ensures that they can correct for any minor material variability. In addition, it was

confirmed that the PAT chemometric models were calibrated across the design spaces using multiple lots of excipients. The models were shown to be robust against normal excipient lot to lot variability.

Studies were conducted to examine the chemical and physical compatibility of the tezacaftor SDD and ivacaftor SDD with the tablet excipients as well as with each other. Open dish stability of 800 mg/g tezacaftor SDD over 6 months at 40ºC / 75% RH showed no chemical or physical incompatibility. The potential of the interactions between tezacaftor and HPMCAS and the crystalisation of tezacaftor in the presence of sodium lauryl sulfate (both components present in ivacaftor SDD) in the FDC tablet product was also addressed.

Tezacaftor/ivacaftor FDC tablets (commercial formulation) were stationed on an open dish stability study at 40ºC / 75% RH for 12 months. The results demonstrate the chemical and physical compatibility of all components of the FDC tablet.

The tablets are easily distinguishable from the Kalydeco and Orkambi tablets, since they have different colour.

The composition of the product proposed for marketing is the same as the pivotal (phase III) clinical formulation. An overview of tezacaftor and ivacaftor formulations used in clinical development has been provided. Formulations included an oral solution (used in 2 studies) and tablets (used in all other studies), either as separate tezacaftor and ivacaftor tablets and/or tezacaftor/ivacaftor FDC tablets.

Manufacturing process of the early phase III clinical studies was a traditional manufacturing process with the same process steps as the proposed continuous manufacturing (CM) process; the later phase III batches were manufactured according to the CM process. The pivotal clinical batch results (regardless the traditional or CM process used) showed comparable batch results.

As part of the pharmaceutical development, the dissolution profiles of the FDC tablet were compared to those obtained with the individual tablets used in Phase 1 and 2 studies. They were found to be similar and therefore were expected to provide comparable exposure and pharmacokinetics to the individual tablets. Based on this dissolution data as well as the Phase 2 results, the 100 mg tezacaftor/ 150 mg ivacaftor FDC tablet was selected for Phase 3 studies. Pharmacokinetic (PK) results from the 100 mg tezacaftor/150 mg ivacaftor FDC tablet in Study 006 and the individual tezacaftor and ivacaftor tablets dosed in Studies 101 and 103 suggested that the FDC tablet provides comparable exposure and PK as the individual tablets.

The product and manufacturing process development were conducted following an enhanced QbD approach in line with ICH Q8. An adequate quality target product profile (QTPP) was defined as basis for the development in line with the finished product properties and its use and relevant CQAs were identified and derived thereof.

Specifically, the QTPP was to develop an immediate release fixed-dose combination tablet of 100mg tezacaftor/150mg ivacaftor for oral administration which is bioavailable, safe and efficacious and has a 24 month shelf life at room temperature packaged in blister

The identified potential tezacaftor finished product intermediate (SDD) CQAs were: appearance, identification, assay, degradation products, particle size, bulk density, residual solvents and physical form. An initial risk assessment was conducted to determine the likelihood that variability in materials and process steps could have an impact on one or more potential CQAs of the SDD. This was followed by a multivariate DOE designed to evaluate process parameters that could have an impact on SDD CQAs. Based on the results from these studies the design spaces and in –process control for the process were established.

The CQAs for ivacaftor SDD were previously established and assessed as part of Kalydeco Marketing Application (EMEA/H/C/002494).

With regards to the FDC tablets, potential CQAs for the tezacaftor active substance, tezacaftor SDD, ivacaftor SDD and the tezacaftor/ivacaftor FDC tablet were identified. An initial risk assessment was performed on the tezacaftor active substance, SDD, and FDC tablet to determine which materials and process steps could potentially impact the CQAs.

Both active spray dried dispersions were assessed as having the potential to impact some CQAs. The ivacaftor SDD physical properties are well understood due to its longer development and commercial history and thus it was assessed as having a low risk.

Risk assessment and prior knowledge were used to design multivariate experiments that evaluate main effects and interactions. These experiments considered the desired manufacturing range (DMR) as well as incoming material specifications and equipment capability. Any differences in scale or equipment between the experiments conducted and the commercial equipment were considered (scale-up and engineering risk assessment) to ensure results are representative of the commercial process and are documented as appropriate. Initial screening designs were performed in a discontinuous manner as specific unit-operation to identify material attributes, dry granulation processing parameters and coating process parameters that may impact finished product CQAs prior to conducting integrated continuous QbD experiments on the continuous manufacturing DLR. Data from QbD studies were analyzed to define the design spaces that ensures all CQAs are within acceptance limits, and process models which describe them. Robustness of the design spaces limits and the models were demonstrated with the pivotal clinical batches, which were commercial scale. The validity of all the design spaces at the same time was confirmed.

The process knowledge gained throughout QbD development formed the basis of the overall product control strategies for active substance and finished product. The control strategy includes control of input material attributes, automated feedback loops to drive each unit operation towards its target set point, monitoring of design spaces parameters throughout manufacturing to ensure product is manufactured within the design spaces, IPC and finished product specifications. This ensures that a quality product will be consistently produced.

The commercial manufacture of the tezacaftor/ivacaftor FDC tablets uses a CM process, starting with the introduction of individual components and ending with film coated tablets, combined with real time release testing (RTRT). The equipment is equipped with both spectroscopic and non-spectroscopic process analytical technology (PAT) which are used for in-process control (IPC) and/or RTRT. The CM system uses gravity feed for material transfer between unit processes. Additionally, a dilute phase pneumatic conveying system is also used to transfer granules and a bucket lift (TRU) conveying system to move core tablets. LIW feeders are used when accurate material dosing is required. The desired quantity of each component is fed into in-line blender 1.

The individual components in blender 1 are mixed and conveyed using an auger system (convective mixing) and the output blend is then fed to the roller compactor. The intragranular (IG) blend is dry granulated using a roller compactor and the resulting ribbons are milled into granules. The granules are conveyed via pneumatic transfer to the granule conditioning unit (GCU) for further milling. The first segregation point for removal of non-conforming material is after the GCU.

Extragranular (EG) excipients are then added using a second set of LIW feeders (feeder bank 2) and these components are fed into in-line blender 2.

The final blend is transferred by gravity to the rotary tablet press for compression, and the resulting tablets are mechanically transferred to a deduster/metal checker followed by the tablet relaxation unit (TRU).

From the TRU the tablets are conveyed to the tablet coaters (perforated pan coating system) for application of a non-functional film coat. The continuous coater incorporated in the DLR system is a sub-batch coater. To accommodate the desired range of line rates of the DLR, two identical continuous film coaters are incorporated in the system, running in parallel.

The second segregation point for non-conforming material is at the TRU. The final coated tablets are discharged out of the coaters into intermediate containers.

Start-up and shut down processes have been described and justified. The residence time distribution (RTD) was assessed and used to develop the segregation strategy of material identified for waste.

Hold times have been studied experimentally and documented at the commercial scale for sieved SDDs and excipients as well as the coating suspension used for manufacture of this product. Based on this study the holding times with no impact to process capability or product quality were defined. These holding times are therefore acceptable.

The IPC for tezacaftor/ivacaftor FDC tablets manufacture have been justified. Adequate acceptance criteria and sampling plans have been defined.

Specifically, mass flow for the components of the FDC tablet is determined gravimetrically by the LIW feeders. SDD IG blend potency is calculated based on the gravimetric dosing of the IG blend components by the LIW feeders (Feeder Bank 1, Feeders 1-4).

Two methods for assessing final blend potency have been established: (1) measurement of tezacaftor and ivacaftor final blend potency by NIR and (2) calculation of tezacaftor and ivacaftor final blend potency using granule potency determined by NIR and feeder mass flow data for the final blend components (Feeder Bank 2, Feeders 5-7). The intention is to manufacture with both methods active to ensure continuous monitoring of the process when the NIR systems are unavailable (e.g. undergoing on-going performance verification). However, only one result from either of the two methods is required to satisfy the minimum IPC sampling plan for manufacture. The methods have been fully validated per ICH Q2 (R1).

Core tablet weight, thickness and hardness are measured on a tablet tester installed at the tablet press.

The capability of the RTRT methods to properly characterize the relevant CQA has been demonstrated by the comparison of the results obtained with the RTRT and the regulatory method.

A post-approval change management protocol (PACMP) relating to the management of changes to models employed for IPC and RTRT for the FDC tablets has been submitted. It defines the model change and associated validation testing, acceptance criteria, and regulatory reporting strategy required for each model.

Two independent *in vitro* dissolution methods were developed for testing 100 mg tezacaftor/ 150 mg ivacaftor FDC tablets, one for each active ingredient. Both dissolution methods have shown discriminating ability against meaningful manufacturing variations and tablet properties, and are considered suitable for their intended use as the primary release and stability quality control methods for tezacaftor/ivacaftor FDC tablets.

Bulk tezacaftor/ivacaftor FDC tablets are packaged in double low-density polyethylene (LDPE) bags inside a heat-sealed foil laminated bag. The material complies with Commission Regulation (EU) No 10/2011.

The container closure system for tezacaftor/ivacaftor fixed dosed combination (FDC) tablets is a thermoform blister consisting of clear Aclar (PCTFE – polychlorotrifluoroethylene) film laminated to PVC (polyvinyl chloride) film and sealed with a blister foil lidding. The aclar/foil blister configuration will be placed into an appropriate secondary container. A declaration of compliance of the material with guidelines on Plastic materials, Commission Regulation (EU) No 10/2011 and/or the relevant European Pharmacopoeia monograph has been provided.

Manufacture of the product and process controls

The preparation of the ivacaftor SDD consists of three steps: mixture preparation, spray drying and secondary drying. This is the same registered for Kalydeco and Orkambi.

A PACMP to manage specific design spaces changes for the tezacaftor SDD spray-drying step resulting from equipment and/or site changes or modifications has been submitted. The protocol defines the experiments, testing, acceptance criteria, and regulatory reporting strategy based on the specific proposed change.

As indicated above, the tezacaftor/ivacaftor FDC tablets are manufactured using a CM process including the feeding and intra-granular (IG) blending of actives and IG excipients, dry granulation and milling, extra-granular (EG) blending of granules and EG excipients, compression and film coating.

The design space limits and IPCs have been justified (see pharmaceutical development section).

The analysis results for 10 batches of tezacaftor SDD used in clinical studies have been presented. All results met the specifications. All batches of tezacaftor SDD met the specifications

Process validation results for intragranular blend uniformity, blend uniformity by dosage form assay, and dissolution of tablets from the beginning, middle and end of a run have been provided.

A continuous process verification (CPV) approach to validation has been implemented for the tezacaftor/ivacaftor FDC product. A process validation scheme has been submitted. At the time of opinion, the DLR has been used for process development activities and for manufacture of 5 clinical finished product batches, and will also be used for commercial manufacture. The clinical batches were manufactured using the same equipment, using similar line rates, and with the same sampling locations as will be used for commercial manufacture. Process performance understanding is further supported by conducting development (QbD) experiments on the same continuous manufacturing line (DLR), and using multivariate analysis to link process parameters to product CQAs and define design spaces within which product quality is assured.

Process parameter and IPC data is collected and reported continuously throughout manufacture, both for the purpose of process monitoring and control and as inputs to calculations for batch release via RTRT. Process capability has been demonstrated via analysis of IPC variability, which has informed the sampling plan and frequency as well as through analysis of process parameter variability, which has demonstrated the ability of the process to operate within design spaces limits. Furthermore, there is a thorough understanding of product quality during start-up and shutdown, as well as before and after pauses. The RTD on the DLR has been characterized, and procedures are in place to allow segregation of all potentially impacted material.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, identification (IR/RTRT), assay (HPLC/RTRT), degradation products (HPLC), uniformity of dosage units (HPLC/RTRT), dissolution (Ph. Eur./RTRT), water content (KF/RTRT), physical form (XRPD/RTRT), and microbial purity (TAMC, TYMC, *E. coli*) (Ph. Eur.).

A RTRT strategy with a contingency plan specifying the use of alternative testing or monitoring approaches on a temporary basis in case of RTR equipment failure has been defined. Satisfactory comparative testing between the RTRT and the Regulatory methods was conducted for the first three commercial batches to be marketed. A post-approval program for parallel testing has been provided and justified. This is in line with the Guideline on Real Time Release Testing (EMA/CHMP/QWP/811210/2009-Rev1).

Chemometric models have been developed in line with the FDA Guidance for Industry: Analytical Procedures and Methods Validation for Drugs and Biologics, 2015 and the CHMP guideline on the use of Near Infrared Spectroscopy (EMEA/CHMP/DVMP/QWP/17760 2009 Rev2). The models were developed using the DLR instrumentation and lab instrumentation equivalent to the DLR systems. Samples encompassing anticipated process variability (process design spaces) and physical, chemical, and compositional material variability were used to calibrate the chemometric models and ensure specificity and robustness. Analytical method descriptions summarizing the PAT data acquisition parameters and the chemometric models have been provided.

The PAT tools used for RTRT have been described.

The **PAT 3** station is sited after the dry granulation step and before the addition of extragranular excipients, and production of the final blend. It consists of two in-line instruments: a laser diffraction unit for determining granule particle size, an attribute used in the chemometric dissolution model required for RTRT; and an in-line NIR sensor for assay of the two active substances in the granule. The results taken together with the data from the LIW feeders of the extragranular excipients are used to predict, as an IPC the potency of the two actives in the final blend.

The **PAT 4** station is sited before tablet compression and consists of an in-line NIR sensor for assay of the two active substances and water content of the final blend.

The **PAT 5** station is sited following tablet compression and consists of two at-line instruments: Raman spectroscopy sensor for determining the polymorphic form of the two active substances, and identification of the two active substances in the drug product; and the Kraemer Tablet Testing system to measure the tablet core weight, thickness and hardness.

A partial least squares model to predict tezacaftor dissolution rate for each segment (about 1/12) of the CM batch was developed. The model has the following inputs:

- average tezacaftor content and average ivacaftor content in final blend is obtained from the **PAT 4** NIR chemometric models.
- average segment granule volume weighted particle size distribution obtained from the **PAT 3** Laser Diffraction system
- the segment tezacaftor SDD and ivacaftor SDD feed factors (i.e. the line feed rate in kg/hr) are obtained from the loss in weight feeders 2 and 1 respectively located in Feeder Bank 1.

- the segment average core tablet weight, thickness, and hardness obtained from the **PAT 5** Kraemer Tablet Testing system.

The model was developed using multiple dissolution samples obtained from manufacturing runs spanning the process design spaces and desired manufacturing range. The samples used for calibration were prepared with various drug substance, spray dried dispersion and excipient lots.

The same approach was taken to develop a RTRT dissolution model for ivacaftor.

The RTRT dissolution methods were verified during a clinical campaign on the DLR according to an approved protocol. Verification of the methods was performed by comparing the RTRT dissolution results with the results obtained by the regulatory dissolution methods for the determination of tezacaftor and ivacaftor. The results obtained met the acceptance criteria as defined in the approved protocol, confirming that the method is suitable for its intended use.

PAT 4 NIR final blend potencies for tezacaftor and ivacaftor together with **PAT 5** core tablet weight are used to determine the tezacaftor and ivacaftor batch content uniformity. The batch average tezacaftor content, the variance in tezacaftor content, the batch average ivacaftor content, and the variance in ivacaftor content in final blend along with the batch average core tablet weight and variance in core tablet weight are subsequently used to calculate the batch content uniformity for tezacaftor and ivacaftor.

A protocol describing model maintenance strategy has been presented.

Analytical methods have been adequately described and validated in line with ICH Q2 (R1), when applicable.

Comparative RTRT and end product regulatory batch data are reported for 22 QbD runs and three confirmatory QbD runs (parallel testing). This included data from the four clinical batches (two small scale, and two batches are or near commercial scale) which were shown to be comparable and compliant with the proposed specification. This data shows that the manufacturing process can manufacture consistently and that the both the RTRT and end product testing data are comparable.

Degradation products are addressed only in the stability specification, and not at batch release. This is accepted because the starting materials are satisfactorily controlled and data from the primary and supportive stability lots showed no degradation products at or above the reporting threshold (0.10%) at all test points under all storage conditions.

A justification to only perform microbial limits testing on commercial stability lots of tezacaftor/ivacaftor FDC tablets has been presented. Data from 7 batches of FDC tablets showing very low bioburden and absence of specified microorganisms using validated compendial microbial limits methods were provided. Water activity testing was performed for 4 of these lots, and showed water activities less than 0.6 (indicating the material is not likely to support microbial growth). In addition, 6 lots of tezacaftor/ivacaftor FDC tablets placed on stability showed no change in microbial content after storage for 12 months at 30°C/75% RH in the intended container closure system. Water activity was tested for 3 of the stability lots, and the results remained below the threshold for microbial growth promotion (0.6) after storage for 12 months at 30°C/75% RH in the intended container closure system. Data available confirm that the tezacaftor/ivacaftor FDC tablets have very low risk of microbial contamination. However, to verify that the risk remains low, the applicant will perform microbial limits testing on commercial stability lots of packaged tezacaftor/ivacaftor FDC tablets to confirm the results

comply with USP <1111>. This approach is accepted because water is not used during the manufacturing process and water content is controlled in the active substance SDDs and excipients.

A justification for the omission of chiral purity, residual solvents, elemental impurities and water from the specification was also provided.

The control of chiral purity of tezacaftor active substance is established according to ICH Q6A (decision tree #5) by applying limits to in the starting material. It has been demonstrated that under the conditions used for the preparation of tezacaftor SDD and tezacaftor/ivacaftor FDC tablets, there is no opportunity to directly epimerize the tezacaftor secondary carbinol chiral center. In addition, there has been no change on stability in chiral purity within method variability. Therefore, chiral purity will be controlled only in starting material.

The levels of residual solvents in tezacaftor/ivacaftor FDC tablets are controlled via ICH Q3C (R6) option 1 limits for residual solvents used in the manufacturing of the tezacaftor and ivacaftor active substances and SDD. All SDD and tablet excipients also meet ICH Q3C (R6) Option 1 limits for residual solvents. These controls ensure the total potential residual solvent content of tezacaftor/ivacaftor FDC tablets comply with the ICH Q3C (R6) requirements.

The potential presence of elemental impurities in tezacaftor/ivacaftor FDC tablet was assessed according to the ICH Q3D using a risk based approach and taking into account the dosing regimen including a 150 mg Kalydeco tablet. It demonstrated that all Class 1 and Class 2A elemental impurities in the tezacaftor/ivacaftor FDC tablets will be consistently below 30% of the established PDEs. The risk assessment also demonstrates that elemental impurities intentionally added in the ivacaftor and tezacaftor drug substances manufacturing processes are controlled to appropriate levels in the drug product. Therefore, no additional controls on elemental impurities in the drug product are required.

A justification to omit water content from the shelf-life specification was also provided. Water is not a CQA for the tablets, but microbial count, the only CQA that could be impacted by water, will be tested directly. In addition, dissolution will also be monitored.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 5 clinical batches manufactured by a discontinuous process and five clinical CM batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

The proposed shelf life and storage condition for the ivacaftor SDD is 24 months when stored in the intended container closure system. This is the same approved for Kalydeco and Orkambi and the same data has been submitted in Symkevi dossier.

The proposed shelf life for tezacaftor SSD is 36 months when stored in the intended container closure system at not more than 30°C. The shelf-life and storage condition are supported by 24 months of formal long-term at 25°C / 60% RH and 6 month at 40°C / 75% RH stability data from three primary pilot and commercial scale batches. Samples were tested for appearance, assay and degradation products, chiral purity (HPLC), water content, physical form, microbial count and specified microorganisms and water activity. All results met the acceptance criteria for the attributes evaluated.

Photostability of tezacaftor SDD was evaluated per ICH Q1B Option 2 on one batch. Samples were tested for appearance, assay, degradation products, physical form and chiral purity (HPLC). The data, showing no changes in the fully exposed test sample and the covered control, confirm that tezacaftor SDD does not require light protective packaging.

The data presented support the proposed shelf life and storage conditions for tezacaftor SDD.

The stability of Symkevi bulk tablets was evaluated. Stability data from one batch of FDC tablets stored in the proposed bulk bag during 12 months at 25°C ± 2°C/60% RH ± 5% RH and 6 months 40°C ± 2°C/75% RH ± 5% RH was provided. The same parameters as in the formal stability studies of the FDC tablets (see paragraph below) were studied. No significant changes were observed. Therefore the proposed holding time of 12 months in the bulk bag is acceptable.

Additionally, stability data on the product has been provided on six production scale (clinical) batches prepared using a batch (discontinuous) manufacturing process and stored for up to 18 months at 25°C/60% RH and 30°C/75% and for 6 months at 40°C/75% RH, in line with ICH requirements. The batches were stored in the proposed blister. Additional supportive stability data from three batches prepared using a CM process and stored for 12 months under long term conditions and 6 months under accelerated conditions were also provided. Samples were tested for appearance, assay (ivacaftor, tezacaftor), degradation products (ivacaftor, tezacaftor), tezacaftor chiral purity, dissolution (ivacaftor, tezacaftor), water content and physical form. Samples stored at 30°C/75% were also tested for microbiology (TAMC, TYMC, E. coli) and water activity. The analytical procedures used were stability indicating.

Stability data showed no trends under all storage conditions for appearance, assay of active substances, degradation products, chiral purity. The X-ray powder diffraction data showed absence of crystalline tezacaftor and absence of crystalline ivacaftor at all test points under all storage conditions. With respect to tezacaftor dissolution, no trends were seen at 25°C/60%RH, a very slight negative trend at 30°C/75%RH and 40°C/60%RH. With respect to ivacaftor dissolution, no trends were seen at all storage conditions. A slight increase in water content was seen under all storage conditions, but all results remained well within the commercial specification acceptance limits.

Photostability as ICH Q1B Option 2 was studied on one batch. Samples were tested for appearance, assay, degradation and chiral purity. The data, showing no changes in the fully exposed test sample and the covered control, confirmed that tezacaftor/ivacaftor tablets do not require light protective packaging.

Symkevi tablets were subjected to stress conditions, which included heat, heat/humidity, treatment under acidic, basic, and oxidative conditions for up to 14 days, and exposure to UV and visible light. The tablets were found to be the least stable under base, oxidative, and in solution exposed to light stress conditions. No significant degradation was observed under all the other stress. The tezacaftor and ivacaftor peaks were found to be spectrally pure in all stressed samples demonstrating that the commercial HPLC method for assay and degradation products determination of tezacaftor/ivacaftor FDC tablets is stability indicating.

To support the independent shelf-life of the FDC tablet from the SDD, an end-to-end stability study was executed to evaluate the impact of aged ivacaftor and tezacaftor SDDs on the physical and chemical stability of the tezacaftor/ivacaftor FDC tablet. The end-to-end study involved aging representative lots of ivacaftor and tezacaftor SDDs packaged in the commercial packaging configuration for 6 months at 40°C/75%RH (“accelerated aging”). The aged SDDs were subsequently used to prepare tezacaftor/ivacaftor FDC tablets, which were packaged in the commercial packaging and placed on stability. During this end-to-end stability study, there were no significant changes in any

of the tezacaftor/ivacaftor FDC tablets CQA's tested on stability through 18 months at 25°C/60%RH and 30°C/75%RH, and 6 months at 40°C/75%RH. Results from this end-to-end stability study established that the shelf-lives of the SDDs and the FDC tablet are independent, and that tezacaftor and ivacaftor SDDs can be used to manufacture FDC tablets at any point in their shelf life with no impact on the physical or chemical stability of the tablets.

Based on available stability data, the proposed shelf-life of 30 months as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No material from animal origin is used in the production of the product.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substances and finished product has been presented in a satisfactory manner.

The applicant has applied QbD principles in the development of the active substances and finished product and their manufacturing processes. Design spaces have been proposed for several steps in the manufacture of the active substances and finished product. The design spaces have been adequately verified.

The manufacture of the FDC tablets uses a continuous dry granulation process starting with the introduction of individual components and ending with film coated tablets.

Following this QbD approach, a real time release testing strategy has been proposed.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

n/a

2.3. Non-clinical aspects

2.3.1. Introduction

Tezacaftor (VX-661) is developed as a CFTR corrector, improving the processing of CFTR in the endoplasmic reticulum and the Golgi apparatus as well as the trafficking of the protein to the membrane. Ivacaftor, already on the market, was shown to be a CFTR potentiator, increasing the chloride transport by the protein present on the membrane. The development of tezacaftor was

supported by safety pharmacology studies conducted in accordance with ICH S7A and S7B guidelines and a toxicology program conducted in accordance with ICH M3(R2) and other relevant ICH guidelines in addition to recommendations stemming from discussions with Regulatory Authorities throughout development. All safety pharmacology, toxicity, and toxicokinetic studies considered pivotal to safety assessment were conducted in compliance with Good Laboratory Practice (GLP) regulations with any exceptions duly noted and were conducted in Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC) accredited facilities.

The pharmacological profile of TEZ alone and in combination with IVA was characterized in electrophysiological and molecular biological studies using primary cultures of human bronchial epithelial (HBE) cells derived from homozygous F508del CF donors (F508del/F508del-HBE) and Fisher rat thyroid (FRT) cells individually expressing normal CFTR, F508del-CFTR, or 31 mutant CFTR forms with defects in the amount and/or function of CFTR. *In vitro* assays performed using cultured HBE and FRT cell monolayers have been used to characterize other CFTR modulators that have demonstrated clinical benefit in people with CF, including IVA, and thus have precedent as non-clinical models to predict the potential for clinical benefit of CFTR modulation in people with CF. No *in vivo* pharmacology studies were conducted with TEZ either alone or in combination with IVA because pharmacologically validated CF animal models have not been established. Secondary pharmacodynamics (PD) studies were conducted to determine TEZ's spectrum of activity towards two closely related misfolded mutant proteins (HERG and Pgp) and to evaluate the potential for pharmacologically-mediated, off-target effects.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In an in vitro competition assay it was shown that tezacaftor indeed binds to the first membrane spanning domain (MSD1, aa 1-437) of CFTR. In addition, it was shown that tezacaftor selectively corrects CFTR as tezacaftor does not correct processing and trafficking of two other mutated and misfolded proteins from the ABC superfamily, G601S-hERG and G268V-PgP.

Due to the lack of an animal model system, in vivo non-clinical efficacy studies to show the activity potential of tezacaftor and/or ivacaftor were not conducted. Instead, two in vitro model systems were used, which is agreed. 1) Primary human bronchial epithelial cells, isolated form CF (double F508del) and non-CF lung explants. Efficacy of tezacaftor and/or ivacaftor in improving processing & trafficking and chloride transport of F508del CFTR was studied 2) FRT cells without background CFTR transfected with a (mutated) CFTR gene, using a single Flp-InTM genomic site. Efficacy of the tezacaftor and/or ivacaftor in improving processing & trafficking and chloride transport of each single CFTR was studied.

In vitro HBE model system

Tezacaftor was able to 'transform' a portion of the majority of immature F508del CFTR mutant to the 'mature' situation as recognized by an increase in molecular weight detectable on protein level on western blot. The ratio of mature/total was related to the amount of the ratio mature/total levels wildtype CFTR levels. The increase in the amount of mature CFTR also resulted in increased chloride transport. The increase in the ratio mature/total CFTR (from 20 to ~45% of normal CFTR) was not equally translated into an increase in chloride transport (from 2% to 8% of normal CFTR, see also section 2.1.4). This suggests that tezacaftor increased the amount of F508del, now correctly edited with oligosaccharides, on the membrane, but did not alter the chloride transport functionality of the mutated CFTR. Ivacaftor may be required to make the F508del CFTR, now present on the membrane, more capable to transport chloride.

Indeed, tezacaftor and ivacaftor both slightly increased the chloride transport by F508del CFTR but the combination of the two was more successful in increasing chloride transport than the sum of the effect of the two compounds separately in HBE cells. The height of the airway surface liquid and the ciliary beat frequency, two other functional parameters to demonstrate efficacy were also statistically significantly improved. The potency (EC50) of tezacaftor in combination with maximally effective concentration of ivacaftor is 0.6 µM and the potency of ivacaftor in the presence of a maximally effective concentration of tezacaftor is 0.006 µM. Addition of 20% human serum, mimicking human situation, shifted the EC50 for tezacaftor (in presence of ivacaftor) from 0.6 µM to 3 µM, and for ivacaftor (in presence of tezacaftor) was shifted from 0.006 µM to 0.013 µM. In addition to the shift in potency, efficacy (magnitude of response) of the combination of TEZ and IVA was improved.

In vitro FRT model system: Tezacaftor/Ivacaftor

The FRT system was used to analyse the effect of Tezacaftor and/or Izacaftor on processing and trafficking and chloride transport of normal CFTR, F508del-CFTR, a number of Residual Function (RF) mutants, splice mutants and a set of Kalydeco responsive gating mutants.

Tezacaftor is a CFTR corrector increasing the amount of CFTR channels on the cell surface. Ivacaftor a CFTR potentiator, increasing the chloride transport. The combined incubation of both drug substances in vitro, leads to an even higher increase in chloride transport. In vitro studies showed that the combination of tezacaftor/ivacaftor is more efficacious then the two drugs separately in increase of chloride transport for the F508del mutant, the RF mutants: E56K, P67L, R74W, D110E, D110H, R117C, E193K, L206W, R352Q, A455E, D579G, S945L, S977F, F1052V, K1060T, A1067T, R1070W, F1074L, D1152H, and D1270N, the Kalydeco responsive gating mutants: G178R, S549N, S549R, G551D, G551S, G1244E, S1251N, S1255P, G1349D and R117H. In vitro the efficacy the tezacaftor/ivacaftor combination for the splice mutants 711+3A->G, 2789+5G->A, 3272-26A->G, or 3849+10kbC->T and E381X was not investigated, but the tezacaftor/ivacaftor combination appeared to be effective for most of these mutants in the clinical study (108).

Secondary pharmacodynamic studies

In vitro off-target evaluation

Tezacaftor and ivacaftor were evaluated for potential off-target effects in a panel of 168 in vitro receptor, channel, and enzyme radioligand binding assays. Tezacaftor showed only significant binding affinity to the sodium channel Site 2 target receptor at concentrations below 10 µM (Ki = 6.6 µM). However, in a functional assay no significant binding to any of the NaV channels; NaV1.1, NaV1.3, NaV1.5, NaV1.7, and NaV1.8, could be determined. Based on Studies 106 and 107, a tezacaftor Cmax

of 6 mg/l is obtained under steady-state conditions when given 100 mg OD to CF patients. With >99% protein bound, the free tezacaftor C_{max} is 0.06 mg/ml, which equals to 0.11 µM. Thus, no secondary pharmacology effects of tezacaftor are anticipated in human. Ivacaftor appeared to stimulate the monoamine transporter and the serotonin receptor (5-HT2C) at sub-micromolar potency. Since ivacaftor has a low potency to cross the blood-brain-barrier, interaction with these targets was considered unlikely upon treatment of patients. Based on Studies 106 and 107, the ivacaftor C_{max} of 1.20 mg/l is obtained under steady-state conditions when given 150 mg OD. With >99% protein bound, the free ivacaftor C_{max} is 0.012 mg/ml, which equals 0.03 µM. Thus, no secondary pharmacology effects of Ivacaftor are anticipated in human.

Pharmacological activity of metabolites

Three tezacaftor metabolites are substantially present in human, M1, M2, and M5. In plasma, tezacaftor and its major circulating metabolites M1- tezacaftor, M2- tezacaftor and M5- tezacaftor accounted for 7%, 15%, 31% and 33% of AUC values of the total radioactivity, respectively. M3-TEZ accounted for 7% of the total radioactivity AUC. Of these, only M1-tezacaftor appears pharmacologically active. The potency of M1- tezacaftor and tezacaftor in the presence of continuous ivacaftor in Cultured F/F^{-} (F508del) HBE Cells were similar with EC_{50} values of 3.24 µM for M1-TEZ and 5.95 µM for TEZ.

Two ivacaftor metabolites are substantially present in human, M1 and M6. In plasma, ivacaftor and its major circulating metabolites M1- ivacaftor and M6- ivacaftor accounted for 12%, 66% and 21% of AUC_{inf}. Of these M1-ivacaftor was pharmacologically active with a 6-fold lower potency than ivacaftor. Mean EC_{50} value was 1.2 µM for M1-IVA and 0.2 µM for IVA.

Safety pharmacology programme

In vitro cardiac current channel testing

Tezacaftor (IC_{50} > 10 µM) and M2-Tezacaftor (IC_{50} > 200 µM) are not considered potent hERG inhibitors and as the clinical free fraction of tezacaftor is 0.11 µM, the hERG channel inhibition by tezacaftor is not regarded clinical relevant.

Ivacaftor inhibited hERG channel (IC_{15} of 5.5 µM), $Ca_v1.2$ (IC_{50} of 1.3 µM) and $K_v1.5$ (IC_{50} of3.4 µM). M6-ivacaftor (10 µM) showed only minimal inhibition of th$CA_v1.2$, hK_vLQT1/minK, and h$Na_v1.5$ (in CHO cells) or hERG and hKir2.1. As the unbound/ free fraction of ivacaftor in human serum is 0.03 µM, the inhibition of hERG and other channels influencing cardiac currents, is not regarded as clinical relevant.

In vivo safety pharmacology

Tezacaftor had no effect on CNS or respiratory function in Sprague Dawley rats dosed 0, 20, 60 or 200 mg/kg. Cardiovascular examination revealed increased ABP (17 to 25%) and decreased QT and QTc intervals (2 to 8%) between 6 to 14 hours after oral administration in 2/4 dogs dosed 250 mg/kg. Since in human, QTc effects were not noted, this observation is not regarded clinical relevant. Fasted Sprague Dawley Rats administered 100 or 200 mg/kg tezacaftor once daily by oral gavage for 4 days, showed significantly delayed gastric emptying of the charcoal test meal, but this effect was not observed in the clinical study.

Ivacaftor had no effect on CNS or respiratory function in Sprague Dawley. Cardiovascular examination revealed a dose-related, but transient increase in the ABP parameters (SBP, DBP, and MAP) at 60 minutes post dose, but was considered non-adverse due to the small magnitude and brief nature of the

response. Fasted Sprague Dawley Rats administered a single dose of 250, 500 or 1000 mg/kg ivacaftor showed statistical significant increases in stomach plus content weight and in GI transit time.

Overall, results from safety pharmacology studies evaluating tezacaftor and ivacaftor and of the secondary pharmacodynamic screening studies suggest a high degree of selectivity and a low potential to have biologically meaningful effects on vital function when tezacaftor and ivacaftor are administered in combination.

Pharmacodynamic drug interactions

Combination safety pharmacology studies involving the co-administration of TEZ and IVA were not performed as the studies conducted on each individual entity were considered adequate and provided no evidence for the potential of additive or synergistic interaction in any of the endpoints evaluated. This is acceptable to the CHMP.

2.3.3. Pharmacokinetics

The nonclinical pharmacokinetics (PK) characteristics of TEZ were investigated in a series of *in vitro* and *in vivo* studies. *In vivo* studies were conducted in CD-1 mice, CByB6F1 mice, Sprague Dawley rats, pigmented Long-Evans rats, New Zealand White rabbits, Golden Syrian hamsters, cynomolgus monkeys and Beagle dogs. With the exception of pigmented rats, hamsters and monkeys, *in vivo* PK parameters for TEZ were evaluated all in species and strains employed in nonclinical safety pharmacology and toxicity studies for TEZ. Most studies were non-GLP and used the oral route of administration, the intended therapeutic route in humans. A similar set of nonclinical PK studies were previously conducted with IVA in support of the development and registration of Kalydeco, and those considered pivotal to assessment of the combination regimen.

Methods of Analysis

Tezacaftor / Ivacaftor

The Applicant provided validation reports for the analytical methods used, demonstrating the suitability of the methods, storage and handling for the purpose of analysis of TEZ and its metabolites (M1-TEZ and M2-TEZ) and of IVA and its metabolites M1-IVA and M6-IVA. Specific and sensitive bioanalytical assays have been developed and validated for the quantitative determination of these compounds in rat, mouse, rabbit and dog plasma. In these methods, biological samples were extracted by liquid–liquid extraction (GLP studies) or by protein precipitation (non-GLP studies) and analysed by LC-MS/MS with stable isotope labeled analogues of the analytes used as internal standards. The assay reproducibility was demonstrated at least once per species / per assay using an incurred samples reanalysis approach during sample analysis. The radiochemical procedures (QWBA, LSC and radiometric detector attached to HPLC) used to detect ^{14}C-TEZ or ^{14}C-IVA and its metabolites ^{14}C-M1-IVA and ^{14}C-M6-IVA are adequate. The radiolabelled compounds are of sufficient chemical and radioactive purity.

Absorption

Tezacaftor

The in-vitro Caco-2 cell transmembrane permeability of tezacaftor is high. The efflux ratio of tezacaftor was greater than 2. Similarly, M1-TEZ exhibited high permeability with an efflux ratio of 0.8 while M2-TEZ exhibited low permeability with an efflux ratio of 3.4. The bidirectional permeability of tezacaftor across Caco-2 cells appears to be influenced by active transport processes. In the presence

of a Pgp inhibitor, the efflux ratio of TEZ but not that of M2-TEZ decreased, indicating that only TEZ is a substrate for Pgp. The permeability of M5-TEZ in MDCK-MDR1 and MDCK-WT cell lines was very low.

Systemic clearance following intravenous administration was lower than hepatic blood flow in mice, rats, dogs and monkeys (~4% - 15% of hepatic blood flow) and the intravenous elimination half-life of tezacaftor was shorter than that of oral administration.

Upon intravenous administration in cynomolgus monkey, tezacaftor demonstrated a low clearance (~4% of hepatic blood flow) and a moderate apparent volume of distribution. In monkeys, the volume of distribution of tezacaftor (0.66 L/kg) was equal to body water. In CF patient study 101, a larger apparent volume of distribution of tezacaftor (271 L) was found, i.e. larger than body water, after oral administration in fed state of TEZ 100 mg once daily in combination with IVA 150 mg every 12 hours.

In mice, after single oral administration, tezacaftor was well absorbed and exhibited low clearance (12.4 ml/min/kg) and a moderate volume of distribution (1.56 L/kg). After repeated administration, there was a decrease of the systemic exposure to tezacaftor in males and females, likely due to enzyme induction.

In rats, the pharmacokinetic pattern of tezacaftor followed a similar pattern as in mice. After single oral administration, tezacaftor was absorbed rapidly and good (53% bioavailability) and exhibited low clearance (7.21 ml/min) and a moderate volume of distribution (1.93 ml/min/kg). The increase in systemic exposure was dose-proportional over the dose range 9.25 to 203 mg/kg, and less than dose proportional at the 600 mg/kg dose level. The dose proportional increase in Cmax and AUC values over the dose range of 9.25 to 203 mg/kg and the consistent t1/2 estimates in the same range indicate linear kinetics in the disposition of TEZ from 9.25 to 203 mg/kg. After repeated administration in rats (7 day-, 1 month-, 3 month-, 6 month-, 12-mounth studies), the exposure of tezacaftor generally increased as the dose increased. The increase in exposure was dose proportional at lower dose levels from 20 to 200 mg/kg/day or 100 mg/kg/day, dependent on study duration, and was less than dose proportional at higher dose levels. No apparent accumulation of tezacaftor was observed, with the exception of the 52-week study at lower dose levels where 2-3 fold accumulation of tezacaftor was found. No meaningful sex-related differences were observed. In pregnant rats, the systemic exposure to tezacaftor was similar to non-pregnant rats at steady state.

Toxicokinetic studies were performed in pregnant and non-pregnant rabbits to assess the exposure to tezacaftor the rabbit reproduction toxicity studies. These 2-week studies showed that repeated administration led to a dose-related exposure to tezacaftor. There was some evidence of accumulation of tezacaftor and M1-TEZ, but of M2-TEZ, in pregnant rabbits.

In dogs, after single oral administration, tezacaftor was good absorbed (43% bioavailability) and exhibited a low clearance (1.95 ml/min/kg) and a low volume of distribution (0.48 L/kg). The increase in systemic exposure was dose-proportional over the tested dose range (3 to 300 mg/kg). After repeated administration in dogs (7-day-, 28-day-, 3-month-, 6-month- and 12-month studies) the exposure of tezacaftor, and the metabolites M1-TEZ or M2-TEZ, increased dose proportional in the tested dose range of 25 to 200 mg/kg/day. In general, no apparent accumulation was noted with tezacaftor or with the metabolites M1-TEZ or M2-TEZ. In addition, there was no evidence for sex difference or evidence for enzyme induction. The absorption of tezacaftor may be improved by the intake of food depending on the formulation used. In a 28-day investigative toxicity study in dogs, it was found that food increased the absorption of TEZ at a high dose level of 100 mg/kg 1.6 and 5 fold using respectively amorphous (spray dried dispersion) and micronized crystalline drug substance.

M2-TEZ, which is a major circulating metabolite in humans, was not formed to a significant amount in rats and dogs, the species of the pivotal toxicology studies. Therefore, M2-TEZ was dosed to rats and

dogs in separate studies. When M2-TEZ was administered subcutaneously at 500 mg/kg in male rats, the AUC0-∞ was 312 µg*h/mL but multiple dose treatment was stopped due to the adverse injection site reactions. When M2-TEZ was administered subcutaneously at 10 mg/kg to dogs, an AUC of 147 µg*h/mL was achieved. Intravenous administration of M2-TEZ to dogs resulted in systemic plasma clearance of 1.32 mL/min/kg. The volume of distribution at steady state was low and the T½ was moderate, with respective values of 0.44 L/kg and 8.0 hr.

Ivacaftor

Ivacaftor was orally rapidly absorbed in mice, rats, rabbits, and dogs, with the extent of absorption ranging from 30% to 100%. Apparent permeability of ivacaftor *in vitro*, using a Caco-2 cell-based assay, was high, which suggests that human intestinal absorption will be high following oral administration.

Ivacaftor and its major metabolite M6 are not a substrate for efflux protein P-gp, while its major metabolite M1 may inhibit P-gp.

Systemic exposure to ivacaftor tended to increase during repeat oral dosing at toxicological dose levels to mice, rats, rabbits and dogs, possibly due to accumulation of ivacaftor in plasma, and Tmax values increased with increasing dose levels, suggesting solubility limited absorption process. Therefore, a number of formulations studies were carried out in the preclinical phase to find an optimal formulation and dosage form.

Food improved the absorption of ivacaftor at a high dose at high dose level of 120 mg/kg; whereas, it was similar at a lower dosage of 10 mg/kg in suspension formulation.

Interspecies comparison of systemic exposure following oral dosing with ivacaftor showed that the systemic exposure to ivacaftor in males and females at the NOAEL dose level at the end of 6-month rat and 12-months dog studies is equivalent to approximately 16 and 20 times; and 12 and 9 times the exposure seen in humans at the proposed therapeutic dose, respectively.

Systemic clearance following intravenous administration was lower than hepatic blood flow in mice, rats, dogs and monkeys and the intravenous elimination half-life of ivacaftor was shorter than that of oral administration, suggesting exposure was limited by absorption.

Low clearance and high fraction absorbed led to high systemic exposure to ivacaftor in all species.

Tezacaftor/Ivacaftor combination

Systemic exposures to tezacaftor and ivacaftor in combination toxicity studies in rats (1 month and 3 months studies) and dogs (1 month study) were similar to the exposures observed when these compounds were dosed individually. In these combination toxicity studies, no relevant differences were observed in systemic exposures or peak plasma concentrations for tezacaftor, ivacaftor and metabolites. The exposure of tezacaftor and ivacaftor generally increased as the dose increased, and the increase in exposure was dose proportional at lower dose levels and was less than dose proportional at higher dose levels. In general, no accumulation of tezacaftor or M1-TEZ was noted. For ivacaftor, M1-IVA and M6-IVA some accumulation was evident in rats, whereas in dogs, some accumulation was observed in males, but not in females.

Distribution

Tezacaftor

Upon intravenous administration tezacaftor demonstrated a moderate volume of distribution. In beagle dogs and cynomolgus monkeys, the volume of distribution of tezacaftor (0.48 - 0.66 L/kg) was equal to body water and in mouse and rat (1.6 – 1.9 L/kg), it was about 2-fold higher than body water. In CF

patient study 101, a larger apparent volume of distribution of tezacaftor (271 L) was found, i.e. larger than body water, after oral administration in fed state of TEZ 100 mg once daily in combination with IVA 150 mg every 12 hours.

Protein binding of tezacaftor is high (>98%) plasma, and similar across species. M1-TEZ, M2-TEZ and M5-TEZ are also highly bound to plasma proteins and similar across species (>97.5%), except M2-TEZ which is less protein bound in mouse plasma (93.6%). These protein binding percentages were independent of concentration, indicating that no saturation of binding was evident up to 10 µM. The unbound fractions were low with minimal differences in percentages unbound across nonclinical species (1.4% - 2.0%) and human (0.9%). Human serum albumin is the major human plasma protein for tezacaftor, M1-TEZ, M2-TEZ and M5-TEZ binding, where whereas alpha-1-acid glycoprotein appears to play a minimal role.

In normal and pregnant rats, ^{14}C-tezacaftor-related material is rapidly distributed across all tissues, with detectable amounts noted in all tissues at 1 hour post dose. The gastrointestinal tract and liver showed the highest levels of radioactivity, at distance followed by the adrenal glands, pancreas, kidneys, heart and lungs. Lower levels were observed in the salivary glands, thyroid, mesenteric lymph nodes, spleen, prostate, thymus, fat, muscle, skin, and urinary bladder, followed by the testes and eyes. Lowest exposures were in the brain, indicating that tezacaftor does not readily cross the blood-brain-barrier. The tissue distribution of tezacaftor in pigmented rats was similar to that in albino rats, suggesting that tezacaftor does not bind to melanin containing tissues (skin, eyes).
The placental transfer was minimal and the exposures of tezacaftor in foetuses was low.

A study with unlabelled tezacaftor that studied the distribution of tezacaftor and M1-TEZ in the brain, lung, liver, kidney, pancreas, testes, fat, skin and spleen showed that the exposure to M1-TEZ in these tissues was up to two times higher than the exposure to tezacaftor. The tissue to plasma AUC ratio for tezacaftor was approximately 6.8 for the liver, 3.7 for the pancreas, 2.5 for the lung, and approximately 0.3 for the skin. For M1-TEZ, the tissue to plasma AUC ratio was highest in the liver (~8.7), and was ~5.3 for the lung, ~0.8 for the brain and ~0.2 in the skin.

Tezacaftor and M1-TEZ lung distribution was similar following single dose or multi-dose administration. A 7-day lung distribution study in rats showed that tezacaftor distributes more to the lung than to the plasma. Tezacaftor was detected in the plasma, lung, trachea, and bronchoalveolar lavage fluid at 2 hours post dose indicating that tezacaftor distributes to the respiratory tract and is excreted from the lung into the epithelial lining fluid. In the lung, the exposure of the lung to M1-TEZ was about 2.5 times greater than the exposure of tezacaftor to the lung, indicating that the retention of M1-TEZ was somewhat higher than of tezacaftor in lung tissue and plasma.

Tezacaftor and ivacaftor are not preferentially distributed into red blood cells.

Ivacaftor

Ivacaftor demonstrated a large apparent volume of distribution, indicative of a high penetration of these drugs into tissues. In cynomolgus monkey, the volume of distribution (0.69 L/kg) was greater than body water. In CF patient study 101, the apparent volume of distribution of ivacaftor was 206 L, after oral administration in fed state of IVA 150 mg every 12 hours in combination with TEZ 100 mg once daily.

Plasma protein binding of ivacaftor and its major metabolites (M1-IVA and M6-IVA) was greater than 98% *in vitro* in mouse, rat, dog, and human plasma and to isolated human plasma protein components. Human serum albumin was the main plasma component involved in the binding of ivacaftor or its metabolites in human plasma.

Ivacaftor was rapidly distributed across all tissues in rats. Tissues in the gastrointestinal tract showed highest ivacaftor exposure, followed by organs of eliminations (liver, kidney), organ of gland systems (adrenal, lymph nodes, pancreas, thyroid, thymus) and lungs. Lowest exposures were noted in the brain, eyes and testes. Ivacaftor was not bound to melanin containing tissues.

The ratio of ivacaftor levels to plasma were 3.80 and 0.939 for the lung and trachea, respectively. Thus, ivacaftor distributes more readily to the lung, trachea and lung epithelial lining fluid than to the plasma when administered orally to male rats. Furthermore, the ratio of the concentration of ivacaftor in the epithelial lining fluid to that in the plasma is 8.13, indicating substantial distribution of the compound to the lung and its excretion to the epithelial lining fluid.

Placental transfer of ivacaftor in rats and rabbits was minimal and the exposures to ivacaftor in foetuses were low. Ivacaftor accumulated in the milk of lactating rats.

Metabolism

Tezacaftor

In vivo metabolism of tezacaftor was investigated in ^{14}C-radiolabel studies in rats and dogs. In rats, main metabolism involved the formation of a dehydrogenation metabolite (M1-TEZ), a phosphate conjugate of M1-TEZ (M5-TEZ), and an oxidation metabolite of M1-TEZ (M2-TEZ). In plasma of rats, primarily unchanged tezacaftor, M1-TEZ (AUCinf 1.29-fold of tezacaftor) and M5-TEZ (AUCinf 0.75-fold of tezacaftor) were found. M2-TEZ was a major component in bile (approximately 25% of dose) but was low in plasma (0.05-fold of TEZ).
In dogs, metabolism mainly involved the formation of glucuronides of tezacaftor and M1-TEZ. In plasma, primarily unchanged tezacaftor, M3-TEZ (glucuronide of tezacaftor) and M12-TEZ (glucuronide of M1-TEZ) were found. M1-TEZ, M2-TEZ and M5-TEZ were low in dog plasma (<5% of total AUC). In bile, most of the radioactivity was associated with M3-TEZ and M11-TEZ (glucuronides of tezacaftor), and M12-TEZ and M13-TEZ (glucuronides of M1-TEZ).
Of the major circulating human metabolites (M1-TEZ, M2-TEZ and M5-TEZ), M1-TEZ and M5-TEZ were formed in significant amounts in rats but only to a low extent in dogs. In mice, the plasma exposure for M1-TEZ and M2-TEZ was 166% and 12.5% relative to TEZ, respectively. At steady state, the exposure to M1-TEZ and M2-TEZ was ~4.2 - 6.0x and ~0.24 - 0.40x relative to TEZ especially at the higher dose levels. As M2-TEZ was not formed to a significant amount in the preclinical species used for the toxicology studies, rats and dogs, M2-TEZ was dosed to rats and dogs in separate studies.

In vitro data indicate that CYP3A4 and CYP3A5 are the predominant cytochrome P450 enzymes involved in the metabolism of tezacaftor and also of M1-TEZ. M1-TEZ was the most abundant metabolite (besides the parent compound) following incubation with liver microsomes or hepatocytes from rat, dog, monkey and human. In the *in vivo* studies, M1-TEZ was also a major metabolite in rats and humans but not in dogs (monkeys were not studied *in vivo*). In dog liver microsome incubations, glucuronidated metabolites were major metabolites, as they were also in dog plasma in the *in vivo* study. However, glucuronidated metabolites M4a and M4b were apparently not detected to a relevant extent in the *in vivo* dog study. M5-TEZ, which is a major *in vivo* metabolite in rats and humans, was not formed in the *in vitro* studies in microsomes / hepatocytes of these species. M5-TEZ was relatively stable in human, dog and rat hepatocytes / liver microsomes. Minimal formation of M1-TEZ and M2-TEZ in these incubations indicate that some of the M5-TEZ (which is phosphorylated M1-TEZ) is converted back into M1-TEZ.

Ivacaftor

The metabolic profile of ivacaftor in both animals and humans are qualitatively similar. Following extensive metabolism, M1-IVA and M6-IVA were major circulating metabolites. M1 is pharmacologically

active metabolite (1/6th of the potency of ivacaftor) and M6 is not considered as an active metabolite (< 1/50th of the potency of ivacaftor). The metabolism of IVA was catalysed primarily by phase I oxidation (M1-IVA, M6-IVA), with minor contribution by phase II glucuronidation and sulfation (M1-IVA sulphate).

Based on *in vitro* data, human CYP3A4 and CYP3A5 are the predominant isozymes involved in the metabolism of ivacaftor and M1-IVA. M6-IVA was not metabolized *in vitro* by any of the human CYPs. *In vitro* inhibition studies suggest that ivacaftor and M1-IVA may have pharmacokinetic interactions with other drugs that are CYP2C8, CYP2C9, CYP3A or P-gp substrates.

The systemic exposure to M1-IVA was higher than to M6, with AUC0-24hr ratios of M1-IVA to ivacaftor ranging from 5% to 24% in mice, 6% to 34% in rats, and 7% to 25% in dogs versus AUC0-24hr ratios of M6-IVA to ivacaftor ranging from 1% to 7% in mice, 1% to 20% in rats and 2% to 10% in dogs. Both M1-IVA and M6-IVA demonstrated dose-limitations to achieving high exposures by intravenous administration in rats, since they are practically insoluble in an aqueous vehicle suitable for repeat-dose studies, and had moderate to high clearance. M1-IVA and M6-IVA had low exposures due to solubility-limited absorption after oral administration in rats in a 100% organic vehicle (PEG400).

Excretion

Tezacaftor

In intact rats, intact dogs and humans the main route of excretion of tezacaftor was via the faeces (75% - 79%, 58% and 72% of dose, respectively). Faecal excretion in intact dogs was relatively low probably due to liquid faeces in some of the animals as also a high amount in the cage rinse (18%) was found. Studies with bile duct cannulated (BDC) rats and dogs showed that large part of faecal excretion was due to excretion via the bile (53% and 50% of dose in orally dosed BDC rats and dogs respectively). Excretion via the urine was low, generally below 10% of dose in rats and dogs and 14% in humans.
In rats, total radioactivity in faeces was excreted primarily as unchanged tezacaftor and M2-TEZ and in bile primarily as M2-TEZ. In dogs, radioactivity in bile was excreted primarily as glucuronides of tezacaftor and of M1-TEZ.

Tezacaftor was excreted in milk of rats with a Cmax in milk of 1.5 times the Cmax in maternal plasma.

Ivacaftor

Faecal elimination is the predominant route of excretion in rat and humans. As the result of extensive metabolism, only 2.5% of the total radioactive dose of ivacaftor was excreted as unchanged parent in humans.

2.3.4. Toxicology

A set of toxicity studies has been conducted with TEZ to determine its toxicological profile. These studies are listed below. A similar set of studies was conducted previously for IVA to support the clinical development and registration of Kalydeco. Given that TEZ is being developed in combination with IVA, the GLP-compliant studies with IVA considered pivotal to the safety assessment of the proposed combination regimen.

Table 1 Repeat-Dose Toxicity Studies

Test Article	Species (Strain)	Study Type (Route)	No. of Animals/ Group	Doses (mg/kg/day)	GLP	References
TEZ	Mouse (CByB6F1)	28-Day[a, b] (gavage)	10/sex	250, 500, or 750	Yes	Report No. VX-661-TX-017
	Rat (Sprague-Dawley)	7-Day (gavage)	5/sex	30, 200, or 600	No	Report No. VRT-893661-TX-004
		28-Day (gavage)	10/sex, 5/sex (R)[c]	20, 60, or 200/100[d]	Yes	Report No. VRT-893661-TX-010
		28-Day (gavage)	5/sex	100 or 150	Yes	Report No. VX-661-TX-001
		3-Month (gavage)	10/sex 5/sex (R)[c]	25, 50, or 100	Yes	Report No. VX-661-TX-010
		6-Month (gavage)	10/sex, 5/sex (R)[c]	25, 50, or 100	Yes	Report No. VX-661-TX-012
		2-Year (gavage)	70/sex	M: 5, 15, or 50 F: 5, 20, or 75	Yes	Report No. VX-661-TX-020
	Dog (Beagle)	7-Day (gavage)	1/sex	10, 50, or 100	No	Report No. VRT-893661-TX-005
		28-Day (gavage)	3/sex, 2/sex (R)[c]	25, 75, 250	Yes	Report No. VRT-893661-TX-011
		28-Day (gavage)	6/sex	60	Yes	Report No. VX-661-TX-002
		28-Day (gavage)	6/sex	100 (fed), 250 (fasted)	Yes	Report No. VX-661-TX-015
		28-Day (gavage)	20/sex, 4/sex (R)[e]	100	Yes	Report No. VX-661-TX-022
		3-Month (gavage)	4/sex 2/sex (R)[c]	50, 150, 450	Yes	Report No. VX-661-TX-011
		3-Month (oral)	4/sex,	5, 25, 50	Yes	Report No. VX-661-TX-016
		6-Month (gavage)	4/sex	2, 10, 100, or 200	Yes	Report No. VX-661-TX-018
		12-Month (gavage)	4/sex	2, 10, 100, or 200	Yes	Report No. VX-661-TX-013
IVA	Rat (Sprague-Dawley)	6-Month (gavage)	15/sex 5/sex (R)[f]	50, 100, and 150	Yes	Report No. VX-770-TX-010
	Dog (Beagle)	12-Month (gavage)	4/sex (6-M) 4/sex (12-M) 4/sex (R)[g]	15, 30, or 60	Yes	Report No. VX-770-TX-011
TEZ and IVA[h]	Rat (Sprague-Dawley)	28-Day (gavage)	15/sex 5/sex (R)[f]	40/5, 60/10, 80/10, 100/100[h]	Yes	Report No. VX-661-TX-004
		3-Month (gavage)	15/sex 5/sex (R)[c]	20/80 40/40, 80/20[h]	Yes	Report No. VX-661-TX-014
	Dog (Beagle)	28-Day (gavage)	4/sex 2/sex (R)[c]	25/2.5, 25/5, 50/5, 100/60[h]	Yes	Report No. VX-661-TX-003

R: recovery; 6-M: 6-month; 12-M: 12-month

[a] 5-day preliminary tolerability study preceded the 28-day study; [b] Carcinogenicity dose-range-findings studies;

[c] Recovery animals included in design for control and high dose groups; [d] Dose reduced on Day 12 due to declining clinical condition and mortality; [e] Recovery animals included in design for control and TEZ-treated groups following 3, 6, 9, and 12 months; [f] Recovery animals included in design for all dose groups; [g] Two 1-month recovery periods (2/sex high dose group) following the 6- and 9-month sacrifices; [h] Combination toxicity studies involving co-administration of TEZ and IVA (TEZ/IVA doses)

Single dose toxicity

Single-dose toxicity studies were not conducted with TEZ in mice or rats, since they are no longer recommended in the ICH M3(R2) guidelines. TEZ was dosed at a single dose up to 2000 mg/kg in male and female mice in a micronucleus assay; the MTD was established at 2000 mg/kg. The single-dose or acute oral toxicity profile of IVA was previously established in GLP-compliant studies (in mice and rats) conducted in support of the registration of Kalydeco. While these studies are not considered pivotal to the safety assessment of the proposed combination regimen, the MTD in mice and rats was established at 2000 and 500 mg/kg, respectively. Thus, the acute oral toxicity of IVA was considered to be of low order, particularly considering the exposures achieved in these studies.

Repeat dose toxicity

Repeat dose oral toxicity studies were conducted in mice, rats and dogs to explore the toxic potential of TEZ following repeated oral exposure up to 52 weeks.

In both rats and dogs, decreased food consumption accompanied by a decrease in bodyweight gain was observed, especially in the first weeks of dosing. In addition, in rats a decrease in erythrocytic parameters and subsequent increase in circulating reticulocytes was observed. However, both these finding did not translate in clinical studies conducted with TEZ and IVA combined therapy. Also observed in both rats and dogs following repeated administration of TEZ was the microscopic finding of minimal to mild dilated lacteals in the villi tips of the duodenum, jejunum and/or ileum. Dilatation of lacteals was considered non-adverse by the applicant in all toxicity studies based on a lack of progression over time and severity of the finding. It should be noted that safety factors for this effect are low or absent: Tezacaftor exposures at the NOAEL in rats (50 mg/kg/day) and dogs (10 mg/kg/day), were 2.2-2.6 fold (rat) or 0.3–0.4 (dogs) fold times the expected exposure (steady-state AUC0-24hr) at the human therapeutic dosage. However, since there is an absence of TEZ-related clinical signs and/or clinical pathology findings that could be related to this effect, it can be concluded that dilated lacteals are unlikely to be relevant for humans.

Repeat-dose toxicity studies previously conducted in support of the registration of Kalydeco and ranging from sub-acute to chronic in duration identified the liver (mice and rats) as the only IVA-related target organ of toxicity. The mechanism of hepatotoxicity is believed to be a rodent-specific phenomenon and not relevant to humans.

Combination repeat-dose toxicity studies involving the co-administration of TEZ and IVA up to 3 months in duration in rats and 28 days in duration in dogs did not produce any unexpected toxicities or interactions. Noteworthy, test article-related microscopic findings in both rats and dogs were non-adverse minimal-to-mild dilated lacteals noted in the duodenum, jejunum, and/or ileum of the small intestine. This was also noted in the repeat-dose toxicity studies conducted with TEZ suggesting no additive or synergistic effects noted with the combination of TEZ/IVA for this finding.

Genotoxicity

The designs of the pivotal GLP-compliant genotoxicity studies evaluating the mutagenic and clastogenic potential of TEZ and those previously conducted for IVA to support registration of Kalydeco are presented in below.

Table 2 Genotoxicity Studies

Test Article	Assay	Test System	Doses	GLP	Reference
TEZ	Bacterial reverse mutation (Ames)	*S. typhimurium* (TA98, TA100, TA1535, and TA1537) *E. coli* (WP2*uvr*A)	1.5 - 5000 µg/plate ± S9 activation	Yes	Report No. VRT-893661-TX-007
	Chromosomal aberration	Chinese Hamster Ovary (CHO) cells	Up to 125 µg/mL 4 h ± S9 activation and 20 h -S9 exposures	Yes	Report No. VRT-893661-TX-008
	In vivo mammalian erythrocyte micronucleus	ICR mice, 5 males/dose level	Oral dosing 500, 1000, and 2000 mg/kg	Yes	Report No. VRT-899661-TX-003
IVA	Bacterial reverse mutation (Ames)	*S. typhimurium* (TA98, TA100, TA1535, and TA1537) *E. coli* (WP2*uvr*A)	1.5-5000 µg/plate ± S9 activation	Yes	Report No. VRT-813077-TX-003
	Chromosomal aberration	Chinese Hamster Ovary (CHO) cells	Up to 3924 µg/mL (10 mM) 4 h ± S9 activation and 20 h -S9 exposures	Yes	Report No. VRT-813077-TX-005
	In vivo mammalian erythrocyte micronucleus	ICR mice, 5 males/dose level	Oral dosing 500, 1000, and 2000 mg/kg[a]	Yes	Report No. VRT-813077-TX-006

[a] Twice daily dosing (250, 500, 1000 mg/kg/dose) separated by 3 h

Both TEZ and IVA were concluded to be negative for mutagenic and clastogenic potential when evaluated in the specified battery of genotoxicity studies. M2-TEZ was also concluded negative for mutagenic and clastogenic potential *in vitro*. Combination genotoxicity studies involving the co-administration of TEZ and IVA were not performed as the studies conducted on each individual entity were considered adequate for hazard identification and assessment of the genetic toxicity risk associated with co-administration.

Carcinogenicity

Tezacaftor was tested in a half year carcinogenicity study in mice and a two year carcinogenicity study in rats. In both studies, tezacaftor was dosed up to the maximum tolerated dose. In mice, minimal decreased body weight, decreased motor activity and hunched posture were observed. Hemangiocarcinoma was minimally significantly increased in males at low dose, but not at higher doses. Due to the lack of dose response, it is agreed that this effect can be considered not toxicologically significant. In addition, mainly non-neoplastic effects in the liver were observed, including, centrilobular hypertrophy which increased in severity over dose at all doses in males and high dose in females. In adrenal glands in males, minimal X-zone degeneration and adreno-cortical hypertrophy was observed. A decrease in corpora lutea was observed in females. In rats, body weight was decreased at high dose throughout the study in absence of a decrease in food consumption.

Benign cholangiomas were observed in 2/70 females at high dose and the increased incidence was statistically significant. However, there was an absence of tezacaftor-related bile duct proliferation and effects on the bile duct were also not observed in repeated dose studies in rat. Marginally and not significantly increased incidences were noted in a dose responsive manner for other tumour types, including malignant pheochromocytomas in males, malignant lymphomas in males, and pars distalis

carcinomas of the pituitary gland in females. Non-neoplastic legions included minimal to mild dilated lymphatics was observed in the ileum, GALT and to a lesser extent, jejunum.

Tezacaftor was not found to be carcinogenic in mouse and rat. Tezacaftor exposure was 1.1-1.8 and 2.1-3.9 fold exposure at the MRHD in human, for mice and rat, respectively. In rat, exposure to Tezacaftor + M1-TEZ was 2.2 and 3.8 fold exposure at MRHD for males and females, respectively.

Ivacaftor was tested in two year carcinogenicity studies in rats and in mice.

In both rat and mice, no neoplastic findings were attributed to ivacaftor. Non-neoplastic findings in the mouse included an increase of myofiber mineralization in the heart and skeletal muscle in females at high dose. This effect was considered to be non-adverse.

Ivacaftor was not found to be carcinogenic in both rat and mouse. At the highest dose tested, ivacaftor exposure was 5-9 and 21-39 fold exposure at the MRHD in human, for mice and rat, respectively.

Reproduction Toxicity

Table 3 Reproductive and Developmental Studies

Test Article	Study Type	Species (Strain)	No. of Animals/Group	Oral Doses (mg/kg/day)	GLP	Reference
TEZ	FEED	Rat (Sprague -Dawley)	25/sex	25, 50, or 100	Yes	Report No. VX-661-TX-021
	EFD[a]	Rat (Sprague -Dawley)	25 F	25, 50, or 100	Yes	Report No. VX-661-TX-008
		Rabbit (NZW)	22 F	10, 25, or 50	Yes	Report No. VX-661-TX-009
	PPND	Rat (Sprague -Dawley)	25 F	25, 50, or 100	Yes	Report No. VX-661-TX-023
IVA	FEED	Rat (Sprague -Dawley)	25/sex	50, 100, or 200	Yes	Report No. VX-770-TX-008
	EFD[b]	Rat (Sprague -Dawley)	25 F	50, 100, or 200	Yes	Report No. VX-770-TX-006
		Rabbit (NZW)	20 F	25, 50, or 100	Yes	Report No. VX-770-TX-007
	PPND	Rat (Sprague -Dawley)	25 F	50, 100, or 200	Yes	Report No. VX-770-TX-009
	Juvenile[b]	Rat (Sprague -Dawley)	20/sex	10, 25, or 50	Yes	Report No. VX-770-TX-025

EFD: embryo-fetal development; F: females; FEED: fertility and early embryonic development; PPND: pre- and postnatal development; NZW: New Zealand White
[a] TK evaluations in satellite rats or main study rabbits included in design for exposure to TEZ, M1-TEZ or IVA
[b] TK evaluations in satellite rats included in design for exposure to IVA and its metabolites (M1 and M6)

Fertility

Tezacaftor did not have an adverse effect on male or female fertility or early embryonic development in rats up to 2.6 fold exposure at the MRHD. At this dose, number of abnormal sperm was slightly increased, but did not affect male fertility and was within historical control.

Ivacaftor was associated with a decrease of overall fertility index and number of pregnancies in females, with significant reductions in number of corpora lutea and implantation sites with subsequent reductions in the average litter size and average number of viable embryos per litter. Ivacaftor was did not affect male fertility. In males significant weight decrease of the seminal vesicles without fluid was observed, but as no effects on male fertility could be determined this is not considered adverse. The ivacaftor margin of safety for female fertility is 0.6 times the MRHD.

Embryo-fetal development

The effect of tezacaftor on embryo-fetal development was tested in rat and rabbit. Maternal toxicity included decreases of body weight and food consumption during treatment, which was partially recovered after treatment in both species. In rat, no adverse effects on the fetus were observed. In the rabbit, at maternal toxic doses fetal weight was decreased. Exposure at the embryo fetal NOAEL was 3.1 and 0.2 fold exposure at MRHD in human, for rat and rabbit, respectively.

Ivacaftor was not teratogenic dosed orally to pregnant rats and rabbits during organogenesis. In rats, at moderate to severe maternal toxic doses, reductions of fetal body weight and increases in variations of skeletal development were observed, including cervical ribs, incompletely ossified ribs, wavy ribs and sternal irregularities. These variations are commonly observed in the presence of maternally toxic doses, and are therefore in this study not considered adverse. In rabbit, extreme maternal toxicity was observed at the high and mid dose tested, leading to morbidity and resulting in abortions and total litter loss. Exposure at the embryo fetal NOAEL was 15 fold exposure at MRHD in human, for both rat and rabbit.

Pre- and postnatal toxicity

In the pre- and postnatal study, tezacaftor induced maternal toxicity at mid and high dose. Due to severe toxicity, the high dose (100 mg/kg/day) was terminated early at lactation day (LD) 17/18 and one animal was euthanized in extremis at GD13 due to severe body weight loss and decreased food consumption. Maternal adverse effects included decreased body weight during gestation and lactation (up to -17%) and decreased food consumption at both mid (50 mg/kg/day) and high dose and thinness at high dose only. In addition at high dose, poor pup survival was observed. Pups showed clinical signs including decreased activity, thin appearance, skin cold to touch and skin discoloured purple in pups during lactation, pre-weaning developmental delays (pinna detachment, eye opening and static righting reflexes), sexual maturation delays (vaginal opening and preputial separation), effect on pup motor activity (increases in total distance travelled), and in F1 female animals lower corpora lutea counts, fewer uterine implantation sites and fewer viable embryos in the GD13 uterine fertility assessments were noted. In addition, at mid dose only, fertility index was low in female F1 animals and effects on oestrous cycle were observed. These effects were not observed at high dose, but cannot be excluded as a tezacaftor induced effect, as exposure at high dose was discontinued early and due to small number of litters at high dose for continuation of the study. The NOAEL for pre and post-natal toxicity and maternal toxicity was 25 mg/kg/day. Exposure at this dose is 0.9 fold exposure at the MRHD.

Ivacaftor exposure was associated with reductions of survival and lactation indices and decreased pup body weight in the pre- and postnatal development study. No developmental effects were observed at the NOAEL of 100 mg/kg/day, which corresponds to an exposure of 15 fold at the MRHD.

Juvenile toxicity

Juvenile toxicity studies have not been conducted with tezacaftor. A juvenile rat study was conducted for a previous application (Kalydeco) to support the treatment of young children less than two year of

age with ivacaftor. Cataracts were seen in juvenile rats dosed with ivacaftor from postnatal day 7 to 35 at dose levels of 10 mg/kg/day (0.12 times the recommend human dose) and higher. This finding has not been observed in older animals and its potential relevance in humans is unknown.

Toxicokinetic data

Toxicokinetic profile of TEZ was evaluated in the 3-month oral (tablet) repeat dose toxicity study.

Local Tolerance

Dermal and ocular local tolerance studies with tezacaftor were performed as part of a handler safety package to aid in setting worker protection levels during manufacture. Tezacaftor was predicted to be a dermal non-irritant in the EPIDERM assay and a mild eye irritant in vivo in the rabbit.

Other toxicity studies

Tezacaftor and ivacaftor were both negative for antigenicity in the murine local lymph node assay.

M2-TEZ subcutaneous repeat-dose toxicity was evaluated in rats and dogs up to 28 days. However, in rats, severe adverse injection site reactions were observed on day 1 and 2 in the middle- and high dose animals. Therefore, animals were necropsied on day 3. M2-TEZ was better tolerated in dogs and clinical observations were limited to the injection sites including epidermal erosion/ulcer and associated inflammation, oedema, and other dermal and/or subcutaneous findings. M2-TEZ was not found to be genotoxic in the Ames assay and chromosomal aberration assay in HPBL cells.

No dedicated genotoxicity tests have been performed for the metabolites M1-TEZ and M5-TEZ. In genotoxicity test S9 metabolic activation is expected to result in TEZ-M1 and TEZ-M5 exposure. Exposure of the M1-TEZ and M5-TEZ metabolites was at a sufficient level in the tezacaftor in vivo mouse chromosome aberration assay and tezacaftor mouse and rat carcinogenicity assays. All genotoxicity tests for tezacaftor were negative, and therefore M1-TEZ and M5-TEZ are also not considered genotoxic. As highest dose tested in the carcinogenicity studies was the MTD, these studies are considered sufficient for studying possible carcinogenicity of M1-TEZ and M5-TEZ.

Tezacaftor metabolite M2-TEZ was tested for embryo-fetal developmental toxicity in pregnant rabbits subcutaneously. The systemic exposure to M2-TEZ increased approximately 10-fold in rats and dogs when the compound was administered subcutaneously relative too orally. At doses with moderate to severe maternal toxicity (local tolerance, body weight gain and food consumption effects) no effects on fetal development or survival were observed. A large part of the observed maternal toxicity was due to adverse effects at the injection site. At the fetal NOAEL M2-TEZ exposure was 213 mg/kg/day, which is 1.8 fold of the exposure at the MRHD.

Impurities are considered toxicologically qualified based on in silico data generated by DEREK and SARAH or data of repeat dose toxicity studies in dog and rat. Four potential impurities (VRT-0826681, VRT-0909604, VRT-0910507, and VRT-0911436) were found negative for genotoxicity.

Tezacaftor was not found to be phototoxic in Balb/c 3T3 mouse fibroblasts.

2.3.5. Ecotoxicity / environmental risk assessment

Table 4 Summary of main study results for Tezacaftor

Substance (INN / Invented Name): Tezacaftor			
CAS-number (if available): 1152311-62-0			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	3.58	Potential PBT: N
PBT-statement :	The compound is not considered as PBT nor vPvB.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.0165	µg/L	> 0.01 threshold: Y
Other concerns (e.g. chemical class)			N

Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	733 L/kg (domestic sludge) 879 L/kg (domestic sludge) 957 L/kg (sandy loam) 920 L/kg (sandy loam) 1116 L/kg (clay)			Geometric mean for sludge: 851 L/kg Geometric mean for soil: 1013 L/kg
Ready Biodegradability Test	OECD 301	not available			not required
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,water}$ 26.9/16.5 d at 20°C $DT_{50,water}$ 57.4/35.2 d at 12°C $DT_{50,total\ system}$ 58.1/22.3 d at 20°C $DT_{50,total\ system}$ 124/48 d at 12°C			Tezacaftor is persistent in water
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	p.m.	µg/L	study report not available
Daphnia sp. Reproduction Test	OECD 211	NOEC	p.m.	µg/L	study report not available
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	p.m.	µg/L	study report not available
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥1000	µg/L	
Phase IIb Studies					
Bioaccumulation/*Species*	OECD 305	BCF	p.m.	L/kg	study report not available
Sediment dwelling organism/*Species*		NOEC	p.m.	mg/kg	study report not available

Table 5 Summary of main study results for Ivacaftor

Substance (INN/Invented Name): Ivafactor			
CAS-number (if available): 873054-44-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	>4.7	Potential PBT: Y
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	>4.7	
	BCF	not available	B/not B
Persistence	ready biodegradability	not available	
	DegT50	$DT_{50,\ system}$ = 1233/261 d (sandy silt loam sediment / sand sediment)	DT_{50} values corrected to 12°C. Conclusion: vP
Toxicity	NOEC algae NOEC crustacea NOEC fish	≥54.7 0.0031 ≥1000	T
	CMR	not investigated	potentially T
PBT-statement :	PBT assessment cannot be finalised.		

Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$	0.026	µg/L	> 0.01 threshold: Y; based on refined Fpen, Fpen refinement currently not acceptable.
Other concerns (e.g. chemical class)			N
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} =2710; 1970; 5900 L/kg	
Ready Biodegradability Test	OECD 301	not available	study not required
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50water}$ 1.7/4.4 d at 20°C $DT_{50water}$ 3.6/9.4 d at 12°C $DT_{50sediment}$ 1329/208 d at 20°C $DT_{50sediment}$ 2836/444 d at 12°C $DT_{50total\ system}$ 581/123 d at 20°C $DT_{50total\ system}$ 1233/261 d at 12°C % shifting to sediment >10%	Significant shifting to sediment observed. Ivacaftor is very persistent in sediment

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	≥54.7	µg/L	growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	3.1 p.m.	µg/L	

Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	p.m.	µg/L	report not available
Activated Sludge, Respiration Inhibition Test	OECD 209	EC10	>1000	µg/L	respiration
Phase IIb Studies					
Bioaccumulation/*Species*	OECD 305	BCF	not available	L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$	p.m.	d	report not available
Soil Micro-organisms: Nitrogen Transformation Test	OECD 216	NOEC	≥0.046	mg/ kg	endpoint potentially insufficient to exclude a risk to soil micro-organisms.
Terrestrial Plants, Growth Test	OECD 208	NOEC	≥1818	mg/ kg	
Earthworm, Acute Toxicity Tests/*Eisenia fetida*	OECD 207	NOEC	≥417	mg/ kg	
Collembola, Reproduction Test/*Folsomia candida*	ISO 11267	NOEC	≥690	mg/ kg	
Sediment dwelling organism/*Species*		NOEC	not available	mg/ kg	normalised to 10% o.c.

A study on bioaccumulation of ivacaftor is not available yet and the PBT assessment cannot be finalised in the current evaluation. Furthermore, the ivacaftor and the tezacaftor ERAs cannot be finalised for the STP, surface water, groundwater, sediment and terrestrial compartment because of the absence of relevant study reports.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for further investigation to be addressed:

- The final updated tezacaftor Phase II ERA report and the reports for the studies discussed should be submitted by 30 September 2018.
- The final updated ivacaftor Phase II ERA report and the reports for the studies discussed should be submitted by 31 March 2019.

2.3.6. Discussion on non-clinical aspects

The FRT system was used to analyse the effect of tezacaftor and/or ivacaftor on processing and trafficking and chloride transport of normal CFTR, F508del-CFTR, a number of RF mutants, splice mutants and a set of Kalydeco responsive gating mutants.

The combination of tezacaftor and ivacaftor is regarded effective *in vitro* when

(1) a statistically significant increase in chloride transport over baseline normal;

(2) a ≥10 pp increase in chloride transport over baseline as a percentage of normal CFTR;

(3) a statistically significant increase in chloride transport compared to treatment with ivacaftor alone, are demonstrated.

To include mutants in the indication based on *in vitro* data only, the applicant would have to convincingly demonstrate that the *in vitro* FRT model is valid. External validation of the model is not accepted. Van Goor and colleagues (2014) also characterised various missense mutations associated

with defects in protein processing or function in FRT cells. There were differences in the baseline values of mature CFTR values (expressed as % of normal CFTR) and of chloride transport (expressed as % of normal CFTR) compared to the data provided in the TEZ/IVA dossier. This may be caused by differences in design e.g. time of addition of the compound.

Furthermore, in addition to this experiment, CFTR mRNA expression in FRT cells was measured. The level of mature CFTR mRNA expression was generally similar between normal and most CFTR mutant forms tested with three exceptions: P47L-, E92K, and A455E-CFTR. The range in baseline chloride transport did not appear to be affected due to differences in CFTR mRNA levels or total protein levels (mature + immature) for most mutant CFTR forms, except for R117C-CFTR (38 ± 5% normal CFTR, being significantly lower) suggesting that the baseline level of chloride transport may be underestimated. In contrast, the estimated total protein levels for E193K-CFTR (177 ± 12% normal CFTR), R352Q-CFTR (178 ± 4% normal CFTR), and D1152H-CFTR (256 ± 16% normal CFTR) were higher compared with normal CFTR, suggesting that the baseline chloride transport may be overestimated by ~1.8 to 2.6 fold for these three mutant CFTR forms. In conclusion, given that Fischer Rat Thyroid (FRT) cells expressing the mutants of interest are proposed as a validated assay to predict possible clinical response in subjects carrying at least one of these mutations, the applicant was requested to describe the experimental conditions of the studies performed of Western Blot and Ussing chamber, including whether mRNA expression for each of the mutants has been quantified. A comparison versus the results published by Van Goor (2014) was also requested, including whether these results support the applicant proposed classification (i.e., functional defect is mainly protein processing, function or both).

As an overall conclusion of the response provided by the applicant, it would appear that the stably transfected FRT cell line is particularly useful for gathering information on the underlying defect of certain CFTR mutant proteins as they allow trans-epithelial ion transport and Western blot studies. However, their relevance of this for the *in vivo* situation is not fully established, given their non-human origin and the high levels of transfected CFTR expression in this system (see section 2.4). In addition, this system seems highly susceptible to the experimental conditions used (e.g. concentration of the test agents, acute versus chronic addition of the test agents, temperature etc). This has been shown by comparing the *in vitro* results available in the public domain in the same system versus the ones reported by the applicant. There seems to be an agreement between both sets of data in terms of which is the functional defect of each of the CFTR mutations considered for approval. However, some discrepancies arise, e.g. the magnitude of the changes observed for some specific mutations. The data presented are not reassuring of an *in vitro – in vivo* correlation and point to limitations of the FRT system to predict clinical efficacy. The scatterplots and clinical response in study 108 may only indicate that a cut-off would have been well chosen, but this could only be concluded in the presence of data on the 'negative' side of the cut-off. Therefore, there continues to be substantial degree of uncertainty over the sufficiency of the in vitro data based identification of on the FRT system to identify mutations using a panel of Fischer rat thyroid (FRT) cells for inclusion within the scope of the indication.

Thus, considering the lack of a multi-pronged approach for the identification of patients with genotypes suitable for treatment, the *in vitro* model used is not sufficiently reliable to predict a clear clinical efficacy in patients with mutations where clinical date are missing.

As a result of these considerations, the indication of Symkevi was restricted to those mutations, where clinical data from patients were presented. In addition, the Kalydeco responsive mutants, were also retracted from the indication, due to the negative clinical data observed in a clinical trial, please refer to section 2.5 for detailed discussion.

In the rat 2-year carcinogenicity study for tezacaftor, the incidence of pars distalis carcinoma in the pituitary gland in female rats was below historical control data. Benign cholangiomas in females, malignant pheochromocytomas in males, and malignant lymphomas in males occurred slightly above historical control. However, as the incidence of these findings was low or considered to be specific to rat as per the published literature, these effects are not relevant for the use in humans. Juvenile toxicity studies have not been conducted with tezacaftor, as the applicant states they are not required to support the current proposed indication for treatment of patients of 12 year and older. This is in line with the guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric use (EMEA/CHMP/SWP/169215/2005), as there are no suggestions that tezacaftor has an effect on the CNS, reproductive organs or bone growth. Based on available data from toxicity studies, it is not expected that tezacaftor is potentially immunotoxic, or that it will have an effect on dependence.

There were no human specific metabolites identified. However, the exposure safety margins of TEZ and IVA metabolite (M1-TEZ, M2-TEZ, M1-IVA and M6-IVA) at the NOAEL in repeat dose toxicity studies were low in some instances. Clinical experience, including placebo-controlled and long-term safety data from TEZ/IVA clinical studies and the established safety profile of ivacaftor, have demonstrated lack of translatability of adverse non-clinical findings. Therefore, the exposure-based margins are considered adequate for the proposed clinical use.

As for the environmental risk assessment, both, tezacaftor and ivacaftor ERA studies were not completed but the applicant agreed to conduct further tests and submit their results post-authorisation.

2.3.7. Conclusion on the non-clinical aspects

In the pharmacodynamic investigation of tezacaftor monotherapy and TEZ/IVA combination, tezacaftor/ivacaftor showed a consistent positive effect on sweat chloride in the investigated subjects with CF homozygous for F508del or heterozygous F508del/G551D or heterozygous for *F508del* and a residual function mutation (F/RF). The pharmacokinetics of tezacaftor and ivacaftor has been investigated to a reasonable degree. However, a number of concerns remain to be resolved via post-authorisation measures and the CHMP considers the following measures necessary to address the non-clinical issues and these have been committed to by the applicant in a letter of recommendation:

- The final updated tezacaftor Phase II ERA report along with final the reports for the ERA studies.
- Results from an in vitro study to evaluate the potential induction of CYP2B6 by M1-TEZ and of CYP1A2 and CYP2B6 by M2-TEZ.
- Results from in vitro studies to investigate the inhibitory effect of TEZ and its metabolites on OCT1 (SLC22A1), MATE1 (SLC47A1), MATE2 (SLC47A), and BSEP (ABCB11).
- Results from in vitro studies to investigate whether IVA and its metabolites are substrates for BCRP.
- Results from an in vivo study to investigate the potential DDI between TEZ/IVA and an OATP1B1 substrate.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 6 Completed and Ongoing Tezacaftor / Ivacaftor Clinical Studies

Study Identifier; Type of Study; Study Status/ Location of Report	Study Design and Type of Control	Objective(s) of the Study	Test Product(s); Dosage Regimen; Route of Administration	Duration of Treatment	Number of Subjects Dosed; Healthy Subjects or Diagnosis of Patients
Biopharmaceutic Studies					
Comparative Bioavailability and Bioequivalence Studies					
VX13-661-004 Phase 1 Completed	Randomized, open-label	Relative BA and food effect of FDC tablet	**TEZ** 50-mg tablet **IVA** 150-mg tablet **TEZ/IVA** TEZ 50-mg/IVA 150-mg FDC tablet TEZ 50 mg and IVA 150 mg, as FDC or separate tablets Oral	Single dose on 3 dosing occasions	18 healthy subjects
Human PK Studies					
Healthy Subject PK and Initial Tolerability Studies					
VX10-661-001 Phase 1 Completed	FIH, randomized, double-blind, SAD and MAD, placebo-controlled	**Part A** Evaluate safety and PK of SAD **Part B** BA of TEZ tablet relative to solution and food effect on PK of tablet **Part C** Define safety and PK of MAD	**TEZ** solution or 50-mg or 100-mg tablet **Part A** TEZ 50, 100, 200, or 300 mg; or matching placebo **Part B** TEZ 100 mg **Part C** TEZ 50, 100, or 200 mg qd; or matching placebo Oral	**Part A** 1 single dose **Part B** 4 single doses **Part C** 28 days	85 total healthy subjects **Part A** 33 subjects **Part B** 16 subjects **Part C** 36 subjects
VX13-661-005 Phase 1 Completed	Open-label	Evaluate PK, ADME	**TEZ** 100 mg/100 µCi ^{14}C-TEZ solution Oral	Single dose	6 healthy subjects
Intrinsic Factor PK Studies					
VX15-661-009 Phase 1 Completed	Open-label	Evaluate the PK and safety of TEZ/IVA and their metabolites in subjects with moderate hepatic impairment compared to matched healthy subjects	**TEZ** 50-mg film-coated tablet **IVA** 150-mg film-coated tablet TEZ 50 mg qd IVA 150 mg qd Oral	10 days	24 subjects total **Cohort 1** 12 subjects with moderate hepatic impairment **Cohort 2** 12 matched healthy subjects
Extrinsic Factor PK Studies					
VX14-661-006 Phase 1 Completed	Open-label	**Cohort 1** Assess the effect of itraconazole (strong CYP3A inhibitor) on PK of TEZ/IVA metabolites **Cohort 2** Evaluate the effect of TEZ/IVA on midazolam and digoxin (probe substrates of CYP3A and P-gp)	**TEZ** 25-mg film-coated tablet **IVA** 50-mg or 150-mg film-coated tablet **TEZ/IVA** TEZ 100-mg/IVA 150-mg film-coated FDC tablet **Cohort 1** TEZ 25 mg qd IVA 50 mg qd Itraconazole 200 mg qd for 5 days **Cohort 2** TEZ 100 mg qd IVA 150 mg q12h Single dose Midazolam 2 mg on 2 dosing occasions Single dose Digoxin 0.5 mg on 2 dosing occasions Oral	**Cohort 1** 28 days **Cohort 2** 19 days	34 healthy subjects
VX15-661-008 Phase 1 Completed	Open-label, 2-period, 1-way crossover	Evaluate the DDI between TEZ/IVA and oral contraceptive	**TEZ/IVA** TEZ 100-mg/IVA 150-mg FDC film-coated tablet **IVA** 150-mg film-coated tablet TEZ 100 mg qd/IVA 150 mg q12h ORTHO-NOVUM 1/35 (EE 35 µg/NE 1000 µg) qd Oral	56 days total (28 days TEZ/IVA)	25 healthy female subjects of childbearing potential
Human PD Studies					
Healthy Subject PD and PK/PD Studies					
VX15-661-010	Randomized,	Evaluate the effect of TEZ on	**TEZ** 50-mg tablets	**Part A**	116 healthy subjects

Phase 1 Completed	placebo- and active-controlled, double-blind, parallel ECG study	QT/QTc interval	**Part A** Cohort 1 TEZ 200 mg qd or matching placebo Cohort 2 TEZ 300 mg qd or matching placebo **Part B** Cohort A TEZ 100 mg qd Days 1 through 7; TEZ 300 mg qd Days 8 through 14 Cohort B Single dose 400 mg moxifloxacin on Day 1 Cohort C Single dose 400 mg moxifloxacin on Day 15 All cohorts received VX-661- and moxifloxacin-matching placebos as appropriate to maintain the blind Oral	7 days **Part B** 16 days total Cohort A 14 days TEZ	
Patient PD and PK/PD Studies					
VX11-661-101 Phase 2 Completed	Randomized, double-blind, placebo-controlled, dose ranging	Safety, PK, PD, and efficacy of TEZ monotherapy and TEZ/IVA	**TEZ** 10- or 50-mg tablet **IVA** 50-, 100-, or 150-mg tablet **Groups 1, 2a, 3a, 5a** TEZ 10, 30, 100, or 150 mg qd; or matching placebo **Groups 2b, 3b, 4, 5b, 6a** TEZ 10, 30, 100, or 150 mg qd; and IVA 50 or 150 mg q12h; or matching placebo **Group 6d** TEZ 50 mg q12h; and	28 days	190 subjects with CF, aged 18 years and older, homozygous for *F508del* or aged 12 years and older, heterozygous for *F508del/G551D*
			IVA 150 mg q12h; or matching placebo **Group 7** TEZ 100 mg qd and physician-prescribed Kalydeco 150 mg q12h Groups 6b, 6c, and 8 not enrolled Oral		
Efficacy and Safety Studies					
Controlled Clinical Studies Pertinent to the Claimed Indication					
VX13-661-103 Phase 2 Completed	Randomized, double-blind, placebo-controlled; open-label extension	Evaluate safety of TEZ/IVA, dose confirming for Phase 3	**TEZ** 50-mg tablet **IVA** 150-mg film-coated tablet **Group 1** TEZ 50 mg q12h and IVA 150 mg q12h; or matching placebo **Group 2** TEZ 100 mg qd and IVA 150 mg q12h; or matching placebo **OLE Phase** TEZ 100 mg qd IVA 150 mg q12h Oral	**Placebo-controlled Phase** 12 weeks **OLE Phase** 40 weeks	67 total subjects with CF, 18 years and older, homozygous for *F508del* **Placebo-controlled Phase** 40 subjects **OLE Phase** 27 subjects
VX14-661-106 Phase 3 Completed	Randomized, double-blind, placebo-controlled, parallel-group	Pivotal efficacy, safety, and PK	**TEZ/IVA** TEZ 100-mg/IVA 150-mg FDC film-coated tablet **IVA** 150-mg film-coated tablet TEZ 100 mg qd/IVA 150 mg q12h or matching placebo Oral	24 weeks	509 subjects with CF, aged 12 years and older, homozygous for *F508del*
VX14-661-107	Randomized, double-blind, placebo-controlled, parallel-	Evaluate efficacy, safety, and PK	**TEZ/IVA** TEZ 100-mg/IVA 150-mg FDC film-coated tablet **IVA** 150-mg film-coated tablet	Approximately 12 weeks	168 subjects with CF, aged 12 years and older, heterozygous for *F508del*
VX14-661-108 Phase 3 Completed	Randomized, double-blind, placebo-controlled, crossover	Pivotal efficacy, safety, and PK	**TEZ/IVA** TEZ 100-mg/IVA 150-mg FDC film-coated tablet **IVA** 150-mg film-coated tablet TEZ 100 mg qd/IVA 150 mg q12h; or IVA 150 mg q12h; or matching placebo Oral	16 weeks total: Two 8-week treatment periods, with a washout of 8 weeks between each treatment period	248 subjects with CF, aged 12 years and older, with *F508del*/RF mutations

Uncontrolled Clinical Studies					
VX14-661-110 Phase 3 Ongoing	Open-label, rollover	Evaluate long-term safety and efficacy	**TEZ/IVA** TEZ 100-mg/IVA 150-mg FDC film-coated tablet **IVA** 150-mg film-coated tablet **Treatment Cohort** TEZ 100 mg qd/IVA 150 mg q12h Oral **Observational Cohort** No study drug administered	Approximately 96 weeks	Approximately 1375 subjects potentially eligible Subjects with CF, homozygous or heterozygous for *F508del* **Treatment Cohort** Subjects 12 years of age and older **Observational Cohort** Subjects <18 years of age
Other Studies					
Extrinsic Factor PK Studies					
VX13-770-017 Phase 1 Completed	Open-label	To evaluate the DDI effects of ciprofloxacin on IVA and on TEZ/IVA; safety and tolerability	**IVA** 150-mg tablet **TEZ** 50-mg tablet **Cohort 1** IVA 150 mg q12h; ciprofloxacin 750 mg q12h **Cohort 2** TEZ 50 mg q12h; IVA 150 mg q12h; ciprofloxacin	**Cohort 1** 14 days **Cohort 2** 20 days	34 healthy subjects

With the response to the CHMP's request, the applicant submitted results and study report of Study VX14-661-109.

Table 7

Ongoing Controlled clinical study					
Study VX14-661-109 Phase 3	Randomized, double-blind, active-controlled	Evaluating efficacy and safety of TEZ/IVA and PK of TEZ, M1-TEZ, IVA, and M1-IVA	TEZ 100 mg qd/IVA 150 mg q12h IVA 150 mg q12h	12 weeks	156 subjects with CF ≥12 years old F/gating genotype

2.4.2. Pharmacokinetics

The pharmacokinetics of tezacaftor (and ivacaftor in combination with tezacaftor) as well as its major metabolites were investigated in both, healthy subjects and CF patients. Studies in healthy subjects were performed to understand dose-proportionality, effect of food on exposure, bioavailability from different formulations, absorption, distribution, metabolism, and excretion (ADME) characteristics, DDI potential of tezacaftor/ivacaftor as CYP3A substrate and a potential CYP3A and P-gp inhibitor, DDI with oral contraceptives, effect of moderate hepatic impairment on PK of tezacaftor/ivacaftor and effect of tezacaftor on the ECG QT interval. Further PK data were obtained from two Phase 2 studies and three Phase 3 studies to assess the effects of demographic characteristics and other covariates on tezacaftor/ivacaftor PK and to characterize the exposure-response relationships (population PK [popPK] and PK/PD).

Both tezacaftor as ivacaftor were analysed using liquid chromatography with MS detection. In general, analytical methods for tezacaftor and its metabolites as well as for ivacaftor and its metabolites were validated with respect to accuracy, specificity and stability. Standard non-compartmental analyses methods were used to determine PK parameters in studies where intensive sampling was conducted (mainly Phase 1 studies). The potential drug-drug interaction between the moderate CYP3A4 inhibitor fluconazole or the mild CYP3A4 inhibitor ciprofloxacin and tezacaftor were simulated using a PBPK model.

Absorption

After administration of the tezacaftor/ivacaftor fixed dose combination (FDC) under fed conditions, maximum plasma concentrations for tezacaftor and ivacaftor were obtained after approximately 4 (2-8) hours and 6 (3-10) hours, respectively. Based on interstudy comparisons, exposure between the tezacaftor/ivacaftor FDC and separate tezacaftor and ivacaftor tablets under steady-state conditions was comparable.

Food was shown to have no relevant effect on exposure to tezacaftor. The known food-effect of ivacaftor (3-fold increased AUC_{inf}, 4-fold increased C_{max}) was confirmed. As a result of the food-effect for ivacaftor, the FDC formulation is recommended to be administered with food.

Distribution

In vitro, both protein binding of tezacaftor, M1-tezacaftor, M2-tezacaftor, and M5-tezacaftor as well as that of ivacaftor, M1-ivacaftor, and M6-ivacaftor is high in human plasma, with approximately 99% bound to plasma proteins. Tezacaftor primarily binds to albumin and ivacaftor primarily to alpha 1-acid glycoprotein and albumin. After oral administration of tezacaftor 100 mg once daily in combination with ivacaftor 150 mg every 12 hours in patients with CF in the fed state, the mean range for apparent volume of distribution of tezacaftor and ivacaftor was approximately 270-300 L and 206-220 L, respectively. Neither tezacaftor nor ivacaftor partition preferentially into human red blood cells.

Tezacaftor is metabolized extensively in humans. *In vitro* data indicate that tezacaftor and M1-tezacaftor are metabolized mainly by CYP3A4 and CYP3A5. Following oral administration of a single dose of 100 mg ^{14}C-tezacaftor to healthy male subjects, M1-TEZ, M2-TEZ, and M5-TEZ were the 3 major circulating metabolites of tezacaftor in humans (contributing to 15%, 31%, and 33% of total radioactivity, respectively). Tezacaftor represents 7% of total radioactivity. M1-TEZ has similar potency to that of tezacaftor and is considered pharmacologically active. M2-TEZ is much less pharmacologically active than tezacaftor or M1-TEZ, and M5-TEZ is not considered pharmacologically active. A minor circulating metabolite, M3-TEZ, is formed by direct glucuronidation of tezacaftor.

It is known that ivacaftor is also metabolized extensively in humans. *In vitro* and *in vivo* data indicate that ivacaftor is metabolized primarily by CYP3A4 and CYP3A5. M1-IVA and M6-IVA are the two major metabolites of ivacaftor in humans. M1-IVA has approximately one-sixth the potency of ivacaftor and is considered pharmacologically active. M6-IVA is not considered pharmacologically active.

Elimination

After single dose administration of 100 mg tezacaftor in healthy volunteers, the mean elimination half-lives for unchanged TEZ, M1-TEZ, M2-TEZ and M5-TEZ were similar and ranged from 109 to 122 h after single dose administration. In the CF patient study 101, tezacaftor clearance under steady-state conditions in CF patients was 1.31 (0.41) l/h, and its elimination half-life was 156 (52.7) h. The $t_{1/2}$ for M1-661 and M2-661 under steady state conditions were 128 (39.5) h and 129 (26.7) h, respectively.

In a mass balance study, a mean of 72.2% of the radioactive TEZ dose was recovered in faeces and 13.7% was recovered in urine through the last collection interval, resulting in a mean overall recovery of 85.9%. Tezacaftor is therefore mainly eliminated via the faeces, either as parent compound (34%) or as M2-TEZ (26% of the administered dose). Renal excretion accounts for approximately 13% of the administered dose (10% as M2-TEZ and 2.5% as M3-TEZ). Less than 1% of the dose is excreted as

parent compound via the urine. These results indicate that the majority of tezacaftor is excreted from the body via faeces following oral administration.

In the CF patient Study 101, ivacaftor clearance under steady-state conditions was 15.7 (6.38) l/h, and its elimination half-life was 9.3 (1.72) h. The $t_{1/2}$ for M1-IVA and M6-IVA were 11.3 (2.12) h and 14.4 (6.14) h, respectively. From the original dossier, it is known that ivacaftor is mainly eliminated as metabolites via the faeces, with negligible renal excretion as parent compound.

Pharmacokinetics of TEZ metabolites has been investigated to a reasonable extent. TEZ metabolites M1-TEZ, M2-TEZ and M5-TEZ have a $t_{1/2}$ that is comparable to that of TEZ. Under steady-state, for each of the metabolites, exposure to M1-TEZ, M2-TEZ and M5-TEZ is approximately 1.5-fold higher than for TEZ.

Dose proportionality and time dependencies

Exposure to tezacaftor (administered alone or in combination with ivacaftor) increase in an approximately dose-proportional manner with increasing doses from 10 mg to 300 mg once daily. The pharmacokinetics of ivacaftor are generally linear with respect to time or dose ranging from 25 mg to 250 mg (Kalydeco SmPC). Considering the lack of relevant PK interaction between ivacaftor and tezacaftor, this is expected also to be the case when given combination with tezacaftor.

The accumulation ratio of 1.5-3 for tezacaftor when given once daily is in line with the $t_{1/2}$ of approximately 155 h. Accumulation ratio's for the tezacaftor metabolites are higher (ranging from 2.9 to 18 for the different metabolites), since t_{max} for these metabolites is later than for tezacaftor (12-72 hours), with comparable $t_{1/2}$ of approximately 130 hours. For this reason, the relative amount of tezacaftor metabolites increases under steady state conditions as compared to single dose, exposure being approximately 1.5 higher than that of tezacaftor.

Special populations

Renal impairment: Renal clearance is likely to play a minimal role in the elimination of TEZ and IVA, and therefore no dose adjustment is necessary for patients with mild to moderate renal impairment. In the absence of clinical data, caution is recommended when administering TEZ and IVA combination therapy to patients with severe renal impairment (creatinine clearance less than or equal to 15 to 29 mL/min) or with end-stage renal disease.

Hepatic impairment: Based on results from Study 009, which showed higher exposure of TEZ (36% for AUC, 20% based on the total increase in active TEZ/TEZ-M1 exposure) and IVA (52% for AUC) in subjects with moderate hepatic impairment, the Applicant proposes that the dose for patients with moderate hepatic impairment (Child-Pugh Class B) should be reduced to 1 TEZ 100 mg/IVA 150 mg tablet once daily. The evening dose of 150 mg IVA should not be taken. With respect to IVA, the proposed dose is in line with the dose advised for IVA as single agent. Despite the fact that data obtained with TEZ/IVA in moderate hepatically impaired patients would support the lack of a dose advice in case of moderate hepatic impairment, considering the therapeutic window of +/-50%, the dose advice is accepted to be aligned with that of IVA given as singe agent, for which additional data with a stronger effect of hepatic impairment are available. No dose adjustment for TEZ and IVA is needed in case of mild hepatic impairment.

Gender, race and weight: No relevant difference in exposure between gender was noted, whereas the effect of race could not be evaluated, since only a very small number of non-white patients was

included in the clinical studies, 97.6% of subjects being White. No major differences in exposure were noted comparing the TEZ AUC in non-White patients with that in White patients. However, information on different races is considered to be very limited, as also reflected in the SmPC. TEZ exposure in different (high and low) weight categories are considered to be within the therapeutic range, and no clinically relevant effects on efficacy or safety are expected.

Age: Only a low number of elderly patients 65-74 years of age (6 patients) were included in the clinical studies conducted for TEZ/IVA. Overall, age does not appear to be a relevant covariate in the pop-PK study.

Pharmacokinetic interaction studies

Substrate in vitro:. Based on *in vitro* data, CYP3A4/5 are the main CYP isoforms involved in TEZ and IVA metabolism. Co-administration with CYP3A4/5 inhibitors or inducers may therefore result in change in TEZ and IVA exposure. With regard to drug transporters, *in vitro*, TEZ is a substrate for the uptake transporter OATP1B1 as well as for efflux transporters P-gp and BCRP. TEZ is no substrate for OATP1B3. M1-TEZ is substrate for P-gp. However, exposure to TEZ is not expected to be affected significantly by concomitant inhibitors of OATP1B1, P-gp, or BCRP due to its high intrinsic permeability and low likelihood of being excreted intact.

Inhibition/induction in vitro: Based on *in vitro* data, TEZ and its metabolites are predicted not to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 and they are not expected to induce CYP1A2, CYP2B6 and CYP3A4. With regard to drug transporters, TEZ does not inhibit transporters P-gp, BCRP, OATP1B3, OCT1, OCT2, OAT1, or OAT3. Only limited inhibition of OATP1B1 (IC_{50} 3.2 µM) was observed *in vitro*. Based on *in vitro* data, IVA has the potential to inhibit CYP2C8, CYP2C9 and P-gp. No induction was noted by IVA and its metabolites. *In vitro* studies showed that IVA is not a substrate for OATP1B1, OATP1B3, or P-gp.

Effect of co-administered drugs on tezacaftor/ivacaftor in vivo: In vivo, co-administration of strong CYP3A inhibitor itraconazole caused a substantial increase in the exposure of TEZ (4-fold) and IVA (16 fold) when administered in combination. Therefore, a reduction in the dose of TEZ and IVA combination therapy is recommended for co-administration with strong CYP3A inhibitors.

Using a PBPK model, the effect of a moderate CYP3A4 inhibitors fluconazole, verapamil and erythromycin on TEZ exposure was investigated. The PBPK model is considered sufficiently validated, comparing simulated exposure data with actual TEZ exposure data with or without itraconazole and ciprofloxacin. Based on the results of these PBPK analyses, in the presence of a moderate CYP3A4 inhibitors (e.g., fluconazole, verapamil, erythromycin), TEZ steady-state AUC and C_{max} are predicted to increase 2.1-fold and 1.7-fold with fluconazole, 1.7- and 1.4-fold with verapamil and 2.6- and 2.0-fold with erythromycin, respectively.

Further, PBPK simulations with the proposed dose in the presence of moderate inhibitors of CYP3A4 (100 mg TEZ every other day), sufficiently assure adequate exposure to TEZ in the presence of these 3 different moderate inhibitors of CYP3A4.

In IVA study 770-010, multiple-dose co-administration of IVA and moderate CYP3A4 inhibitor fluconazole increased IVA exposure approximately 3-fold and increased M1-IVA exposure approximately 2-fold. These results indicate that fluconazole would cause a clinically relevant increase in TEZ and IVA exposures. Therefore, a reduction in the dose of TEZ and IVA combination therapy is recommended for co-administration with moderate CYP3A inhibitors. For ivacaftor, the dose reduction was already known from the Kalydeco dossier. In case of co-administration of the CYP3A4 inhibitor

ciprofloxacin, no clinically relevant increase was noted for TEZ and IVA. Therefore, no dose adjustment is needed upon ciprofloxacin co-medication.

Co-administration of the strong CYP3A inducer rifampicin substantially decreased IVA exposure (Study 770-009), which is consistent with IVA being a sensitive CYP3A substrate. Although not investigated, TEZ exposure would also be expected to decrease with co-administration of strong CYP3A inducers, although it is not a sensitive CYP3A substrate based on the smaller (<5-fold) effect of itraconazole on TEZ compared to IVA. Nevertheless, co-administration of medicinal products that strongly induce CYP3A (e.g., rifampicin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort) with the combination of TEZ and IVA are not recommended as they may decrease the IVA and TEZ exposures and limit the effectiveness of the combination. These recommendations are consistent with the labelling for IVA monotherapy.

Effect of TEZ/IVA on co-administered drugs in vivo. Administration of TEZ/IVA did not have a clinically relevant effect on the PK of CYP3A4 substrate midazolam. These results indicate that no dose adjustment is necessary when co-administering TEZ/IVA with a CYP3A substrate. Administration of TEZ/IVA increased P-gp substrate digoxin exposure approximately 1.3-fold compared with digoxin administered alone. These results are similar to the effect of IVA alone on digoxin (Study 770-016) and suggest a weak inhibition of P-gp by TEZ/IVA. Caution and appropriate monitoring are recommended when co-administering TEZ/IVA with sensitive P-gp substrates, e.g., digoxin, cyclosporine, everolimus, sirolimus, tacrolimus, or other medicinal products that are substrates of P-gp with narrow therapeutic windows. No significant DDI between ethinyl estradiol (EE) and norethindrone estradiol (NE) and TEZ/IVA was observed when the oral contraceptive was co-administrated with TEZ/IVA in healthy subjects. The results are consistent with DDI results between IVA and oral contraceptives in healthy subjects (Study 770-005). These results indicate that co-administration with TEZ/IVA is not expected to reduce the effectiveness of hormonal contraceptives.

Because based on *in vitro* studies IVA and M1-IVA may have the potential to inhibit CYP2C9, caution and monitoring is recommended when substrates of this isozyme with narrow therapeutic index (such as warfarin) are co-administered with TEZ/IVA.

Pharmacokinetics using human biomaterials

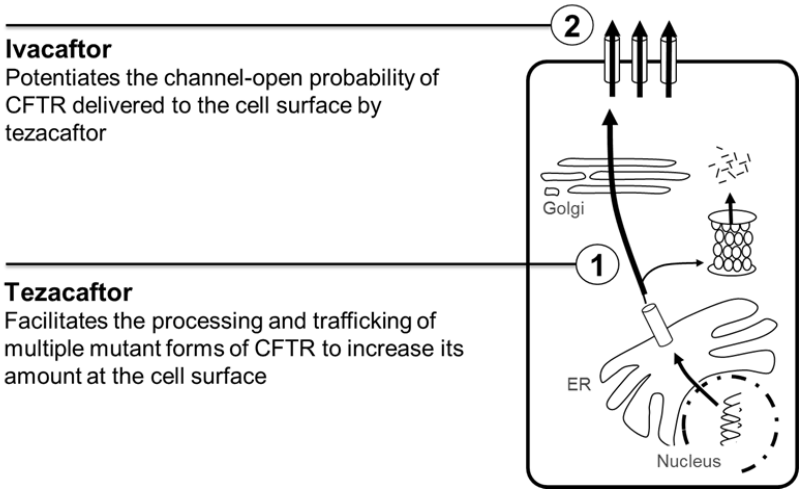
Not applicable

2.4.3. Pharmacodynamics

Mechanism of action

Tezacaftor is a broad-acting CFTR corrector that facilitates the cellular processing and trafficking of normal or multiple mutant forms of CFTR (including F508del-CFTR) to increase the amount of functional CFTR protein delivered to the cell surface, resulting in increased chloride transport. Ivacaftor is a CFTR potentiator that potentiates the channel-open probability (or gating) of CFTR at the cell surface to increase chloride transport. For ivacaftor to function CFTR protein must be present at the cell surface. Ivacaftor can potentiate the CFTR protein delivered to the cell surface by tezacaftor, leading to a further enhancement of chloride transport than either agent alone. The combined effect of tezacaftor and ivacaftor is increased quantity and function of CFTR at the cell surface, resulting in increases in chloride transport, airway surface liquid height, and ciliary beat frequency.

Figure 4 Mechanisms of Action of Tezacaftor and Ivacaftor



Primary and Secondary pharmacology

Effects on Sweat Chloride

Sweat chloride concentration is a direct measure of CFTR function in the sweat gland that is used as a PD marker of on-target activity of CFTR modulators. Sweat chloride was included in the Phase 2 studies, Study 101 and 103, and in the Phase 3 studies, Study 106 and Study 108, as a measure of the effect of TEZ/IVA on CFTR activity. The studies included CF patients with different mutations.

Patients with CF heterozygous for F508del/G551D: In study 101, the effect of TEZ 100 mg qd/IVA 150 mg q12h was evaluated in F/G551D subjects who were taking physician-prescribed Kalydeco (IVA 150 mg q12h) before enrolling in the study. Subjects were randomized to receive TEZ 100 mg qd or placebo, and all subjects continued taking Kalydeco. For the VX-661 + ivacaftor group, the within-group decrease in sweat chloride was -7.02 mmol/L (P = 0.053) compared to 10.18 mmol/L (P= 0.1066) for Kalydeco (placebo group) alone; the difference in sweat chloride relative was -17.20 mmol/L (P = 0.0238). The proportion of subjects with ≥10 mmol decrease in sweat chloride at the average through Day 28 were 0 subjects (Placebo + ivacaftor) and 4 (30.8%) subjects for VX-661 + ivacaftor.

Patients with CF homozygous for F508del: The changes in sweat chloride were measured in patients with CF homozygous for F508del in three studies. In study 101, different doses of TEZ alone of 10, 30, 100, and 150 mg qd and in combination with ivacaftor were tested. IVA 150 mg q12h was selected because it is the approved Kalydeco dose for patients aged 12 years and older, and there is no clinically meaningful DDI between TEZ and IVA. A reduction in the mean sweat chloride compared to baseline was observed in all groups, with the exception of TEZ 10 mg qd. The largest effect is seen with TEZ 100 mg either as monotherapy or combination therapy. In the monotherapy groups, the least square (LS) means absolute change in sweat chloride for the monotherapy ranged from + 3.92 to -20.43. For the combined therapy, the least square mean absolute change ranged from -2.63 to -6.04, see table below.

Table 8 Sweat Chloride (mmol/L): Absolute Change From Baseline Through Day 28 by MMRM, Full Analysis Set (Groups 1 through 5)

	Baseline Statistics		Day 28 Statistics[a]		Absolute Change Through Day 28[b,c]			Treatment Difference (vs. Pooled Placebo)[b,d]		Treatment Difference (vs. Corresponding VX-661 group)[b,d]	
Treatment	N	Mean	N	Mean	N	LS Mean	*P* Value	Difference (95% CI)	*P* Value	Difference (95% CI)	*P* Value
Pooled Placebo	24	102.34	23	100.54	24	-0.86	0.5006	NA	NA	NA	NA
VX-661 10 mg qd	8	98.28	7	106.14	8	3.92	0.0817	4.77 (-0.30, 9.84)	0.0647	NA	NA
VX-661 30 mg qd	8	102.70	6	101.33	6	-4.76	0.0610	-3.91 (-9.50, 1.68)	0.1686	NA	NA
VX-661 100 mg qd	8	102.21	8	87.06	8	-20.43	<0.0001	-19.58 (-24.57, -14.59)	<0.0001	NA	NA
VX-661 150 mg qd	9	103.69	9	98.11	9	-10.46	<0.0001	-9.60 (-14.38, -4.82)	0.0001	NA	NA
VX-661 10 mg qd/ IVA 150 mg q12h	18	107.13	17	101.94	18	-5.06	0.0010	-4.20 (-8.10, -0.31)	0.0348	-8.98 (-14.37, -3.58)	0.0013
VX-661 30 mg qd/ IVA 150 mg q12h	18	102.32	17	95.06	18	-6.00	0.0001	-5.14 (-9.03, -1.25)	0.0101	-1.23 (-7.05, 4.58)	0.6751
VX-661 100 mg qd/ IVA 150 mg q12h	17	103.31	15	97.87	17	-6.04	0.0002	-5.19 (-9.16, -1.21)	0.0110	14.39 (9.09, 19.69)	<0.0001
VX-661 150 mg qd/ IVA 150 mg q12h	17	101.21	16	98.16	17	-2.63	0.0898	-1.77 (-5.71, 2.17)	0.3745	7.83 (2.75, 12.91)	0.0028

Sources: Table 14.2.2.1.1 and Table 14.2.2.1.2

CI: confidence interval; LS: least squares; MMRM: mixed-effects model for repeated measures; N: number of subjects; NA: not applicable; *P*: probability; q12h: every 12 hours; qd: daily; vs: versus

[a] Statistics are from the Day 28 Visit (Table 14.2.2.1.2).

[b] Obtained from MMRM with dependent variable absolute change from baseline, fixed effects for treatment, categorical visit (Day 7, Day 14, Day 21, and Day 28), and treatment-by-visit interaction, with adjustment for continuous baseline values of sweat chloride, using a compound symmetry covariance matrix.

[c] LS mean change from baseline and *P* value for within-group comparison.

[d] Difference between treatments for the LS mean change from baseline and *P* value for between-treatment comparison.

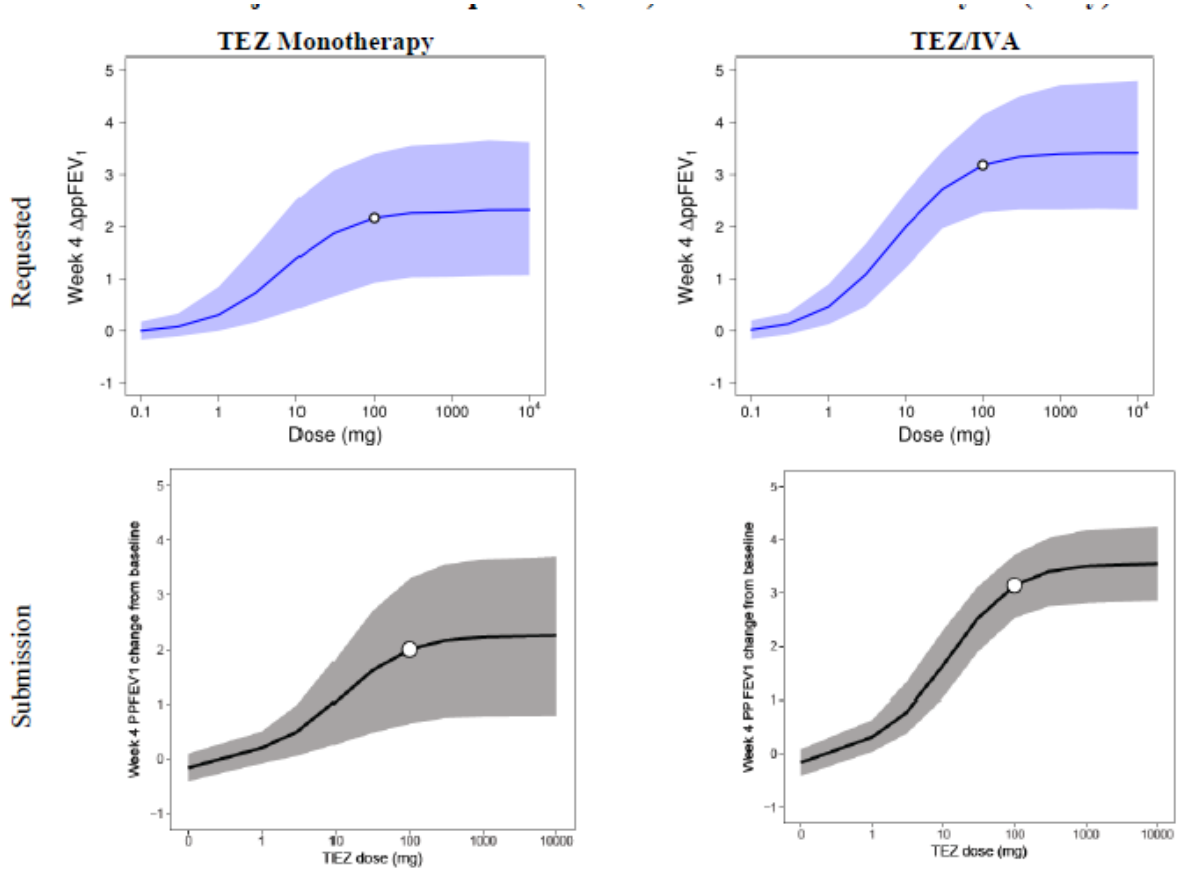
In a responder analysis the proportion of subjects with ≥10 mmol decrease in sweat chloride through Day 28 was 2 (11.8%) subjects for VX-661 100 mg qd/IVA 150 mg q12h, 5 (27.8%) for subjects for VX-661 50 mg q12h/IVA 150 mg q12h. In study 101, ppFEV1 was also measured as pharmacodynamic parameter; these results are discussed in more detail in section on dose response studies. Study 103 was a multicenter, 2-part study in subjects 18 years of age or older with CF, homozygous for the F508del-CFTR mutation. Two doses were included, VX-661 doses of 50 mg q12h (Group 1) and 100 mg qd (Group 2) both combined with IVA 150 mg q12h. The within-group LS mean for average absolute change level from baseline in sweat chloride through Week 12 was -4.7 mmol/L (P = 0.0163) for Group VX-661 100 mg qd/ IVA 150 mg q12h (n=15), and -10.6 mmol/L (P = 0.0011) for Group VX-661 50 mg q12h/IVA 150 mg q12h (n=6), and 1.9 mmol/L (P = 0.2872) for Overall Placebo (n=18). The LS mean treatment difference for Group VX-661 100 mg qd/ IVA 150 mg q12h versus Overall Placebo was -6.5 mmol/L (P = 0.0161). The LS mean absolute change from baseline in sweat chloride level was -6.6 mmol/L (P = 0.0002) during the 40-week OLE Phase.

In the clinical study 106 in patients with CF homozygous for F508del, the difference in sweat chloride compared to placebo was -9.1 (P<0.0001) and -10.1 (-11.4, -8.8) (P<0.0001) after 4 weeks and 12 weeks of treatment, respectively.

Relationship between plasma concentration and effect

Exposure-response (E-R) analyses used clinical data from Studies 101, 103, and 106. The exposure-response (E-R) modelling incorporated all TEZ monotherapy data from the Phase 2 Study 101. In addition to the on-treatment data, post-treatment washout data (the largest amount of which was collected in Study 101 following the 4-week treatment period) also contributed to the E-R analysis. Due to the long terminal elimination of TEZ, these data provided additional response data for exposures similar to the TEZ 10 mg qd dose. The difference between TEZ/IVA and TEZ is provided in

the model with data of study 101, 103 and 106 (grey colour) and with only data study 101 (see figure below).



Source: Data on file and Report N021

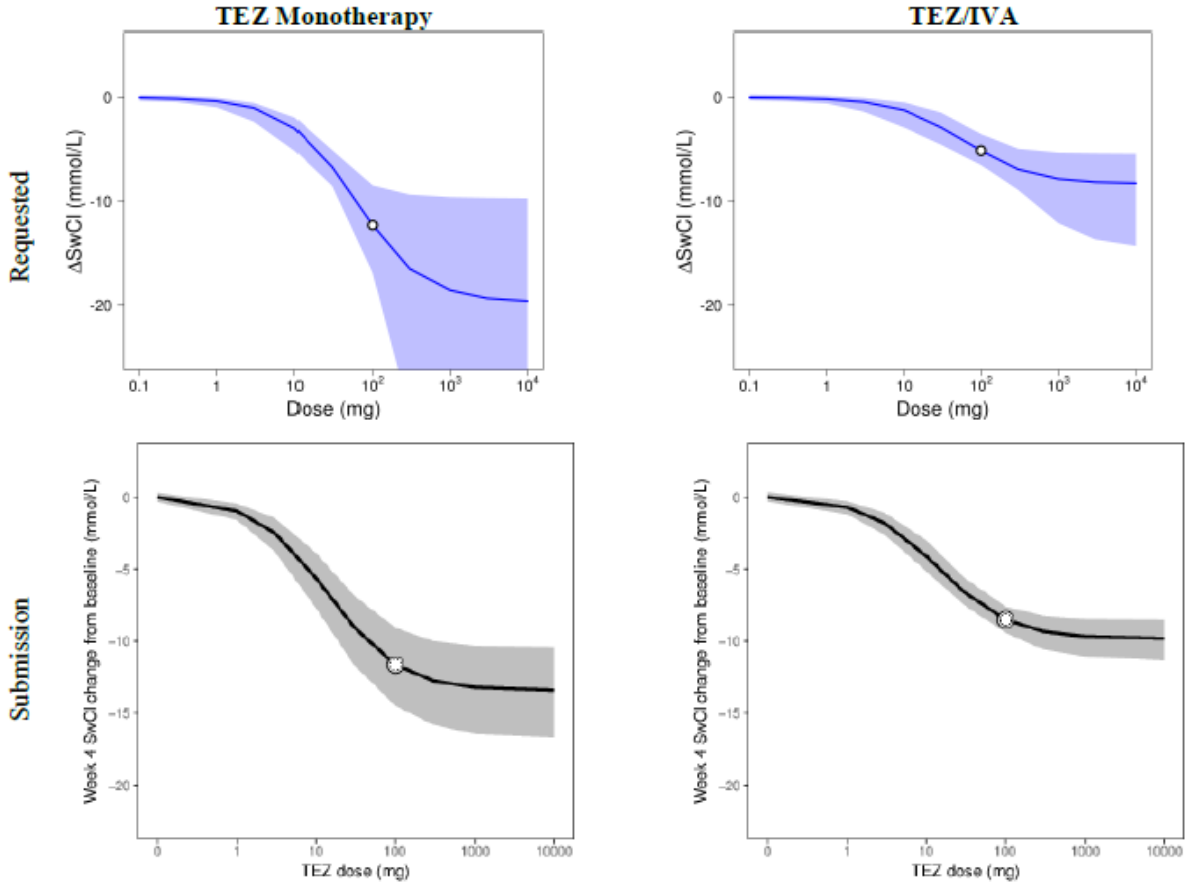
Notes: Requested analysis included data from placebo arms, TEZ monotherapy arms, and TEZ/IVA arms where TEZ was dosed qd and IVA was dosed at 150 mg q12h. This analysis does not include the screening data.

The line is the median and shaded area is the 95%CI for the simulated mean change from baseline. The results are summarized from 1000 replicate simulated populations of 3000 individuals each. The white dot marks the typical change from baseline for TEZ 100 mg qd dosed as monotherapy or in combination with IVA 150 mg q12h.

Covariates for this simulation were re-sampled from Study 106 subjects (*F/F* genotype).

Figure 5 Comparison of Modelled Dose-Response Relationships for ppFEV1 in F/F Subjects for the Requested (Blue) and Submission Analyses (Grey)

The figure below presents the decreases in SwCl for TEZ/IVA and TEZ alone.



Source: Data on file and Report N021
Notes: Requested analysis included data from placebo arms, TEZ monotherapy arms, and TEZ/IVA arms where TEZ was dosed qd and IVA was dosed at 150 mg q12h.

The line is the median and shaded area is the 95%CI for the simulated mean change from baseline. The results are summarized from 1000 replicate simulated populations of 3000 individuals each. The white dot marks the typical change from baseline for TEZ 100 mg qd dosed as monotherapy or in combination with IVA 150 mg q12h. Covariates for this simulation were re-sampled from Study 106 subjects (*F/F* genotype).

Figure 6 Comparison of Modelled Dose-Response Relationships for Sweat Chloride in F/F Subjects for the Requested (Blue) and Submission Analyses (Grey)

Patients heterozygous for F508del and a residual function mutation (F/RF): In Study VX14-661-108, the LS mean treatment difference versus placebo for the absolute change in sweat chloride from study baseline to the average of Week 4 and Week 8 was -9.5 mmol/L (P<0.0001) for TEZ/IVA and -4.5 mmol/L (P<0.0001) for IVA. The LS mean treatment difference for the absolute change in sweat chloride from study baseline to the average of Week 4 and Week 8 was -5.1 mmol/L in favour of TEZ/IVA compared to IVA (P<0.0001).

Relationship between plasma concentration and effect

Population PK analyses were conducted on pooled data from Studies 101, 103, 106, 107, and 108 (Study N021). For these analyses, a 2-compartment popPK model with absorption driven by a sequential zero-order/ first-order process was used to describe the PK of TEZ. PopPK analyses for IVA

were conducted with a prior popPK model. In the same Study N021, nonlinear mixed-effects models were developed to describe the exposure-response (PK/PD) relationship for the absolute change in ppFEV1 and sweat chloride for F/F subjects. These PK/PD analyses pooled data from Studies 101, 103, and 106.

QT/QTC Evaluation

Potential QTc prolongation has been evaluated in Study VX15-661-010 in 116 healthy volunteers. Study 010 was a randomized, active and placebo-controlled, double-blind, parallel arm, study, conducted in 2-part (Parts A and B). The objective of Part A was designed to evaluate the safety and tolerability of multiple ascending doses of TEZ; the objective of Part B was to evaluate the effects of therapeutic and supratherapeutic doses of TEZ compared with placebo on the QTc interval. A mixed-effects model for repeated measures (MMRM) was used for testing the treatment difference of the ΔQTcF between the therapeutic dose and placebo was tested using. Prolongation was declared negative if the upper limit of the 1-sided 95% CI for the mean difference of the therapeutic dose versus placebo fell below 10 msec for every time point. In Part A, no subject had an increase of QTcF >30 msec. The upper limit of the 2-sided 90% CI for the mean difference of the 100-mg dose versus placebo fell below 10 msec at every time point. In Part B, no subject had an increase of QTcF >60 msec. The upper limits of the 2-sided 90% CIs for the mean difference in ΔQTcF between the VX-661 300-mg dose and placebo, fell below 10 msec at every time point for Day 14. The positive control (moxifloxacin) behaved appropriately (positive QTc signal); the study had assay sensitivity to allow for conclusions on QTc prolongation.

There were no clinically relevant trends in standard ECG parameters, including no clinically significant increases or decreases over time in mean heart rate in subjects receiving TEZ 200-mg and 300-mg doses, compared to subjects receiving placebo or moxifloxacin. There were no obvious differences between the therapeutic and supratherapeutic TEZ doses.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The pharmacokinetics of tezacaftor (and ivacaftor in combination with tezacaftor) as well as its major metabolites were investigated both in healthy subjects and CF patients. For the bioanalysis, non-chiral assays were used. Analytical methods for tezacaftor and its metabolites as well as for ivacaftor and its metabolites were adequately validated, with accuracy, specificity and stability meeting appropriate requirements.

The dose advice for TEZ in the presence of various inhibitors of CYP3A4 was supported by a PBPK model. The PBPK model-predicted TEZ and M1 plasma-concentration-time curves in the absence and presence of itraconazole or fluconazole, as well as the prediction of the $t_{1/2}$ were presented. The PBPK model was validated for baseline tezacaftor PK and the combination of tezacaftor and the strong CYP3A4 inhibitor itraconazole as well as the mild CYP3A4 inhibitor ciprofloxacin. This is considered sufficient by the CHMP. In addition, the applicant provided further qualifications for the PBPK model, i.e., other substrates have been studied with itraconazole and fluconazole in the platform, e.g., midazolam, simvastatin, and zolpidem.

However, the CHMP considered that insufficient information was provided on the effect of genetic variations related to pharmacokinetics. Both TEZ and IVA are mainly metabolised by CYP3A4. For this enzyme, a relevant and relatively abundant variant with reduced activity has been reported, i.e., CYP3A4 *22. The Applicant did not make clear if high ratio's in trough levels for TEZ and IVA and their

metabolites which were identified could be related to the occurrence of e.g. a CYP3A4*22 genotype in the patients involved. Instead, the variation in Ctrough and the lack of concordance between the deviation from average levels for TEZ and IVA in the same patient was used as argument that CYP3A4*22 is not important for the high ratio's that were observed at certain occasions. Such conclusion is not possible based on the provided data, since the applicant did not demonstrate that the CYP3A4*22 genotype indeed was present in the patients at stake nor if there were other CYP3A4*22 patients in the study population. In the absence of such data, and bearing in mind that dose modifications are proposed for TEZ/IVA in combination with moderate (and strong) inhibitors of CYP3A4, a potential effect of CYP3A4 variants on exposure to TEZ and IVA cannot be excluded. Therefore, the applicant committed in the post authorisation phase to either provide the CYP3A4 genotype of the patients included in the already submitted clinical studies, followed by further analysis of potential relationship between exposure (AUC, Cmax and Ctrough) and genotype, or provide additional *in vivo* data in healthy subjects, comparing exposure (AUC, Cmax and Ctrough) to TEZ and IVA in patients with CYP3A4*22 genotype and subjects with CYP3A4 wild-type phenotype.

With respect to hepatic impairment, based on results from Study 009, which showed higher exposure of TEZ (36% increase for AUC, 20% based on the total increase in active TEZ/TEZ-M1 exposure) and IVA (52% increase for AUC) in subjects with moderate hepatic impairment, the dose for patients with moderate hepatic impairment (Child-Pugh Class B) should be reduced to 1 TEZ 100 mg/IVA 150 mg tablet once daily. The evening dose of 150 mg IVA should not be taken. With respect to IVA, the proposed dose is in line with the dose advised for IVA as single agent. This is reflected in the SmPC. The lack of a dose-adjustment for TEZ in case of moderate hepatic impairment is agreed by the CHMP.

The TEZ exposures in different weight categories are considered to be within the therapeutic window, and no clinically relevant effects on efficacy or safety are expected. The total number of patients over 65 years of age included in the clinical studies is limited. No patients over 75 years of age have been included. Overall, age does not appear to be a relevant covariate in the pop-PK study N021. Based on the overview of the number of adolescents per study, and the plot showing simulated AUC vs age based on the pop-PK Study N021 model, comparing TEZ exposure in the age range 12-17 and >17 years of age, no clinically relevant increase in TEZ exposure is observed in adolescents as compared to adult patients. Further, exposure to IVA in adolescents, when given in combination with 100 mg TEZ is comparable to that in adults.

Based on actual study data, IVA and M1-IVA C_{max} and AUC_{0-12h} were approximately 30% higher after administration of TEZ/IVA than after administration of IVA alone. This increase is somewhat higher than reported based on the Pop-PK model (17% increase). However, this increase is not expected to result in clinically relevant changes in safety of IVA, as compared to the situation where IVA is given as single agent.

Based on contemporary regulatory requirements, the potential for drug-drug interactions should be evaluated for a new drug and the relevant metabolites. This was not fulfilled with respect to induction of CYP1A2 and 2B6 for M1-TEZ and M2-TEZ, based on the assumption that nowadays the likelihood that TEZ/IVA is combined with a relevant drug is low. However, the applicant has initiated an *in vitro* induction study regarding potential induction of CYP2B6 by M1-TEZ and of CYP1A2 and CYP2B6 by M2-TEZ, results of which will be submitted post-approval. This is agreed by the CHMP.

The possible DDI between TEZ and M1-TEZ, M2-TEZ and M5-TEZ metabolites and warfarin due to displacement of warfarin from protein binding sites might not be clinically relevant due to the low hepatic extraction ratio of warfarin. Since monitoring of INR is already advised in the SmPC due to the fact that ivacaftor may inhibit CYP2C9, this is considered sufficient.

With regard to drug transporters, TEZ appears to inhibit OATP1B1 *in vitro* (IC_{50} 3.2 µM). Since the TEZ I/IC50 for OATP1B1 is higher than the criteria of 0.02 and co-administration of an OATP1B1 substrate drug in the future cannot be excluded, an *in vivo* study investigating the potential DDI between TEZ/IVA and an OATP1B1 substrate will be conducted by the Applicant and will be submitted post-approval. Further, as requested in the *Guideline on the Investigation of Drug Interactions (CPMP/EWP/560/95/Rev. 1)* and since future combination with OCT1, MATE and BSEP substrate drugs cannot be excluded, the applicant has initiated an *in vitro* study investigating the inhibitory effect of TEZ and its metabolites on OCT1 (SLC22A1), MATE1 (SLC47A1) and MATE2 (SLC47A) and BSEP (ABCB11) results of which will be submitted post-approval. Finally, an *in vitro* test for substrate characteristics towards BCRP is considered a basic requirement for new drugs like ivacaftor (in combination with tezacaftor). Effects of BCRP on IVA metabolites M1-IVA and M6-IVA cannot be excluded. Therefore, investigations elucidating whether ivacaftor and its metabolites are substrate for BCRP have been initiated by the applicant and results will be submitted post-approval, which is agreed by the CHMP.

Pharmacodynamics

The proposed mechanism of action is based on *in vitro* experiments where the combination of tezacaftor and ivacaftor caused a statistically significant increase in chloride transport over ivacaftor alone in the mutations that are proposed for approval, as described in section 5.1 of the SmPC. Changes in sweat chloride as a pharmacodynamic parameter for the activity of a CTFR modulator was investigated in the Phase II in Study 101 and 103, and in Phase 3 in Study 106 in subjects with CF, who are homozygous for F508del, and in Phase 3 in Study 108 in subjects heterozygous for F508del and a residual function mutation (F/RF). Study 101 included also subjects with CF, who are heterozygous F508del/G551D.

TEZ 100 mg qd//IVA 150 mg q12h showed a reduction (improvement) in mean sweat chloride levels in all investigated populations. In the two pivotal studies 106 and 108 the reduction in sweat chloride observed was in the same range as observed with Orkambi, already authorised for treatment of patients with homozygous for F508del. In study 108, in subjects heterozygous for F508del, the reduction in sweat chloride concentration was also higher with TEZ/IVA than IVA supporting the combination. The effect was maintained during the open label period of 40 weeks in study 103 in 27 patients. The reduction is considered relevant for patients with F/F mutations from the perspective that mutations with residual CFTR activity have sweat chloride levels approximately 10% lower (improved) than severe mutations and have disease manifestations that are either less severe or demonstrate a delay in onset compared with the most severe mutations.

TEZ 100 mg qd/IVA 150 mg q12h was also compared with different doses of TEZ monotherapy. For sweat chloride TEZ monotherapy at 100 mg and 150 mg qd appeared more effective than the combination at reducing sweat chloride. Inconsistences are acknowledged between the combination and the monocomponent tezacaftor and also between the TEZ monotherapy groups. Evaluation of treatment differences versus pooled placebo across cohorts demonstrated also inconsistency between sweat chloride and FEV1 data. Overall, however, the results for ppFEV1 demonstrated quite consistently a greater effect for TEZ/IVA combination with the highest response for TEZ 100 mg qd /IVA 150 mg q12h and a clinically relevant difference with TEZ 100 mg.

Results of population PK/PD analyses suggested an exposure-response (E-R) relationship for change in ppFEV1 as a function of TEZ exposure at a fixed IVA dose of 150 mg q12h, and estimated TEZ 100 mg qd/IVA 150 mg q12 to be near the maximum achievable response.

The E-R analyses indicated that the combination has an added value over monotherapy of tezacaftor in ppFEV1 in subjects with the F/F genotype. The combining data from studies 101, 103 and 106, for E-R analysis, comparing TEZ monotherapy versus TEZ/IVA in combination was considered not valid, given that studies 103 and 106 lacked a TEZ monotherapy comparator arm and post-treatment washout data from TEZ/IVA treated patients, in order to provide additional response data for exposures similar to the TEZ 10 mg qd dose. Therefore additional E-R analyses were provided in the 2nd RSI. In the re-analysis, the results for ppFEV1 were confirmed: 44% greater median change from baseline ppFEV1 with TEZ/IVA compared with TEZ (versus 60% difference in the previous analysis). The 95% CI was wide: -25% to 373%. The model predicted a within-group ppFEV1 response of 3.2 percentage points (95% CI: 2.2, 4.4) in Study 101, consistent with the observed within-group response of 3.4 percentage points (95% CI: 2.7, 4.0) in study 106. The re-analysed E-R data for sweat chloride again demonstrate a greater reduction in sweat chloride with TEZ monotherapy versus TEZ/IVA. For sweat chloride, the TEZ/IVA sweat chloride response in Study 106 was under-predicted using the model developed on the data from Study 101, i.e. -5.2 mmol/L (95% CI: -6.9,-3.4) whereas the improvement observed in Study 106 was -9.9 mmol/L (95% CI: -10.9, -8.9). Thus overall, the model, within the limitations, appears to be more accurate for FEV1 than sweat chloride. This is consistent with the known variability in measurements of sweat chloride.

The interpretation of the results of study 101 is limited by the 4 week duration of the study.

The effect of IVA in subjects with the F/F genotype was been investigated before (study 104). A small, not relevant difference in the adjusted mean absolute change from baseline for sweat chloride values of -2.87 mmol/L (P = 0.0384) has been observed.

For the secondary pharmacology, potential QTc prolongation of tezacaftor has been evaluated in Study VX15-661-010 in 116 healthy volunteers. As the study had assay sensitivity, the results allow for a conclusion on QTc prolongation. As at all time point the treatments differences fell below the predefined 10 msec and normality can be assumed as the median and mean are almost equal for almost all time points, it is concluded that tezacaftor at supratherapeutic dose did not prolong the QTcF interval in healthy subjects. The conduct of a dedicated QTc study with only TEZ is considered justified because tezacaftor has only a modest effect on the exposure of IVA. Since IVA has been shown not to prolong the QTc interval at supratherapeutic doses of 450 mg q12h, the increased IVA exposure in combination with TEZ is not considered relevant with respect to the probability to influence the QTc.

2.4.5. Conclusions on clinical pharmacology

In the pharmacodynamic investigation of tezacaftor monotherapy and TEZ/IVA combination, tezacaftor/ivacaftor showed a consistent positive effect on sweat chloride in the investigated subjects with CF homozygous for F508del or heterozygous F508del/G551D or heterozygous for *F508del* and a residual function mutation (F/RF). Nevertheless, the inferior effect of TEZ/IVA compared with TEZ on sweat chloride in study 101 is not completely understood. There appears to be no sufficient reason to exclude the possibility that TEZ as monotherapy may have clinically relevant pharmacodynamic activity, particularly when there are also discrepancies within the *in vitro* data and there is evident complexity in the mechanisms involved in correcting the CFTR function. The results of exposure-response modelling, submitted to support clinical superiority of TEZ/IVA over TEZ are limited, since the model appears to be more accurate for FEV1 than sweat chloride, but there are limitations for interpretation because of the very wide confidence intervals around the predicted responses. Please refer to section 2.5.

The pharmacokinetics of tezacaftor and ivacaftor has been sufficiently investigated, although some concerns remain to be resolved via post-authorisation measures, related to special patient populations/pharmacogenetics and drug-drug interactions.

The CHMP considers the following recommendations necessary to address the issues related to pharmacology:

- The Applicant should either provide the CYP3A4 genotype of the patients included in the already submitted clinical studies, followed by further analysis of potential relationship between TEZ and IVA exposure (AUC, Cmax and Ctrough) and genotype, or provide additional in vivo data in healthy subjects, comparing exposure (AUC, Cmax and Ctrough) to TEZ and IVA in patients with CYP3A4*22 genotype and subjects with CYP3A4 wild-type phenotype. The final study report should be submitted by 30 April2019.

2.5. Clinical efficacy

The TEZ/IVA clinical package comprises 6 clinical studies in total: two 2 dose finding studies, three placebo-controlled phase 3 efficacy and safety studies and one long term open label study evaluating safety and efficacy. Phase 2 PD study (study 101) is handled as a dose ranging study and is described in this section. The development programme for CF in patients aged 12 years and older enrolled a different patient population per clinical study:

- Study 106: subjects homozygous for *F508del* (F/F)
- Study 108: subjects heterozygous for *F508del* and a residual function mutation (F/RF).
- Study 107: subjects heterozygous for *F508del* and a minimal function mutation that is nonresponsive to TEZ and/or IVA (F/MF).
- Study 110: subjects homozygous or heterozygous for the F508del-CFTR mutation and who participated in Studies 103, 106, 107, 108, 109, 111, or other Vertex Pharmaceuticals Incorporated (Vertex) studies investigating TEZ in combination with IVA.

Studies 106 and 108 are the key efficacy studies supporting the proposed indication. Study 110 is the extension study and is still ongoing; the results of an interim analysis were submitted.

Study 107 was prematurely stopped based on a prespecified futility analysis when approximately 50% of subjects completed the study.

As referred to in the introductory section, the Applicant has communicated that Study 109 in F508del/gating patients failed to meet its primary endpoint and therefore clinical superiority for TEZ/IVA versus IVA cannot be concluded. The applicant removed the gating mutations from the claimed indication and product information during the assessment procedure.

2.5.1. Dose response studies

Two Phase 2 studies VX11-661-101 (Study 101) and VX13-661-103 (Study 103) evaluated different doses TEZ monotherapy and TEZ/IVA combination therapy.

- Study 101 was a randomized, multicenter, double-blinded, placebo-controlled study that evaluated TEZ and TEZ/IVA at multiple dose levels in adult subjects with F/F genotype and in adult and adolescent subjects with F/G551D.

- Study 103 was a multicenter, 2-part study in subjects 18 years of age or older with CF, homozygous for the F508del-CFTR mutation.

In both studies, the primary objectives were to evaluate the safety, tolerability, and the secondary objectives to evaluate the efficacy (assessed by percent predicted FEV1 [ppFEV1] and Cystic Fibrosis Questionnaire-Revised [CFQ-R] Respiratory domain), PD and PK of TEZ and TEZ/IVA.

CF patients 18 years or older with the F/F genotype

Increases in ppFEV1 for the VX-661 monotherapy groups were variable and not dose-dependent. The increases for the VX-661/IVA groups were dose-dependent, with the highest increase for the proposed dose TEZ 100 mg qd/IVA 150 mg q12h. The group that showed the greatest improvement in absolute change in ppFEV1 compared to placebo was TEZ 100 mg qd/IVA 150 mg q12h (3.89 %, P = 0.0101). No additional benefit was observed at the higher TEZ dose of 150 mg qd/IVA 150 mg q12h (ppFEV1 3.75 %; P = 0.0125), see table below. These results were consistent with the Phase 2/3 PK/PD analysis showing that exposures observed with the clinical dose of TEZ (100 mg qd) were on the flat part of dose-response curve.

Table 9 Results for ppFEV1: Absolute Change From Baseline Through Day 28 (Percentage Points) by MMRM, Full Analysis Set (Groups 1 Through 5)

	Baseline Statistics		Day 28 Statistics[a]		Absolute Change Through Day 28[b,c]			Treatment Difference (vs. Pooled Placebo)[b,d]		Treatment Difference (vs. Corresponding VX-661 Group)[b,d]	
						LS		Difference		Difference	
Treatment	n	Mean	n	Mean	N	Mean	*P* Value	(95% CI)	*P* Value	(95% CI)	*P* Value
Pooled Placebo	24	57.78	23	57.07	24	-0.14	0.8845	NA	NA	NA	NA
VX-661 10 mg qd	8	64.25	7	65.18	8	3.49	0.0375	3.63 (-0.16, 7.42)	0.0605	NA	NA
VX-661 30 mg qd	8	61.43	8	61.58	8	1.63	0.3229	1.76 (-1.99, 5.52)	0.3536	NA	NA
VX-661 100 mg qd	8	62.53	8	64.01	8	1.60	0.3300	1.74 (-2.01, 5.50)	0.3603	NA	NA
VX-661 150 mg qd	9	56.91	9	59.33	9	2.54	0.1042	2.68 (-0.92, 6.27)	0.1429	NA	NA
VX-661 10 mg qd/ IVA 150 mg q12h	18	61.84	17	62.98	18	1.30	0.2368	1.44 (-1.43, 4.31)	0.3230	-2.19 (-6.11, 1.74)	0.2725
VX-661 30 mg qd/ IVA 150 mg q12h	19	61.95	17	63.36	19	2.90	0.0082	3.03 (0.19, 5.88)	0.0369	1.27 (-2.61, 5.15)	0.5181
VX-661 100 mg qd/IVA 150 mg q12h	17	58.73	15	62.24	17	3.75	0.0014	3.89 (0.94, 6.83)	0.0101	2.14 (-1.82, 6.11)	0.2867
VX-661 150 mg qd/IVA 150 mg q12h	17	59.83	16	63.23	17	3.61	0.0019	3.75 (0.82, 6.68)	0.0125	1.07 (-2.73, 4.88)	0.5782

Sources: Table 14.2.5.2.1 and Table 14.2.5.2.2

CI: confidence interval; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: number of subjects; NA: not applicable; *P*: probability; $ppFEV_1$: percent predicted forced expiratory volume in 1 second, q12h: every 12 hours; qd: daily; vs: versus

[a] Statistics are from the Day 28 Visit (Table 14.2.5.2.2).

[b] Obtained from MMRM with dependent variable absolute change from baseline, fixed effects for treatment, categorical visit (Day 7, Day 14, Day 21, and Day 28), and treatment-by-visit interaction, with adjustment for continuous baseline values of $ppFEV_1$, using a compound symmetry covariance matrix.

[c] LS mean change from baseline and *P* value for within-group comparison.

[d] Difference between treatments for the LS mean change from baseline and P value for between-treatment comparison.

The within-group LS mean for average absolute change from baseline in ppFEV1 through Week 12 in study 103 was 3.0 % (95% CI: 0.4, 5.5; P = 0.0226) for TEZ 100 mg/IVA 150 mg, 0.9 % (95% CI: -3.1, 5.0; P = 0.6437) for TEZ 50 mg/IVA 150 mg, and 0.9 % (95% CI: -1.7, 3.5; P = 0.4801) for Overall Placebo. The LS mean treatment difference for TEZ 100 mg/IVA 150 mg versus Overall Placebo was 2.1 % (95% CI: -1.5, 5.7; P = 0.2536). An alternative regimen with the same total daily dose of TEZ was also evaluated in Studies 101 and 103 (TEZ 50 mg q12h/ IVA 150 mg q12h), but resulted in a lower mean change in ppFEV1 versus placebo. The results of study 101 and Study 103 are presented in the following table:

Table 10 Study VX11-661-101 and Study VX13-661-103: Key Efficacy Data for the Phase 3 Regimen (TEZ 100 mg qd/IVA 150 mg q12h)

	Study 101		Study 103	
Endpoint	Subjects ≥18 years with the F/F genotype N = 17	Subjects ≥12 years with the F/G551D genotype N = 14	Placebo-controlled Phase N = 15	OLE N = 27
Absolute change in $ppFEV_1$	3.75 percentage points ($P = 0.0014$)	4.60 percentage points ($P = 0.0120$)	3.0 percentage points ($P = 0.0226$)	2.7 percentage points ($P = 0.0232$)
Absolute change in CFQ-R respiratory domain score	5.15 points ($P = 0.0933$)	3.79 points ($P = 0.1679$)	1.0 point ($P = 0.7510$)	-0.6 points ($P = 0.7983$).
Absolute reduction in sweat chloride	-6.04 mmol/L ($P = 0.0002$)	-7.02 mmol/L ($P = 0.0530$)	-4.7 mmol/L ($P = 0.0163$)	-6.6 mmol/L ($P = 0.0002$)
Absolute change in weight and BMI	N/A	N/A	N/A	1.0 kg ($P = 0.1071$) and 0.33 kg/m^2 ($P = 0.1226$)

Sources: Study VX11-661-101 CSR; Study V13-661-103 CSR
BMI: body mass index; CFQ-R: Cystic Fibrosis Questionnaire Revised; IVA: ivacaftor; $ppFEV_1$: percent predicted force expiratory volume in 1 second; TEZ: tezacaftor; OLE: open-label extension phase; N/A: not applicable
Note: Analyses for Study 101 were through Day 28. Analyses for Study 103 Placebo-controlled phase were through Week 12. Analyses for Study 103 OLE phase were through Week 40. Data are shown for the within group changes.

CF patients 12 years or older with the F/G551D genotype (study 101) (Group 7 (18 patients))

The TEZ/IVA group had increases in mean ppFEV1 of 4.60 % (P = 0.0120; Day 28; within-group), with a treatment difference of 3.20 % compared to placebo (P = 0.3646), see table below.

Table 11 Results for ppFEV1: Absolute Change From Baseline Through Day 28 by MMRM, Full Analysis Set (Group 7)

	Baseline Statistics		Day 28 Statistics[a]		Absolute Change Through Day 28[b,c]			Treatment Difference (vs. Group 7 Placebo)[b,d]	
Treatment[d]	n	Mean	n	Mean	N	LS Mean	*P* Value	Difference (95% CI)	*P* Value
Placebo + Kalydeco	4	62.61	4	61.78	4	1.40	0.6502	NA	NA
VX-661 100 mg qd + Kalydeco	14	59.14	14	64.22	14	4.60	0.0120	3.20 (-4.10, 10.51)	0.3646

Sources: Table 14.2.5.2.7 and Table 14.2.5.2.8
CI: confidence interval; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample;
NA: not applicable; *P*: probability; $ppFEV_1$: percent predicted forced expiratory volume in 1 second
qd: daily; vs: versus
Note: All subjects received physician-prescribed Kalydeco for at least 28 days before the Screening Visit through the Safety Follow-Up Visit.
[a] Data are from the Day 28 Visit (Table 14.2.5.2.8)
[b] Obtained from MMRM with dependent variable absolute change from baseline, fixed effects for treatment, categorical visit (Day 7, Day 14, Day 21, and Day 28), and treatment-by-visit interaction, with adjustment for continuous baseline values of $ppFEV_1$, using a compound symmetry covariance matrix.
[c] LS mean change from baseline and *P* value for within-group comparison.
[d] Difference between treatments for the LS mean change from baseline and *P* value for between treatment comparison.

Dosing in adolescents

The use of the adult dosing regimen in subjects with CF who are 12 to 17 years of age in the Phase 3 studies was based on equivalence of severity of disease and allometric scaling of doses. Both TEZ and IVA are predominantly eliminated by metabolism via the CYP3A4/5 pathway. The maturity of the CYP enzymes in adolescents is similar to adults, and thus metabolism of TEZ and IVA are expected to be similar in adolescents and adults. Based on the historical data on weight and age in subjects with CF from the IVA Phase 3 program and the US CF Foundation Registry, weights in the adolescent population are only slightly lower than those of the adult CF population. No dose adjustment is thus needed.

2.5.2. Main studies

Studies 106 and 108 are the core efficacy studies supporting the proposed indication. Study 106 investigated the efficacy of TEZ/IVA in subjects homozygous for F508del (F/F), while Study 108 investigated it in subjects heterozygous for F508del and a residual function mutation (F/RF).

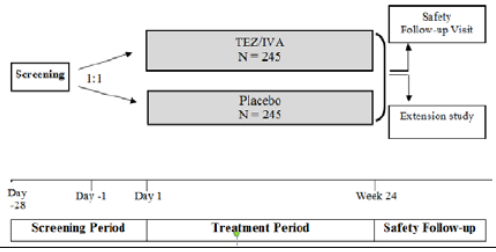
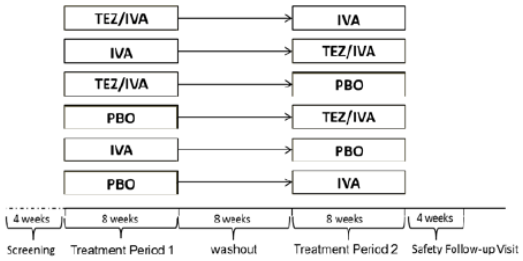
Title of studies

Study VX14-661-106 **Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Tezacaftor in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation**
Study VX14-661-108 **A Phase 3, Randomized, Double-blind, Placebo-controlled, Crossover Study to Evaluate the Efficacy and Safety of Ivacaftor and VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Heterozygous for the F508del-CFTR Mutation, and a Second Allele With a CFTR Mutation Predicted to Have Residual Function**

Methods

Design

Table 12 Design of pivotal studies 106 and 108 for Symkevi

Study VX14-661-106 *Core efficacy study to support the indication statement*		
Objectives • Evaluate the efficacy of TEZ/IVA through Week 24 in F/F subjects • Evaluate the safety of TEZ/IVA • Investigate PK of TEZ, M1-TEZ, M2-TEZ, IVA, and M1-IVA	Design Randomized (1:1), double-blind, placebo-controlled 	Population 510 subjects with CF ≥12 years old Males and females F/F genotype ppFEV$_1$ ≥40 to ≤90
Study VX14-661-108 *Core efficacy study to support the indication statement*		
Objectives • Evaluate the efficacy of TEZ/IVA and IVA monotherapy through 8 weeks of treatment in F/RF subjects • Evaluate safety of TEZ/IVA and IVA monotherapy • Investigate PK of TEZ, M1-TEZ, IVA, and M1-IVA	Design Randomized (1:1:1:1:1:1), double-blind, placebo-controlled, 2-period, 3-treatment, crossover 	Population 248 subjects with CF ≥12 years old Males and females F/RF genotype ppFEV$_1$ ≥40 to ≤90

Study Participants

Key inclusion criteria were for both studies, aged 12 years or older and FEV1 ≥40% and ≤ 90% of predicted normal for age, sex, and height. In study 106 participants were to be homozygous for the F508del-CFTR mutation, while in study 108 the patients were heterozygous for F508del and a mutation that results in RF of the CFTR protein (F/RF). Diagnoses of CF had to be confirmed, in study 106 by a sweat chloride value ≥60 mmol/L, while in study 108, by a sweat chloride value ≥60 mmol/L OR if the sweat chloride value was <60 mmol/L, documented evidence of chronic sinopulmonary disease.

Key exclusion criteria for Studies 106 and 108 decreased potential confounders of study endpoint evaluations. The main exclusion criteria were similar in both trials:

- Abnormal liver function defined as any 2 or more of the following: ≥3 x upper limit of normal (ULN) aspartate transaminase (AST), ≥3 x ULN alanine transaminase (ALT), ≥3 x ULN gamma-glutamyl transferase (GGT), ≥3 x ULN alkaline phosphatase (ALP), or ≥2 x ULN total bilirubin
- Abnormal liver function defined as any increase of ≥5 x ULN AST or ALT
- Abnormal renal function defined as glomerular filtration rate ≤50 mL/min/1.73 m2 (calculated by the Modification of Diet in Renal Disease Study Equation) for subjects ≥18 years old and ≤45 mL/min/1.73 m2 (calculated by the Counahan-Barratt equation) for subjects aged 12 to 17 years (inclusive)

- An acute upper or lower respiratory infection, PEx, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1 (first dose of study drug)
- A 12-lead ECG demonstrating QTc >450 msec at screening.
- Colonization with organisms associated with a more rapid decline in pulmonary status (e.g., Burkholderia cenocepacia, Burkholderia dolosa, and Mycobacterium abscessus)

Treatments

Study VX14-661-106

Test product, dose and mode of administration: 100-mg TEZ/150-mg IVA, film-coated fixed-dose combination (FDC) tablet AND 150-mg IVA, film-coated tablet.

Reference therapy, dose and mode of administration: 0-mg TEZ/0-mg IVA, placebo film-coated tablet AND 0-mg IVA, placebo film-coated tablet.

Study VX14-661-108

Table 13 *Study VX14-661-108*

Treatment	Time	Drug(s) and Dose(s) Administered Route of Administration
TEZ/IVA	AM	TEZ 100-mg/IVA 150-mg fixed-dose tablet IVA-matching placebo tablet, oral
	PM	IVA 150-mg tablet, oral
IVA	AM	TEZ/IVA-matching placebo tablet IVA 150-mg tablet, oral
	PM	IVA 150-mg tablet, oral
Placebo	AM	TEZ/IVA-matching placebo tablet IVA-matching placebo tablet, oral
	PM	IVA-matching placebo tablet, oral

AM: morning; IVA: ivacaftor; PM: evening; TEZ: tezacaftor.

Objectives

Study VX14-661-106

Primary: To evaluate the efficacy of tezacaftor (TEZ) in combination with ivacaftor (IVA) through Week 24 in subjects with cystic fibrosis (CF) who are homozygous for the F508del mutation on the CFTR gene

Secondary: To evaluate the safety of TEZ in combination with IVA through Week 24, to investigate the pharmacokinetics (PK) of TEZ and its metabolites, M1-TEZ and M2-TEZ, and IVA and its metabolite, M1-IVA.

Study VX14-661-108

Primary: To evaluate the efficacy of VX-661 (tezacaftor [TEZ]) in combination with ivacaftor (IVA) and IVA monotherapy through 8 weeks of treatment in subjects with cystic fibrosis (CF) who are heterozygous for F508del and a mutation that results in residual function (RF) of the CFTR protein (F/RF).

Secondary: To evaluate the safety of TEZ in combination with IVA (TEZ/IVA) through 8 weeks of treatment, to evaluate the safety of IVA monotherapy through 8 weeks of treatment, to investigate the pharmacokinetics (PK) of TEZ and its metabolite M1 (M1-TEZ), and IVA and its metabolite M1 (M1-IVA)

Outcomes/endpoints

The primary endpoint in studies 106 and 108 was absolute change from baseline in ppFEV1.

Table 14 Efficacy Endpoints in Phase 3 Studies 106 and 108

Endpoint	Study 106	Study 108
$ppFEV_1$: absolute change	X (primary)	X (primary)
ppFEV1: relative change	X (key secondary)	X (secondary)
PEx: number	X (key secondary)	X (other)
BMI	X (key secondary)	
CFQ-R respiratory domain score	X (key secondary)	X (key secondary)
PEx: time to first	X (secondary)	X (other)
Sweat chloride concentration	X (secondary)	X (secondary)
BMI-z-score	X (secondary)	
Body weight	X (secondary)	
Body weight z-score		
Height z-score		
Rate of change in $ppFEV_1$		
Exocrine pancreatic function		
Serum IRT concentration	X (other)[a]	X (other)
FE-1		X (other)

Sources: Studies 106, 108, 110 CSRs

BMI: body mass index; CRQ-R: Cystic Fibrosis Questionnaire-Revised; FE-1: fecal elastase-1; IRT: immunoreactive trypsinogen; PEx: pulmonary exacerbation; ppFEV1: percent predicted forced expiratory volume in 1 second
Note: Key secondary endpoints are the endpoints that are part of the testing strategy and hence controlled for Type 1 error rate.

For the F/RF population, endpoints that are expected to require longer than 8 weeks of therapy to determine a treatment effect were included as study 108 assessments and evaluated with additional long-term data in Study 110 (i.e., pulmonary exacerbations [PEx], body mass index [BMI], and weight). Spirometry was performed pre-bronchodilator according to ATS standard in compliance with withholding of bronchodilators. For adolescents, the standards of Hankinson and Wang applied. For the CFQ-R 3 different versions of CFQ-R forms were used:

- CFQ-R for Children Ages 12 and 13 version had a total of 35 questions to form 8 domains.
- CFQ-R for Adolescents and Adults version (subjects 14 years old and older) had a total of 50 questions to form 12 domains.
- CFQ-R for Parents/Caregivers version (subjects 13 years old and younger) had a total of 44 questions to form 11 domains.

Pulmonary exacerbation is defined as a clinical deterioration in respiratory status necessitating a change in antibiotic therapy (IV, inhaled, or oral) for any 4 or more of the following signs or symptoms: change in sputum; new or increased haemoptysis; increased cough; increased dyspnoea;

malaise, fatigue, or lethargy; temperature above 38°C (equivalent to approximately 100.4°F); anorexia or weight loss; sinus pain or tenderness; change in sinus discharge; change in physical examination of the chest; decrease in lung function by at least 10%; or radiographic changes indicative of pulmonary infection.

Sample size

Study VX14-661-106

The study was powered for both the primary endpoint (absolute change from baseline in ppFEV1) and a secondary endpoint of clinical interest (relative risk of PExs). The primary efficacy endpoint was the absolute change from baseline in ppFEV1 through Week 24. The null hypothesis to be tested was that the mean absolute change from baseline in ppFEV1 through Week 24 was the same for TEZ/IVA and placebo groups. Assuming a common SD of 8% in each treatment group, a sample size of 220 subjects in each treatment group was to have at least 90% power to detect a treatment difference of 2.5% in ppFEV1 between treatment groups, using a 2-sided significance level of 0.05. If the above null hypothesis was rejected, the efficacy of TEZ/IVA was considered established.

Assuming the PEx rate for placebo was 0.5 events in 24 weeks, with 220 subjects in each treatment group, the power to detect a 40% reduction in the PEx rate in the active arm versus the placebo arm was approximately 92%. The power to detect a 33% reduction in the PEx rate was about 78%. This power calculation was based on an R simulation with 10000 replications. To adjust for a 10% dropout, a total sample size of approximately 490 subjects was needed

Study VX14-661-108

The primary efficacy endpoint was the absolute change in ppFEV1 from study baseline to the average of the Week 4 and Week 8 measurements in each Treatment Period. The null hypotheses to be tested was that the mean absolute change from study baseline in ppFEV1 to the average of the Week 4 and Week 8 measurements was the same for (i) TEZ/IVA and placebo; and (ii) IVA monotherapy and placebo.

Assuming an SD of 7 percentage points, 30 subjects per sequence were needed to have at least 90% power to detect a 3 percentage point treatment difference between TEZ/IVA and placebo when the mean values of the primary endpoint were being compared. A 2-sided significance level of 0.05 was used in the sample size calculations. Accounting for the testing strategy, the proposed sample size yielded approximately an 85% chance of observing a statistically significant difference between IVA monotherapy and placebo for the primary endpoint, under the assumption that IVA monotherapy is also 3 percentage points better than placebo. The sample size estimate was based on 10,000 simulation runs with an incomplete block design assuming no dropouts. In the simulation, the correlation between responses to the 2 treatments within a subject was assumed to be zero. After adjusting for an assumed dropout rate of 10%, the sample size was increased to 34 subjects per sequence (204 total subjects).

Randomisation

Study VX14-661-106

Approximately 490 subjects (245 per arm) who meet eligibility criteria will be stratified by age at Screening Visit (<18 versus ≥18 years of age), sex (male versus female), and percent predicted FEV1 severity determined during the Screening Period (<70 versus ≥70), and then randomized (1:1) to

either TEZ/IVA or placebo. An interactive web response system (IWRS) will be used for randomization following a list of randomization codes generated by a designated vendor.

Study VX14-661-108

Subjects who met the eligibility criteria were randomized (1:1:1:1:1:1) to 1 of the 6 treatment sequences. Randomization was stratified by age at the Screening Visit (<18 versus ≥18 years of age), FEV1 severity (determined at the Screening Visit; <70% versus ≥70% predicted), and type of RF mutation on the second CFTR allele (Class V non-canonical splice mutation versus Classes II to IV RF mutation). An interactive web response system (IWRS) was used to assign subjects to treatment and to ensure enrolment of at least 25% of subject with Classes II to IV RF mutations.

Blinding (masking)

Study VX14-661-106

This is a double-blind study. The blinded data review before database lock is considered acceptable (ICH E9, section 7).

Study VX14-661-108

This was a double-blind study. Blinding measures are considered sufficient to have the study team blinded, although if individual physicians in the trial may have known the allocation based on spirometry, sweat chloride, FE-1 and IRT results. However, the treatment discontinuation is very low (at least 96.3% completed treatment in both periods, see subject disposition), so this is considered not to have impacted the results.

Statistical methods

Models

Primary, key secondary, and other secondary efficacy endpoints that were continuous variables measured repeatedly were analysed based on a mixed-effects model for repeated measures (MMRM) in Study 106. Primary, key secondary and other secondary efficacy endpoints that were continuous variables were analysed based on a mixed-effects model (MEM) in Study 108.

Endpoints that were anticipated to demonstrate rapid onset (i.e., ppFEV1, CFQ-R) were assessed "through" the final treatment period assessment in order to incorporate all assessments while on treatment. Endpoints which were anticipated to demonstrate a more gradual onset (e.g., BMI, weight) were assessed "at" the final treatment period assessment. All efficacy analyses were also summarized for each time point of assessment.

Testing Approach

Study 106: A hierarchical fixed-sequence testing strategy was used to control the overall type I error rate of 0.05 for the primary and key secondary endpoints. After the primary endpoint, the key secondary endpoints were tested in the following order: relative change from baseline in ppFEV1, number of PEx, absolute change from baseline in BMI at Week 24, and absolute change from baseline in CFQ-R through Week 24.

Study 108: To control the overall Type I error rate with multiple treatment comparisons (TEZ/IVA versus placebo, and IVA versus placebo) for both primary and key secondary efficacy endpoints, a gatekeeping approach was used where statistical significance could be claimed for the key secondary

endpoint (CFQ-R respiratory domain) only if the primary endpoint (absolute change in ppFEV1) achieved statistical significance, and statistical significance of IVA versus placebo could be claimed only if TEZ/IVA versus placebo for the same endpoint was significant. Each of the hypothesis tests defined within the testing hierarchies was conducted at the significance level (alpha) of 0.05 (2-sided).

As Study 108 was a 2-period cross-over design, carryover effect and treatment-by-period interaction for the primary analysis were assessed. Carryover effect for the primary analysis was assumed to be negligible due to the adequately long washout period of 8 weeks. Based on the results from the model for the primary analysis and the other sensitivity analyses, no statistical evidence suggested that there was a carryover effect.

Results

Participant flow

Study VX14-661-106

A total of 510 subjects were randomized: 259 subjects in the placebo group and 251 subjects in the TEZ/IVA group. One subject in the placebo group did not receive any study drug dose due to a PEx before the Day 1 visit. Of the 509 subjects who received at least 1 dose of study drug, 475 (93.3%) completed dosing. The percentage of subjects who discontinued treatment due to AE was low in both treatment groups (TEZ/IVA: 2.8%; placebo: 3.1%). A total of 231 (92.0%) subjects in the TEZ/IVA group and 230 (89.1%) subjects in the placebo group rolled over into the Treatment Cohort of Study 110.

Table 15 Participants flow in study 106

Disposition/Reason	Placebo N = 259 n (%)	TEZ/IVA N = 251 n (%)	Total N = 510 n (%)
All Subjects Set[a]	259	251	510
Randomized Set[b]	259	251	510
Safety Set[c]	258	251	509
FAS[d]	256	248	504
Completed treatment regimen	240 (93.0)	235 (93.6)	475 (93.3)
Prematurely discontinued treatment	18 (7.0)	16 (6.4)	34 (6.7)
Reason for discontinuation from treatment			
AE	8 (3.1)	7 (2.8)	15 (2.9)
Subject refused further dosing (not due to AE)	5 (1.9)	5 (2.0)	10 (2.0)
Did not meet eligibility criteria	3 (1.2)	3 (1.2)	6 (1.2)
Physician decision	0	1 (0.4)	1 (0.2)
Required prohibited medication	2 (0.8)	0	2 (0.4)
Completed study	241 (93.4)	236 (94.0)	477 (93.7)
Prematurely discontinued study	17 (6.6)	15 (6.0)	32 (6.3)
Reason for discontinuation from study			
AE	8 (3.1)	4 (1.6)	12 (2.4)
Withdrawal of consent (not due to AE)	6 (2.3)	7 (2.8)	13 (2.6)
Lost to follow-up	0	0	0
Death	0	0	0
Other non-compliance	0	0	0
Physician decision	0	1 (0.4)	1 (0.2)
Study termination by sponsor	0	0	0
Other	3 (1.2)	3 (1.2)	6 (1.2)
Rollover to Study VX14-661-110			
Yes	233 (90.3)	231 (92.0)	464 (91.2)
Treatment cohort	230 (89.1)	231 (92.0)	461 (90.6)
Observational cohort[e]	3 (1.2)	0	3 (0.6)
No	0	0	0

Source: Table 14.1.1

AE: adverse event; *CFTR*: CF transmembrane conductance regulator gene; FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; TEZ: tezacaftor

Notes: Percentages are based on the Safety Set. If a subject discontinued treatment or study for multiple reasons, the subject was counted in each category but counted only once in the total number of subjects who prematurely discontinued treatment.

[a] The All Subjects Set was defined as all subjects who were randomized or received at least 1 dose of the study drug. Treatment assignment was based on the randomized treatment, or on the actual treatment for subjects who were dosed but not randomized (if any).

[b] The Randomized Set was defined as all subjects who were randomized. Treatment assignment was based on the randomized treatment.

[c] The Safety Set was defined as all subjects who received at least 1 dose of the study drug. Treatment assignment was based on the actual treatment received.

[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. Treatment assignment was based on the randomized treatment.

[e] The 3 subjects who rolled over into the Observational Cohort later became part of the Treatment Cohort in Study 110.

Study VX14-661-108

A total of 248 subjects were enrolled at 81 study sites in North America, Europe, Israel, and Australia. Among the 248 subjects who were randomly assigned to treatment, 246 subjects received at least 1 dose of study drug in Period 1 (81 received placebo, 81 received IVA, and 84 received TEZ/IVA). In Period 1, 243 (98.8%) of the 246 subjects who received at least 1 dose of study drug completed treatment; 3 (1.2%) subjects (2 in the placebo group and 1 in the TEZ/IVA group) prematurely discontinued study drug and withdrew from the study. Seven other subjects discontinued from the study during the 8-week Washout Period between Period 1 and Period 2.

In Period 2, 235 subjects received at least 1 dose of study drug, and 234 (99.6%) subjects completed treatment; 1 (0.4%) subject in the IVA group prematurely discontinued treatment during Period 2. Overall, 227 (92.3%) subjects enrolled in the treatment cohort of the extension study, and no subjects enrolled in the observational cohort in the extension study.

Table 16 Participants flow in study 108

Disposition/Reason	Placebo n (%)	IVA n (%)	TEZ/IVA n (%)	Total n (%)
All Subjects Set[a]	165	164	167	248
FAS[b]	161	156	161	244
Randomized Set	165	164	167	248
Safety Set[c]	162	157	162	246
Period 1				
FAS	80	81	83	244
Safety Set	81	81	84	246
Completed treatment regimen	79 (97.5)	81 (100.0)	83 (98.8)	243 (98.8)
Prematurely discontinued treatment[d]	2 (2.5)	0	1 (1.2)	3 (1.2)
Reason for treatment discontinuation				
AE	1 (1.2)	0	0	1 (0.4)
Noncompliance with study drug	1 (1.2)	0	0	1 (0.4)
Pregnancy (self or partner)[d]	0	0	1 (1.2)[e]	1 (0.4)
Prematurely discontinued study	6 (7.4)	2 (2.5)	2 (2.4)	10 (4.1)
Reason for discontinuation from study				
AE	2 (2.5)	1 (1.2)	0	3 (1.2)
Withdrawal of consent (not due to AE)	2 (2.5)	0	0	2 (0.8)
Lost to follow-up	1 (1.2)	0	0	1 (0.4)
Other noncompliance	1 (1.2)	1 (1.2)	1 (1.2)	3 (1.2)
Other	0	0	1 (1.2)	1 (0.4)
Period 2				
FAS	81	75	78	234
Safety Set	81	76	78	235
Completed treatment regimen	81 (100.0)	75 (98.7)	78 (100.0)	234 (99.6)
Prematurely discontinued treatment	0	1 (1.3)	0	1 (0.4)
Reason for treatment discontinuation				
AE	0	1 (1.3)	0	1 (0.4)
Prematurely discontinued study	0	1 (1.3)	0	1 (0.4)
Reason for discontinuation from study				
AE	0	1 (1.3)	0	1 (0.4)
Completed treatment in both periods	156 (96.3)	154 (98.1)	158 (97.5)	234 (95.1)
Completed study	156 (96.3)	154 (98.1)	159 (98.1)	235 (95.5)
Rollover to Extension Study VX14-661-110	149 (92.0)	149 (94.9)	155 (95.7)	235 (95.5)
Treatment cohort	149 (92.0)	149 (94.9)	155 (95.7)	227 (92.3)
Observational cohort	0	0	0	0

Recruitment

Study 106 was conducted at 91 sites in the US, Canada, and Europe. Study period was from 30 January 2015 (date first eligible subject signed the informed consent form) up to 20 January 2017 (date last subject completed the last visit). Study 108 was conducted at 81 sites in North America, Europe, Israel, and Australia. Study period was from 27 March 2015 (date first eligible subject signed the informed consent form) up to 16 February 2017 (date last subject completed the last visit).

Conduct of the study

The Study 106 protocol was amended 3 times, see below. All the changes are considered not to have affected the size and interpretation of effects substantially.

Table 17 Summary of Study VX14-661-106 Protocol Amendments

Protocol Version	Date	Comments
1.0	14 November 2014	Original version
2.0	26 March 2015	Addition of CFQ-R assessment at Week 8, Week 16, and the Safety Follow-up Visit
3.0	08 June 2015	Addition of postdose spirometry and ophthalmologic examinations in subjects <18 years old
4.0	06 May 2016	Previous exclusion criterion 8 excluded subjects who had discontinued LUM/IVA pivotal studies to minimize potential bias. Exclusion criterion 8 was revised to additionally exclude subjects who received LUM/IVA (Orkambi) commercially, through an expanded access program, or through a clinical study.

CFQ-R: Cystic Fibrosis Questionnaire-Revised; LUM/IVA: lumacaftor/ivacaftor

The original protocol of study 108 was amended 2 times and major changes for each of the amendments are summarized the below table.

Table 18 Section of Summary of Study VX14-661-108 Protocols

Protocol version Date of version	***Major Amendments***
Version 2.0 ***06 August 2015***	Added ophthalmologic examination at the Early Termination of Treatment Visit or Safety Follow-up Visit for subjects <18 years of age at Screening and further instructions regarding examination Added spirometry assessments in subjects <18 years of age at Screening at 2 and 4 hours after dosing on Day 1 and Day 15 of each Treatment Period and further instructions regarding assessment Changed sweat chloride from the key secondary endpoint to a secondary endpoint; changed CFQ-R respiratory domain from a secondary endpoint to a key secondary endpoint

	Added washout requirements for subjects who have previously used a commercially available CFTR modulator. Added detail about the criteria used to determine eligible CTFR mutations; updated criteria to require all mutations to be potentially responsive to IVA monotherapy: Revised list of eligible mutations: removed P205S, A1067T, and R1070Q, and added E831X Revised the formula for calculating the number of days hospitalized for PEs
Version 3.0 ***10 June 2016***	Subjects whose screening genotype results do not confirm study eligibility will not be included in the FAS because they are not in the target population for the study. Reduced the sample size from 300 subjects (50 subjects per sequence) to approximately 204 subjects (34 subjects per sequence), based on the change to the testing strategy (see below). The revised power calculations with a sample size of 204 subjects are provided. Moved the relative change in ppFEV1 from a key secondary endpoint to a secondary endpoint and removed from the testing hierarchy because relative change provides similar information to the absolute change in ppFEV1 (the primary endpoint). Specified that the annualized duration of hospitalizations due to PExs will be calculated using data up to Week 8 in each Treatment Period. Removed responder analysis for ppFEV1 because it is difficult to interpret in the absence of an identified and validated minimal clinically important difference in the ppFEV1. Removed the statistical comparison of TEZ/IVA and IVA monotherapy from the testing strategy to be consistent with the primary objective. The testing strategy was accordingly replaced with a single, stepwise hierarchical approach.

After the database lock, a post-hoc analysis to investigate cross-over effects were performed: change of study baseline to average of week 4 and 8 in period 1 and in period 2. The major amendments are acceptable.

Baseline data

Subject demography and baseline characteristics, including baseline lung function and CFQ-R Respiratory Domain, were well-balanced across treatment groups and were generally similar in Studies 106 and 108, as stated in the below table**.**

Subjects with the F/F genotype (Study 106) typically have CF that has an earlier onset and is more rapidly progressive than with subjects with the F/RF genotype (Study 108). Consistent with this, the Study 106 population versus the Study 108 population was younger (mean age of 26.3 versus 34.8 years), had higher mean baseline sweat chloride values (100.9 versus 69.9 mmol/L), had lower mean BMI (21.04 versus 24.22 kg/m2), had higher use of inhaled antibiotics (58.7% versus 31.2%).

Table 19 Studies 106 and 108: Key Subject Demography and Baseline Characteristics, Full Analysis Set Outcomes of Study VX14-661-106

Characteristic	Study 106		Study 108 (Period 1)[c]		
	Placebo N = 256 n (%)	TEZ/IVA N = 248 n (%)	Placebo N = 80 n (%)	IVA N = 81 n (%)	TEZ/IVA N = 83 n (%)
Age at screening (years)					
Mean (min, max)	25.7 (12, 61)	26.9 (12, 64)	32.6 (12, 72)	36.3 (12, 69)	35.6 (12, 68)
Age groups at screening (years), n (%)					
<18	58 (22.7)	58 (23.4)	11 (13.8)	12 (14.8)	11 (13.3)
≥18	198 (77.3)	190 (76.6)	69 (86.3)	69 (85.2)	72 (86.7)
Sex, n (%)					
Male	131 (51.2)	127 (51.2)	34 (42.5)	41 (50.6)	35 (42.2)
Female	125 (48.8)	121 (48.8)	46 (57.5)	40 (49.4)	48 (57.8)
Region, n (%)					
North America	68 (26.6)	59 (23.8)	39 (48.8)	36 (44.4)	45 (54.2)
Europe[a]	188 (73.4)	189 (76.2)	41 (51.3)	45 (55.6)	38 (45.8)
Weight (kg)					
Mean (min, max)	58.9 (33.0, 107.0)	58.1 (29.0, 93.0)	69.7 (42.0, 112.0)	71.1 (40.0, 156.9)	67.7 (43.0, 127.0)
BMI (kg/m^2)[b]					
Mean (min, max)	21.12 (14.47, 32.24)	20.96 (13.67, 30.04)	24.56 (15.59, 36.99)	24.51 (15.19, 49.65)	23.61 (16.18, 42.43)
Residual function mutation, n (%)					
Non-canonical splice	NA	NA	48 (60.0)	48 (59.3)	50 (60.2)
Missense	NA	NA	32 (40.0)	33 (40.7)	33 (39.8)
$ppFEV_1$ at baseline					
Mean (min, max)	60.4 (27.8, 96.2)	59.6 (30.3, 91.1)	62.1 (35.1, 93.5)	62.8 (35.0, 92.2)	61.8 (34.6, 91.4)
$ppFEV_1$ categories at baseline, n (%)					
<40	24 (9.4)	23 (9.3)	6 (7.5)	8 (9.9)	8 (9.6)
≥40 to <70	152 (59.4)	157 (63.3)	48 (60.0)	46 (56.8)	48 (57.8)
≥70 to ≤90	73 (28.5)	65 (26.2)	25 (31.3)	26 (32.1)	25 (30.1)
>90	7 (2.7)	2 (0.8)	1 (1.3)	1 (1.2)	2 (2.4)
Missing	0	1 (0.4)	NA	NA	NA
Sweat chloride at baseline (mmol/L)					
Mean (min, max)	100.5 (42.0, 125.5)	101.3 (38.5, 140.0)	70.7 (19.0, 135.0)	74.9 (11.0, 112.5)	64.1 (12.5, 119.0)

CFQ-R Respiratory at baseline					
Mean (min, max)	69.9 (16.7, 100.0)	70.1 (6.7, 100.0)	67.8 (16.7, 94.4)	70.0 (16.7, 100.0)	66.5 (16.7, 100.0)
Colonization of *Pseudomonas aeruginosa*, n (%)					
Positive	182 (71.1)	185 (74.6)	48 (60.0)	45 (55.6)	52 (62.7)
Use of dornase alfa[c], n (%)	185 (72.3)	165 (66.5)	54 (67.5)	49 (60.5)	47 (56.6)
Use of azithromycin[c], n (%)	141 (55.1)	135 (54.4)	38 (47.5)	31 (38.3)	32 (38.6)
Use of inhaled antibiotic[c], n (%)	160 (62.5)	136 (54.8)	23 (28.8)	27 (33.3)	26 (31.3)
Use of bronchodilator[c], n (%)	234 (91.4)	222 (89.5)	71 (88.8)	68 (84.0)	74 (89.2)
Use of inhaled bronchodilator[c], n (%)	234 (91.4)	221 (89.1)	71 (88.8)	67 (82.7)	74 (89.2)
Use of inhaled hypertonic saline[c], n (%)	133 (52.0)	126 (50.8)	39 (48.8)	36 (44.4)	43 (51.8)
Use of inhaled corticosteroids[c], n (%)	162 (63.3)	139 (56.0)	45 (56.3)	48 (59.3)	50 (60.2)
Pancreatic insufficient[d], n (%)					
Yes	NA	NA	11 (13.8)	11 (13.6)	11 (13.3)

Sources: Study 106 CSR/Table 14.1.3 and Table 14.1.4; Study 108 CSR/Table 14.1.3 and Table 14.1.4

AE: adverse event; BMI: body mass index; CFQ-R: Cystic Fibrosis Questionnaire-Revised; IVA: ivacaftor; n: number of subjects; FEV_1: forced expiratory volume in 1 second; SD: standard deviation; TEZ: tezacaftor

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

[a] For Study 106 Europe includes Switzerland. For Study 108, subjects in Israel and Australia have been presented under Europe.

[b] BMI = Weight/(Height × Height) kg/m^2.

[c] Includes medications started before the first dose of study drug in the study and continuing during the treatment period.

[d] Fecal elastase-1 <200 µg/g. Fecal elastase was not collected in Study 106 because F/F subjects are expected to be pancreatic insufficient.

[e] Data from Study 108 Treatment Period 1 were presented to represent the baseline characteristics of the study population. No meaningful differences were observed in Treatment Period 1 and 2 for any treatment group.

Study 106: the number of obese and undernourished subjects was similar across treatment groups, both for adolescents (<18 years of age) and for adults (≥ 18 years of age). Approximately 30% of the all patients was undernourished (defined as BMI < 18.5 Kg/m^2), while for adolescents approximately 70% were undernourished. Approximately 98% of subjects in Study 106 had exocrine pancreatic insufficiency and up to 97% of these subjects received pancreatic enzyme replacement therapy.

Study 108: baseline characteristics for ppFEV1, CFQ-R respiratory domain score, and sweat chloride concentrations were compared for period 1 and 2 period using paired-t-tests. The within-subject differences of Period 1 and Period 2 baselines in ppFEV1, CFQ-R respiratory domain score, and sweat chloride were consistently negligible across treatments and support the lack of carryover effect. Overall, 30% of the patients received pancreatic enzymes in a population of patients in which 13.5% were identified as pancreatic insufficient defined as faecal elastase-1 concentration <200 µg/g).

Numbers analysed

Study VX14-661-106

Of the 509 subjects who received at least 1 dose of study drug, 475 (93.3%) completed dosing. The percentage of subjects who discontinued treatment due to AE was low in both treatment groups (TEZ/IVA: 2.8%; placebo: 3.1%). A total of 231 (92.0%) subjects in the TEZ/IVA group and 230 (89.1%) subjects in the placebo group rolled over into the Treatment Cohort of Study 110.

Outcomes and estimation

Study VX14-661-106

The efficacy analysis was performed on the Full Analysis Set (FAS): all randomized subjects who carry the intended CFTR allele mutation and have received at least 1 dose of study drug. A total of 510 subjects were randomized: 259 subjects in the placebo group and 251 subjects in the TEZ/IVA group. One subject in the placebo group did not receive any study drug dose due to a PEx before the Day 1 visit. Of the 509 subjects who received at least 1 dose of study drug, 475 (93.3%) completed dosing. The percentage of subjects who discontinued treatment due to AE was low in both treatment groups (TEZ/IVA: 2.8%; placebo: 3.1%). A total of 19 (3.7%) subjects had protocol deviations (IPDs).

Primary endpoint

The LS mean treatment difference between the TEZ/IVA and placebo groups was 4.0 % (95% CI: 3.1, 4.8) and was statistically significant in favour of TEZ/IVA (P<0.0001).

Table 20 MMRM Analysis of Absolute Change From Baseline in ppFEV1 Through Week 24, Full Analysis Set

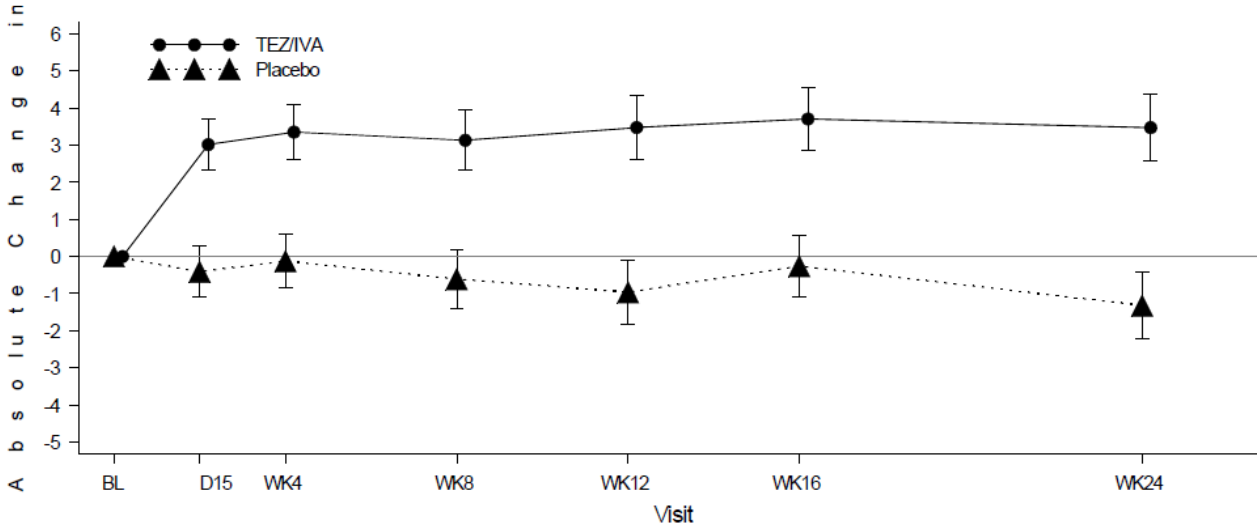
Statistic	Placebo N = 256	TEZ/IVA N = 248
Baseline		
n	256	247
Mean (SD)	60.4 (15.7)	59.6 (14.7)
Absolute change through Week 24		
n	256	245
LS mean (SE)	-0.6 (0.3)	3.4 (0.3)
95% CI of LS mean	(-1.3, 0.0)	(2.7, 4.0)
P value within treatment	0.0601	<0.0001
LS mean difference (95% CI)	NA	4.0 (3.1, 4.8)
P value versus placebo	NA	<0.0001

Source: Table 14.2.1.2.1.1

BL: baseline; CI: confidence interval; D: Day; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; ppFEV1: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor; WK: Week

Notes: The analysis included all measurements up to Week 24, whether assessed on treatment or after treatment discontinuation. The 95% CIs are from an MMRM that included treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex (male versus female), age group at screening (<18 versus ≥18 years old), BL ppFEV1, and BL ppFEV1-by-visit interaction. An unstructured covariance structure was used to model the within-subject errors. A Kenward-Roger approximation was used for the denominator degrees of freedom. BL was defined as the most recent non-missing measurement before the first dose of study drug.

A plot of the average absolute change from baseline in ppFEV1 through Week 24 is provided in below.



Source: Figure 14.2.1.1.1
BL: baseline; CI: confidence interval; D: Day; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; ppFEV1: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor; WK: Week
Notes: The analysis included all measurements up to Week 24, whether assessed on treatment or after treatment discontinuation. The 95% CIs are from an MMRM that included treatment, visit, and treatment-by-visit interaction as fixed effects with adjustments for sex (male versus female), age group at screening (<18 versus ≥18 years old), BL ppFEV1, and BL ppFEV1-by-visit interaction. An unstructured covariance structure was used to model the within-subject errors. A Kenward-Roger approximation was used for the denominator degrees of freedom. BL was defined as the most recent non-missing measurement before the first dose of study drug.

Figure 7 Absolute Change From Baseline in ppFEV1 at Each Visit, Full Analysis Set

Key Secondary Efficacy Variables

Relative Change From Baseline in Percent Predicted FEV1 Through Week 24: The key secondary endpoint of relative change from baseline in ppFEV1 through Week 24 analysed by MMRM was met. The LS mean treatment difference between the TEZ/IVA and placebo groups was 6.8% (95% CI: 5.3, 8.3) and was statistically significant in favour of TEZ/IVA (P<0.0001). Within group, the LS mean relative change in ppFEV1 through Week 24 was statistically significant in the TEZ/IVA group (6.3%; P<0.0001) but not in the placebo group (-0.5%; P = 0.3823).

Number of Pulmonary Exacerbations Through Week 24: The number of pulmonary exacerbations (PExs) through Week 24 was analysed using a negative binomial regression model. The model-based event rate of PExs was in the TEZ/IVA group 0.64 events per year and in the placebo group 0.99 events per year. The rate reduction in PExs was statistically significant in favour of TEZ/IVA as assessed by the rate ratio of 0.65 (95% CI: 0.48, 0.88; P = 0.0054). In addition, treatment with TEZ/IVA was associated with lower event rate per year of pulmonary exacerbations requiring IV antibiotic therapy (0.32) compared to placebo (0.59). The rate ratio versus placebo was 0.53 (95%CI: 0.34, 0.82; P = 0.0042).

Absolute Change From Baseline in BMI at Week 24: The absolute change from baseline in BMI at Week 24 was analysed using an MMRM model. At Week 24, the within-group improvement was statistically significant for the TEZ/IVA group (P = 0.0004) and for the placebo group (P = 0.0134). Although the LS mean absolute change from baseline in BMI was numerically greater in the TEZ/IVA group (0.18 kg/m^2) than in the placebo group (0.12 kg/m^2) at Week 24, the treatment difference was not statistically significant (P = 0.4127). Therefore, the hierarchical multiple testing procedure was stopped.

Absolute Change From Baseline in CFQ-R Respiratory Domain Score through Week 24: The last key secondary endpoint in the testing hierarchy was a self-reported measure of respiratory symptoms, the CFQ-R respiratory domain score, analysed by MMRM through Week 24. The pooled CFQ-R "Children Ages 12 and 13" and "Adolescents and Adults" versions were used for the analysis.

Treatment with TEZ/IVA resulted in improvements in the CFQ-R respiratory domain score. Within group, the LS mean absolute change from baseline in the pooled CFQ-R respiratory domain score through Week 24 was 5.0 points (P<0.0001) in the TEZ/IVA group and -0.1 points (P = 0.8889) in the placebo group. The LS mean treatment difference between the TEZ/IVA and placebo groups in pooled CFQ-R respiratory domain score was 5.1 points (95% CI: 3.2, 7.0; nominal P<0.0001).

Other Secondary Efficacy Variables

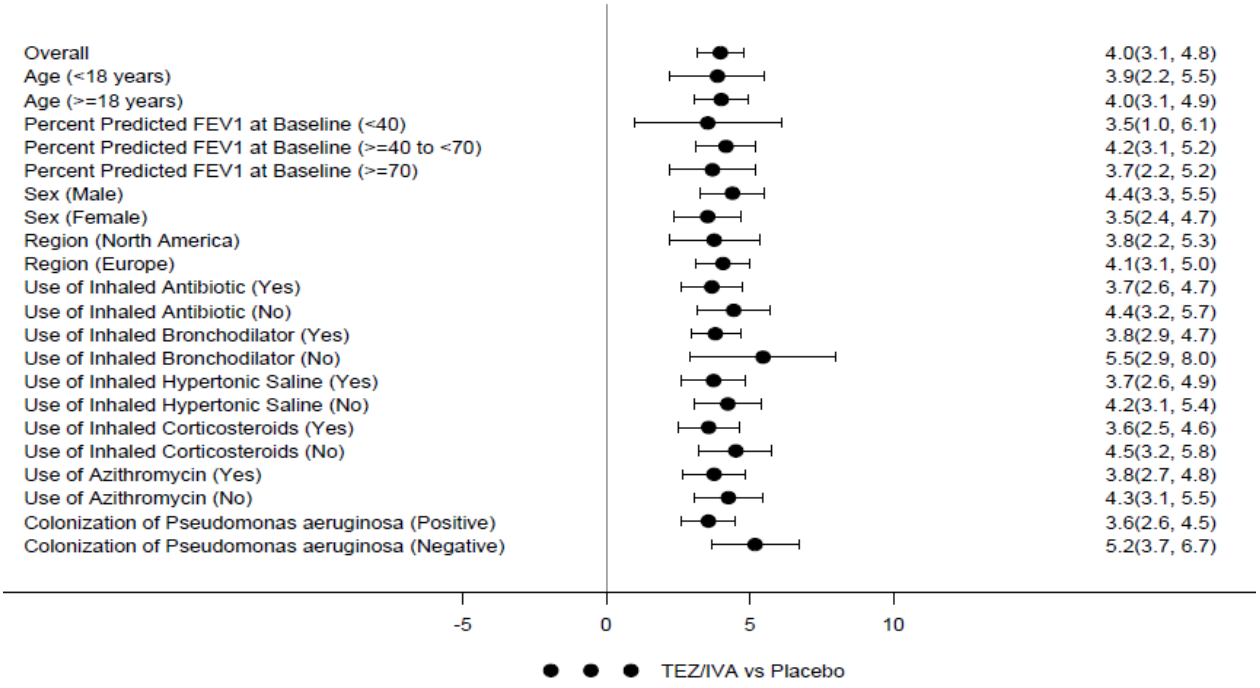
Time-to-First Pulmonary Exacerbation Through Week 24: TEZ/IVA reduced the risk of PEx compared to placebo, with a hazard ratio of 0.637 (P = 0.0069). The 75th percentile of event-free time of the time-to-first PEx was 14.6 weeks in the placebo group and 22.6 weeks in the TEZ/IVA group. The hazard ratio was 0.553 (0.357, 0.857; P= 0.0080) for time-to-first pulmonary exacerbation requiring IV antibiotic therapy. The estimated week 24 event-free rate (95% CI) was 0.87 (0.82, 0.91) in the TEZ/IVA group and 0.79 (0.73, 0.83) in the placebo group. Number of planned hospitalisations were 7 and 17 for TEZ/IVA and placebo respectively resulting in an observed event rate of 0.06 vs 0.13. For unplanned hospitalisations, the number of hospitalisations was 10 and 19 for TEZ/IVA and placebo respectively with an event rate of 0.08 vs 0.15.

Subgroup analysis

In the age group < 18 years, the LS mean treatment difference between the TEZ/IVA and placebo groups for the absolute change from baseline in ppFEV1 through Week 24 was 3.9 % (95% CI: 2.2, 5.5) and was statistically significant in favour of TEZ/IVA (P<0.0001). In the age group ≥ 18 years, the LS mean treatment difference between the TEZ/IVA and placebo groups was 4.0 % (95% CI: 3.1, 4.9; P<0.0001).

Consistent and significant effect in ppFEV1 favouring TEZ/IVA compared to placebo were observed across all prespecified subgroups: age (<18 or ≥18 years old), sex, baseline lung function (ppFEV1 <40, ≥40 to <70, or ≥70 %), region (North America or Europe), P. aeruginosa infection, and baseline use of common CF medications (i.e., azithromycin and inhaled antibiotics, bronchodilators, corticosteroids, and hypertonic saline).

Table 21 Forest Plot of LS Mean Difference between treatments with 95% CI for Absolute Change From Baseline in Percent Predicted FEV1 through Week 24 by Subgroup Full Analysis Set



Study VX14-661-108

The efficacy analysis was performed on the Full Analysis Set (FAS): all randomized subjects who carry the intended CFTR allele mutation and have received at least 1 dose of study drug. Among the 248 subjects who were randomly assigned to treatment, 246 subjects received at least 1 dose of study drug in Period 1 (81 received placebo, 81 received IVA, and 84 received TEZ/IVA). One subject assigned to placebo and 1 subject assigned to IVA in Period 1 were later deemed to be screen failures and did not receive treatment. In Period 2, 81 subjects received placebo, 76 subjects received IVA, and 78 subjects received TEZ/IVA. Across both periods, 162 subjects received at least 1 dose of placebo, 157 subjects received at least 1 dose of IVA, and 162 subjects received at least 1 dose of TEZ/IVA.

Table 22 Subject Disposition, All Subjects Set

Disposition/Reason	Placebo n (%)	IVA n (%)	TEZ/IVA n (%)	Total n (%)
All Subjects Set[a]	165	164	167	248
FAS[b]	161	156	161	244
Randomized Set	165	164	167	248
Safety Set[c]	162	157	162	246
Period 1				
FAS	80	81	83	244
Safety Set	81	81	84	246
Completed treatment regimen	79 (97.5)	81 (100.0)	83 (98.8)	243 (98.8)
Prematurely discontinued treatment[d]	2 (2.5)	0	1 (1.2)	3 (1.2)
Reason for treatment discontinuation				
AE	1 (1.2)	0	0	1 (0.4)
Noncompliance with study drug	1 (1.2)	0	0	1 (0.4)
Pregnancy (self or partner)[d]	0	0	1 (1.2)[e]	1 (0.4)
Prematurely discontinued study	6 (7.4)	2 (2.5)	2 (2.4)	10 (4.1)
Reason for discontinuation from study				
AE	2 (2.5)	1 (1.2)	0	3 (1.2)
Withdrawal of consent (not due to AE)	2 (2.5)	0	0	2 (0.8)
Lost to follow-up	1 (1.2)	0	0	1 (0.4)
Other noncompliance	1 (1.2)	1 (1.2)	1 (1.2)	3 (1.2)
Other	0	0	1 (1.2)	1 (0.4)
Period 2				
FAS	81	75	78	234
Safety Set	81	76	78	235
Completed treatment regimen	81 (100.0)	75 (98.7)	78 (100.0)	234 (99.6)
Prematurely discontinued treatment	0	1 (1.3)	0	1 (0.4)
Reason for treatment discontinuation				
AE	0	1 (1.3)	0	1 (0.4)
Prematurely discontinued study	0	1 (1.3)	0	1 (0.4)
Reason for discontinuation from study				
AE	0	1 (1.3)	0	1 (0.4)
Completed treatment in both periods	156 (96.3)	154 (98.1)	158 (97.5)	234 (95.1)
Completed study	156 (96.3)	154 (98.1)	159 (98.1)	235 (95.5)
Rollover to Extension Study VX14-661-110	149 (92.0)	149 (94.9)	155 (95.7)	235 (95.5)
Treatment cohort	149 (92.0)	149 (94.9)	155 (95.7)	227 (92.3)
Observational cohort	0	0	0	0

Overall, 234 (95.1%) of 246 of subjects in the safety set completed the treatment regimen in both periods. Eleven subjects (6 in the placebo group, 3 in the IVA group, and 2 in the TEZ/IVA group) withdrew from the study (10 subjects during Period 1 or during washout and 1 subject during Period 2). One additional subject who completed treatment with TEZ/IVA in Period 1 did not receive treatment in Period 2 but completed all visits in Period 2.

In Period 1, 243 (98.8%) of the 246 subjects who received at least 1 dose of study drug completed treatment; 3 (1.2%) subjects (2 in the placebo group and 1 in the TEZ/IVA group) prematurely discontinued study drug and withdrew from the study. Seven other subjects discontinued from the study during the 8-week Washout Period between Period 1 and Period 2. In Period 2, 235 subjects received at least 1 dose of study drug, and 234 (99.6%) subjects completed treatment; 1 (0.4%) subject in the IVA group prematurely discontinued treatment during Period 2.

Overall, 227 (92.3%) subjects enrolled in the treatment cohort of the extension study, and no subjects enrolled in the observational cohort in the extension study (Study VX14-661-110).

A total of 14 subjects were identified who had IPDs. Subjects could have IPDs in more than 1 category. A review of the results for the subjects with IPs did not suggest that the IPDs had a clinically meaningful effect on the study conclusions. As most subjects completed treatment in both periods, subject demography and baseline characteristics in Period 2 were similar to those for Period 1.

Primary endpoint

Absolute Change From Study Baseline in ppFEV1 to the Average of Week 4 and Week 8: treatment with TEZ/IVA and IVA resulted in statistically significant improvement in ppFEV1 compared to placebo. The LS mean treatment difference versus placebo for absolute change in ppFEV1 from study baseline to the average of Week 4 and Week 8 was 6.8 % (95% CI: 5.7, 7.8; P<0.0001) for the TEZ/IVA group and 4.7 % (95% CI: 3.7, 5.8; P<0.0001) for the IVA group. TEZ/IVA treatment resulted in statistically significant improvement in ppFEV1 compared to IVA. The LS mean treatment difference for the absolute change in ppFEV1 from study baseline to the average of Week 4 and Week 8 was 2.1 % (95% CI: 1.2, 2.9; P<0.0001) in favour of TEZ/IVA.

Table 23 Linear Mixed Effects Model for Absolute Change From Study Baseline in ppFEV1 to the Average of Week 4 and Week 8 Measurements, Full Analysis Set

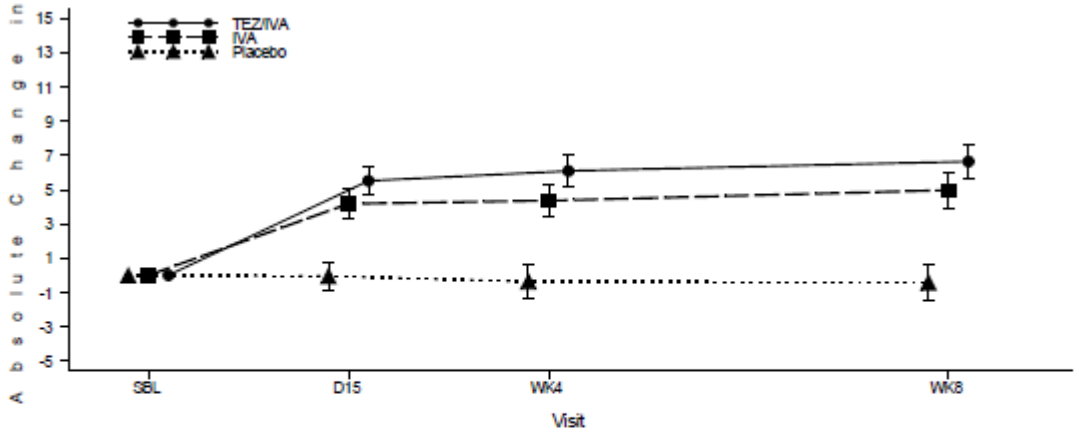
	Placebo N = 161	IVA N = 156	TEZ/IVA N = 161
Study Baseline			
n	161	156	161
Mean (SD)	62.2 (14.3)	62.1 (14.6)	62.1 (14.7)
Average absolute change at Week 4 and Week 8			
n	160	156	159
LS mean (SE)	-0.3 (0.5)	4.4 (0.5)	6.5 (0.4)
95% CI of LS mean	(-1.2, 0.6)	(3.5, 5.3)	(5.6, 7.3)
LS mean treatment difference versus placebo, (95% CI)	NA	4.7 (3.7, 5.8)	6.8 (5.7, 7.8)
P value versus placebo	NA	<0.0001	<0.0001
P value within Treatment	0.5035	<0.0001	<0.0001
LS mean treatment difference versus. IVA, (95% CI)	NA	NA	2.1 (1.2, 2.9)
P value versus IVA	NA	NA	*P*<0.0001

Source: Table 14.2.1.2.1

CI: confidence interval; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; IVA: ivacaftor; LS mean: least squares mean; n: size of subsample; N: total sample size; SE: standard error; TEZ: tezacaftor.

Notes: The FAS was defined as all randomized subjects who have received at least 1 dose of study drug. The FAS was used for efficacy analyses in which subjects were analyzed according to their randomized treatment group. Subjects were excluded from the FAS if they were found to have the incorrect genotype. Week 4 and Week 8 measurements after treatment discontinuation from the treatment period in which discontinuation occurred were included in the analysis.

[a] The following mixed effects model was used: treatment, period, and study baseline $ppFEV_1$ as fixed effects and subject as a random effect; Covariance Structure = CS with different structure parameters for sequences with and without placebo, DF = Kenward-Roger.



Source: Figure 14.2.1.1
CI: confidence interval; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; IVA: ivacaftor; LS mean: least squares mean; MMRM: mixed-effect model repeated measures; TEZ: tezacaftor; UN: unstructured
Notes: Analysis included all measurements up to Week 8, both on-treatment measurements and measurements after treatment discontinuation. A UN covariance structure was used to model the within-subject errors. A Kenward-Roger approximation was used for the denominator degrees of freedom.

Figure 8 MMRM Analysis of Absolute Change From Study Baseline in ppFEV1 at Each Visit, Full Analysis Set

Sensitivity Analysis for the Primary Efficacy Endpoint

A sensitivity analysis for the primary efficacy endpoint was performed using an MMRM model with treatment, period, visit within period, treatment-by-visit interaction, and ppFEV1 at study baseline as the covariates. Using this model, the LS mean treatment difference for the TEZ/IVA group versus placebo for the absolute change from study baseline in ppFEV1 to the average of Week 4 and Week 8 was 6.8 % (95% CI: 5.6, 8.0; P<0.0001). Treatment with TEZ/IVA also demonstrated statistically significant improvement in absolute change in ppFEV1 compared to IVA. The LS mean treatment difference for the IVA group versus placebo for the absolute change from study baseline in ppFEV1 to the average of Week 4 and Week 8 was 5.1 % (95% CI: 3.8, 6.3; P<0.0001)

Key Secondary Efficacy Variable

Absolute Change from Study Baseline in CFQ-R Respiratory Domain to the Average of Week 4 and Week 8: The minimum clinically important difference (MCID) for the CFQ-R respiratory domain score is 4 points. Treatment with TEZ/IVA and IVA resulted in statistically significant improvement in absolute change in CFQ-R respiratory domain score compared to placebo, and mean CFQ-R respiratory domain scores increased by more than 4 points in the TEZ/IVA and IVA groups. Compared to placebo, the LS mean treatment difference from study baseline to the average of Week 4 and Week 8 was 11.1 points (95% CI: 8.7, 13.6; P<0.0001) for TEZ/IVA and 9.7 points (95% CI: 7.2, 12.2; P<0.0001) for IVA.

Table 24 Linear Mixed Effects Model for Absolute Change From Study Baseline in CFQ-R Respiratory Domain to the Average of Week 4 and Week 8, Full Analysis Set

	Placebo N = 161	IVA N = 156	TEZ/IVA N = 161
Study Baseline			
n	161	156	161
Mean (SD)	68.7 (18.3)	67.9 (16.9)	68.2 (17.5)
Average absolute change to the average at Week 4 and Week 8			
n	160	156	161
LS mean (SE)	-1.0 (1.0)	8.7 (1.0)	10.1 (1.0)
95% CI of LS mean	(-2.9, 1.0)	(6.8, 10.7)	(8.2, 12.1)
P value within treatment	0.3265	<0.0001	<0.0001
LS mean difference versus placebo, 95% CI	NA	9.7 (7.2, 12.2)	11.1 (8.7, 13.6)
P value versus placebo	NA	<0.0001	<0.0001
LS mean difference versus IVA, 95% CI	NA	NA	1.4 (-1.0, 3.9)
P value versus IVA	NA	NA	0.2578

Source: Table 14.2.4.2

CFQ-R: Cystic Fibrosis Questionnaire- Revised; CI: confidence interval; IVA: ivacaftor; LS mean: least squares mean; n: size of subsample; N: total sample size; SD: standard deviation; SE: standard error; TEZ: tezacaftor.

Notes: Week 4 and Week 8 measurements after treatment discontinuation from the treatment period in which discontinuation occurred were included in the analysis. The following mixed effects model was used: treatment, period, study baseline CFQ-R respiratory domain score as fixed effects and subject as a random effect; Covariance Structure = CS with different structure parameters for sequences with and without placebo; DF = Kenward-Roger.

The absolute change in CFQ-R respiratory domain score was numerically greater in the TEZ/IVA group than the IVA group. The LS mean treatment difference for absolute change in CFQ-R respiratory domain from study baseline to the average of Week 4 and Week 8 was 1.4 points (95% CI: -1.0, 3.9; P = 0.2578), in favour of TEZ/IVA.

Other Secondary Efficacy Variables

Relative Change in ppFEV1 from Study Baseline to the Average of Week 4 and Week 8: Results for relative change in ppFEV1 were consistent with the result for the primary analysis. Treatment with TEZ/IVA and IVA resulted in improvement in relative change in ppFEV1 compared to placebo. The LS mean treatment difference versus placebo for the relative change in ppFEV1 from study baseline to the average of Week 4 and Week 8 was 11.4% (95% CI: 9.6, 13.2; P<0.0001) for TEZ/IVA and 8.1% (95% CI: 6.3, 9.9; P<0.0001) for IVA. The relative change in ppFEV1 was greater in TEZ/IVA than IVA. The LS mean treatment difference for the relative change in ppFEV1 from study baseline to the average of Week 4 and Week 8 was 3.3% in favour of TEZ/IVA (95% CI: 1.8, 4.8; P<0.0001)

Treatment with TEZ/IVA and IVA reduced sweat chloride concentrations compared to placebo: The LS mean treatment difference versus placebo for the absolute change in sweat chloride from study baseline to the average of Week 4 and Week 8 was -9.5 mmol/L (95% CI: -11.7, -7.3; P<0.0001) for TEZ/IVA and -4.5 mmol/L (95% CI: -6.7, -2.3; P<0.0001) for IVA. The reduction in sweat chloride concentration was greater in TEZ/IVA than IVA. The LS mean treatment difference for the absolute change in sweat chloride from study baseline to the average of Week 4 and Week 8 was -5.1 mmol/L in favour of TEZ/IVA (95% CI: -7.0, -3.1; P<0.0001).

Additional Efficacy Variables and Other Endpoints

- Additional Spirometry Variables

Analysis of additional lung function parameters, including (predose) FEV1, FVC, ppFVC, FEF25%-75%, ppFEF25%-75%, FEV1/FVC ratio, and ppFEV1/FVC ratio were also performed. Improvements were observed for both TEZ/IVA and IVA compared to placebo for all parameters. To evaluate changes in small airways, the effect on ppFEF25%-75% was analysed. The mean (SD) absolute change from study baseline to the average of Week 4 and Week 8 in ppFEF25%-75% was 7.8 % (10.6) in the TEZ/IVA group, 6.6 % (10.3) in the IVA group, and -0.1 % (7.9) in the placebo group.

- Analysis of Response in CFQ-R Respiratory Domain

The MCID for the CFQ-R respiratory domain score is considered to be 4 points. The percentage of subjects who had an increase of at least 4 points was higher for TEZ/IVA and IVA compared to placebo. At the average of Week 4 and Week 8, the percentages of subjects who exceeded the improvement threshold was 65.2% in the TEZ/IVA group, 58.3% in the IVA group, and 32.9% in the placebo group. The odds ratio versus placebo was 7.418 (95% CI: 3.649, 15.080; P<0.0001) for TEZ/IVA, and 4.847 (95% CI: 2.447, 9.605; P<0.0001) for IVA. The odds ratio for TEZ/IVA versus IVA was 1.530 (95% CI: 0.849, 2.759; P = 0.1562).

- Variables Related to BMI

Increases in BMI and weight were observed in all treatment groups at Week 8. The mean absolute change from study baseline in BMI at Week 8 was 0.34 kg/m^2 for TEZ/IVA, 0.47 kg/m^2 for IVA, and 0.18 kg/m^2 for placebo.

- Pulmonary Exacerbations

PEx events occurred in 11 (6.8%) subjects in the TEZ/IVA group, 9 (5.8%) subjects in the IVA group, and 19 (11.8%) subjects in the placebo group. The estimated event rate of PEx was lower for TEZ/IVA (0.34 events per year) and IVA (0.29 events per year) than for placebo (0.63 events per year). Compared to placebo, the rate ratio was 0.54 (95% CI: 0.26, 1.13; P = 0.1031) for TEZ/IVA and 0.46 (95% CI: 0.21, 1.01; P = 0.0532) for IVA. The rate ratio was 1.18 (95% CI: 0.49, 2.87; P = 0.7131) for TEZ/IVA compared to IVA.

Table 25 Generalized Linear Mixed Model Analyses for the Number of PExs During PEx Analysis Period, Full Analysis Set

Statistic	Placebo N = 161	IVA N = 156	TEZ/IVA N = 161
Number of subjects with events, n(%)	19 (11.8)	9 (5.8)	11 (6.8)
Total number of days (years)	10268 (30.56)	10137 (30.17)	10378 (30.89)
Number of events (observed event rate per year)	20 (0.65)	9 (0.30)	11 (0.36)
Estimated event rate per year*	0.63	0.29	0.34
Rate ratio versus placebo, 95% CI	NA	0.46 (0.21, 1.01)	0.54 (0.26, 1.13)
P value versus placebo	NA	0.0532	0.1031
Rate ratio versus IVA, 95% CI	NA	NA	1.18 (0.49, 2.87)
P value versus IVA	NA	NA	0.7131

Source: Table 14.2.2.1

CI: confidence interval; IVA: ivacaftor; n: size of subsample; N: number of subjects; NA: not applicable; PEx: pulmonary exacerbation; PEx Analysis Period: Time from the first dose in the treatment period to the last efficacy assessment up to Week 8 of the same treatment period; ppFEV1: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor.

Notes: Total number of days = PEx analysis period end date − PEx analysis period start date + 1 for all subjects in the FAS. Total number of years is calculated by dividing this quantity by 336. Observed event rate per year is calculated as the total number of events divided by total number of years.

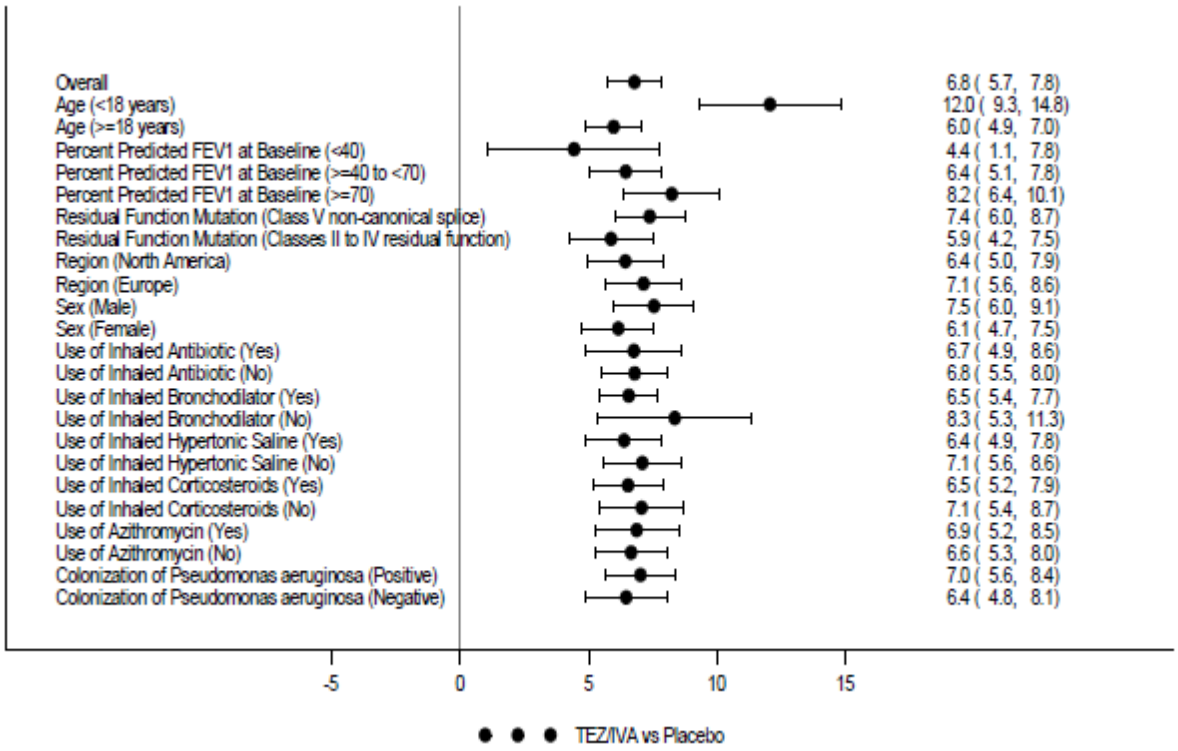
* Generalized linear mixed model for number of events: treatment, period, study baseline percent predicted FEV1 as fixed effects and subject as a random effect; Distribution: Negative binomial, link: log; offset = log of PEx analysis period duration in years. PEx was defined as a new event or change in antibiotic therapy for ≥4 sinopulmonary signs/symptoms (as listed in Section 9.5.7.8.1).

Subgroup analysis

Subgroup Analysis of Primary Efficacy Endpoint

For the FAS, subgroup analyses of the primary endpoint were performed using a model similar to that for the primary analysis, but included an additional covariate for the relevant grouping factor as well as a term for grouping factor by treatment interaction. All of the subgroup analyses demonstrated that TEZ/IVA and IVA treatment resulted in statistically significant improvement over placebo in mean absolute change from study baseline in ppFEV1 to the average of Week 4 and Week 8 regardless of age, baseline lung function, region, use of common CF medications, P. aeruginosa colonization, and RF mutation group (Class V non-canonical splice or Classes II to IV missense). Regarding gender, the treatment effect for TEZ/IVA versus IVA was greater in males (2.6 pp) compared with females (1.6 pp). The subgroup analysis of sweat chloride and CFQ-R in males and females were consistent with the primary analysis. For TEZ/IVA, the mean treatment differences for absolute change in ppFEV1 through the average of Week 4 and Week 8 compared to placebo ranged from 4.4 (95% CI:1.1, 7.8) to 12.0 (95% CI:9.3, 14.8) % across subgroups (P<0.05). For IVA, the mean treatment differences for absolute change in ppFEV1 to the average of Week 4 and Week 8 compared to placebo ranged from 3.6 % (95% CI: 1.9, 5.2) to 8.0 % (95% CI: 5.2, 10.7) across subgroups (P<0.05).

Table 26 Forest Plot of LS Mean Difference for Absolute Change From Study Baseline in ppFEV1 to Average of Week 4 and Week 8 by Subgroup, Full Analysis Set



Source: Figure 14.2.1.3
IVA: ivacaftor; ppFEV1: percent predicted forced expiratory volume in 1 second; LS: least squares; ppFEV1: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor
Note: The forest plot is based on data from Table 14.2.1.2.1 and Table 14.2.1.2.3.

Clinical data for splice mutations were analysed as a subgroup for the primary endpoint of ppFEV1 and demonstrated a treatment effect compared to placebo of 7.4 % (95% CI: 6.0, 8.7; P <0.0001). The treatment effect for the splice mutation subgroup compared to IVA monotherapy was 1.9 % (95% CI: 0.8, 3.0; P = 0.0008), confirming the contribution of TEZ in this sub-population. Summary statistics by RF Mutation are provided below.

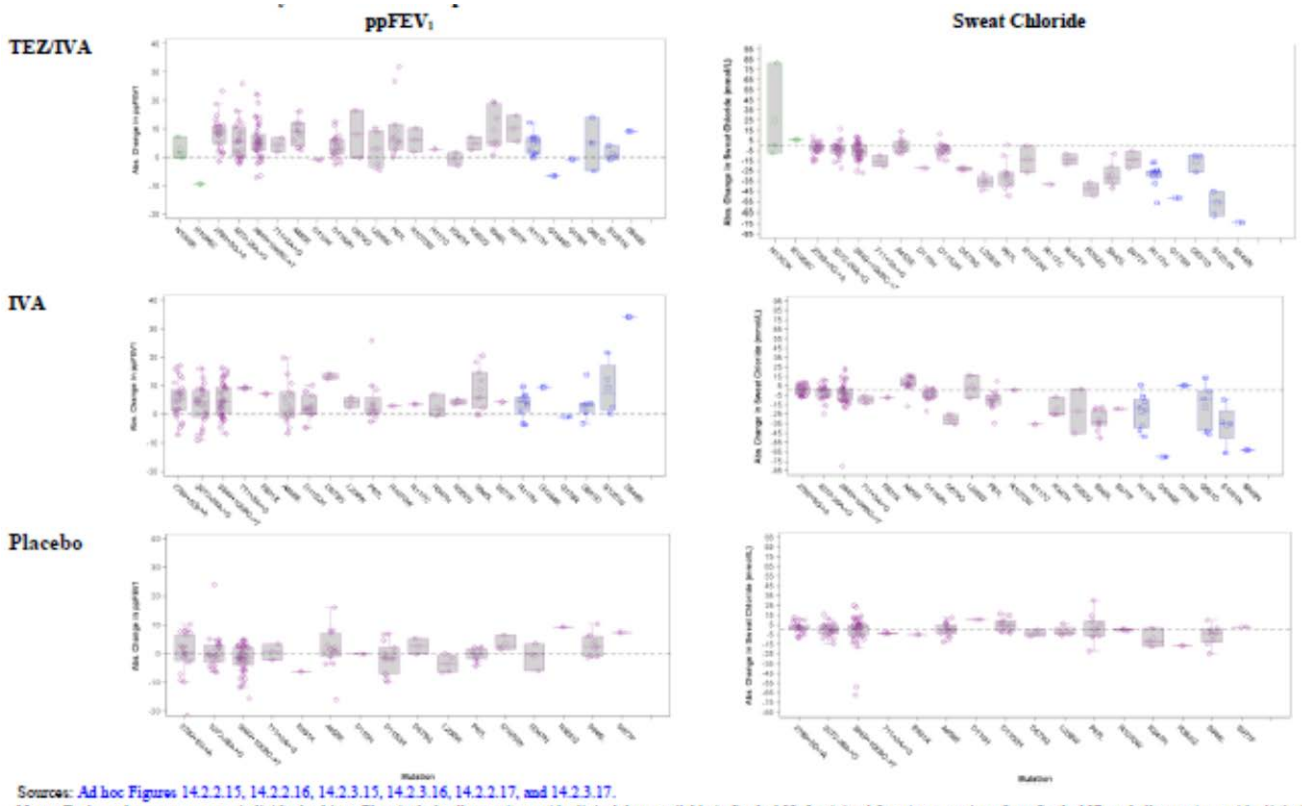
Table 27 Summary Statistics for Absolute Change from Study Baseline in Percent Predicted FEV1 to the Average of Week 4 and Week 8 by RF Mutation Full Analysis Set

RF Mutation	Statistic	Placebo*	IVA	TEZ/IVA
F508del/2789+5G->A	n	160	28	25
	Mean (SD)	-0.4 (5.9)	5.1 (6.4)	8.6 (5.6)
	Median	-0.3	5.4	8.8
	Min, Max	-23.8, 24.0	-7.1, 17.0	-1.5, 23.4
	Mean Diff vs Placebo, 95% CI	-	5.6 (3.2, 8.0)	9.0 (6.5, 11.5)
F508del/3272-26A->G	n	160	23	23
	Mean (SD)	-0.4 (5.9)	3.5 (6.6)	5.7 (6.9)
	Median	-0.3	4.5	5.3
	Min, Max	-23.8, 24.0	-9.1, 16.0	-2.1, 25.9
	Mean Diff vs Placebo, 95% CI	-	3.9 (1.2, 6.5)	6.1 (3.5, 8.8)
F508del/3849+10kbC->T	n	160	40	43
	Mean (SD)	-0.4 (5.9)	5.1 (5.9)	5.8 (6.3)
	Median	-0.3	4.3	5.0
	Min, Max	-23.8, 24.0	-6.8, 16.2	-7.2, 22.3
	Mean Diff vs Placebo, 95% CI	-	5.5 (3.5, 7.6)	6.2 (4.2, 8.2)
F508del/711+3A->G	n	160	2	2
	Mean (SD)	-0.4 (5.9)	9.2 (0.5)	4.3 (3.4)
	Median	-0.3	9.2	4.3
	Min, Max	-23.8, 24.0	8.9, 9.6	2.0, 6.7
	Mean Diff vs Placebo, 95% CI	-	9.6 (1.4, 17.9)	4.8 (-3.5, 13.0)
F508del/A455E	n	160	14	11
	Mean (SD)	-0.4 (5.9)	3.7 (7.5)	8.5 (4.3)
	Median	-0.3	1.2	9.3
	Min, Max	-23.8, 24.0	-6.6, 19.7	2.6, 16.1
	Mean Diff vs Placebo, 95% CI	-	4.1 (0.8, 7.5)	9.0 (5.4, 12.5)
F508del/D110H	n	160	0	1
	Mean (SD)	-0.4 (5.9)	-	-1.0 (-)
	Median	-0.3	-	-1.0
	Min, Max	-23.8, 24.0	-	-1.0, -1.0
	Mean Diff vs Placebo, 95% CI	-	-	-0.6 (-12.2, 11.1)
F508del/D1152H	n	160	15	21
	Mean (SD)	-0.4 (5.9)	2.4 (4.3)	3.8 (3.9)
	Median	-0.3	1.8	3.0
	Min, Max	-23.8, 24.0	-5.0, 10.2	-2.5, 12.5
	Mean Diff vs Placebo, 95% CI	-	2.8 (-0.2, 5.9)	4.2 (1.6, 6.8)
F508del/D579G	n	160	2	2
	Mean (SD)	-0.4 (5.9)	13.3 (1.2)	8.1 (11.7)
	Median	-0.3	13.3	8.1
	Min, Max	-23.8, 24.0	12.4, 14.1	-0.2, 16.4
	Mean Diff vs Placebo, 95% CI	-	13.7 (5.5, 22.0)	8.5 (0.2, 16.9)
F508del/E831X	n	160	1	0
	Mean (SD)	-0.4 (5.9)	7.1 (-)	-
	Median	-0.3	7.1	-
	Min, Max	-23.8, 24.0	7.1, 7.1	-
	Mean Diff vs Placebo, 95% CI	-	7.5 (-4.2, 19.1)	-
F508del/L206W	n	160	2	4
	Mean (SD)	-0.4 (5.9)	4.2 (2.4)	3.0 (7.5)
	Median	-0.3	4.2	3.2
	Min, Max	-23.8, 24.0	2.5, 5.9	-4.5, 10.2
	Mean Diff vs Placebo, 95% CI	-	4.6 (-3.6, 12.8)	3.4 (-2.5, 9.3)

F508del/P67L	n	160	12	11
	Mean (SD)	-0.4 (5.9)	4.3 (7.7)	9.4 (10.4)
	Median	-0.3	1.6	5.8
	Min, Max	-23.8, 24.0	-2.5, 25.7	0.0, 31.9
	Mean Diff vs Placebo, 95% CI	-	4.7 (1.2, 8.3)	9.8 (6.0, 13.7)
F508del/R1070W	n	160	1	2
	Mean (SD)	-0.4 (5.9)	2.9 (-)	6.1 (5.8)
	Median	-0.3	2.9	6.1
	Min, Max	-23.8, 24.0	2.9, 2.9	2.0, 10.1
	Mean Diff vs Placebo, 95% CI	-	3.3 (-8.3, 15.0)	6.5 (-1.8, 14.7)
F508del/R117C	n	160	1	1
	Mean (SD)	-0.4 (5.9)	3.5 (-)	2.9 (-)
	Median	-0.3	3.5	2.9
	Min, Max	-23.8, 24.0	3.5, 3.5	2.9, 2.9
	Mean Diff vs Placebo, 95% CI	-	3.9 (-7.7, 15.6)	3.3 (-8.3, 15.0)
F508del/R347H	n	160	3	2
	Mean (SD)	-0.4 (5.9)	2.5 (3.9)	-0.5 (3.1)
	Median	-0.3	1.3	-0.5
	Min, Max	-23.8, 24.0	-0.6, 6.9	-2.8, 1.7
	Mean Diff vs Placebo, 95% CI	-	2.9 (-3.8, 9.7)	-0.1 (-8.4, 8.1)
F508del/R352Q	n	160	2	2
	Mean (SD)	-0.4 (5.9)	4.4 (1.3)	4.9 (3.2)
	Median	-0.3	4.4	4.9
	Min, Max	-23.8, 24.0	3.5, 5.3	2.6, 7.1
	Mean Diff vs Placebo, 95% CI	-	4.8 (-3.4, 13.1)	5.3 (-3.0, 13.5)
F508del/S945L	n	160	9	7
	Mean (SD)	-0.4 (5.9)	8.8 (7.9)	9.6 (7.7)
	Median	-0.3	5.9	5.4
	Min, Max	-23.8, 24.0	-0.2, 20.5	0.7, 19.5
	Mean Diff vs Placebo, 95% CI	-	9.2 (5.1, 13.2)	10.0 (5.5, 14.6)
F508del/S977F	n	160	1	2
	Mean (SD)	-0.4 (5.9)	4.3 (-)	10.1 (6.5)
	Median	-0.3	4.3	10.1
	Min, Max	-23.8, 24.0	4.3, 4.3	5.5, 14.7
	Mean Diff vs Placebo, 95% CI	-	4.7 (-7.0, 16.3)	10.5 (2.2, 18.8)

The comparison of TEZ/IVA and IVA for ppFEV1 was in favour of TEZ/IVA, overall and for the majority of predefined subgroups. Overall, the LS mean treatment difference for the TEZ/IVA group versus IVA for the absolute change from study baseline in ppFEV1 to the average of Week 4 and Week 8 was 2.1 percentage points (95% CI: 1.2, 2.9; P <0.0001).

On request of the CHMP, box-and-whisker plots with jitters were submitted by the applicant during the assessment. The plots demonstrated the variability in response between subjects with the same mutation, see below.



Sources: Ad hoc Figures 14.2.2.15, 14.2.2.16, 14.2.3.15, 14.2.3.16, 14.2.2.17, and 14.2.3.17.

Notes: Each marker represents an individual subject. Plots include all mutations with clinical data available in Study 108, 2 minimal function mutations from Study 107, and all mutations with clinical data available in Study 109. Only subjects without prior IVA use are included for Study 109. Baseline was defined as the last assessment before the first dose of study drug during the treatment period (Studies 107 and 108) or the Run-In Period (Study 109).

Figure 9 Box-and-Whisker Plot of Absolute Change from Baseline in ppFEV1 and Sweat chloride for Residual Function, Gating (IVA-naïve), and Minimal Function Mutations by Treatment Group

Mixed Model

At request of the CHMP, mixed models to describe the between- and within- mutation variance and to investigate the possibility to predict generalisation to mutations that were not enrolled were also submitted.

The linear mixed effect model included the absolute change from study baseline in ppFEV1 or sweat chloride to the average of the Week 4 and Week 8 measurements as the dependent variable, treatment as a fixed effect, and mutation as a random effect. Compared to placebo, improvements in ppFEV1 were larger for TEZ/IVA and IVA. In addition, improvements with TEZ/IVA were larger than with IVA. Placebo behaved as expected for all mutations, with estimated mean changes from baseline for ppFEV1 close to 0 percentage points. The results based on the linear mixed effects model are consistent with the pre-planned primary analysis model. Furthermore, the results of the model suggest a consistent treatment benefit of TEZ/IVA for all individual mutations in the proposed indication. The between-mutation variability is quite small (1.7 percentage points, SD = 1.3) compared with the within-mutation variance (37.3 percentage points, SD = 6.1).

Based on the linear mixed model, the range of mean responses for mutations that were eligible but not enrolled in Study 108 were predicted. For subjects treated with TEZ/IVA, the range of the mean increase for a mutation is 5.1 to 8.5 percentage points based on the model. For any mutation that was eligible for Study 108, the mean response is predicted to be 4.6 percentage points or greater for TEZ/IVA with 95% probability. For IVA, the mean response for a randomly selected mutation would be 2.7 percentage points or greater with 95% probability. For sweat chloride for subjects treated with

TEZ/IVA, the range of the mean improvement for a mutation is -2.6 to -28.5 mmol/L based on the model.

Ancillary analyses

In the age group < 18 years, the LS mean treatment difference between the TEZ/IVA and placebo groups for the absolute change from baseline in ppFEV1 through Week 24 was 3.9 percentage points (95% CI: 2.2, 5.5) and was statistically significant in favour of TEZ/IVA (P<0.0001). In the age group ≥ 18 years, the LS mean treatment difference between the TEZ/IVA and placebo groups it was 4.0 percentage points (95% CI: 3.1, 4.9; P<0.0001). Consistent and significant effects in ppFEV1 favouring TEZ/IVA compared to placebo were observed across all pre-specified subgroups: age (<18 or ≥18 years old), sex, baseline lung function (ppFEV1 <40, ≥40 to <70, or ≥70 percentage points), region (North America or Europe), P. aeruginosa infection, and baseline use of common CF medications (i.e., azithromycin and inhaled antibiotics, bronchodilators, corticosteroids, and hypertonic saline).

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 28 Summary of efficacy for trial 106

Title: A Phase 3, Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Efficacy and Safety of VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the *F508del*-CFTR Mutation			
Study identifier	EudraCT Number: 2014-004837-13; VX14-661-106		
Design	Randomized, double-blind, placebo-controlled, parallel-group, multicenter study in subjects 12 years old and older with CF who are homozygous for the F508del-CFTR mutation.		
	Duration of main phase:		24 weeks ± 5 days
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		As extension part, patients rolled over to a separate study
Hypothesis	Superiority		
Treatments groups	Symkevi + ivacaftor		100 mg TEZ/150 mg IVA daily for 24 weeks + 150 mg IVA daily for 24 weeks, N = 251
	Placebo		0 mg TEZ/0 mg IVA daily for 24 weeks + 0 mg IVA daily for 24 weeks, N=259
Endpoints and definitions	Primary endpoint	ppFEV1	absolute change from baseline in ppFEV1 through Week 24
	Key Secondary	ppFEV1	Relative change in ppFEV1 from baseline through Week 24 (%)
	Key Secondary	PEx	Number of pulmonary exacerbations from baseline through Week 24
	Key Secondary	BMI	Absolute change in BMI from baseline at Week 24 (kg/m^2)
	Key Secondary	CFQ-R	Absolute change in CFQ-R Respiratory Domain Score from baseline through Week 24
Database lock	21 February 2017.		

Results and Analysis

Analysis description	**Primary Analysis – absolute change in lung function as measured by ppFEV1** Adult and adolescent patients with cystic fibrosis (CF) who are homozygous for the F508del mutation on the CFTR gene and have FEV1 ≥40% and ≤ 90% of predicted normal were included.		
Analysis population and time point description	Full Analysis Set (FAS): all randomized subjects who carry the intended CFTR allele mutation and have received at least 1 dose of study drug. 24 weeks		
Descriptive statistics and estimate variability	Treatment group	placebo	TEZ/IVA
	Number of subject	256	248
	LS mean ppFEV1 (absolute change from baseline)	-0.6	3.4
	95% CI of LS mean	-1.3, 0.0	2.7, 4.0
	LS mean ppFEV1 (relative change from baseline)	-0.5	6.3
	95% CI of LS mean	-1.7, 0.6	5.1, 7.4
	PEx	122	78
	Estimated event rate per year	0.97	0.64
	LS mean BMI (absolute change from baseline)	0.12	0.18
	95% CI of LS mean	0.03, 0.22	0.08, 0.28
	LS mean CFQ-R Respiratory domain (Absolute Change From Baseline	-0.1	5.0
	95% CI of LS mean	-1.6, 1.4	(3.5, 6.5)

Effect estimate per comparison	Primary endpoint	Comparison groups	TEZ/IVA versus placebo
		LS mean difference absolute change ppFEV1	4.0
		95% CI	3.1, 4.8
		P-value	<0.0001
	Key secondary endpoint	Comparison groups	TEZ/IVA versus placebo
		LS mean difference relative change ppFEV1	6.8%
		95% CI	5.3, 8.3
		P-value	<0.0001
	Key secondary endpoint	Comparison groups	TEZ/IVA versus placebo
		Rate reduction in PExs	0.65
		95% CI	0.48, 0.88
		P-value	0.0054
	Key secondary	Comparison groups	TEZ/IVA versus placebo

	endpoint	LS mean difference BMI	0.06
		95% CI	-0.08, 0.19
		P-value	0.4127
	Key secondary endpoint	Comparison groups	TEZ/IVA versus placebo
		LS mean difference CFQ-R (points)	5.1
		95% CI	3.2, 7.0
		P-value	N/A[a]
Notes	[a] The treatment difference for the LS mean absolute change from baseline in BMI was not statistically significant (*P* = 0.4127). Therefore, the hierarchical multiple testing procedure was stopped.		
Analysis description	**Secondary analysis** As other secondary efficacy endpoints, time-to-first pulmonary exacerbation, absolute change in sweat chloride from baseline, absolute change in BMI z-score from baseline (in subjects <20 years of age at time of screening) and absolute change in body weight from baseline were investigated. They all showed a positive effect for TEZ/IVA compared to placebo. **Ancillary analysis** The Forest Plot for the subgroups analysed, shows a consistent beneficial effect for TEZ/IVA compared to placebo. The lowest point estimate is 3.5 difference in the group of patients with low baseline FEV1 (ppFEV1 < 40%) and female sex.		

Table 29 Summary of efficacy for trial VX14-661-108

Title: A Phase 3, Randomized, Double-blind, Placebo-controlled, Crossover Study to Evaluate the Efficacy and Safety of Ivacaftor and VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Heterozygous for the F508del-CFTR Mutation, and a Second Allele With a CFTR Mutation Predicted to Have Residual Function			
Study identifier	Eudra CT Number: 2014-004788-18; VX14-661-108		
Design	Randomized, double-blind, placebo-controlled, 6 treatment sequences, incomplete crossover. Randomization (1:1:1:1:1:1) was stratified by age (<18 versus ≥18 years), FEV1 severity (<70% versus ≥70% predicted), and type of RF mutation on the second CFTR allele (Class V noncanonical splice mutation versus Classes II to IV missense RF mutation)		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		2 Treatment Periods (8 weeks each), and Washout Period (8 weeks), not applicable not applicable
Hypothesis	Superiority of 3 percentage point treatment difference between TEZ/IVA and placebo for the mean values of the primary endpoint		
Treatments groups	placebo		2 x 8 weeks, N=165
	ivacaftor		2 x 8 weeks, N=164
	Tezacaftor/ivacaftor		2 x 8 weeks, N=167
Endpoints and definitions	Primary endpoint	ppFEV1	Absolute change from study baseline in ppFEV1 to the average of Week 4 and Week 8
	Key Secondary endpoint	CFQ-R	Absolute Change from Study Baseline in CFQ-R Respiratory Domain to the Average of Week 4 and Week 8
Database lock	14 March 2017		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Full analysis Set (FAS): all randomized subjects who carry the intended CFTR mutations and had received at least 1 dose of study drug. Week 4-8 per treatment period			
Descriptive statistics and estimate variability	Treatment group	placebo	ivacaftor	Tezacaftor/ivacaftor
	Number of subject	161	156	161
	LS mean change in ppFEV1	-0.3	4.4	6.5
	95% CI	-1.2, 06	3.5,5.3	5.6,7.3
	LS mean change in CFQ-R	-1	8.7	10.1
	95% CI	-2.9,1.0	6.8 10.7	8.2,12.1

Effect estimate per comparison	LS mean change in ppFEV1	Comparison groups	TEZ/IVA versus placebo
		LS mean difference	6.8
		95% CI	5.7, 7.8
		P-value	<0.0001
		Comparison groups	TEZ/IVA versus IVA
		LS mean difference	2.1
		95% CI	1.2, 2.9
		P-value	<0.0001
	LS mean change in CFQ-R	Comparison groups	TEZ/IVA versus placebo
		LS mean difference	11.1
		95% CI	8.7 13.6
		P-value	<0.0001
		Comparison groups	TEZ/IVA versus IVA
		LS mean difference	1.4
		95% CI	-1.0, 3.9
		P-value	0.2578
Notes			

Analysis description	**Secondary analysis** As other secondary efficacy endpoints, relative Change in ppFEV1, absolute change in sweat chloride concentrations, additional Spirometry Variables, BMI and pulmonary exacerbations were measured. They all showed a positive effect for TEZ/IVA compared to placebo, while relative change in ppFEV1, sweat chloride and the additional spirometry variables showed a positive effect for TEZ/IVA compared to IVA. **Ancillary analyses:** The Forest Plot for the subgroups analysed, shows a consistent beneficial effect for TEZ/IVA compared to placebo. The lowest point estimate is 4.4 difference in the group of patients with low baseline FEV1 (ppFEV1 < 40%). The highest results are observed in the group of age < 18 years (12.0), FEV1 ≥70% or no use of bronchodilator (8.3). The number of patients per specific RF mutation is very small. Nevertheless the effects observed are supportive with the overall effects except for the deletions F508del/D110H and F508del/E831X.

Analysis performed across trials (pooled analyses and meta-analysis)

No additional across analysis were performed.

Clinical studies in special populations

The clinical studies were primarily based on the genetic mutation and analysed. Hence, the results are presented in the clinical studies. Clinical data for splice mutations were analysed as a subgroup for the primary endpoint of ppFEV1 and demonstrated a treatment effect compared to placebo of 7.4 % (95% CI: 6.0, 8.7; P <0.0001). The treatment effect for the splice mutation subgroup compared to IVA monotherapy was 1.9 % (95% CI: 0.8, 3.0; P = 0.0008), confirming the contribution of TEZ in this sub-population.

Adolescents and adults were included together in the trials. Subgroup analyses of the primary endpoint were done using a model similar to that for the primary analysis. On request of the CHMP, additional subanlyses in adolescents have been submitted also for study 110. The following results are based on MMRM analyses with the baseline defined as the last non-missing assessment before the first dose of TEZ/IVA in Study 110 for all treatment groups.

Adolescent subjects with CF with F/F mutation from parent study 106: A total of 109 adolescent patients (< 18 years old) out of 459 patients were included in study 110, 55 patients previously treated with placebo (PBO-TEZ/IVA group) and 54 previously treated with TEZ/IVA (TEZ/IVA group). The mean absolute change (SE) from baseline in ppFEV1 for subjects <18 years old was 5.3 (0.7) percentage points in the PBO-TEZ/IVA group and -0.8 (0.8) pp in the TEZ/IVA group. For subjects aged 18 years or older, the mean (SE) was 3.6 (0.5) pp and −0.3 (0.5) pp, respectively.

In study 110, the mean absolute change (SE) from baseline in BMI-z value for subjects <18 years old was 0.10 (0.05) kg/m^2 in the PBO-TEZ/IVA group and −0.04 (0.05) kg/m^2 in the TEZ/IVA group. The mean (95%CI) absolute change in BMI for the overall population was 0.23 kg/m^2 (0.06) and 0.00 kg/m^2 (0.06), respectively.

In study 110, the mean absolute change (SE) from baseline in weight-z value for subjects <18 years old was 0.06 (0.04) kg in the PBO-TEZ/IVA group and −0.02 (0.04) kg in the TEZ/IVA group. The mean (95%CI) absolute change in weight for the overall population was 0.9 (0.2) kg and 0.2 (0.2) kg respectively.

Adolescent subjects with CF with F/RF mutation from parent study 108: A total of 32 adolescent patients (< 18 years old) out of 226 patients were included in study 110, 14 patients previously treated with placebo (PBO-TEZ/IVA group), 8 patients previously treated with ivacaftor (IVA-TEZ/IVA group) and 10 previously treated with TEZ/IVA.

Mean (SD) weight z-scores (provided for subjects less than 20 years of age at screening of the parent study) were 0.24 (1.42), -0.12 (1.11), and 0.22 (1.16) respectively and mean (SD) BMI z-scores were 0.14 (1.26), -0.22 (1.03), and 0.03 (1.22)respectively at Study 110 baseline. At Study 110 baseline, the majority of subjects less than 18 years old with ppFEV1 below 70 were in the PBO-TEZ/IVA and IVA-TEZ/IVA groups (i.e., 57.1% and 62.5% vs. 40% in the TEZ/IVA group).

The mean absolute change (SE) from baseline in ppFEV1 for subjects <18 years old was 7.2 (1.2) percentage points in the PBO-TEZ/IVA group and 1.6 (1.6) percentage points in the IVA-TEZ/IVA group 0.7 (1.5 pp in the TEZ/IVA group. For subjects aged 18 years or older, the mean (SE) change was 4.4 (0.7) pp and 2.5 (0.7) pp and 0.0 (0.7), respectively.

In study 110, the mean absolute change (SE) from baseline in BMI-z value for subjects <18 years old was 0.04 (0.05) in the PBO-TEZ/IVA group and -0.13 (0.07) in the IVA-TEZ/IVA group and 0.16 (0.06) in the TEZ/IVA group. The mean absolute change (SE) from baseline in weight-z value for subjects <18 years old was not provided.

Overall, subgroup analyses showed statistically significant and consistent changes in ppFEV1 regardless of age, sex, baseline lung function, geographic region, use of common CF medications, and P. aeruginosa colonization. There were limited data from elderly patient (6 patients ≥65 years of age at screening in study 108) as reflected in the SmPC.

Supportive studies

Two supportive studies are submitted in the addition to the two pivotal studies and two dose finding studies: Study VX08-770-104 (Study 104) and Study VX14-661-110 (Study 110).

Study 104 was a randomized, double-blind, placebo-controlled, parallel-group, study that evaluate the safety and efficacy of IVA monotherapy in subjects with the F/F genotype. This study was already submitted as a variation in the ivacaftor dossier.

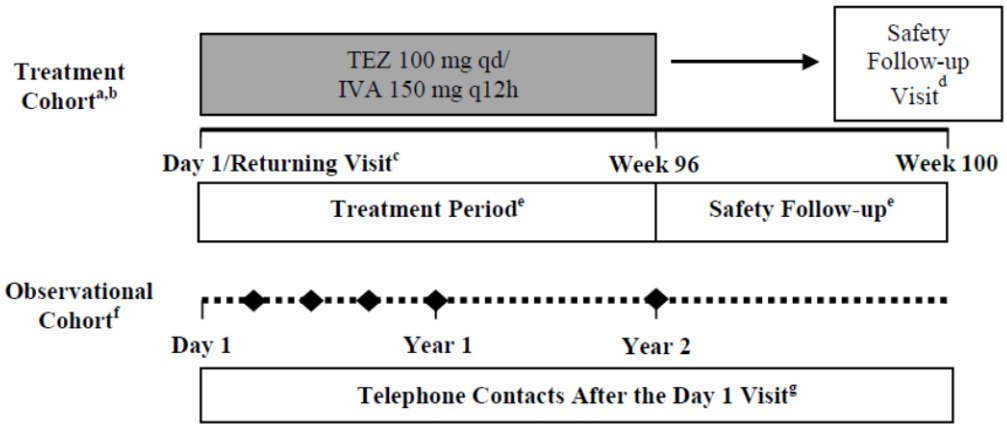
Study 110 is an open label uncontrolled extension study to support durability of efficacy and safety in subjects who complete Studies 103, 106, 107, 108 and 109. Study 110 is of importance as it provides long term data on efficacy and safety. The study is still ongoing and the results of an interim analysis are submitted.

The results of a third study (Study VX14-661-107) are also submitted, but this study was not considered a fully supportive study by the Applicant, because it was prematurely stopped because results of a planned interim analysis met the pre-defined futility rule. During the evaluation, results from Study VX14-661-109 were also provided.

Study VX14-661-110: open label extension study. Interim analysis 1 (70% of the enrolled patients analysed)

Study 110 is an open-label rollover study that enrolled subjects from the Phase 2 and 3 studies of TEZ/IVA (studies 103, 106, 107, 108, 109, 111, or other Vertex Pharmaceuticals Incorporated (Vertex) studies investigating TEZ in combination with IVA).

Study 110 has a Treatment Cohort and an Observational Cohort. Subjects were eligible to enrol in the Treatment Cohort if they completed study drug treatment in the previous study and met the eligibility criteria. Subjects in the Treatment Cohort receive TEZ/IVA for approximately 96 weeks. Subjects remained on their stable medication regimens for CF defined as the regimen subjects followed for at least 28 days before the first dose of study drug in Study 106 or 108. Subjects in the Observational Cohort did not receive study drug.



IVA: ivacaftor; q12h: every 12 hours; qd: daily; TEZ: tezacaftor
Notes: All subjects received a TEZ 100-mg/IVA 150-mg fixed-dose combination tablet qd in the morning and an IVA 150-mg tablet qd in the evening.

Figure 10 Study design VX14-661-110

Main Inclusion Criteria

1. Male and female subjects 12 years of age and older with CF who are homozygous or heterozygous for the F508del-CFTR mutation
2. The following criteria applied to the Treatment and Observational Cohorts:

- Elected to enroll in the Treatment Cohort
    - Completed study drug treatment during the Treatment Period in a parent study (Studies 103, 106, 107, 108, or 109), Study 111, or other Vertex studies investigating TEZ in combination with IVA (but not Studies 101, 112, and 113)
    - Subjects who had study drug interruptions, but completed study visits up to the last scheduled visit of the Treatment Period were eligible.
    - Subjects who had a study drug interruption at the last scheduled visit of the Treatment Period of the parent study, subjects who required interruption to be continued or initiated at Day 1 in Study 110, or subjects who resumed study drug in the parent study after a study drug interruption due to elevated transaminases but who did not complete at least 4 weeks of rechallenge with study drug (due to the timing of the rechallenge versus the time remaining in the Treatment Period of the parent study)

were required to meet eligibility criteria and to receive approval from the Vertex medical monitor in order to be enrolled into the Study 110 Treatment Cohort.

- Subjects re-enrolling in the Treatment Cohort met all of the following criteria:
    - Previously received at least 4 weeks of study drug before discontinuing Study 110 to participate in another qualified Vertex study, which was defined as a Vertex study of investigational CFTR modulators that allowed participation of subjects in Study 110.
    - Completed the last required visit of another qualified Vertex study before or during the Returning Visit in Study 110. (If > 60 days from the Returning Visit in Study 110, approval of the medical monitor was required.) Subjects who discontinued Study 110 to screen for another qualified Vertex study, and did not enroll into the other study, were eligible to re-enroll in Study 110.
    - Subjects who discontinued Study 110 more than once to participate in another qualified Vertex study did not re-enroll in Study 110 a second time.
- Subjects entering the Observational Cohort met the following criteria:
    - <18 years of age (age on the date of informed consent/assent in the parent study)
    - Completed study drug treatment during the Treatment Period in a parent study (Studies 103, 106, 107, 108, or 109), Study 111, or in other parent Vertex studies investigating TEZ in combination with IVA (Note: Studies 101, 112, and 113 were not eligible parent studies), not elected for the Study 110 Treatment Cohort;
    - subjects from Study 111 or in other parent Vertex studies investigating TEZ in combination with IVA), but did not meet eligibility criteria for enrollment into the Treatment Cohort

Main Exclusion criteria and List of study prohibitions and cautions for food and medication were similar as for study 106 and study 108. Commercially available CFTR modulators (Kalydeco and Orkambi) were prohibited from 30 days before screening through the end of each study.

Efficacy evaluation

The evaluation of the long-term efficacy of TEZ/IVA for subjects in the Treatment Cohort was a secondary objective; for efficacy assessment spirometry, weight, height, body mass index (BMI), CF questionnaire-revised (CFQ-R), 12-Item Short Form Survey (SF-12), and documentation of other events related to outcomes (e.g. pulmonary exacerbations [PEx]) were measured. Spirometry and pulmonary exacerbation (PEx) were defined as in parent clinical studies. Following additional instruction applied for CFQ-R for the age

- Subjects who were 12 and 13 years of age at Day 1 completed the CFQ-R Child version themselves, and their parents/caregivers completed the CFQ-R Parent version, on all visits, regardless of whether the subject subsequently turned 14 years of age during the study.
- Subjects who turned 14 years of age during their participation in the parent study and had their Day 1 Visit for Study 110 on the same day as the last parent study visit completed the CFQ-R per the parent protocol requirement. At Day 15 and all subsequent visits, these subjects completed the CFQ-R Adolescent/Adult version themselves.

- Subjects 14 years of age and older at Day 1 who did not have their Day 1 Visit for Study 110 on the same day as the last parent study visit completed the Adolescent/Adult version of the questionnaire themselves at all visits.

Efficacy Analysis Sets

Efficacy analysis sets in Study 110 were based on the parent study. The efficacy analysis sets were defined differently for PEx analysis and other efficacy analyses, following the same principles as specified in the integrated summary of efficacy (ISE) statistical analysis plan (SAP).

The All Subjects Set: all subjects who enrolled or received at least 1 dose of study drug in the Study 110 Treatment Cohort from parent Studies 103, 106, 107, and 108.

Safety Set: all subjects within the All Subjects Set who received at least 1 dose of study drug in Study 110. Percentages were calculated relative to the number of subjects in the Safety Set.

Efficacy Analysis Populations for all efficacy analyses:

Study 106/110 Efficacy Analysis Population and PEx Efficacy Analysis Population

TEZ/IVA : Subjects randomized to TEZ/IVA in Study 106 and who received TEZ/IVA in Study 110

PBO-TEZ/IVA: Subjects randomized to placebo in Study 106 and who received TEZ/IVA in Study 110

Study 108/110 PE Efficacy Analysis Population

TEZ/IVA: Subjects randomized to IVA-TEZ/IVA sequence or PBO-TEZ/IVA sequence in Study 108 and who received treatment in Period 2 of Study 108 and who received TEZ/IVA in Study 110.

IVA/TEZ/IVA: Subjects randomized to TEZ/IVA-IVA sequence or PBO-IVA sequence in Study 108 and who received treatment in Period 2 of Study 108 and who received TEZ/IVA in Study 110

PBO-TEZ/IVA: Subjects randomized to TEZ/IVA-IVA sequence or PBO-IVA sequence in Study 108 and who received treatment in Period 2 of Study 108 and who received TEZ/IVA in Study 110 and subjects randomized to TEZ/IVA-PBO sequence or IVA-PBO sequence in Study 108 and who received treatment in Period 2 of Study 108 and who received TEZ/IVA in Study 110.

Study 108/110 PEx Efficacy Analysis Populations

TEZ/IVA: Subjects randomized to IVA-TEZ/IVA sequence or PBO-TEZ/IVA sequence in Study 108 and who received treatment in Period 2 of Study 108

IVA-TEZ/IVA: Subjects randomized to TEZ/IVA-IVA sequence or PBO-IVA sequence in Study 108 and who received treatment in Period 2 of Study 108 and who received TEZ/IVA in Study 110. Subjects in TEZ/IVA-IVA sequence who did not enroll in Study 110 treatment cohort will also be included in this group if they received treatment in Period 1.

PBO-TEZ/IVA: Subjects randomized to TEZ/IVA-PBO sequence or IVA-PBO sequence in Study 108 and who received treatment in Period 2 of Study 108 and who received TEZ/IVA in Study 110. Subjects in TEZ/IVA-PBO sequence who did not enroll in Study 110 treatment cohort will also be included in this group if they received treatment in Period 1.

VX14-661-110 Study results

For the F/F population, 459 subjects received TEZ/IVA in Study 110. Of these, 231 subjects switched from placebo in Study 106 to TEZ/IVA in Study 110 (PBO-TEZ/IVA group), and 228 subjects continued to receive TEZ/IVA (TEZ/IVA group). At the time of the IA, 14 subjects (6.1%) in the PBO-TEZ/IVA group and 8 subjects (3.5%) in the TEZ/IVA group had discontinued treatment. For the F/RF population, 222 subjects received TEZ/IVA in Study 110. Of these, 78 subjects received placebo in Study 108 Period 2 (PBO-TEZ/IVA group), 69 subjects received IVA in Study 108 Period 2 (IVA-TEZ/IVA group), and 75 subjects received TEZ/IVA in Study 108 Period 2 (TEZ/IVA group). At the time of the IA, 3 subjects (1.4%) had discontinued treatment (1 subject in each group). As of the IA1 data cut date, 870 subjects had been enrolled in Study 110 from 4 parent studies as follows: 462 (53.3%) subjects from Study 106, 223 (25.7%) subjects from Study 108, 159 (18.3%) subjects from Study 107, and 23 (2.7%) subjects from Study 103. No subjects were enrolled in the Observational Cohort.

Of the 867 subjects who received at least 1 dose of study drug in Study 110 (i.e., the Safety Set), 185 (21.3%) prematurely discontinued treatment. The majority of discontinuations were due to the early termination of Study 107 for futility; 154 (17.8%) subjects discontinued treatment in Study 110 due to study termination by Sponsor. The percentages of subjects who discontinued treatment due to AE (0.7%) or discontinued the study due to AE (0.5%) were low.

Table 30 Subject Disposition (Study 110 Treatment Cohort), All Subjects Set

Disposition/Reason	Placebo-TEZ/IVA n (%)	Active-TEZ/IVA[a] n (%)	Total n (%)
All Subjects Set	391	479	870
Safety Set	390	477	867
Prematurely discontinued treatment	95 (24.4)	90 (18.9)	185 (21.3)
AE	5 (1.3)	1 (0.2)	6 (0.7)
Subject refused further dosing (not due to an AE)	4 (1.0)	6 (1.3)	10 (1.2)
Lost to follow-up	1 (0.3)	2 (0.4)	3 (0.3)
Death	0	0	0
Did not meet eligibility criteria	0	1 (0.2)	1 (0.1)
Noncompliance with study drug	0	0	0
Other noncompliance	0	1 (0.2)	1 (0.1)
Physician decision	1 (0.3)	1 (0.2)	2 (0.2)
Requires prohibited medication	1 (0.3)	0	1 (0.1)
Pregnancy (self or partner)	2 (0.5)	1 (0.2)	3 (0.3)
Study termination by sponsor	78 (20.0)	76 (15.9)	154 (17.8)
Other	3 (0.8)	1 (0.2)	4 (0.5)
Prematurely discontinued study	15 (3.8)	13 (2.7)	28 (3.2)
AE	3 (0.8)	1 (0.2)	4 (0.5)
Withdrawal of consent (not due to an AE)	4 (1.0)	3 (0.6)	7 (0.8)
Lost to follow-up	2 (0.5)	2 (0.4)	4 (0.5)
Death	0	0	0
Other noncompliance	1 (0.3)	2 (0.4)	3 (0.3)
Physician decision	1 (0.3)	1 (0.2)	2 (0.2)
Study termination by sponsor	0	0	0
Other	4 (1.0)	4 (0.8)	8 (0.9)
Subjects from each of the following parent studies			
Study 103	0	23 (4.8)	23 (2.7)
Study 106	232 (59.5)	230 (48.2)	462 (53.3)
Study 107	80 (20.5)	79 (16.6)	159 (18.3)
Study 108	78 (20.0)	145 (30.4)	223 (25.7)

Of the 222 subjects in the Study 108/110 ES, 3 (1.4%) subjects prematurely discontinued treatment, and no subjects discontinued treatment due to AE. Of the 459 subjects in the Study 106/110 ES, 22 (4.8%) subjects prematurely discontinued treatment, and 4 (0.9%) subjects discontinued treatment due to AE.

Study period was from 31 August 2015 (date first eligible subject signed the informed consent form) up to 06 March 2017 (data cut date of interim analysis). The original protocol (v1.0, dated 19 May 2015) was amended once.

Demographics and Other Baseline Characteristics

The used baseline was the baseline measurements of the parent studies. Demographic and other baseline characteristics, including mean values and distributions, were similar across placebo/TEZ-IVA and active treatment/TEZ-IVA groups. In Study 106/110 Efficacy Set, the median age of subjects was 25 years (range: 12, 64). A total of 51.6% of subjects were male. The majority of subjects had baseline ppFEV1 ≥40 to <70 (61.7%) or ≥70 to ≤90 (27.2%). Median BMI was 20.72 kg/m^2 (range: 13.67, 32.24). In study 108/110 Efficacy Set, the median age of subjects was 35 years (range: 12,

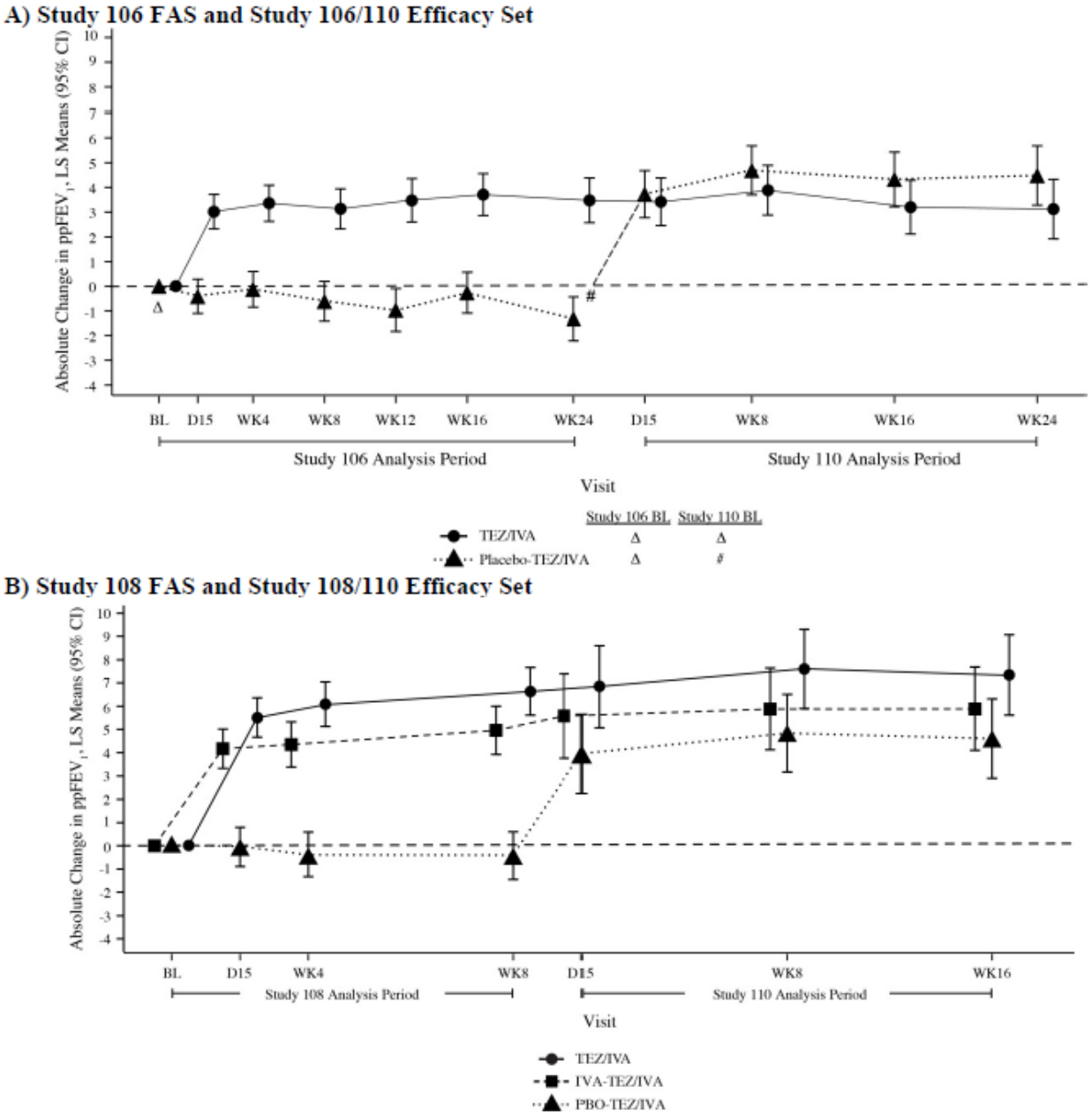
72). A total of 46.8% of subjects were male. The majority of subjects had baseline ppFEV1 ≥40 to <70 (58.1%) or ≥70 to ≤90 (31.1 %). Median BMI was 23.53 kg/m^2 (range: 15.19, 49.65). The most common medical history and prior medications used were consistent with the expectations for a population with CF.

There were 26 IPDs prior to the cut-off date for IA1. None of these IPDs were considered to adversely affect subjects or the interpretation of study results. Twelve subjects had IPDs due to <80% study drug compliance; 7 subjects >70%, 3 subjects >50%, and 1 subject each had 48.8% and 4.7% compliance. The most common reasons were treatment interruption i.e., to take a prohibited concomitant medication, a non-LFT-related AE, or for both of these reasons. The subject with 48.8% compliance had treatment interruption due to renal failure.

VX14-661-110 outcomes and estimation

Absolute change in ppFEV1 from baseline: At Week 24 of Study 110, in F/F subjects, the LS mean absolute change from baseline in ppFEV1 was 3.1 % (95% CI: 1.9, 4.3; P<0.0001) in the TEZ/IVA group after 48 weeks treatment in total. Subjects who went from placebo to TEZ/IVA the LS mean absolute change in ppFEV1 from baseline in ppFEV1 was 4.5 % (95% CI: 3.3, 5.7; P<0.0001) in the PBO-TEZ/IVA group. For F/RF subjects who received TEZ/IVA in Study 108 Period 2, at Week 16, the LS mean absolute change from baseline in ppFEV1 was 5.9 percentage points (95% CI: 4.1, 7.7; P<0.0001) in the IVA-TEZ/IVA group and 7.4 percentage points (95% CI: 5.6, 9.1; P<0.0001) in the TEZ/IVA group. For subjects in the PBO-TEZ/IVA group who received placebo in Period 2 of Study 108 at Week 16 the LS mean absolute change in ppFEV1 from baseline in ppFEV1 was 4.6 percentage points (95% CI: 2.9, 6.3; P <0.0001) in the PBO-TEZ/IVA group.

An additional increase in ppFEV1 was observed for subjects who received IVA in Study 108 Period 2 and began receiving TEZ/IVA in Study 110 (see figure below); this increase in ppFEV1 from Study 108 Week 8 was observed as early as Day 15 of Study 110, and the improvement in ppFEV1 from Study 108 baseline was sustained at Week 16 (5.9 %; 95% CI: 4.1, 7.7; P<0.0001). The magnitude and trend of improvement in ppFEV1 observed in Study 110 in patients who received placebo in the parent study were similar to those observed for subjects who received TEZ/IVA in Studies 106 or 108.



Source: ISE/Figure 3.2.1.1 and Figure 3.2.1.2
BL: baseline; CI: confidence interval; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; PBO: placebo; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

Notes: The MMRM analysis for Study 110 analysis period is restricted to the last visit at which the total number of subjects was approximately 70% of subjects in the parent study (106 or 108) FAS.
Study 106: During Study 106, the last non-missing measurement before the first dose of study drug in Study 106 was used to calculate the change from baseline. For subjects in the PBO-TEZ/IVA group, the last non-missing measurement before the first dose of study drug in Study 110 was used to calculate the change from baseline during study 110.
Study 108: For both the Study 108 and 110 Analysis Periods, baseline was the most recent non-missing measurement before the first dose of study drug in Study 108. Treatment assignment in the period of Study 110 was based on assigned treatment in Period 2 of Study 108. Study 108 Analysis Period includes Treatment Periods 1 and 2, and subjects were included in more than 1 treatment group during the Study 108 Analysis Period

Figure 11 MMRM Analyses of Absolute Change From Baseline in ppFEV1 at Each Visit

Relative change in ppFEV1 from baseline

Study 106/110 Efficacy Set

The mean ppFEV1 showed a relative improvement in the TEZ/IVA group during Study 106, and this improvement was maintained through Week 24 in Study 110 (P<0.0001 at all time points in both studies). At Week 24 of Study 110, the LS mean relative change from baseline in ppFEV1 was 5.9% (95% CI: 3.7%, 8.0%; P<0.0001) in TEZ/IVA group.

Subjects in the PBO-TEZ/IVA group who began receiving TEZ/IVA in Study 110 showed a relative improvement in ppFEV1 as early as Day 15 of Study 110, and the improvements in ppFEV1 were sustained through Week 24 (P<0.0001 at all time points in Study 110). At Week 24 of Study 110, the LS mean relative change from baseline in ppFEV1 was 8.8% (95% CI: 6.6%, 10.9%; P <0.0001) in the PBO-TEZ/IVA group.

Study 108/110 Efficacy Set

The mean ppFEV1 showed a consistent relative improvement in the IVA-TEZ/IVA and TEZ/IVA groups during Study 108, and this improvement was maintained (TEZ/IVA) or showed further increase (IVA-TEZ/IVA) through Week 16 in Study 110 (*P*<0.0001 at all-time points in both studies). At Week 16 of Study 110, the LS mean relative change from baseline in ppFEV1 was 10.3% (95% CI: 7.2%, 13.3%; *P* <0.0001) in the IVA-TEZ/IVA group and 12.6% (95% CI: 9.7%, 15.5%; *P* <0.0001) in the TEZ/IVA group.

Subjects in the PBO-TEZ/IVA group who received placebo in Period 2 of Study 108 showed a relative improvement in ppFEV1 as early as Day 15 of Study 110, and the improvements in ppFEV1 were sustained through Week 16 (*P*<0.0001 at all time points in Study 110). At Week 16 of Study 110, the LS mean relative change from baseline in ppFEV1 was 8.5% (95% CI: 5.6%, 11.3%; *P* <0.0001) in the PBO-TEZ/IVA group.

Number of Pulmonary Exacerbations

Subjects in the 106/110 PE analysis set (F/F population) who received TEZ/IVA in Study 106 maintained a lower event rate per year of PEx (0.72) compared to the placebo group in Study 106 (0.99). Subjects in the 106/110 PE analysis set who received placebo in Study 106 had lower event rate per year of PEx (0.58) in Study 110 compared to the placebo group in Study 106 (0.99). The event rate per year of PEx was similar to that of the TEZ/IVA group in Study 106. Subjects in the 108/110 PE analysis set (F/RF population) who received TEZ/IVA in Study 108 had a lower PEx event rate per year in Study 110 (0.20) than during Study 108 (0.34). Subjects in the 108/110 PE analysis set who received placebo in Study 108 had a lower PEx event rate per year (0.34) in Study 110 than in the placebo group in Study 108 (0.63). The PEx event rate per year was similar to that of the TEZ/IVA group in Study 108. Subjects in 108/110 PE analysis set who received IVA in Study 108 had a low PEx event rate per year in Study 110 (0.39), see below**.**

Table 31 Study 110 PE Analysis Period: Pulmonary Exacerbations, Study 106/110 and Study 108/110 PE Analysis Sets

	Study 106/110		Study 108/110		
Endpoint	PBO-TEZ/IVA N = 231	TEZ/IVA N = 248	PBO-TEZ/IVA N = 80	IVA-TEZ/IVA N = 75	TEZ/IVA N = 78
Pulmonary Exacerbations					
Number of subjects with events, n (%)	64 (27.7)	106 (42.7)	13 (16.3)	15 (20.0)	11 (14.1)
Total number of days (years)[a]	61490 (183.01)	103644 (308.46)	16003 (47.63)	15086 (44.90)	20516 (61.06)
Total number of events	105	229	15	16	11
Estimated event rate per year	0.58	0.72	0.34	0.39	0.20
95% CI	(0.44, 0.75)	(0.59, 0.88)	(0.19, 0.61)	(0.22, 0.70)	(0.10, 0.39)
Pulmonary Exacerbations Requiring Hospitalization					
Number of subjects with events, n (%)	25 (10.8)	43 (17.3)	5 (6.3)	4 (5.3)	3 (3.8)
Total number of days (years)[a]	61490 (183.01)	103644 (308.46)	16003 (47.63)	15086 (44.90)	20516 (61.06)
Total number of events	34	81	5	4	3
Estimated event rate per year	0.18	0.22	0.08	0.07	0.04
95% CI	(0.11, 0.28)	(0.15, 0.31)	(0.02, 0.28)	(0.02, 0.26)	(0.01, 0.17)
Pulmonary Exacerbations Requiring IV Antibiotic Therapy					
Number of subjects with events, n (%)	36 (15.6)	59 (23.8)	5 (6.3)	4 (5.3)	2 (2.6)
Total number of days (years)[a]	61490 (183.01)	103644 (308.46)	16003 (47.63)	15086 (44.90)	20516 (61.06)
Total number of events	57	124	5	5	2
Estimated event rate per year	0.27	0.33	0.07	0.08	0.02
95% CI	(0.19, 0.40)	(0.24, 0.45)	(0.02, 0.29)	(0.02, 0.30)	(0.00, 0.14)

Sources: ISE/Table 3.5.1.1, Table 3.5.3.1, Table 3.5.4.1, Table 3.5.1.2, Table 3.5.3.2, Table 3.5.4.2

CI: confidence interval; IVA: ivacaftor; n: number of subjects; PBO: placebo; PE: pulmonary exacerbation; TEZ: tezacaftor

Notes: PE Analysis Period: For subjects who enrolled in Study 110, refers to the time period from the first dose of TEZ/IVA in Study 106, Study 108 (Period 2), or Study 110 (for subjects who were not randomized to TEZ/IVA in Study 106 or Study 108 [Period 2]) to the last efficacy assessment in Study 110. For subjects who did not enroll in Study 110, refers to the time period from the first dose of TEZ/IVA in Study 106 or Study 108 to the last efficacy assessment.

[a] Total number of days = PE Analysis Period end date - PE Analysis Period start date + 1. Total number of years is calculated by dividing this quantity by 336 days.

During the assessment, the applicant also submitted additional analysis of the pulmonary exacerbation rates of second interim analysis (IA2). The number of PExs was estimated using a negative binomial regression model. The PEx Analysis Period included all time that a given subject was on active treatment, which may have begun in either Study 106, Study 108 or Study 110. For patients with F/F mutation (study 106), the event rate of PEx was 0.64 events per year in the TEZ/IVA group and 0.99 events per year in the placebo group. For IA1 and IA2, the PEx event rate was 0.72 events per year. In Study 108, the PEx event rate was for the TEZ/IVA group 0.34 events per year and for the placebo

group 0.63 events per year. At the time of IA2 of Study 110, the PEx event rate was 0.22 events per year at a total group exposure to TEZ/IVA of 115 years.

Table 32 Study 110 PEx Analysis Period: PEx Results, Study 106/110 (F/F) and Study 108/110 (F/RF) PEx Analysis Sets

	Study 106/110			Study 108/110			
Endpoint	PBO-TEZ/IVA N = 231	TEZ/IVA N = 248	Total N = 479	PBO-TEZ/IVA N = 81	IVA-TEZ/IVA N = 74	TEZ/IVA N = 78	Total N = 233
Pulmonary Exacerbations							
Number of subjects with events, n (%)	101 (43.7)	128 (51.6)	229 (47.8)	30 (37.0)	27 (36.5)	24 (30.8)	81 (34.8)
Total number of days (years)[a]	112385 (334.48)	156867 (466.87)	269252 (801.35)	35287 (105.02)	31889 (94.91)	38697 (115.17)	105873 (315.10)
Total number of events	221	339	560	52	33	33	118
Observed event rate per year	0.66	0.73	0.70	0.50	0.35	0.29	0.37
Estimated event rate per year	0.65	0.72	0.69	0.38	0.26	0.22	0.29
95% CI	(0.52, 0.80)	(0.60, 0.87)	(0.59, 0.80)	(0.24, 0.61)	(0.15, 0.44)	(0.13, 0.37)	(0.19, 0.43)
Pulmonary Exacerbations Requiring Hospitalization or IV Antibiotic Therapy							
Number of subjects with events, n (%)	67 (29.0)	75 (30.2)	142 (29.6)	9 (11.1)	10 (13.5)	11 (14.1)	30 (12.9)
Total number of days (years)[a]	112385 (334.48)	156867 (466.87)	269252 (801.35)	35287 (105.02)	31889 (94.91)	38697 (115.17)	105873 (315.10)
Total number of events	121	179	300	17	14	12	43
Observed event rate per year	0.36	0.38	0.37	0.16	0.15	0.10	0.14
Estimated event rate per year	0.33	0.35	0.34	0.06	0.06	0.04	0.06
95% CI	(0.25, 0.45)	(0.27, 0.46)	(0.28, 0.42)	(0.02, 0.22)	(0.02, 0.22)	(0.01, 0.15)	(0.02, 0.17)

Sources: ISE2 Adhoc Tables 3.5.3.1 and 3.5.3.2; ISE2 Tables 3.5.1.1 and 3.5.1.2

CI: confidence interval; IVA: ivacaftor; n: number of subjects; PBO: placebo; PE: pulmonary exacerbation; TEZ: tezacaftor

Notes: PE Analysis Period: For subjects who enrolled in Study 110, refers to the time period from the first dose of TEZ/IVA in Study 106, Study 108 (Period 2), or Study 110 (for subjects who were not randomized to TEZ/IVA in Study 106 or Study 108 [Period 2]) to the last efficacy assessment in Study 110. For subjects who did not enroll in Study 110, refers to the time period from the first dose of TEZ/IVA in Study 106 or Study 108 to the last efficacy assessment.

[a] Total number of days = PE Analysis Period end date - PE Analysis Period start date + 1. Total number of years is calculated by dividing this quantity by 336 days.

Pulmonary exacerbation requiring hospitalizations: Similar to results for the number of PEx for subjects in the 106/110 PE analysis set (F/F population), the event rate for PEx requiring hospitalization remained low for subjects who received TEZ/IVA in Study 106 (0.22) and was reduced from 0.29 in Study 106 to 0.18 in Study 110 for subjects who received placebo in Study 106. The event rate for PEx requiring hospitalization was low for all 3 groups of subjects in the 108/110 PE analysis set (F/RF population) in Study 110.

Pulmonary exacerbation requiring IV antibiotics: Similar to results for the number of PEx for subjects in the 106/110 PE analysis set (F/F population), the event rate for the PEx requiring IV antibiotics remained low for subjects who received TEZ/IVA in Study 106 (0.33) and was reduced from 0.54 in Study 106 to 0.27 in Study 110 for subjects who received placebo in Study 106. The event rate for the number of PEx requiring IV antibiotics was low for all 3 groups in Study 110 for subjects in the 108/110 PE analysis set (F/RF population).

Natural History PEx Data

Table 33 Prevalence Of Pulmonary Exacerbations From 2012 to 2014 Among CF Patients Homozygous for *F508del* or Heterozygous for *F508del* With an RF Mutation Aged ≥12 years, US CFF Patient registry

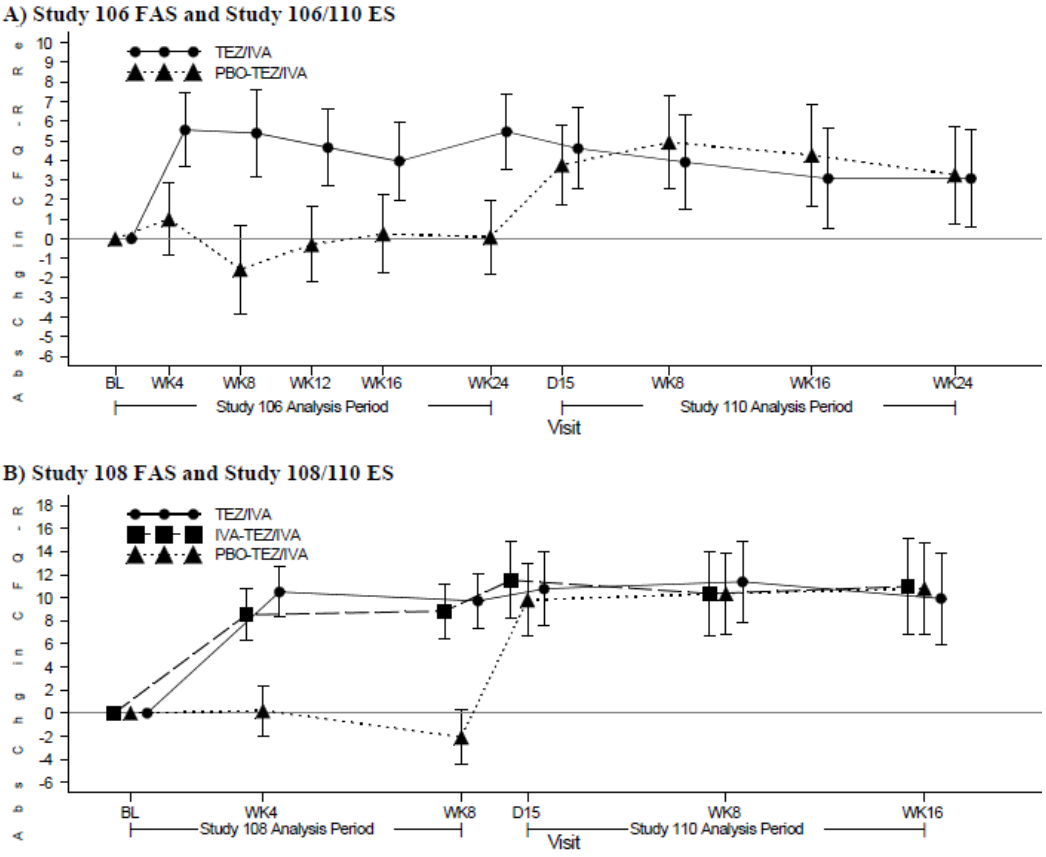
	Homozygous *F508del* Patients Aged ≥12 Years Old as of January 1, 2012		Heterozygous F508del Residual function patients ≥12 Years Old as of January 1, 2012[a]	
Year	Population	Number of Subjects With Events (Risk [%])	Population	Number of Subjects With Events (Risk [%])
2012	8086	3,852 (47.6)	834	225 (27.0)
2013	7599	3,693 (48.6)	775	242 (31.2)
2014	7329	3,629 (49.5)	747	236 (31.6)

Source: CFF Registry Data on file

[a] The CFF Registry included the following RF mutations: E56K, E193K, K106, P67L, R74W, D110E, D110H, R117C, R352Q, A455E, D579G, E831X, S945L, S977F, F1052V, R1070W, F1074L, D1152H, L206W, R347H, D1270N, 2789+5G→A, 3849+10kbC→T, 3272−26A→G, 711+3A→G

Time-to-first pulmonary exacerbation: For subjects in the 106/110 PE analysis set (F/F population), the estimated exacerbation-free probability for subjects who received TEZ/IVA in Study 106 was 0.602 after 48 weeks of TEZ/IVA treatment. For subjects who received placebo in Study 106, the estimated exacerbation-free probability at Week 24 in Study 110 was 0.752, which was higher than the estimated exacerbation-free probability at Week 24 for treatment with placebo (0.649) and similar to the estimated exacerbation-free probability at Week 24 of Study 106 for subjects who received TEZ/IVA (0.749). For subjects in the 108/110 PE analysis set (F/RF population), the estimated exacerbation-free probability for subjects who received TEZ/IVA in Study 108 was 0.857 after 24 weeks ofTEZ/IVA treatment. The estimated exacerbation-free probability at Week 24 in Study 110 was 0.863 for subjects who received placebo in Study 108 and 0.751 for subjects who received IVA in Study 108.

Respiratory Symptoms (Measured by CFQ-R Respiratory Domain Score): CFQ-R was also evaluated in Study 110. For subjects who received TEZ/IVA in Study 106 or Study 108 Period 2, improvements in CFQ-R respiratory domain score continued through all visits in Study 110. Subjects who received placebo in Study 106 and began treatment with TEZ/IVA in Study 110 had improvements as early as Day 15 (within-group change = 3.8 points) that were sustained through Week 24 of Study 110. Subjects who received placebo in Study 108 Period 2 and begin treatment with TEZ/IVA in Study 110 had improvements as early as Day 15 (within-group change = 9.8 points) that were sustained through Week 16 of Study 110. The magnitude and trend of improvement in CFQ-R respiratory domain score observed for subjects receiving the first dose of TEZ/IVA in Study 110 were similar to those observed for subjects who received the first dose of TEZ/IVA in Study 106 and Study 108, respectively, see below.



Sources: ISE Figure 3.4.1.1 (Study 106); ISE Figure 3.4.1.2 (Study 108)
BL: baseline; CI: confidence interval; D: day; ES: Efficacy Set; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; PBO: placebo; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor; Wk: week
Study 106: During Study 106, the last non-missing measurement before the first dose of study drug in Study 106 was used to calculate the change from baseline. For subjects in the PBO-TEZ/IVA group, the last non-missing measurement before the first dose of study drug in Study 110 was used to calculate the change from baseline during study 110.
Study 108: For both the Study 108 and 110 Analysis Periods, baseline was the most recent non-missing measurement before the first dose of study drug in Study 108. Treatment assignment in this period was based on assigned treatment in Period 2 of Study 108. Study 108 Analysis Period includes Treatment Periods 1 and 2, and subjects were included in more than 1 treatment group during the Study 108 Analysis Period.

Figure 12 MMRM Analyses of Absolute Change From Baseline in Pooled CFQ-R Respiratory Domain Score at Each Visit

At Week 24 in Study 106, the proportion of patients who had at least a 4 point increase in CFQ-R respiratory domain score was 51.3% in the TEZ/IVA group and 35.7% in the placebo group. In subjects who received TEZ/IVA for 48 weeks, the proportion of subjects who met or exceeded the MCID at Study 106 Week 24 was 48.6% through 24 weeks of additional TEZ/IVA treatment in Study 110.

F/RF subjects treated with either TEZ/IVA or IVA in Study 108 had a numerical increase of 2.6 points in CFQ-R Respiratory Domain Score after 16 weeks of TEZ/IVA treatment. Additionally, F/RF subjects who received placebo in Study 108 had an improvement of 11.3 points in CFQ-R Respiratory Domain Score after they received TEZ/IVA for 16 weeks in Study 110. The proportion of patients who met or exceeded the MCID at the conclusion of Study 108 (53.9%) was maintained through an additional 16 weeks of TEZ/IVA treatment in Study 110 (62.2%)

Absolute change from baseline in BMI: For subjects in the 106/110 efficacy set (F/F population), BMI continued to increase for both groups in Study 110. For subjects who received TEZ/IVA in Study 106, the within-group change in BMI was 0.26 kg/m^2 at Week 24 of Study 110 compared to 0.18 kg/m^2 at

Week 24 of Study 106. For subjects who received placebo in Study 106, the within-group change in BMI was 0.26 kg/m^2 at Week 24 of Study 110 compared to 0.12 kg/m^2 at Week 24 of Study 106. For subjects in the 108/110 efficacy set (F/RF population), at IA2, BMI increased an additional 0.53 kg/m^2 for subjects who received TEZ/IVA in Period 2 of Study 108, compared 0.35 kg/m^2 for subjects who received placebo in Period 2 of Study 108 and 0.16 kg/m2 for subjects who received ivacaftor in Period 2 of Study 108.

Absolute change from baseline in weight: For subjects in the 106/110 efficacy set (F/F population), weight continued to increase for both groups in Study 110. For subjects who received TEZ/IVA in Study 106, the within-group change in weight was 0.7 kg at Week 24 of Study 106 compared to 1.2 kg at Week 24 of Study 110. For subjects who received placebo in Study 106, the within-group change in weight was 0.6 kg at Week 24 of Study 106 compared to 1.0 kg at Week 24 of Study 110.

For subjects in the 108/110 efficacy set (F/RF population), weight continued to increase for all 3 groups in Study 110. For subjects who received TEZ/IVA in Period 2 of Study 108, the within-group change in weight was 1.1 kg at Week 8 of Study 108 compared to 2.3 kg at Week 16 of Study 110. For subjects who received placebo in Period 2 of Study 108, the within-group change in weight was 0.6 kg at Week 8 of Study 108 compared to 1.7 kg at Week 16 of Study 110. For subjects who received IVA in Period 2 of Study 108, the within-group change in weight was 1.4 kg at Week 8 of Study 108 compared to 2.1 kg at Week 16 of Study 110.

Interim analysis 2 (100% of the enrolled patients analysed)

With the responses to the CHMP's requests, summarised data of a second interim analysis (IA2) of data from 100% of the subjects from Study 106 completing 24 weeks and subjects from Study 108 completing 16 weeks of the 96 weeks is submitted. For this analysis, the baseline is defined as the last non-missing assessment before the first dose of TEZ/IVA in Study 110. The results are presented as LS estimates.

For F/F subjects from parent study 106, the results were following:

At Week 24 of Study 110, in F/F subjects the LS mean absolute change (SD) from baseline in ppFEV1 for subjects in PBO-TEZ/IVA group was 4.2 pp (0.5) and for subjects in the TEZ/IVA group -0.2 pp (0.5).

The estimated event rate per year of PEx was 0.65 (95% CI 0.52, 0.80) and 0.72 (95% CI 0.60, 0.87) in PBO-TEZ/IVA and TEZ/IVA groups, respectively).

The estimated event rate per year of PEx requiring hospitalisation or IV antibiotic therapy was 0.33 (95% CI 0.25, 0.45) and 0.35 (95% CI 0.27, 0.46) in PBO-TEZ/IVA and TEZ/IVA groups, respectively).

The change in CFQ-R was 3.3 (1.0) points in the PBO-TEZ/IVA group, and 0.4 (1.0) points in TEZ/IVA group.

The change in BMI was 0.23 kg/m^2 (0.06) in the PBO-TEZ/IVA group and 0.00 kg/m^2 (0.06) in TEZ/IVA group, while the change in weight was 0.9 kg (0.20 in the PBO-TEZ/IVA group, and 0.2 kg (0.20) in TEZ/IVA group.

For F/RF subject from parent study 108, the results were following:

At Week 16 of Study 110, in F/RF subjects the LS mean absolute change from baseline in ppFEV1 for subjects in PBO-TEZ/IVA group was 4.9 pp (0.6), for subjects in IVA-TEZ/IVA group 2.4 pp (0.7) and for subjects in the TEZ/IVA group 0.0 pp (0.6).

The event rate per year of PEx was 0.38 (95% CI 0.24, 0.61) in the PBO-TEZ/IVA group, IVA-TEZ/IVA 0.26 (95% CI 0.15, 0.44) and 0.22 (95% CI 0.13, 0.37) in TEZ/IVA group).

The estimated event rate per year of PEx requiring hospitalisation or IV antibiotic therapy was 0.06 (95% CI 0.02, 0.22) 0.06 (95% CI 0.02, 0.22) and 0.04 (95% CI 0.01, 0.15) in PBO-TEZ/IVA, IVA-TEZ/IVA and TEZ/IVA groups, respectively).

The change in CFQ-R was 8.1 (1.6) points in the PBO-TEZ/IVA group while in the group IVA-TEZ/IVA 3.9 (1.7) points and 4.4 (1.6) points in TEZ/IVA group.

The change in BMI was 0.35 (0.11) kg/m^2 in the PBO-TEZ/IVA group, in the IVA-TEZ/IVA 0.15 kg/m^2 (0.11) and 0.54 kg/m^2 (0.11) in TEZ/IVA group.

Results for adolescents are described in section on specific populations.

Study VX08-770-104

Study VX08-770-104 (Study 104) was a randomized, double-blind, placebo-controlled, parallel-group, 16-week study (Part A) with a 96-week, OLE (Part B) to evaluate the safety and efficacy of IVA monotherapy in subjects with the F/F genotype.

Part A was a 16-week, 4:1 randomised, double-blind, placebo-controlled, parallel-group Phase 2 study of ivacaftor (150 mg every 12 hours) in 140 patients with CF age 12 years and older who were homozygous for the F508del mutation in the CFTR gene and who had FEV1 ≥ 40% predicted.

Subjects were eligible to participate in Part B in case of:

- An increase of ≥10% relative to baseline ppFEV1 at 1 or more time points
- A decrease from baseline in sweat chloride concentration of ≥15 mmol/L at both the Day 15 and Week 8 visits.

Efficacy measures were considered secondary endpoints and included absolute change in ppFEV1, sweat chloride, CFQ-R, pulmonary exacerbations, weight, and rate of decline in percent predicted FEV1. The study was discontinued by the sponsor following results obtained from a pre-specified evaluation of the Part B data.

PART A, EFFICACY RESULTS (placebo controlled phase)

For the primary endpoint, absolute change of ppFEV1, the adjusted mean was 1.53 % in the ivacaftor group and -0.18 % in the placebo group. The estimated treatment difference for ivacaftor versus placebo was 1.72 % (95% CI: -0.6349, 4.0754); this difference was not statistically significant (P = 0.1509). For the secondary endpoint, the adjusted mean in sweat chloride values was greater in the VX-770 group (-2.74 mmol/L) than in the placebo group (0.13 mmol/L); this difference was nominally statistically significant (nominal: P = 0.0384). The changes in sweat chloride occurred by Day 15 and were sustained for the duration of the 16-week treatment period. The treatment difference on respiratory symptoms, as measured by the change in CFQ-R respiratory domain of VX-770 administration compared to placebo was 1.31 points. An effect of VX-770 administration on weight, as measured by the change in weight, weight-for-age z-score, BMI, and BMI-for-age z-score over 16 weeks of treatment was not observed in this study (treatment difference 0.07 kg/m^2.

PART B, EFFICACY RESULTS (OLE Phase)

A total of 38 patients rolled over to the OLE phase, 5 patients who received placebo and 38 who received VX-770. The rate of decline from Part A baseline through Week 64 in percent predicted FEV1 was 5.7445% in the placebo/VX-770 group and -1.0738% in the VX-770/VX-770 group (treatment difference -6.8183% (95% CI: -14.6503, 1.0136, P = 0.0876). The rate of decline in percent predicted FEV1 from Part B baseline through Week 64 was 5.3409% in the placebo/VX-770 group and -5.2994% in the VX-770/VX-770 group. The estimated treatment difference for the VX-770/VX-770 group versus the placebo/VX-770 group was -10.6402 (95% CI: -20.4402, -0.8402; P = 0.0336); the clinical significance of this finding is uncertain because both groups received VX-770 for the duration of Part B.

For subjects treated with VX-770 for 64 weeks (VX-770/VX-770 group), the marginal decrease in mean absolute change in sweat chloride that was observed from baseline to Week 16 in Part A was not sustained through Week 64. There were no differences for the change in CFQ-R respiratory domain score, the yearly rate of pulmonary exacerbations or weight.

Study VX14-661-107

Study VX14-661-107 (study 107) was a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study in subjects with CF who are heterozygous for the F508del-CFTR mutation and with a second CFTR mutation that is not likely to respond to TEZ and/or IVA therapy. TEZ 100 mg once daily qd)/IVA 150 mg q12h was administered for up to 12 weeks.

CFTR mutations that are not likely to respond to VX-661 and/or ivacaftor therapy were defined using 3 major sources: biological plausibility for the mutation to respond (i.e., class), evidence of clinical severity on a population basis based on the patient registry CFTR, and *in vitro* testing. The clinical severity criteria (average sweat chloride >86 mmol/L, %PI >50%) do not specifically apply to the individual subjects to be enrolled in this study, but were used to classify the mutation status:

Truncation mutations	• %PI >50% and/or SwCl- >86 mmol/L • no full-length protein
Canonical splice mutations	• %PI >50% and/or SwCl- >86 mmol/L • no or little mature mRNA
Frameshift mutations	• %PI >50% and/or SwCl- >86 mmol/L • garbled or truncated protein
Class II, III, IV mutations not responsive to ivacaftor or VX-661*	• %PI >50% and/or SwCl- >86 mmol/L OR • not responsive *in vitro* to ivacaftor or VX-661

%PI: percentage of subjects who are pancreatic insufficient; SwCl-: sweat chloride
* mutations that responded with chloride transport <10% of wild-type CFTR were considered minimal function and nonresponsive

The rationale of this study was if a positive treatment effect of the TEZ /IVA combination could be demonstrated, a large number of patients would benefit.

Efficacy results

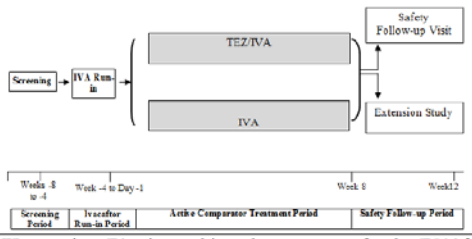
The LS mean treatment difference for the absolute change from baseline in ppFEV1 through Week 12 for the TEZ/IVA group versus the placebo group was 1.2 % (95% CI: -0.3, 2.6; P value: 0.1176). The

LS mean treatment difference for the TEZ/IVA group versus the placebo group by visit was similar to the difference observed through Week 12 and ranged from 0.6 to 1.9 %. Treatment with TEZ/IVA did not demonstrate statistically significant treatment differences in the absolute change in ppFEV1 from baseline through Week 12. The 1-sided 80% UCB for LS mean treatment difference in the absolute change in ppFEV1 from baseline through Week 12 was 1.79 %, which was below the predefined futility boundary of 2.5% and the 1-sided 80% UCB for LS mean within treatment difference in the absolute change in ppFEV1 from baseline through Week 12 for the TEZ/IVA group was 1.52 %, which was below the futility boundary of 1.75 %. There were no clinically relevant differences for the change in CFQ-R respiratory domain score (2.1 points), the number (event rate per year) of pulmonary exacerbations (23 [0.98] events) vs 22 [0.97] events), BMI (-0.08 kg/m^2), BMI z-score (-0.05). The within-group LS mean absolute change from baseline in sweat chloride through Week 12 was greater in the TEZ/IVA group (-4.7 mmol/L) compared with the placebo group (-1.2 mmol/L), however the difference is not clinically relevant.

Study VX14-661-109

The results of this study were submitted during the assessment procedure. Study VX14-661-109 compared TEZ/IVA with IVA in 156 subjects aged 12 years and older with CF who are heterozygous for the F508del-CFTR mutation and a second CFTR allele with a gating defect that is clinically demonstrated to be IVA-responsive. The objectives and design are presented in the table below.

Table 34 Summary of design of study 109

Objectives	Design	Population
• Evaluate the efficacy of TEZ/IVA through Week 8 in F/gating subjects • Evaluate the safety of TEZ/IVA • Investigate PK of TEZ, M1-TEZ, IVA, and M1-IVA	Randomized (1:1), double-blind, active-controlled 	200 subjects with CF[b] ≥12 years old Males and females F/gating genotype $ppFEV_1$ ≥40 to ≤90 for subjects who have received IVA within 28 days; $ppFEV_1$ ≥40% and ≤75% for subjects who have not received IVA within 28 days

F/F: subjects homozygous for the *F508del-CFTR* mutation; F/gating: subjects heterozygous for the *F508del-CFTR* mutation and a second mutation with a gating defect that is clinically demonstrated to be IVA responsive; F/RF: subjects heterozygous for the *F508del-CFTR* mutation and a second mutation associated with residual function; F/MF: subjects heterozygous for the *F508del-CFTR* mutation and a second mutation resulting in minimal function; IVA: ivacaftor; TEZ: tezacaftor

[a] Study 107 enrolled 168 subjects out of the protocol-specified number of 300 subjects. The study was stopped based on a prespecified futility analysis when approximately 50% of subjects completed the study. Data from subjects enrolled in Study 107 will be included in the pooled safety database for TEZ/IVA. Study 107 will not be included as a supporting efficacy study for the proposed indication.

[b] Study 109 .is currently subject to a PIP modification that proposes to modify the total number of subjects enrolled.

The primary endpoint was the average absolute change in ppFEV1 through Week 8 of the Active Comparator Treatment Period (the baseline was the conclusion of the Run-in Period). The majority of subjects were White (96.7%). A total of 56.0% of subjects were male. The overall median age was 32.0 years (range: 12 to 71 years), with 18 (12.0%) subjects in the 12 to <18 years old subgroup. Demographic parameters were similar between the TEZ/IVA and IVA groups and similar in the Active Comparator Treatment Period (ACTP) and the IVA Run-in Period. Subjects were using similar concomitant medications during the IVA Run-in Period.

Within group, the mean treatment difference in absolute change in $ppFEV_1$ from baseline through Week 8 was 0.2 percentage points (95% CI: -0.5, 1.0; *P* = 0.5355) in the IVA group and 0.5 percentage points (95% CI: -0.2, 1.3; *P* = 0.1548) in the TEZ/IVA group. The LS mean treatment

difference between the TEZ/IVA and IVA groups for absolute change in ppFEV1 from baseline through Week 8 was 0.3 percentage points (95% CI: -0.8, 1.4; *P* = 0.5846).

Key secondary endpoints were relative changes in ppFEV1 and change in CFQ-R. Change in sweat chloride was a secondary efficacy endpoint. Treatment with TEZ/IVA resulted in a greater reduction (improvement) in sweat chloride concentration compared to IVA. The mean treatment difference between the TEZ/IVA and IVA groups in absolute change in sweat chloride from study baseline through Week 8 was -5.8 mmol/L (95% CI: -10.7, -0.9; P = 0.0216). The relative change in ppFEV1 and change in CFQ-R between the TEZ/IVA and IVA group were similiar.

***In vitro –in vivo* relationship**

In vitro studies were used to identify mutations that are likely to respond to TEZ/IVA in a clinical setting.

In vitro models

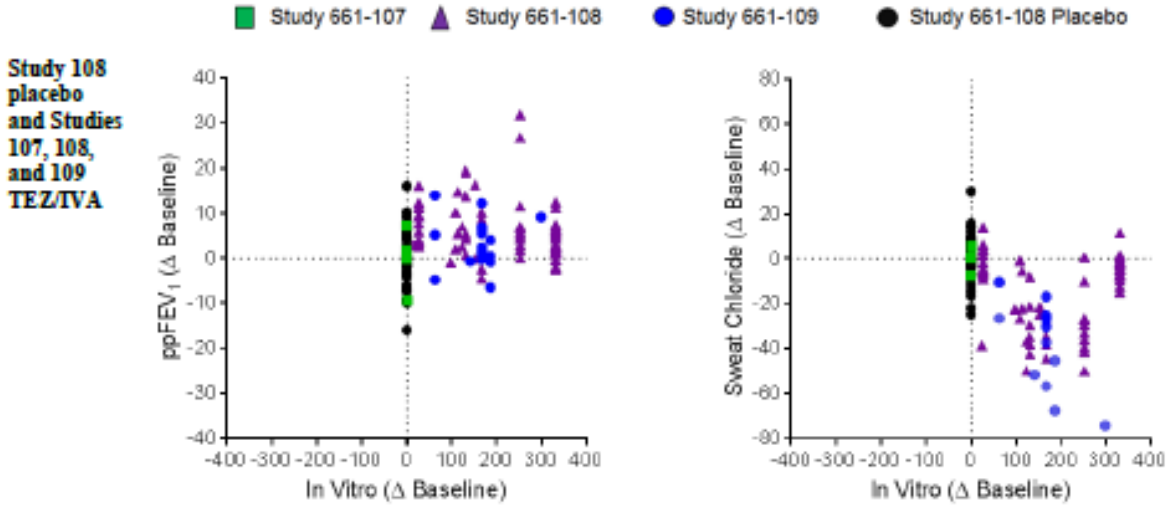
HBE cells and FRT *in vitro* model systems were used to understand the biology of CFTR mutations and effect of CFTR modulators on chloride transport: both models are well-established *in vitro* models for the studying CF (refer for details to non clinical assessment). In the FRT *in vitro* model, the F508del-CFTR response to TEZ/IVA, which represents the response of a single allele, did not reach the threshold of an increase in chloride transport over baseline of ≥10 % of normal.

Residual Function and IVA-Responsive Gating Mutations: The FRT model was used to evaluate the effect of TEZ/IVA on the CFTR mutations eligible for Studies 108 (and 109). Normal CFTR, the 20 missense RF CFTR forms eligible for Study 108, and the 10 IVA-responsive mutations eligible for Study 109 responded to TEZ/IVA with an increase in chloride transport of at least 10 % higher than normal CFTR. The 5 splice mutations eligible for Study 108 produce both correctly and aberrantly spliced CFTR transcripts; thus epithelial cells with these mutations express normal CFTR on the surface, although at reduced levels. FRT cells which express normal CFTR respond to TEZ/IVA with increased chloride transport, supporting that these 5 splice mutations will be responsive *in vivo*.
Of the 25 CFTR mutations eligible for Study 108, subjects with 17 mutations were enrolled. The ppFEV1 response in this group is used to support the ability of the *in vitro* model to predict clinical response to TEZ/IVA. The Study 108 subgroup analysis in subjects with splice mutations demonstrated a clinical response to TEZ/IVA. R347H-CFTR mutant was excluded based on an in vitro increase in chloride transport below the pre-defined threshold of 10%. All 9 mutations eligible for Study 108, for which no subjects were enrolled, were responsive to TEZ/IVA in the FRT model system. These 9 mutations were initially included in the proposed label. The 10 gating mutations eligible for Study 109 were responsive to TEZ/IVA *in vitro* and had a greater increase in chloride transport for TEZ/IVA than IVA and were initially proposed for the indication. In the response to the 1ste RSI, they are removed as the consequence of the results of the finalised study 109, which showed no difference in clinical response between ivacaftor and tezacaftor/ivacaftor.

TEZ/IVA-nonresponsive CFTR mutations: In vitro responses are also used as model for prediction of negative clinical responses. Many mutations included in Study 107 are not amenable to *in vitro* study due to the lack of any CFTR protein produced (truncation mutations). Two mutations in Study 107 (R1066C and N1303K) result in CFTR protein with processing and trafficking defects, and these CFTR forms were not responsive to TEZ/IVA in vitro in the FRT assay. These *in vitro* results were confirmed by the outcomes of Study 107.

In the response to the CHMP's request, scatterplots of the *in vitro* and *in vivo* responses were submitted, see figure below. The scatterplots show the *in vitro* response in the FRT assay and clinical

endpoints (i.e. ppFEV1, sweat chloride) for individual subjects in Study 108, 109 (ivacaftor naive) and 107 (R1066c, N1303K). The 5 splice mutations from Study 108 (i.e., 711+3A→G, 2789+5G→A, 3272-26A→G, or 3849+10kbC→T, and E831X) were not included in the scatterplots because FRT cells expressing the different splice mutations were not generated.



Sources: Study 108 Ad hoc Figures 14.2.2.17, 14.2.3.17, 14.2.2.32, and 14.2.3.32.

Notes: Each marker represents an individual subject on the y-axis and the mean value of chloride transport in the FRT assay for the mutation carried by that individual. Plots include all mutations in the proposed label with clinical data available in Study 108 and that have chloride transport data available in the FRT assay (*A455E, L206W, R117C, D110H, P67L, R1070W, S945L, S977F, D579G, R352Q*, and *D1152H*), 2 minimal function mutations from Study 107 (*N1303K* and *R1066C*), and all mutations with clinical data available in Study 109 (*G1244E, R117H, G551D, G178R, S1251N, G1349D*, and *S549N*). Change from baseline for $ppFEV_1$ and sweat chloride are provided for individual subjects within-group. Baseline was defined as the last assessment before the first dose of study drug during the treatment period (Studies 107 and 108) or the Run-In Period (Study 109).

Figure 13 Scatterplot of Clinical Response (ppFEV1 and Sweat Chloride) Versus In Vitro Chloride Transport for Residual Function, Gating (IVA-Naïve Subjects), and Minimal Function Mutations by Treatment Group

2.5.3. Discussion on clinical efficacy

At the time of the submission, tezacaftor/ivacaftor was claimed to be indicated in a combination regimen with ivacaftor 150 mg tablets "*the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro and/or clinical evidence (see section 5.1).* A table with these mutations was included in section 5.1 of the SmPC.

Hence, the proposed indication reflected the populations that were clinically investigated i.e. patients with CF who are homozygous for the F508del mutation, and patients with CF who are heterozygous for the F508del/residual function mutation, for which clinical data is collected. In addition, inclusion of CFTR mutations with residual function identified as responsive to TEZ/IVA was based on *in vitro* data models and was also initially proposed by the applicant.

For the *in vitro* test, HBE and mainly FRT models were used. These models were suggested by the applicant to be useful as support for distinguishing patients with CFTR mutations expected to benefit from treatment for which no extensive clinical data would be available. The use of *in vitro* data would

then be justified by a scientific understanding of the molecular basis of CFTR dysfunction, the known mechanism of action of the drug and the HBE/FRT models which the applicant asserts to be considered robust and established. A 10% increase in chloride transport was specified without clinical validation that this threshold of response would be decisive to predict clinical efficacy. The stably transfected FRT cell line appears to be particularly useful for gathering information on the underlying defect of certain CFTR mutant proteins. However, their relevance for the *in vivo* clinical situation can be questionable given their non-human origin and the high artificially overexpressed levels of transfected CFTR mutant protein in this system (refer to non-clinical part for a detailed discussion).

Scatterplots were provided with the results of all patients with residual function mutations in study 108, of the treatment naïve patients in study 109 with gating mutations and of the patients with minimal function mutations R1066C and N1303K in Study 107 as for these patients/mutations baseline ppFEV1 and in vitro data were available. Although, the majority of data points for individual subjects fall into the upper right quadrant for ppFEV1 and lower right quadrant for sweat chloride suggesting that the cut-off may have been be well chosen, the absence of the 'negative' side complicates the interpretation of the validity. Moreover, the absence of a scatter around a diagonal does not demonstrate a correlation between chloride transport and ppFEV1 increase, nor does it indicate a clinically relevant increase in ppFEV1. Furthermore, while IVA alone mostly appears to produce smaller increases from baseline in chloride transport compared to TEZ/IVA, there appears to be a similar spread of ppFEV1 and sweat chloride values for IVA monotherapy as for TEZ/IVA. The wide spread of the clinical response within a certain mutation is clearly demonstrated in the box-and-whisker plots.

For generalisability/extrapolation purposes regarding mutations not clinically investigated, a Mixed Model analyses were requested by the CHMP and were provided by the applicant. When comparing the predicted means with the observed medians (and constructing a range based on +/-1.96 times the within mutation SD), the model seems to overestimate the effect size for the majority of mutations with small sample size (< 10) and to predict well for mutations with a larger sample size (≥10). Thus the model is driven by the mutations with larger number of patients. This is confirmed in the threshold analysis: in 6 out of the 10 mutations with a low number of patients, the predicted percentage of patients with ≥ 2% improvement is higher than observed.

As the consequence of the above shortcomings of the *in vitro* model itself and the unclear relation between *in vitro* and *in vivo* results, the CHMP concluded that the originally proposed clinical indication including mutations based on *in vitro* evidence solely is not sufficiently justified. Further investigations for validation of this model with FRT cell or other in vitro systems would be needed. The applicant is encouraged to discuss the validation of the in vitro models (FRT cells or primary human cells) as well as the *in vitro-in vivo* relation within an EMA/CHMP qualification advice, during post-authorisation phase.

Design and conduct of clinical studies

Dose finding studies

Multiple doses of tezacaftor alone and combinations of tezacaftor with ivacaftor have been investigated in two phase II studies: study 101 (a dose ranging study in adult subjects with F/F genotype and in adult and adolescent subjects with F/G551D) and study 103 (a dose confirming study in adult CF patients, homozygous for the F508del-CFTR mutation). The same dosing was used in adolescents as for adults based equivalence of severity of disease and similar maturity of the CYP enzymes. The specified primary efficacy analysis variable/endpoint was the absolute change in sweat chloride (mmol/L) from baseline through Day 28. Given the acceptance of sweat chloride as a diagnostic

criterion and an important pharmacodynamic indicator of disease severity in CF, this is considered appropriate. Absolute change from baseline in ppFEV1 was evaluated as a secondary endpoint. The use of MMRM as the primary analysis is generally not supported in the presence of missing data, but in the context of an exploratory study this is less of a concern.

Main studies

Efficacy and safety have been evaluated in 5 phase III studies in CF patients aged 12 years and older. Study 106 in subjects homozygous for *F508del* (F/F) and study 108 in subjects heterozygous for *F508del* and a residual function mutation (F/RF) are the core efficacy studies. Study 110 was designed to support persistence of efficacy and long-term safety. Results are currently submitted as an interim analysis. The supportive studies Study 107 investigated TEZ/IVA in subjects heterozygous for *F508del* and a minimal function mutation that is not likely nonresponsive to TEZ and/or IVA (F/MF), while study 770-104 investigated ivacaftor monotherapy in subjects with the F/F genotype. The recently ended Study 109 compared TEZ/IVA versus IVA in patients with the F508del/gating genotype.

All main studies were randomised double-blind placebo-controlled multicentre studies except open-label, single-arm extension study 110. Studies 101, 109 and 108 were also active controlled by ivacaftor. Placebo was deemed necessary, because no CFTR modulators were approved for the F/F population at the time of study initiation and for adequate assessment of the benefit in the absence of an approved CFTR modulator in subjects with F/RF genotypes. The ivacaftor control arm allowed for assessment of contribution of tezacaftor to ivacaftor. Study 110 included a Treatment Cohort and an Observational Cohort. The in-and exclusion criteria for the dose-response studies, studies 101 and 103, and pivotal trials 106 and 108 were largely similar, except for the genotype mutations. In all studies the patients were 12 years and older. Patients had to have FEV1 ≥40% and ≤ 90% and stable CF. Diagnosis of CF was confirmed with standard methods of sweat chloride testing.

In study 108, the definition of 'residual function' is unusual as *in vitro* responsiveness requirement has been added. Patients needed to have a residual function based on population-level clinical phenotypic data and *in vitro* responsiveness to ivacaftor. Although the used criteria are acceptable for identifying patients, it is questionable if the term 'residual function' should have been used. Moreover, given the heterogeneity of the mutations with residual function, further characterisation in terms of the functional class as well as whether all of them are disease-causing are presented as requested, although summarily. Compared to class II (containing F508 homozygotes), classes IV and V had a significantly lower mortality rate and milder clinical phenotype.[1] Patients with CF and a RF mutation have a reduced rate of lung function decline compared to those homozygous for F508del (−0.82 compared to −1.77)[2] However, patients with an RF mutation still demonstrate progressive lung disease, particularly during adolescence.

The exclusion criteria were acceptable and in line with the risks (adverse events) known from Kalydeco (ivacaftor) and Orkambi (lumacaftor/ivacaftor). The duration of the dose finding studies 101 and 103 of 28 days and 12 weeks + 40 weeks OLE, respectively, is acceptable. The 24 week treatment period of pivotal study 106 is in line with the EMA guideline on CF (CHMP/EWP/9147/08) and in accordance with the CHMP's scientific advice. Pivotal study 106 had a parallel design. Study 108 had a cross-over design with two 8 week treatment periods with a wash-out period of 8 weeks in between. The wash-out period is justified from a pharmacokinetic perspective, while clinically a comparison for the baseline values of ppFEV1, CFQ-R and sweat chloride per period further excluded a carry-over effect.

[1] McKone EF, Goss CH, Aitken ML. CFTR genotype as a predictor of prognosis in cystic fibrosis. Chest. 2006;130:1441-7.
[2] Sawicki GS, Konstan M, McKone E, Moss RB, Johnson C, Lubarsky B, Suthoff E, Millar S, Pasta DJ, Mayer-Hamblett N, Goss C, Morgan W. Rate of Lung Function Decline in Patients with Cystic Fibrosis (CF) Having a Residual Function Gene Mutation. American Journal of Respiratory and Critical Care Medicine; p:A4847; 2017 American Thoracic Society.

Furthermore, the duration of treatment is very short, thus a difference may not have been captured within the trial. Long term data are provided from Study 110 with a duration of approximately 96 weeks.

Endpoints

All studies included the following endpoints: absolute change in ppFEV1, change of sweat chloride, height and weight, CFQ-R, pulmonary exacerbations and BMI. Depending on the type of study and the objectives of the study, primary and secondary endpoints were appointed. The primary endpoints in the phase II studies were change of sweat chloride in study 101 and absolute change in ppFEV1 in study 103, primarily for the purpose of PD assessments and dose finding, respectively. These endpoints are acceptable to the CHMP.

For the pivotal studies 106 and 108, the primary endpoint is absolute change in ppFEV1. FEV1 is the advocated primary endpoint in EMA's guideline on CF (CHMP/EWP/9147/08). Rate of decline in FEV1 has been demonstrated to correlate with survival and to be the strongest clinical predictor of mortality, while FEV1 is repeatable and, adjusted for age and sex, has been shown to be a cofactor for mortality. However, in study 108, the average of ppFEV1 from Week 4 to Week 8 is used. The results of a post-hoc of analysis using of the mixed-effects model at Week 8 alone were consistent with the primary analysis. The key secondary endpoints in study 106 (relative change in ppFEV1, number of pulmonary exacerbations, absolute change in BMI, change in CFQ-R respiratory domain score) and in study 108 (absolute change in CFQ-R, with the remaining as secondary endpoints) are all accepted endpoints in CF clinical trials. Each of them is able to measure a different aspect of the disease, and together able to support a benefit for CF patients. In extension Study 110, the same endpoints were used as in the parent studies.

Statistical methods

The analysis methods for the continuous repeated measures data e.g. ppFEV1 and CFQ-R, and the rates and timing of exacerbations are appropriate. Head-to-head comparisons of TEZ/IVA to IVA in study 108 were removed via protocol amendment from the set of endpoints for which type I error was protected, so these cannot be statistically significant in a formal sense. The applicant explained that the comparison of TEZ/IVA vs IVA was considered of interest, but not reason is provided for the removal of statistical testing. As for Symkevi no mutations are proposed that already registered for Kalydeco, this decision is acceptable.

Efficacy data and additional analyses

Dose regimen

For the CF patients 18 years or older with *F/F mutation* (n=194 included in study 101, ppFEV1 increased more with TEZ 100 mg qd /IVA 150 mg q12h compared to TEZ 150 mg qd/IVA 150 mg q12h (4.44 % vs. 4.13 %) and to VX-661 50 mg q12h/IVA 150 mg q12h (3.66 % vs 2.31 %). There was no clear evidence of a TEZ dose response on ppFEV1.

In study 101 there was discrepancy between sweat chloride and ppFEV1 outcomes, with TEZ monotherapy achieving consistently superior reductions in sweat chloride compared with TEZ/IVA; whereas change in ppFEV1 was superior with TEZ/IVA versus TEZ at the proposed combination dose. As discussed in the PD section, overall, the results for ppFEV1 demonstrated quite consistently a greater effect for TEZ/IVA combination with the highest response for TEZ 100 mg qd /IVA 150 mg q12h and a clinically relevant difference with TEZ 100 mg. However, there was no clear dose response to TEZ monotherapy at 10 mg q.d., which appeared to produce improvement in ppFEV1 not dissimilar

to that with the combination. For sweat chloride TEZ monotherapy at 100 mg and 150 mg qd appeared more effective at reducing sweat chloride than the combination, but there were inconsistences between the combination and the monocomponent tezacaftor and also between the TEZ monotherapy dose groups. Evaluation of treatment differences versus pooled placebo across cohorts demonstrated also inconsistency between sweat chloride and FEV1 data. However, in all groups the number of patients in the groups was low, either 8 (monotherapy) or 16 (combination therapy).

Exposure-response modelling results submitted to support clinical superiority of TEZ/IVA over TEZ was not fully reassuring. *In vitro* data were not conclusive either. There was a discrepancy between the patch clamp data and the Ussing chamber chloride conductance data when F508del is expressed in the same FRT cell system. Moreover, the patch clamp data are not aligned with the *in vivo* data in study 101 which appeared to demonstrate an effect of tezacaftor monotherapy in reduction of sweat chloride, which the applicant acknowledges, is not fully understood.

The effect of IVA in subjects with the F/F genotype was been investigated in study 104. The estimated treatment difference for ivacaftor versus placebo was 1.72 % (95% CI: -0.6349, 4.0754, P = 0.1509) suggesting that the effects of TEZ/IVA in study 106 (LS mean absolute change from baseline for placebo -0.6 and for TEZ/IVA 3.4) is partly due to effect of ivacaftor. For the 18 CF patients 12 years or older with *F/G551D* in study 101, change in sweat chloride was -7.02 mmol/L for TEZ 100 mg qd + Kalydeco, with a treatment difference of -17.2 mmol/L compared to Placebo + Kalydeco (P = 0.0238). A clinically relevant response was also observed in ppFEV1 within treatment and compared to Kalydeco alone.

In the response to the CHMP's request during evaluation, summarised data of a second interim analysis (IA2) of study 110 were provided. These follow up data could be analysed for all subjects (685), for patients with F/F mutation after 24 weeks and after 16 weeks for subject with F/RF mutation of the 96 weeks of the study. For the vast majority of the patients when rolling over the OLE study, dosing was not interrupted. Although interruption was up to 198 days, this is not expected to be of importance because of the small number of patients with interruption i.e. 20 subjects from Study 106 and 16 patients from Study 108.

Adolescents

The same dosing was used in adolescents as for adults based equivalence of severity of disease and similar maturity of the CYP enzymes. A comparable exposure was confirmed by simulated AUC vs age based on the pop-PK model.

CF patients 12 years or older with the F/F genotype

In the pivotal study 106 in 510 patients the baseline demographics, characteristics and concomitant medication appeared to be balanced overall. Missing data for the repeated measurements data were not an issue (less than 10%). The LS mean treatment difference in absolute change in ppFEV1 between the TEZ/IVA and placebo groups was 4.0 % (95% CI: 3.1, 4.8) in favour of TEZ/IVA (P<0.0001). The obtained difference between TEZ/IVA and placebo was above the predefined threshold (2.5 %) and also above the definition of clinical relevance of 2.5 % as determined as the average natural decline in CF patients (Report of the workshop on endpoints for cystic fibrosis clinical trials (EMA/769571/2012)). Results from MMRM analysis demonstrated a statistically significant improvement in absolute change in ppFEV1 compared to placebo already on Day 15 of 3.4 %. These improvements were sustained during the treatment period, with an increasing difference with placebo because of the gradual decrease in the placebo group of -1.3 % at week 24, in line with an expected

yearly loss of approximately 2.5%. The post–hoc sensitivity analyses supported the primary analysis, also by 95% CI and statistical significance.

A requested ANCOVA model with an imputation method for the missing data yielded a LS mean treatment difference in $ppFEV_1$ similar in magnitude to the LS mean treatment difference of 5.0 percentage points in the ANCOVA analysis with no imputations and remains highly statistically significant.

The inclusion of patients with $ppFEV_1$ <40, despite the exclusion criterion, is caused by a difference in ppFEV1 at screening and at baseline study visit.

Consistent and significant effects in ppFEV1 favouring TEZ/IVA were observed across all pre-specified subgroups: age, sex, baseline lung function, region, P. aeruginosa infection, and baseline use of common CF medications. The lowest point estimate of 3.5 % difference in the groups of patients with ppFEV1 < 40% and in female sex is still above clinical relevance.

The results of the key secondary endpoint, relative change from baseline in ppFEV1, support the primary endpoint. However, this parameter is not independent from the primary endpoint. For the other key secondary endpoint pulmonary exacerbations, the event rate was lower in the TEZ/IVA group (0.64 events per year) than in the placebo group (0.99 events per year). The rate reduction of 0.35 in PEx was statistically significant in favour of TEZ/IVA. This reduction of 35.3 % is considered clinically relevant. The hazard ratio for time-to-first pulmonary exacerbation requiring IV antibiotic therapy was also in favour of TEZ/IVA (0.553; P= 0.0080) as were the number of planned and unplanned hospitalisations. However, numbers of patients with exacerbations were low.

The secondary endpoint hierarchy was broken by the results of BMI. For this important extra-pulmonary parameter, the LS mean absolute change from baseline was numerically greater in the TEZ/IVA group (0.18 kg/m2) than in the placebo group (0.12 kg/m2). The LS mean (95% CI) of change from baseline in BMI was 0.06 (-0.08, 0.19; P= 0.4127). Therefore, the hierarchical multiple testing procedure was stopped.

In additional analyses in undernourished subjects (those with a weight- or a BMI-for-age z score below 0) improvement in BMI was numerically greater with placebo compared with TEZ/IVA and numerically less with TEZ/IVA (0.15 kg/m2) in under-nourished patients compared with the overall patient population in study 106 (0.18 kg/m2). However, the responder analysis of under-nourished patients who achieved a target BMI (defined for subjects <20 years as meeting a BMI-z-score was ≥ 0 and for subjects ≥20 years as meeting BMI value greater than the median baseline BMI value for healthy subjects) revealed more responders in the TEZ/IVA compared with placebo group, indicating a trend benefit on nutritional status with TEZ/IVA.

The last key secondary endpoint in the testing hierarchy was the CFQ-R respiratory domain score. The LS mean treatment difference between the TEZ/IVA and placebo groups in pooled CFQ-R respiratory domain score was 5.1 points (95% CI: 3.2, 7.0; nominal P<0.0001).

The reduction in sweat chloride is modest, given that homozygous F508del/F508del patients have baseline sweat chloride in the region of 100 mmol/L. Based on natural history data, mutations with residual CFTR activity that have sweat chloride levels approximately 10% lower (improved) than severe mutations have disease manifestations that are either less severe or demonstrate a delay in onset compared with the most severe mutations. Therefore, the reduction is acceptably relevant.

Preliminary results of open label extension study 110 at the time of the first interim analysis suggest that the efficacy observed in Study 106 is mirrored: an improvement of ppFEV1 is already observed at Day 15 for patients on previous placebo treatment and at Week 24 the LS mean absolute change from

baseline in ppFEV1 was 3.1 % (95% CI: 1.9, 4.3; P<0.0001) in the TEZ/IVA group and 4.5 % (95% CI: 3.3, 5.7; P<0.0001) in the PBO-TEZ/IVA group. Thus, both groups achieved a clinically relevant improvement from baseline. However, the initially observed improvement lowered in the TEZ/IVA group. Nevertheless, two different baselines are used for subjects enrolled from study 106 into study 110. For subjects who used tezacaftor/ivacaftor in study106, the baseline corresponds to the baseline of study 106, while for those who used placebo in study106, the baseline considered is that of study 110.

Summary results of a second interim analysis using study 110 baseline were submitted with 100% of patients. A loss of 0.5 percentage points in ppFEV1 was observed during the additional 24 weeks. This was considered acceptable as it is lower than the annual loss in this group of patients with F/F mutation i.e., −1.91 (95%CI, -1.82, −1.72) points using the Global Lung Initiative (GLI) equations[3]. The rate of decline is higher in adolescents compared to adults i.e. annual loss of −2.05 (95%CI, −2.15, −1.94). Furthermore, the time period spans from 2006 to 2014, while the standard of care since then has considerably changed. As a comparison, in the Cystic Fibrosis Foundation Patient Registry (CFFPR) the estimated annualised rate of lung function decline was −2.29 (95%CI, −2.56, −2.03) in the period from 2012 to 2014 and in the 2008-2009-2010 data set of the European Cystic Fibrosis Society Patient Registry −1.52 (−1.72, −1.31) in the 2008-2009-2010. Compared to this data from registries the results achieved by the treatment with TEZ/IVA could be considered relevant. The F/F subjects, who received TEZ/IVA during Study 106, maintained the improvements in BMI achieved in Study 106 during the extension period of Study 110. Further analyses of the data of the second interim analysis with using MMRM analysis showed similar trends.

The percentage of undernourished subjects in the adolescent group was considerably higher than in the adult group (69.8% vs. 17.5% respectively). This finding is in line with the nutritional decline that has been reported by several studies during adolescence and that commonly persists into early adult life. In study 106, no clinically meaningful within-group and between groups changes in the LS mean BMI z-score at Week 24. The absolute change in mean from baseline in BMI z-score for subjects <18 years was 0.10 (0.00, 0.19) in the PBO-TEZ/IVA group and −0.04 (−0.13, 0.06) in the TEZ/IVA group from Study 110 baseline at IA2. The mean (95%CI) absolute change in BMI for the overall population was 0.23 kg/m2 (0.11, 0.34) and 0.00 kg/m2 (−0.11, 0.11) respectively. Further analyses of the data of all adolescents patients with using MMRM analysis showed similar trends.

The initial improvement in CFQ-R was partly maintained (-1.3 point), but after 1 year the difference with baseline is near clinical relevance. The responder analysis supported a benefit in favour of TEZ/IVA as 51.3% patients were responders after 24 weeks (study 106), only reduced to 108/228 (48.6%) after 48 weeks (study 110). #

In Study 106, the event rate of PEx was 0.64 events per year in the TEZ/IVA group and increased to 0.72 after 24 weeks in Study 110. With this increase in the duration of TEZ/IVA exposure the PEx rate was still lower than the rate in the placebo group in Study 106. Moreover, in patients who started TEZ/IVA in either Study 106 (parent study) or Study 110, the risk of PEx that led to hospitalization or IV antibiotic treatment was 29.6%, while in the CFF Registry, the risk of PEx ranged from 47.6% to 49.5% from 2012 to 2014. All exacerbation related parameters remained substantially better in the two interim analyses (event rate of 0.72) compared to the placebo treated arm in study 106 (event rate of 0.99). Thus the positive effect is considered to be sustained.

[3] G Sawicki, MW Konstan, E McKone, RB Moss, B Lubarsky, E Suthoff, S Millar, DJ Pasta, N Mayer-Hamblett, CH Goss, W Morgan. Rate of lung function decline in patients with Cystic fibrosis (cf) having a residual function Gene mutation. Thorax 2017;72(Suppl 3):A1–278.

In study 104, a small not relevant difference in the adjusted mean absolute change from baseline through Week 16 in ppFEV1 has been observed between the ivacaftor group (1.5377%) and placebo group (-0.1826%) with an estimated treatment difference of 1.7203% (p = 0.1509). A similar picture was observed for sweat chloride values with a difference of -2.87 mmol/L (P = 0.0384). In the open label extension phase, subjects treated with ivacaftor for 64 weeks (IVA/IVA), the small improvement in FEV1 in the parent part was not sustained through Week 64. The efficacy of ivacaftor alone is not established in CF patients with F/F genotype.

CF patients 12 years or older heterozygous for the F508del-CFTR mutation, and a second allele with residual function

In the pivotal study 108, 81 subjects received placebo in Period 1 and 81 in Period 2, 81 subjects received IVA in Period 1 and 76 in Period 2, and 84 received TEZ/IVA in Period 1 and 78 in Period 2. Overall baseline demographics, characteristics and concomitant medication were overall balanced, but there were more females than males in the placebo and TEZ/IVA arms compared with the IVA arm where males and females were more evenly represented. There were more females than males in all study arms but the greatest imbalance between males and females (more females) was in the TEZ/IVA and placebo groups, with a lesser imbalance in IVA arm. A total of 23 patients had baseline sweat chloride levels within the normal range. In that case patients had to have documented evidence of chronic sinopulmonary disease. The status of chronic lung infection due to P. aeruginosa was not collected, but the concomitant use of inhaled antibiotics was collected for a period of 28 days prior to the screening and during the study. This may not reflect the incidence of subjects with a history of infection over the past 2 years, as some infections would be expected to resolve prior to enrolment. Therefore, the results of subgroup analysis by colonization with Pseudomonas do not accurately reflect the effect of treatment in study 108.

The majority of the patients were patients with canonical splice mutations. These mutations are not tested for responsiveness to ivacaftor and the applicant argued that these mutations produce both correctly and aberrantly spliced CFTR transcripts; thus epithelial cells with these mutations express normal CFTR on the surface, although at reduced levels. FRT cells, which express normal CFTR, respond to TEZ/IVA with increased chloride transport, supporting that these 5 splice mutations will be responsive *in vivo*. The inclusion is considered acceptable as indeed, *in vitro* responsiveness cannot provided.

The LS mean treatment difference of ppFEV1 compared to placebo was 6.8 %(95% CI 5.7, 7.8, P<0.0001) and to IVA was 2.1 % (95% CI: 1.2, 2.9; P<0.0001) in favour of TEZ/IVA. The sensitivity analysis is supportive for the primary analysis as the obtained difference between TEZ/IVA and placebo was above the predefined threshold and was statistically significant. The multiple testing procedure for study 108 is not proven to protect type I error, but due to the strong statistical significance, many conceivable multiplicity procedures would produce similar results, so this is not considered critical.

An ad hoc analysis was performed on individual RF mutations for ppFEV1. Although the response of splice mutations as a group was confirmed, the results showed that for some genotypes ivacaftor monotherapy seems to be a better option and that for some patients ppFEV1 did not improve.
The clinical relevance of responses of the mutations with clinical data was determined by using different thresholds and the annual loss of ppFEV1 of -1.05 with most rapid loss in the 18 to 24–year age group (-1.38 (0.39) (excluding R117H)[4].

[4] Sawicki, G., Konstan, M.W., McKone, E., Moss, R.B., et al. Rate of lung function decline in patients with cystic fibrosis (CF) having a residual function gene mutation. Thorax. 2017;72(Suppl 3):A1-278.

Given the fact that the applicant powered the sample size to detect a 3 percentage point treatment difference between TEZ/IVA and placebo, the 2% was chosen as a reasonable difference compared with placebo to have an impression of responders. The applicant proposed an additional threshold analysis of changes in ppFEV1 ≥0 percentage points, as it was considered that any improvement or stabilization in this measure would be considered clinically meaningful as CF subjects with RF mutations experience annual declines in ppFEV1. Although this is agreed in general, for studies of duration of 8 week treatment a stabilisation cannot fully appointed to a treatment effect yet. Furthermore, in the subanalysis of the mutations in study 108 when taken a clinically relevance as for the null hypothesis i.e. 3 % only three mutation would not fulfil this threshold, while when using 2%, this concerns 2 mutations.

For following mutations, sufficient clinical evidence is considered present: *2789+5G->A*, *3272-26A->G*, *3849+10kbC->T, A455E*, *D1152H*, *P67L*, and *S945L*. Because of the very limited data, *711+3A→G, D579G , L206W, R1070W, R117C, R352Q,* and *S977F* do not fulfil the requirement of robust clinical data and the modelling did not add new insights to overcome this issue. However, *711+3A→G, R1070W, R117C, R352Q,* and *S977F* fulfil the criteria for passing the different thresholds and might also be considered acceptably established. For the mutations *D579G* and *L206W*, although patient numbers are very low, 50% of the patients have a clinically relevant response. Given the rarity of these mutations and the difficulty of obtaining what would ordinarily be deemed robust clinical data, the sparse but promising data are considered sufficient for these mutations to be included in the indication of Symkevi.
Independent of the method for threshold or calculation, the mutations *D110H* does not meet any criterion and has been removed from the clinical indication. The R347H mutation was already excluded from the indication based on an *in vitro* increase in chloride transport below the pre-defined threshold of 10%.

The rationale for the need for TEZ in a TEZ/IVA combination can be considered somewhat more persuasive for patients with missense mutations that express misfolded CFTR protein. Patients with missense mutations demonstrated a greater mean treatment difference in both ppFEV1 and sweat chloride for TEZ/IVA versus IVA (difference of 2.3 pp ppFEV1 and -8.5 sweat chloride for missense mutations; versus 1.9 ppFEV1 and -3.0 sweat chloride for splice mutations). However*, in vitro* data through FRT cell data are absent for non-canonical splice mutations as DNA constructs are not available. Patients with such mutations were nonetheless included in study 108. The rationale behind inclusion was that non-canonical splice mutations result in low levels of normally folded CFTR protein.

For the key secondary endpoint CFQ-R Respiratory Domain, the difference of TEZ/IVA compared to placebo of 11.1 points and the difference compared to baseline of 10.1 points is clinically relevant as it is above the threshold of 4 points. The percentage of subjects who had an increase of at least 4 points was higher for TEZ/IVA and IVA compared to placebo: 65.2%, 58.3%, and 32.9% respectively with a favourable odds ratio for TEZ/IVA of 7.418 and 1.530 against placebo and IVA, respectively.
Absolute change in Sweat Chloride (-9.5 mmol/L) and change of BMI (0.34 kg/m^2) were all supportive for TEZ/IVA. Pulmonary exacerbations occurred in 11 (6.8%) subjects in the TEZ/IVA group, 9 (5.8%) subjects in the IVA group, and 19 (11.8%) subjects in the placebo group.

The estimated event rate of PEx was lower for TEZ/IVA (0.34 events per year) and IVA (0.29 events per year) than for placebo (0.63 events per year). Although suggestive for a benefit, exacerbation rate is not a reliable parameter measured over such a short time.

In sub-analyses, TEZ/IVA and IVA treatment resulted in statistically significant improvement over placebo regardless of age, sex, baseline lung function, region, use of common CF medications, and P.

aeruginosa colonization. The lowest point estimate is 4.4 difference in the group of patients with low baseline FEV1 (ppFEV1 < 40%). The inclusion of patients with $ppFEV_1$ <40, despite the exclusion criterion, is caused by a difference in ppFEV1 at screening and at baseline study visit. Although TEZ/IVA showed clinically relevant differences over placebo, the benefit over ivacaftor monotherapy is small (2.1 percentage points), but is relevant, in relation to an overall estimated annualized ppFEV1 rate of decline of –1.05 percentage point in F/RF patients. The male and female subgroups had trends that were consistent with this finding.

For pulmonary exacerbations, the reduction of event rate was even higher with monotherapy IVA. In the secondary endpoint CFQ-R a numerical higher but not relevant score was observed, but the responder analysis showed a somewhat more distinctive difference (65.2 versus 58.3). Thus, there is a clinical benefit over ivacaftor in this population of patients with F/RF mutations. For sweat chloride and pulmonary exacerbation rate there were no meaningful differences. Taking all data together, there is a benefit for TEZ/IVA over ivacaftor monotherapy. Some support is derived from study 101 in patients with F/G551D mutations taking TEZ on top of physician described Kalydeco, who had an improvement in ppFEV1 of 3.20 percentage points compared to Kalydeco alone, but the duration of the treatment period was rather short (28 days).

The preliminary results of study 110 support the effect maintenance. At Week 16, all groups achieved a clinically relevant improvement from baseline for absolute change from baseline in ppFEV1: 5.9 % (95% CI: 4.1, 7.7; P<0.0001) in the IVA-TEZ/IVA group, 7.4 % (95% CI: 5.6, 9.1; P<0.0001) in the TEZ/IVA group and 4.6 % (95% CI: 2.9, 6.3; P <0.0001) in the PBO-TEZ/IVA group. Improvement of ppFEV1 was observed at Day 15 for patients on previous placebo treatment as was in the parent study. Results of ppFEV1 of the second interim analysis (IA2) showed maintenance of the improvements observed during the parent study (0.1 percentage points). The event rate per year of pulmonary exacerbation was 0.34 for PBO-TEZ/IVA, 0.39 for IVA-TEZ/IVA and 0.20 for TEZ/IVA in the study 108/110 PEx efficacy set. This is lower than the event rate for the placebo group in Study 108 (0.63). However, the time was very short to allow for firm conclusions.

The results of the CFQ-R respiratory domain score for the 108/110 efficacy set seems reassuring although patient are treated only for 24 or 16 weeks with TEZ/IVA. Symptomatic improvement is not so well maintained over the longer term in F/F patients compared to F/RF patients. After 16 weeks of TEZ/IVA treatment a numerical increase of 2.6 points in CFQ-R Respiratory Domain Score after 16 weeks of TEZ/IVA treatment was observed. The proportion of patients who met or exceeded the MCID at the conclusion of Study 108 (53.9%) was maintained through an additional 16 weeks of TEZ/IVA treatment in Study 110 (62.2%) and also supports the maintenance of effect.

A gain in BMI and weight is consistently present from the start with treatment of TEZ/IVA, with an additional improvement in BMI of 0.53 (1.11) at week 16 of Study 110. The pivotal study faces the concern of the short duration and would not fulfil the requirement as laid down in the CF guideline. However, the 16 weeks extension data provided supportive evidence up to 24 weeks. Moreover, as already indicated in the CHMP SA support can also be derived for the data in other populations; the similar pattern of effect to the CF patients with F/F mutation and the similar early improvement at Day 15 supports extrapolation of the results in CF patients with F/F mutation to subject with F/RF mutation.

All patients

The number of patients ≥ 65 years old are not presented but are limited. There were 6 patients in this age group in the clinical studies. No notable trends were observed in these subjects compared to the overall study population. However, as the follow up of the benefit in elderly is warranted, it is part of the regular follow-up within the RMP.

Withdrawal effect

Studies 101 and 103 provide information about treatment withdrawal on ppFEV1. Changes in ppFEV1 after discontinuation of treatment showed that the improvements in ppFEV1 during 4 weeks of TEZ/IVA treatment were lost 1 to 4 weeks after discontinuation of dosing. However, as preservation of lung function by a CTFR modifier will need much longer time than 1 month, this loss of effect is not considered indicative for long term effects.

Assessment of paediatric data on clinical efficacy

Adolescents were included together with adults in the trials. Subgroup analyses of the primary endpoint were done using a model similar to that for the primary analysis. Subgroup analyses showed statistically significant and consistent changes in ppFEV1 regardless of age. The changes in ppFEV1 were similar (study 106) or better (study 108).

In adolescents with F/F mutation, the decline in ppFEV1 in the TEZ/IVA group is higher compared to adults (−0.8 vs. −0.3) in study 110, but the gain observed in subjects in the PBO-TEZ/IVA group in study 110 is higher (5.3 pp) than that observed in the parent study 106 at week 24 (3.5 pp) despite disease progression may have occurred. The change in weight- and BMI-z scores in subjects in the PBO-TEZ/IVA group was higher than observed in study 106. Overall, the treatment effect of tezacaftor/ivacaftor on body weight and BMI in study 106 week 24 or in study 110 week 24 was modest.

For adolescents heterozygous for F508del/pre-specified residual function mutations, the improvement seen in the parent study 108 was kept or increased after 16 weeks of treatment with tezacaftor/ivacaftor in study 110.

2.5.4. Conclusions on the clinical efficacy

CF patients 12 years or older with the F/F genotype

Although there is overall consistency in FEV1 response to TEZ/IVA between Phase II and Phase III studies, TEZ/IVA was not compared with TEZ alone in Phase III. In Phase II, where TEZ monotherapy was evaluated, the data did not consistently demonstrate superiority of TEZ/IVA over TEZ alone in ppFEV1 across all TEZ doses and was undermined by small patient numbers. The Phase II data indicated consistently greater reductions in sweat chloride with TEZ monotherapy compared with TEZ/IVA that has not been adequately explained. There are some discrepancies in the *in vitro* results, with some data supporting a need for IVA and other data suggesting no gain from addition of IVA. Furthermore, the failure of TEZ/IVA to increase chloride conductance in FRT cells with adequate (overexoressed) levels of F508del is at odds with the result of study 106. The absence of pivotal study evidence comparing TEZ/IVA versus TEZ in F508del CFTR patients leaves a number of important questions unanswered. Nevertheless, the TEZ/IVA efficacy is supported by a clinically relevant and statistically significant improvement in ppFEV1 compared to placebo. The results of the primary analysis were confirmed by the sensitivity analysis and by the secondary endpoints such as number/rate of exacerbations. Consistent and significant effects on ppFEV1 favouring TEZ/IVA were observed across all pre-pecified subgroups. In addition, in a comparison with natural history data, the benefit of the treatment is established. Altogether, the data point to the maintenance of the effect seen in the parent study 106 after a period of treatment with tezacaftor/ivacaftor of approximately 48 weeks.

CF patients 12 years or older heterozygous for the F508del-CFTR mutation, and a second allele with residual function

The approved indication reflects the currently available evidence collected in patients. The actual and precise relationship of the extent of *in vitro* responsiveness and *in vivo* effectiveness in patients with CF is still unclear and therefore inclusion of CFTR mutations identified as responsive to TEZ/IVA based only on the FRT *in vitro* model is not agreeable to the CHMP and hence, was not pursued by the applicant.

From the clinical data, efficacy is supported by a clinically relevant and statistically significant improvement in ppFEV1 compared to placebo. The improvement in CFQ-R Respiratory Domain of 11.1 points is impressive and substantially above MCID of 4 points during 24 weeks in total. The majority of the patients treated with TEZ/IVA achieved an improvement of 4 points. The secondary endpoints supported the results of the primary endpoint. Thus overall, the benefit of TEZ/IVA compared to placebo is considered demonstrated. Due to the statistical approach statistical significance cannot be declared against ivacaftor. However, overall the data of measuring are short. The similar pattern of effect to the CF patients with F/F mutation and the similarity in early improvement at Day 15 provides further support. In addition, as for the patients with F/FF mutation a comparison with natural history data, the benefit of the treatment is established.

TEZ/IVA was also numerically better than IVA alone, indicating the additional effect of tezacaftor to ivacaftor. However, the benefit over ivacaftor monotherapy is small (2.1 percentage points), but is considered relevant, in relation to an overall estimated annualized ppFEV1 rate of decline of –1.05 percentage point in F/RF patients. Taking all data together, there appears to be a benefit for TEZ/IVA over ivacaftor.

Finally, the CHMP agreed that Symkevi can be indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the *F508del* mutation or who are heterozygous for the *F508del* mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene: *P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T*.

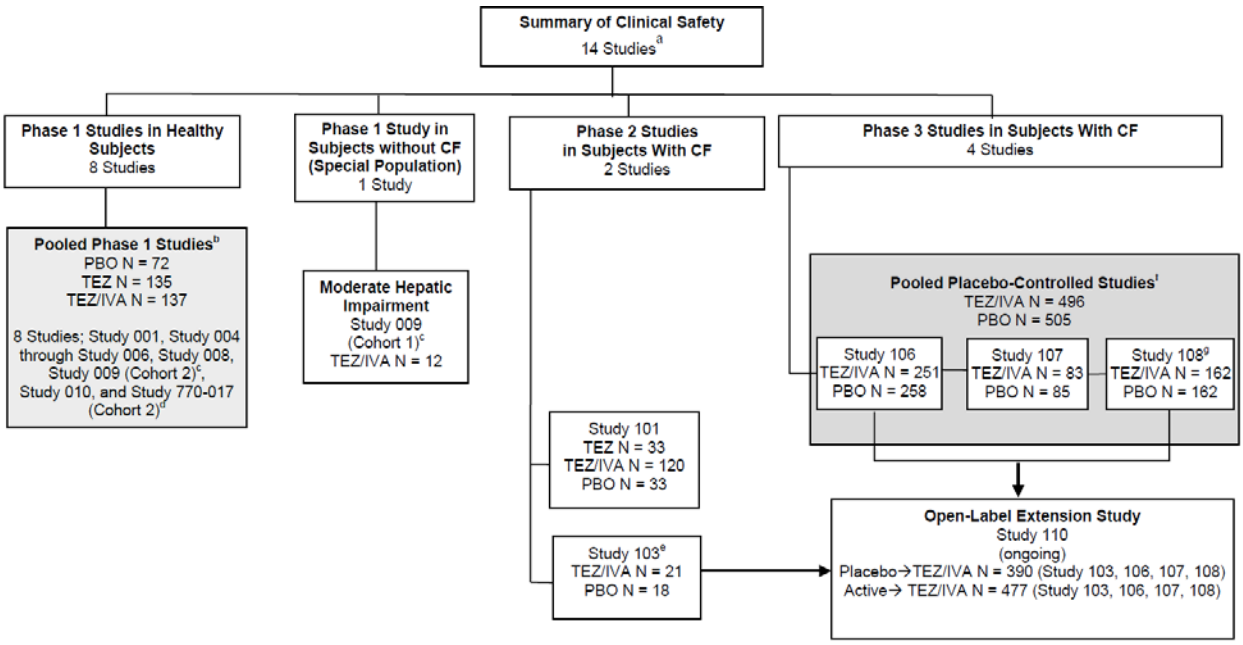
The CHMP considers the following measures necessary to address issues related to long term efficacy and safety, which was included in RMP as a category 3 study:

- Study 110, a phase 3 open label rollover study in subjects aged 12 years and older homozygous or heterozygous for the *F508del-CFTR* mutation.

2.6. Clinical safety

The safety analysis included all safety data available from 14 clinical studies with tezacaftor (TEZ) monotherapy or tezacaftor in combination with ivacaftor (TEZ/IVA), see **Figure 14** below. The core safety data consisted of pooled analyses of the 3 completed Phase 3 studies of TEZ/IVA combination therapy (Studies 106, 107 and 108) and was called the Phase 3-controlled Safety Set (PC-SS). In the core safety data set PC-SS, the majority of patients was White, and 18 years of age or older. The median age was approximately 28 years, and 20% of patients was <18 years in both arms. The proportion of males and females was similar. Baseline disease characteristics show that the proportion of patients distributed across the different ranges of percent predicted FEV1 were similar across the TEZ/IVA and placebo groups. Use of concomitant CF medications was similar between the placebo and TEZ/IVA groups. Long-term safety of TEZ/IVA in patients with CF was presented from open label

extension Study 110 (OLE-SS) and from patients with ≥48 weeks of TEZ/IVA exposure during the parent study and/or Study 110 (long term safety data set, LT-SS).



CF: cystic fibrosis; IVA: ivacaftor; OLE: open-label extension; PBO: placebo; SCS: Summary of Clinical Safety; TEZ: tezacaftor
Notes: Figure includes the number of subjects in the safety set of each study or pooled safety set as of the database lock date. Shaded boxes denote analysis of pooled safety data.
[a] Includes 13 completed studies and 1 ongoing OLE study (Study 110) for which an interim analysis (data cut-off date: 06 March 2017) has been performed.

Figure 14 Overview of 14 Clinical Studies Included in the Safety Analysis.

Patient exposure

In the TEZ/IVA pooled-placebo controlled Phase 3 studies (PC-SS), 496 patients received TEZ/IVA and 505 patients received placebo. Mean treatment duration was 16 weeks in both groups.

Table 35 Summary of Exposure: Placebo-controlled Safety Set (PC-SS)

Duration of Exposure	Statistic	Placebo N = 505	TEZ/IVA N = 496
Total exposure	Patient years	157.3	154.2
Exposure duration (weeks)	Mean (SD)	16.3 (7.5)	16.2 (7.7)
	Median	12.7	12.6
	Min, max	1.9, 25.0	0.3, 26.4
Exposure duration by interval, n (%)			
≤2 weeks		2 (0.4)	6 (1.2)
>2 to ≤4 weeks		5 (1.0)	2 (0.4)
>4 to ≤8 weeks		113 (22.4)	113 (22.8)
>8 to ≤16 weeks		140 (27.7)	137 (27.6)
>16 to ≤24 weeks		174 (34.5)	155 (31.3)
>24 weeks		71 (14.1)	83 (16.7)
Number of subjects by study			
Study 106		258	251
Study 107		85	83
Study 108		162	162

Source: ISS/Table 2.1.1.6
IVA: ivacaftor; PC-SS: Placebo-controlled Safety Set; SD: standard deviation; TEZ: tezacaftor.
Notes: Duration of study drug exposure (weeks) = (last dose date – first dose date + 1)/7, regardless of any interruptions in dosing. Patient years = duration of study drug exposure (days)/365.25. The PC-SS includes all subjects who received at least 1 dose of TEZ/IVA or placebo in Studies 106, 107, or 108. Subjects from Study 108 may receive 2 periods of treatment due to the cross-over design and therefore may be counted in more than 1 column.

Mean exposure duration was approximately 2-fold in OLE Study 110 (33.5 weeks), and 4-fold in safety data set LT-SS (69 weeks,). A total of 326 patients have been exposed to TEZ/IVA for at least 48 weeks.

Table 36 Summary of Exposure: Long-term Safety Set (LT-SS)

Duration of Exposure	Statistic	Total N = 326
Total exposure	Patient years	431.4
Exposure duration (weeks)	Mean (SD)	69.0 (15.3)
	Median	67.7
	Min, max	48.0, 115.9
Exposure duration by interval, n (%)		
≥48 to ≤60 weeks		108 (33.1)
>60 to ≤72 weeks		109 (33.4)
>72 to ≤84 weeks		52 (16.0)
>84 to ≤96 weeks		36 (11.0)
>96 weeks		21 (6.4)

Source: ISS/Table 2.2.2.2
IVA: ivacaftor; TEZ: tezacaftor; SD: standard deviation
Notes: Duration of study drug exposure (weeks) = (last dose date – first dose date + 1)/7, regardless of any interruptions in dosing. Patient years = duration of study drug exposure (days)/365.25. Includes the subjects in the Placebo-Controlled and Open-Label Integrated Safety Set with ≥48 weeks of TEZ/IVA treatment.

Adverse events

Nearly all patients in the TEZ/IVA (82.3%) and placebo (86.9%) groups of the PC-SS experienced at least one treatment-emergent AE. Across all AE categories defined in table below, incidences of AEs were either similar between the TEZ/IVA and placebo group, or lower in the TEZ/IVA group. Given the 2- and 4-fold increased durations of exposure in the OLE-SS and LT-SS compared to that of the pooled Phase III PC-SS, the incidences of AEs in the OLE-SS and LT-SS did not show any meaningful increases.

Table 37 Overview of Adverse Events: Placebo-controlled Safety Set (PC-SS)

Category	Placebo N = 505 n (%)	TEZ/IVA N = 496 n (%)
Total number of AEs	2223	1875
Subjects with any AEs	439 (86.9)	408 (82.3)
Subjects with Grade 3 or 4 AEs	43 (8.5)	35 (7.1)
Subjects with SAEs	75 (14.9)	50 (10.1)
Subjects with related SAEs[a]	7 (1.4)	5 (1.0)
Subjects with AEs leading to treatment discontinuation	10 (2.0)	8 (1.6)
Subjects with AEs leading to treatment interruption	18 (3.6)	12 (2.4)
Subjects with AEs leading to death	0	0

Source: ISS/Table 2.1.2.1.1
AE: adverse event; IVA: ivacaftor; PC-SS: Placebo-controlled Safety Set; SAE: serious adverse event; TEZ: tezacaftor
Notes: When summarizing number of events, a subject with multiple events is counted multiple times. When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category. The PC-SS includes all subjects who received at least 1 dose of TEZ/IVA or placebo in Studies 106, 107, or 108. Subjects from Study 108 may receive 2 periods of treatment due to the cross-over design and therefore may be counted in more than 1 column.
[a] Related AEs and SAEs include related, possibly related, and missing categories.

Common adverse events: The most common AEs (at least 15% incidence in either treatment group) were infective pulmonary exacerbation (PEx) of CF and cough, both occurring more frequently in the placebo group. Of the AEs with an incidence of at least 5% in either treatment group, the only events that were numerically higher in the TEZ/IVA group than in the placebo group were headache (13.7% versus 11.3%), nasopharyngitis (11.5% versus 9.7%), and nausea (7.7% versus 6.7%; see table below). The type of AEs in the long term safety data sets was similar to the pooled Phase 3 PC-SS. All of the proposed TEZ/IVA ADRs appear as ADRs on the Kalydeco label. ADRs that appear on the Kalydeco label that did not meet the criteria for TEZ/IVA ADRs are abdominal pain, diarrhoea, oropharyngeal pain, nasal congestion, rash, and upper respiratory tract infection.

Table 38 AEs with an incidence of at least 5% in either treatment group by preferred term (PC-SS)

Preferred Term	Placebo N = 505 n (%)	TEZ/IVA N = 496 n (%)
Subjects with any AEs	439 (86.9)	408 (82.3)
Infective pulmonary exacerbation of cystic fibrosis	153 (30.3)	117 (23.6)
Cough	141 (27.9)	108 (21.8)
Headache	57 (11.3)	68 (13.7)
Nasopharyngitis	49 (9.7)	57 (11.5)
Sputum increased	65 (12.9)	57 (11.5)
Haemoptysis	56 (11.1)	48 (9.7)
Pyrexia	49 (9.7)	41 (8.3)
Fatigue	51 (10.1)	38 (7.7)
Nausea	34 (6.7)	38 (7.7)
Oropharyngeal pain	44 (8.7)	36 (7.3)
Diarrhoea	34 (6.7)	31 (6.3)
Dyspnoea	36 (7.1)	30 (6.0)
Abdominal pain	34 (6.7)	29 (5.8)
Nasal congestion	28 (5.5)	24 (4.8)

Source: ISS/Table 2.1.2.2.3
AE: adverse event; IVA: ivacaftor; PC-SS: Placebo-controlled Safety Set; PT: preferred term; TEZ: tezacaftor
Notes: A subject with multiple events within a category is counted only once in that category. Table is sorted in descending order of TEZ/IVA column by PT. The PC-SS includes all subjects who received at least 1 dose of TEZ/IVA or placebo in Studies 106, 107, or 108. Subjects from Study 108 may receive 2 periods of treatment due to the cross-over design and therefore may be counted in more than 1 column. MedDRA Version 19.1.

Related adverse events: In the PC-SS, the incidences of AEs considered by the investigator to be related to study drug were similar between the placebo group (22.2%) and TEZ/IVA group (23.6%), see table below. The incidences of related AEs across SOCs and PTs were also similar between the placebo and TEZ/IVA groups. A similar safety profile regarding related AEs was observed in the OLE-SS and LT-SS analyses.

Table 39 Incidence of AEs by Relationship (PC-SS)

Category	Placebo N = 505 n (%)	TEZ/IVA N = 496 n (%)
Subjects with any AEs	439 (86.9)	408 (82.3)
Subjects with AEs by strongest relationship		
Related	10 (2.0)	5 (1.0)
Possibly Related	102 (20.2)	112 (22.6)
Unlikely Related	114 (22.6)	96 (19.4)
Not Related	213 (42.2)	195 (39.3)

Source: ISS/Table 2.1.2.1.1
AE: adverse event; IVA: ivacaftor; PC-SS: Placebo-controlled Safety Set; SAE: serious adverse event; TEZ: tezacaftor
Notes: When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category. Related AEs include related and missing categories. The PC-SS includes all subjects who received at least 1 dose of TEZ/IVA or placebo in Studies 106, 107, or 108. Subjects from Study 108 may receive 2 periods of treatment due to the cross-over design and therefore may be counted in more than 1 column.

Adverse events by severity: The majority of AEs in both the placebo and TEZ/IVA treatment groups were mild or moderate in severity. There were no imbalances in the incidence of mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4) AEs between the placebo and TEZ/IVA group; see table below.

Table 40 Incidence of AEs by Severity: PC-SS

Category	Placebo N = 505 n (%)	TEZ/IVA N = 496 n (%)
Subjects with any AEs	439 (86.9)	408 (82.3)
Subjects with AEs by maximum severity		
Mild	190 (37.6)	199 (40.1)
Moderate	206 (40.8)	174 (35.1)
Severe	42 (8.3)	34 (6.9)
Life-threatening	1 (0.2)	1 (0.2)

Source: ISS/Table 2.1.2.1.1
AE: adverse event; IVA: ivacaftor; PC-SS: Placebo-controlled Safety Set; TEZ: tezacaftor
Notes: When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category. The PC-SS includes all subjects who received at least 1 dose of TEZ/IVA or placebo in Studies 106, 107, or 108. Subjects from Study 108 may receive 2 periods of treatment due to the cross-over design and therefore may be counted in more than 1 column.

There were no imbalances in the incidence of Grade 3 or Grade 4 AEs in the TEZ/IVA group (7.1%) relative to the placebo group (8.5%). Most of the Grade 3 or 4 AEs were respiratory and gastrointestinal events, please refer to the table below. Infective PEx of CF and haemoptysis were the only Grade 3 or 4 AEs that had an incidence of at least 1% in either treatment group.

Table 41 Incidence of Severe (Grade 3) or Life-threatening (Grade 4) Adverse Events That Occurred in At Least 2 Subjects in Any Treatment Group by Preferred Term: PC-SS

Preferred Term	Placebo N = 505 n (%)	TEZ/IVA N = 496 n (%)
Subjects with any Grade 3 or 4 AEs	43 (8.5)	35 (7.1)
Infective pulmonary exacerbation of cystic fibrosis	19 (3.8)	18 (3.6)
Haemoptysis	5 (1.0)	4 (0.8)
Distal intestinal obstruction syndrome	1 (0.2)	2 (0.4)
Pneumonia	1 (0.2)	2 (0.4)
Blood creatine phosphokinase increased	2 (0.4)	1 (0.2)
Aspartate aminotransferase increased	2 (0.4)	0
Fatigue	2 (0.4)	0

Source: ISS/Table 2.1.2.2.5
AE: adverse event; IVA: ivacaftor; MedDRA: Medical Dictionary for Regulatory Activities; PC-SS: Placebo-controlled Safety Set; PT: Preferred Term; TEZ: tezacaftor
Notes: A subject with multiple events within a category is counted once under the maximum severity in that category. The PC-SS includes all subjects who received at least 1 dose of TEZ/IVA or placebo in Studies 106, 107, or 108. Subjects from Study 108 may receive 2 periods of treatment due to the cross-over design and therefore may be counted in more than 1 column. Table is sorted in descending order of TEZ/IVA column by PT. MedDRA Version 19.1.

Two subjects in the PC-SS had life-threatening (Grade 4) AEs that were considered possibly related to study drug by the investigator including 1 patient in the placebo group (mental status changes, acute respiratory failure, pneumothorax, infective PEx of CF, and pneumonia) and 1 patient in the TEZ/IVA group (haemoptysis). Grade 3 (severe) or Grade 4 (life-threatening) AEs occurred in 10.3% of patients in the OLE-SS and 16.3% of patients in the LT-SS. In the OLE-SS, no imbalances were observed in the incidences of Grade 1-4 AEs between the Placebo-TEZ/IVA and Active-TEZ/IVA group. The type of the most common Grade 3-4 AEs in the long term safety data sets was similar to the PC-SS.

Adverse Events by Time of Onset: An analysis of AEs over time was done using the longest placebo-controlled study, Study 106. Over 8-week intervals, the onset of AEs was generally higher in the first 8 weeks of treatment in both the TEZ/IVA and placebo groups. There were no clinically meaningful trends or patterns in the incidence of AEs by time.

Serious adverse event/deaths/other significant events

The incidence of SAEs was higher in the placebo group (14.9%) than in the TEZ/IVA group (10.1%). The only SAEs that occurred in ≥1% of patients in either treatment group were infective PEx of CF (6.7% TEZ/IVA vs. 10.3% placebo) and hemoptysis (1% vs. 1.2%).

Table 42 Incidence of Serious Adverse Events That Occurred in At Least 2 Subjects in Any Treatment Group by Preferred Term: PC-SS

Preferred Term	Placebo N = 505 n (%)	TEZ/IVA N = 496 n (%)
Subjects with any SAEs	75 (14.9)	50 (10.1)
Infective pulmonary exacerbation of cystic fibrosis	52 (10.3)	33 (6.7)
Haemoptysis	6 (1.2)	5 (1.0)
Distal intestinal obstruction syndrome	0	3 (0.6)
Pneumonia	3 (0.6)	2 (0.4)
Influenza	2 (0.4)	1 (0.2)
Pulmonary function test decreased	3 (0.6)	0
Abdominal pain	2 (0.4)	0
Acute kidney injury	2 (0.4)	0
Constipation	2 (0.4)	0

Source: ISS/Table 2.1.2.3.3

IVA: ivacaftor; MedDRA: Medical Dictionary for Regulatory Activities; PC-SS: Placebo-controlled Safety Set; PT: Preferred Term; SAE: serious adverse event; TEZ: tezacaftor

Notes: A subject with multiple events within a category is counted only once in that category. Table is sorted in descending order of TEZ/IVA column by PT. The PC-SS includes all subjects who received at least 1 dose of TEZ/IVA or placebo in Studies 106, 107, or 108. Subjects from Study 108 may receive 2 periods of treatment due to the cross-over design and therefore may be counted in more than 1 column. MedDRA Version 19.1.

There were no deaths reported in the TEZ/IVA clinical development program.

Adverse Events of Special Interest

Liver-related Adverse Events: Due to transaminase elevations being common in CF, and observed in some patients while receiving Kalydeco, a comprehensive review of the PC-SS data was conducted for AEs associated with elevated transaminases. The incidences of subjects with elevated transaminase events were low and similar between the placebo (3.6%) and TEZ/IVA (3.4%) groups. There were also low incidences of elevated transaminase events leading to discontinuation in the placebo (0.4%) and

TEZ/IVA (0.2%) groups. The majority of the elevated transaminase events were mild or moderate in severity. There were no elevated transaminase events that were considered serious. The incidences of subjects with other AEs in the hepatobiliary SOC were similar between the placebo (0.8%) and TEZ/IVA (0.4%) groups. There were no SAEs in the hepatobiliary SOC. The incidence and patterns of events for subjects who received ≥48 weeks of TEZ/IVA (LT-SS) remained lowed (6.7%) and similar to the incidence in subjects in PC-SS (3.6% in the placebo group and 3.4% in the TEZ/IVA group).

Respiratory Adverse Events and Spirometry: Due to the warning and precaution about respiratory AEs in the label for Orkambi, which has the same mechanism of action as TEZ/IVA, respiratory AEs and serial post-dose spirometry were evaluated in the TEZ/IVA Phase 3 studies. The incidence of subjects with respiratory events was numerically lower for TEZ/IVA (11.3%) than placebo (14.7%). No individual respiratory events occurred in a greater incidence in subjects in the TEZ/IVA group than in the placebo group. All respiratory events were mild to moderate in severity. No subjects in the TEZ/IVA group had an event leading to discontinuation. A subanalysis of PTs related to respiratory symptoms (i.e., chest discomfort, dyspnea, and respiration abnormal) demonstrated a lower incidence in TEZ/IVA (8.9%) than placebo (11.5%). No apparent pattern of time course in the onset of respiratory events or respiratory symptoms was identified from the Study 106 or Study 110 data.

In the PC-SS, subjects <18 years of age had postdose spirometry assessments to detect any postdose decline in ppFEV1. On Days 1 and 15, the postdose (2 and 4 hour) ppFEV1 values showed no evidence of decline from the pre-dose ppFEV1 for the placebo or TEZ/IVA groups. A subgroup analysis of AEs by baseline lung disease (baseline ppFEV1 <40, ≥40 to<70, or ≥70) found a trend of lower incidence of respiratory adverse events for subjects receiving TEZ/IVA compared to placebo for all subgroups, including those with the most severe lung disease (ppFEV1 <40).

Laboratory findings

Overall, there were no clinically important adverse trends attributable to TEZ/IVA dosing identified in vital sign assessments, haematology parameters, lipid/vitamin or amylase/lipase values in patients in the pooled Phase 3 placebo controlled safety set. Furthermore, in the placebo controlled safety set, there were no clinically meaningful differences in any ECG parameter between TEZ/IVA and placebo.

Earlier safety data in healthy volunteers suggest that VX-661 and its major metabolites may have low potential for drug-induced QT prolongation. A QT/QTc study was performed and showed no clinically relevant trends in standard ECG parameters, including no clinically significant increases or decreases over time in mean HR in patients receiving TEZ, compared to patients receiving placebo or moxifloxacin. There were no obvious differences between the therapeutic and supratherapeutic TEZ doses. No evidence was observed for QT prolongation, and no subject receiving TEZ at therapeutic and supratherapeutic doses had QTcF interval of >450 msec, or increase of >60 msec.

Due to existing warnings and precautions for IVA related to cataracts, ophthalmologic assessments were performed. Only Study 106 was long enough (24-week treatment duration) to allow detection of treatment-emergent cataracts. In this study, the incidences of treatment-emergent cataracts (not present at baseline) were 5.2% in the placebo group and 6.9% in the TEZ/IVA group. The incidence of resolved cataracts (present at baseline and not present at the follow-up exam) were 25% in the placebo group and 33% in the TEZ/IVA groups. There were no SAEs or discontinuations due to cataracts in the TEZ/IVA group.

In order to investigate whether the findings of lacteal dilation in nonclinical species translated to a human finding of small bowel dysfunction, Study 103 included VCE assessments to evaluate the appearance of the small bowel at screening and after 12 weeks of dosing. There was no evidence of

clinically meaningful changes in gastrointestinal function observed in VCE at Week 13, or in laboratory data or AEs after up to a minimum of 40 weeks and maximum of 48 weeks of treatment (OLE phase) with TEZ/IVA.

Phase 3 studies included monitoring of nutritional laboratory values (vitamins, lipids), and no meaningful findings related to decreased nutritional status were observed. No evidence of BMI decrease was observed in patients who received up to 48 weeks of treatment with TEZ/IVA in Phase 3 studies.

Safety in special populations

Age: Of 1001 patients who received study drug, 199 patients (19.8%) were ≥12 to <18 years of age years of age. The safety profile of TEZ/IVA was similar between these patients and patients ≥18 years of age. Data in patients ≥65 years old are limited.

Gender: Approximately equal proportions of females (50.5%) and males (49.5%) were included in the PC-SS. The most common AEs by PT for males and females were similar to the most common AEs observed in patients overall. The only SAE to occur in >10% of patients overall in any group was infective PEx of CF, which had a higher incidence for females than males.

Race: A subgroup analysis by race was not conducted for any of the Pooled Safety Sets, as the number of subjects in the other racial subgroups was too small for reliable comparative analyses.

Renal Impairment: Renal clearance was not expected to play a major role in the elimination of TEZ and IVA. No dose adjustment is recommended for patients with mild or moderate renal impairment in section 4.2 of the SmPC. Caution is recommended in patients with severe renal impairment or end-stage renal disease.

Hepatic Impairment: Hepatic metabolism plays a major role in the elimination of TEZ and IVA. Moderate hepatic impairment increased TEZ and IVA exposures, and a reduced dose is recommended. There is no experience with TEZ/IVA with severe hepatic impairment. Therefore, its use is not recommended in section 4.2 of the SmPC, unless the benefits outweigh the risks. In such cases, TEZ/IVA should be used in a reduced dose.

CFTR Genotype: There were no meaningful differences in safety profile of TEZ/IVA in Studies 106, 107, or 108. The frequency of AEs in the two pivotal Phase 3 studies (Study 106: patients homozygous for the *F508del* mutation and Study 108: patients heterozygous for the *F508del-CFTR* mutation, with a second *CFTR* mutation predicted to have residual function) were summarized in the tables below.

Table 43 Overview of Adverse Events, Safety Set Study 106

	Placebo N = 258 n (%)	TEZ/IVA N = 251 n (%)	Total N = 509 n (%)
Number of AEs (total)	1526	1201	2727
Subjects with any AEs	245 (95.0)	227 (90.4)	472 (92.7)
Subjects with related AEs	66 (25.6)	64 (25.5)	130 (25.5)
Subjects with AEs by strongest relationship			
Related	5 (1.9)	1 (0.4)	6 (1.2)
Possibly related	61 (23.6)	63 (25.1)	124 (24.4)
Unlikely related	50 (19.4)	49 (19.5)	99 (19.4)
Not related	129 (50.0)	114 (45.4)	243 (47.7)
Subjects with AEs by maximum severity			
Mild	99 (38.4)	114 (45.4)	213 (41.8)
Moderate	117 (45.3)	91 (36.3)	208 (40.9)
Severe	29 (11.2)	21 (8.4)	50 (9.8)
Life-threatening	0	1 (0.4)	1 (0.2)
Subjects with Grade 3/4 AEs	29 (11.2)	22 (8.8)	51 (10.0)
Subjects with SAEs	47 (18.2)	31 (12.4)	78 (15.3)
Subjects with related SAEs	3 (1.2)	5 (2.0)	8 (1.6)
Subjects with AEs leading to treatment discontinuation	8 (3.1)	7 (2.8)	15 (2.9)
Subjects with AEs leading to treatment interruption	8 (3.1)	2 (0.8)	10 (2.0)
Subjects with AEs leading to death	0	0	0

Source: Table 14.3.1.1.1

AE: adverse event; IVA: ivacaftor; MedDRA: Medical Dictionary for Regulatory Activities; n: size of subsample; N: total sample size; PT: preferred term; SAE: serious AE; TEZ: tezacaftor

Notes: AEs were coded using MedDRA Version 19.1. A subject with multiple events within a category was counted only once in that category. Related means study drug regimen-related and included the related, possibly related, and missing categories.

Table 44 Overview of Adverse Events, Safety Set Study 108

	Placebo N = 162 n (%)	IVA N = 157 n (%)	TEZ/IVA N = 162 n (%)
Number of AEs (total)	447	342	422
Subjects with any AEs	126 (77.8)	114 (72.6)	117 (72.2)
Subjects with related AEs	38 (23.5)	31 (19.7)	37 (22.8)
Subjects with AEs by strongest relationship			
Related	5 (3.1)	2 (1.3)	3 (1.9)
Possibly related	33 (20.4)	29 (18.5)	34 (21.0)
Unlikely related	25 (15.4)	23 (14.6)	30 (18.5)
Not related	63 (38.9)	60 (38.2)	50 (30.9)
Subjects with AEs by maximum severity			
Mild	63 (38.9)	55 (35.0)	58 (35.8)
Moderate	54 (33.3)	51 (32.5)	55 (34.0)
Severe	8 (4.9)	8 (5.1)	4 (2.5)
Life-threatening	1 (0.6)[a]	0	0
Subjects with Grade 3 or Grade 4 AEs	9 (5.6)	8 (5.1)	4 (2.5)
Subjects with SAEs	14 (8.6)	10 (6.4)	8 (4.9)
Subjects with related SAEs	2 (1.2)	2 (1.3)	0
Subjects with AEs leading to treatment discontinuation	1 (0.6)	2 (1.3)[b]	0
Subjects with AEs leading to treatment interruption	6 (3.7)[a]	5 (3.2)	2 (1.2)
Subjects with AEs leading to death	0	0	0

Sources: Table 14.3.1.1, Listing 16.2.1, Listing 16.2.5.2.1, and Listing 16.2.7.1.

AE: adverse event; CF: cystic fibrosis; CPK: creatine phosphokinase; IVA: ivacaftor; MedDRA: Medical Dictionary for Regulatory Activities; n: size of subsample; N: total sample size; PEx: pulmonary exacerbation; SAE: serious adverse event; TEZ: tezacaftor.

Notes: AEs were coded using MedDRA Version 19.1. When summarizing the number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percentage of subjects, a subject with multiple events within a category was counted only once in that category. Related AEs include related and possibly related categories.

[a] One subject had multiple life-threatening AEs (mental status changes, acute respiratory failure, pneumothorax, infective PEx of CF, and pneumonia) that were each considered serious. The study drug was interrupted, and the subject completed the study.

[b] The case report form from another subject incorrectly noted that the subject discontinued treatment for an SAE of blood CPK increased; however, the event occurred 1 day after the last dose of IVA in the Treatment Period, and this subject actually completed Treatment Period 1. The subject did subsequently withdraw from the study during the Washout Period due to the event and did not participate in Period 2.

Baseline ppFEV1: there were no clinically meaningful differences in the pattern of adverse events rates related to severity of lung disease at baseline between TEZ/IVA and placebo.

Geographic Region: There were no clinically meaningful trends associated with geographic region.

Use in Pregnancy and Lactation: The effects of TEZ and IVA on conception, pregnancy, and lactation in humans are largely unknown. Given the limited data available on pregnancy outcomes after TEZ/IVA exposure during pregnancy or lactation, TEZ/IVA combination therapy should not be used during pregnancy or lactation unless the potential benefit is considered to outweigh the potential risk.

Safety related to drug-drug interactions and other interactions

Please refer to discussion regarding pharmacokinetic interactions (CYP3A inducer/inhibitor interactions).

Discontinuation due to adverse events

Discontinuation of study drug: The rate for AE leading to treatment discontinuation was low and balanced in the PC-SS: 2.0% for placebo and 1.6% for TEZ/IVA. The only AE occurring in at least 2 patients leading to treatment discontinuation that had a higher incidence in the TEZ/IVA group (0.4%; 2 patients) than the placebo group (0 patients) was abdominal pain.

Interruption of study drug: The incidence of AEs leading to treatment interruption was low and balanced between the placebo (3.6%) and TEZ/IVA (2.4%) group. There were no AEs leading to treatment interruption occurring in >1% of patients in either treatment group. The only AE occurring in at least 2 patients leading to treatment discontinuation that had a higher incidence in the TEZ/IVA group was distal intestinal obstruction syndrome (DIOS) (0.6%, 3 patients vs. 0 patients in the placebo group. The 3 events of DIOS were considered not related to treatment.

Post marketing experience

Symkevi has not been marketed and thus, there is no post marketing experience.

2.6.1. Discussion on clinical safety

Patient population and exposure

Main safety data was derived from pooled analyses of the 3 completed Phase 3 studies of TEZ/IVA combination therapy (Studies 106, 107 and 108). In this Phase III controlled safety set (PC-SS), 496 patients received TEZ/IVA and 505 patients received placebo. Mean treatment duration was 16 weeks in both groups. Long-term safety of TEZ/IVA in patients with CF was presented from open label extension Study 110 (OLE-SS). Furthermore, long-term safety data was presented separately for a selection of these patients, i.e. those with minimal 48 weeks of TEZ/IVA exposure (long term safety data set, LT-SS). Mean treatment duration was approximately 2-fold in the OLE Study (33.5 weeks) compared to the PC-SS, and 4-fold in the LT-SS (69 weeks). More than 100 patients (i.e. n=326) have been exposed to TEZ/IVA combination therapy for at least 48 weeks in line with the guidelines on minimum exposure data for safety analyses of long-term therapy. In response to the CHMP's request, the applicant recalculated exposure duration, accounting for interruptions and discontinuations. Recalculated exposure data were, similar to original exposure data, well balanced between treatment arms.

Adverse events, serious adverse events and deaths

Nearly all patients in both arms of the PC-SS experienced at least one treatment-emergent AE (82.3% of patients in the TEZ/IVA arm and 86.9% in the placebo arm). The most common AEs (respiratory and gastrointestinal events) in patients who received TEZ/IVA in clinical studies were mild to moderate in severity and were common manifestations typical for patients with CF. The only TEAEs with an incidence of at least 5% in either treatment group, that were numerically higher in the TEZ/IVA group than in the placebo group, were headache (13.7% versus 11.3%), nasopharyngitis (11.5% versus 9.7%), and nausea (7.7% versus 6.7%). Related AEs occurred in similar frequencies between the TEZ/IVA (23.6%) and placebo group (22.2%). In response to the CHMP's request, the applicant provided further reassurance that the incidences of related AEs in the TEZ/IVA group were consistently lower or similar to the incidence in the placebo group in the PC-SS. There was no increase in the incidence of related AEs in the OLE-SS and LT-SS, when considering the increased exposure in the long term safety sets. Grade 3-4 AEs were also reported with similar frequencies in both arms. Infective PEx

of CF and haemoptysis were the only Grade 3 or 4 AEs that had an incidence of at least 1% in either treatment group.

Analysis of AEs over time was done using the longest placebo controlled study 106. In this study, the onset of AEs was generally higher in the first 8 weeks of treatment in both arms. The rate for AE leading to treatment discontinuation (1.6% TEZ/IVA vs. 2% placebo) or treatment interruption (2.4% vs. 3.6%) in the PC-SS was low and balanced. Infective PEx of CF was the most common AE leading to treatment discontinuation, which could be expected for patients with CF.

The incidence of SAEs was lower in the TEZ/IVA group (10.1%), than in the placebo group (14.9%), driven largely by a reduced incidence of infective PEx of CF events in subjects in the TEZ/IVA group. There were no serious liver-related or respiratory AEs, as previously observed with Kalydeco or Orkambi.

No deaths were reported in the TEZ/IVA clinical development program.

The long term safety data sets OLE-SS and LT-SS showed increased frequencies of (related AEs), Grade 3-4 AEs, SAEs and AEs leading to treatment discontinuation with TEZ/IVA compared to the pooled Phase III PC-SS. However, it is agreed with the applicant that this is probably related to the increased mean exposure in the long term safety data sets (2-4 fold compared to the PC-SS). Moreover, the placebo-TEZ/IVA arm in the OLE-SS, that received TEZ/IVA for a much shorter time period compared to the Active-TEZ/IVA arm, showed a similar pattern. The type of AEs was similar to the pooled Phase 3 PC-SS, and consistent with AEs commonly observed in subjects with CF. As in the pooled Phase 3 PC-SS, the majority of subjects had AEs that were mild or moderate in the long term safety data sets. A few immunological events have been reported, but none of the events that occurred among patients treated with TEZ/IVA were considered related to TEZ/IVA or resulted in treatment discontinuation, and all of these events were attributed to alternative aetiologies.

Adverse events of special interest

Hepatic toxicity is a known adverse event for Kalydeco and Orkambi. Liver-related AEs occurred in similar frequencies in the TEZ/IVA and placebo treatment groups in the PC-SS, and no serious elevated transaminase events were observed. However, in the Symkevi trials, exclusion criteria for patients with pre-existing liver function impairments were more stringent compared to the Orkambi trials. In the Symkevi trials patients were excluded when 2 out of the defined impairments were present while in the Orkambi trial this was the case for 3 out of these impairments. It is therefore not possible to directly compare the risk for hepatic toxicity in Orkambi and Symkevi. Despite the low incidence of liver related AEs in the current clinical trials with TEZ/IVA, it is therefore endorsed that a warning regarding the potential risk for elevated transaminases has been included in section 4.4 of the SmPC (similar to Kalydeco and Orkambi), and that it has been included as important potential risk in the summary of safety specifications in the RMP.

Due to the warning and precaution about respiratory AEs in the label for Orkambi, respiratory AEs and serial post-dose spirometry were evaluated in the TEZ/IVA Phase 3 studies. No clinically meaningful trends in the respiratory-related AEs or postdose spirometry data were observed, including those for patients with ppFEV1 <40 at baseline.

Safety in special populations

No clinically relevant differences in safety profile of TEZ/IVA between patients ≥12 to <18 years of age and ≥18 years of age have been observed. Upon request the applicant presented safety data of patients ≥65 years. It is acknowledged that data in the elderly population (>65 years) were very limited, as cystic fibrosis leads to a shortened life expectancy. Only 6 patients in the 3 placebo-

controlled Phase 3 clinical studies were aged 65 years or older at screening. Of these 6 patients, 4 received TEZ/IVA. Due to the small number of patients in this age group, no final conclusions regarding safety can be drawn. It is nevertheless reassuring that no apparent new safety signals were observed.

The patient populations in the respective individual studies of the PC-SS differ substantially, as patients from numerous genotypes were included. Patients homozygous for the F508del mutation, as included in Study 106 generally have a relatively rapid disease progression, whereas mutations that result in a more modest reduction in CFTR mediated chloride transport (residual function CFTR mutation), may result in CF that is more slowly progressive. It is therefore anticipated that patients included in Study 108 might show a better safety profile compared to patients in Study 106. As this might influence the overall safety profile as observed in the PC-SS, the safety results have been assessed for the 3 separate Phase III Studies as well.

The individual study reports of the three Phase III studies included in the integrated PC-SS analysis showed that AEs and SAEs indeed occurred most frequently in Study 106 (90.4% AE and 12.4% SAE Study 106 vs. 72.2% and 4.9% Study 108). However, a similar pattern is observed in the placebo arms of these studies. Moreover, differences in related (S)AEs and Grade 3-4 AEs between the three studies were less pronounced. In addition, the longer duration of study 106 compared to study 108 is prone to a higher incidence of AEs due to the longer exposure. Altogether, it is reassuring that as observed with the integrated PC-SS, the safety profile of TEZ/IVA treatment in the individual studies was similar or sometimes even better compared to the respective placebo arms.

The applicant also proposed to conduct a non-interventional post-authorization safety study (PASS) as per GVP Module VIII (EMA/813938/2011 Rev 3*). This registry study is expected provide further reassurance on the safety profile of the tezacaftor/ ivacaftor combination but the lack of a concurrent non-treated cohort is a significant unavoidable methodological limitation of the study. Taking into account that no new significant safety concerns have so far been identified with tezacaftor/ ivacaftor, the experience to date with ivacaftor, and the methodological limitations with the proposed registry study, it is accepted that the study be included in the RMP as a category 3 study.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

No significant new or additional safety concerns were identified with the addition of TEZ to IVA. The safety profile of TEZ/IVA appeared similar across studies. There were no latent, late onset safety issues or risks identified in the long term safety sets. TEZ/IVA was well tolerated with low discontinuation rates due to AEs.

The CHMP considers the following measure necessary to address issues related to safety, which is included in the RMP as category 3 study:

- A non-interventional post-authorization safety study (PASS). This registry study is expected provide further reassurance on the safety profile of the tezacaftor/ ivacaftor combination but the lack of a concurrent non-treated cohort is a significant unavoidable methodological limitation of the study. The protocol is expected to be submitted by the end of December 2018.

2.7. Risk Management Plan

Safety concerns

Important identified risks	• None
Important potential risks	• Hepatotoxicity • Concomitant use of TEZ/IVA with strong CYP3A inhibitors or inducers • Cataract
Missing information	• Use in pregnant and lactating women • Long-term safety • Patients with moderate or severe hepatic impairment • Patients with ppFEV$_1$ < 40

Pharmacovigilance plan

Study / activity **Type, title and category (1-3)**	**Objectives**	**Safety concerns addressed**	**Status** **(planned, started)**	**Date for submission of interim or final reports (planned or actual)**
VX14-661-110 (Study 110) Category 3	To evaluate the safety and efficacy of long-term treatment with TEZ in combination with IVA in subjects aged 12 years and older with CF, homozygous or heterozygous for the *F508del-CFTR* mutation	• Hepatotoxicity • Concomitant use of TEZ/IVA with strong CYP3A inhibitors or inducers • Cataract • Long-term safety	Ongoing	Final report July 2020
VX17-661-117 (Study 117) Category 3 (Protocol to be submitted by the end of December 2018)	To evaluate • the safety outcome in the real-world setting, • CF disease progression in patients treated with TEZ/IVA in the real-world setting, as measured by changes	• Hepatotoxicity • Use in pregnant and lactating women • Long-term safety • Patients with hepatic impairment • Patients with ppFEV$_1$ <40	Planned	Annual interim reports December 2019/2020/2021/2022 Final Report December 2023

	over time in lung function and nutritional status, • frequency and outcome of pregnancy in female patients • drug utilisation and to characterise potential off-label use			

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hepatotoxicity	**Routine risk minimisation measure:** SmPC Section 4.4 SmPC Section 4.4 where advice is given on monitoring LFTs. PL Section 3 and 4. **Additional risk minimisation measures:** No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** • Study 110 • Study 117 (PASS)
Concomitant use of TEZ/IVA with strong CYP3A inhibitors or inducers	**Routine risk minimisation measure:** SmPC Sections 4.2, 4.4, and 4.5 SmPC Sections 4.2 and 4.5 where dose reductions are recommended when TEZ/IVA is co-administered with a strong inhibitor of CYP3A. PL Section 2. **Additional risk minimisation measures:** No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** • Study 110
Cataract	**Routine risk minimisation measure:** SmPC Sections 4.4 and 5.3 SmPC Section 4.4 where advice is given on recommended ophthalmological examinations. PL Section 2. **Additional risk minimisation measures:** No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** • Study 110
Use in pregnant and lactating women	**Routine risk minimisation measure:** SmPC Sections 4.6 and 5.3 SmPC Section 4.6 where advice is given to avoid the use of	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only

	Symkevi during pregnancy and to determine the use during breastfeeding after taking into account the benefit of breastfeeding the child and the benefit of therapy for the woman. PL Section 2. **Additional risk minimisation measures:** No risk minimisation measures	Pregnancy follow-up form **Additional PV activities:** • Study 117 (PASS)
Long-term safety	**Routine risk minimisation measure:** SmPC Sections 4.8 and 5.1 SmPC Sections 4.8 and 5.1 describe the available clinical evidence, including the number and extent of exposure in clinical studies. **Additional risk minimisation measures:** No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** • Study 110 • Study 117 (PASS)
Patients with moderate or severe hepatic impairment	**Routine risk minimisation measure:** SmPC Sections 4.2, 4.4, and 5.2. SmPC Section 4.2 where advice is given on dose adjustment based on severity of hepatic impairment. PL Section 3. **Additional risk minimisation measures:** No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** • Study 117 (PASS)
Patients with $ppFEV_1$ <40	**Routine risk minimisation measure:** SmPC Section 5.1 **Additional risk minimisation measures:** No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** • Study 117 (PASS)

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.6 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 12 Feb 2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of tezacaftor with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers tezacaftor contained in the fixed combination medicinal product - Symkevi - to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union. Ivacaftor was considered to be a known active substance.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Labelling exemptions

A request to omit all particulars from the immediate labelling has been submitted by the applicant and has been found unacceptable by the QRD Group for the following reasons:

The product will be marketed as film-coated tablets supplied in blisters sealed in a wallet card. The company requested to omit printing of the minimum particulars on the blister foil as patients will not be able to see it, and separation from the wallet card would obliterate any printing on the blister, making it illegible.

The QRD Group rejected the request to omit completely particulars on the blister foil since there is no guarantee that the blister cannot be separated from the wallet. The Group requested to have the minimum particulars to be printed on the blister foil as follows: Invented name, strength, INN, EXP and Lot.

A request of translation exemption of the immediate labelling has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

The only particulars which would need translation on the blister foil are the INN, EXP and Lot. The Group agreed to have these particulars in English only.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

2.10.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Symkevi (tezacaftor / ivacaftor) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Cystic Fibrosis is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality, and at present, there is no cure. CF is caused by mutations in the CFTR gene that result in absent or deficient function of the CFTR protein at the cell surface that regulates salt and water absorption and secretion. The failure to regulate chloride transport results in the accumulation of thick, sticky mucus in the bronchi of the lungs, loss of exocrine pancreatic function, impaired intestinal absorption, reproductive dysfunction, and elevated sweat chloride concentration. Lung disease is the primary cause of morbidity and mortality in people with CF.

The claimed indication is:

Symkevi is indicated in a combination regimen with Kalydeco (ivacaftor 150 mg tablet) for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro and/or clinical evidence (see section 5.1).

In section 5.1 the list of approved mutations was displayed.

The proposed indication was not acceptable to the CHMP, due to the lack of reliable clinical data for some mutations. Since the inclusion of mutations based on *in vitro* data is not agreeable, there is no need for a reference to an explanatory table in section 5.1 of the SmPC. Hence, the wording was amended as follows:

Symkevi is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who are heterozygous for the F508del mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T.

Symkevi (TEZ/IVA) consists of two substances, tezacaftor and ivacaftor, that work by improving activity of CFTR in the lungs. Treatment with Symkevi is expected to thin the abnormal secretions, reduce symptoms of the disease and improve lung function. For the patients with CF heterozygous for the F508del/RF mutation, the indication reflects the clinical data collected in patients with RF-CFTR mutations identified as responsive to TEZ/IVA in *in-vitro* data models.

3.1.2. Available therapies and unmet medical need

The vast majority of CF therapies target the symptoms of the disease such as nutritional supplements, antibiotics, and mucolytics. A few years ago, CFTR modulators became available which have the potency to modify the progress of the disease. Two CFTR modulators are approved for the treatment of CF in the EU, Kalydeco (ivacaftor) and Orkambi (lumacaftor/ivacaftor).

KALYDECO

- Kalydeco tablets are indicated for the treatment of patients with cystic fibrosis (CF) aged 6 years and older and weighing 25 kg or more who have one of the following gating (class III) mutations in the *CFTR* gene: *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N* or *S549R.*
- Kalydeco tablets are also indicated for the treatment of patients with cystic fibrosis (CF) aged 18 years and older who have an *R117H* mutation in the *CFTR* gene
- Kalydeco granules are indicated for the treatment of children with cystic fibrosis (CF) aged 2 years and older and weighing less than 25 kg who have one of the following gating (class III) mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N* or *S549R*

ORKAMBI

- Orkambi is indicated for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who are homozygous for the F508del mutation in the CFTR gene.

Symkevi (tezacaftor + ivacaftor) is a combination therapy combining the CFTR corrector tezacaftor, a compound designed to move the defective CFTR protein to the proper place in the airway cell surface, with the CFTR potentiator ivacaftor, which helps facilitate the opening of the chloride channel on the cell surface to allow chloride and sodium (salt) to move in and out of the cell. The distinction between correctors and potentiators is nonetheless questioned in the scientific literature due to the interdependence of chloride channel opening and CFTR subcellular localisation on protein folding.

Symkevi targets several CFTR genotypes for which approved modulator therapies are not available. The F508del/Residual Function (RF) mutations represent ~ 9% of the CF population. The patients who harbour a mutation with a residual function are characterised by slower disease progression than the homozygous F508 population, but they will eventually experience the clinical consequences of CF including a reduced lifespan. However, it is difficult to quantify the difference in survival or the development of irreversible damage over a short trial period considering the slower progression of disease.

TEZ/IVA is also claimed to be an alternative for patients, who are homozygous for F508del and cannot tolerate or take LUM/IVA because of serious adverse events or certain concomitant medications, respectively.

3.1.3. Main clinical studies

Efficacy and safety of Symkevi was supported by three key trials. The trials investigated tezacaftor 100 mg qd/ivacaftor 150 mg q12h.

Study 106 in CF patients 12 years or older is a randomized, double-blind, placebo-controlled, parallel-group study in subjects homozygous for the F508del-CFTR mutation. A total of 510 subjects were randomized. Placebo was used as the control treatment. Study 106 was powered for ppFEV1 and pulmonary exacerbations and provided 24 weeks data.

Study 108 in CF patients 12 years or older is a phase 3, randomized, double-blind, placebo- and active controlled, crossover study in subjects aged 12 years and older, heterozygous for the F508del-CFTR mutation, and a second allele with a CFTR mutation predicted to have residual function. Alongside

placebo, ivacaftor was deemed necessary because *in vitro* and clinical data supported the potential efficacy of IVA monotherapy. Study 108 was powered for ppFEV1 and provided 8 weeks data.

Study 110 is an open-label rollover study that enrolled subjects from the Phase 2 and 3 studies of TEZ/IVA. This study is designed to support persistence of efficacy and long-term safety and is part of the RMP. An interim analysis is submitted allowing for evaluation of the persistence of efficacy. As of the interim (IA1) cut-off date, 870 subjects had been enrolled from 4 parent studies among 462 subjects from Study 106 with additional 24 week treatment and 223 subjects from Study 108 with additional 16 week treatment. Data from 70% of the enrolled patients were analysed. Summarised data of a second interim analysis (IA2) of study 110 became available from 100% of the enrolled patients during the assessment.

Two additional studies are submitted providing results for further insight about mutations possibly beneficial for treatment with TEZ/IVA: Study 104 in CF patients 12 years or older with the F/F genotype and study 107 in CF patients 12 years or older heterozygous for the F508del-CFTR mutation, and a second allele not likely to respond to TEZ/IVA or ivacaftor therapy (F508del/NR).

Study 109 was also submitted, which compared TEZ/IVA with IVA in 156 subjects aged 12 years and older with CF who are heterozygous for the F508del-CFTR mutation and a second CFTR allele with a gating defect that is clinically demonstrated to be IVA-responsive. However, this study failed to show beneficial effect over ivacaftor.

Dose finding was performed in two phase 2 studies. Study 101 and Study 103 evaluated different doses TEZ monotherapy and TEZ/IVA combination therapy in adult subjects with F/F genotype and study 101 also in adult and adolescent subjects with F/G551D.

Potential QTc prolongation has been evaluated in Study VX15-661-010 in 116 healthy volunteers for therapeutic and supratherapeutic doses of TEZ compared with placebo and moxifloxacin.

3.2. Favourable effects

CF patients 12 years or older with the F/F genotype

Changes in sweat chloride test, representing a pharmacodynamic parameter for the activity of a CTFR modulator, showed a decrease of -9.9 in the group treated with TEZ/IVA versus 0.2 for the placebo group. TEZ/IVA (n= 510) showed a statistically highly significant mean treatment difference in absolute change of ppFEV1 from baseline through week 24 of 4.0 % compared to placebo; 3.4% for TEZ/IVA and – 0.6% for placebo (P<0.0001), a difference that was already observed on Day 15. The improvements were sustained during the treatment period (3.5 % at week 24), while in the placebo group a gradual decrease of -1.3 % has been observed. In patients with ppFEV1 < 40%, an increase of 3.5 % in ppFEV1 was observed. Preliminary results of the open label extension study 110 support the maintenance of the effect as an absolute change from baseline in ppFEV1 of 3.1 % in the TEZ/IVA group and 4.5 % in the PBO-TEZ/IVA group at week 24 was observed. An improvement of ppFEV1 was already demonstrated at Day 15 in patients on previous placebo treatment. In adolescents, the mean (95%CI) absolute change from Study 110 baseline in ppFEV1 at week 24 in study 110 was 5.3 percentage points (3.9, 6.8) in the PBO-TEZ/IVA group and -0.8 pp (−2.3, 0.7) in the TEZ/IVA group.

Consistent improvements in ppFEV1 favouring TEZ/IVA were observed across all prespecified subgroups: age, sex, baseline lung function, region, Pseudomonas aeruginosa infection, and baseline use of common CF medications. The lowest point estimate was a 3.5 % difference in the group of patients with ppFEV1 < 40% and in females. No CI of any subgroup crossed 0.

For the secondary endpoints, the estimated event rate of pulmonary exacerbations was lower in the TEZ/IVA group (0.64 events per year) compared with the placebo group (0.99 events per year) being statistically significant. The difference between the TEZ/IVA and placebo groups in CFQ-R respiratory domain score was 5.1 points, i.e. 5.0 and -0.1 for TEZ/IVA and placebo respectively (P<0.0001). As indicative for nutritional status, the absolute change in BMI was numerically favourable for TEZ/IVA when compared to placebo: an increase of 0.18 kg/m^2 compared to 0.12 kg/m^2, respectively (p = 0.4127). The increase in BMI continued to 0.26 kg/m^2 in study 110. In adolescents, the mean (95%CI) absolute change from Study 110 baseline at week 16 in study 110 in BMI Z-value was 0.10 (0.00, 0.19) in the PBO-TEZ/IVA group and −0.04 (−0.13, 0.06) in the TEZ/IVA group and in weight-z value 0.06 (0.04) kg in the PBO-TEZ/IVA group and −0.02 (0.04) kg in the TEZ/IVA group. Further analyses of the data of the second interim analysis with all adolescent patients with using MMRM analysis showed similar trends. The other secondary endpoints were overall supportive, some only numerically, some were statistically significant.

In study 104 in 94 patients, the LS mean absolute change from baseline through Week 16 in ppFEV1 was in the ivacaftor group 1.5377% and in the placebo group -0.1826% (P = 0.1509). In the open label extension phase, the improvement in FEV1 in the parent part was not sustained through Week 64. The difference in decrease in sweat chloride was -2.87 mmol/L between the ivacaftor group and the placebo group (P = 0.0384).

CF patients 12 years or older heterozygous for the F508del-CFTR mutation, and a second allele with residual function

TEZ/IVA treatment (n=162) resulted in an increase in absolute change in ppFEV1 averaged for Week 4 and Week 8 of 6.5% with a difference of 6.8 % compared to placebo (n=162). The LS mean treatment difference compared to IVA (n = 157) was 2.1 % in favour of TEZ/IVA, both comparisons being statistically significant. The sensitivity analysis showed similar results. In patients with ppFEV1 < 40%, an increase of 4.4 % in ppFEV1 was observed. In patients ≤ 18 years , the mean (95%CI) absolute change from baseline in ppFEV1 at week 24 in study 110 was 7.2 pp (4.8, 9.7) in the PBO-TEZ/IVA group, 1.6 pp (−1.5, 4.8) in the IVA-TEZ/IVA group and 0.7 (−2.2, 3.6) in the TEZ/IVA group. Consistent improvements in ppFEV1 favouring TEZ/IVA were observed across the pre-specified subgroups, age, sex, baseline lung function, region, use of common CF medications, P. aeruginosa colonization.

For the key secondary endpoint CFQ-R Respiratory Domain, the LS mean difference of TEZ/IVA compared to placebo was 11.1 points and compared to baseline of 10.1 points (both statistically significant). The LS mean difference with IVA was 1.4. The percentage of subjects who had an increase of at least 4 points was higher for TEZ/IVA and IVA when compared to placebo: 65.2%, 58.3%, and 32.9%, respectively. Differences in absolute change in sweat chloride and BMI were higher in TEZ/IVA compared to placebo. The change in sweat chloride was -9.9, -4.5 and 0.2 mmol/l for TEZ/IVA, IVA and placebo respectively, while for BMI 0.34, 0.47 and 0.18 kg/m^2. The results of the CFQ-R respiratory domain score of 9.9 points appears reassuring for 24 week (TEZ/IVA) or 16 weeks (PBO-TEZ/IVA, IVA-TEZ/IVA) treatment with TEZ/IVA. A gain in BMI (0.34 kg/m^2) and weight is consistently apparent when patients start with treatment of TEZ/IVA. In study 110, the mean absolute change (SE) from Study 110 baseline in BMI-z value for subjects <18 years old was 0.04 (0.05) in the PBO-TEZ/IVA group and -0.13 (0.07) in the IVA-TEZ/IVA group and 0.16 (0.06) in the TEZ/IVA group.

Interim results of study 110 in 70%of the patients showed that the improvements in ppFEV1 during the placebo controlled phase was further improved with 0.1 percentage points in patients treated with TEZ/IVA in study 108. For CFQ-R a further increase of 2.6 points was demonstrated. The PEx event rate was lower for the TEZ/IVA group (0.34 events per year) than for the placebo group (0.63 events

per year). In Study 110, subjects who continued TEZ/IVA in Study 110 maintained a low PEx event rate of 0.20 events per year at the time of IA1 and 0.22 events per year at the time of IA2. The risk of PEx that led to hospitalization or IV antibiotic treatment was 12.9%, while in the CFF Registry the risk of PEx ranged from 27.0% to 31.6% from 2012 to 2014. However, the exacerbation rate even annualised, is not a reliable parameter measured over such a short time period, i.e., 8 weeks in study 108 and 16 weeks in study 110.

In Study 101, patients with F/G551D mutations taking TEZ on top of physician described Kalydeco showed an improvement in ppFEV1 of 3.20 percentage points compared to Kalydeco alone, demonstrating a treatment benefit in a gating mutation.

CF patients 12 years or older heterozygous for the F508del-CFTR mutation, and a second mutation that is not likely to respond to TEZ and/or IVA therapy (F508del/NR)

In study 107 in patients with F508del/NR mutation, the difference in absolute change in ppFEV1 between TEZ/IVA and placebo group was 1.2 % (95% CI: -0.3, 2.6; P = 0.1176). The 1-sided 80% UCB was below the predefined futility boundary of 2.5%.

3.3. Uncertainties and limitations about favourable effects

Dose regimen and drug-drug interactions

When TEZ/IVA was compared with TEZ alone across a range of TEZ and IVA doses in Phase II, (study 101) in patients homozygous for the F508del-CFTR mutation, the proposed combination regimen TEZ 100 mg qd/IVA 150 mg q12h demonstrated the greatest improvement in ppFEV1. However, a low dose of TEZ alone (10 mg q.d.) apparently demonstrated an effect on ppFEV1 that was not dissimilar to the combination in the proposed higher dose regimen, leaving a question over the possibility of a negative pharmacodynamic interaction between TEZ and IVA. The lack of robustness of the study due to small patient numbers does not allay this concern. Moreover, a greater reduction in sweat chloride was demonstrated with TEZ monotherapy, compared with the TEZ/IVA combination, at the highest doses. For ppFEV1, the treatment effects for the combination therapy compared to placebo ranged from 1.44 to 3.89, and for the monotherapy from 1.74 to 3.63, with the greatest treatment effect at the lowest TEZ dose of 10 mg qd. The model, within the limitations, appears to be more accurate for FEV1 than sweat chloride but cannot be considered conclusive. The need for IVA in a FDC combination of TEZ/IVA to treat F/F patients is not considered to be established and the absence of a pivotal study evidence comparing TEZ/IVA versus TEZ in F508del CFTR patients leaves a number of important questions unanswered.

Both, TEZ and IVA, are substrate for CYP3A4, an enzyme for which potentially important genetic variation has been reported (i.e. CYP3A4*22) that may lead to TEZ and IVA exposures comparable to those obtained when given in combination with strong inhibitors of CYP3A4. For this reason, either additional information on the genetic profile of patients included in the studies with respect to this enzyme, or additional in vivo data in healthy subjects should be provided. In both situations, further analysis of the potential relationship between TEZ and IVA exposure (AUC, Cmax and Ctrough) and genotype in subjects with CYP3A4*22 genotype and subjects with CYP3A4 wild-type phenotype is being requested. Based on the outcome of this analysis, potential consequences of such pharmacogenetic variations related to CYP3A4 for exposure and/or dose advice should be further discussed. Additional information will be provided post-approval on the substrate, inhibiting and inducing characteristics of TEZ and metabolites, as well as IVA and its metabolites, and towards a number of enzymes and transporters, in order to be able to predict potential consequences for drug-

drug interactions. These results will be submitted in post-authorisation phase (included in the RMP) and this is agreed by the CHMP.

All patients

Only 6 patients ≥ 65 years of age were included, all in study 108 for patients with F/RF mutations, which is also reflected in the SmPC.

Only interim data from study 110 is available for a total treatment duration of up to 48 weeks for patients with F/F genotype and 24 weeks for patients with F/RF genotype, although the study is planned to provide up to a follow-up safety and efficacy duration of 120 and 104 weeks respectively. The applicant committed to report the full data from this study in the post-authorisation phase.

CF patients 12 years or older with the F/F genotype

The reduction in sweat chloride is only modest, given that homozygous F508del/F508del patients have baseline sweat chloride in the region of 100 mmol/L. Based on natural history data, mutations with residual CFTR activity with sweat chloride levels of approximately 10% lower than severe mutations, such as homozygous F508del/F508del patients, have less severe disease manifestations or demonstrate a delay in onset. The reduction is therefore acceptably relevant. In the second interim analysis of the open label extension study 110, using study 110 baseline, a loss of 0.5 percentage points in ppFEV1 was observed during the additional 24 weeks. This appears acceptable as it is lower than the annualized loss in this group of patients with F/F mutation i.e., −1.91 percentage points[5].

The initial improvement in CFQ-R was partly maintained (-1.3 point). In the responder analysis 51.3% patients treated with TEZ/IVA were responders after 24 weeks (study 106) and 48.6% after 48 weeks (study 110) compared with placebo 35.7%. The percentage of undernourished adolescents was considerably higher compared to the adults (69.8% vs. 17.5% respectively). In this group of undernourished patients no clinically meaningful within-group changes in BMI z-score were observed. The event rate of PEx was 0.72 after 24 weeks in Study 110. Moreover, in patients who started TEZ/IVA in either Study 106 (parent study) or Study 110, the risk of PEx that led to hospitalization or IV antibiotic treatment was 29.6%.

CF patients 12 years or older heterozygous for the F508del-CFTR mutation, and a second allele with residual function

For study 108, patients with mutations were eligible based on *in vitro* evidence of responsiveness to TEZ/IVA defined as a 10% increase in chloride transport. The Fischer Rat thyroid cell lines, expressing potential mutations of residual function and possibly predicting a clinical response, were claimed by the applicant as a validated test environment. However, there is no clinical validation that this threshold of response is sufficient to predict clinical efficacy. The scatterplots provided were not conclusive to show a reliable relationship for the extend of *in vitro* and *in vivo* responsiveness.

For all individual mutations, the number of patients is low. This limits the interpretation of the results. For following mutations, sufficient clinical evidence is considered present: *2789+5G->A*, *3272-26A->G*, *3849+10kbC->T, A455E*, *D1152H*, *P67L*, and *S945L*.

Despite the very limited data, *711+3A→G, D579G , L206W, R1070W, R117C, R352Q,* and *S977F* a clinically relevant response was observed in a number of patients. Given the rarity of these mutations

[5] G Sawicki, MW Konstan, E McKone, RB Moss, B Lubarsky, E Suthoff, S Millar, DJ Pasta, N Mayer-Hamblett, CH Goss, W Morgan. Rate of lung function decline in patients with Cystic fibrosis (cf) having a residual function Gene mutation. Thorax 2017;72(Suppl 3):A1–278.

and the difficulty of obtaining what would ordinarily be deemed robust clinical data, the sparse but promising data are considered sufficient. However, no patient with the mutation *D110H* had a beneficial clinical response. Mutation R347H was already excluded from the indication based on an in vitro increase in chloride transport below the pre-defined threshold of 10%.

Overall, the characterisation of the study population with respect to some relevant factors is not as accurate as it would have been desirable. This applies to the status of chronic lung infection due to P. aeruginosa and the use of pancreatic enzymes.

For the primary analysis of the absolute change in ppFEV1, the multiple testing procedure for study 108 is not proven to protect type I error, but due to the strong statistical significance, many conceivable multiplicity procedures would produce similar results. Therefore, this is not considered critical and no further pursued. The results of a second interim analysis of study 110 showed trends in maintenance of effect, in ppFEV1, CFQ-R respiratory domain and BMI. The improvement in ppFEV1 of 3.20 percentage points compared to Kalydeco alone in patients with F/G551D mutations has been observed in a short period of only 28 days.

All populations

A withdrawal effect has been observed 1 to 4 weeks after treatment discontinuation of dosing. However, as preservation of lung function by a CTFR modifier will need much longer time than 1 month, this loss of effect is not considered indicative for long term effects.

3.4. Unfavourable effects

Treatment-emergent AEs were reported for nearly all patients in both arms of the Phase III placebo-controlled safety data set PC-SS (82.3% of patients in the TEZ/IVA arm vs. 86.9% in the placebo arm). TEAEs with an incidence of at least 5% in either treatment group, that were numerically higher in the TEZ/IVA group than in the placebo group, were headache (13.7% versus 11.3%), nasopharyngitis (11.5% versus 9.7%), and nausea (7.7% versus 6.7%). Related AEs occurred in 23.6% of patients treated with TEZ/IVA and in 22.2% treated with placebo.

Grade 3-4 AEs were reported for 7.1% (TEZ/IVA) vs. 8.5% (placebo) of patients. Infective PEx (3.6% vs. 3.8%) of CF and haemoptysis (0.8% vs. 1.0%) were the only Grade 3 or 4 AEs that had an incidence of at least 1% in either treatment group. SAES were reported for 10.1% (TEZ/IVA) vs. 14.9% (placebo). The SAEs that occurred in ≥1% of patients in either treatment group were infective PEx of CF (6.7% vs. 10.3%) and haemoptysis (1.0% vs. 1.2%). Related SAEs occurred in 1.0% (TEZ/IVA) vs. 1.4% (placebo). Related SAEs that occurred in 2 or more patients in either treatment group were haemoptysis (0.4% vs. 0%) and infective PEx of CF (0.2% vs. 0.6%).

The long-term safety data sets OLE-SS and LT-SS showed increased frequencies of (related AEs), Grade 3-4 AEs, SAEs and AEs leading to treatment discontinuation with TEZ/IVA compared to the pooled Phase III PC-SS. Of note: the placebo-TEZ/IVA arm in the OLE-SS showed a similar pattern and the mean exposure in the long-term safety data sets was increased 2-4 fold compared to the PC-SS.

Discontinuations due to AEs occurred in 1.6% (TEZ/IVA) vs. 2% (placebo). Of the events occurring in at least 2 patients, the AE leading to treatment discontinuation that had a higher incidence in the TEZ/IVA group (0.4%; 2 patients) than the placebo group (0 patients) was abdominal pain.

3.5. Uncertainties and limitations about unfavourable effects

The safety data package, while in principle adequate for the current approval, is still lacking in sufficient patient-years of exposure to inform about long latency or rare adverse effects. This information will become available during post-marketing pharmacovigilance. The restricted indication is considered adequate.

3.6. Effects Table

Table 45 Effects Table for Symkevi: data cut-off: 25 July 2017

Effect	Short Description	Unit	Treatment	Control 1	Control 2	Uncertainties / Strength of evidence	References
Favourable Effects							
CF patients with the F508/F508 genotype							
			TEZ/IVA		**Placebo**		
ppFEV1	Absolute change baseline –wk 24	%	3.4	N/A	-0.6	Clinically relevant	1*
CFQ-R	Absolute change baseline –wk 24	Points	5.0	N/A	-0.1	Clinically relevant	1
PEx	Estimated Event rate – baseline wk 24	Number /year	0.64	N/A	0.97	Relevant	1
BMI	Absolute change baseline –wk 24	Kg/m^2	0.18	N/A	0.12	Numerical difference with placebo	1
Sweat chloride	Absolute change baseline –wk 24	mmol/L	-9.9	N/A	0.2		1
CF patients with F508del/RF genotype							
			TEZ/IVA	**IVA**	**Placebo**		
ppFEV1	Absolute change baseline-wk 8	%	6.5	4.4	- 0.3	Relevant difference with placebo, but not in all mutations	
CFQ-R	Absolute change baseline-wk 8	Points	10.1	8.7	- 1.0	Relevant difference with placebo. Small difference with IVA	
PEx	Estimated Event rate baseline-wk 8	Number /year	0.34	0.29	0.63	Clinical relevant to placebo but not with IVA	2**
BMI	Absolute change baseline-wk 8	Kg/m^2	0.34	0.47	0.18	Numerical difference with placebo	2
Sweat chloride	Absolute change baseline-wk 8	mmol/L	-9.9	-4.9	-0.4		2

Effect	Short Description	Unit	Treatment	Control 1	Control 2	Uncertainties / Strength of evidence	References
Unfavourable Effects							
TEAEs	Proportion of patients in PC-SS *Headache* *Nasopharyngitis* *Nausea*	%	82.3 13.7 11.5 7.7	***	86.9 11.3 9.7 6.7	Pooled Phase III safety data for patients with different CFTR genotypes. See clinical AR for individual study results. No differences between adults and adolescents	
Related TEAEs		%	23.6		22.2		
Grade 3-4 TEAEs		%	7.1		8.5		
SAEs	*Overall* *Related*	%	10.1 1		14.9 1.4		
Discontinuations due to AE		%	1.6		2.0		

*1 refers to study 106, **2 refers to study 108.
*** not applicable, as data refer to pooled Phase III placebo-controlled safety data set, see clinical AR for individual study results including Study 108 with ivacaftor monotherapy safety results.
Abbreviations: TEAE: treatment emergent adverse event; PC-SS: Phase III-controlled safety set

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

FEV1 as a surrogate endpoint is a well-established endpoint and reduction of decline of FEV1 is related to improved survival. Pulmonary exacerbations and decline of lung function have an impact on survival in cystic fibrosis and reduce health-related quality of life. Preservation of lung function alongside reductions of the rate of pulmonary exacerbations are the main goals of treatment of cystic fibrosis. BMI as an important parameter for the nutritional status; this reflects the extra-pulmonary effects. The dose regimen for adolescents is established in both the clinical studies and the PoP PK model.

CF patients 12 years or older homozygous for the F508del-CFTR mutation

Importance of the favourable effects

The observed difference between TEZ/IVA and placebo in absolute change of ppFEV1 is above the predefined threshold of clinical relevance (2.5 %) in the context of the natural decline in CF patients (Report of the workshop on endpoints for cystic fibrosis clinical trials (EMA/769571/2012)) in the pivotal study 106 as well as in the extension study 110. The results in study 110 in the patients on previous placebo treatment in study 106 mirror the results of study 106, showing the consistency of the results. The maintenance of effect is shown by the results of the patients who received active

treatment for 48 weeks, still being above 3%. The rate reduction of 0.35 in pulmonary exacerbations is also relevant.

Strength of the evidence

The primary analysis provided evidence for the efficacy of TEZ/IVA in absolute change in ppFEV1 (p <0.0001, 95% CI 3.1, 4.8). The sensitivity analysis confirmed the robustness of the results. Furthermore, consistent improvements in ppFEV1 favouring TEZ/IVA were observed across all prespecified subgroups with the lowest point estimate still clinically relevant. The results of the primary parameter are supported by the majority of the secondary endpoints, rate reduction in PExs (P-value 0.0054, 95% CI 0.48, 0.88), BMI (p > 0.05), and CFQ-R respiratory domain. The data of the extension study 110 confirmed the results as similar results were demonstrated in the previously placebo treated patients; the patients who continued treatment with TEZ/IVA kept more or less the improvements already experienced during the parent study. It has been confirmed that ivacaftor alone is not efficacious in CF patients with F/F mutation (study 104).

Impact of the uncertainties

The proposed combination dose regimen is questioned given that tezacaftor as monotherapy has not been investigated in the phase 3 program. The in vitro discrepancies, study 101 data and the exposure-response analyses fail to substantiate a need for IVA in a TEZ/IVA combination to treat homozygous F508del patients. Based on the second interim analysis of the open label extension study, the data suggest the maintenance of the effect seen as observed in the parent study. However, an accurate and precise interpretation of the data would require a control group as the disease progresses over time. The conclusions are based on summary results, making an indisputable value judgement currently not possible.

CF patients 12 years or older heterozygous for the F508del-CFTR mutation, and a second allele with residual function

Importance of the favourable effects

The obtained difference of TEZ/IVA in absolute change in absolute change of ppFEV1 of 6.8 % is above the predefined threshold (3.0 %) and also above accepted clinical relevance in both the parent study 108 as in the extension study 110 establishing the benefit of TEZ/IVA over 24 weeks in total. The improvement in CFQ-R Respiratory Domain of 11.1 points is impressive and substantially above MCID of 4 points. The majority of the patients treated with TEZ/IVA achieved an improvement of 4 points. During the extension phase of 16 weeks, the improvement was maintained.

Strength of the evidence

The primary analysis provided evidence for the efficacy of TEZ/IVA in ppFEV1 (p <0.0001, 95% CI 5.7, 7.8). The sensitivity analysis confirmed the primary analysis. In addition, the improvements in ppFEV1 favouring TEZ/IVA were consistent across the pre-specified subgroups. The improvements of ppFEV1 in the extension study at Day 15 for patients on previous placebo treatment is similar as in the parent study. All these results confirm the robustness and consistency of the primary analysis.

The (key) secondary endpoints support the results found in the primary endpoint.

The data of the extension study 110 appears to confirm the results as similar results were demonstrated in the previously placebo treated patients; the patients who continued treatment with TEZ/IVA kept more or less the improvements already experienced during the parent study.

The results of Study 107 confirmed that TEZ/IVA is not efficacious in patients who have the F508del-/MF mutation, indicating that the aimed population is CF patients with F/RF mutation.

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

Impact of the uncertainties

In patients with F/RF mutations, the combination regimen for study 108 was informed by *in vitro* data alone. While the *in vitro* data suggest that TEZ on its own has substantial chloride transport enhancing activity that is separable from a corrector function, the Phase III study 108 data indicate a modest incremental clinical benefit for the TEZ/IVA combination versus IVA alone. This suggests that TEZ is making a relatively modest contribution to the clinical effect with the TEZ/IVA combination in the F/RF patients.

For the primary analysis, the multiple testing procedures hampered the protection of type I error, but due to the strong statistical significance, many conceivable multiplicity procedures would produce similar results. Therefore, this is not considered critical.

Data are only available up to 24 weeks. Especially the placebo controlled phase is short (8 weeks). However, the 16 weeks extension data provided supportive evidence of sustained effect as well as a pattern similar to the CF patients with F/F mutation. Also the previous placebo treated group switched to active treatment showed a similar effect as the initial TEZ/IVA group. The maintenance of effect in CF patients with F/F mutation is accepted as support for CF patients heterozygous for the F508del-CFTR mutation, and a second allele with residual function group. Although the data of the extension study 110 appears to confirm the results as similar results were demonstrated in the previously placebo treated patients, only 70% of the patients enrolled were analysed. Hence the data of a second interim analysis was submitted analysing 100% of the patients. Overall the results were in line with the results of the first interim analysis.
Although TEZ/IVA showed clinically relevant differences over placebo, the benefit over ivacaftor monotherapy is small and sometimes even not reaching clinical relevance. For ppFEV1 the treatment difference was 2.1 %, but this is still considered relevant in relation to an overall estimated annualized ppFEV1 rate of decline of –1.05 percentage point in F/RF patients. Although for pulmonary exacerbations the reduction of event rate was higher with monotherapy IVA, the events rates are not reliable because of the short time of 8 weeks measurements.
For the secondary endpoint CFQ-R the responder analysis showed a distinctive difference (65.2 versus 58.3), Altogether, there is a clinical benefit over ivacaftor in this population of patients with F/RF mutations. The rationale for the need for TEZ in a TEZ/IVA combination can be considered somewhat more persuasive for patients with missense mutations.

Although, the overall the study met its primary endpoint, for the separate mutations, the number of patients is low. This limits the interpretation of the results per mutation.

No significant new or additional safety concerns were identified with the addition of TEZ to IVA. The safety profile of TEZ/IVA appeared similar across studies. There were no latent, late onset safety issues or risks identified in the long term safety sets. TEZ/IVA was well tolerated with low discontinuation rates due to AEs. Long term safety will be evaluated in the post-marketing setting.

3.7.2. Balance of benefits and risks

CF patients 12 years or older homozygous for the F508del-CFTR mutation

The primary analysis in the placebo controlled study 106 provided evidence for the efficacy of TEZ/IVA and demonstrated that TEZ/IVA provides clinical benefit to CF patients with F/F mutation. The results in this study are sufficiently robust and the statistical approach is considered sound. The data from study 110 are confirmative of the maintenance of the effect in 70% of the available patients. The results of the second interim analysis in 100 % of the population are in line with the first interim analysis. In study 101, the data including exposure-response analyses do not provide reassurance of a need for IVA in a TEZ/IVA combination, to treat homozygous F508del patients. Although there is overall consistency of response to TEZ/IVA in FEV1 between Phase II and Phase III studies, TEZ/IVA was not compared with TEZ alone in Phase III, which leaves questions over superiority of the combination, particularly given the apparently greater reduction in sweat chloride with TEZ monotherapy, compared with TEZ/IVA, at higher doses, in study 101. The non-robustness of the Phase II study (101) data, due to the small patient numbers in each treatment group, cannot be used to allay concern in this regard. The absence of TEZ monotherapy evaluation at Phase III, to address the need for IVA in a TEZ/IVA combination question, remains of concern.

In addition to the lack of clarity in the clinical data, the scientific literature points to the interdependence of chloride channel gating and CFTR protein localization on protein folding, which makes the distinction between corrector and potentiator action somewhat unclear. From *in vitro* results, the mechanistic argumentation has been strengthened but is not sufficiently convincing because of discrepancy between the patch clamp data and the Using chamber chloride conductance data and between patch clamp data and the in vivo data in study 101. However, this ongoing uncertainty is set against i) the level of unmet need in F508del homozygous patients who cannot tolerate LUM/IVA or where LUM/IVA is inadvisable; and ii) demonstration of superiority for TEZ/IVA over placebo in homozygous F508del patients resulting in relevant improvements in this population. Nevertheless, this should not be interpreted as an endorsement of lack of need for future clinical investigation into this important and as yet unresolved issue for these patients.

Data from other studies confirmed that monotherapy with ivacaftor alone is not efficacious in CF patients homozygous for the F508del-CFTR mutation. The overall safety profile of Symkevi in CF patients 12 years or older homozygous for the F508del-CFTR mutation is considered acceptable.

CF patients 12 years or older heterozygous for the F508del-CFTR mutation, and a second allele with residual function

The primary analysis for ppFEV1 in the placebo and active controlled study provided evidence for the efficacy of TEZ/IVA in ppFEV1 as well as for other clinical endpoints compared to placebo. The primary analysis is sufficiently robust. The statistical approach is overall sound.

In addition, the benefit can only be considered established for the mutations that are supported by clinical data. All mutations initially proposed to be included in the indication based on *in vitro* responsiveness to TEZ/IVA could not be sufficiently justified by the applicant. A relationship between the extent of *in vitro* responsiveness in FRT cells and clinical response could not be established either. Further investigations for validation of this model with FRT cell, or other in vitro systems, as well as the in vitro-in vivo relation would be needed in case of inclusion of mutation based on *in vitro* data only.

As the pivotal study faces the concern of the short duration and also only limited data of the extension study are available, the overall data are covering only 24 weeks. The data of the important parameters are confirmative of maintenance of the effect based on the summary results. In addition, the data overall mirror the pattern observed in the CF patients with F/F mutation. Therefore, the maintenance of effect is considered established. Because TEZ/IVA is a new therapy with an indication that includes genotypes eligible or ivacaftor treatment, the comparison to ivacaftor is of importance. The clinical relevance of the differences over ivacaftor was small, but relevant. Overall the safety profile in CF patients 12 years or older heterozygous for the F508del-CFTR mutation, and a second allele with residual function is considered acceptable.

3.7.3. Additional considerations on the benefit-risk balance

CF patients 12 years or older homozygous for the F508del-CFTR mutation

For these patients, a combination of a corrector and a potentiator has been established in principle by the combination of lumacaftor and ivacaftor (Orkambi). For Orkambi in its registration trials, the results of ppFEV1 were an increase in ppFEV1 from baseline of 2.16 % and 2.85% at 24 weeks (see EPAR Orkambi). Thus, there is a difference compared to TEZ/IVA (3.4 % from baseline) presented by cross trial comparison.

The long term data are quite similar i.e. 3.25% for Orkambi compared to 3.1% for TEZ/IVA at 48 weeks.

TEZ/IVA offers a CFTR modulator alternative for patients who cannot tolerate Orkambi because of adverse events or who could not take Orkambi because of DDIs.

3.8. Conclusions

The overall B/R of Symkevi is positive in the following indication:

Symkevi is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who are heterozygous for the F508del mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Symkevi is not similar to Bronchitol, Cayston, Tobi Podhaler and Kalydeco within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Symkevi is favourable in the following indication:

Symkevi is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who are heterozygous for the F508del mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272 26A→G, and 3849+10kbC→T.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

1. At the request of the European Medicines Agency;
2. Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that tezacaftor is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union. Ivafactor is considered to be a known active substance.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0193/2017 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.