Assessment report

Kalydeco

International non-proprietary name: ivacaftor

Procedure No. EMEA/H/C/002494/II/0063/G

Note

Variation 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
BQL	below the quantifiable limit
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	CF transmembrane conductance regulator protein
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
Cl	chloride ion
CPK	creatine phosphokinase
Ctrough	concentration at the end of the dosage interval
CYP	cytochrome P450
CYP3A	cytochrome P450 3A
DBP	diastolic blood pressure
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form
ERS	European Respiratory Society
EU	European Union
F508del	CFTR protein lacking the phenylalanine normally found at position 508 of the wildtype protein
F*508del*	*CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type gene
F/F	*F508del/F508del* mutation
F/G551D	*F508del/G551D* mutation
F/MF	*F508del/*minimal function mutation
F/NR tezacaftor/ivacaftor	*F508del* and another allele not likely to responsive to
F/RF	*F508del*/residual function mutation
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
FE-1	fecal elastase-1
FEF25-75%	forced midexpiratory flow rate
FEV1	forced expiratory volume in 1 second

FRT	Fischer rat thyroid
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GPS	Global Patient Safety
ICH	International Council for Harmonization
IPD	important protocol deviations
IRB	institutional review board
IRT	immunoreactive trypsinogen
IV	intravenous
IVA	ivacaftor
LC-MS/MS	liquid chromatography–mass spectrometry/mass spectrometry
LFT	liver function test
LLN	lower limit of normal
LLOQ	lower limit of quantification
LUM	lumacaftor
LUM/IVA	lumacaftor/ivacaftor
LS	least squares
M1-IVA	M1-ivacaftor
M1-TEZ	M1-tezacaftor
Max	maximum value
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum value
MCID	minimum clinically important difference
MF	minimal function
MMRM	mixed-effects model for repeated measures
N	total sample size
n	size of subsample
NA	not applicable
OLE	open-label extension
NBQL	Number below the quantifiable limit
NPD	nasal potential difference
P	probability
PBO	placebo
PD	pharmacodynamics
PE/PEx	pulmonary exacerbation
PK	pharmacokinetics
PN	preferred name
ppFEV1	percent predicted forced expiratory volume in 1 second

PT	Preferred Term
q12h	every 12 hours
qd	daily
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's formula
RF	residual function
SAE	serious adverse event
SD	standard deviation
SE	standard error
SOC	standard of care
SOP	standard operating procedures
TE	treatment-emergent
TEAE	treatment-emergent adverse event
TEZ	tezacaftor
TEZ/IVA	tezacaftor 100 mg qd/ivacaftor 150 mg q12h
ULN	upper limit of normal
UN	unstructured
US	United States
VX-661	tezacaftor
VX-770	ivacaftor
WHO-DDE	World Health Organization Drug Dictionary Enhanced

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Vertex Pharmaceuticals (Europe) Ltd. submitted to the European Medicines Agency on 30 August 2017 an application for a group of variations.

The following variations were requested in the group:

Variations requested		Type	Annexes affected
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB
B.II.e.5.a.2	Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	Type IB	A, I, IIIA and IIIB
B.II.e.5.a.2	Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	Type IB	A, I, IIIA and IIIB

1) C.I.6.a (type II) - Extension of Indication to include the combination regimen of the ivacaftor 150 mg evening dose and tezacaftor/ivacaftor;
2) B.IIe.5.a.2 (type IB) - to add a blister card pack presentation containing 28-tablets for the 150 mg film-coated tablets (EU/1/12/782/005);
3) B.IIe.5.a.2 (type IB) - to add a blister pack presentation containing 28-tablets for the 150 mg film-coated tablets (EU/1/12/782/006).
As a consequence, section 4.1, 4.2, 4.4, 4.5, 4.8, 6.5 and 8 of the SmPC are updated. Annex A, the Package Leaflet and Labelling are updated in accordance.
An updated RMP (version 7.10) is included.

The requested group of variations proposed amendments to the Annex A, Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Kalydeco, was designated as an orphan medicinal product EU/3/08/556 on 8 August 2018. Kalydeco was designated as an orphan medicinal product in the following indication: treatment of cystic fibrosis.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0147/2017 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0147/2017 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Protocol assistance

The MAH did not seek Protocol Assistance at the CHMP. Scientific advice was given on development of Symkevi.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Concepcion Prieto Yerro

Timetable	Actual dates
Submission date	30 August 2017
Start of procedure:	16 September 2017
CHMP Rapporteur Assessment Report	30 November 2017
PRAC Rapporteur Assessment Report	21 November 2017
PRAC members comments	22 November 2017
Updated PRAC Rapporteur Assessment Report	24 November 2017
PRAC Outcome	30 November 2017
CHMP members comments	4 December 2017
CHMP updated Rapporteur Assessment Report	11 December 2017
1st Request for supplementary information (RSI)	14 December 2017
MAH responses	18 January 2018
Restart of procedure:	22 January 2018
CHMP Rapporteur Assessment Report	6 March 2018
CHMP members comments	12 March 2018
Updated CHMP Rapporteur Assessment Report	19 March 2018
2nd Request for supplementary information (RSI)	22 March 2018
MAH responses	29 April 2018
Restart of procedure:	2 May 2018
PRAC Rapporteur Assessment Report	7 May 2018
PRAC members comments	10 May 2018
CHMP Rapporteur Assessment Report	22 May 2018

Timetable	Actual dates
PRAC Outcome	18 May 2018
CHMP members comments	22 May 2018
Updated CHMP Rapporteur Assessment Report	28 May 2018
3rd Request for supplementary information (RSI)	31 May 2018
MAH responses	5 June 2018
Restart of procedure:	6 June 2018
PRAC Rapporteur Assessment Report	18 June 2018
CHMP Rapporteur Assessment Report	18 June 2018
CHMP members comments	18 June 2018
PRAC members comments	18 June 2018
PRAC Outcome	14 June 2018
Updated PRAC Rapporteur Assessment Report	n/a
Updated CHMP Rapporteur Assessment Report	25 June 2018
4th Request for supplementary information (RSI)	28 June 2018
MAH responses	3 July 2018
Restart of procedure:	4 July 2018
PRAC Rapporteur Assessment Report	11 July 2018
CHMP Rapporteur Assessment Report	16 July 2018
CHMP members comments	19 July 2018
PRAC members comments	16 July 2018
PRAC Outcome	12 July 2018
Updated PRAC Rapporteur Assessment Report	19 July 2018
Updated CHMP Rapporteur Assessment Report	23 July 2018
Opinion	26 July 2018
The CHMP adopted a report on similarity of Kalydeco with Bronchitol, TOBI Podhaler and Cayston (Appendix 1)	26 July 2018

2. Scientific discussion

2.1. Introduction

Cystic fibrosis (CF) is an autosomal recessive disease caused by mutations in the *CFTR* gene that result in absent or deficient function of the CFTR protein at the cell surface. CFTR 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 tissues results in a multisystem pathology. In the lungs, obstruction of airways with thick mucus, establishment of a chronic bacterial infection in the airways, and damaging inflammatory responses are all thought to play a role in causing irreversible structural changes in the lungs and respiratory failure. Progressive loss of lung function is the leading cause of mortality.

Over 2000 CFTR variants have been discovered but only around 200 have been characterised in terms of disease liability due to the extreme rarity of most of them.

Until very recently available CF treatments target the downstream consequences of diminished CFTR function, particularly those related to the lung and/or the pancreatic manifestations of the disease. However, the understanding of the different molecular mechanisms of CFTR dysfunction provided the scientific basis for the development of targeted drugs for mutation-specific therapy of CF. Modulators of CFTR are aimed at rescuing the expression and/or function of mutated CFTR.

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, as acknowledged in the scientific literature, 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. Furthermore, compounds with both potentiator and corrector activity have been identified. Kalydeco (ivacaftor, IVA) and Orkambi (lumacaftor/ivacaftor, LUM/IVA) are the CFTR modulators approved for CF patients with specific mutations. Clinical efficacy of ivacaftor monotherapy has been established in some Class III mutations that cause defects in channel gating as well as in the Class IV mutation *R117H* which also has a defect in channel gating. 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 drug-drug interactions. It is therefore suggested that patients homozygous for *F508del* could benefit from new treatment options with improved efficacy/safety profile than that of LUM/IVA. For patients with the residual function mutations, no CFTR modulators are currently approved in the EU so far.

The proposed therapeutic indication for Kalydeco 150 mg film-coated tablets was:

Kalydeco tablets are also indicated in a combination regimen with Symkevi for the treatment of patients with cystic fibrosis (CF) aged 12 years and older. For indicated CFTR mutations, refer to the

Summary of Product Characteristics of Symkevi.

The claimed indication for Symkevi 100 mg/150 mg film-coated tablets (EMEA/H/C/004682/0000) 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).

More explicitly, the TEZ/IVA combination therapy was proposed to be dosed orally each day in 2 tablets as follows:

- Morning dose: 1 fixed-dose combination 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.

The list of proposed mutations for approval was suggested to be cross referenced from the indication statement to Section 5.1 of the SmPC of Symkevi.

2.2. Quality aspects

The MAH has applied for two additional pack sizes for the finished product:

- Blister pack containing 28 film-coated tablets for the 150 mg film-coated tablets (EU/1/12/782/005)
- Blister card pack containing 28 film-coated tablets for the 150 mg film-coated tablets (EU/1/12/782/006)

During the procedure the MAH has decided that the blister pack presentation containing 28-tablets for the 150 mg film-coated tablets is no longer pursued.

Documentation to be supplied:

1. *Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate) including revised product information as appropriate.*

Sections 3.2.P.7 Container Closure System–Tablet, 6.5 of the SmPC, Annex A, Package Leaflet and Labelling have been updated in accordance.

2. *Justification for the new/remaining pack-size, showing that the new/remaining size is/are consistent with the dosage regimen and duration of treatment as approved in the summary of product characteristics*

The new pack size proposed for Kalydeco (ivacaftor 150 mg) film-coated tablets is a 28-tablet pack in an Aclar/PVC/Alu blister. The existing approved pack size is a 56-tablet pack.

The currently approved posology for Kalydeco monotherapy is one tablet taken orally every 12 hours; a one-day supply is therefore two tablets. The presently-approved pack size of 56 tablets is sufficient for 28 days, or four weeks of treatment.

Vertex has submitted a Marketing Authorisation Application for Symkevi (tezacaftor 100 mg/ivacaftor 150 mg) fixed dose combination (product ref: H0004682) to the EMA on the 25 July 2017. Symkevi will be used in a combination regimen with Kalydeco (ivacaftor 150 mg) film-coated tablets. The

proposed posology for the Symkevi/Kalydeco combination regimen is one Symkevi tablet in the morning and one Kalydeco tablet in the evening. A four week supply of Kalydeco tablets for the proposed Symkevi/Kalydeco combination regimen is therefore 28 tablets.

The purpose of this Type IB B.IIe.5.a)2 variation is to register the additional Kalydeco 28-tablet pack required to provide patients receiving the Symkevi/Kalydeco combination regimen with the correct number of Kalydeco tablets for a four week treatment period.

3. *Declaration that stability studies will be conducted in accordance with the relevant guidelines for products where stability parameters could be affected. Data to be reported only if outside specifications (with proposed action).*

In accordance with Commission Regulation (EC) No 71212012, B.JI.e.5 a) 1 required documentation, the Marketing Authorisation Holder declares that the stability parameters for Kalydeco (ivacaftor) are not affected by the new pack size and are the same as the previously approved.

2.3. Non-clinical aspects

This is an application for the combined use of ivacaftor (as an evening dose) with Symkevi. Since Kalydeco is already authorised and its nonclinical profile is known, the main part of the information in this section refers to results from newly performed tests on tezacator.

2.3.1. Pharmacology

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 CFTR potentiator, e.g. the already authorised ivacaftor, is a small molecule that potentiates the channel open probability (channel gating activity) of both normal and some mutant forms of CFTR at the cell surface to enhance chloride transport. Because the channel gating activity of both normal and some mutant forms of CFTR delivered to the cell surface by CFTR correctors can be potentiated by CFTR potentiators, CFTR correctors and potentiators provide complementary therapeutic approaches to enhance chloride transport in people with CF. Tezacaftor (TEZ) is a new CFTR corrector being developed in combination with IVA (TEZ/IVA) for the treatment of CF.

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:

- 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.

- FRT cells without background CFTR were 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 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). 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 Ivacaftor on processing and trafficking and chloride transport of normal CFTR, F508del-CFTR, a number of Residual Function mutants and a set of Kalydeco responsive gating mutants. The combined incubation of both drug substances *in vitro*, leads to an even higher increase in chloride transport. As stated by the MAH, *in vitro* studies showed that the combination of Tezacaftor/Ivacaftor is more efficacious than the two drugs separately in increase of chloride transport for 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. The F508del-CFTR appeared not responsive in the FRT system as it did not exceed the criterion of ≥10 pp increase in chloride transport. The *in vitro* efficacy of the combination for the splice mutants 711+3A->G, 2789+5G->A, 3272-26A->G, or 3849+10kbC->T and E381X was not investigated.

Secondary pharmacodynamic studies

Tezacaftor showed only significant binding affinity to the sodium channel Site 2 target receptor at concentrations below 10 µM (K_i = 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 TEV C_{max} 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 was evaluated in a similar panel of *in vitro* receptor, channel and enzyme radioligand assays. Sub-micromolar potency was identified for two targets: the monoamine transporter and the serotonin receptor (5-HT2C). 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, a IVA 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.

Safety pharmacology programme

Tezacaftor: As recommended in the ICH S7A and ICH S7B Guidelines, a comprehensive program of safety pharmacology studies was conducted to assess TEZ effects on vital organ systems and potential for adverse PD effects: an *in vitro* study to investigate potential interactions with the human cardiac IKr human ether-a-go-go related gene (hERG) channel and in vivo studies evaluating the effects on several vital organ systems including the CNS and respiratory, CV and GI systems. These studies were considered pivotal to the human safety assessment and were conducted in compliance with GLP regulations.

Tezacaftor inhibited hERG potassium current by (Mean ± SEM) 16.6 ± 3.7% (significantly) at 10 µM (n = 4) and the IC_{50} was estimated to be greater than 10 µM. M2-Tezacaftor inhibited hERG current by 2.4 ± 0.8% at 10 µM (n = 3) and the IC_{50} was estimated to be greater than 300 µM. Tezacaftor and M2-Tezacaftor are not considered potent hERG inhibitors. As the clinical free fraction of tezacaftor is 0.11 µM, the hERG channel inhibition by tezacaftor is not regarded clinical relevant. Tezacaftor had no effect on CNS or respiratory function in Sprague Dawley rats dosed 0, 20, 60 or 200 mg/kg. Cardiovascular examination was done in conscious telemetered beagle dogs' dose after single doses of tezacaftor (0, 25, 75 and 250 mg/kg). Increased ABP (17 to 25%) and decreased QT and QTc intervals (2 to 8%) generally between 6 to 14 hours after oral administration the high dose were only observed in 2 of 4 dogs, but were consistent between the 2 animals. The exposure level (AUC_{0-24h}) in dogs after single dose of 75 mg/kg is ~3 fold the AUC in CF patients when given 100 mg of TEZ. Since in human, QTc effects were not noted, this observation is not likely to be clinically 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. No safety margin has been established for this effect but it was not observed in the clinical study.

Ivacaftor: A comprehensive program of safety pharmacology studies in line with the ICH guidances mentioned above was previously conducted for IVA in support of the registration of Kalydeco. The effects of IVA on a number of voltage gated and non-voltage gated ion channels were limited to moderate inhibition of Cav1.2 and Kv1.5 channels, in addition to a concentration-dependent inhibition of hERG channel tail current. However, these ion channel effects were not considered clinically relevant given that IVA is highly protein bound across all species and the free fraction at therapeutic exposures in the combination regimen are relatively low (approximately 4 nM). Most conclusions from these *in vitro* studies were confirmed *in vivo*, where with exception of a noted dose-related decrease in GI motility and stomach emptying, IVA did not produce any adverse PD effects on the CNS, respiratory system, or CV system *in vivo*.

Effects on the GI system were observed only at doses ≥500 mg/kg in rats, with no evidence of GI motility dysfunction noted in the chronic repeat-dose toxicity studies evaluating IVA at doses as high as 150 mg/kg/day in rats and 60 mg/kg/day in dogs. Together these data suggest that GI motility dysfunction is not likely to occur at therapeutic dose levels in humans.

Tezacaftor/Ivacaftor: Combination safety pharmacology studies involving the co-administration of TEZ and IVA were not performed because the studies conducted on each individual entity were considered adequate and provided no evidence for potential for additive or synergistic interaction in any of the endpoints evaluated. This is acceptable to the CHMP; potential adverse effects of the combination on CNS, cardiovascular, respiratory and GI systems can also be assessed in the combination repeat dose toxicity studies.

Pharmacologic Profiles of Metabolites

Tezacaftor Metabolites: TEZ has 3 major metabolites in humans: M1-TEZ (VRT-0996107), M2-TEZ (VRT-1189001), and M5-TEZ (VRT-1074233). The pharmacologic activity of these metabolites was evaluated in vitro using F/F-HBE. In plasma, TEZ 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. Of these, M1-tezacaftor and M2-tezacaftor appears pharmacologically active. The potency of M1-TEZ and TEZ in the presence of continuous IVA 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 tezacaftor. M2-TEZ had lower potency than TEZ (about 5-fold less than TEZ: EC_{50} of 1.5 μM for M2-TEZ and 0.3 μM for TEZ) and lower maximum efficacy than TEZ (37 ± 4% the maximum efficacy of TEZ).

Ivacaftor Metabolites (M1-IVA and M6-IVA): 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-ivacaftor and 0.2 μM for ivacaftor.

2.3.2. Pharmacokinetics

The absorption, distribution, metabolism, and elimination properties of tezacaftor (TEZ) and ivacaftor (IVA) have been investigated in CD-1 and Tg.rasH2 mice, Sprague-Dawley rats, New Zealand White rabbits, Beagle dogs and Cynomolgus monkeys as single entities, and in combination in rats and dogs. Most studies were carried out using the oral route of administration, the intended therapeutic route in humans. In order to provide sufficient solubility and exposure for nonclinical studies, a 500 mg/g TEZ spray-dried dispersion (SDD) using HPMCAS as physical stabilizer was developed and dosed in all GLP studies.

Methods of analysis: Validation reports for the analytical methods used were provided, demonstrating the suitability, 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: The permeability of TEZ and its metabolites were evaluated in the Caco-2 cells and in the MDCK-MDR1 cell bidirectional assay. The *in vitro* studies demonstrated that TEZ and M1-TEZ have high passive permeability, whereas M2-TEZ and M5-TEZ have low passive permeability. TEZ and M1-TEZ

are Pgp substrate, and M2-TEZ may be a Pgp substrate. Summaries of plasma PK parameters for TEZ and IVA, administered alone or in combination in laboratory animals following single and repeated administration are presented in Tables below. When co-administered in combination studies in rats and dogs, systemic exposures to TEZ and IVA were similar to exposures achieved when these compounds were administered individually. The exposure of TEZ and IVA 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. No significant sex differences (<2-fold) in exposure were observed for either TEZ or IVA. Upon repeat dose oral administration, accumulation was not consistently observed for TEZ; whereas, accumulation was evident for IVA. In mice, TEZ exposure was reduced upon repeat dose oral administration, likely due to cytochrome P450 induction. The presence of food improved the absorption of TEZ. The oral bioavailability of TEZ increased ~ 4.0 to 6.2 folds in the presence of food compared to fasted animals with capsules, and the increase was less, ~1.4 to 1.8 folds for tablets.

Table 1 TEZ Plasma PK Parameters after Oral Administration in GLP Toxicity Studies

Species	Sampling Period	Sex/N	Dose Level[a] (mg/kg)	C_{max} (µg/mL)	AUC_{0-24h} (µg·h/mL)
Mouse (28-Day study)	Day 1	M/44	250	17.6	261
			500	35.8	280
			750	44.8	334
		F/44	250	18.1	226
			500	29.9	239
			750	52.3	285
	Day 28	M/44	250	12.2	92.9
			500	17.9	86.1
			750	16.2	117
		F/44	250	10.1	96.2
			500	17.2	115
			750	21.3	160
Rat (pregnant)	Day 1 (GD 6)	F/8	25	5.80	79.3
			50	13.1	183
			100	19.1	315
	Day 11 (GD 17)	F/8	25	7.57	80.4
			50	11.1	165
			100	19.4	276
Rat (6-month study)	Day 1	M/11	25	5.82	60.1
			50	11.6	148
			100	27.2	370
		F/11	25	6.98	84.3
			50	13.6	189
			100	29.3	420
	Day 180	M/11	25	7.04	86.7
			50	13.5	174
			100	17.4	226
		F/11	25	10.1	113
			50	19.3	236
			100	20.0	337
Rabbit (pregnant)	Day 1 (GD 7)	F/4	10	0.66	3.87
			25	1.72	9.86
			50	4.00	25.6
	Day 14 (GD 20)	F/4	10	0.71	4.52
			25	2.42	17.4
			50	6.63	107

Species	Sampling Period	Sex/N	Dose Level [a] (mg/kg)	C_{max} (µg/mL)	AUC_{0-24h} (µg·h/mL)
Dog (12-month study)	Day 1	M/8	2	0.99	5.73
			10	6.21	38.1
			100	69.2	725
			200	91.9	1130
		F/8	2	0.87	4.24
			10	6.34	38.7
			100	62.6	669
			200	94.1	1130
	Day 364	M/8	2	1.12	9.34
			10	7.83	59.8
			100	78.6	852
			200	107	1450
		F/8	2	1.24	8.84
			10	7.72	58.2
			100	83.6	983
			200	143	2080

Sources: Reports VX-661-TX-017, VX-661-TX-008, VX-661-TX-012, VX-661-TX-009 and VX-661-TX-013

F: female; GD, gestation day; M: male; N: number; PK: pharmacokinetic

[a] Once daily dosing for repeated administration.

Table 2 IVA Plasma PK Parameters after Oral Administration in GLP Toxicity Studies

Species	Sampling Period	Sex/N	Dose Level [a] (mg/kg)	C_{max} (µg/mL)	AUC_{0-24h} (µg·h/mL)
Mouse (3-month study)	Day 1	M/36	100	7.48	53.0
			300	11.6	135
			600	9.55	159
			1000	15.1	270
		F/36	100	7.63	57.4
			300	14.9	216
			600	14.0	225
			1000	17.3	337
	Day 90	M/36	100	6.67	61.8
			300	12.8	159
			600	14.5	208
			1000	21.1	301
		F/36	100	12.4	81.9
			300	14.4	198
			600	27.9	188
			1000	21.9	299
Rat (pregnant)	Day 1 (GD 7)	F/6	50	3.88	64.1
			100	7.25	133
			200	12.1	203
	Day 11 (GD 17)	F/6	50	11.5	205
			100	15.4	332
			200	24.6	NA
Rat (6-month study)	Day 1	M/9	50	5.69	110
			100	12.5	212
			150	16.6	306
		F/9	50	5.71	123
			100	21.8	331
			150	18.1	343
	Day 181	M/9	50	21.9	445
			100	19.0	339
			150	27.5	476
		F/9	50	29.3	561
			100	35.1	666
			150	41.0	734
Rabbit (pregnant)	Day 1 (GD 7)	F/3	25	1.62	24.2
			50	2.88	47.2
			100	7.81	129
	Day 13 (GD 19)	F/3	25	2.29	41.9
			50	6.69	114
			100	16.8	338

Species	Sampling Period	Sex/N	Dose Level [a] (mg/kg)	C_{max} (µg/mL)	AUC_{0-24h} (µg·h/mL)
Dog (12-month study)	Day 1	M/8[b]	15	3.60	65.5
			30	5.69	98.5
			60	9.27	159
		F/8[b]	15	2.08	32.5
			30	4.67	72.4
			60	6.06	101
	Day 365	M/8[b]	15	11.6	230
			30	16.4	320
			60	18.7	351
		F/8[b]	15	10.6	213
			30	10.8	184
			60	14.2	254

Sources: Reports VX-770-TX-012, VX-770-TX-006, VX-770-TX-010, VX-770-TX-007, and VX-770-TX-011
F: female; GD: gestation day; M: male; N: number; NA: not available due to moribund condition of animals at 24 hours (samples not collected); PK: pharmacokinetic
[a] Once daily dosing for repeated administration.
[b] N=12 in the 60 mg/kg dose group.

Table 3 Plasma pharmacokinetic parameters for TEZ, M1-TEZ, IVA, M1-IVA and M6-IVA in a 28-day repeat dose toxicity study in dogs

Analyte	Dose (TEZ/IVA) (mg/kg)	Study Day	Male AUC$_{0-24h}$ (µg·h/mL)	Cmax (µg/mL)	tmax (h)	Female AUC$_{0-24h}$ (µg·h/mL)	Cmax (µg/mL)	tmax (h)
TEZ	25/2.5	1	89.3	12.8	1.75	91.0	10.9	3.75
		28	152	17.8	1.63	137	16.0	2.13
	25/5	1	52.1	8.70	1.63	67.0	11.4	2.00
		28	126	17.1	2.25	119	14.8	1.63
	50/5	1	137	13.7	2.75	297	31.3	3.00
		28	301	33.7	2.50	371	39.8	3.00
	100/60	1	357	33.7	4.08	482	42.4	6.00
		28	460	48.1	2.50	412	44.4	2.75
M1-TEZ	25/2.5	1	7.44	1.15	1.25	10.3	1.27	3.75
		28	12.1	1.42	0.875	14.8	1.49	1.63
	25/5	1	5.28	0.889	1.50	6.59	1.17	2.00
		28	8.65	1.03	1.75	9.49	0.959	1.38
	50/5	1	11.3	1.29	7.75	28.0	2.66	3.00
		28	17.0	1.63	2.25	26.5	2.55	2.75
	100/60	1	22.4	2.21	2.58	28.1	2.83	4.67
		28	15.7	1.56	3.17	14.6	1.54	2.50
IVA	25/2.5	1	15.2	0.994	5.50	13.8	0.902	5.50
		28	37.4	2.32	4.50	18.9	1.18	4.13
	25/5	1	22.6	1.71	3.50	26.5	1.99	5.00
		28	54.2	3.32	5.00	36.5	2.33	2.63
	50/5	1	14.0	1.03	9.50	25.6	1.64	5.00
		28	49.4	2.73	6.00	52.0	3.40	4.00
	100/60	1	184	11.2	8.67	226	13.4	10.7
		28	572	30.2	7.33	249	15.7	4.67
M1-IVA	25/2.5	1	1.33	0.177	3.25	1.51	0.213	3.00
		28	3.27	0.348	2.00	1.88	0.232	1.50
	25/5	1	3.02	0.363	2.63	2.37	0.345	2.25
		28	5.61	0.507	1.75	2.47	0.275	1.00
	50/5	1	1.14	0.129	8.00	2.06	0.176	5.00
		28	3.40	0.284	3.75	4.05	0.405	2.50
	100/60	1	14.5	1.02	6.33	11.5	0.798	8.67
		28	51.5	2.77	6.08	10.4	0.775	2.33
M6-IVA	25/2.5	1	0.301	0.0218	5.00	0.402	0.0320	5.00
		28	0.959	0.0644	4.50	0.715	0.0580	4.50
	25/5	1	0.541	0.0434	4.50	0.604	0.0474	4.50
		28	0.898	0.0589	3.50	0.674	0.0478	2.50
	50/5	1	0.310	0.0299	9.00	0.419	0.0327	10.0
		28	0.705	0.0450	10.0	1.18	0.0752	3.50
	100/60	1	2.38	0.160	16.0	2.24	0.139	14.0
		28	8.37	0.455	2.75	2.45	0.149	4.42

Distribution: Protein binding of TEZ and IVA is high (>98%) in mouse, rat, dog, monkey, and human plasma. M1-TEZ, M2-TEZ, M5-TEZ, M1-IVA, M6-IVA are also highly bound to plasma proteins and similarly across species (>97.5%), except that M2- TEZ is less protein-bound in mouse plasma (93.6%). Human serum albumin is the major human plasma protein for TEZ, M1-TEZ, M2-TEZ, M5-TEZ, M1-IVA and M6-IVA binding. Besides human serum albumin, IVA is also highly bound to other human plasma proteins (AAG, HGG). TEZ and IVA do not preferentially partition into red-blood cells.

When orally administered to rats, both TEZ and IVA were rapidly distributed across most tissues. GI tract, liver, adrenal glands, kidney, pancreas, heart and lungs showed the highest mean maximum concentrations of radioactivity. The lowest exposures were observed in the brain, eyes, and testes. Neither TEZ nor IVA bind to melanin-containing tissues (skin and/or eyes). Placental transfer of both

[14]C-TEZ and ^{14}C-IVA was observed in pregnant rats, and both were shown to be excreted in the milk of lactating rats.

In a tissue distribution study conducted with non-radiolabelled TEZ at 30 mg/kg, both TEZ and M1-TEZ distribution was determined in brain, lung, liver, kidney, pancreas, testes, fat, skin and spleen. The tissue to plasma AUC ratio for TEZ was highest in liver (~7.0) and lowest in brain (0.08). The lung to plasma AUC ratio was approximately 2.5, and the skin to plasma AUC ratio was approximately 0.3 for TEZ. For M1-TEZ, the tissue to plasma AUC ratio was highest in the liver (~8.7), and was ~5.3 for the lung, ~0.08 for the brain and ~0.2 in the skin.

Metabolism: Both phase I and phase II pathways were involved in the metabolism of TEZ, including oxidation, glucuronidation, phosphorylation and various combinations thereof. Following administration of ^{14}C-TEZ to rats, most of the circulating radioactivity was associated with unchanged TEZ, M1-TEZ (dehydrogenation metabolite) and M5-TEZ (phosphate conjugate of M1-TEZ). M1-TEZ is a pharmacologically active major human metabolite of TEZ. M2-TEZ, a major disproportionate human metabolite of TEZ that is significantly less active than TEZ, was the major excreted metabolite in rats. M5-TEZ is a major circulating metabolite of TEZ in humans and in rats. M5-TEZ is a phase II metabolite (phosphate conjugate of M1-TEZ) that was poorly permeable to cell membranes and pharmacologically inactive. TEZ in vitro metabolic profiles were qualitatively similar in all species studied, with major metabolites identified from the in vivo studies in rats and humans summarized in figure below.
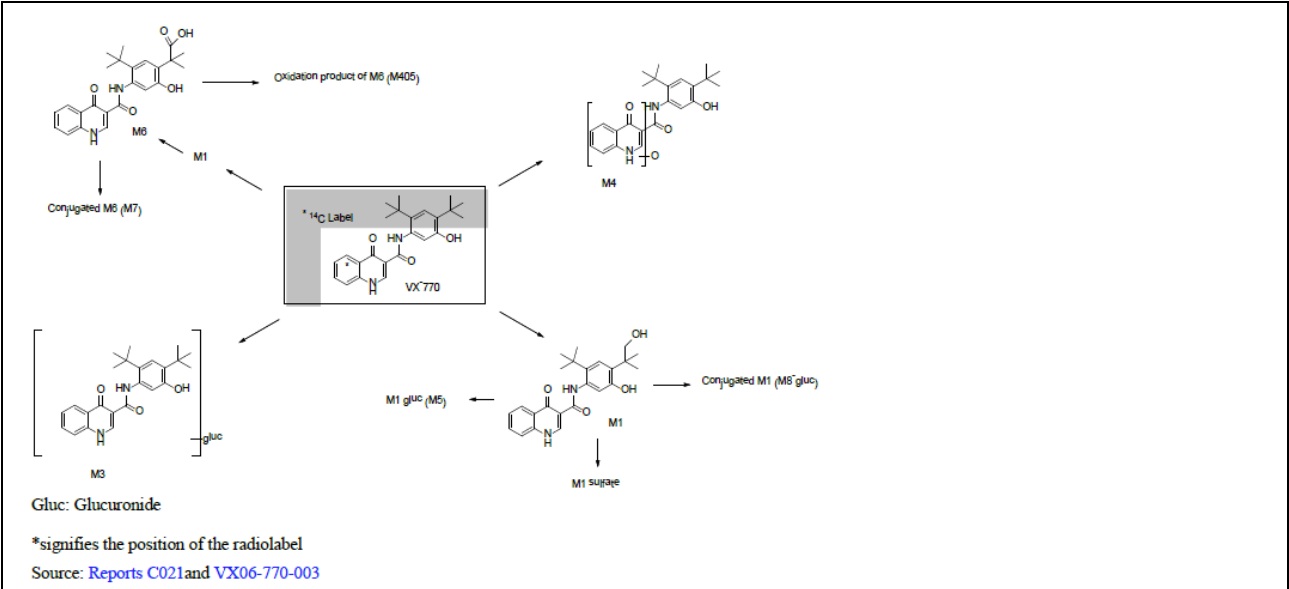
Figure 1 Proposed metabolic pathway of TEZ in rats and humans

*signifies the position of the radiolabel
Source: Reports K247 and VX13-661-005
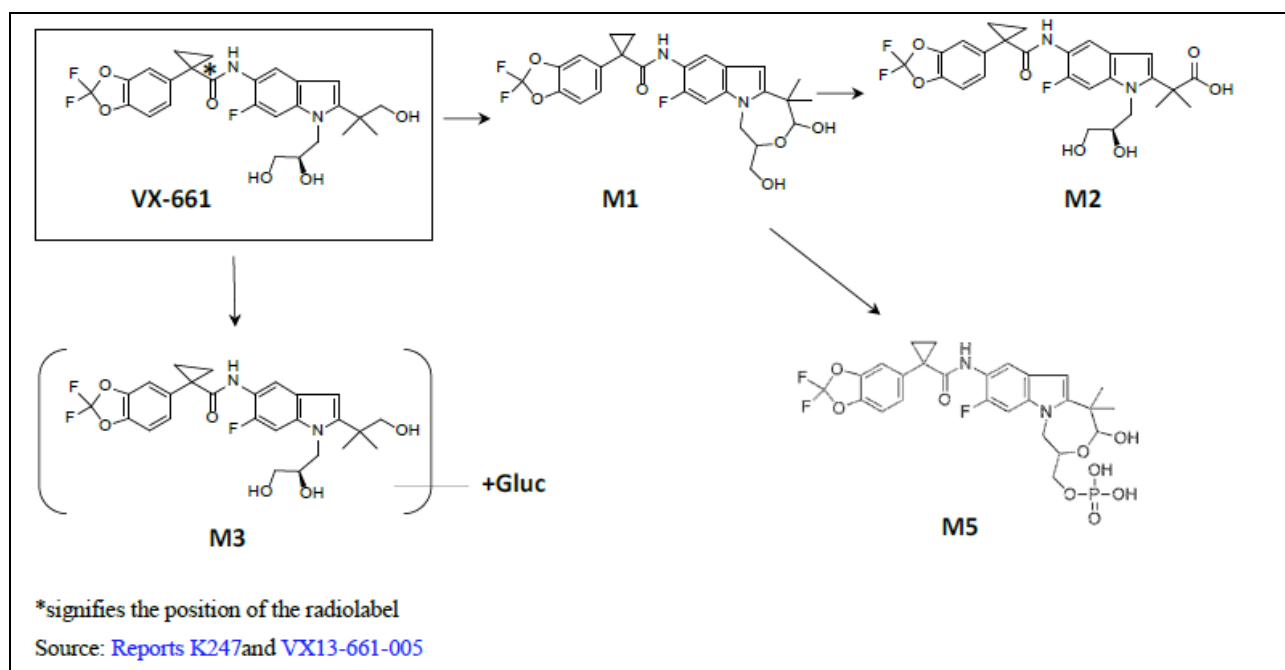
The IVA metabolites, M1-IVA (M1-IVA; significantly less pharmacologically active than IVA) and M6-IVA (M6-IVA; pharmacologically inactive), were prominent circulating metabolites in all species studied. Metabolites identified from in vivo studies in rats and humans are summarized in Figure 2. The metabolism of IVA was catalysed primarily by phase I metabolic enzymes, with minor contribution by phase II conjugation enzymes. IVA was primarily metabolized to M1-IVA and M6-IVA by oxidation.

Other minor metabolites observed were products of structural modification (oxidation and/or conjugation) of M1-IVA or M6-IVA. A direct conjugation of IVA led to M3 metabolite formation, which was observed in plasma and urine.

Figure 2 Proposed metabolic pathway of IVA in rats and humans

Gluc: Glucuronide

*signifies the position of the radiolabel

Source: Reports C021and VX06-770-003

The extent of metabolism was evaluated in 8 major human recombinant cytochrome P450 (CYPs) and hepatocytes from multiple species, including rat, dog, monkey and human. In a panel of 8 recombinant CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP3A5), TEZ when tested at 1 and 10 µM, was stable over 1 hour incubation except for significant metabolic turnover in CYP3A4/5, which suggests that CYP3A4/5 is likely involved in the oxidative metabolism of TEZ (Table 4).

Table 4 TEZ Metabolism by Human Recombinant CYPs

Concentration of TEZ	% Remaining after 60 minutes Supersome Incubation							
	CYP1A2	CYP2B9	CYP2C8	CYP2C9	CYP2C19	CYP2D6	CYP3A4	CYP3A5
1 µM	108 (5)	93 (10)	90 (13)	93 (11)	107 (8)	89 (8)	6 (1)	21 (2) *
10µM	98 (3)	101 (4)	98 (5)	92 (16)	88 (23)	124 (15)	13 (4)	25 (1) *

Source: Reports G028 and M231

n=3, mean (SD), *n=2, mean (SEM)

In a panel of 8 CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP3A5), M1-TEZ tested at 1 µM, was stable over 1 hour incubation except for metabolic turnover in CYP3A4/5, which suggests that CYP3A4/5 is likely involved in the oxidative metabolism of M1-TEZ CYP3A4/5 was involved in transformation of M1-TEZ to M2-TEZ. In addition, M2-TEZ was detected in human liver cytosol preparations incubated with M1-TEZ in the presence but not absence of NAD+, suggesting that aldehyde dehydrogenase might be involved in converting M1-TEZ to M2-TEZ (Table 5).

Table 5 M1-TEZ Metabolism by Human Recombinant CYPs

Concentration of M1-TEZ	% Remaining after 60 minutes Supersome Incubation							
	CYP1A2	CYP2B9	CYP2C8	CYP2C9	CYP2C19	CYP2D6	CYP3A4	CYP3A5
1 µM	96 (3)	89 (10)	94 (4)	95 (4)	95 (2)	94 (7)	68 (1)	17 (1)

Source: Reports H076 and M231
n=3, mean (SD)

Excretion: In intact rats, intact dogs and humans, the main route of excretion of tezacaftor is 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 C_{max} in milk of 1.5 times the C_{max} in maternal plasma.

Faecal elimination is the predominant route of excretion of ivacaftor 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.

Pharmacokinetic drug interactions

Transporter substrate potential in vitro: In vitro studies were performed to evaluate if TEZ, M1-TEZ, M2-TEZ and M5-TEZ were substrates for hepatic uptake transporters (OATP1B1, OATP1B3) and efflux transporters (P-gp and breast cancer resistance protein, BCRP). Based on these, TEZ is a substrate for the uptake transporter OATP1B1, but not for OATP1B3. TEZ is also a substrate for efflux transporters P-gp and BCRP. M1-TEZ and M2-TEZ are substrate for P-gp. Furthermore, M2-TEZ is substrate for OATP1B1 and OATP1B3. M1-TEZ and M5-TEZ are not substrates for OATP1B1 or OATP1B3.

CYP induction potential in vitro: TEZ is predicted to have low potential to cause DDIs via CYP induction. In human hepatocyte assay, TEZ did not induce CYP1A2 and CYP2B6 mRNA. Induction of CYP3A4 mRNA was observed, but considering unbound C_{max} at therapeutic dose, TEZ is not likely to be a significant inducer in the clinic. In human hepatocyte assay, M1-TEZ did not induce CYP1A2 or CYP3A4 at clinically relevant concentration and M2-TEZ did not show induction of CYP3A4 mRNA. M5-MEZ did not induce CYP1A2 and CYP2B6 and showed weak CYP3A4 mRNA induction. In cryopreserved human hepatocytes TEZ had no substantial impact on the metabolism of IVA. The prediction of low induction risk is supported by the observation that systemic exposures to TEZ and IVA when co-administered were similar to the exposures achieved when dosed individually in rats, dogs and humans, as well as the result from clinical DDI study with midazolam (a CYP3A substrate).

CYP inhibition potential in vitro: The inhibition of cytochrome P450 enzymes by TEZ and its major human circulating metabolites (M1-TEZ, M2-TEZ and M5-TEZ) were assessed by using pooled human liver microsomes. The IC_{50} values for inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4 and CYP3A5 were ≥25 µM for TEZ, were ≥12 µM for M1-TEZ, and were ≥ 75 µM for M2-TEZ and M5-TEZ. Based on the free C_{max} of TEZ and its metabolites of approximately 0.11 µM or less no *in vivo* inhibition of CYPS by these substances are expected.

Transporter inhibition potential in vitro: Bidirectional transport studies were conducted with Madin-Darby Canine Kidney (MDCK) cells overexpressing human MDR1. Inhibition of Pgp in MDCK-hMDR1

cells was evaluated by monitoring the inhibition of the Pgp mediated transport for digoxin (10 µM) at varying test compound concentrations (0 - 100 µM). The IC_{50} values were 28.6 µM for TEZ, >30 µM for M1-TEZ and >100 µM for M2-TEZ and M5-TEZ. At oral dose of 100 mg QD of TEZ, the C_{max} of TEZ at steady state is 12.5 µM, and C_{max}/IC_{50} >0.1, suggesting potential drug-drug interaction due to Pgp inhibition in the clinic. Therefore, a clinical DDI study with digoxin was conducted for TEZ in combination with IVA, and the result suggests minimal contribution of TEZ to Pgp inhibition. The potential of TEZ, M1-TEZ, M2-TEZ and M5-TEZ to inhibit the transport of probe substrate by human BCRP, OAT1, OAT3 and OCT2 was evaluated at 10 µM concentration. The probe substrate for these transporters were 2 µM p-aminohippurate (OAT1), 10 µM p-aminohippurate (OAT3), 10 µM metformin (OCT2) and 25 nM genistein (BCRP). Percent inhibition was below 27% for all 4 transporters tested, with the exception of 51% inhibition observed for TEZ on OAT3. A follow-up dose In IVA study 770-010study was carried out and IC_{50} was determined to be > 60 µM. Thus, the DDI potential for TEZ, M1-TEZ, M2-TEZ and M5-TEZ through inhibition of BCRP, OAT1, OAT3 and OCT2 is predicted to be low. TEZ, M1-TEZ, M2-TEZ and M5-TEZ inhibited atorvastatin uptake into OATP1B1 overexpressed HEK-293 cells in a concentration-dependent manner with IC_{50} values of 3.24 µM, 6.22 µM, 7.60 µM, and 11.4 µM, respectively. TEZ, M1-TEZ, M2-TEZ and M5-TEZ inhibited atorvastatin uptake into OATP1B3 overexpressed HEK-293 cells in a concentration-dependent manner with IC_{50} values of 28.8 µM, 19.8 µM, 21.5 µM, and 12.9 µM, respectively. The DDI potential for TEZ, M1-TEZ, M2-TEZ and M5-TEZ through inhibition of uptake transporters OATP1B1 and OATP1B3 is predicted to be low, as calculated R-values were less than 1.25 with exposure achieved at clinical dose of TEZ 100 mg QD.

In IVA study 770-010IVA and M1-IVA are not substrates for OATP1B1 or OATP1B3. M6-IVA is substrate for OATP1B1 and OATP1B3. IVA is not a substrate of Pgp. M1-IVA appears to be a Pgp substrate, while M6-IVA does not appear to be a Pgp substrate, but potentially could be a substrate for other efflux transporters. BCRP is not expected to influence IVA PK because it is highly permeable ($P_{app\,(A \rightarrow B)}$ = 11.9 x 10^{-6} cm/sec in Caco-2 cells), is well-absorbed upon oral administration, and is not excreted unchanged. However, an in vitro test for substrate characteristics towards BCRP is considered a basic requirement for new drugs. Further, effects of BCRP on IVA metabolites M1-IVA and M6-IVA cannot be excluded. Therefore, investigations elucidating whether ivacaftor and its substrates are substrate for BCRP have been initiated by the MAH and results will be submitted post-approval. In vitro studies showed that IVA and M1-IVA have a potential for DDI through inhibition of CYP2C8, CYP2C9 and CYP3A. M6-IVA did not inhibit any CYP enzymes significantly with in vitro IC_{50} values ≥ 63 µM. IVA is predicted to have low potential to cause DDIs via CYP induction. In human hepatocytes, IVA, M1-IVA and M6-IVA were not inducers of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A4/5.

IVA has the potential to inhibit Pgp with IC_{50} of 0.17 µM, and BCRP with IC_{50} of 12.4 µM. IVA is not expected to inhibit OATP1B1, OATP1B3, OCT1, OCT2, OAT1, or OAT3. M1-IVA showed inhibition of Pgp (IC_{50} 8.2 µM), but not M6- IVA. M1-IVA and M6-IVA showed weak inhibition of OATP1B1 and OATP1B3, with low predicted DDI risk due to low unbound C_{max} at the therapeutic dose (R-values <1.004).

2.3.3. Toxicology

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 (mouse and rat) conducted in support of the initial MAA for 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 species 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, these finding were not seen in clinical studies conducted with TEZ and IVA combined therapy. Also observed in both rats and dogs 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 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: TEZ 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 is unlikely to be relevant for humans.

Repeat-dose toxicity studies were 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. In a 3 month combination toxicity study, the death of a rat was attributed to the oral administration of 80/20 mg/kg/day TEZ/IVA. This animal showed a marked reduction in food consumption and body weight in addition to other effects. The systemic exposure detected in this animal was reported to be approximately 4 and 19 times the exposures noted in patients at the daily clinical dose of 100 mg TEZ and 300 mg IVA, respectively. In the 28-day TEZ/IVA combination toxicity study conducted in dogs, no effects on body weight or food consumption were noted at doses up to 100/60 mg/kg/day of TEZ/IVA where the relative exposure to TEZ and IVA were 5- and 19-fold the clinical exposures at a daily dose of 100 mg TEZ and 300 mg IVA. In addition, body weight changes (i.e. increases in mean BMI and weight) observed in patients treated with the combination of TEZ/IVA were similar to those who received placebo. Thus, the degree of reduced body weight and food consumption observed in the rat that died in the 28 day toxicity study with TEZ/IVA did not seem to translate to patients treated with TEZ/IVA.

Genotoxicity

Tezacaftor and ivacaftor were found to be negative in the Ames assay, *in vitro* chromosomal aberration assay and *in vivo* micronucleus test.

Carcinogenicity

TEZ was concluded to be non-carcinogenic in the 26-week Tg.rasH2 transgenic mouse carcinogenicity assay at doses up to 500 mg/kg/day (highest dose), which provides similar exposure level to TEZ (1.1-1.8 fold) that those reached in patients at the Maximum Recommended Human Dose (MRHD).

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. 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. The company provided historical control data and discussed the relevance of tumour findings of 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. 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 and the effects are considered rat specific in literature, these effects are not considered relevant for human.

IVA was also concluded to be non-carcinogenic in the 2-year rodent bioassays at doses up to 200 mg/kg/day in mice and 50 mg/kg/day in rats (highest doses tested for each species). At the highest dose tested, ivacaftor exposure was 10.3-18.7 and 42.8-78.3 fold exposure at the MRHD in human, for mice and rat, respectively.

Non-neoplastic findings with either TEZ or IVA were either considered non-adverse and/or species-specific and not relevant to humans.

Combination carcinogenicity studies involving the co-administration of TEZ and IVA were not performed as the studies conducted on each individual entity were considered adequate to assess the carcinogenic risk associated with co-administration and provided no evidence for potential for additive or synergistic interaction. This is acceptable to the CHMP.

Reproduction toxicity

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 mated with treated males, 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 in treated females. In males significant weight decrease of the seminal vesicles without fluid was observed. The ivacaftor margin of safety for male and female fertility is 4 times the systemic exposure of ivacaftor and its metabolites in adult humans at the MRHD (animal pharmacokinetic data from studies VX-770-TX-010 and VX-770-TX-006 and human pharmacokinetic data from study G198).

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 moribundity and resulting in abortions and total litter loss.

Prenatal and postnatal development, including maternal function: 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 approximately 3 fold at the MRHD, based on the AUC for IVA and its metabolites. M1 and M6 were not measured in the reproductive toxicity studies, so the metabolite values were extrapolated from the ratio of M1 and M6 to IVA in females in the 6-month rat study (VX-770-TX-010) (ratios of M1:IVA at 100 mg/kg/day and 150 mg/kg/day were 10% and 9%, respectively, so average is 10%; ratios of M6:IVA at 100 mg/kg/day and 150 mg/kg/day were 3% and 4%, respectively, so average is 4%).Studies in juvenile animals.

Juvenile toxicity studies conducted in rats to support the treatment of young children less than two year of age with ivacaftor (Kalydeco) identified the eye (lens opacities/cataracts) as a target organ of IVA-related toxicity; the aetiology of this finding remains unknown and ocular effects were not detected in repeat-dose studies conducted in older mice, rats, or dogs.

Local tolerance

Dermal and ocular local tolerance studies with tezacaftor were performed worker safety testing. 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

Phototoxicity: Potential phototoxicity of tezacaftor was tested by measuring relative reduction in viability of Balb/c 3T3 mouse fibroblasts exposed to tezacaftor and ultraviolet radiation (+UVR). Tezacaftor was tested at concentrations of 1.00, 1.78, 3.16, 5.62, 10.0, 17.8, 376 and 56.2 µg/mL. Tezacaftor did not demonstrate phototoxic potential in this assay and therefore does not appear to present any risk of phototoxicity in humans.

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

Studies on metabolites: Major metabolites of tezacaftor identified in human are M1-TEZ, M2-TEZ and M5-TEZ. The M1-TEZ metabolite was not evaluated independently in toxicity studies. The rationale for not doing so was supported by the facts that M1-TEZ exposures in rats were considered to be high enough at the tezacaftor NOAEL in rats to provide adequate toxicology coverage for human exposures at intended therapeutic dose levels. M1-TEZ metabolite exposure ratios at the NOAELs in the longest duration non-clinical studies compared to human at a dose of 100 mg QD were 4-fold for rats and 1-fold for dogs. The M5-TEZ metabolite is a no pharmacologically active Phase 2 and was also detected at levels in a rat oral PK study that were estimated at steady state to be approximately 1.5-fold compared to human at a dose of 100 mg QD. M2-TEZ is classified as a major disproportionate human metabolite at steady-state . M2-TEZ was evaluated independently in separate repeat-dose toxicity, genotoxicity, and embryo-fetal development (EFD).

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.

Metabolites of IVA were not evaluated independently in toxicity studies in support of the registration of Kalydeco. This was because M1-IVA exposures in male rats were considered to be high enough at the IVA NOAEL in rats to provide adequate toxicology coverage for human exposures at intended therapeutic dose levels, chemical synthesis of M1-IVA and M6-IVA beyond small mg quantities was prohibitive, M1-IVA and M6-IVA had limited exposure after oral administration due to a combination of solubility-limited absorption with moderate to high clearance, and while both M1-IVA and M6-IVA demonstrated some exposure upon IV administration, both were practically insoluble in aqueous vehicles suitable for IV dosing in repeat-dose studies.

Studies with tezacaftor metabolite M2-TEZ: Repeat-dose toxicity, genotoxicity and reproductive developmental toxicity studies were conducted with the metabolite M2-TEZ. M2-TEZ was evaluated independently in separate repeat-dose toxicity, genotoxicity, and embryo-fetal development (EFD) studies discussed below. 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 M2-TEZ associated effects on fetal development or survival were observed at doses that suppose exposure level 1.8 fold the exposure at the MRHD.

Studies on impurities: 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. No specified impurities were identified in the IVA SDD drug product. All other impurities were controlled to the applicable ICH Q3 limits.

2.3.4. Ecotoxicity/environmental risk assessment

Table 6 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 7 Summary of main study results for Ivacaftor

Substance (INN/Invented Name): Ivacaftor			
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	preliminary value, report could not be fully assessed in absence of a value for the water solubility.
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	mg/L	respiration

Phase IIb Studies					
Bioaccumulation/*Species*	OECD 305	BCF	not available	L/kg	%lipids:
Aerobic and anaerobic	OECD 307	DT50	p.m.	d	report not

					available
transformation in soil		%CO_2			
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.

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.

2.3.5. 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, 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 MAH would have to convincingly demonstrate that the in vitro FRT model is valid. In this respect, the MAH claimed that this system in which a single CFTR form is expressed was a validate assay to predict possible clinical response in subjects carrying at least one of the mutations of interest. Given that Van Goor and colleagues (2014) also characterised various missense mutations associated with defects in protein processing or function in FRT cells in response to ivacaftor alone, the MAH was requested to describe the experimental conditions used in Western Blot and Ussing chamber studies, 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.

Differences were observed in the baseline values of mature CFTR protein (expressed as % of normal CFTR) and of chloride transport (expressed as % of normal CFTR) compared to the data provided in the TEZ/IVA dossier. It was concluded, however, that these differences may be caused by the experimental conditions used in the studies performed, a fact that could not be circumvented. In addition, an unexpected result was observed in the FRT cell system regarding the F508del-CFTR mutant as tezacaftor/ivacaftor failed to increase chloride transport by ≥ 10% over baseline which is inconsistent with the results of study 106 where homozygous *F508del* patients demonstrated a clinical

benefit for TEZ/IVA over placebo suggesting that there may be a gene dosage effect that *in vivo* is important.

As an overall conclusion of the response provided by the MAH, it is considered that the stably transfected FRT cell line is useful for gathering information on the underlying defect of certain CFTR mutant proteins as they allow transepithelial ion transport and Western blot studies. However, the relevance of the results observed *in vitro* for the *in vivo* situation is not fully established, given the non-human origin of the cell line, the high levels of transfected CFTR expression in this system (see section 2.4) and the fact that only a single allele can be expressed. 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 MAH. There seems to be an overall 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 the cut-off of 10 pp over baseline expressed as a percentage of normal CFTR in the FRT cell line 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 MAH 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 MAH agreed to conduct further tests and submit their results post-authorisation.

2.3.6. Conclusion on the non-clinical aspects

In the pharmacodynamic investigation of tezacaftor monotherapy and TEZ/IVA combination, tezacaftor/ivacaftor showed a consistent positive effect 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. Some concerns remain to be resolved via post-authorisation measures and these have been committed to by the applicant in a letter of recommendation.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The MAH 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

The MAH states that all the clinical studies submitted in the dossier have been conducted according to ICH-GCP principles and the declaration of Helsinki.

• **Tabular overview of 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	Open-label	Evaluate the PK and safety of TEZ/IVA and their metabolites in subjects with moderate hepatic	**TEZ** 50-mg film-coated tablet **IVA** 150-mg film-coated tablet	10 days	24 subjects total **Cohort 1**
Completed		impairment compared to matched healthy subjects	TEZ 50 mg qd IVA 150 mg qd Oral		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
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

Study	Design	Objective(s)	Treatments	Duration	Subjects
Phase 1 Completed	placebo- and active-controlled, double-blind, parallel ECG study	QT/QTc interval	**Part A** <u>Cohort 1</u> TEZ 200 mg qd or matching placebo <u>Cohort 2</u> TEZ 300 mg qd or matching placebo **Part B** <u>Cohort A</u> TEZ 100 mg qd Days 1 through 7; TEZ 300 mg qd Days 8 through 14 <u>Cohort B</u> Single dose 400 mg moxifloxacin on Day 1 <u>Cohort C</u> 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

Study	Design	Objective(s)	Treatments	Duration	Subjects
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

Study	Design	Objective(s)	Treatments	Duration	Subjects
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 MAH submitted results and study report of Study VX14-661-109.

Ongoing Controlled clinical study (not submitted)					
Study VX14-661-109 Phase 3	Randomized, double-blind, active-controlled	Evaluating efficacy and safety of TEZ/IVA vs. 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 both in 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 2 Phase 2 studies (Studies 101, 103) and 3 Phase 3 studies (Studies 106, 107, and 108) 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/ pharmacodynamics [PK/PD]).

Table 8 below provides an overview of the clinical pharmacology studies conducted throughout tezacaftor/ivacaftor clinical development.

Table 8 List of Clinical Pharmacology Studies

Study Number	Study Description
Studies in Healthy Subjects	
Study 001	Single-dose and multiple-dose escalation study including a bioavailability study of a TEZ tablet formulation relative to solution
Study 004	Relative BA and food effect of a fixed-dose combination tablet of TEZ and IVA compared to TEZ and IVA formulated as separate tablets
Study 005	Mass balance study to investigate the absorption, distribution, metabolism, and excretion of TEZ
Study 006	DDI study of the effect of itraconazole on the PK of TEZ in combination with IVA and the effect of TEZ in combination with IVA on the PK of midazolam and digoxin
Study 008	DDI study of the effect of TEZ in combination with IVA on oral hormonal contraceptives
Study 009	PK and safety of TEZ in combination with IVA in subjects with moderate hepatic impairment
Study 010	ECG study to evaluate the effect of TEZ on the QT/QTc interval
Study 770-017	DDI study of multiple-dose ciprofloxacin on the multiple-dose PK of IVA and the multiple-dose PK of TEZ in combination with IVA
Studies in Subjects with CF	
Study 101	Safety, efficacy, PK, and PD of TEZ monotherapy and TEZ/IVA combination therapy (F/F and F/G551D subjects)
Study 103	Safety, efficacy, PK, and PD of TEZ in combination with IVA (F/F subjects)
Study 106	Efficacy and safety of TEZ in combination with IVA (F/F subjects)
Study 107	Efficacy and safety of TEZ in combination with IVA (F/F and F/not responsive [NR] subjects)
Study 108	Efficacy and safety of TEZ in combination with IVA (F/F and F/RF subjects)
Study 110	Open-label rollover study for Studies 103, 106, 107, 108, 109, and 111 to evaluate the safety and efficacy of long-term treatment with TEZ in combination with IVA
Study 770-104	Safety and Efficacy of IVA (F/F subjects)

Absorption

Tezacaftor is considered to be a BCS Class 2 (low solubility/high permeability) compound, using the criteria described in the Biopharmaceutics Classification System. Tezacaftor and M1-TEZ are P-glycoprotein (P-gp) substrates. Both M2-TEZ and M5-TEZ had low apparent permeability. Studies with Caco-2 and recombinant MDCK-MDR1 cells indicate that IVA and M6-IVA are not substrates of P-gp and that M1-IVA is a P-gp substrate. Tezacaftor is orally available, with a median time to maximum concentration (tmax) of approximately 3 hours in healthy subjects (100-mg tablet, under fed conditions). Cmax and AUC (AUC0-24) of TEZ increased approximately dose-proportionally following doses of 50 to 300 mg qd (Study 001). After a single dose of TEZ 50 mg/IVA 150 mg FDC in the fed state, the median (range) tmax for TEZ was approximately 4 hours (2 to 6 hours), and the median (range) tmax for IVA was approximately 6 hours (3 to 10 hours; Study 004). The median (range) tmax values were similar after a single dose of TEZ 100 mg/IVA 150 mg FDC in the fed state in: TEZ: 4 hours (2 to 8 hours); IVA: 6 hours (4 to 8 hours; Study 006 Cohort 2 Day 6). In Study 001 Part B, a high-fat meal had no significant effect on the TEZ AUC0-∞ from either tablet or solution formulation but reduced the Cmax of both formulations by approximately 30%.

Administration of food with the TEZ 50 mg/IVA 150 mg FDC formulation had no clinically relevant effect on TEZ exposures but significantly increased IVA exposures: IVA Cmax increased 4-fold and IVA AUC0-∞ increased 3-fold (Study 004). These results are consistent with the food effect observed for

IVA monotherapy and the dosing recommendations for IVA monotherapy. As a result, 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 more than 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.

Elimination

In vitro data indicate that tezacaftor and M1-tezacaftor are metabolized extensively by human CYP3A4 and CYP3A5. Following oral administration of a single dose of 100 mg 14C-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. Based on data from the original ivacaftor dossier, 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.

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 t1/2 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, after administration of 100 mg tezacaftor QD and 150 mg ivacaftor q12h, 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 t1/2 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 t1/2 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 in combination with tezacaftor.

The accumulation ratio of 1.5-3 for tezacaftor when given once daily is in line with the t1/2 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

Impaired renal function: A dedicated study in subjects with renal impairment has not been performed during the clinical development of tezacaftor in combination with ivacaftor. This is also the case for ivacaftor as a single agent. Less than 1% of the administrated tezacaftor dose was excreted in urine as unchanged drug. Similarly, there was minimal elimination of ivacaftor and its metabolites in urine (6.6% of total radioactivity was recovered in the urine) with less than 0.01% as unchanged parent (Kalydeco SmPC). Therefore, renal clearance is likely to play a minimal role in the elimination of tezacaftor and ivacaftor, 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 tezacaftor and ivacaftor in 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.

Impaired hepatic function: The majority of tezacaftor is excreted from the body via faeces following oral administration and is primarily metabolized via dehydrogenation, oxidation, and glucuronidation in the liver. Ivacaftor is also predominately cleared via a hepatic route. Based on the results of the hepatic impairment study with ivacaftor alone, a dose reduction (from 150 mg q12h to 150 mg qd) during ivacaftor monotherapy is recommended in patients with moderate hepatic impairment (Kalydeco SmPC). The impact of mild to moderate hepatic impairment on tezacaftor/ivacaftor exposure *in vivo* was assessed in subjects with Child-Pugh Class B liver disease (study 009). Based on results from this study, which showed higher exposure of tezacaftor (36% for AUC, 20% based on the total increase in active TEZ/TEZ-M1 exposure) and ivacaftor (52% for AUC) in subjects with moderate hepatic impairment, the company proposed that the dose for patients with moderate hepatic impairment (Child-Pugh Class B) should be reduced to a single tablet of tezacaftor 100mg/ivacaftor 150 mg once daily. The evening dose of 150 mg ivacaftor should not be taken as also reflected in the SmPC. The impact of mild hepatic impairment (Child-Pugh A) on the PK of TEZ/IVA has not been studied, but the increase in exposure is expected to be less than that observed in subjects with moderate hepatic impairment. Therefore, no dose adjustment is deemed necessary for patients with mild hepatic impairment. Similarly, the impact of severe hepatic impairment (Child-Pugh C) on the PK of tezacaftor/ivacaftor has not been studied, but the increase in exposure is expected to be more than that observed in subjects with moderate hepatic impairment. The dose for patients with severe hepatic impairment should be reduced to a single tablet of tezacaftor 100mg/ivacaftor 150 mg once daily (or

less frequently). The evening dose of 150 mg ivacaftor should not be taken as also reflected in the SmPC. Caution is recommended when tezacaftor/ivacaftor is used in patients with severe hepatic impairment.

Gender: An exploratory assessment in Study 001 suggested no sex-related effect on TEZ PK. In the population PK analysis, female sex was a statistically significant covariate (13% increase in TEZ CL/F; 95% CI: 7%, 19%); however, the effect is not considered clinically meaningful. Regarding ivacaftor as a single agent, females had a similar CL/F when compared to males, with a point estimate of 1.03 (95% CI: 0.920, 1.14).

Race: The effect of race on PK of tezacaftor could not be adequately evaluated due to the small number of non-White subjects. The information on different races is considered to be very limited, as reflected in the SmPCs.

Weight:

Tezacaftor: In the population PK analysis, body weight was a predictor of variability in tezacaftor clearance. Tezacaftor CL/F was 1.32 L/h (95% CI: 1.19, 1.47) for a 70-kg subject, using allometric scaling with a fixed coefficient of 0.75. Using this scaling, tezacaftor CL/F for a 40-kg subject would be 34.3% lower than that for a 70-kg subject.. No clinically relevant effects on efficacy or safety are expected and therefore no dose adjustment based on weight is deemed necessary.

Ivacaftor: In the IVA popPK model, body weight was the only significant predictor of IVA disposition (Report K199). No dose modification based on weight was deemed necessary for subjects aged 12 years or older.

Age: only a low number of elderly patients 65-74 years of age (13 patients) were included in the clinical studies conducted for tezacaftor/ivacaftor. This is also the case for ivacaftor as a single agent. Overall, age does not appear to be a relevant covariate in the pop-PK study. The recommended dose of tezacaftor in combination with ivacaftor is the same for adolescents and adult subjects. Adolescent subjects aged 12 to less than 18 years were enrolled in the clinical studies and PK samples collected from them. A population PK approach was used to evaluate the effect of age on TEZ PK parameters.

Pharmacokinetic interaction studies

Substrate in vitro

Based on *in vitro* data, CYP3A4/5 are the main CYP isoforms involved in tezacaftor and ivacaftor metabolism. Co-administration with CYP3A4/5 inhibitors or inducers may therefore result in change in tezacaftor and ivacaftor exposure. With regard to drug transporters, *in vitro*, tezacaftor is a substrate for the uptake transporter OATP1B1 as well as for efflux transporters P-gp and BCRP. Tezacaftor is no substrate for OATP1B3. M1-tezacaftor is substrate for P-gp. However, exposure to tezacaftor 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, tezacaftor 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, tezacaftor 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, ivacaftor has the potential to inhibit CYP2C8, CYP2C9 and P-

gp. No induction was noted by ivacaftor and its metabolites. *In vitro* studies showed that ivacaftor 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 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 moderate CYP3A4 inhibitors, tezacaftor 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 of tezacaftor (i.e., 100 mg TEZ every other day) in the presence of moderate inhibitors of CYP3A4, sufficiently assure adequate exposure to tezacaftor in the presence of these 3 different moderate inhibitors of CYP3A4.

In a previous ivacaftor study from the ivacaftor application (Study 770-010), multiple-dose co-administration of ivacaftor and moderate CYP3A4 inhibitor fluconazole increased ivacaftor 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 ivacaftor exposure (Study 770-009), which is consistent with ivacaftor being a sensitive CYP3A substrate. Although not investigated, tezacaftor 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 tezacaftor compared to ivacaftor. 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 tezacaftor and ivacaftor are not recommended as they may decrease the tezacaftor and ivacaftor exposures and limit the effectiveness of the combination. These recommendations are consistent with the labelling for ivacaftor monotherapy.

TEZ/IVA co-administered with 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-administered 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

Pharmacokinetic drug interactions are part of the non-clinical part of this assessment report.

2.4.3. Pharmacodynamics

Mechanism of action

The claimed indication for Kalydeco 150 mg tablets in a combination regimen with tezacaftor/ivacaftor is for the treatment of subjects (adult and adolescents) with cystic fibrosis homozygous for *F508del* and for the treatment of subjects who are heterozygous for the *F508del* mutation and who have a certain, pre-specified second mutation of residual function of the *CFTR* gene. Tezacaftor is said to be a CFTR corrector that facilitates the cellular processing and trafficking of normal or multiple mutant forms of 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 enhances 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.

Two *in vitro* systems have been used to support the two indications above mentioned. In human bronchial epithelial cells (HBE) cells, which are derived from CF-patient donors, the functional impact and response to CFTR modulators for both CFTR alleles that the patient had are evaluated. Because HBE cells are primary cell lines, it is not possible to obtain HBE cell lines expressing all *CFTR* mutations. Therefore, Fisher Rat Thyroid (FRT) cell lines were engineered to express a single CFTR form to study TEZ/IVA-responsiveness of less prevalent mutations, including residual function and gating mutations. In the FRT system, CFTR function is driven by the type of mutation that is introduced and reflects on the contribution of only a single CFTR form, as compared with HBE cells in which function of CFTR represents the contributions from two alleles.

Primary and secondary pharmacology

Primary pharmacology

Effects on Sweat Chloride: Sweat chloride was included in the Phase II studies, Study 101 and 103, and in the Phase 3 studies, Study 106 and Study 108, as a measure of the effect of tezacaftor/ivacaftor on CFTR activity. The studies included CF patients with different mutations. Patients with CF heterozygous for *F508del/G551D:* In study 101 (Group 7), the effect of TEZ 100 mg qd/IVA 150 mg q12h was assessed 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 tezacaftor/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 was 0 subjects (Placebo + Kalydeco) and 4 (30.8%) subjects for tezacaftor + ivacaftor.

Patients with CF homozygous for *F508del* (F/F): The changes in sweat chloride were measured in patients with CF homozygous for *F508del* in 3 studies.

In study 101, different doses of tezacaftor alone of 10, 30, 100, and 150 mg once daily and in combination with ivacaftor were tested. Ivacaftor 150 mg twice daily was selected because it is the approved Kalydeco dose for patients aged 12 years and older, and there is no clinically meaningful drug-drug interaction between tezacaftor and ivacaftor.

A reduction in the mean sweat chloride compared to baseline was observed in all groups, with the exception of tezacaftor 10 mg once daily. The largest effect is seen with tezacaftor 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 mmol/L. For the combined therapy, the least square mean absolute change ranged from -2.63 to -6.04 mmol/L.

In a responder analysis the proportion of subjects with ≥10 mmol decrease in sweat chloride through Day 28 was 2 (11.8%) subjects for tezacaftor 100 mg once daily/ivacaftor 150 mg every 12 hours, 5 (27.8%) for subjects for tezacaftor 50 mg q12h/ivacaftor 150 mg q12h.

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, tezacaftor doses of 50 mg q12h (Group 1) and 100 mg qd (Group 2) both combined with ivacaftor 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 mmol/L (P<0.0001) and −10.1 mmol/L (-11.4, -8.8) (P<0.0001) after 4 weeks and 12 weeks of treatment, respectively.

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).

Secondary pharmacology

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. PK/PD modelling

Population PK analyses were conducted on pooled data from Studies 101, 103, 106, 107, and 108. 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.

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. 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. Due to limited IVA dose-ranging data, the contribution of IVA was modelled as a binary effect.

During evaluation, additional comparative TEZ versus TEZ/IVA exposure-response data (for ppFEV1 and SwCl) were requested by the CHMP for study 101 alone, excluding TEZ/IVA washout data as a surrogate for TEZ monotherapy exposure. Figures 3-4 show the difference between TEZ/IVA and TEZ based on data from study 101, 103 and 106 (grey colour) and with only data from study 101 (blue) for ppFEV 1 and sweat chloride respectively.

Figure 3 Comparison of Modeled Dose-Response Relationships for ppFEV$_1$ in F/F Subjects for the Requested (Blue) and Submission Analyses (Grey)
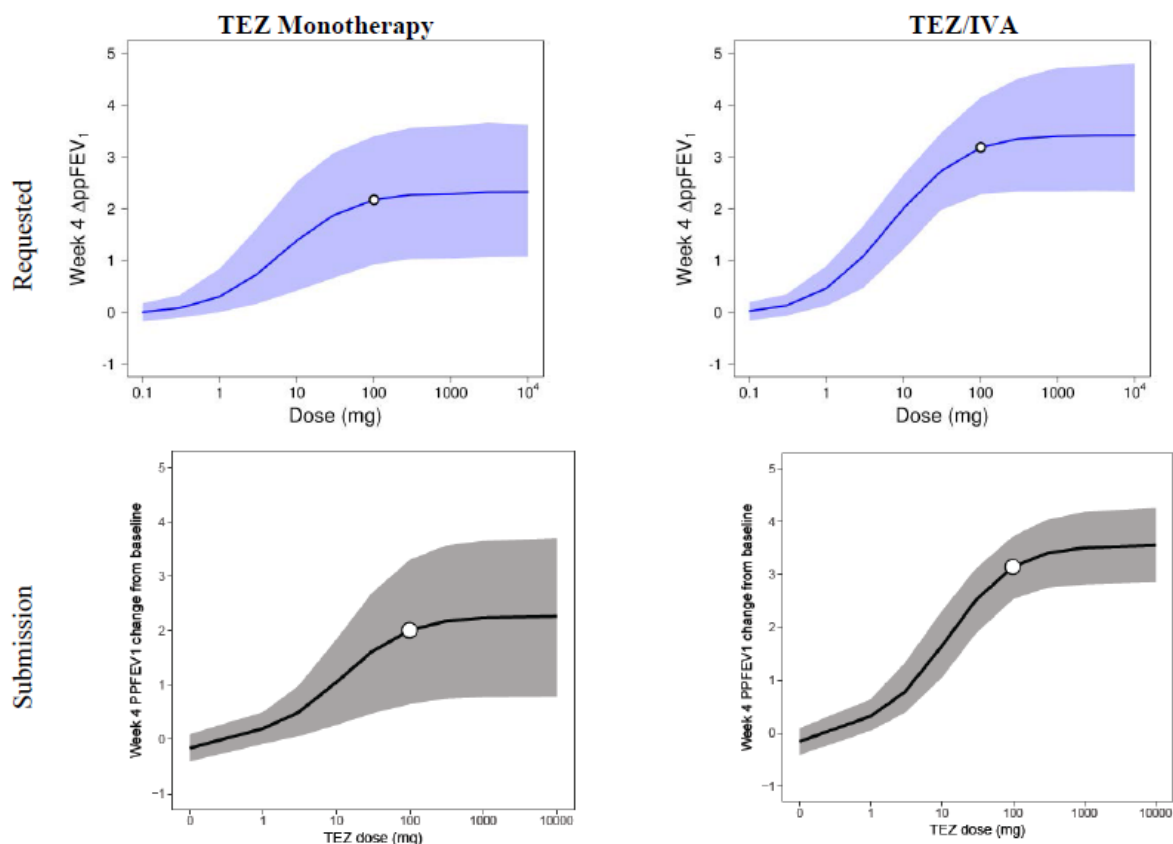
Source: Data on file and Report N021

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 4 Comparison of Modeled Dose-Response Relationships for Sweat Chloride in F/F Subjects for the Requested (Blue) and Submission Analyses (Grey)
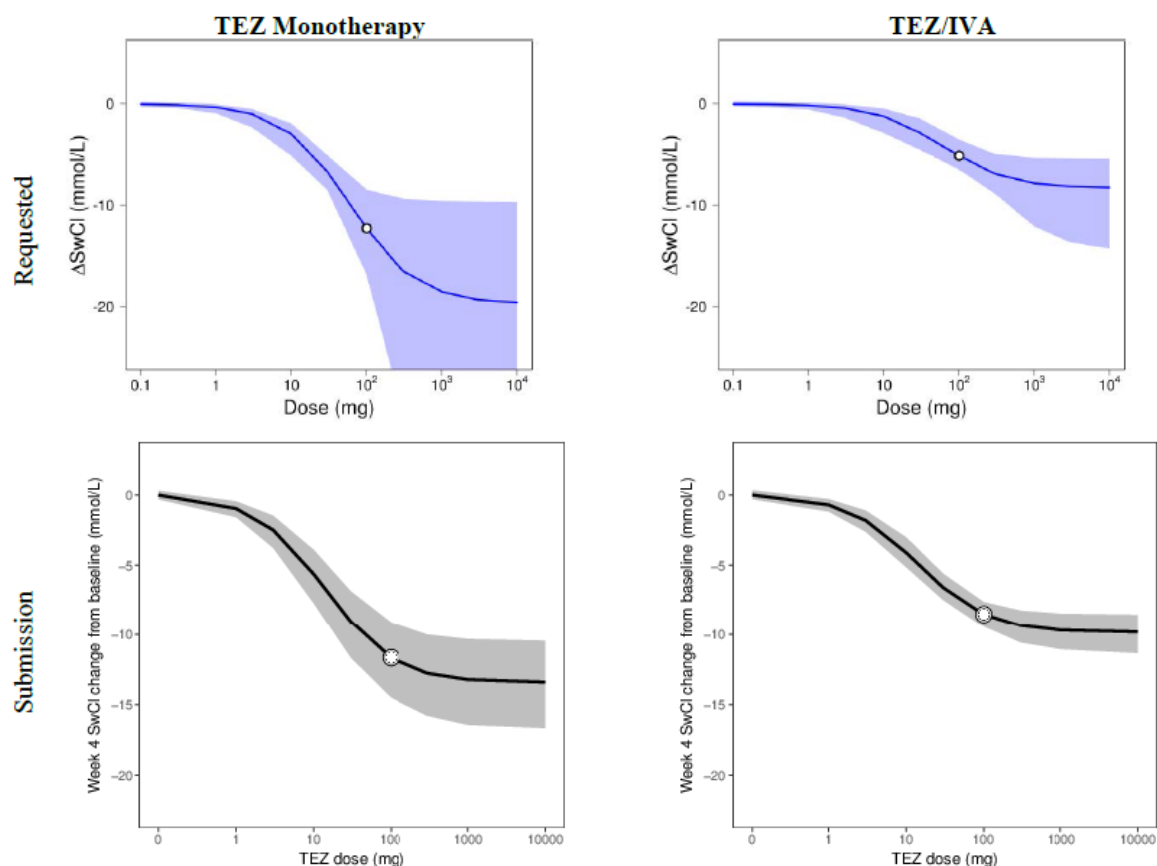
Source: Data on file and Report N021
Notes: Requested analysis included data from placebo arms, TEZ monotherapy arms, and TEZ/IVA arms where TEZ was dosed qd and IVA was dosed at 150 mg q12h.
The line is the median and shaded area is the 95%CI for the simulated mean change from baseline. The results 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).

2.4.5. 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 MAH 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. At present, it remains unclear 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 MAH 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. Therefore, 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 MAH 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, section 4.2. 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.

No changes were proposed for section 5.2 of the SmPC of Kalydeco. The MAH was requested to further substantiate this approach by providing PK parameters of ivacaftor alone and in combination with tezacaftor and discuss the clinical relevance (or lack of it) in view of these PK parameters. Based on actual study data (interstudy comparisons), IVA and M1-IVA Cmax and AUC0-12h 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. Therefore, the approach taken for the clinical pharmacology

program of tezacaftor/ivacaftor in which most of the PK attributes of ivacaftor have been assumed to be similar to those of the single ivacaftor agent is considered acceptable to the CHMP.

Based on current regulatory requirements, the potential for drug-drug interactions should be evaluated for a new drug and the relevant metabolites. The MAH has not fulfilled this requirement 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, it cannot be excluded that in the future new drugs will be marketed that indeed may be combined with TEZ/IVA and are substrate for a relevant enzyme. The MAH 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 (IC50 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 should be conducted. 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 MAH 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 MAH and results will be submitted post-approval, which is agreed by the CHMP.

Pharmacodynamics

The proposed mechanism of action is based on *in vitro* studies in two systems, human bronchial epithelial cells (HBE) cells and stably transfected Fisher Rat Tyroid (FTR) cells that express a single CFTR mutant to study the response of less prevalent mutations to tezacaftor, ivacaftor and the combination. A search has been done in CFTR2 (www.cftr2.org) for all the *CFTR* mutations with residual function that are being proposed for approval. The following is a brief summary of the findings:

•   Out of the 25 residual function mutations that were initially proposed for approval, *E193K-*, *K1060T-*, and *A1067T-CFTR* mutations cannot be found in CFTR2. Clinical data are either not available from study 108.

•   *R74W-* (complex allele), *D110E-*, *D579G-*, *S977F-*, *F1052-*, *R1070W-* (complex allele), *D1257H-*, and *D1270N-CFTR* mutations are mutations of varying clinical consequences. The remaining ones are expected to result in CF when combined with another CF-causing variant.

•   No clinical data are available from study 108 for subjects carrying the following mutations, *E56K-*, *R74W-*, *D110E-*, *E193K-*, *F1052V-*, *K1060T-*, *A1067T-*, *F1074L-*, and *D1270N-CFTR*. Very limited clinical data are available for other mutations such as *D110H* and *R117C*.

- For the five splice mutations proposed sufficient clinical data are available from study 108 with the exception of *E831X* (n=1, ivacaftor-treated subject) and *711+3A->G* (n=2). All the splice mutations considered are expected to result in CF when combined with another CF-causing variant. None of these mutations could be assessed *in vitro* in the FRT cell system.

Change in sweat chloride (as a biomarker of CFTR activity) in response to treatment with tezacaftor alone or in combination with ivacaftor was investigated in the phase 2 studies 101 and 103, and in the phase 3 studies 106 (subjects homozygous *F508del*), and 108 (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 has shown 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. 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 reduction is considered relevant for patients with F/F mutations from the perspective that mutations with residual function 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 mono-component 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. To account for this, post-treatment washout data from TEZ/IVA treated patients were included in the model in order to provide additional response data for exposures similar to the TEZ 10 mg qd dose. This was not considered acceptable and therefore additional E-R analyses were provided on request of the CHMP. 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 extremely wide however: −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 for 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 101.

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 to conclude on the potential for QTc prolongation. As at all time points 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.

2.4.6. 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). However, the inferior effect of TEZ/IVA compared with TEZ on sweat chloride in study 101 is not completely understood. The demonstrated inconsistencies in study 101 are still not 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 CFTR function. Therefore the possibility that tezacaftor may be beneficial on its own in subjects with *F508del-CFTR* cannot be confidently excluded. However, this ongoing uncertainty is set against i) the high level of unmet need in *F508del* homozygous patients who cannot tolerate LUM/IVA or where LUM/IVA is inadvisable; and ii) the demonstration of superiority for TEZ/IVA over placebo in homozygous *F508del* patients resulting in relevant improvements in this population. The pharmacokinetics of tezacaftor and ivacaftor has been investigated to a reasonable degree. Several concerns will be resolved via post-authorisation measures, which have been committed to by the MAH in a letter of recommendations.

2.5. Clinical efficacy

The clinical package for TEZ/IVA to be administered together with IVA, comprises of six clinical studies in total, consisting of one phase 2 PD study, one phase 2 dose finding study, three placebo-controlled phase 3 efficacy and safety studies and one long term open label study evaluating safety and efficacy. The phase 2 PD study (study 101) is handled as a dose ranging study and described in this section.

Dose finding studies: Study VX11-661-101 (study 101) evaluated TEZ monotherapy and TEZ/IVA co-therapy in subjects with cystic fibrosis (CF) who are homozygous for the *F508de-CFTR* mutation or heterozygous for *F508del* and have *G551D* mutation. Study VX13-661-103 (Study 103) evaluated different doses of TEZ/IVA with long-duration of dosing (52 weeks in total).

Efficacy and safety studies: Each of the 5 phase III studies CF in patients aged 12 years and older enrolled a different patient population:

- Study 103: subjects homozygous for *F508del* (F/F)

- 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 with CF who are homozygous or heterozygous for the F508del-CFTR mutation and who participated in Studies VX13-661-103, VX14-661-106, VX14-661-107, VX14-661-108, VX-14-661-109, VX14-661-111, or other Vertex Pharmaceuticals Incorporated (Vertex) studies investigating TEZ in combination with IVA.

Studies 106 and 108 are the core efficacy studies supporting the proposed indication. *In vitro* response to TEZ/IVA provides evidence of response of eligible mutations without clinical data available. Study 107 was stopped because results of a planned interim analysis met the pre-defined futility rule. Study 110 is an open label uncontrolled extension study to support durability of efficacy and safety in subjects who completed Studies 103, 106, 107, 108 and 109. Study 110 was ongoing at the time of filing. During the evaluation, the MAH communicated to the CHMP that Study 109 in patients with F508del/CFTR-gating mutations failed to meet its primary endpoint and therefore clinical superiority for TEZ/IVA versus IVA could not be concluded. As a consequence, during the evaluation, gating mutations (including *R117H*) were excluded from the originally proposed indication.

2.5.1. Dose response studies

Two Phase 2 studies, Study VX11-661-101 (Study 101) and Study VX13-661-103 (Study 103), evaluated different doses of TEZ monotherapy and TEZ/IVA combination therapy in CF subjects with homozygous or heterozygous for *F508del* mutation.

Study 101 was a randomized, multicenter, double-blinded, placebo-controlled study that evaluated the pharmacokinetics (PK), pharmacodynamics (PD), efficacy, and safety of TEZ and TEZ/IVA at multiple dose levels in adult subjects with F/F genotype and in adult and adolescent subjects with F/G551D. Subjects were randomised across a range of dose combinations as shown in the following table.

Table 9

Table 2-1 Study Design: Study VX11-661-101			
Population With CF	**Group Name**	**Dosing (Active or Matched Placebo)**	**Planned Number of Subjects (Active: Placebo)[a]**
Subjects homozygous for *F508del*, ≥18 years old	Group 1	VX-661 10 mg qd	N = 10 (8:2)
	Group 2a	VX-661 30 mg qd	N = 10 (8:2)
	Group 2b	VX-661 10 mg qd/IVA150 mg q12h	N = 20 (16:4)
	Group 3a	VX-661 100 mg qd	N = 10 (8:2)
	Group 3b	VX-661 30 mg qd/IVA 150 mg q12h	N = 20 (16:4)
	Group 4	VX-661 100 mg qd/IVA 150 mg q12h	N = 20 (16:4)
	Group 5a	VX-661 150 mg qd	N = 10 (8:2)
	Group 5b	VX-661 150 mg qd/IVA 150 mg q12h	N = 20 (16:4)
	Group 6a	VX-661 100 mg qd/IVA 50 mg q12h	N = 20 (16:4)
	Group 6b[b]	VX-661 100 mg qd/IVA 100 mg qd	N = 20 (16:4)
	Group 6c[b]	VX-661 100 mg qd/IVA 50 mg qd	N = 20 (16:4)
	Group 6d	VX-661 50 mg q12h/IVA 150 mg q12h	N = 20 (16:4)
Subjects heterozygous for *F508del/G551D*, ≥12 years old	Group 7	VX-661 100 mg qd (in combination with physician-prescribed Kalydeco)[c]	N = 20 (16:4)
Subjects heterozygous for *F508del*/residual function mutation, ≥12 years old	Group 8 (optional)[b]	VX-661 100 mg qd/IVA 150 mg q12h	N = 20 (16:4)

CF: cystic fibrosis; *CFTR*: cystic fibrosis transmembrane conductance regulator; IVA: ivacaftor; N: sample size; q12h: every 12 hours; qd: daily
[a] Subjects in all treatment groups were randomized 4:1 (active:placebo).
[b] Groups 6b and 6c were not enrolled due to rules prespecified in the protocol (Appendix 16.1.1/Section 9.1). Optional Group 8 was not initiated because there was a need to collect additional clinical data in studies that were more adequately designed to study this population.
[c] Subjects must have been receiving physician-prescribed Kalydeco (IVA 150 mg q12h) for at least 28 days before the Screening Visit through the Safety Follow-up Visit.

The primary efficacy variable is the absolute change in sweat chloride (mmol/L) from baseline through Day 28 (analysed based on an MMRM). Other endpoints included FEV1 (L), ppFEV1 (value, and absolute and relative change from baseline [to each visit and average through Day 28]. A model to assess the off treatment period was also be produced and analysed the change from Day 28 through Day 56), CFQ-R.

Results

Overall, 194 subjects were randomised in study 101. Four subjects discontinued the study before receiving their first dose of study drug; therefore, the FAS included 190 subjects: 172 in Groups 1 to 6d (33 subjects in the placebo group, 33 subjects in the VX-661 monotherapy group, and 106 subjects in the VX-661/IVA group) and 18 subjects in Group 7 (4 subjects in the Placebo + Kalydeco group and 14 subjects in the VX-661 + Kalydeco group).

A total of 179 (94.2%) subjects completed study drug treatment, and 185 (97.4%) subjects completed the study/Safety Follow-Up Visit. The most common reason for discontinuation from study drug treatment across all treatment groups was an AE (5 [2.6%] subjects overall).

In Groups 1 to 6d, 2 (6.1%) subjects in the placebo group, 1 (3.0%) subject in the VX-661 monotherapy group, and 8 (7.5%) subjects in the VX-661/IVA group discontinued study treatment. In Group 7, all 18 subjects completed study drug treatment and completed the study.

CF patients 18 years or older with the F508del/F508del genotype (F/F)

Table below summarizes the absolute change from baseline through Day 28 in sweat chloride (mmol/L) by MMRM treated with various dose levels of VX-661 monotherapy and VX-661 in combination with IVA 150 mg q12h (Groups 1 through 5).

Table 10 Sweat Chloride (mmol/L): Absolute Change from Baseline Through D28 by MMRM, Full analysis Set (Groups 1 through 5)

Treatment	Baseline Statistics N	Baseline Statistics Mean	Day 28 Statistics[a] N	Day 28 Statistics[a] Mean	Absolute Change Through Day 28[b,c] N	Absolute Change Through Day 28[b,c] LS Mean	Absolute Change Through Day 28[b,c] P Value	Treatment Difference (vs. Pooled Placebo)[b,d] Difference (95% CI)	Treatment Difference (vs. Pooled Placebo)[b,d] P Value	Treatment Difference (vs. Corresponding VX-661 group)[b,d] Difference (95% CI)	Treatment Difference (vs. Corresponding VX-661 group)[b,d] 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.

Spirometry was evaluated as a secondary efficacy outcome in Groups 1-5. Table below shows the mean absolute change in ppFEV1 through Day 28 in all VX-661 groups and all VX-661/IVA groups when analysed within-group and compared to placebo.

Table 11 PpFEV1: Absolute Change From Baseline Through Day 28 (Percentage Points) by MMRM, Full Analysis Set (Groups 1 Through 5)

Treatment	Baseline Statistics n	Baseline Statistics Mean	Day 28 Statistics[a] n	Day 28 Statistics[a] Mean	Absolute Change Through Day 28[b,c] N	Absolute Change Through Day 28[b,c] LS Mean	Absolute Change Through Day 28[b,c] P Value	Treatment Difference (vs. Pooled Placebo)[b,d] Difference (95% CI)	Treatment Difference (vs. Pooled Placebo)[b,d] P Value	Treatment Difference (vs. Corresponding VX-661 Group)[b,d] Difference (95% CI)	Treatment Difference (vs. Corresponding VX-661 Group)[b,d] 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.

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 a higher TEZ dose of 150 mg qd/ IVA 150 mg q12h (ppFEV1 3.75 %; P =0.00125).

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.

CF patients 12 years or older with the F508del/G551D genotype (study 101) (Group 7, n=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). Table below summarises the absolute change from baseline through day 28 in ppFEV1 by MMRM (Full Analysis Set).

Table 12

Treatment[d]	Baseline Statistics		Day 28 Statistics[a]		Absolute Change Through Day 28[b,c]			Treatment Difference (vs. Group 7 Placebo)[b,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.

In study 103 (18 years of age or older with the F/F genotype), subjects were enrolled into 2 groups. Within each group, the subjects were randomized to active treatment or placebo in a 1:1 ratio.

Group 1: Active: VX-661 50 mg q12h + IVA 150 mg q12h or placebo

Group 2: Active: VX-661 100 mg qd + IVA 150 mg q12h or placebo

The placebo-controlled, randomized, double-blind part of the study evaluated safety, efficacy, and PK of TEZ/IVA when administered for 12 weeks followed by an open-label extension of TEZ/IVA administered for 40 weeks. The within-group LS mean for average absolute change from baseline in ppFEV1 through Week 12 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 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.

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 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.

2.5.2. Main studies

Studies 106 and 108 are the key 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 Study

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

Study design

Figure 5 Design of pivotal studies 106 and 108 for Symkevi

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 m^2 (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 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.

Spirometry was performed pre-bronchodilator according to ATS standard in compliance with withholding of bronchodilators. For adolescents the standards of Hankinson and Wang were 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 96.43% completed treatment in both periods, see subject disposition), so this is considered not to have impacted the results.

Statistical methods

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

In study 106, 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%).

In study 108, all 248 subjects randomized to treatment sequence were included in the All Subjects and Randomized Sets. The Safety Set included 246 randomized subjects who received at least 1 dose of

study drug. Two subjects who were randomized and received treatment but did not have eligible CFTR mutations were excluded from the efficacy analysis. Consequently, the FAS included 244 subjects: 161 who received placebo, 156 who received IVA, and 161 who received TEZ/IVA.

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 15 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 16 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

With very few exceptions, subject demography and baseline characteristics 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), and had higher use of inhaled antibiotics (58.7% versus 31.2%) that were started within 28 days prior to the screening period until the safety follow-up visit (study 106) or during the first treatment period (study 108).

The status of the subjects at enrolment regarding chronic lung infection due to *P. aeruginosa* was not collected. Instead, what was collected was whether the subjects had been tested positive to any respiratory pathogen in the two years prior to the initiation of the trials. Therefore, the characteristic "Colonisation of *P aeruginosa*" should not be understood as if the subjects quoted in table below were all colonised by *P aeruginosa* at the time of the study entry or during it.

In study 106, 1.0% of patients overall were obese (defined as a BMI > 30 kg/m2) while 29.6% were undernourished (defined as BMI < 18.5 Kg/m2). No adolescent subjects were obese but the percentage of undernourished subjects in this age group was considerably higher than in the adult group (69.8% vs. 17.5% respectively). Approximately 98% of subjects in Study 106 had exocrine pancreatic insufficiency and up to 97% of these subjects received pancreatic enzyme replacement therapy.

In study 108, the baseline value of sweat chloride in the TEZ/IVA group in both periods is around 10 mEq/l less than in the other two groups (i.e., around 66 mEq/l in both periods vs. 70 mEq/l on placebo and 75 mEq/l on ivacaftor). In Period 1 of study 108 the percentage of subjects with sweat chloride less than 30 mEq/l was 18.1% in the TEZ/IVA group vs. 5.0% and 4.9% on placebo and ivacaftor respectively. Within-subject comparisons of Period 1 and Period 2 baselines for ppFEV1, CFQ-R respiratory domain score, and sweat chloride concentrations were compared 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 while only 13.5% were identified as pancreatic insufficient (defined as faecal elastase-1 concentration <200 µg/g). A total of 146 subjects (59.8%) had a Class V non-canonical splice mutation, and 98 (40.2%) had Class II to IV mutations.

Table 17 Key Subject Demography and Baseline Characteristics, Full Analysis Set

Characteristic	Study 106		Study 108 (Period 1)[e]		
	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.

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 in study 106 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).

Overall, 461 (90.6%) subjects enrolled in the treatment cohort of the extension study, and 3 (0.6%) subjects enrolled in the observational cohort in the extension study (Study VX14-661-110).

Primary endpoint

The LS mean treatment difference between the TEZ/IVA and placebo groups was 4.0 percentage points (95% CI: 3.1, 4.8) and was statistically significant in favour of TEZ/IVA (P<0.0001) (see table 18).

Table 18 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 cumulative distribution plot of the average absolute change from baseline in ppFEV1 through Week 24 is provided in figure below.

Figure 6 Absolute change from baseline in ppFEV1 through Week 24
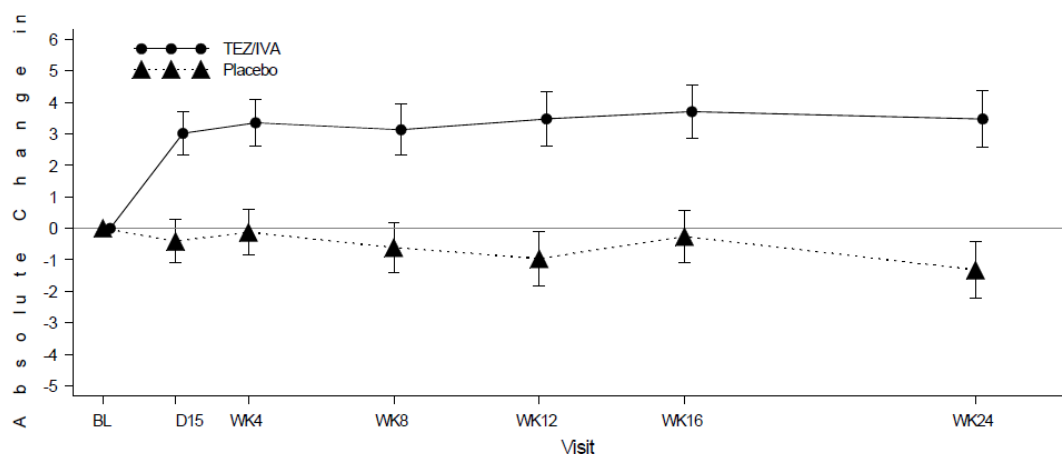
Source: Figure 14.2.1.1.1

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.

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 PEx through Week 24: The number of pulmonary exacerbations (PExs) through Week 24 was analysed using a negative binomial regression model. TEZ/IVA treatment was associated with a lower event rate per year of pulmonary exacerbations (0.64) compared to placebo (0.99). The rate ratio versus placebo was 0.65 (95% CI: 0.48, 0.88; P = 0.0054). In addition, treatment with TEZ/IVA was associated with a 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. The LS mean treatment difference between the TEZ/IVA and placebo groups was −0.04 kg/m2 (95% CI: −0.15, 0.07, P = 0.4127). Therefore, the hierarchical multiple testing procedure was stopped at the level of BMI. Although a statistically significant treatment difference was not achieved, the 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.

In response to the CHMP's request, the MAH provided an analysis of change from baseline for undernourished subjects (defined as subjects < 20 years of age with a baseline BMI-z-score <0; subjects ≥ 20 years of age with a baseline BMI < 18.5 kg/m^2) and an analysis of undernourished subjects who met or exceeded a target BMI (i.e., for subjects < 20 years if their BMI-z-score was ≥ 0; for subjects ≥ 20 years if their BMI value was greater than the median baseline BMI value for healthy subjects ≥20 years [healthy being defined as those with BMI ≥18.5 kg/m^2)].

At week 24 of study 106, the LS mean change from baseline in BMI in undernourished subjects in the placebo group was 0.30 (Min, Max: -1.71, 2.11) while in the TEZ/IVA group the LS mean change was 0.15 (Min. Max: -2.23, 1.63). The responder analysis showed that the percentage of undernourished subjects who met or exceeded the target BMI at Week 24 was 28.6% in the placebo group versus 32.4% in the TEZ/IVA group.
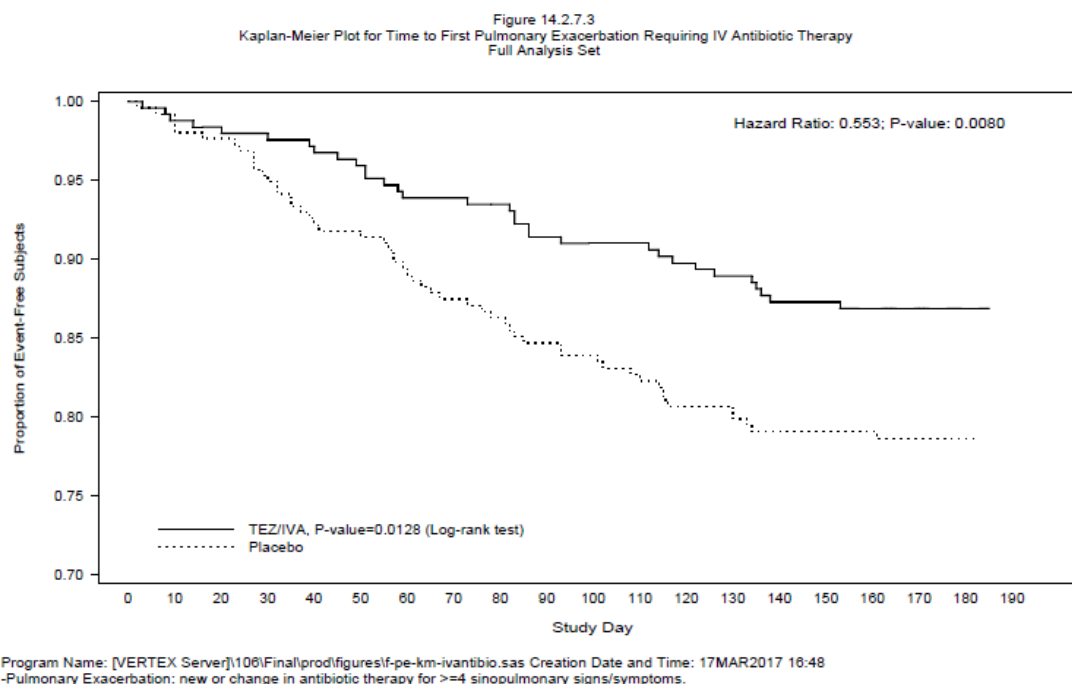
Absolute change from baseline in CFQ-R Respiratory Domain Score through Week 24: The last key secondary endpoint in the testing hierarchy was a self-reported measure of respiratory symptoms, the CFQ-R respiratory domain score, analysed by MMRM through Week 24. The pooled CFQ-R "Children Ages 12 and 13" 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 (95% CI: 0.459, 0.884; 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. No statistically significant differences versus placebo were detected in the time to first pulmonary exacerbation leading to hospitalisation (hazard ratio versus placebo 0.78 [95%CI: 0.44, 1.36; P = 0.3801]).

Figure below presents the survival curves by treatment group for time-to-first pulmonary exacerbation that required IV antibiotic therapy.

Figure 7 Survival curves by treatment group for time-to-first pulmonary exacerbation that required IV antibiotic therapy

Figure 14.2.7.3
Kaplan-Meier Plot for Time to First Pulmonary Exacerbation Requiring IV Antibiotic Therapy
Full Analysis Set

Program Name: [VERTEX Server]\106\Final\prod\figures\f-pe-km-ivantibio.sas Creation Date and Time: 17MAR2017 16:48
-Pulmonary Exacerbation: new or change in antibiotic therapy for >=4 sinopulmonary signs/symptoms.

Absolute change in BMI z-score from baseline at Week 24 (in subjects <20 years of age at time of screening): The absolute change from baseline in BMI z-score at Week 24 for subjects <20 years old at screening (80 subjects in the TEZ/IVA group and 76 subjects in the placebo group) was analysed using an MMRM model. No clinically meaningful within-group changes in the LS mean BMI z-score at Week 24 were observed in the TEZ/IVA (-0.06) or placebo (-0.02) groups; the LS mean treatment difference was −0.04 (95% CI: -0.15, 0.07; P = 0.4713).

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 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 was 4.0 % percentage points (95% CI: 3.1, 4.9; P<0.0001).

Consistent results 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), and baseline use of common CF medications (i.e., azithromycin and inhaled antibiotics, bronchodilators, corticosteroids, and hypertonic saline).

Figure below shows the Forest Plot of LS mean difference between treatments with 95% CI for absolute change from baseline in ppFEV1 through Week 24 by subgroup full Analysis Set.

Figure 8 Forest Plot of LS mean difference between treatments with 95% CI for absolute change from baseline in ppFEV1 through Week 24 by subgroup full Analysis Set

Overall	4.0(3.1, 4.8)
Age (<18 years)	3.9(2.2, 5.5)
Age (>=18 years)	4.0(3.1, 4.9)
Percent Predicted FEV1 at Baseline (<40)	3.5(1.0, 6.1)
Percent Predicted FEV1 at Baseline (>=40 to <70)	4.2(3.1, 5.2)
Percent Predicted FEV1 at Baseline (>=70)	3.7(2.2, 5.2)
Sex (Male)	4.4(3.3, 5.5)
Sex (Female)	3.5(2.4, 4.7)
Region (North America)	3.8(2.2, 5.3)
Region (Europe)	4.1(3.1, 5.0)
Use of Inhaled Antibiotic (Yes)	3.7(2.6, 4.7)
Use of Inhaled Antibiotic (No)	4.4(3.2, 5.7)
Use of Inhaled Bronchodilator (Yes)	3.8(2.9, 4.7)
Use of Inhaled Bronchodilator (No)	5.5(2.9, 8.0)
Use of Inhaled Hypertonic Saline (Yes)	3.7(2.6, 4.9)
Use of Inhaled Hypertonic Saline (No)	4.2(3.1, 5.4)
Use of Inhaled Corticosteroids (Yes)	3.6(2.5, 4.6)
Use of Inhaled Corticosteroids (No)	4.5(3.2, 5.8)
Use of Azithromycin (Yes)	3.8(2.7, 4.8)
Use of Azithromycin (No)	4.3(3.1, 5.5)
Colonization of Pseudomonas aeruginosa (Positive)	3.6(2.6, 4.5)
Colonization of Pseudomonas aeruginosa (Negative)	5.2(3.7, 6.7)

TEZ/IVA vs Placebo

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 (see table below).

Table 19 Study 108 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

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.

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).

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 percentage points (95% CI: 5.7, 7.8; P<0.0001) for the TEZ/IVA group and 4.7 percentage points (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 percentage points (95% CI: 1.2, 2.9; P<0.0001) in favour of TEZ/IVA (see table and figure below).

Table 20 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.

Figure 9 MMRM Analysis of Absolute Change From Study Baseline in ppFEV1 at Each Visit, Full Analysis Set
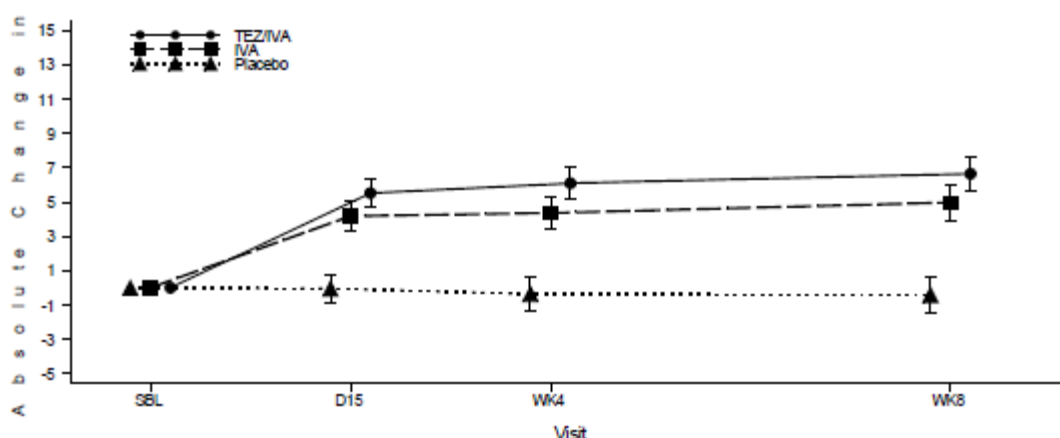
Source: Figure 14.2.1.1
CI: confidence interval; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; IVA: ivacaftor; LS mean: least squares mean; MMRM: mixed-effect model repeated measures; TEZ: tezacaftor; UN: unstructured
Notes: Analysis included all measurements up to Week 8, both on-treatment 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.

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 percentage points (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 percentage points (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. 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. 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: 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)

Absolute Change in Sweat Chloride from Study Baseline to the Average of Week 4 and Week 8: 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. 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/m2 for TEZ/IVA, 0.47 kg/m2 for IVA, and 0.18 kg/m2 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.

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, gender, 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 percentage points (95% CI: 9.3, 14.8) across subgroups (P<0.05). 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), see tables below.

Table 21 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
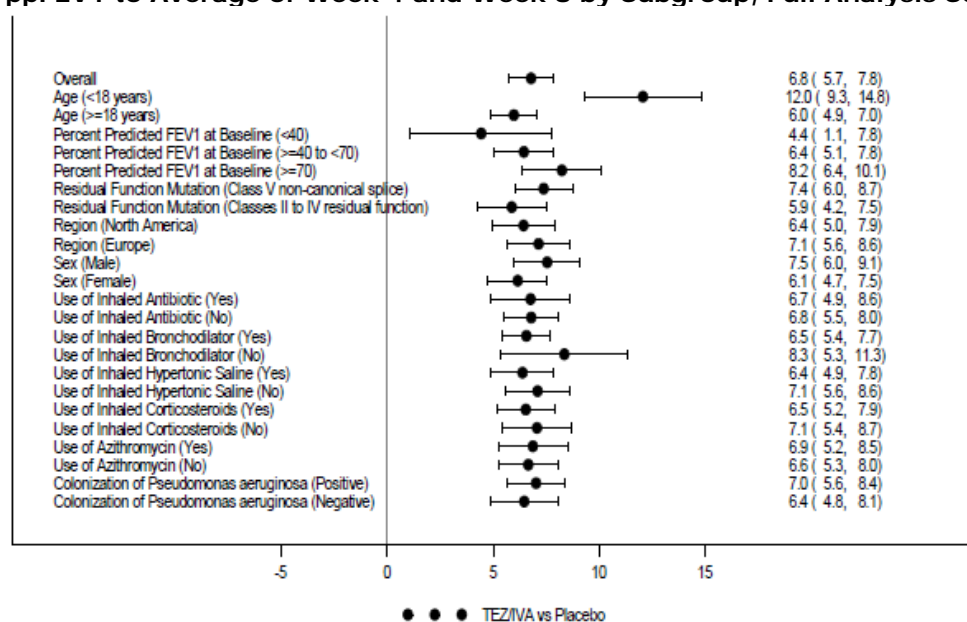
IVA: ivacaftor; ppFEV1: percent predicted forced expiratory volume in 1 second; LS: least squares; ppFEV1: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

Note: The forest plot is based on data from Table 14.2.1.2.1 and Table 14.2.1.2.3.

Table 22 Study 108 Subgroup Analysis for Absolute Change From Baseline in ppFEV1 at the Average of Week 4 and Week 8 Measurements for TEZ/IVA Compared to IVA, Full Analysis Set
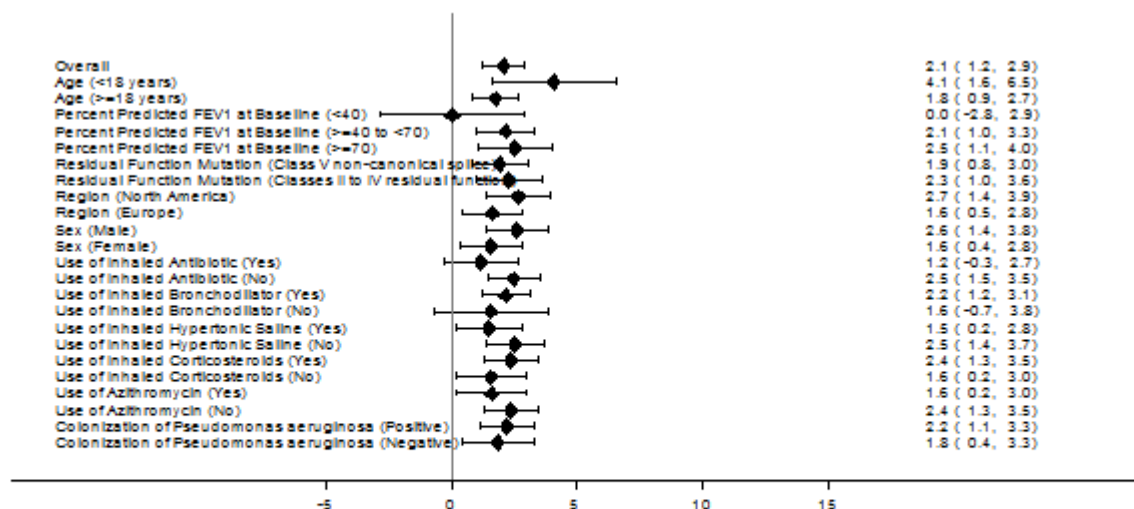
Source: Study 108 CSR/Figure 14.2.1.3

ppFEV1: percent predicted forced expiratory volume in 1 second; CI: confidence interval; IVA: ivacaftor; TEZ: tezacaftor

Notes: LS mean treatment differences (95% CI) in the subpopulations are presented.

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 percentage points (95% CI: 6.0, 8.7; P <0.0001). The treatment effect for the splice mutation subgroup compared to IVA monotherapy was 1.9 percentage points (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 in table below.

Table 23 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	IVA/TEZ
2789+5G->A	N Mean (SD) Median Min, Max Mean Diff vs Placebo, 95% CI	160 -0.4 (5.9) -0.3 -23.8, 24.0	28 5.1 (6.4) 5.4 -7.1, 17.0 5.6 (3.2, 8.0)	25 8.6 (5.6) 8.8 -1.5, 23.4 9.0 (6.5, 11.5)
3272-26A->G	N Mean (SD) Median Min, Max Mean Diff vs Placebo, 95% CI	160 -0.4 (5.9) -0.3 -23.8, 24.0	23 3.5 (6.6) 4.5 -9.1, 16.0 3.9 (1.2, 24.0)	23 5.7 (6.9) 5.3 -2.1, 25.9 6.1 (3.5, 8.8)
3849+10kbC->T	N Mean (SD) Median Min, Max Mean Diff vs Placebo, 95% CI	160 -0.4 (5.99 -0.3 -23.8, 24.0	40 5.1 (5.9) 4.3 -6.8, 16.3 5.5 (3.5, 7.6)	43 5.8 (6.3) 5.0 -7.2, 22.3 6.2 (4.2, 8.2)
711+3A->G	N Mean (SD) Median Min, Max Mean Diff vs Placebo, 95% CI	160 -0.4 (5.9) -0.3 -23.8, 24.0	2 9.2 (0.5) 9.2 8.9, 9.6 9.6 (1.4, 17.9)	2 4.3 (3.4) 4.3 2.0, 6.7 4.8 (-3.5, 13.0)
A455E	N Mean (SD) Median Min, Max Mean Diff vs Placebo, 95% CI	160 -0.4 (5.9) -0.3 -23.8, 24.0	14 3.7 (7.5) 1.2 -6.6, 19.7 4.1 (0.8, 7.5)	11 8.5 (4.3) 9.3 2.6, 16.1 9.0 (5.4, 12.5)
D110H	N Mean (SD) Median Min, Max Mean Diff vs Placebo, 95% CI	160 -0.4 (5.9) -0.3 -23.8, 24.0	0 - - - -	1 -1.0 (-) -1.0 -1.0, -1.0 -0.6 (-12.2, 11.1)
D1152H	N Mean (SD) Median Min, Max Mean Diff vs Placebo, 95% CI	160 -0.4 (5.9) -0.3 -23.8, 24.0	15 2.4 (4.3) 1.8 -5.0, 10.2 2.8 (-0.2, 5.9)	21 3.8 (3.9) 3.0 -2.5, 12.5 4.2 (1.6, 6.8)
D579G	N Mean (SD)	160 -0.4 (5.9)	2 13.3 (1.2)	2 8.1 (11.7)

	Median Min, Max Mean Diff vs Placebo, 95% CI	-0.3 -23.8, 24.0	13.3 12.4, 14.1 13.7 (5.5, 22.0)	8.1 -0.2, 16.4 8.5 (0.2, 16.9)
E831X	N Mean (SD) Median Min, Max Mean Diff vs Placebo, 95% CI	160 -0.4 (5.9) -0.3 -23.8, 24.0	1 7.1 (-) 7.1 7.1, 7.1 7.5 (-4.2, 19.1)	0 - - - -
L206W	N Mean (SD) Median Min, Max Mean Diff vs Placebo, 95% CI	160 -0.4 (5.9) -0.3 -23.8, 24.0	2 4.2 (2.4) 4.2 2.5, 5.9 4.6 (-3.6, 12.8)	4 3.0 (7.5) 3.2 -4.5, 10.2 3.4 (-2.5, 9.3)
P67L	N Mean (SD) Median Min, Max Mean Diff vs Placebo, 95% CI	160 -0.4 (5.9) -0.3 -23.8, 24.0	12 4.3 (7.7) 1.6 -2.5, 25.7 4.7 (1.2, 8.3)	11 9.4 (10.4) 5.8 0.0, 31.9 9.8 (6.0, 13.7)
R1070W	N Mean (SD) Median Min, Max Mean Diff vs Placebo, 95% CI	160 -0.4 (5.9) -0.3 -23.8, 24.0	1 2.9 (-) 2.9 2.9, 2.9 3.3 (-8.3, 15.0)	2 6.1 (5.8) 6.1 2.0, 10.1 6.5 (-1.8, 14.7)
R117C	N Mean (SD) Median Min, Max Mean Diff vs Placebo, 95% CI	160 -0.4 (5.9) -0.3 -23.8, 24.0	1 3.5 (-) 3.5 3.5, 3.5 3.9 (-7.7, 15.6)	1 2.9 (-) 2.9 2.9, 2.9 3.3 (-8.3, 15.0)
R347H*	N Mean (SD) Median Min, Max Mean Diff vs Placebo, 95% CI	160 -0.4 (5.9) -0.3 -23.8, 24.0	3 2.5 (3.9) 1.3 -0.6, 6.9 2.9 (-3.8, 9.7)	2 -0.5 (3.1) -0.5 -2.8, 1.7 -0.1 (-8.4, 8.1)
R352Q	N Mean (SD) Median Min, Max Mean Diff vs Placebo, 95% CI	160 -0.4 (5.9) -0.3 -23.8, 24.0	2 4.4 (1.3) 4.4 3.5, 5.3 4.8 (-3.4, 13.1)	2 4.9 (3.2) 4.9 2.6, 7.1 5.3 (-3.0, 13.5)
S945L	N Mean (SD) Median Min, Max Mean Diff vs Placebo, 95%	160 -0.4 (5.9) -0.3 -23.8, 24.0	9 8.8 (7.9) 5.9 -0.2, 20.5 9.2 (5.1, 13.2)	7 9.6 (7.7) 5.4 0.7, 19.5 10.0 (5.5, 14.6)

	CI			
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)
*R347H-CFTR mutation excluded from the indication based on an in vitro increase in chloride transport below the pre-defined threshold of 10%.				

Upon request of CHMP, individual subject-level data from Study 108 were presented in box-and-whisker plots (including jitters) by mutation for ppFEV1 and sweat chloride. The plots demonstrated the variability in response between subjects with the same mutation (see figure below).

Figure 10 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

Figure 1   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
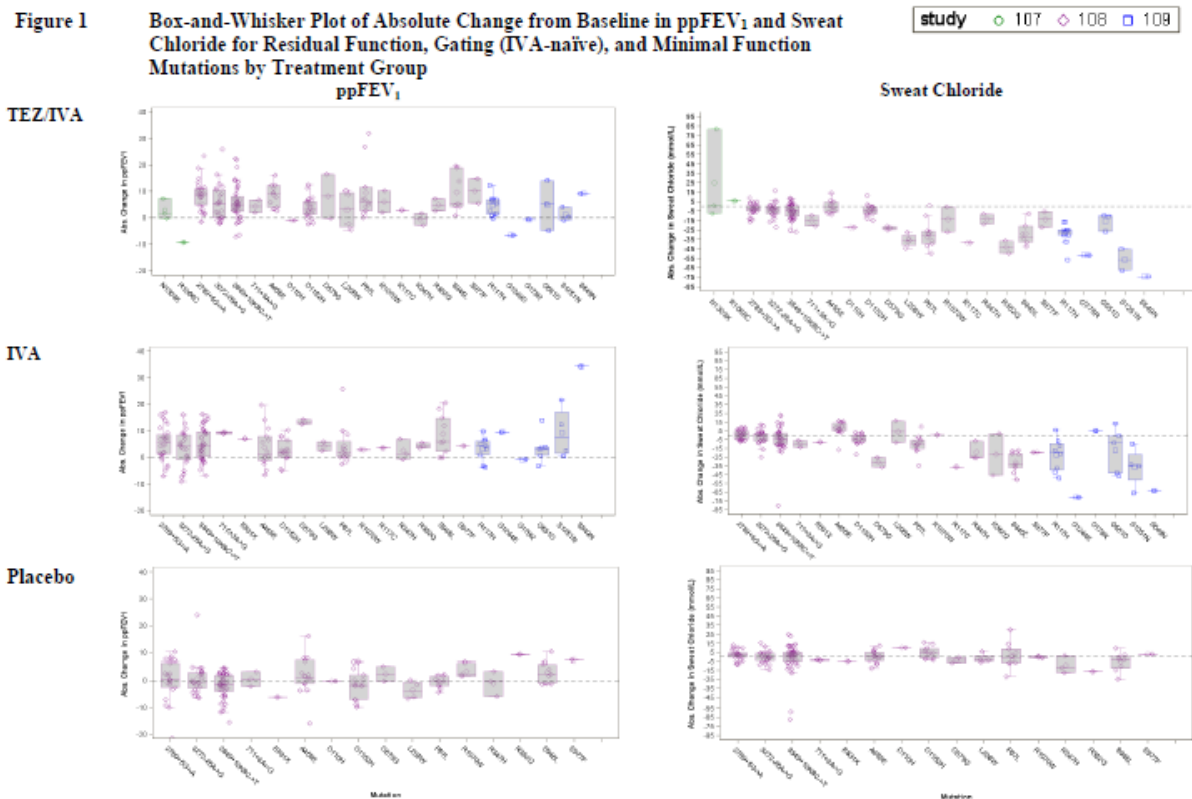
Sources: Ad hoc Figures 14.2.2.15, 14.2.2.16, 14.2.3.15, 14.2.3.16, 14.2.2.17, and 14.2.3.17.
Notes: Each marker represents an individual subject. Plots include all mutations with clinical data available in Study 108, 2 minimal function mutations from Study 107, and all mutations with clinical data available 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).

Mixed model

At request of the CHMP, mixed models to describe the between- and within-mutation variance and investigate the possibility to predict generalisation to mutations not enrolled in study 108 were 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 was 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.

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 24 Summary of efficacy for trial VX14-661-106

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		
Design	Randomized, double-blind, placebo-controlled, parallel-group, multicenter study in subjects 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 in 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	
	Placebo	0 mg TEZ/0 mg IVA daily for 24 weeks + 0 mg IVA daily for 24 weeks	
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 through Week 24
	Key Secondary	BMI	Absolute change in BMI from baseline at Week 24 (kg/m2)
	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
	BMI	0.12	0.18
	SD	0.05	0.05
	CFQ-R	-0.1	5.0
	SD	0.8	0.8

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 endpoint	Comparison groups	TEZ/IVA versus placebo
		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. Most of them 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 25 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		
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:	2 Treatment Periods (8 weeks each), and Washout Period (8 weeks),	
	Duration of Run-in phase:	not applicable	
	Duration of Extension phase:	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 groups each 8 weeks, N=165	
	Ivacaftor	2 groups each weeks, N=164	
	Tezacaftor/ivacaftor	2 groups each 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	**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. 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 pp (95% CI: 6.0, 8.7; P <0.0001). The treatment effect for the splice mutation subgroup compared to IVA monotherapy was 1.9 pp (95% CI: 0.8, 3.0; P = 0.0008), confirming the contribution of TEZ in this sub-population.

In all phase 3 studies together, there were 6 patients over 65 years of age at screening.

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. 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 status (documented within two years prior to enrolment into the pivotal studies).

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 MAH, 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 (Interim analysis 1, IA1, 70% patients analysed)

Study VX14-661-110 (study 110) is an open-label rollover study that enrolled subjects from the Phase 2 and 3 studies of TEZ/IVA. An interim analysis (IA1, dated 6 March 2017) was submitted at the time of MAA. A second interim analysis (IA2) was submitted upon CHMP's request.

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 will 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 study 108. Subjects in the Observational Cohort did not receive study drug. A schematic of the study design is shown in figure below.

Figure 11 Study design VX14-661-110
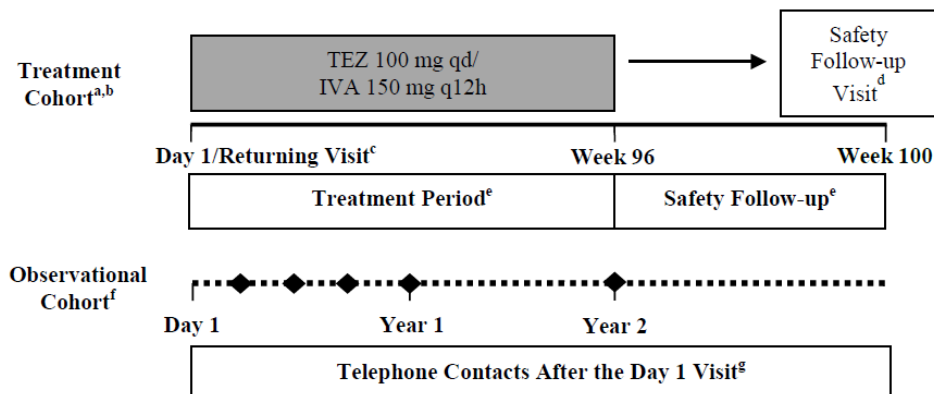
IVA: ivacaftor; q12h: every 12 hours; qd: daily; TEZ: tezacaftor
Notes: All subjects received a TEZ 100-mg/IVA 150-mg fixed-dose combination tablet qd in the morning and an IVA 150-mg tablet qd in the evening.

The primary objective of study 110 is to evaluate the long-term safety and tolerability of TEZ in combination with IVA in subjects with CF, homozygous or heterozygous for the *F508del-CFTR* mutation who are in the Treatment Cohort. Secondary objective was to evaluate the long-term efficacy of TEZ in combination with IVA for subjects in the Treatment Cohort.

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. The Efficacy Analysis Populations for all efficacy analyses except the PEx analyses were: Study 106/110 Efficacy Set (ES) and Study 108/110 ES. They included all subjects who entered the Treatment Cohort of Study 110. Treatment groups for data presentations are defined in table below.

Table 26 Study 110 Efficacy Analysis Population and Treatment Group Assignments

Analysis Population Name	Treatment Group	Description
Study 106/110 ES	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 ES	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-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

ES: Efficacy Set; IVA: ivacaftor (VX-770); PBO: placebo; PEx: pulmonary exacerbation; TEZ: tezacaftor (VX-661)

The PEx efficacy analysis populations for the PEx analysis were: Study 106/110 Pulmonary Exacerbation (PE) Analysis Set and Study 108/110 PE Analysis Set. They included subjects who received TEZ/IVA during either the parent study or during Study 110. Treatment groups for data presentations are defined in table below.

Table 27 PEx Efficacy Analysis Populations and Treatment Group Assignments

Analysis Population Name	Treatment Group	Description
Study 106/110 PE Analysis Set	TEZ/IVA	Subjects randomized to TEZ/IVA in Study 106 and received treatment.
	PBO-TEZ/IVA	Subjects randomized to placebo in Study 106 and who received TEZ/IVA in Study 110.
Study 108/110 PE Analysis Set	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 were also 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 were also included in this group if they received treatment in Period 1.

IVA: ivacaftor (VX-770); PBO: placebo; PEx: pulmonary exacerbation; TEZ: tezacaftor (VX-661)

The PEx Analysis Period for subjects from Studies 106 and 108 who enrolled in Study 110 is represented by the shaded portion in figure below.

Table 28 PEx Analysis Period for Subjects who Enrolled in Study 110

Subjects From Study 106		
TEZ/IVA DB	TEZ/IVA OLE	
Placebo DB	TEZ/IVA OLE	
Subjects From Study 108		
TEZ/IVA DB P1	IVA DB P2	TEZ/IVA OLE
IVA DB P1	TEZ/IVA DB P2	TEZ/IVA OLE
TEZ/IVA DB P1	Placebo DB P2	TEZ/IVA OLE
Placebo DB P1	TEZ/IVA DB P2	TEZ/IVA OLE
IVA DB P1	Placebo DB P2	TEZ/IVA OLE
Placebo DB P1	IVA DB P2	TEZ/IVA OLE

Source: Study 110/SAP v2.0/Section 8.2.2
DB: double-blind; P1: Treatment Period 1; P2: Treatment Period 2; OLE: Open-label Extension (Study 110); PEx: pulmonary exacerbation
Note: Shaded text represents the PEx Analysis Period for subjects from Studies 106 and 108 who enrolled in Study 110.

Continuous endpoints during the Study 110 Analysis Period were analysed using a separate MMRM for subjects in the Study 110 analysis population. However, the MMRM analysis for the Study 110 Analysis Period was restricted to the last visit at which the total number of subjects still on study was approximately 70% of the subjects from the parent study (Studies 106 or 108). The MMRM was used for the following analyses:

- Absolute change from baseline in percent predicted forced expiratory volume in 1 second (ppFEV1)

- Relative change from baseline in ppFEV1

- Absolute change from baseline in BMI

- Absolute change from baseline in CFQ-R respiratory domain score

- Absolute change from baseline in body weight

The efficacy analysis baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to the first dose of study drug in the parent studies for all subjects, except for subjects randomized to the placebo arm in Study 106. The efficacy analysis baseline for subjects randomized to the Study 106 placebo arm was defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to the first dose of study drug in Study 110. The parent study baseline was used to calculate the absolute and relative change from baseline unless otherwise specified.

Study 110 was not designed or powered to assess the difference of TEZ/IVA effects for subjects transitioning from the various treatments in Study 106 or 108 to TEZ/IVA in Study 110. All *P* values provided for within-group changes are therefore nominal.

Results

Subject disposition

At the time of the interim analysis 1 (IA1) data cut (06 March 2017), 870 subjects were enrolled and 867 subjects had received at least 1 dose of TEZ/IVA in the Study 110 Treatment Cohort from the

following parent studies: 23 subjects from Study 103, 462 subjects from Study 106, 159 subjects from Study 107, and 223 subjects from Study 108. No subjects were enrolled in the Observational Cohort at the time of IA1. Overall subject disposition for the Study 110 Treatment Cohort is summarized in table below.

Table 29 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 867 subjects who received at least 1 dose of study drug in Study 110, 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 AEs (0.7%) or discontinued the study due to AEs (0.5%) were low. The total number of subjects with data was approximately 70% of subjects in the Efficacy Set (ES) for the respective parent study (Study 106/110 ES or Study 108/110 ES).

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).

Demographics and baseline characteristics

Baseline demographics and disease characteristics are provided in IA1 for 459 subjects in Study 106/110 ES. Out of these, 231 were subjects randomised to placebo in the parent study 106 (PCBO-TEZ/IVA group) and 228 were randomised to TEZ/IVA in the parent study (TEZ/IVA group). In Study 108/110 ES, data are provided for a total of 222 subjects distributed as follows: 78 in the PBO-TEZ/IVA group, 69 subjects in the IVA-TEZ/IVA group, and 75 subjects in the TEZ/IVA group. The baseline demographic and disease characteristics data presented below were derived from Study 106 and study 108.

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/m2 (range: 13.67, 32.24).

In the 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/m2 (range: 15.19, 49.65). The most common medical history and prior medications used were consistent with the expectations for a population with CF. The different disease phenotype of both study populations (e.g., most subjects with residual function mutations are pancreatic sufficient when compared to patients homozygous for *F508del*) is reflected by these data.

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.

- **Outcomes and estimation of efficacy variables (secondary endpoints, IA1)**

At the time of data cut for IA1, approximately 70% of subjects that rolled over from Study 106 had completed the Week 24 Visit in Study 110 and approximately 70% of subjects that rolled over from Study 108 had completed the Week 16 Visit in Study 110.

Absolute change in ppFEV1 from baseline: For subjects who received placebo in study 106, the within-group mean absolute change in ppFEV1 from study 110 baseline at Week 24 of Study 110 was 4.5 percentage points (95% CI: 3.3, 5.7; nominal P<0.0001) compared to 3.4 pp at week 24 of study 106 in the TEZ/IVA group. For subjects randomised to TEZ/IVA in study 106, at Week 24 of study 110, the within-group mean absolute change in ppFEV1 from study 106 baseline was 3.1 pp (95% CI: 1.9, 4.3; nominal P<0.0001) after 48 weeks treatment in total.

For subjects who received placebo in Period 2 of Study 108 (PCBO-TEZ/IVA group), at Week 16 of study 110 the within-group mean absolute change in ppFEV1 from study 108 baseline was 4.6 pp (95% CI: 2.9, 6.3; nominal P <0.0001) compared to 6.5 pp at week 24 of study 108 in the TEZ/IVA group. For subjects who received TEZ/IVA in Study 108 Period 2, the within-group mean absolute change in ppFEV1 from study 108 baseline at Week 16 of study 110 was 5.9 pp (95% CI: 4.1, 7.7; nominal P<0.0001) in the IVA-TEZ/IVA group and 7.4 pp (95% CI: 5.6, 9.1; nominal P<0.0001) in the
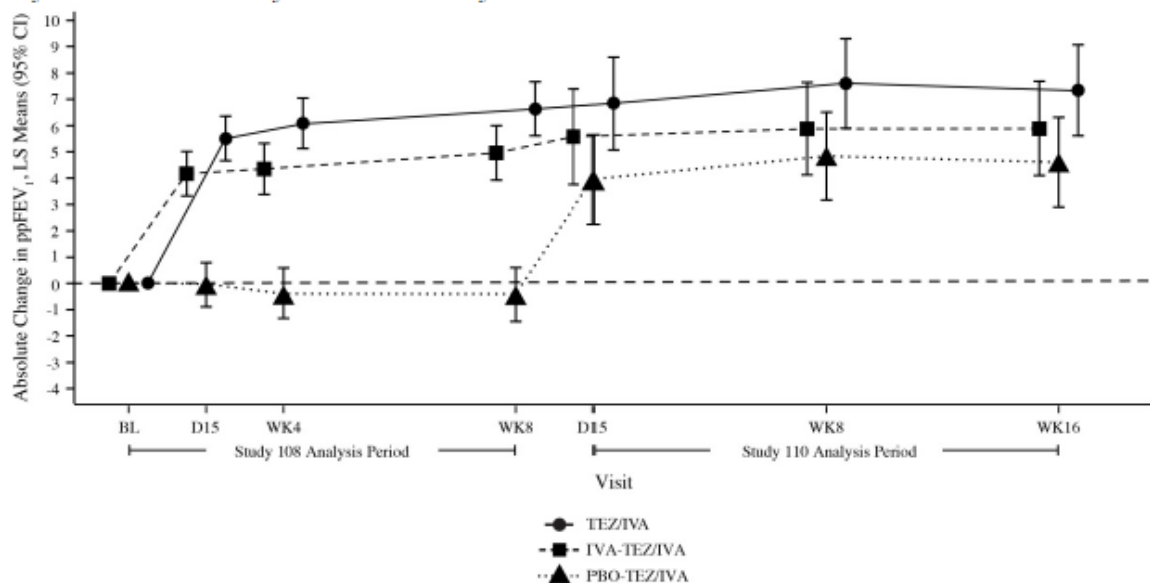
TEZ/IVA group. Results from MMRM analysis of the absolute change from baseline in ppFEV1 are shown in figures below for both efficacy sets of study 110.

Figure 12 Results from MMRM analysis of the absolute change from baseline in ppFEV1

A) Study 106 FAS and Study 106/110 Efficacy Set
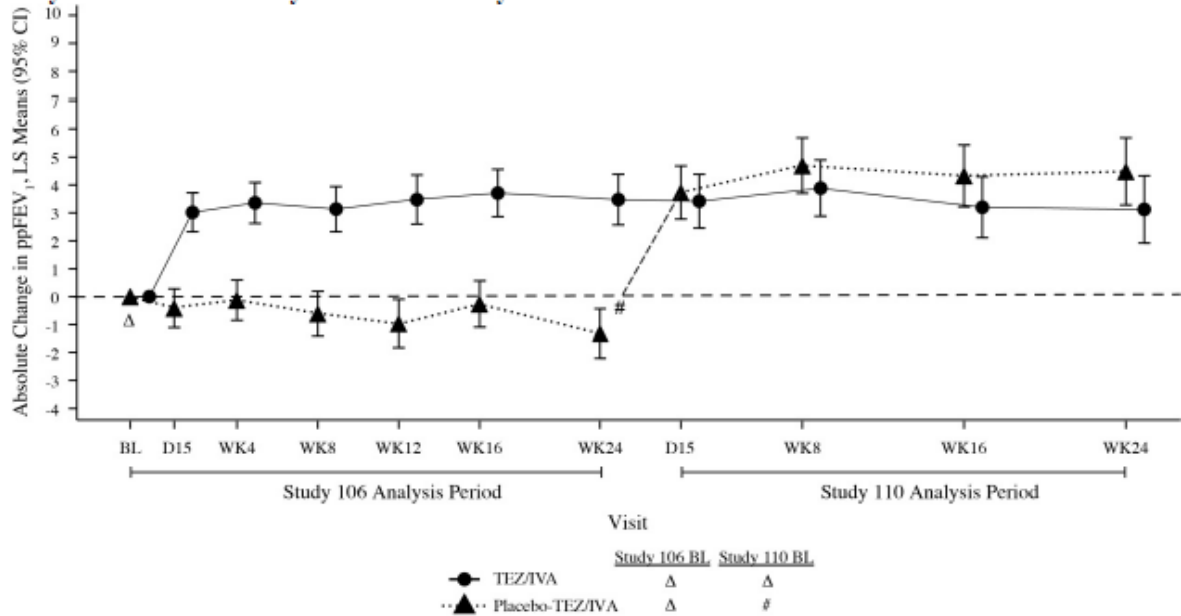
B) Study 108 FAS and Study 108/110 Efficacy Set

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

Number of Pulmonary Exacerbations: Tables below show the results of pulmonary exacerbations for both PEx efficacy analysis populations.

Table 30 Results of pulmonary exacerbations for both PEx efficacy analysis populations (106/110 and 108/110)

	Study 106/110		Study 108/110		
	PBO-TEZ/IVA	TEZ/IVA	PBO-TEZ/IVA	IVA-TEZ/IVA	TEZ/IVA
Endpoint	N = 231	N = 248	N = 80	N = 75	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.

Subjects in the 106/110 PE analysis set who received placebo in Study 106 had an estimated event rate per year of PEx of 0.58 (95% CI: 0.44, 0.75) in Study 110 that was lower than the event rate in the placebo (0.99) and TEZ/IVA groups (0.64) in Study 106. Subjects in the 106/110 PE analysis set who received TEZ/IVA in Study 106 maintained an estimated annualised event rate of pulmonary

exacerbations of 0.72 (95% CI: 0.59, 0.88) that was slightly higher than the event rate observed at week 24 of study 106 (0.64) and lower than the event rate per year of PEx in the placebo group in Study 106 (0.99).

Subjects in the 108/110 PE analysis set who received placebo in Study 108 had a similar estimated event rate of PEx per year (0.34, [95% CI: 0.19, 0.61]) in Study 110 than the estimated event rate at week 8 of study 108 in the TEZ/IVA group (0.34). The event rate was lower than the one estimated in the PCBO group at week 8 of study 108 (0.63). Subjects in the IVA-TEZ/IVA group of the Study 108/110 PE Analysis Set had a higher estimated event rate per year of pulmonary exacerbations (0.39 [95% CI: 0.22, 0.70]) than the IVA group at week 8 of study 108 (0.29). Subjects in the 108/110 PE analysis set who received TEZ/IVA in Study 108 had a lower PEx event rate per year in Study 110 (0.20, [95% CI: 0.10, 0.39]) than during Study 108 (0.34).

Regarding PEx that require IV antibiotic therapy, for subjects in the PCBO-TEZ/IVA group of the Study 106/110 PE Analysis Set, the event rate was decreased from 0.54 in study 106 to 0.27 (95% CI: 0.19, 0.40). Subjects in the TEZ/IVA group of the Study 106/110 PE Analysis Set had a higher estimated event rate per year (0.39 [95% CI: 0.22, 0.70]) than in study 106 (0.29). 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).

Time-to-first pulmonary exacerbation: For subjects who received placebo in Study 106, the estimated exacerbation-free probability at Week 24 in Study 110 was 0.75 (95% CI: 0.68, 0.81), which was higher than the estimated exacerbation-free probability at Week 24 of Study 106 in the placebo group (0.65) and similar to the estimated exacerbation-free probability at Week 24 of Study 106 for subjects who received TEZ/IVA (0.75). 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 0.60 (95% CI: 0.53, 0.66) after 48 weeks of TEZ/IVA treatment.

For subjects who received the first dose of TEZ/IVA in Study 110, the estimated exacerbation-free probability at Week 16 of the PE Analysis Period (reflecting 16 weeks of treatment in Study 110) was 0.88 (95% CI: 0.78, 0.94) in the PBO-TEZ/IVA group and 0.83 (95% CI: 0.71, 0.90) in the IVA-TEZ/IVA group. 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 0.86 (95% CI: 0.75, 0.92) after 24 weeks of TEZ/IVA treatment.

Absolute change from baseline in BMI: For subjects who received placebo in Study 106, the within-group change in BMI from study 110 baseline was 0.26 kg/m2 (95% CI: 0.12, 0.40) at Week 24 of Study 110 compared to 0.18 kg/m2 at Week 24 of Study 106 in the TEZ/IVA group. For subjects who received TEZ/IVA in Study 106, the within-group change in BMI from study 106 baseline was 0.26 kg/m2 (95% CI: 0.12, 0.39) at Week 24 of Study 110.

In response to the CHMP's request, the MAH provided an analysis of change from baseline for undernourished subjects and an analysis of undernourished subjects who met or exceeded a target BMI. At week 24 of study 110, the LS mean change from study 110 baseline in BMI in undernourished subjects in the PCBO-TEZ/IVA group was 0.73 (Min, Max: -2.77, 2.86) while in the TEZ/IVA group the LS mean change from study 106 baseline was 0.38 (Min, Max: -1.25, 2.40). The responder analysis showed that the percentage of undernourished subjects who met or exceeded the target BMI at Week 24 was 35.2% in the PCBO-TEZ/IVA group versus 33.8% in the TEZ/IVA group.

Figure below shows the MMRM analyses of absolute change from baseline in BMI (kg/m2) at each visit, Study 106 FAS and Study 106/110 ES.

Figure 13 MMRM analyses of absolute change from baseline in BMI (kg/m2) at each visit, Study 106 FAS and Study 106/110 ES
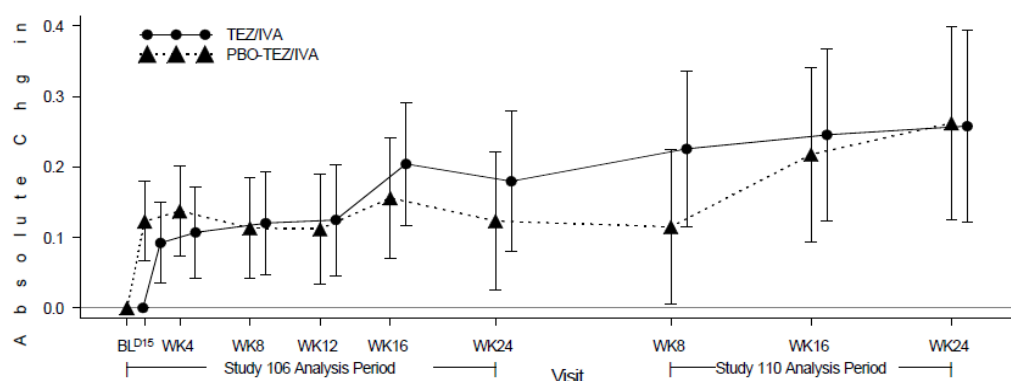
Source: Figure 14.2.3.1.1

Notes: The MMRM analysis for the Study 110 analysis period was performed on the Study 106/110 ES and was restricted to the last visit at which the total number of subjects with data was approximately 70% of subjects in the Study 106/110 ES. BL was generally defined as the last non-missing measurement before the first dose of study drug in Study 106; however, changes during the Study 110 analysis period for subjects in the PBO-TEZ/IVA group were based on the Study 110 BL (most recent non-missing measurement before the first dose of study drug in Study 110); the Study 110 BL time point is not depicted in the figure.

For subjects who received placebo in Period 2 of Study 108, the within-group change in BMI from study 108 baseline was 0.52 kg/m2 (95% CI: 0.21, 0.83) at Week 16 of Study 110 compared to 0.34 kg/m2 at Week 8 of Study 108 in the TEZ/IVA group. For subjects who received IVA in Period 2 of Study 108, the within-group change in BMI from study 108 baseline was 0.60 kg/m2 (95% CI: 0.27, 0.93) at Week 16 of Study 110. For subjects who received TEZ/IVA in Period 2 of Study 108, the within-group change in BMI from study 108 baseline was 0.74 kg/m2 (95% CI: 0.43, 1.06) at Week 16 of Study 110.

Absolute change from baseline in weight: For subjects who received placebo in Study 106, the within-group change in weight from study 110 baseline was 1.0 kg (95% CI: 0.6, 1.4) at Week 24 of Study 110 compared to 0.7 kg at Week 24 of Study 106 in the TEZ/IVA group. For subjects who received TEZ/IVA in Study 106, the within-group change in weight from study 106 baseline was 1.2 kg (95% CI: 0.8, 1.6) at Week 24 of Study 110. For subjects who received placebo in Period 2 of Study 108, the within-group change in weight from study 108 baseline was 1.7 kg (95% CI: 0.8, 2.6) at Week 8 of Study 108 compared to 1.0 kg at Week 8 of Study 108 in the TEZ/IVA group. For subjects who received IVA in Period 2 of Study 108, the within-group change in weight from study 108 baseline was 2.1 kg (95% CI: 1.1, 3.1) at Week 16 of Study 110. For subjects who received TEZ/IVA in Period 2 of Study 108, the within-group change in weight from study 108 baseline was 2.3 kg (95% CI: 1.4, 3.3) at Week 16 of Study 110.

Absolute Change in the CFQ-R Respiratory Domain Score: Subjects in the PBO-TEZ/IVA group who began receiving TEZ/IVA in Study 110 showed at Week 24 of Study 110, a within-group mean absolute change in CFQ-R respiratory domain score from study 110 baseline of 3.3 points (95% CI: 0.8, 5.7) compared to 5.5 points in the TEZ/IVA group at week 24 of study 106. For subjects in the TEZ/IVA group at Week 24 of Study 110, the mean absolute change from study 106 baseline in CFQ-R respiratory domain score was 3.1 points (95% CI: 0.6, 5.5).

Subjects in the PBO-TEZ/IVA group who received placebo in Period 2 of Study 108 showed at Week 16 of Study 110, a within-group change in the mean absolute change in CFQ-R respiratory domain score from study 108 baseline of 10.8 points (95% CI: 6.9, 14.7) compared to 10.1 points in the TEZ/IVA group at the average of week 4 and week 8 in study 108. At Week 16 of Study 110, the LS mean

absolute change from study 108 baseline in CFQ-R respiratory domain score was 11.0 points (95% CI: 6.8, 15.1) in the IVA-TEZ/IVA group and 9.9 points (95% CI: 6.0, 13.9) in the TEZ/IVA group.

- **Outcomes and estimation of efficacy variables (secondary endpoints, IA2)**

With the responses to the CHMP's request during the evaluation, a second interim analysis (IA2) of study 110 was submitted. In this second interim analysis (IA2), baseline is defined as the last non-missing assessment before the first dose of TEZ/IVA in Study 110 for all "treatment" groups while in the first interim analysis (IA1) the parent study baseline was used to calculate the absolute change from baseline in continuous variables, except for subjects randomized to the placebo arm in Study 106. In IA1, for placebo subjects in the parent study 106, the efficacy analysis baseline was defined as the most recent non-missing measurement collected prior to the first dose of study drug in Study 110.

The start of the PEx Analysis Period for subjects from Studies 106 and 108 who enrolled in Study 110 was similar. The only difference between IA1 and IA2 for the PE Analysis Sets was the duration of exposure to TEZ/IVA which was longer at the time of IA2 (as the data cut for IA2 was on 14 November 2017 and the data cut for IA1 was on 06 March 2017).

For F/F subjects from parent study 106, the results (expressed as mean within-group changes [95% CI] for all variables except for pulmonary exacerbations) were as follows:

At Week 24 of Study 110, the LS mean absolute change from baseline in ppFEV1 for subjects in PBO-TEZ/IVA group was 4.2 pp (3.3, 5.1) while for subjects in the TEZ/IVA group the mean change was −0.2 pp (-1.1, 0.7). For adolescents subjects (less than 18 years old), these figures were 5.3 pp (3.9, 6.8) and -0.8 (-2.3, 0.7) in the PCBO-TEZ/IVA and TEZ/IVA groups, respectively.

The estimated event rate per year of PEx was 0.65 (0.52, 0.80) and 0.72 (0.60, 0.87) in PBO-TEZ/IVA and TEZ/IVA groups, respectively. The estimated evet rate per year of pulmonary exacerbations that require intravenous therapy was 0.32 (0.24, 0.42) in the PCBO-TEZ/IVA group and 0.35 (0.27, 0.45) in the TEZ/IVA group.

The change in BMI was 0.23 kg/m2 (0.11, 0.34) in the PBO-TEZ/IVA group, and 0.00 kg/m2 (-0.11, 0.11) in the TEZ/IVA group, while the change in weight was 0.9 kg (0.5, 1.2) in the PBO-TEZ/IVA group, and 0.2 kg (-0.1, 0.6) in TEZ/IVA group.

The change in BMI z-score restricted to adolescent subjects was 0.10 (0.00, 0.19) and -0.04 (-0.13, 0.06) in the in the PCBO-TEZ/IVA and TEZ/IVA groups, respectively. Regarding weight z-score, these figures were 0.06 (-0.01, 0.14) and -0.02 (-0.09, 0.05).

The change in CFQ-R was 3.3 points (1.4, 5.3) in the PBO-TEZ/IVA group, and 0.4 points (-1.3, 2.4). 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 sustained through 24 weeks of additional TEZ/IVA treatment in Study 110 (48.6%).

For F/RF subjects from parent study 108, the results (expressed as mean within-group changes [95% CI] for all variables except for pulmonary exacerbations) were as follows:

At Week 16 of Study 110, the LS mean absolute change from baseline in ppFEV1 for subjects in PBO-TEZ/IVA group was 4.9 pp (3.7, 6.2), for subjects in the IVA-TEZ/IVA group this value was 2.4 pp (1.1, 3.7) and 0.0 (-1.2, 1.3) for subjects in the TEZ/IVA group. These figures for adolescent subjects were as follows: 7.2 (4.8, 9.7), 1.6 (-1.5, 4.8), and 0.7 (-2.2, 3.6) respectively.

The change in the respiratory domain of CFQ-R was 8.1 points (18.7) in the PBO-TEZ/IVA group while in the IVA-TEZ/IVA group it was 3.9 points (0.6, 6.5) and 4.4 points (1.2, 7.6) in TEZ/IVA group. 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%).

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

The change in BMI was 0.35 kg/m2 (0.14, 0.56) in the PBO-TEZ/IVA group, 0.15 kg/m2 (-0.07, 0.38), in the IVA-TEZ/IVA group and 0.54 kg/m2 (0.32, 0.76) in TEZ/IVA group. Mean changes in body weigth were 1.0 kg (0.5, 1.6), 0.6 (0.0, 1.2), and 1.5 (0.9, 2.1) in the PBO-TEZ/IVA, IVA-TEZ/IVA, and TEZ/IVA groups respectively. Analysis of within-group changes in BMI z-scores in adolescent subjects show the following results: 0.04 (-0.07, 0.14), -0.13 (-0.26, 0.01), and 0.16 (0.04, 0.28) in the PCBO-TEZ/IVA, IVA-TEZ/IVA, and TEZ/IVA groups respectively. Regarding the within-group mean change in weigth z-score, these figures were as follows 0.02 (-0.09, 0.12), -0.06 (-0.20, 0.08), and 0.13 (0.01, 0.26) respectively.

The MAH was requested to contextualise the results of change in ppFEV1 and rate of pulmonary exacerbations in patients with cystic fibrosis with the mutations of interest. To that end, two sets of data were provided.

The rate of decline in ppFEV1 was retrospectively analysed by Sawicki et al. (2017) in the Cystic Fibrosis Foundation Patient Registry (CFFPR). Patients in the CFFPR from 2006 to 2014 with a residual function mutation heterozygous for *F508del* were compared to patients homozygous for *F508del* *(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.)*. Residual function mutations were identified based on clinical or *in vitro* evidence of residual ion transport. Annual rates of ppFEV1 decline were estimated over 2-year periods using all available measurements using the 2012 Global Lung Initiative equations. In homozygous *F508del* subjects the estimated annual rate of decline in ppFEV1 overall (subjects aged 6 years or older) was −1.91 (SE, 0.05), with the most rapid rate of decline observed in the 18-24 year group (−2.52 [0.09]). For heterozygous subjects (excluding those with an *R117H-CFTR* mutation), the estimated annual rate of decline in ppFEV1 overall (subjects aged 6 years or older) was −1.05 (0.39). Similarly, the most rapid rate of decline was observed in the young adult group (−1.85 [SE not provided]). In the 13-17 year group the annual rate of decline in ppFEV1was −2.37 (*F508del* homozygous subjects) and −0.57 (heterozygous subjects excluding those with an *R117H-CFTR* mutation).

Regarding the natural history data of pulmonary exacerbations, the MAH provided unpublished data on the rate of these events from the CFF Patient Registry. The definition of pulmonary exacerbation as used in the registry, i.e. requiring IV antibiotics or hospitalization was used to compare the rate of pulmonary exacerbations leading to hospitalization or IV antibiotic treatment from Studies 106/110 and 108/110 at the time of IA2 to the natural history data. The annual risk of PEx from CFF Registry data are provided in table below.

Table 31 Prevalence of pulmonary exacerbations from 2012to 2014 among CF patients for homozygous for F508del or heterozygous for F508del with an RF mutation aged >12 years

Year	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]	
	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

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 (NR) to TEZ and/or IVA therapy. TEZ 100 mg once daily qd)/IVA 150 mg q12h was administered for up to 12 weeks.

The rationale for designating NR second allele mutations is based on the following:

- biologic plausibility due to a predicted lack of full-length CFTR protein (e.g., nonsense, noncanonical splice, and frameshift mutations)

- evidence of clinical severity on a population basis based on the patient registry CFTR2 (average sweat chloride >86 mmol/L, percentage of patients with pancreatic insufficiency [%] is >50%), and

- *in vitro* testing (mutations that responded with chloride transport <10% of wild-type CFTR were considered minimal function and NR).

Efficacy Results
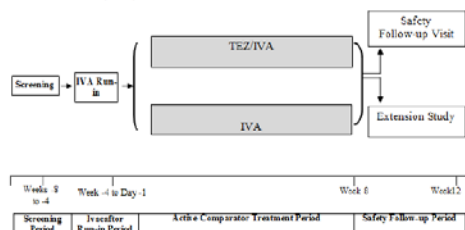
The LS mean treatment difference for the absolute change from baseline in ppFEV1 through Week 12 for the TEZ/IVA group versus the placebo group was 1.2 % (95% CI: -0.3, 2.6; P value: 0.1176). The LS mean treatment difference for the TEZ/IVA group versus the placebo group by visit was similar to the difference 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/m2), 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 evaluation. 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 figure below.

Table 32 Summary of design of study 109

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 ppFEV1 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 similar.

Based on the above results, patients with gating mutations were removed from the originally claimed indication.

In vitro-in vivo relationship

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

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 (refer for details to the 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 with residual function 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. The R347H-CFTR mutant was excluded from the indication based on an in vitro increase in chloride transport below the pre-defined threshold of 10%. Out of these 26 mutations of residual function, there were 9 for which no subjects were enrolled in study 108; all of these mutations were responsive to TEZ/IVA in the FRT model system. These 9 mutations were initially included in the proposed label. Additionally, for some mutations the number of subjects enrolled in study 108 was very limited (e.g., E831X and D110H). 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 response to the 1st RSI, they were 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 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 response to the CHMP's request, scatterplots of the in vitro and in vivo responses were submitted on request of the CHMP (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.

Figure 14 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
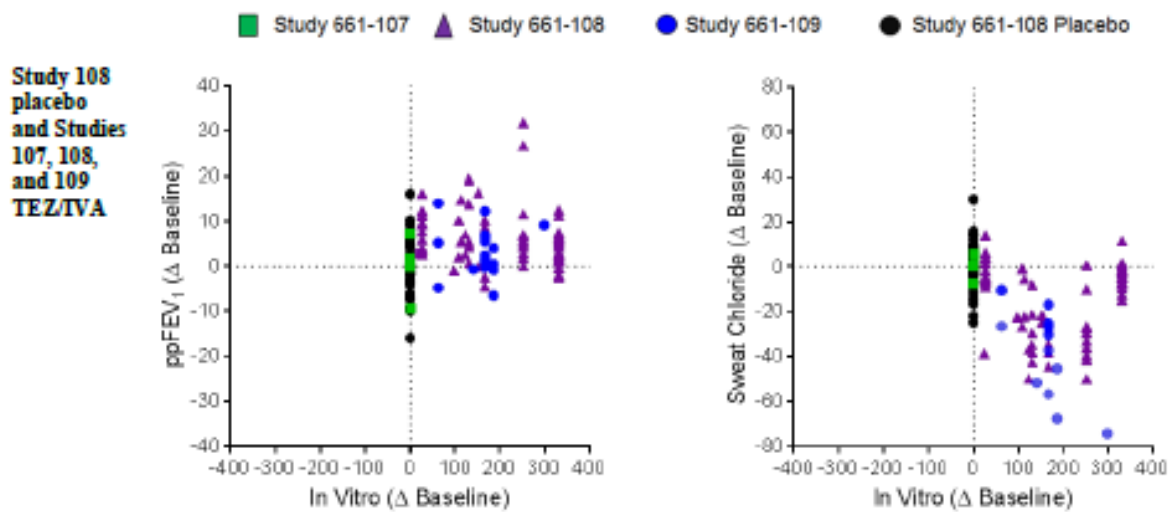
Sources: Study 108 Ad hoc Figures 14.2.2.17, 14.2.3.17, 14.2.2.32, and 14.2.3.32.
Notes: Each marker represents an individual subject on the y-axis and the mean value of chloride transport in the FRT assay for the mutation carried by that individual. Plots include all mutations in the proposed label 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 ppFEV₁ 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).

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 "*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).* A table with these mutations was included in section 5.1 of the SmPC.

Hence, the proposed indication for heterozygous subjects did not reflect the population that was clinically investigated in study 108, i.e. patients with CF who are heterozygous for the *F508del*/residual function mutation. 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 MAH.

For the responsiveness *in vitro*, HBE and mainly FRT models were used. These models were suggested to be useful as support for distinguishing patients with *CFTR* mutations expected to benefit from treatment for which clinical data are not 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 MAH 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 is very questionable given their non-human origin and the high artificially overexpressed levels of transfected CFTR mutant protein in this

system (please refer to non-clinical part for a detailed discussion).

Scatterplots were provided with the results of all patients in study 108, of the ivacaftor-naive patients in study 109, and of the patients with 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 well chosen, in the absence of 'negative' data it is difficult to conclude on the validity of the threshold. Moreover, the absence of a scatter around a diagonal demonstrated the lack of a correlation between chloride transport and ppFEV1 increase as well as the lack of 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 to mutations that were not clinically investigated, Mixed Model analyses were requested by the CHMP and were provided by the MAH. 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 the larger number of patients. This is confirmed in the threshold analysis as in 6 out of the 10 mutations with a small number of subjects, 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 MAH 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 the post-authorisation phase.

Design and conduct of clinical studies

<u>Dose-finding studies</u>

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 on 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 marker of CFTR activity, 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.

<u>Main studies</u>

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 long-term safety and maintenance of effect. Results of study 110 are currently submitted as an interim analysis. The supportive studies Study 107 investigated TEZ/IVA in subjects heterozygous for *F508del* and a minimal function (MF) mutation that is likely nonresponsive to TEZ and/or IVA (F/MF), while study 770-104 investigated ivacaftor monotherapy in subjects with the F/F genotype. Study 109 (ongoing at the time of MAA filing and closed during the CHMP assessment process) compared TEZ/IVA versus IVA in patients with the *F508del*/gating genotype (F/pre-specified gating mutations).

All main studies were randomised, double-blind, and placebo-controlled except the open-label, single-arm extension study 110. Studies 101, 103, 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 of subjects enrolled. 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. While for study 106, a confirmed diagnosis of CF defined as a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis was requested, for study 108 if the sweat chloride value was <60 mmol/L, there must have been a documented evidence of chronic sinopulmonary disease. This is acceptable due to differences between the two study populations with patients with residual function mutations expected to have less severe disease than that of *F508del* homozygous patients.

In study 108, patients needed to have a pre-specified mutation of residual function based on population-level clinical phenotypic data and *in vitro* responsiveness to ivacaftor. Given the heterogeneity of the mutations with residual function, further characterisation in terms of the functional class as well as whether all of them were disease-causing were presented as requested, although summarily. Compared to class II (e.g., *F508del*), classes IV and V had a significantly lower mortality rate and milder clinical phenotype. Patients with CF and a RF mutation (excluding subjects with an *R117H-CFTR* mutation) have a reduced rate of lung function decline compared to *F508del* homozygous subjects (−1.05 compared to −1.91). However, patients with an RF mutation still demonstrate progressive lung disease.

The duration of the dose finding studies 101 and 103 of 28 days and 12 weeks, respectively, is acceptable for the objective of the trials. 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. Treatment duration is however very short, thus a difference may not have been captured in the trial. Longer-term data will be provided by Study 110 with a duration of approximately 96 weeks. A first interim analysis (Interim analysis 1, IA1) was submitted including data from 70% of subjects up to 24 weeks (subjects who rolled over from the parent study 106) or up to 16 weeks (subjects who rolled over from the parent study 108. Upon CHMP's request, a second interim analysis (IA2) of study 110 was submitted in which within-group changes in continuous variables were calculated using as baseline the last non-missing assessment before the first dose of TEZ/IVA in Study 110, while in the first interim analysis (IA1) the parent study baseline was used to calculate the absolute changes from baseline, except for subjects randomized to

the placebo arm in Study 106.

Endpoints

All studies included the following endpoints: absolute change in ppFEV1, change of sweat chloride, height and weight, respiratory domain of 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 analysis 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 percent predicted FEV1, number of pulmonary exacerbations, absolute change in body mass index (BMI), change in the respiratory domain score of the CFQ-R) and in study 108 (absolute change in CFQ-R, with the remaining as additional endpoints given the short duration of the treatment period) are all accepted endpoints in clinical trials on CF, although the relative change in ppFEV1 is clearly dependent on the absolute change in ppFEV1. Each of them is able to measure a different aspect of the disease, and together able to support a benefit for CF patients. In the extension study 110, the same endpoints of efficacy (secondary) 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 considered statistically significant in a formal sense. The MAH explained that the comparison of TEZ/IVA vs IVA was considered of interest, but no reason is provided for the removal of statistical testing. As for Symkevi no mutations that are already registered for Kalydeco in the EU are proposed, this decision is acceptable. Finally, no convincing methods to investigate carry-over in study 108 were planned, but on request of CHMP a post-hoc analysis was performed. The protocol amendments made appeared to be acceptable.

Efficacy data and additional analyses

Dose regimen

For CF patients 18 years or older with F/F mutation (n=194 included in study 101, ppFEV1 increased more with TEZ100 mg qd/IVA 150 mg q12h compared to TEZ 150 mg qd/IVA 150 mg q12h (4.44 pp vs. 4.13 pp) and to VX-661 50 mg q12h/IVA 150 mg q12h (3.66 pp vs 2.31 pp). 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 to 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 and TEZ monotherapy at 10 mg qd which appeared to produce improvement in ppFEV1 not dissimilar to that with the combination. TEZ monotherapy at 100 mg and 150 mg qd appeared more effective than the combination at reducing sweat chloride, but there were inconsistences 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. However, in all groups the number of patients in the groups was small, e.i. 8 (monotherapy) or 16 (combination therapy).

Exposure-response modelling, submitted to support clinical superiority of TEZ/IVA over TEZ was also not reassuring. *In vitro* data were not conclusive either. There is 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 discrepant with the *in vivo* data in study 101 which appeared to demonstrate an effect of tezacaftor on its own to reduce sweat chloride which the MAH 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 percentage points (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 pp and for TEZ/IVA 3.4 pp) 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.

Adolescents

The same dosing was used in adolescents as for adults based on similar disease severity 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 homozygous for F508del (F/F)

In the pivotal study 106 (n=510), baseline demographics, disease characteristics and concomitant medication appear to be balanced overall. Thirty percent (29.6%) of patients were undernourished (defined as a BMI z-score <0 for subjects <20 years of age and as a BMI <18.5 kg/m^2 for subjects ≥ 20 years of age). The percentage of undernourished subjects in the adolescent age group was 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. The inclusion of patients with ppFEV1 <40, despite the exclusion criterion, is caused by a difference in ppFEV1 at screening and at the baseline study visit and it is therefore considered not potentially biased. In study 106, a total of 47 subjects had a decrease in ppFEV1 below 40 pp from screening to baseline. Out of these 47 subjects, 38 (80.9%, 21 subjects on placebo and 17 on TEZ/IVA) received inhaled antibiotics prior to Day 1. Most of these subjects continued to receive them at day Day 1 and afterwards.

The status of chronic lung colonisation due to *P. aeruginosa* was not collected at the time of study enrolment. *Pseudomonas* lung colonisation was documented by the finding of *P. aeruginosa* within two years prior to the start of the study.

Missing data for repeated measures was 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 percentage

points (pp) (95% CI: 3.1, 4.8) in favour of TEZ/IVA (P<0.0001). In adolescent subjects (n=58 per treatment group), the mean treatment difference in the TEZ/IVA group vs. placebo for the absolute change in ppFEV1 from baseline through week 24 was 3.9 pp (95% CI: 2.2, 5.5). The obtained difference between TEZ/IVA and placebo in the overall population of study 106 was above the predefined threshold (2.5 pp) and also above the definition of clinical relevance of 2.5 percentage points quoted 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 that was evident at Day 15 of 3.4 pp. This improvement was sustained during the treatment period, with an increasing difference with placebo because of the gradual decrease in the placebo group of -1.3 pp at week 24. 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 shows a treatment difference in ppFEV1 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 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.

The estimated annual event rate ratio of pulmonary exacerbations for TEZ/IVA versus placebo was 0.65 (95% CI 0.48, 0.88; p = 0.0054). The estimated annual event ratio of pulmonary exacerbations requiring IV antibiotic therapy (which is considered a marker of severity) was 0.53 (95% CI: 0.34, 0.82; P = 0.0042). Regarding pulmonary exacerbations leading to hospitalisation, no statistically significant differences versus placebo were detected (rate ratio versus placebo 0.78 [95% CI: 0.44, 1.36; P = 0.3801]). In additional secondary efficacy evaluation, subjects in the TEZ/IVA group had a longer time-to-first pulmonary exacerbation than subjects in the placebo group, with a hazard ratio of 0.637 favouring the TEZ/IVA group (P = 0.0069). The 75th percentile of pulmonary exacerbations-free time was 14.6 weeks in the placebo group and 22.6 weeks in the TEZ/IVA group. For pulmonary exacerbations that require intravenous therapy, less than 25% of patients in each group had such an event during the study period.

The secondary endpoint hierarchy was broken by the results of BMI. For this important extra-pulmonary parameter the mean absolute change was numerically greater in the TEZ/IVA group (0.18 kg/m2) than in the placebo group (0.12 kg/m^2) at Week 24, but the treatment difference was not statistically significant. The mean treatment difference between groups in the absolute change from baseline in BMI was 0.06 (95% CI: -0.08, 0.19; P= 0.4127). Therefore, the hierarchical multiple testing procedure was stopped at the level of BMI.

In additional analyses in undernourished subjects, the mean change from baseline in BMI was numerically greater with placebo (0.30 kg/m^2) than with TEZ/IVA (0.15 kg/m^2). The responder analysis of under-nourished patients who achieved a target BMI revealed a slightly higher percentage of responders in the TEZ/IVA group (32.4%) compared to the placebo group (26.8%).

The last key secondary endpoint in the testing hierarchy (after BMI) 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).

Other secondary endpoints were overall supportive, although some only numerically. 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. The reduction is therefore acceptably relevant.

No clinically meaningful within-group changes in the mean BMI z-score were observed in the TEZ/IVA (n= 80, 0.06) or placebo (n = 76, −0.02) groups in subjects under 20 years of age; the mean between-group treatment difference was -0.04 (95% CI: -0.15, 0.07; P = 0.4713).

Consistent and significant benefits in ppFEV1 favouring TEZ/IVA were observed across all prespecified subgroups: age, sex, baseline lung function, region, *P. aeruginosa* colonisation (documented within the two years prior to study start but not at the time of enrolment into the study), and baseline use of common CF medications. The lowest point estimate of 3.5 pp difference in the groups of patients with ppFEV1 < 40% and in female sex is still above clinical relevance.

Preliminary results of the open label extension study 110 at the time of the first interim analysis 1 (including approximately 70% of the subjects who had completed the Week 24 Visit in Study 110) seem suggestive for the maintenance of the effect. The efficacy picture in Study 106 is mirrored in the PCBO-TEZ/IVA group of study 110. At week 24 of study 110 (IA1), the mean absolute change from study 110 baseline in ppFEV1 was 4.5 pp (95% CI: 3.3, 5.7) in the PBO-TEZ/IVA group. The mean absolute change from study 106 baseline at week 24 of study 110 was 3.1 pp (95% CI: 1.9, 4.3) in the TEZ/IVA group. Thus, both groups achieved a clinically relevant improvement from baseline of the parent study (TEZ/IVA group) or of study 110 (PCBO-TEZ/IVA group).

The second interim analysis (IA2) showed a loss of 0.2 percentage points in ppFEV1 during the additional 24 weeks of treatment with tezacaftor/ivacaftor in the TEZ/IVA group. This is considered reasonable as the decline in ppFEV1 after 48 weeks of treatment with tezacaftor/ivacaftor is below the estimated annual rate of decline experienced by untreated (with CFTR modulators) *F508del* homozygous subjects according to the data discussed by the MAH (Sawicki et al. 2017) which is −1.91 (including subjects aged 6 years and older).

In Study 106 week 24, the annualised event rate of PEx requiring intravenous antibiotic therapy was 0.29 in the TEZ/IVA group and increased to 0.35 after 24 weeks in Study 110 (IA2). 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 (0.54). 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% overall, while in the CFF Registry the risk of PEx (also defined as those requiring IV antibiotics or hospitalization) ranged from 47.6% to 49.5% from 2012 to 2014. These natural history data on pulmonary exacerbations have been generated in the CFFPR and are on file (i.e., not available in the public domain yet). The results in study 110 are not unexpected given that the percentage of subjects with pulmonary exacerbations requiring intravenous therapy was less than 25% in each group of study 106 at week 24.

A limited gain in BMI was observed at week 24 of study 106 in the TEZ/IVA (0.18 kg/m^2) group vs. the placebo group (0.12 kg/m^2). At week 24 of study 110 the mean within-group change increased to 0.23 kg/m^2 (95% CI: 0.11, 0.34) in the PCBO-TEZ/IVA group while no additional gain was observed in the TEZ/IVA group as shown by a mean within-group change of 0.00 (-0.11, 0.11). An analysis restricted to undernourished subjects showed that at week 24 of study 110, the LS mean change from study 110 baseline in BMI in the PCBO-TEZ/IVA group was 0.73 kg/m^2 (Min, Max: -2.77, 2.86) while in the TEZ/IVA group the LS mean change from study 106 baseline was 0.38 kg/m2 (Min, Max: -1.25, 2.40). In the responder analysis the percentage of undernourished subjects who met or exceeded the target BMI at Week 24 was 35.2% in the PCBO-TEZ/IVA group versus 33.8% in the TEZ/IVA group.

The improvement observed in the CFQ-R respiratory domain at week 24 of study 106 in the TEZ/IVA group (5.5 points) was partially maintained at week 24 of study 110 as shown by a mean within-group change of 0.4 points while in the PCBO-TEZ/IVA group the mean change was 3.3 (1.4, 5.3). The responder analysis further support a benefit in favour of TEZ/IVA as 51.3% patients were responders after 24 weeks (study 106), only reduced to 48.6% after 48 weeks (study 110) of treatment with TEZ/IVA.

As specific data for adolescents were not provided with IA1, these were requested within the interim analysis 2 (IA2). At screening of the parent study 106 there were 116 subjects from 12 to less than 18 years old. Out of these, at the time of IA2, 55 subjects were analysed in the PCBO-TEZ/IVA group and 54 in the TEZ/IVA group. The majority of subjects had baseline ppFE ≥ 40 to <70 (44.0%) or ≥70 to ≤ 90 (48.6%).

The MMRM analysis of the absolute change in ppFEV1 from study 110 baseline at Week 24 of study 110 shows a mean within-group change of −0.8 pp (95% CI: −2.3, 0.7) in the TEZ/IVA group compared to −0.3 (−1.2, 0.7) in subjects ≥ 18 years old. In the PCBO-TEZ/IVA group, this figure was 5.3 pp (3.9, 6.8). Regarding BMI z-score, at week 24 of study 110, the mean within-group change in the PCBO-TEZ/IVA was 0.10 (95% CI: 0.00, 0.19) while in the TEZ/IVA group this figure was -0.04 (95% CI: -0.13, 0.06). The analysis above mentioned limited to undernourished patients is relevant for this age subset given that the percentage of undernourished subjects in the adolescent group was considerably higher than in the adult group (69.8% vs. 17.5% respectively). Overall, these results suggest that young subjects homozygous for *F508del* are at higher risk of lung status decline as a loss of 0.8 pp in ppFEV1 is seen at week 24 of study 110 in the TEZ/IVA group compared to -0.3 in the adult population.

For *F508del* homozygous patients, the place in treatment of a combination of a corrector and a potentiator has already been established by the combination of lumacaftor and ivacaftor (Orkambi). The initial improvement of ppFEV1 is higher with tezacaftor/ivacaftor than with Orkambi in its registration trials (1.68 pp and 2.63 pp at 24 weeks, see EPAR Orkambi).

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 (1.54%) and placebo group (-0.18%) with an estimated treatment difference of 1.72% (p = 0.15). A similar picture was observed for sweat chloride values with a difference of -2.87 mmol/L (P = 0.038). 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, and a second allele with residual function (F/RF)

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. Baseline demographics, disease characteristics and concomitant medication were overall balanced, but there were more females than males in all study arms with the greatest imbalance between males and females (more females) in the TEZ/IVA and placebo groups, with a lesser imbalance in the IVA arm. A total of 23 patients had baseline sweat chloride levels within the normal range. All of them were heterozygous *F508del/D1152H* (n= 16) or *F508del/3849+10kbC->T* (n=7). In that case patients had to have documented evidence of chronic sinopulmonary disease.

Twenty-eigth percent (28.6%) of subjects in the placebo group, 34% on ivacaftor, and 31.1% on tezacaftor/ivacaftor received pancreatic enzymes while the number of those with a diagnosis of exocrine pancreatic insufficiency (defined as faecal elastase-1 concentration <200 µg/g) is considerably lower (13.8%, 13.6%, and 13.3% respectively) a discrepancy that remains unexplained.

The inclusion of patients with ppFEV1 <40%, despite the exclusion criterion, is caused by a difference in ppFEV1 at screening and at baseline study visit. In study 108, 22 subjects had a decrease in ppFEV1 below 40 pp from screening to baseline. Out of these 22 subjects, 13 (59.1%, 2 subjects on placebo, 5 on ivacaftor and 6 on TEZ/IVA) received inhaled antibiotics at some point between screening and baseline but all of them could stop treatment with inhaled antibiotics before Day 1.

The status of chronic lung colonisation due to *P. aeruginosa* was not collected at the time of study enrolment. The sub-analysis by this factor was based on the finding of *P. aeruginosa* within the two years prior to the study start. This may not reflect the true incidence of subjects with chronic lung infection as some infections would be expected to resolve prior to enrolment. Therefore, the results of subgroup analysis by colonization with *Pseudomonas* may not accurately reflect the effect of treatment in study 108.

The majority of the patients were heterozygous F508del/non-canonical splice mutations. These mutations were not tested for *in vitro* responsiveness to ivacaftor as required in study 108. The inclusion of these mutations was justified by the MAH based on the fact that they 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 be shown in FRT cells but in other systems.

The LS mean treatment difference of ppFEV1 compared to placebo was 6.8 pp (95% CI: 5.7, 7.8; P<0.0001) and to IVA was 2.1 pp (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.

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 found by Sawicki et al (2017) excluding subjects with an *R117H-CFTR* mutation with most rapid loss in the 18 to 24−year age group (−1.85, excluding *R117H*). Given the fact that the MAH powered the sample size to detect a 3 percentage point treatment difference between TEZ/IVA and placebo, 2 percentage points was chosen as a reasonable difference compared with placebo to have an impression of responders. An additional threshold analysis of changes in ppFEV1 ≥0 percentage points was proposed by the MAH because 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 sub-analysis of the mutations in study 108 when taken a clinically relevance as for the null hypothesis i.e. 3% only three mutations would not fulfil this threshold, while when using 2% this concerns 2 mutations.

For the 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 strictly the requirement

of robust clinical data and the modelling did not add new insights to overcome this issue. However, *CFTR* mutations *711+3A→G, R1070W, R117C, R352Q, and S977F* fulfil the criteria for passing the different thresholds of ppFEV1 and might also be considered acceptably established. For 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. Independent of de method for threshold or calculation, mutation *D110H* does not meet any criterion. Mutation *R347H* was never proposed for the indication due to 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 mmol/l for missense mutations; versus 1.9 pp ppFEV1 and -3.0 mmol/l 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 mean treatment difference of TEZ/IVA compared to placebo of 11.1 points (95% CI: 8.7, 13.6) 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 7.42 and 1.53 against placebo and IVA, respectively. Mean absolute change in sweat chloride (-9.5 mmol/l) and change in BMI (0.34 kg/m2) were all supportive for TEZ/IVA. Pulmonary exacerbations occurred in 11 (6.8%), 9 (5.8%), and 19 (11.8%) subjects in the TEZ/IVA, IVA, and placebo groups, respectively. The estimated event rate of PEx was lower for the TEZ/IVA (0.34 events per year) and the IVA (0.29 events per year) groups than for the placebo group (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 (documented within two years prior to study start). 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 in ppFEV1 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. The reduction of the estimated event rate was even higher with ivacaftor monotherapy (0.29 events oer year) than for TEZ/IVA (0.34 events per year). However, as previously discussed, the exacerbation rate is not a reliable parameter measured over such a short time.

In the secondary endpoint CFQ-R a numerical higher but not clinically relevant score was observed (mean treatment difference of TEZ/IVA vs. IVA of 1.4 points), but the responder analysis showed a somewhat more distinctive difference (65.2% versus 58.3%). 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 prescribed 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 at the time of first interim analysis (IA1), including 70% of the sample size of study 108 who had completed the Week 16 visit in study 110, support the maintenance of the effect. At Week 16 of interim analysis 1, all groups achieved a clinically relevant improvement from baseline of the parent study for absolute change in ppFEV1: 5.9 pp (95% CI: 4.1, 7.7) in the IVA-TEZ/IVA group, 7.4 pp (5.6, 9.1) in the TEZ/IVA group and 4.6 pp (2.9, 6.3) in the PBO-TEZ/IVA group. Improvement of ppFEV1 was evident at Day 15 for patients on previous placebo treatment. Results from the second interim analysis (IA2) show that at week 16 of study 110 the mean within-group change was 0.0 pp (-1.2, 1.3) in the TEZ/IVA group, i.e., the effect achieved in the parent study 108 is kept at week 16 of study 110 although further gain over that achieved in the parent study is not observed at the time of the interim analysis 2.

The results of the CFQ-R respiratory domain score for the 108/110 efficacy set are reassuring but these patients are only treated for 24 or 16 weeks with TEZ/IVA. 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.

The annualised event rate of pulmonary exacerbations 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 (IA1). This is lower than the event rate for the placebo group in Study 108 (0.63). However, the overall time was still too short for measuring exacerbations, i.e., 8 weeks in study 108 and 16 weeks in study 110. At IA2 of Study 110, the low PEx event rate was maintained at 0.22 events per year in the TEZ/IVA group. Thus, the PEx rate was unchanged between IA1 and IA2. The event rate of pulmonary exacerbations requiring IV antibiotic therapy is low given the usually milder disease of subjects with CFTR mutations with residual function.

A gain in BMI and weight is consistently present from the start of treatment of TEZ/IVA, with an additional mean (SD) improvement in BMI of 0.54 kg/m^2 (95% CI: 0.32, 0.76) at Week 16 of Study 110 (IA2) in the TEZ/IVA group while in the PCBO-TEZ/IVA group the mean change was 0.35 kg/m^2 (0.14, 0.56).

In study 110 IA2 there were 32 adolescent subjects (< 18 years old). Fourteen (14) were analysed in the PCBO-TEZ/IVA group, 8 in the IVA-TEZ/IVA group, and 10 in the TEZ/IVA group. Their mean (SD) BMI z-scores were 0.14 (1.26), −0.22 (1.03), and −0.03 (122) respectively. All subjects had baseline ppFEV1 40 to <70 (53.1%) or ≥70 to ≤ 90 (46.9%). At baseline, the majority of subjects less than 18 years old with ppFEV1 below 70 were in the PCBO-TEZ/IVA and IVA-TEZ/IVA groups (i.e., 57.1% and 62.5% respectively vs. 40% in the TEZ/IVA group).

Results from mixed-effects model for repeated measures (MMRM) analysis of the absolute change from baseline in ppFEV1 for subjects <18 years old at screening of the parent study show that the mean within-group absolute change from baseline at study 110 week-16 in ppFEV1 was 7.2 pp (95% CI: 4.8, 9.7) in the PCBO-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 compared to 4.4 pp, 2.5 pp, and 0.0 pp in adult subjects. In terms of BMI z-score, the mean change was as follows: 0.04 (−0.07, 0.14) in the PCBO-TEZ/IVA group, −0.13 (−0.26, 0.01) in the IVA-TEZ/IVA group, and 0.16 (0.04, 0.28) in the TEZ/IVA group. Of note, the mean (SD) BMI z-scores at baseline were 0.14 (1.26), −0.22 (1.03), and −0.03 (1.22) respectively suggesting a benefit for adolescents treated with tezacaftor/ivacaftor. However, numbers are small and these data should be interpreted with caution.

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.

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 (N= 168 patients), the difference in absolute change in ppFEV1 between TEZ/IVA and placebo group was 1.2 pp (95% CI: -0.3, 2.6; P = 0.1176). The 1-sided 80% upper confidence bound (UCB) was below the predefined futility boundary of 2.5pp. The study has been prematurely stopped because of lack of efficacy.

All patients

The number of patients ≥ 65 years old was initially not presented. There were 6 patients in this age group, all of them enrolled in study 108. 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 pivotal 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). Adolescent data were, however, not specifically discussed for study 110. Adolescents are at higher risk of lung function and nutritional status decline. This is the reason why analyses of various efficacy endpoints restricted to them were requested in the frame of the interim analysis 2 of study 110. These have been discussed, see above.

2.5.4. Conclusions on the clinical efficacy

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

Although there is consistency of responses in FEV1 between phase II and phase III studies, suggesting superiority of the combination, this is in contrast to the sweat chloride results. The absence of evidence comparing TEZ/IVA versus TEZ in homozygous *F508del-CFTR* patients leaves a number of questions unanswered. However, this ongoing uncertainty is set against i) the level of unmet need in *F508del* homozygous patients who cannot tolerate or take LUM/IVA or where LUM/IVA is inadvisable; and ii) the demonstration of superiority for TEZ/IVA over placebo in homozygous *F508del* patients resulting in relevant improvements in this population.

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 benefits in ppFEV1 favouring TEZ/IVA were observed across all pre-specified subgroups. In addition, in a comparison with natural history data, the benefit of the treatment seems established although some uncertainty remains regarding that the data provided to put in context the results of the treatment with tezacaftor/ivacaftor in study 106 and in study 110 are not fully available in the public domain.

The results of the first interim analysis (IA1) of study 110, an open label extension study, 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 in the TEZ/IVA group. The results of interim analysis 2 (IA2) suggest that further gain over that achieved after 24 weeks of treatment with tezacaftor/ivacaftor in study 106 is not obtained. Data for adolescents were provided in the frame of IA2. Overall, these results suggest that young subjects homozygous for *F508del* are at higher risk of lung and nutritional status decline.

Compared to Orkambi in its registration trials, the results of ppFEV1 appear better, but for the long term data, this still needs to be confirmed when additional analysis of data of study 110 are available (e.g., data beyond 24 weeks).

The results of study 104 confirmed that ivacaftor alone is not efficacious in subjects with F/F genotype.

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

The current proposed indication reflects the 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 pursued anymore.

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 (average of week 4 and week 8) is above the MCID of 4 points and apparently sustained for up to 24 weeks in total. Other (non-key) 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, continuous treatment duration with TEZ/IVA was too short to assess maintenance of efficacy. 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/F mutation a comparison with natural history data, the benefit of the treatment seems established. Some uncertainty remains regarding the fact that the data provided to put in context the results of the treatment with tezacaftor/ivacaftor in study 108 and in study 110 are not fully available in the public domain.

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 (excluding subjects with an *R117H-CFTR* mutation). Taking all data together, there appears to be a benefit for TEZ/IVA over ivacaftor.

The results for most of the mutations with clinical data are considered sufficient.

Finally, the CHMP agreed that Kalydeco 150 mg tablets can be indicated in combination regimen with Symkevi 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.*

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 Figure 15 below.

Figure 15 Overview of Studies (N=14) Included in SCS
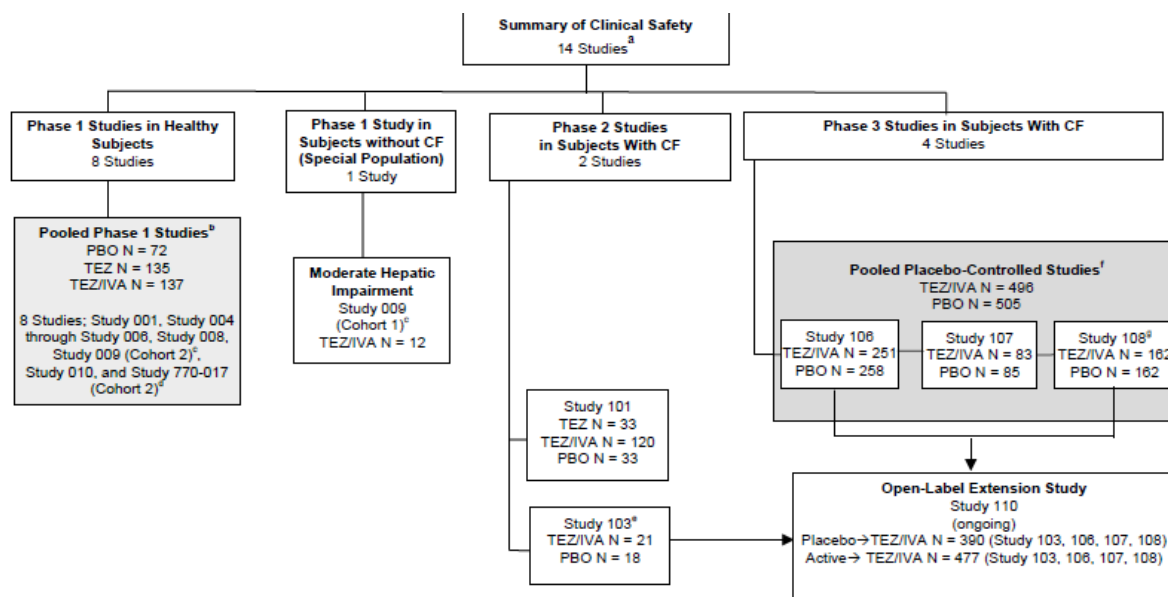
Sources: ISS/Table 2.1.1.1, 2.1.1.6, and 2.3.1.1, Study 009 CSR/Table 14.1.1, Study 101 CSR/Table 14.1.6, Study 103 CSR/Table 14.1.8, and Study 110 IA CSR/Table 14.1.1
CF: cystic fibrosis; IVA: ivacaftor; OLE: open-label extension; PBO: placebo; SCS: Summary of Clinical Safety; TEZ: tezacaftor
Notes: 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.

Three safety datasets were defined.

Phase 3-controlled Safety Set (PC-SS): Main safety data is derived from 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). The 3 Phase III studies were designed to evaluate the efficacy and safety of TEZ 100 mg once daily in combination with IVA 150 mg every 12 hours versus placebo for up to 24 weeks.

Long term safety data sets (OLE-SS and LT-SS): Long-term safety of TEZ/IVA in patients with CF was presented from open label extension Study 110 (OLE-SS) and from all patients with ≥ 48 weeks of TEZ/IVA exposure during the parent study and/or Study 110 (long term safety data set, LT-SS).

Supportive studies: Supportive analyses included pooled safety data from 8 Phase 1 studies in healthy subjects, and safety data from two individual Phase II studies.

Patient exposure

Pooled safety Analysis of Phase III Placebo-controlled Studies (PC-SS): Total exposure (patient years, [PY]), total number of subjects included in the PC-SS, number of subjects by study, and number of subjects by exposure duration interval were well balanced between the placebo and TEZ/IVA groups (see table below). The mean (SD) treatment duration was similar for the placebo (16.3 [7.5] weeks) and the TEZ/IVA (16.2 [7.7] weeks) groups. There were 245 (48.5%) subjects in the placebo group and 238 (48.0%) subjects in the TEZ/IVA group who had >16 weeks exposure.

Table 33 Summary of Exposure: Placebo-controlled Safety Set

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.

Study 110 Interim Analysis (OLE-SS): Study drug exposure for subjects in the OLE-SS is summarized in the Table 34. Exposure durations include duration of study drug exposure in Study 110 only; study drug exposure during the parent studies is not included. A total of 867 subjects were exposed to TEZ/IVA in the OLE-SS: 390 subjects (45.0%) in the Placebo-TEZ/IVA group who had received placebo in the parent study treatment period before enrolling in Study 110 and 477 subjects (55.0%) in the Active-TEZ/IVA group who had received active study drug (either IVA or TEZ/IVA) in the parent study treatment period before enrolling in Study 110. Mean exposure duration for subjects in the OLE-SS (includes duration of study drug exposure in Study 110 only; exclusive of the exposure duration in the parent studies) was 33.5 weeks overall (32.5 weeks in the Placebo-TEZ/IVA group and 34.3 weeks in the Active-TEZ/IVA group). Thus, mean exposure duration for subjects in the OLE-SS is approximately 2-fold that of subjects in the pooled Phase 3 PC-SS (16.3 weeks).

Table 34 Summary of Exposure: OLE Safety Set

Duration of Exposure	Statistic	Placebo-TEZ/IVA N = 390	Active-TEZ/IVA N = 477	Total N = 867
Total exposure	Patient years	242.6	314.0	556.6
Exposure duration (weeks)	Mean (SD)	32.5 (19.3)	34.3 (18.8)	33.5 (19.0)
	Median	29.0	33.0	30.7
	Min, max	0.1, 79.1	1.7, 76.1	0.1, 79.1
Exposure duration by interval, n (%)				
>0 to ≤8 weeks		33 (8.5)	35 (7.3)	68 (7.8)
>8 to ≤16 weeks		65 (16.7)	62 (13.0)	127 (14.6)
>16 to ≤24 weeks		61 (15.6)	72 (15.1)	133 (15.3)
>24 to ≤36 weeks		75 (19.2)	90 (18.9)	165 (19.0)
>36 to ≤48 weeks		67 (17.2)	86 (18.0)	153 (17.6)
>48 to ≤60 weeks		44 (11.3)	83 (17.4)	127 (14.6)
>60 weeks		45 (11.5)	49 (10.3)	94 (10.8)

Source: Study 110 IA CSR/Table 14.1.7
IVA: ivacaftor; OLE; open-label extension; 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. Exposure durations include duration of study drug exposure in Study 110 only; exposure in parent studies is not included.

Long-term Safety Set (LT-SS): Study drug exposure is summarised for subjects in the LT-SS in the Table 35. In accordance with ICH E1 guidelines, the LT-SS was designed to evaluate safety in subjects who have approximately 1 year of exposure to TEZ/IVA. A total of 326 subjects were included in the LT-SS and received ≥48 weeks of TEZ/IVA treatment during the parent study and/or Study 110. Median exposure for subjects in the LT-SS was 67.7 weeks; mean (SD) exposure duration was 69.0 (15.3) weeks, ranging from 48 to 116 weeks. Thus, mean exposure duration for subjects in the LT-SS was approximately 4-fold that of the pooled Phase 3 PC-SS (16.3 weeks).

Table 35 Summary of Exposure: Long-term Safety Set

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

AEs were collected continuously during all studies. An AE was defined as any untoward medical occurrence in a subject during the study; the event did not necessarily have a causal relationship with the active treatment. TEAEs were defined as any AEs that increased in severity or that were newly developed at or after the first dose of study drug through the end of the treatment-emergent period. For consistency, AEs from all studies included in the pooled safety sets were aligned to MedDRA Version 19.1.

Pooled Analysis of Phase 3 Placebo-controlled Studies (PC-SS): Across all endpoints, incidences of AEs were either similar between the placebo and TEZ/IVA groups or lower in the TEZ/IVA group. The overall percentage of subjects with AEs was higher in the placebo group (86.9%) versus the TEZ/IVA group (82.3%). There were no deaths. The percentage of subjects with SAEs was lower in the TEZ/IVA group (10.1%) than in the placebo group (14.9%). The percentages of subjects with Grade 3 (severe) and Grade 4 (life-threatening) AEs, related SAEs, AEs leading to treatment discontinuation and AEs leading to treatment interruptions were low and similar between the placebo and TEZ/IVA group (see table 36).

Table 36 Overview of the Adverse Events: Placebo-controlled Safety Set

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.

Study 110 Interim Analysis (OLE-SS): The overall percentage of subjects with AEs in the OLE-SS (82.2%) was similar to the placebo (86.9%) and TEZ/IVA (82.3%) groups in the pooled Phase 3 PC-SS. There were no deaths reported in the OLE-SS. Given the approximately 2-fold increased duration of exposure in the OLE-SS compared to the PC-SS, the percentage of subjects in the OLE-SS with SAEs was comparable (20.0%) to the percentage of subjects with SAEs in the placebo (14.9%) and TEZ/IVA (10.1%) groups in the pooled Phase 3 PC-SS, despite an approximately 2-fold higher mean exposure duration to TEZ/IVA in the OLE-SS. The percentages of subjects with Grade 3 (severe) and Grade 4 (life-threatening) AEs, related SAEs, and AEs leading to treatment discontinuation in the OLE-SS were low and similar to the pooled Phase 3 PC-SS, see table 37.

Table 37 Overview of the Adverse Events: OLE Safety Set

Category	Placebo-TEZ/IVA N = 390 n (%)	Active-TEZ/IVA N = 477 n (%)	Total N = 867 n (%)
Total number of AEs	1622	1947	3569
Subjects with any AEs	320 (82.1)	393 (82.4)	713 (82.2)
Subjects with Grade 3 or 4 AEs	43 (11.0)	46 (9.6)	89 (10.3)
Subjects with SAEs	76 (19.5)	97 (20.3)	173 (20.0)
Subjects with related SAEs[a]	9 (2.3)	7 (1.5)	16 (1.8)
Subjects with AEs leading to treatment discontinuation	5 (1.3)	2 (0.4)	7 (0.8)
Subjects with AEs leading to treatment interruption	19 (4.9)	30 (6.3)	49 (5.7)
Subjects with AEs leading to death	0	0	0

Source: Study 110 IA CSR/Table 14.3.1.1

AE: adverse event; IVA: ivacaftor; OLE-SS: Open-label Extension 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 OLE-SS includes all subjects who received at least 1 dose of TEZ/IVA in Study 110. Data are summarized for the Study 110 treatment-emergent period only (defined in Section 2.1).

[a] Related AEs and SAEs include related, possibly related, and missing categories.

Long-term Safety Set (LT-SS): Mean exposure duration for subjects in the LT-SS was approximately 4-fold that of the pooled Phase 3 PC-SS. There were no deaths reported in the LT-SS. The percentage of subjects with SAEs was 29.1%, and the percentage of subjects with Grade 3 (severe) and Grade 4 (life-threatening) AEs was 16.3%. A low percentage of subjects had related SAEs (1.8%) and AEs leading to treatment discontinuation (0.3%).

Serious adverse event/deaths/other significant events

Respiratory events and elevated transaminases were specified to be of particular interest due to a risk of transient decline in FEV1 following treatment initiation with Orkambi and elevated transaminases in patients receiving Kalydeco who have pre-existing hepatic enzyme elevation and also in some patients receiving Orkambi.

Transaminase elevations: These are common in CF due to the disease, and have also been documented in some patients receiving Kalydeco and Orkambi. A comprehensive review of the PC-SS data was conducted for AEs associated with elevated transaminases, AEs related to hepatobiliary events, and liver function test laboratory changes (i.e., alanine aminotransferase [ALT], aspartate aminotransferase [AST]). During the placebo-controlled Phase 3 studies (up to 24 weeks), the incidence of maximum transaminase (ALT or AST) >8, >5, or >3 x the upper limit of normal (ULN) were similar between Symkevi in combination with ivacaftor- and placebo-treated patients; 0.2%, 1.0%, and 3.6% in Symkevi in combination with ivacaftor-treated patients, and 0.4%, 1.0%, and 3.4% in placebo-treated patients. One patient (0.2%) on therapy and 2 patients (0.4%) on placebo permanently discontinued treatment for elevated transaminases. The majority of the elevated transaminase events were mild or moderate in severity. There were no elevated transaminase events that were considered serious. No patients treated with Symkevi in combination with ivacaftor experienced a transaminase elevation >3 x ULN associated with elevated total bilirubin >2 x ULN. 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. Respiratory events in the PC-SS were collectively assessed and included the following PTs: asthma, bronchial hyperreactivity, bronchospasm, wheezing, chest discomfort, dyspnea, and respiration abnormal. 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 sub-analysis of PTs related to respiratory symptoms (i.e., chest discomfort, dyspnoea, and respiration abnormal) also 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 predose 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).

Adverse drug reactions: AEs that were identified as potential ADRs and occurred in at least 3% of subjects who received TEZ/IVA and that had at least a 1% greater incidence than in the placebo group were headache, nasopharyngitis, nausea, sinus congestion, and dizziness. These are proposed for inclusion as adverse reactions in the SmPC. A similar safety profile regarding related AEs was observed in the OLE-SS and LT-SS analyses.

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 38 Incidence of Adverse Events by Severity: Placebo-controlled Safety Set

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. Infective pulmonary exacerbations of CF and hemoptysis were the only Grade 3 or 4 AEs that had an incidence of at least 1% in either treatment group. Similarly, the majority of subjects in the OLE-Safety Set had AEs that were mild or moderate. Grade 3 (severe) or Grade 4 (life-threatening) AEs occurred in 10.3% of patients. 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-TEZ/IVA and Active-TEZ/IVA group. The only Grade 3 or Grade 4 AE that was reported in >1% of all patients in the OLE-SS was infective PEx of CF (4.6%).

The majority of subjects in the LT-SS (78.8%) had AEs that were mild or moderate, similar to the incidence in the pooled Phase 3 PC-SS (placebo group [78.4%], TEZ/IVA group [75.2%]). Grade 3 or 4 AEs occurred in 16.3% of subjects in the LT-SS.

The second most common Grade 3 or 4 AE was gastroenteritis, occurring in 1.2% of patients in the LT-SS. All other Grade 3 or 4 AEs occurred in <1% of subjects. As noted above, 2 patients in the LT-SS had Grade 4 life-threatening AEs (2 suicide attempts) during Study 110.

Other significant events: The incidence of SAEs was higher in the placebo group (14.9%) than in the TEZ/IVA group (10.1%; see table 39). The only SAEs that occurred in ≥1% of patients in either treatment group were infective PEx of CF and haemoptysis. The incidence of infective PEx of CF was higher in the placebo group (10.3%) than in the TEZ/IVA group (6.7%); the incidence of haemoptysis was similar between the placebo (1.2%) and the TEZ/IVA (1.0%) group.

Table 39 Incidence of Serious Adverse Events that Occurred in at least 2 subjects in any treatment group by preferred term: Placebo-controlled safety set

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.

Related SAEs: The incidence of related SAEs was similar between the placebo group (1.4%) and TEZ/IVA group (1.0%). Related SAEs that occurred in 2 or more patients in either treatment group were hemoptysis (0% in the placebo group and 0.4% in the total TEZ/IVA group) and infective PEx of CF (0.6% in the placebo group and 0.2% in the total TEZ/IVA group). In the OLE-SS, SAEs were reported in 20.3% of patients in the Active-TEZ/IVA arm and 19.5% in the Placebo-TEZ/IVA arm. The most common SAEs (occurring in at least 2 patients) were infective PEx of CF (117 [13.5%] patients), hemoptysis (16 [1.8%] patients), distal intestinal obstruction syndrome (DIOS, 7 [0.8%] patients), constipation (4 [0.5%] patients), abdominal pain (3 [0.3%] patients), and influenza (3 [0.3%] patients). SAEs considered related to treatment that occurred in more than 2 patients were infective PEx of CF (5 [0.6%] patients) and blood creatine phosphokinase (CPK) increased (2 [0.2%] patients). Overall, 29.1% of patients in the LT-SS had an SAE. SAEs considered related to treatment occurred in 6 (1.8%) patients in the LT-SS, similar to the incidence in patients in the pooled Phase 3 PC-SS (1.4% in the placebo group and 1.0% in the TEZ/IVA group). SAEs that occurred in more than 2 patients in the LT-SS were similar to those that occurred in the pooled Phase 3 PC-SS and the OLE-SS, and included infective PEx of CF (63 [19.3%] patients), hemoptysis (11 [3.4%] patients), influenza (4 [1.2%] patients), DIOS (3 [0.9%] patients), and pneumonia (3 [0.9%] patients). As in the OLE-SS, the only SAE considered related to treatment to occur in more than 2 patients in the LT-SS was infective PEx of CF (3 [0.9%] patients). There were no deaths reported in the TEZ/IVA clinical development program.

Laboratory findings

The descriptive statistics and threshold analyses for clinical laboratory parameters (serum chemistry, haematology, and coagulation studies), vital signs, physical examinations, and ECGs assessed in PC-SS showed minor differences between the TEZ/IVA and placebo groups that were not considered to be clinically meaningful. Patients with CF are chronically ill, experience frequent infections, take numerous medications, and have disease-related metabolic abnormalities. Thus, fluctuations in laboratory parameters are common. The incidence of laboratory abnormalities resulting in reports of adverse events was generally similar between the TEZ/IVA and placebo groups.

In the PC-SS, 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 relevant differences between the therapeutic and supra-therapeutic 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.

Results of study 103 confirmed that 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.

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 (presents 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. Baseline and follow-up ophthalmological examinations are

recommended in paediatric patients initiating ivacaftor treatment, either in monotherapy or in a combination regimen with tezacaftor/ivacaftor, as stated in the SmPC of Kalydeco.

Safety in special populations

Age: Of 1001 patients who received study drug, 199 patients (19.8%) were ≥12 to <18 years of age. The safety profile of TEZ/IVA was largely similar in patients ≥12 to <18 years of age and adults. The incidence of SAEs in the TEZ/IVA group was slightly higher (4% difference between groups) in adolescent patients ≥12 to <18 years of age compared to adults >18 years, but the incidences were lower than in the placebo arms of each subgroup. AEs that were at least 5% more common in subjects ≥12 to <18 years of age than in subjects ≥18 years of age in the TEZ/IVA group were cough, infective PEx of CF, and headache. Of these, only the incidence of headache was slightly higher in subjects in the TEZ/IVA group than in the placebo group within each age subgroup. AEs that were at least 5% more common in subjects ≥18 years of age than in subjects ≥12 to <18 years of age in the TEZ/IVA group were nasopharyngitis and haemoptysis. Only the incidence of nasopharyngitis was slightly higher in the TEZ/IVA group compared to placebo within each age subgroup.

Safety data in patients ≥65 years old are limited because the Phase 3 studies of TEZ/IVA did not include sufficient numbers of patients in this age group.

Gender: Approximately equal numbers of females (506 [50.5%]) and males (495 [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 subjects overall. The only SAE to occur in >10% of subjects overall in any group was infective PEx of CF, which had a higher incidence for females than males, consistent with the overall trend observed for all AEs. However, the incidences of infective PEx of CF were lower for both sexes with TEZ/IVA treatment (male: 20.2%; female: 26.9%) compared to placebo (male: 25.4%; female: 35.0%).

Overall, there were no clinically meaningful trends associated with sex in subjects receiving TEZ/IVA in the pooled Phase 3 placebo-controlled studies. While there was a higher overall incidence of females who had AEs than males, the incidences of subjects with AEs were typically lower in the TEZ/IVA groups than in the placebo groups, suggesting that this difference was unlikely attributable to TEZ/IVA treatment.

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. PK studies of TEZ/IVA have not been done in subjects with moderate (creatinine clearance 30 to 59 mL/min) or severe (creatinine clearance 15 to 29 mL/min) renal impairment. Therefore, a safety assessment of TEZ/IVA in subjects with renal impairment was not conducted. 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, as per the SmPC recommendation.

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 and ivacafotr should not be administered in the evening.

CFTR Genotype: Based on the similar safety profile observed with approved CFTR modulators across genotypes, all genotypes were pooled for the placebo-controlled database to provide the largest possible safety database. There were no meaningful differences in safety profile of TEZ/IVA in Studies 106, 107, or 108.

Baseline ppFEV1: Pooled placebo-controlled Phase 3 studies enrolled subjects with FEV1 ≥40% and ≤90% of predicted normal for age, sex, and height at screening. Patients were stratified at randomization for ppFEV1 <70% and ≥70% at screening. To assess the impact of pp FEV1 on safety, subgroup analyses were conducted in patients with ppFEV1 ≥40 and <70, patients with ppFEV1 ≥70 and in patients with ppFEV1 <40 at baseline. The majority (61.3%) had baseline ppFEV1 ≥40 to <70%, followed by those with baseline ppFEV1 ≥70 (29.4%). Although patients were excluded if they had a ppFEV1 <40% at screening, some patients (9.2%) had ppFEV1 <40% at baseline (43 placebo patients; 49 TEZ/IVA patients). The numbers of patients in each ppFEV1 category were similar in the TEZ/IVA and IVA groups.

The incidence of patients with AEs leading to treatment discontinuation was low (≤2.1%) and similar to placebo (≤2.6%) across all ppFEV1 subgroups for patients receiving TEZ/IVA. Overall, 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 (European, including Australia and Israel [61.5%] vs. North American [38.5%]) in subjects in the pooled Phase 3 PC-SS.

Pregnancy and lactation: The effects of TEZ and IVA on conception, pregnancy, and lactation in humans are not known as no adequate and well-controlled studies of TEZ and IVA in pregnant or lactating women have been conducted. There were 5 pregnancies reported in phase 3 trials; the outcome is known for 3 of them. Three healthy children were born. For the remaining two, the outcome is not known due to lost to follow-up and to lack of agreement to sign pregnancy informed consent form. 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, as stated in the SmPC.

Safety related to drug-drug interactions and other interactions

Please refer to earlier discussion regarding PK interactions (CYP3A inducer/inhibitor interactions). No additional safety information regarding interactions has been identified in the pooled safety database.

Discontinuation due to adverse events

Discontinuation of study drug: The rate for AE leading to treatment discontinuation in the PC-SS was 2.0% for the placebo group and 1.6% for TEZ/IVA. In the PC-SS, the AEs leading to discontinuation that occurred in at least 2 patients in either treatment group were abdominal pain, alanine aminotransferase increased, blood alkaline phosphatase increased, fatigue, headache, and oropharyngeal pain. Of these events occurring in at least 2 patients, the only 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.

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 in the PC-SS. There were no AEs leading to treatment interruption occurring in >1% of patients in either treatment group. The AEs that

occurred in at least 2 patients that led to treatment interruption in either group were distal intestinal obstruction syndrome (DIOS), alanine aminotransferase increased, infective PEx of CF, hemoptysis, abdominal pain, nausea, and aspartate aminotransferase increased. Of these, DIOS was the only AE that occurred in a higher incidence in patients in the TEZ/IVA group (0.6%, 3 patients) than the placebo group (0 patients). The 3 events of DIOS were considered not related to treatment.

Post marketing experience

TEZ/IVA is not marketed in any EU country. As of June 2017, IVA monotherapy (Kalydeco) is approved for the treatment of CF in patients as young as 2 years old with certain *CFTR* mutations in Australia, Canada, EU, Israel, Liechtenstein, New Zealand, Switzerland, and the US. The age groups and genotypes included in the indication differ by region.

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 CHMP's request during the evaluation, the MAH recalculated exposure duration, accounting for interruptions and discontinuations. Recalculated exposure data were, similar to original exposure data, well balanced between treatment arm, which was reassuring.

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 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%). The MAH's response to the CHMP's questions provided 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 hemoptysis were the only Grade 3 or 4 AEs that had an incidence of at least 1% in either treatment group.

Blood creatinine phosphokinase increased has been reported by patients who received Orkambi but it was not considered an adverse reaction (due to similar incidence on placebo arm). In the PC-Safety

Set, 3 subjects reported a Grade 3 or Grade 4 adverse event of blood creatinine phosphokinase increased (2 on placebo; 1 on TEZ/IVA).

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, however, 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/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 MAH 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.

During the evaluation, the MAH clarified that 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 etiologies.

Adverse events of special interest

Hepatic toxicity is a known adverse event for Kalydeco and Orkambi. In the current application, 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 post-dose spirometry data were observed, including those for patients with ppFEV1 <40 at baseline.

Safety in special populations

Age: 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. It is acknowledged that data in the elderly population (>65 years) were very limited, as CF 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.

CFTR genotype: 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.

From the perspective of the current procedure, i.e., administration of ivacaftor in combination with tezacaftor, study 108 is the only that allows a direct comparison of ivacaftor monotherapy vs. the combination. This comparison is of interest, since all mutations that are registered for Kalydeco were investigated in clinical trials and are proposed for the indication. It is therefore reassuring that the frequency and type of AEs was largely similar between TEZ/IVA and IVA monotherapy. The presented data even suggested a numerical difference in favour of TEZ/IVA with regard to grade 3-4 AEs, SAEs and AEs leading to discontinuation.

Pregnancy/lactation: the effects of TEZ/IVA on conception, pregnancy, and lactation are unknown. It is advised that TEZ/IVA should be used during pregnancy or breast-feeding only if the potential benefits are considered to outweigh the potential risks, as per the SmPC.

As part of the marketing authorisation of Symkevi, the MAH also proposed category 3 for Study 117, as 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.

2.6.2. Conclusions on clinical safety

During the development programme of Kalydeco to be co-administered with Symkevi, no significant new or additional safety concerns were identified with the addition of TEZ to IVA.

Overall, 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. As IVA is a component of the TEZ/IVA regimen, similar

recommendations to those in place for Kalydeco are proposed including routine monitoring of transaminases (in all patients) and baseline and follow-up eye examination (in paediatric patients). The safety data remain limited and further characterisation of the safety profile in paediatric patients is required in the post authorisation setting.

2.6.3. PSUR cycle

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.

2.7. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 7.10 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 7.10 with the following content:

Safety concerns

Important identified risks	None
Important potential risks	• Hepatotoxicity • Cataract • Concomitant use of IVA with strong CYP3A inhibitors or inducers • Cardiac arrhythmias
Missing information	• Use in pregnant and lactating women • Use in children between 2 to 11 years old • Safety in patients with cardiac diseases • Patients with moderate or severe hepatic impairment

CYP: cytochrome P450; IVA: ivacaftor

Pharmacovigilance plan

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional PV activities which are Conditions of the MA (key to benefit risk)				
None				
Category 2 – Imposed mandatory additional PV activities which are Specific Obligations in the context of a conditional MA under exceptional circumstances (key to benefit risk)				
None				
Category 3 – Required additional PV activities (by the competent authority)				
None				

Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Hepatotoxicity	**Routine risk minimisation measure:** SmPC Section 4.4 where advice is given on monitoring LFTs. SmPC Section 4.8 PL Section 4 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** None
Cataract	**Routine risk minimisation measure:** SmPC Section 4.4 where advice is given on recommended ophthalmological examinations SmPC Section 5.3 PL Section 2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** None
Concomitant use of IVA with strong CYP3A inhibitors or inducers	**Routine risk minimisation measure:** SmPC Section 4.2 where dose reductions are recommended when co-administered with a strong inhibitor of CYP3A. SmPC Section 4.4 PL Section 2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** None
Cardiac arrhythmias	**Routine risk minimisation measure:** SmPC Section 5.3 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** None
Use in pregnant and lactating women	**Routine risk minimisation measure:** SmPC Section 4.6 where advice is given on to use Kalydeco during pregnancy only if clearly needed and during breastfeeding if the potential benefit outweighs the potential risks. PL Section 2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only Pregnancy follow-up form **Additional PV activities:** None
Use in children between 2 to 11 years old	**Routine risk minimisation measure:** SmPC Section 4.2 where the posology is described SmPC Sections 4.8 and 5.2 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:** None
Safety in patients with cardiac disease	**Routine risk minimisation measure:** SmPC Section 5.3 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** None

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Patients with moderate or severe hepatic impairment	**Routine risk minimisation measure:** SmPC Section 4.2 where advice is given on dose adjustment based on severity of hepatic impairment SmPC Section 5.2 PL Section 3 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** None

CYP: cytochrome P450, PL: Patient Leaflet; SmPC: Summary of Product Characteristics

2.8. *Update of the Product information*

As a consequence, section 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1, 5.2, 5.3, 6.4, 6.5, 6.6, 7 and 8 of the SmPC are updated. Annex A, the Package Leaflet and Labelling are updated in accordance.
Annex II has been modified to remove a condition already fulfilled.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, which were reviewed by QRD and accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative.

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Kalydeco. The bridging report submitted by the MAH has been found acceptable.

2.8.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Kalydeco (ivacaftor) is included in the additional monitoring list as it has a PASS imposed either at the time of authorisation or afterwards; [REG Art 9(4)(cb), Art 10a(1)(a), DIR Art 21a(b), Art 22a(1)(a)];

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 for Kalydeco 150 mg film-coated tablets in combination with Symkevi is:

Kalydeco tablets are also indicated in a combination regimen with Symkevi for the treatment of patients with cystic fibrosis (CF) aged 12 years and older. For indicated CFTR mutations, refer to the Summary of Product Characteristics of Symkevi.

The proposed indication was not acceptable to the CHMP, due to the lack of reliable clinical data for some mutations. Hence, the indication was restricted to those mutations where sufficient clinical information has been provided by the MAH:

Kalydeco tablets are also indicated in a combination regimen with tezacaftor 100 mg/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 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 may have the potential to modify the progression 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 homogeneous 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

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, because no CFTR modulators were approved at the time the study was conducted. Study 106 was powered for ppFEV1 and pulmonary exacerbations. Study 106 provided 24 weeks data.

Study 108 in CF patients 12 years or older is a phase 3, randomized, double-blind, placebo- and ivacaftor-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 support 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 long-term safety and maintenance of efficacy. An interim analysis was submitted allowing for evaluation of the persistence of efficacy beyond the treatment duration in the pivotal studies. As the date of data cut of the first interim analysis (IA1), 870 subjects had been enrolled from 4 parent studies among which 462 subjects from Study 106 with additional 24 week treatment and 223 subjects from Study 108 with additional 16 week treatment. Upon CHMP request, a second interim analysis (IA2) of study 110 was submitted in which within-group changes in continuous variables were calculated using as baseline the last non-missing assessment before the first dose of TEZ/IVA in Study 110, while in the first interim analysis (IA1) the parent study baseline was

used to calculate the absolute changes from baseline for all "treatment" groups, except for subjects randomized to the placebo arm in Study 106. As specific data for adolescent subjects were not discussed within IA1, these were requested with IA2.

Two additional studies were submitted providing results for further mutations possibly beneficial from treatment of Symkevi, i.e., study 104 in CF patients 12 years or older with the *F508del/F508del* genotype in which ivacaftor monotherapy was assessed 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 *F508del/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. Similarly, a dedicated QTc study of ivacaftor monotherapy was assessed at the time of MAA of Kalydeco.

3.2. Favourable effects

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

Changes in sweat chloride were assessed as a marker of the activity of CFTR. The mean change in sweat chloride was -9.9 mmol/l and 0.2 mmol/l for TEZ/IVA and placebo groups respectively. In study 106 (n= 510), TEZ/IVA showed a statistically significant mean treatment difference in absolute change of ppFEV1 from baseline through week 24 of 4.0 percentage points (pp) compared to placebo i.e., for TEZ/IVA 3.4 pp and for placebo – 0.6 pp, a difference that was evident at Day 15. The improvement was sustained during the treatment period (3.5pp at week 24), while in the placebo group a gradual decrease of -1.3 pp has been observed. In patients with ppFEV1 < 40%, an increase of 3.5 pp in ppFEV1 was observed. In adolescent subjects in study 110, the mean treatment difference in the TEZ/IVA group vs. placebo for the absolute change in ppFEV1 from baseline through week 24 was 3.9 pp (95% CI: 2.2, 5.5).

For key secondary endpoints, the estimated event rate of pulmonary exacerbations was 0.64 events per year in the TEZ/IVA group compared to the placebo group (0.99 events per year). The rate ratio vs. placebo was statistically significant. TEZ/IVA treatment was also associated with a 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).

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 although the treatment difference was not statistically significant (p = 0.4127).

The 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 other (non-key) secondary endpoints were overall supportive, although some only numerically.

Consistent improvements in ppFEV1 favouring TEZ/IVA were observed across all pre-specified subgroups: age, sex, baseline lung function, region, *Pseudomonas aeruginosa* colonisation (documented within the 2 years prior to study), and baseline use of common CF medications. The lowest point estimate was 3.5 pp difference in the group of patients with ppFEV1 < 40% and in females. No confidence interval of any subgroup crossed 0.

Preliminary results of study 110 from the first interim analysis (IA1) mirror the results of study 106 in the PCBO-TEZ/IVA group as shown by a within-group mean change from study 110 baseline of 4.5 pp in ppFEV1 at week 24 of study 110. Similar improvements to those observed in subjects randomised to TEZ/IVA in the parent study 106 were observed for key secondary endpoints of efficacy in this group in study 110. In the TEZ/IVA group, the mean absolute change from study 106 baseline in ppFEV1 was 3.1 pp. In adolescents, the same trend was observed in the PCBO-TEZ/IVA group, i.e., the mean within-group absolute change from study 110 baseline in ppFEV1 was 5.3 percentage points (95% CI: 3.9, 6.8) while the mean absolute change in BMI z-score was 0.10 (95% CI: 0.00, 0.19).

In study 104 in 94 patients, the LS mean absolute change from baseline through Week 16 in ppFEV1 was in the ivacaftor group 1.54 pp and in the placebo group -0.18 pp (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

In study 108, TEZ/IVA (n = 162) treatment resulted in an increase in absolute change in ppFEV1 averaged for Week 4 and Week 8 of 6.5 pp with a mean difference of 6.8 pp (95% CI: 5.7, 7.8) compared to placebo (n =162) which was statistically significant. The mean treatment difference compared to IVA (n = 157) was 2.1 pp (95% CI: 1.2, 2.9) in favour of TEZ/IVA. The sensitivity analysis showed similar results. In patients with ppFEV1 < 40%, an increase of 4.4 pp in ppFEV1 was observed. In adolescents, the mean treatment difference in the TEZ/IVA group vs. placebo for the absolute change in ppFEV1 through the average of Week 4 and Week 8 compared to placebo was 12.0 pp (95% CI: 9.3, 14.8).

For the key secondary endpoint CFQ-R Respiratory Domain, the mean treatment difference of TEZ/IVA compared to placebo was 11.1 points (95% CI: 8.7, 13.6) which was also statistically significant. The mean treatment difference versus IVA was 1.4 points (95% CI: -1.0, 3.9). 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.

For other secondary parameters, differences in absolute change in sweat chloride and BMI were higher in TEZ/IVA compared to placebo. The absolute change in sweat chloride was -9.5, -4.5 and 0.2 mmol/l for TEZ/IVA, IVA and placebo groups respectively while the respective changes for BMI were 0.34, 0.47 and 0.18 kg/m^2. 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, and *P. aeruginosa* colonization (documented within the 2 years prior to study start).

Preliminary results of study 110 from the first interim analysis (IA1) mirror the results of study 108 in the PCBO-TEZ/IVA group as shown by a within-group mean change from study 108 baseline of 4.4 pp (95% CI: 2.9, 6.3) in ppFEV1 at week 16 of study 110. Similar improvements to those observed in subjects randomised to TEZ/IVA in the parent study 108 were observed for key secondary endpoints of

efficacy in this group. In the TEZ/IVA group, the mean absolute change from study 108 baseline in ppFEV1 was 7.4 pp (95% CI: 5.6, 9.1).

Results of the second interim analysis (IA2) of study 110 showed that the improvement achieved in ppFEV1 in the placebo group of study 108 was maintained at week 16 of study 110 in the TEZ/IVA group. The mean intragroup change in ppFEV1 at the average of week 4 and week 8 of study 108 was 6.5 pp in the TEZ/IVA group, while at week 16 of study 110 no differences were seen with respect to the within-change observed in study 108. For CFQ-R the mean within-change from baseline at week 16 of study 110 was still 4.4 points (95% CI: 1.2, 7.6) in the TEZ/IVA group compared to a mean within-group change of 10.1 points in study 108. In Study 110, subjects who continued TEZ/IVA maintained a low pulmonary exacerbation event rate of 0.20 at IA1 and 0.22 at IA2. The risk of PEx that led to hospitalization or IV antibiotic treatment was 12.9%, while in the CFF Registry the annual risk of PEx in need of hospitalisation or IV therapy ranged from 27.0% to 31.6% from 2012 to 2014.

In adolescents, the mean absolute change from baseline at study 110 week-16 in ppFEV1 was 7.2 pp (95% CI: 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 as compared to adults, i.e., 4.4 pp (3.1, 5.7), 2.5 pp (1.1, 3.8), and 0.0 pp (−1.3, 1.3) respectively. Overall, better results are observed in adolescents. Regarding BMI z-score, the mean absolute change from baseline at study 110 week-16 were 0.04 (95% CI: −0.07, 0.14) in the PBO-TEZ/IVA group, −0.13 (−0.26, 0.01) in the IVA-TEZ/IVA group, and 0.16 (0.04, 0.28) in the TEZ/IVA group. The mean absolute change in BMI (kg/m2) for the overall population was 0.35 kg/m2 (95% CI: 0.14, 0.56), 0.15 kg/m2 (−0.07, 0.38), and 0.54 kg/m2 (0.32, 0.76) respectively.

In Study 101, patients with *F/G551D* mutations taking TEZ on top of physician prescribed 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 pp (95% CI: -0.3, 2.6; P = 0.1176). The 1-sided 80% UCB was below the predefined futility boundary of 2.5 pp.

3.3. Uncertainties and limitations about favourable effects

Dose regimen and drug-drug interactions

When testing multiple combinations of tezacaftor and ivacaftor (study 101) in patients homozygous for the *F508del-CFTR* mutation, the regimen TEZ 100 mg qd/IVA 150 mg q12h was favourable in ppFEV1 compared to other dose combinations as well as compared to the almost all TEZ monotherapy groups. However, the greatest reduction in absolute change in sweat chloride has been observed in some monotherapy groups of tezacaftor (ranging from +3.92 to −20.43 mmol/l). A clear dose response could not be observed for ppFEV1. The treatment effect of the combination therapy compared to placebo ranged from 1.44 to 3.89 pp, and for the monotherapy from 1.74 to 3.63 pp, with the greatest treatment effect at the lowest TEZ dose of 10 mg once daily. The model, within the limitations, appears to be more accurate for ppFEV1 than for sweat chloride but cannot be considered conclusive.

In F/RF patients, the combination regimen for study 108 was supported by *in vitro* data only. 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, C_{max} and C_{trough}) and genotype in subjects with CYP3A4*22 genotype and subjects with CYP3A4 wild-type phenotype should be provided. 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.

All patients

Overall, the characterisation of the study population with respect to some relevant factors is not as accurate as it would have been desirable. This mainly applies to the status of chronic lung colonisation due to *P. aeruginosa* which was not known at the time of study entry. While for subjects enrolled in study 108 it is expected that this percentage is relatively low, this is not the case for patients homozygous for *F508del*. In study 108, discrepancies have been found between the number of subjects declared as having exocrine pancreatic insufficiency based on faecal elastase-1 values and those receiving exogenous pancreatic enzymes.

Only 6 patients ≥ 65 years of age were included in the phase III program, all were in study 108.

Only interim data from study 110 are available for a total treatment duration of up to 48 weeks for patients with F/F genotype and up to 24 weeks for patients with F/RF genotype, although the study is planned to provide up to a follow-up duration of 120 and 104 weeks respectively. A second interim analysis was requested by CHMP where baseline was defined as study 110 baseline for all "treatment" groups of study 110. Some uncertainties remain regarding the datasets used for the various analyses that have been provided as part of IA2. Study 110, however, was not designed or powered to assess the difference of TEZ/IVA effects for subjects transitioning from the various treatments in Study 106 or 108 to TEZ/IVA in Study 110, i.e., it is a descriptive in nature. All P values provided for within-group changes of the MMRM analyses performed are nominal. Furthermore, this study is expected to provide data beyond 24 weeks or 16 weeks of treatment with TEZ/IVA for homozygous F508del subjects and for heterozygous F508del/pre-specified residual function mutations, respectively.

CF patients 12 years or older homozygous for F508del (Study 106)

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.

The secondary endpoint hierarchy was broken by the results of BMI, the fourth endpoint in the testing hierarchy (after the absolute and the relative change in ppFEV1 and the rate of pulmonary exacerbations) for which the difference between treatments groups was not statistically significant, i.e., the mean treatment difference between groups was 0.06 kg/m^2 (95% CI: -0.08, 0.19; P = 0.4127). The percentage of undernourished subjects was considerably higher in the adolescent group than in the adult group (69.8% vs. 17.5% respectively). No clinically meaningful changes in BMI z-score were observed either. The mean between-group treatment difference was -0.04 (95% CI: -0.15, 0.07).

The last endpoint in the testing hierarchy, the respiratory domain of CFQ-R cannot be claimed as statistically significant.

In the second interim analysis (IA2) of the open label extension study 110, using study 110 as baseline, a loss of 0.2 pp in ppFEV1 was observed in the TEZ/IVA group during the additional 24 weeks of treatment. In adolescent subjects, the loss was slightly higher, i.e., -0.8 pp. 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 overall and -2.37 pp in the 13-17 year group (Sawicki 2017).

The event rate of pulmonary exacerbations requiring IV antibiotic therapy was 0.35 in the TEZ/IVA group after 24 weeks of additional treatment in Study 110 (IA2) as compared to 0.29 at week 24 of study 106. In F/F subjects who began receiving TEZ/IVA in either Study 106 (parent study) or Study 110, the average duration of follow-up was 1.67 years per subject and the risk of PEx that led to hospitalization or IV antibiotic treatment was 29.6%, while in the CFF Registry, the annual risk of PEx ranged from 47.6% to 49.5% from 2012 to 2014. This is not unexpected given that the percentage of subjects with pulmonary exacerbations requiring intravenous therapy was less than 25% in each group at week 24 of study 106.

In study 110 week 24, subjects in the TEZ/IVA maintained the limited improvement in BMI seen at week 24 of study 106 as no differences were seen with respect to the within-change observed in study 106. The mean within-group change in BMI from baseline at study 110 week-24 in BMI z-score for adolescent subjects was -0.04 (-0.13, 0.06) in the TEZ/IVA group.

The initial improvement in CFQ-R was partly maintained (0.4 points). 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%.

CF patients 12 years or older heterozygous for the F508del-CFTR mutation, and a second allele with residual function (study 108)

For study 108, mutations were eligible based on *in vitro* evidence of responsiveness to ivacaftor defined by a 10% increase in chloride transport AND on the availability of population-level phenotypic data compatible with residual CFTR activity.

The Fischer Rat thyroid (FRT) cell lines expressing mutations of residual function, and possibly predicting a clinical response, was claimed by the MAH as a validated assay. However, there is no clinical validation that the threshold of at least 10% increase in in vitro chloride transport is sufficient to predict clinical efficacy. The scatterplots provided were not conclusive to show a relationship for the extent of *in vitro* responsiveness and *in vivo.*

For most of the mutations, the number of patients was small limiting the interpretation of the results.

For the following mutations, it is considered that sufficient clinical evidence is 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* CFTR mutants do not fulfil strictly the requirement of robust clinical data and the modelling did not add new insights to overcome this issue. However, mutations *711+3A→G, R1070W, R117C, R352Q,* and *S977F* fulfil the criteria for passing the different thresholds of responder analysis ppFEV1 > 2% or ppFEV1 ≥ 0%, mean and median of the subanalysis, and are also considered acceptably established. For 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. Regardless of the method for threshold or calculation, mutation *D110H* does not meet any criteria. The *R347H-CFTR*

mutation (which was eligible for study 108) was never proposed to be part of the indication based on an *in vitro* increase in chloride transport below the pre-defined threshold of 10%.

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 it is not further pursued. Head-to-head comparisons of TEZ/IVA vs. IVA were removed from the testing hierarchy in study 108 and therefore treatment differences between these two groups cannot be considered statistically significant in a formal sense.

The analysis of the event rate of pulmonary exacerbations in study 108 was annualised. However, the exacerbation rate even if 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.

The results of a second interim analysis of study 110 showed trends in maintenance of effect in ppFEV1, CFQ-R respiratory domain and BMI. However, the conclusion is based on interim results of study 110. 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 and could not be confirmed in the pivotal study 109.

Adolescents

The number of adolescent subjects was 116 in study 106 while it was 34 in study 108. The small number of adolescent subjects in study 108 calls for a word of caution when interpreting the results in this age group. Adolescent data were not specifically discussed in the first interim analysis of study 110 in spite of the fact that subjects in this age subset are at higher risk of lung function decline. Similarly, a decline in nutritional status is usually seen in adolescents that can be attributed to various factors. In study 106, the percentage of under-nourished subjects was higher in the adolescent group than in adult group. No meaningful changes in BMI-for-age z-score were seen in adolescent subjects in the TEZ/IVA group in study 106.

As a consequence, subgroup analyses of change of ppFEV1 and BMI z-score were requested as part of the interim analysis 2 of study 110. These suggest that young subjects homozygous for *F508del* are at higher risk of lung status decline as a loss of 0.8 pp in ppFEV1 is seen at week 24 of study 110 in the TEZ/IVA group compared to -0.3 in the adult population.

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 to inform long term administration, is still lacking in sufficient patient-years of exposure to inform long latency or rare adverse effects. This information will become available during post-marketing pharmacovigilance. Thirteen subjects older than 65 years have been enrolled in the clinical program, with 6 of them enrolled in study 108. 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. However, no apparent new safety signals were observed in these subjects. Out of the 5 pregnancies reported in phase 3 trials, the outcome is known for 3 of them. Three healthy children were born. For the remaining two, the outcome is not known due to lost to follow-up and to lack of agreement to sign pregnancy informed consent form. There is still limited experience in pregnant women, as stated in the SmPC.

3.6. Effects Table

Table 40 Effects Table for Kalydeco indicated in combination with Symkevi for treatment of patients with CF aged 12 years and older who are homozygous for the *F508del* mutation or who have at least 1 mutation in *CFTR* gene that is responsive to TEZ/IVA based on in vitro data and/or clinical evidence* 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 (study 106)							
			TEZ/ IVA		Place-bo		
ppFEV1	Absolute change baseline –wk 24	Percentage points (pp)	3.4	N/A	-0.6	Clinically relevant	1*
PEx	Estimated event rate through week 24	Number /year	0.64	N/A	0.97	Clinically relevant but the definition allows for the use of oral antibiotics.	1

Effect	Short Description	Unit	Treatment	Control 1	Control 2	Uncertainties/ Strength of evidence	References
PEx that require IV antibiotic therapy	Estimated event rate through week 24	Number /year	0.54	N/A	0.29	Clinically relevant. Less than 25% of patients in each group had such an event at week 24 of study 106 which is below that expected based on unpublished data from the CFFPR.	
BMI	Absolute change baseline –wk 24	Kg/m^2	0.18	N/A	0.12	Testing hierarchy broken (p>0.05) Limited improvement but better trend for TEZ/IVA.	1
CFQ-R	Absolute change baseline –wk 24	Points	5.0	N/A	-0.1	Last endpoint in the testing hierarchy after BMI. Statistical significance cannot be claimed. Treatment difference above the MCID (≥ 4 points)	1
Sweat chloride	Absolute change baseline –wk 24	mmol/L	-9.9	N/A	0.2		1

CF patients with F508del/RF genotype (study 108)

			TEZ/ IVA	IVA	Place-bo		
ppFEV1	Absolute change baseline W8	pp	6.5	4.4	- 0.3	Relevant difference with placebo, but not in all mutations. Small difference with IVA but still relevant (when compared to the rate of decline estimated in the CFFPR of −1.05).	2*
CFQ-R	Absolute change form baseline W8	Points	10.1	8.7	- 1.08	Relevant difference with placebo. Small difference with IVA.	2
PEx	Estimated event rate up to week 8	Number /year	0.34	0.29	0.63	Short period to estimate pulmonary exacerbations. Relevant difference with placebo but not with IVA	2
BMI	Absolute change baseline-wk 8	Kg/m^2	0.34	0.47	0.18	Short period to asses BMI. Relevant difference with placebo but not with IVA	2

Effect	Short Description	Unit	Treatment	Control 1	Control 2	Uncertainties/ Strength of evidence	References
Sweat chloride	Absolute change baseline-wk 8	mmol/L	-9.9	-4.9	0.4		2
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		

Abbreviations: PEx: Pulmonary exacerbations; TEAE: treatment emergent adverse event; PC-SS: Phase III-controlled safety set
Notes:
*1 refers to study 106, 2 refers to study 108 and 3 refers to study 110.
** 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.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The FEV1 as a surrogate endpoint is a well-established endpoint and slowing the rate 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. Body weight is related to lung function and improving this extra-pulmonary endpoint is also a clinical relevant objective of the treatment of cystic fibrosis. The dose regimen for adolescents has been established in the clinical studies and supported by population PK model. Adolescents are at a higher risk of lung function decline. Similarly, a decline in nutritional status is usually seen in this age subset that can be attributed to various factors.

CF patients 12 years or older homozygous for the F508del-CFTR mutation

<u>Importance of the favourable effects</u>

The observed difference between TEZ/IVA and placebo of 4.0 pp in absolute change of ppFEV1 is above the predefined threshold (2.5 pp) and also above the definition of clinical relevance 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. The interim results in study 110 in the patients on previous placebo treatment in study 106 mirror the results of week 24 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 3pp. A rate reduction of 0.35 was seen in pulmonary exacerbations. For pulmonary exacerbations that require IV antibiotic therapy the rate reduction was 0.25. These are positive findings given the impact these events have in the quality of life and disease progression.

<u>Strength of the evidence</u>

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 pre-specified subgroups with the lowest point estimate still clinically relevant. The results of the primary parameter are supported by some of the secondary endpoints, namely the rate reduction in pulmonary exacerbations (95% CI: 0.48, 0.88; P = 0.0054). Changes in BMI although not statistically significant, favour TEZ/IVA numerically. A responder analysis of under-nourished patients based on the achievement of a target BMI revealed more responders in the TEZ/IVA compared with placebo group (i.e., 32.4% vs. 26.8% respectively at week 24 of study 106) which is particularly relevant for adolescent subjects as most undernourished subjects were in this age group. Also, numerically, the change in the respiratory domain score of CFQ-R favours TEZ/IVA (p-value N/A).

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 overall more or less the changes experienced during the parent study. It has been confirmed that ivacaftor alone is not efficacious in CF patients with F/F mutation (study 104).

<u>Impact of the uncertainties</u>

The proposed dose regimen is questioned especially from the perspective 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 ivacaftor to treat homozygous *F508del* patients.

The secondary endpoint hierarchy was broken at the level of BMI. For this important extra-pulmonary parameter no clinically meaningful within-group changes in the mean BMI were observed in the TEZ/IVA or placebo groups (95% CI: -0.08, 0.19; P = 0.4127). This also applies to the adolescent group in which no meaningful differences in BMI z-scores between treatment groups were seen either.

The respiratory domain of the CFQ-R was the last key secondary endpoint in the testing hierarchy and therefore, although the change favours TEZ/IVA group, the result cannot be formally declared as statistically significant.

For pulmonary exacerbations that require intravenous therapy, less than 25% of patients in each group had such an event during the parent study period which is below the annual risk reported in the CFF Patient Registry (around 45%, unpublished data). In particular, in the placebo group the percentage of subjects with pulmonary exacerbations that require intravenous therapy was 21.1% (n=54). This may partially reflect the fact that study duration is still too short to properly assess pulmonary exacerbations.

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 although additional improvement is not

usually observed over that achieved in the parent study. This conclusion is based on interim results of study 110. Further data from this study are expected beyond 24 weeks of treatment with TEZ/IVA. An accurate and precise interpretation of the data would require a control group as the disease progresses over time.

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

<u>Importance of the favourable effects</u>

The obtained difference of TEZ/IVA in absolute change of ppFEV1 of 6.8 pp is above the predefined threshold (3.0 pp) 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 substantially above the 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.

<u>Strength of the evidence</u>

The primary analysis provided evidence for the efficacy of TEZ/IVA in ppFEV1 (95% CI 5.7, 7.8; p <0.0001). The sensitivity analysis confirmed the primary analysis. In addition, the improvements in ppFEV1 favouring TEZ/IVA were consistent across the prespecified subgroups. The improvement 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 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.

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 anymore for the indication of TEZ/IVA.

<u>Impact of the uncertainties</u>

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 procedure 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). This short treatment duration hampers a proper assessment of the rate of pulmonary exacerbations and body weight. However, the 16 weeks extension data provided show that the previous placebo treated group when switched to active treatment experienced a similar effect as the initial TEZ/IVA group. The

patients who continued treatment with TEZ/IVA kept overall the changes experienced during the parent study. This conclusion is based on interim results of study 110. Further data from this study are expected beyond 16 weeks of treatment with TEZ/IVA. An accurate and precise interpretation of the data would require a control group as the disease progresses over time.

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 pp, but this is still considered relevant in relation to an overall estimated annualized ppFEV1 rate of decline of −1.05 percentage points in F/RF patients (excluding subjects with an *R117H-CFTR* mutation). Although for pulmonary exacerbations the reduction of event rate was higher with monotherapy IVA, the event rate is not reliable because of the short-time period of treatment (8 weeks).

For the secondary endpoint respiratory domain of 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, study 108 met its primary endpoint overall, for some of the individual mutations, the number of patients is small. This limits the interpretation of the results per mutation.

No significant new or additional safety concerns were identified with the addition of tezacaftor to ivacaftor. The safety profile of the combination appeared similar across studies. There were no latent, late onset safety issues or risks identified in the long term safety sets analysed. Tezacaftor and ivacaftor in combination were overall well tolerated with low discontinuation rates due to adverse events.

3.7.2. Benefit-risk balance

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 is demonstrated that TEZ/IVA provides clinical benefit to CF patients with F/F mutation particularly in what refers to pulmonary function as shown by the treatment difference in the absolute change in ppFEV1 and the reduction in pulmonary exacerbations. A modest effect is seen in the group of TEZ/IVA-treated patients as well as in under-nourished patients in terms of BMI improvement. The statistical approach is overall sound. The interim results of study 110 of all the important parameters are indicative of the maintenance of the effect in 70% of the available patients. Further data from this study are expected beyond 24 weeks of treatment with TEZ/IVA.

In study 101, the data and the exposure-response analyses do not provide full reassurance of a need for IVA to treat homozygous *F508del* patients. Although there is consistency of response in FEV1 between phase II and phase III studies, suggesting superiority of the combination, this is in contrast to the sweat chloride results, and there remain uncertainties and inconsistencies.

These data cannot be disregarded as clinically irrelevant when the scientific literature points to the interdependence of chloride channel gating and CFTR protein localization on protein folding, which blurs the distinction between corrector and potentiator action. 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 Ussing 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) the clear demonstration of superiority for TEZ/IVA over placebo in homozygous *F508del* patients resulting in relevant improvements in this population. However, 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. However, a benefit can only be considered established for the mutations that are supported by clinical data. The mutations proposed to be included in the indication based only on *in vitro* responsiveness to TEZ/IVA have not been sufficiently justified. A relationship between the extent of *in vitro* responsiveness in FRT cells and clinical response could not be established.

The pivotal study 108 faces the concern of the short duration while data are available in the extension study 110 up to 24 weeks of continuous treatment with TEZ/IVA only in subjects who received TEZ/IVA in the second treatment period of study 108. The data of the first interim analysis of study 110 are indicative of maintenance of the effect in 70% of the available patients. Further data from this study are expected beyond 16 weeks of treatment with TEZ/IVA.

Because TEZ/IVA is a new therapy with an indication that includes genotypes eligible for 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 pre-specified 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 Kalydeco 150 mg tablets is positive in the following extended indication:

Kalydeco tablets are also indicated in a combination regimen with tezacaftor 100 mg/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 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

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		Type	Annexes affected
B.II.e.5.a.2	Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	Type IB	A, I, II, IIIA and IIIB
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	A, I, II, IIIA and IIIB

1) C.I.6.a (type II) - Extension of Indication to include the combination regimen with tezacaftor 100 mg/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*;
2) B.IIe.5.a.2 (type IB) - to add a blister card pack presentation containing 28-tablets for the 150 mg film-coated tablets (EU/1/12/782/005);
As a consequence, section 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1, 5.2, 5.3, 6.4, 6.5, 6.6, 7 and 8 of the SmPC are updated. Annex A, the Package Leaflet and Labelling are updated in accordance.
An updated RMP (version 7.10) is included.

The group of variations leads to amendments to the Annex A, Annex II, Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in

accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

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.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Long-term effectiveness study to compare disease progression among children with CF who have a specified CFTR gating mutation and are aged 2 through 5 years at the time of Kalydeco treatment initiation versus disease progression among concurrent matched cohort of children with CF who have never received Kalydeco treatment.	Final Report: December 2023

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0147/2017 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Kalydeco is not similar to Bronchitol, TOBI Podhaler and Cayston within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.
See appendix 1.

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

1) C.I.6.a (type II) - Extension of Indication to include the combination regimen with tezacaftor 100 mg/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*;
2) B.IIe.5.a.2 (type IB) - to add a blister card pack presentation containing 28-tablets for the 150 mg film-coated tablets (EU/1/12/782/005);

As a consequence, section 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1, 5.2, 5.3, 6.4, 6.5, 6.6, 7 and 8 of the SmPC are updated. Annex A, the Package Leaflet and Labelling are updated in accordance.
An updated RMP (version 7.10) is included.

The group of variations leads to amendments to the Annex A, Annex II, Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Summary

Please refer to Scientific Discussion 'Kalydeco-H-C-2494-II-63-G'.

Attachments

1.   SmPC, Annex II, Labelling and Package Leaflet (changes highlighted) as adopted by the CHMP on 26 July 2018.

Appendix

1.   CHMP AR on similarity dated 26 July 2018.

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by 9 August 2018. The principles to be applied for the deletion of CCI are published on the EMA website at
   http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/03/WC500124536.pdf.

2. The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

3. If the approved RMP is using Rev. 2 of the 'Guidance on the format of the RMP in the EU' and the RMP 'Part VI: Summary of the risk management plan' has been updated in the procedure, the MAH is reminded to provide to the EMA Procedure Assistant by Eudralink a PDF version of the 'Part VI: Summary of the risk management plan' as a standalone document, within 14 calendar days of the receipt of the CHMP Opinion. The PDF should contain only text and tables and be free of metadata, headers and footers.

4. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, or prior to the next regulatory activity, whichever is first. For additional guidance see chapter 4.1 of the *Harmonised Technical Guidance for eCTD Submissions in the EU*.