10 July 2020
EMA/385871/2020 Rev.1
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kaftrio

International non-proprietary name: ivacaftor / tezacaftor / elexacaftor

Procedure No. EMEA/H/C/005269/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Background information on the procedure 7
1.1. Submission of the dossier 7
1.2. Steps taken for the assessment of the product 8
2. Scientific discussion 9
2.1. Problem statement 9
2.1.1. Epidemiology 10
2.1.2. Aetiology and pathogenesis 10
2.1.3. Clinical presentation and diagnosis. 11
2.1.4. Management 12
2.2. Quality aspects 13
2.2.1. Introduction 13
2.2.2. Active Substance 14
2.2.3. Finished Medicinal Product 24
2.2.4. Discussion on chemical, pharmaceutical and biological aspects 31
2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects 32
2.2.6. Recommendation for future quality development 32
2.3. Non-clinical aspects 32
2.3.1. Introduction 32
2.3.2. Pharmacology 33
2.3.3. Pharmacokinetics 36
2.3.4. Toxicology 41
2.3.5. Ecotoxicity/environmental risk assessment 46
2.3.6. Discussion on non-clinical aspects 49
2.3.7. Conclusion on non-clinical aspects 57
2.4. Clinical aspects 57
2.4.1. Introduction 57
2.4.2. Pharmacokinetics 58
2.4.3. Pharmacodynamics 63
2.4.4. Discussion on clinical pharmacology 64
2.4.5. Conclusions on clinical pharmacology 66
2.5. Clinical efficacy 66
2.5.1. Dose-response studies 69
2.5.2. Main studies 72
2.5.3. Discussion on clinical efficacy 112
2.5.4. Conclusions on clinical efficacy 124
2.6. Clinical safety 124
2.6.1. Discussion on clinical safety 154
2.6.2. Conclusions on clinical safety 158
2.7. Risk Management Plan 158
2.8. Pharmacovigilance 162
2.9. New Active Substance 162
2.10. Product information 162

2.10.1. User consultation 162
2.10.2. Additional monitoring 162
3. Benefit-Risk Balance 162
3.1. Therapeutic Context 162
3.1.1. Disease or condition 162
3.1.2. Available therapies and unmet medical need 163
3.1.3. Main clinical studies 163
3.2. Favourable effects 164
3.3. Uncertainties and limitations about favourable effects 166
3.4. Unfavourable effects 167
3.5. Uncertainties and limitations about unfavourable effects 169
3.6. Effects Table 170
3.7. Benefit-risk assessment and discussion 172
3.7.1. Importance of favourable and unfavourable effects 172
3.7.2. Balance of benefits and risks 175
3.7.3. Additional considerations on the benefit-risk balance 177
3.8. Conclusions 177
4. Recommendations 177

List of abbreviations

ADR	adverse drug reaction
AE	adverse event
ALT	alanine transaminase
ARAUC	accumulation ratio of AUC
AST	aspartate transaminase
AUC	area under the concentration versus time curve
AUC_T	AUC during a dosing interval
BA	bioavailability
BL	baseline
BMI	body mass index
BP	blood pressure
bpm	beats per minute
C_{avg}	average concentration during a dosing interval at steady-state
CF	cystic fibrosis
CFF-TDN	Cystic Fibrosis Foundation Therapeutics Development Network
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFQ-R RD	Cystic Fibrosis Questionnaire-Revised Respiratory Domain
CFTR	cystic fibrosis transmembrane conductance regulator gene
CFTR	cystic fibrosis transmembrane conductance regulator protein
CI	confidence interval
CK	creatine kinase
C_{max}	maximum observed concentration
C_{min}	minimum observed concentration
CSR	clinical study report
CYP	cytochrome P450
C-QTc	concentration-QTc
DBP	diastolic blood pressure
DDI	drug-drug interaction
ECFS-CTN	European Cystic Fibrosis Society Clinical Trials Network
ECG	electrocardiogram
EE	ethinyl estradiol
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOP2	End-of-Phase 2
E-R	exposure-response
EU	European Union
F/F	homozygous for F508del
F/G	heterozygous for F508del and a gating mutation
F/MF	heterozygous for F508del and an MF mutation
F/RF	heterozygous for F508del and a residual function mutation

F508del	CFTR gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
FEV_1	forced expiratory volume in 1 second
G	gating
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HBE	human bronchial epithelial
HR	heart rate
IA	interim analysis
iFAS	interim Full Analysis Set
INR	international normalized ratio
IV	intravenous
IVA	ivacaftor
LFT	liver function test
LN	levonorgestrel
LS	least squares
LUM	lumacaftor
MA-FAS	Meta-analysis Full Analysis Set
MCID	minimum clinically important difference(s)
MF	minimal function
MMRM	mixed-effects model for repeated measures
NDA	New Drug Application (US)
OATP1B1	organic anion transporting polypeptide B1
OATP1B3	organic anion transporting polypeptide B3
ODD	orphan drug designation
OE	ophthalmological examination
OLE	open-label extension
OL-FAS	Open-label Full Analysis Set
PD	pharmacodynamic
PDCO	European Medicines Agency Pediatric Committee
PEx	pulmonary exacerbation
P-gp	P-glycoprotein
PIP	pediatric investigation plan
PK	pharmacokinetic
PMR	post-marketing requirement
popPK	population PK
$ppFEV_1$	percent predicted forced expiratory volume in 1 second
PT	Preferred Term
PY	patient-year
q12h	every 12 hours

qd	once daily
qod	every other day
QT	QT interval
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's formula
RF	residual function
SAE	serious adverse event
SBP	systolic blood pressure
SCS	summary of clinical safety
SD	standard deviation
SE	standard error
SwCl	sweat chloride
t½	terminal phase half-life
TC	triple combination
TEAEs	treatment-emergent adverse events
TEZ	tezacaftor
t_{max}	time of maximum concentration
UK	United Kingdom
ULN	upper limit of normal
US	United States
VX-445 :	elexacaftor

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Vertex Pharmaceuticals (Ireland) Limited submitted on 14 October 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Kaftrio, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 13 December 2018.

Kaftrio was designated as an orphan medicinal product EU/3/18/2116 on 14 December 2018 in the following condition: Treatment of cystic fibrosis.

The applicant applied for the following indication:

"Kaftrio is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene."

The legal basis for this application refers to:

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

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0091/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-002324-PIP01-17 was not yet completed as some measures were deferred.

Similarity

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

New active Substance status

Based on the CHMP review of the available data, the CHMP considers that ivacaftor/tezacaftor/elexacaftor is a new active substance as elexacaftor is not a constituent of a medicinal product previously authorised within the European Union and it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any EU authorised active substance.

Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
25 January 2018	EMA/CHMP/SAWP/9006/2018	Karin Janssen van Doorn, David Brown

The Protocol Assistance pertained to the following clinical aspects:

- Adequacy of the proposed clinical development plan to support an initial marketing authorisation application (MAA) for CF patients aged 12 and older heterozygous for the *F508del* mutation and a "MF" mutation, including a single 24-week pivotal randomized, double-blind, placebo-controlled Phase 3 study in approximately 360 F/MF subjects with the primary endpoint absolute change in ppFEV1 at Week 4. The study would also assess the effect on pulmonary exacerbation rate. Specific questions were raised on the use of an interim analysis of the 4-week primary endpoint to support the MAA submission, and the proposed safety database.
- Acceptability of the proposed clinical development plan to support an expansion of the MAA indication to patients with CF aged 12 years and older who have the *F508del* mutation on at least 1 allele, including a randomized, double-blind, active comparator-controlled (TEZ/IVA), 4-week Phase 3 study in CF subjects, aged 12 years and older, with the F/F genotype with the primary endpoint absolute change in ppFEV1 at Week 4.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Peter Kiely

The application was received by the EMA on	14 October 2019
Accelerated Assessment procedure was agreed-upon by CHMP on	19 September 2019
The procedure started on	31 October 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	2 January 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	23 December 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	8 January 2020
In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 January 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	28 January 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	27 March 2020

The timetable was reverted to a standard timetable due to the Applicant request for a 3 months clock stop finally reduced to 2 months	
A GCP inspection at 2 investigators sites in Germany and Czech Republic between 18-28 November 2019. The outcome of the inspection carried out was issued on 16 January 2020.	
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	5 May 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	14 May 2020
The Rapporteurs circulated the updated Joint Assessment Report on the responses to the List of Questions to all CHMP members on	21 May 2020
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	28 May 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	1 June 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	10 June 2020
The Rapporteurs circulated the updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	18 June 2020
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	23 June 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Kaftrio on	25 June 2020
The CHMP adopted a report on similarity of Kaftrio with Kalydeco, Symkevi, Bronchitol, and Tobi Podhaler on	25 June 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive revised opinion for granting a marketing authorisation to Kaftrio on	10 July 2020
The CHMP adopted a corrected report on similarity of Kaftrio with Kalydeco, Symkevi, Bronchitol, and Tobi Podhaler on	10 July 2020

2. Scientific discussion

2.1. Problem statement

The claimed indication reads as follows:

Kaftrio is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene.

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. The *CFTR* protein is an epithelial chloride channel responsible for aiding in the regulation of salt and water absorption and secretion. The failure to regulate chloride transport in these organs results in the multisystem pathology associated with CF.

In people with CF, loss of chloride transport due to defects in the *CFTR* protein 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.

F508del, is the most common disease-causing mutation (84.7% of the individuals in the US and 81.1% of the individuals in Europe)[1,2]. With the proposed indication, this would result in treatment possibility in a vast majority of the patients.

2.1.1. Epidemiology

CF affects approximately a total of 31,000 individuals in the US and a total of 42.000 in the EU (excluding the data from Russia, Turkey and Israel)[1,2]. The incidence and prevalence of CF varies between racial groups; CF is considerably more common in the Caucasian populations of North America and Europe than in Asian and African populations. In Europe, the median age of all CF patients is 18.5 years (with youngest patient being diagnosed just after birth and the oldest patients being 88.4 years of age). Despite advances in treatment, the current median age of death in a patient with CF was approximately 31 years in 2018, and the future predicted median age of survival is approximately 47 years[1,2].

2.1.2. Aetiology and pathogenesis

The *CFTR* protein is an epithelial chloride ion (CL-) channel located in the epithelia of multiple organs, including lungs, pancreas, intestinal tract, liver, and vas deferens, that is responsible for aiding in the regulation of salt and water absorption and secretion. More than 2000 mutations in the *CFTR* gene have been identified.

CFTR mutations can be classified according to the mechanisms by which they disrupt *CFTR* function.

- Class I mutations: Defective protein production
- Class II mutations: Defective protein processing
- Class III mutations: Defective regulation
- Class IV mutations: Defective chloride conduction
- Class V mutations: Reduced amounts of functional *CFTR* protein (less transcription)

Class I, II and III usually lead to a classic (severe) CF phenotype with pancreatic insufficiency.

Class IV and V are mostly associated with a milder expression of the disease.

[1] Cystic Fibrosis Foundation. Patient Registry: 2018 Annual Data Report. Bethesda, MD: Cystic Fibrosis Foundation; 2019.

[2] European Cystic Fibrosis Society. 2017 ECFS Patient Registry Annual Data Report. Karup, Denmark: European Cystic Fibrosis Society; 2019.

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

More than 2000 mutations of the CFTR gene have been identified. Most of these mutations are not associated with CF disease or are very rare. Currently, the CFTR2 database (an online resource that provides clinical and nonclinical data about CF-associated *CFTR* mutations) contains information on 412 of these identified mutations, with sufficient evidence to define 346 mutations as disease causing.

CF-causing mutations can be divided into 2 groups based on the extent of loss of chloride transport caused by the mutation. In general, a complete or near complete loss of *CFTR* chloride transport is referred to as "minimal function" of *CFTR* (class I, II and III). A less complete loss of *CFTR*-mediated chloride transport is referred to as "residual function" of *CFTR* (class IV and V).

The applicant uses slightly different definitions, especially when considering "minimal function" mutations.

- Gating mutations (G) result in a *CFTR* protein with a primary defect of low channel open probability compared to normal *CFTR.* (comparable to Class III)
- Residual function (RF) mutations result in a more modest reduction in *CFTR*-mediated chloride transport than Class I mutations or minimal function mutations. (comparable to Class IV)
- Minimal function (MF) mutations produce (1) no *CFTR* protein or (2) a *CFTR* protein that is not responsive to IVA and TEZ/IVA *in vitro*. (comparable to Class I) (see Table 8 overview of MF mutations used in study 102)

For convenience, in this assessment report the definitions of the Applicant will be used, and 4 different CF population are described:

- Homozygous for *F508del* (F/F)
- Heterozygous for *F508del* and a minimal function mutation (F/MF)
- Heterozygous for *F508del* and a gating mutation (F/G)
- Heterozygous for *F508del* and a residual function mutation (F/RF)

2.1.3. Clinical presentation and diagnosis.

CF is diagnosed when both of the following criteria are met:

- Clinical symptoms consistent with CF in at least one organ system (CLASSIC), or positive newborn screen or genetic testing for siblings of patients with CF

  AND

- Evidence of *CFTR* dysfunction (any of the following):
  - Elevated sweat chloride ≥60 mmol/L (CLASSIC)
  - Presence of two disease-causing mutations in *CFTR*, one from each parental allele
  - Abnormal nasal potential difference

Around 2 % of patients lack one or more of the "CLASSIC" features. They may have milder clinical symptoms and/or normal to intermediate sweat chloride results. These patients can still be diagnosed with CF if they meet genetic or functional criteria[3].

2.1.4. Management

Existing treatments for CF can be broadly classified in 2 groups: (1) therapies that manage the symptoms, complications, and comorbidities of the disease (e.g., antibiotics, mucolytics, pancreatic enzyme replacement therapy) and (2) *CFTR* modulators (i.e., correctors and potentiators) which target the underlying cause of the disease. Concomitant administrations of these two groups is recommended to maintain and improve lung function, reduce the risk of infections and exacerbations, and improve quality of life.

(1) CF therapies currently available, including nutritional supplements, antibiotics, and mucolytics, target the downstream consequences and symptoms of the disease. These therapies are predominantly generic medicines authorized at a national level, apart from agents for the management of chronic pulmonary infections due to Pseudomonas aeruginosa.

(2) *CFTR* modulators are small molecules that target specific defects caused by mutations in the *CFTR* gene. Correctors (tezacaftor and lumacaftor) facilitate the cellular processing and trafficking of *CFTR* to increase the quantity of *CFTR* at the cell surface. Potentiators (ivacaftor) increase the channel open probability (channel gating activity) of the *CFTR* protein delivered to the cell surface to enhance chloride transport. A combination of a corrector and a potentiator, should results in sufficient levels of *CFTR* at the surface, which is then enhanced for its gating function. Kalydeco (ivacaftor, IVA), Orkambi (lumacaftor/ivacaftor, LUM/IVA) and Symkevi (tezacaftor/ivacaftor, TEZ/IVA) are *CFTR* modulators approved for CF patients with specific mutations. Not all *CFTR* genotypes are indicated for approved modulator therapies, and not all patients are able to tolerate the therapy.

Therefore, the applicant continued to develop additional modulators that would drive higher levels of *CFTR* function from *F508del-CFTR* mutation. According to the Applicant, if a *CFTR* modulator regimen had a large enough effect on *F508del-CFTR,* then the presence of a single *F508del* allele alone would be sufficient to derive significant clinical benefit. That single regimen would be effective in all patients with at least one *F508del* allele, regardless of the mutation on the second allele. If the second allele is also responsive, any benefit derived from that allele would be in addition to the substantial benefit derived from the robust effect on *F508del-CFTR*. Importantly, for patients who have one *F508del* allele and are currently being treated with *CFTR* modulators (i.e. F/G and F/RF patients), their F*508del* allele seems not being fully leveraged because approved regimens primarily target the gating (IVA) or RF (IVA and TEZ/IVA) allele with limited modulation of the single *F508del* allele; these patients too would benefit from additional, highly effective modulation of their *F508del*.

About the product

Kaftrio belongs to the pharmacotherapeutic group of other respiratory system products with ATC code R07AX. Kaftrio is a triple combination product which contains the new *CFTR* modulator elexacaftor (VX-445), and the known *CFTR* modulators ivacaftor and tezacaftor.

Tezacaftor, as *CFTR* corrector, facilitates the cellular processing and trafficking of *CFTR* (including *F508del-CFTR*) to increase the amount of functional CFTR protein delivered to the cell surface, resulting in increased chloride transport. Ivacaftor, as a *CFTR* potentiator, potentiates the channel-

[3] Farrell PM, White TB, Ren CL, et al. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. J Pediatr 2017; 181S:S4.

open probability (or gating) of *CFTR* at the cell surface to increase chloride transport. Elexacaftor, as next-generation *CFTR* corrector, also facilitates the cellular processing and trafficking of *CFTR*. The product is considered to have a different chemical structure and a different mechanism of action as the first generations of *CFTR* correctors (TEZ, LUM) and potentiator (IVA).

The combination of elexacaftor, tezacaftor and ivacaftor should result in increased quantity and function of *CFTR* at the cell surface, resulting in increases in chloride transport, airway surface liquid height, and ciliary beat frequency.

The proposed posology for Kaftrio is as follows:

- Morning dose: 2 fixed-dose combinations (FDC) tablets (each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg), supplied as an orange, film-coated tablet.
- Evening dose: 1 tablet containing 150 mg of ivacaftor, supplied as a blue, film-coated tablet.

Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest in two subpopulations (F/MF and F/F) of the intended indication.

This was based on:

1) Unmet need: Although for a majority of the intended target population approved treatment are available, these treatments can limit disease progression to a certain extent. Therefore, an unmet need could still be present. For the F/MF population, no modulator treatment is approved and therefore the unmet need could be acknowledged.
2) Efficacy: In the F/MF and F/F population benefits are observed for the triple combination compared to placebo, for lung function, sweat chloride and CFQ-R RD. These data appeared to support the claim that the triple combinations will be able to address the unmet need in these populations. No efficacy data were presented for the F/G and F/RF populations.

However, during assessment the CHMP concluded that it was no longer appropriate to pursue accelerated assessment, since the applicant requested a 3 months clock stop ultimately reduced to 2 months. Therefore, the conditions for accelerated assessment could no longer be met.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as fixed dose combination (FDC) film-coated tablets containing 75 mg of ivacaftor, 50 mg of tezacaftor and 100 mg of elexacaftor.

The other ingredients of the table core are: hypromellose (E464), hypromellose acetate succinate, sodium laurilsulfate (E487), croscarmellose sodium (E468), microcrystalline cellulose (E460(i)) and magnesium stearate (E470b.

The ingredients of the tablet film coat are: hypromellose (E464), hydroxypropyl cellulose (E463), titanium dioxide (E171), talc (E553b), iron oxide yellow (E172) and iron oxide red (E172).

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

Of note, the ivacaftor and tezacaftor active substances are identical to those used in Kalydeco (ivacaftor) tablets and granules (EMEA/H/C/002494), Orkambi (lumacaftor/ivacaftor) tablets (EMEA/H/C/003954) and Symkevi (tezacaftor/ivacaftor) tablets (EMEA/H/C/004682), already approved in the EU. During the manufacture of the finished product, ivacaftor and tezacaftor active substances are fully dissolved in a spray-drying solvent system and spray-dried to stabilise their amorphous forms into an intermediate, known as the spray-dried dispersion (SDD). The ivacaftor and tezacaftor SDDs used in the manufacture of Kaftrio are the same as those used in the manufacture of the named approved products.

2.2.2. Active Substance

Ivacaftor

Full information has been provided in the dossier for this active substance.

The applicant has confirmed that "the quality data supporting the ivacaftor active substance and SDD used in the manufacture of the Kaftrio FDC finished product is identical to that submitted and currently approved for Kalydeco (EMEA/H/C/002494) and Symkevi (EMEA/H/C/004682)". Therefore, detailed assessment of the already approved data supporting ivacaftor active substance and SDD has not been conducted within this marketing authorisation review.

General information

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

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

The compound has the following molecular structure:

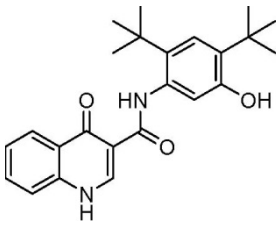


Figure 1: ivacaftor structure

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

Ivacaftor has a non-chiral molecular structure.

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

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

Ivacaftor active substance shows polymorphism. Development studies resulted in the discovery of 25 forms, 2 hydrates, and 19 solvated forms. Techniques and approaches used to generate polymorphic forms included crash cooling, rapid solvent evaporation, anti-solvent addition precipitation, slurry techniques, thermal treatment of amorphous material, and chemical process development. XRPD, solid

state NMR, and synchrotron radiation were used to distinguish the forms. Spectroscopic methods (FTIR, Raman, solid state NMR), thermal analyses (thermal gravimetric analysis, differential scanning calorimetry), and moisture sorption/desorption analysis were used to characterize the individual neat polymorphs.

The active substance produced by the proposed manufacturing process consists of a mixture of two major crystalline neat polymorphic forms. This is attributed to the fact that both forms nucleate under the process conditions used during the final crystallization step and conversion of one form into the other is slow and not typically completed before isolation of the active substance. The control of the final isolation and drying conditions ensures that mixtures of the neat crystalline forms is consistently produced. Nevertheless, the polymorphic form of ivacaftor during the synthesis of the active substance is not a critical quality attribute (CQA) since during the manufacture of the finished product, ivacaftor is fully dissolved in a spray-drying solvent system to provide an amorphous intermediate, the SDD, which is then converted to the final finished product. Therefore, ivacaftor's physical form is only a CQA for ivacaftor SDD (spray dried dispersion) and the final tablets, since it is critical to maintain the amorphous form to ensure bioavailability.

Manufacture, characterisation and process controls

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

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

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

Although the design spaces were developed at small laboratory scales, a design space verification protocol providing demonstration of the risk of scale dependence of the parameters which define each design space was submitted. For the first three design spaces the assessment concluded that there is low risk of scale dependence and, therefore, the ranges defined at laboratory scale are applicable to commercial scale. This is supported by confirmatory experiments and scale up/down calculations conducted at pilot scale at the higher risk points in the design space. For the fourth design space, the engineering-based assessment determined that there is a higher risk of scale dependence than for the other three design spaces. Data were collected from the commercial scale and multiple confirmatory experiments, supported by appropriate engineering modelling, and scale up/down calculations were conducted. The robustness of the process has been confirmed with the manufacture of fifteen large-scale batches of ivacaftor active substance, which have consistently met the acceptance criteria for all active substance CQAs. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design spaces.
Ivacaftor active substance is packaged inside a low density polyethylene (LDPE) bag and secured with an appropriate closure (twist tie or equivalent). The bag is then placed inside a second LDPE bag and

secured appropriately; the closed LDPE bags are placed into a secondary container suitable for storage and shipping. The LDPE is compliant with the Directive 2002/72/EC and the European Pharmacopoeia Monograph 3.1.3 "Polyolefins".

Specification

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

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

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

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

Stability

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

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

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

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

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

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 48 months in the proposed container closure system, which is the one authorised in Kalydeco and Orkambi.

Tezacaftor

Full information has been provided in the dossier for this active substance. The applicant has confirmed in their cover Letter that "the quality data supporting the tezacaftor active substance and SDD used in the manufacture of the Kaftrio FDC finished product is identical to that submitted and currently approved for Symkevi 100/150 mg film-coated tablets (EMEA/H/C/004682 - EU/1/18/1306/001)". This has been supplemented in Kaftrio dossier with additional batch analysis and stability data. Therefore, detailed assessment of the already approved data supporting tezacaftor active substance and SDD has not been conducted within this marketing authorisation review.

General information

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

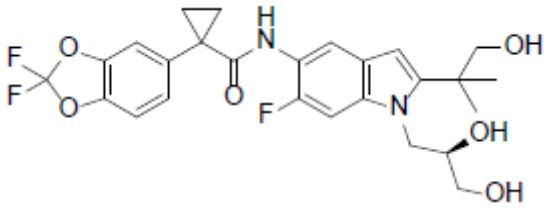


Figure 2: tezacaftor structure

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

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

Tezacaftor is a non-hygroscopic white to off-white crystalline solid. The substance is practically insoluble in aqueous solvents and more soluble in organic solvents. Because of its poor solubility in water, a SDD, where the active substance is in an amorphous form to provide sufficient oral bioavailability was developed (see finished product section).

Physical characterization of tezacaftor was conducted by X-ray powder diffraction, differential scanning calorimetry, thermal gravimetric analysis and dynamic vapour sorption. The physical form of tezacaftor active substance manufactured by the proposed commercial process is the most thermodynamically stable crystalline neat form. To understand the polymorph landscape of tezacaftor, a comprehensive polymorph screening for neat forms, solvates, and hydrates was conducted. Two neat forms were found. No hydrate has been found from multiple aqueous-based solvent systems.

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

Manufacture, characterisation and process controls

The commercial manufacturing process for the synthesis of tezacaftor involves seven steps from commercially available well-defined starting materials with acceptable specifications and several crystallizations.

The selected starting materials in the synthesis are approvable, in view of ICH Q11 and its Q&A, and the CHMP guideline on chemistry of the active substance (EMA/454576/2016); sufficient justification and discussion for the choice of these compounds is provided. The names and addresses of the starting material manufacturers/suppliers are laid down in the dossier. This also holds regarding the synthesis routes of the starting materials applied by the manufacturers/suppliers. Two active substances manufacturers which use the same route of synthesis are proposed. After the initial marketing authorisation for Symkevi, the applicant submitted a variation to make some changes to the manufacturing process of tezacaftor while maintaining consistent solution yields. The procedure for downstream steps remained the same. This change does not have any effect on the quality of the active substance.

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

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

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

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

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

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

Detailed information regarding the manufacturing process development of tezacaftor active substance has been presented. The changes made during development are considered minor and are not expected to impact on the quality of the active substance.

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

Specification

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

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

Specifically, the absence for a control of chiral purity has been justified on the basis that tezacaftor contains a single chiral center, which is a secondary carbinol. The tezacaftor enantiomer, arises from an enantiomeric impurity in one of the starting materials. The downstream chemistry does not promote racemization of the stereocentre, and no racemization was observed during tezacaftor active substance stability studies. In order to accomplish racemization, a multi-step procedure with specific conditions would be required. Therefore, the control of chiral purity of tezacaftor active substance is established according to ICH Q6A (decision tree #5) by applying limits in the starting material as supported by development studies. The carry over studies and design spaces studies showed that the stereo-chemical enantiomers, if formed, do not carry through the synthesis and that the limit established at starting material level is adequate. This justification is acceptable.

Elemental impurities are controlled in line with ICH Q3D.

All solvents are control well below the option 1 limit in draft ICH Q3C (R6).

Water content is not a CQA of tezacaftor because the crystalline active substance is non-hygroscopic , and water does not affect active substance stability or finished product manufacture.

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

Likewise, particle size of tezacaftor is not a CQA because the active substance is completely dissolved in the spray drying solvent system as the first step of the SDD manufacture.

Tezacaftor has not been shown to be bactericidal or bacteriostatic. However, the active substance manufacturing process follows classic chemical synthesis which is hostile to microorganisms. In addition, the microbial limits and water activity test results from 3 representative active substance lots presented show very low bioburden, absence of specified microorganisms using validated compendial microbial limits methods, and water activities less than 0.6 (consistent with the fact that the active substance has low hygroscopicity and indicating the material is not likely to support microbial growth).

The primary stability showed that water activity levels remain below the threshold for microbial growth promotion (0.6), and no change in microbial content after storage for 12 months at 25°C/60% RH in the intended container closure system. These combined data indicate that tezacaftor active substance possesses very low risk of microbial contamination and microbial testing of commercial lots is not necessary.

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

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

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

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

Batch analysis data on 21 pilot or commercial scale batches of the active substance used for non-clinical studies, clinical studies, and formal stability studies, or intended for future clinical or commercial use were provided for the approval for Symkevi. In addition, data from 11 commercial scale batches manufactured using the revised manufacturing process have been provided in the MAA dossier for Kaftrio. All the results are within the proposed specifications and consistent from batch to batch.

Stability

Stability data from three commercial scale batches of active substance from one of the proposed manufacturers stored in the intended commercial package for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: appearance, assay, organic impurities, chiral purity (HPLC), water content (KF titration), physical form (XRPD), microbial limits (USP <61> and <62>), specified microorganisms (*E. coli*) and water activity (USP <1112>). All results met the acceptance criteria for the attributes evaluated and no trends were observed. Water activity levels remained below the threshold for microbial growth promotion (0.6), and no change in microbial content after storage for 24 months at 25°C/60% RH in the intended container closure system was observed. The stability data show that tezacaftor active substance is stable when packaged in the intended container closure system under all storage conditions.

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

Results on stress studies including heat (80°C), heat/humidity (80°C/75%RH), treatment under acidic (0.2N HCl, ambient), basic (0.2N NaOH, ambient), and oxidative (0.02% H_2O_2, ambient) conditions for up to 14 days, and exposure to UV and visible light (solid and solution) were also provide on one batch. Tezacaftor was found to be the least stable under the oxidative condition and when exposed to light stress conditions in solution. Results from the primary stability studies demonstrate that none of the degradation products observed under these stress conditions are found at or above the reporting threshold when the active substance is packaged and stored according to label requirements. No degradation was observed when tezacaftor was exposed to the other stress conditions listed above.

All tezacaftor samples from this study were tested for spectral peak purity. The tezacaftor peak was found to be spectrally pure in all stressed samples demonstrating that the commercial HPLC method for assay and organic impurities determination of tezacaftor active substance is stability indicating.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 36 months when stored in the proposed container at no more than 30°C.

Elexacaftor

General information

The chemical name of elexacaftor (also known as VX-445) is *N*-(1,3-dimethyl-1H-pyrazole-4-sulfonyl)-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1*H*-pyrazol-1-yl]-2-[(4*S*)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide corresponding to the molecular formula $C_{26}H_{34}F_3N_7O_4S$. It has a molecular weight of 597.66 g/mol and the following structure:

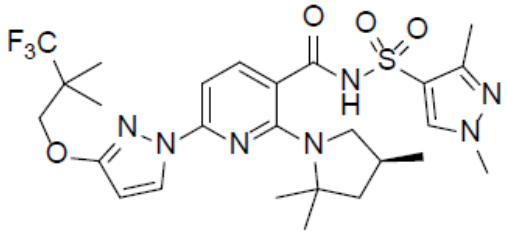


Figure 3: active substance structure

The chemical structure of elexacaftor was elucidated by a combination of elemental analysis, MS, NMR (^{1}H and ^{13}C), IR, Raman and UV-Vis. XRD, DSC, TGA and DVS were used to determine the physical characteristics of elexacaftor.

Elexacaftor is a crystalline non-hygroscopic white solid. Elexacaftor is practically insoluble in water and buffer solutions from pH 1.0 to pH 8.0. It is also practically insoluble in fasted and fed states simulated intestinal fluid at room temperature and 37 ^{0}C.

Elexacaftor exhibits stereoisomerism due to the presence of one chiral centre (with *S*-configuration). The asymmetric centre is a saturated hydrocarbon with no proximal functionality, hence it does not support or stabilize a transition state to promote racemization. Additionally, enantiomeric purity is controlled routinely by chiral HPLC in one of the starting materials. This has been adequately justified in line with ICH Q6A (see specifications section).

With regards to polymorphism the physical form of elexacaftor is the crystalline neat form.
The screening conducted showed that VX-445 forms solvates with methanol, ethanol and isopropyl acetate. No hydrate was found to form in multiple aqueous based solvent systems. The physical form selected for elexacaftor is the thermodynamically stable form and stable during the proposed manufacturing process.

Manufacture, characterisation and process controls

This active substance is synthesized in six chemical steps using four well defined starting materials with acceptable specificationswhich have been adequately justified in line with ICH Q11.

The manufacturing process has been developed using a combination of conventional univariate studies and elements of QbD such as risk assessment, DOE studies, and kinetic modelling. The materials and process for the manufacture of elexacaftor were assessed as part of the initial risk assessment. When the assessment indicated a medium or high risk, further experimentation and assessment on the

effects of parameters on elexacaftor CQAs were conducted. Based on the results from these studies, the critical parameters for this process were defined and the design spaces were established.

The scale dependent phenomena for steps with design space or a known scale-up risk for each step, have been discussed and considered acceptable. These included solids suspension, liquid blending and liquid-liquid dispersion. All were within the design space limits on a commercial scale; the QbD studies to define limits and assess criticality are deemed appropriate. , it is concluded that adequate methodology for design space scale verification has been used and confirm the adequacy of the proposed design spaces for commercial manufacture. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design spaces.

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

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised. The relevant spike/purge experiments have been undertaken and adequate limits have been set for each impurity.

In-silico analysis was performed and identified six compounds as potential or known genotoxic impurities. Risk assessments using purge factor calculations were performed demonstrating that these are eliminated by the process and justifying their control strategy.

Elemental impurities are controlled to the ICH Q3D limit in intermediate specification and indirectly controlled *via* the specification for residue on ignition in the active substance.

Solvents used early in the process are controlled according to ICH Q3C in the relevant intermediate specification after their last use. All solvents used in latter stages are controlled in the final active substance specification in line with ICH Q3C.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. The proposed commercial manufacturing process uses the same bond making and breaking steps as the original process. Changes included change of some reaction solvents, addition of water swashes, addition of some IPC and changes to the crystallization conditions, among others. Changes introduced have been presented in sufficient detail and have been justified. It has been demonstrated that the change(s) did not have a significant impact on the quality of the product. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged inside a LPDE bag and secured with an appropriate closure (twist tie or equivalent). The clear translucent bag is then placed inside a second black opaque LDPE bag and secured appropriate. The closed LDPE bags are placed into a secondary container suitable for storage and shipping. The LDPE resin used to manufacture the bags is suitable to be in contact with food and complies with the requirements of Commission Regulation (EU) No 10/2011 and the Ph.Eur. Monograph 3.1.3 "Polyolefins".

Specification

The active substance specification includes tests for: appearance, identification (IR, Ph. Eur.), assay (HPLC), organic impurities (HPLC), residue on ignition/sulphated ash (Ph.Eur.), residual solvents (GC), physical form (Ph. Eur.) and particle size distribution (laser diffraction). These are the CQAs of elexacaftor.

The acceptance criteria for the specified enantiomeric impurity supported by atoxicology study (refer to non-clinical part). The acceptance criteria for other organic impurities have been in line with the ICH Q3A qualification threshold for active substances with a maximum daily dose of ≤2g.

ICH Q3C option 1 limits are used for all solvents except for solvents where no ICH limits are provided. For solvents without ICH limits, limits were established as per ICH Q3C calculation for a 10g daily dose and literature PDE data of 6.2mg/day.

Physical form is confirmed by IR spectroscopy. This is the thermodynamically stable form, which has been consistently manufactured.

The particle size is controlled by the manufacturing process conditions and was measured throughout development by laser light diffraction. As requested by the CHMP the applicant tightened the specification limit and included a 3-tier limit in line with active substance particle size data for batches used in pivotal clinical trials along with ongoing clinical studies.

The absence for a test for chiral purity has been justified based on the fact that it is controlled at the level of the starting material. Additionally, during the manufacturing process or storage the conditions needed for racemization do not occur. This strategy is supported by development studies and release and stability data.

Aluminum is used as a reagent in the preparation of an intermediate. According to ICH Q3D, aluminium is considered to have low inherent toxicity and low risk to human health therefore it is not included in the specification and it is indirectly controlled through the residue on ignition specification in the intermediate and the active substance. Other elemental impurities used in the process are controlled to ICH Q3D limits.

Water content has been omitted from the specification since it is not a critical quality attribute of elexacaftor, which is a crystalline non-hygroscopic active substance.

The absence of specification for microbial purity has been justified by the low water activity <0.6 and the low bioburden results in four active substance stability batches.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurity testing has been presented. The method for assay and organic impurities by HPLC have been demonstrated to be stability indicating based on forced degradation studies

Batch analysis data has been provided from multiple batches of the active substance used in non-clinical, clinical and stability studies as well as four commercial size batches manufactured at the production site. All batches comply with specification including the additional quality attribute chiral purity which is not included in the specification.

Stability

Stability data from three commercial scale and one supportive pilot scale batches of active substance from the proposed manufacturer(s) stored in the intended commercial package for up to 12 months under long term (25 ºC / 60% RH and 30 ºC / 65% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* appearance, assay, organic impurities, chiral purity (HPLC), water content (KF titration), physical form (Ph. Eur.), microbial limits (TAMC, TYMC, *E.coli*) (Ph. Eur.), and water activity. The analytical methods used were the same as for release and were stability indicating. The results indicate that the chiral purity and polymorphic form remain the same on

stability. All results remained well within the acceptance limits and no trends were observed. The re-test period is justified.

Photostability testing following the ICH guideline Q1B was performed on one pilot scale batch. Samples were tested for appearance, assay, organic impurities and chiral purity. Changes in appearance and unspecified impurities were observed in the exposed sample therefore the active substance has to be stored in light protective packaging (outer LDPE black bag) for long term storage.

Elexacaftor was subjected to stress conditions including heat and heat/humidity for 21 days, treatment under acidic, basic and oxidative conditions for 7 days and exposure to UV and visible light. Samples were tested for assay and total impurities. Samples were most sensitive to acidic and oxidative conditions The results demonstrated that the methods for assay and organic impurities determination are stability indicating.

Vertex has committed to monitoring the stability of the primary lot and one supportive lot of the active substance through 60 months under the protocol.

Vertex has also committed to monitoring the stability of 3 commercial lots from the first commercial campaign of VX-445 from each site under the stability protocol and thereafter a minimum of 1 lot per year at each site according to the post approval stability protocol provided.

Any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 24 months stored in the proposed container in order to protect from light. The active substance does not need a specific storage temperature condition.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Kaftrio is an immediate-release film coated tablet for oral administration. The tablet is a fixed dose combination (FDC) of the active ingredients ivacaftor, tezacaftor, and elexacaftor. The ivacaftor/tezacaftor/elexacaftor FDC tablets contain 75 mg of ivacaftor, 50 mg of tezacaftor, and 100 mg of elexacaftor and have a total tablet target weight of 502.64 mg. They are orange film coated tablets, debossed with "T100" on one face and plain on the other face.

The QbD strategy applied to the finished product is the same as that for Orkambi and Symkevi.
The quality target product profile (QTPP) was to develop immediate release FDC tablets of elexacaftor/tezacaftor/ivacaftor (100mg/50mg/75mg) for oral administration, bioavailable, safe and efficacious and with at least 24-month shelf-life at room temperature in the proposed container.

Potential CQAs for the elexacaftor substance, tezacaftor SDD, ivacaftor SDD and the FDC tablet were described. The CQAs for the FDC tablets are: appearance, identification, assay, degradation products, dissolution, uniformity of dosage units, physical form, residual solvents, microbial limits, elemental impurities and chiral purity.

Upon CHMP request, the applicant has provided a justification regarding the acceptability of the dosage form and its physical properties to the intended patient population.

Both ivacaftor and tezacaftor active substances are provided as individual amorphous SDDs. Elexacaftor is provided as a crystalline powder. As indicated above, the applicant declared that ivacaftor and tezacaftor active substances and SDDs used in this Kaftrio submission are identical to the

ones used and approved for Kalydeco (ivacaftor), Orkambi (ivacaftor/lumacaftor) and Symkevi (ivacaftor/tezacaftor).

Ivacaftor is a stable crystalline material of high purity with well characterized physical and chemical properties. While crystalline ivacaftor is chemically and physically stable, it practically insoluble in aqueous media and has low bioavailability. Various approaches to obtain materials with better aqueous solubility were explored including salts, co-crystals, and an amorphous form. Given the acceptable chemical and physical stability of the neat amorphous form combined with its significantly improved dissolution rate and bioavailability as compared to a crystalline form, the amorphous form was selected as the most appropriate active substance form for development. The physical stability of amorphous ivacaftor in aqueous systems is significantly improved when a molecular amorphous dispersion is formed with a stabilizing polymeric material. The crystalline active substance is therefore spray dried to make an amorphous SDD prior to manufacturing the final tablet. As mentioned above, this is the same approach used in the approved Kalydeco, Orkambi and Symkevi products.

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

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

Tezacaftor active substance is provided as a crystalline solid which is practically insoluble in water and buffer solutions from pH 1.0 to pH 9.0. The amorphous form of tezacaftor was selected as the most appropriate physical form for development due to increased solubility as compared to a crystalline form. The physical stability of amorphous tezacaftor in solution is significantly improved with the addition of a polymer to the amorphous dispersion. The crystalline active substance is therefore spray dried with a polymerto produce an amorphous SDD finished product intermediate. Tezacaftor SDD is packaged inside a LDPE bag/liner which is placed inside a second LDPE bag/liner. The closed LDPE bag/liners are then sealed in a foil laminated bag with desiccant.

Elexacaftor active substance is the new active substance (NAS) component of the proposed FDC tablets. The clinically relevant physicochemical properties of this active substance were discussedAs indicated in the active substance section, the crystalline form is the most thermodynamically stable form and was selected for development. This form is stable during finished product manufacture.

The applicant has not discussed rationale for the choice of excipients and their content in the finished product; however, it can be accepted that prior knowledge has been used to help define the qualitative and quantitative composition. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. Compliance with EU colouring in medicinal products regulation is confirmed for the colours. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.The impact of critical material attributes (CMAs) has been discussed, and the applicant has confirmed that there are no expected impacts to product CQAs or process dynamics, material flow, diversion, or process performance when excipients are used within their respective specifications and defined by the product composition.

Multiple lots of each excipient were used during development and clinical manufacture with no impact observed on processability or product quality due to lot-to-lot variation. This lack of observed impact is also supported through prior knowledge gained during the development, clinical, and commercial manufacturing experience with Symkevi and Orkambi, which share many of the same excipients.

As with Symkevi and Orkambi NIR final blend chemometric models, the Kaftrio FDC final blend NIR chemometric model calibration sets include spectra obtained throughout the design space using multiple lots of excipients. Models are robust against normal excipient lot to lot variability.

The rationale supporting Avicel grades is presented and it is agreed that compendial specifications are sufficient, considering the degree of (parametric) control exerted by the equipment and the equipment configuration details registered.

Compatibility was investigated by placing proposed Kaftrio FDC tablets on an open dish stability study at 40ºC/75%RH for 6 months. The results demonstrate the chemical and physical compatibility of all components of the FDC tablet.

A summary of elexacaftor, tezacaftor, ivacaftor, and deuterated ivacaftor formulations used in clinical development, along with the trials they were used in has been provided. The final FDC formulation proposed for commercial use was evaluated in a bioavailability study (Study VX17-445-005) and dosed in Phase 3 studies.

The FDC finished product was developed using a continuous manufacturing (CM) process on a Continuous Manufacturing Development and Launch Rig (DLR). The FDC tablet is manufactured using a dry granulation process

Similarly to Orkambi and Symkevi, initial clinical supplies were manufactured using a discontinuous process, and both the discontinuous and continuous processes were used to manufacture material for pivotal clinical trials. Both tablets have the same composition and utilize the same manufacturing process (process steps), although one was made using a discontinuous process and the other the continuous process. Several of the unit operations utilize exactly the same equipment (roller compactor, press and film coater). The continuous blending process utilizes a different mechanism for blending compared to the discontinuous process, however both blending processes produce uniform blends, as demonstrated by blend uniformity testing, and result in comparable FDC finished product. The continuous process has been used for development and Phase 3 clinical resupply batches, formal stability batches, QbD DOE experiments, and is the proposed commercial process.

The *in*-vitro dissolution methods for each active substance were independently developed. Extensive investigations were performed to ensure the methods were adequately discriminating. This included evaluation of actives solubility in various media (considering surfactant, buffer, pH, and paddle speed), selection of media that ensure sink conditions and show discrimination with respect to material/tablet attributes and processing parameters and selection of media that enable the selection of an appropriate reporting time point. The discriminatory power of each method was evaluated with respect to material attributes and tablet properties, including the active bulk density and crystallinity, excipient level, active particle size, ribbon solid fraction, granule particle size and tablet hardness.

It is acknowledged that the methods for ivacaftor and tezacaftor are identical to those for already approved products.

The dissolution methods have collectively shown discriminating ability against meaningful manufacturing and material attribute variations and are considered suitable for their intended use as primary release and stability quality control methods for the FDC tablets.

The submitted dossier is the third CM dossier for the applicant. The CM process starts with the introduction of formulation components and ending with film coated tablets. The FDC product was developed using dry granulation on Vertex's continuous manufacturing platform (DLR) already used for Orkambi and Symkevi manufacture.

The DLR is controlled by a process control system responsible for user access control. The process control system displays active unit operations, the status of IPCs and CPPs, process trends, and alerts.

All principles of continuous manufacturing (from the stages feeding, materials handling, blending, dry granulation, milling, compression, and film-coating), material flow through the system and residence time distribution (RTD) have been described.

The start-up and shut-down procedures as they cascade through the process have also been described.

In the continuous process, material is tracked using the Product Key (PK) concept. It is explained that specific PKs having IPC results outside the acceptance criteria will be removed from the process. Segregation points have been presented and justified. The segregation approach has also been described taking into consideration the RTD and the equipment design.

Specific aspects of the process have been discussed in more detail, including process and equipment design considerations, feedback loops, etc. Specific operational considerations have also been described.

The CM process control strategy consists of four levels: unit operation control(s) to set point, design space monitoring, in-process controls and product specifications.

The DLR is equipped with process analytical technology with some being used for in-process control (IPC),. Process parameters and design space limits are monitored in real-time, and any excursions are detected and alerted in real-time. In-process controls and limits are defined, as is the finished product specification.

The primary mechanism by which the quality of the finished product is assured is parametric control.

A key part of the control strategy is 'typical final blend potency' IPC method to control homogeneity and potency of the blend prior to compression.

During the review a major objection on the ability of the NIR method to correctly categorise samples was raised. CAPAs have been implemented, and the initial risk assessment has been updated and mitigation steps implemented. The applicant confirmed that parallel testing has been performed and 100% agreement between the HPLC results and NIR results was achieved for each of the models. The applicant was requested and committed to perform it on all five batches in the next campaign. It will be extended to additional five batches if any of the initial five do not meet the parallel testing acceptance criteria.

The NIR model principles, development and validation, maintenance and life-cycle management are all discussed. A PACMP has been submitted to manage NIR model updates. The model is critical to product quality and is considered a high-impact model. The PACMP has been agreed.

The IPC sampling plan is discussed and justified, and is driven primarily by parametric control; therefore, equipment and process design and operational considerations as well as input materials controls feature more prominently.

Risk assessment, prior knowledge, and DOEs were subsequently used to design multivariate experiments that evaluate main effects and interactions on the CQAs. These experiments consider the desired manufacturing range (DMR) as well as incoming material specifications and equipment capability. Any differences in scale or equipment between the experiments conducted and the commercial equipment were considered (scale-up and engineering risk assessment) to ensure results are representative of the commercial process.

Experimental designs were conducted in a multivariate manner for the granulation and compression unit operations. Separately, a unit-operation specific experiment was conducted for the film-coating process. Intragranular and extragranular blending speeds were fixed, based on initial risk assessment evaluation, and considered of low risk to the resulting finished product quality, on standard rotations.

The primary packaging is a blister consisting of PCTFE (polychlorotrifluoroethylene)/PVC (polyvinyl chloride) with a paper backed aluminium foil lidding. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The commercial manufacturing process for the tezacaftor SDD and ivacaftor SDD is the same as for Symkevi and Kalydeco.

Briefly, the preparation of the ivacaftor SDD consists of three steps: mixture preparation, spray drying and secondary drying, followed by packaging.

The manufacture of the tezacaftor SDD is a multi- step process comprising solution preparation, spray drying, secondary drying and sieving and bulk packaging.

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

As mentioned above, Kaftrio FDC tablets are manufactured using a CM process. The process steps include feeding, blending, dry granulation and milling, compression, and coating. A fixed line rate has been defined and is used. During the review the CHMP raised a major objection since the level of detail of the manufacturing process description and control strategy was considered insufficient, taking into consideration the parametric control strategy and the findings during development. This was satisfactorily addressed by the applicant. Vertex has confirmed that all batches supplied to European markets will meet and be released to all specifications for incoming materials, starting materials, elexacaftor, and finished product agreed upon during review and reflected in the final dossier.

As described in the previous section, the manufacturing process was developed in accordance with the enhanced approach in ICH Q8. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design space for compression and coating. The design space is specific to the equipment train and equipment configuration.

A third PACMP to manage changes to the FDC tablets design space and sites of manufacture during the product lifecycle has been provided and is acceptable.

Comprehensive information regarding process controls has been provided. The NIR method is a qualitative method, used to discriminate between samples inside and outside the limits. The limits reflectthe proposed finished product assay specification. The NIR acquisition method is adequately described and supported. The model justification is extensive and is intended to ensure that adequate variability is incorporated. The content uniformity method defined in the specification is used for reference analyses. Model validation considers ICH Q2 and the EU NIR Guidelines. The model is considered high impact, directly affecting product quality.

The intended commercial batch size has been defined.

Major steps of the manufacturing process have been validated by a number of studies.
The manufacturing process is considered to be non-standard. A continuous process verification (CPV) approach as per the EMA Guideline on Process Validation for Finished Products–Information and Data to be Provided in Regulatory Submissions (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1, Corr.1) has been followed. A CPV scheme is provided in 3.2.R.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (IR), assay (HPLC), degradation products (HPLC), uniformity of dosage units (Ph. Eur.), dissolution for the three active substances (Ph. Eur.), water content (KF) and microbial limits (Ph. Eur.).

The proposed release specifications are typical for an oral solid dose product and comply with ICH Q6A and P. Eur. Monograph for tablets.

The applicant adopted a QbD approach to set specifications for the FDC finished product. Under this approach, specifications are not considered the primary means of control and are not solely based on historical data available. FDC tablet quality is achieved and assured by design of a well-controlled, robust manufacturing process. The tests included in the specification provide additional verification that specific CQAs have been met.

The specified organic impurities in the FDC tablet are degradation of elexacaftor. The acceptance criterion for one of the specified impurities is supported by a toxicology study. The acceptance criterion for additional specified and unspecified degradation products are in line with ICH Q3B. In addition, no other degradation products have been observed.

Water content is determined at release only. Water content is not a CQA of the FDC tablets. However, an acceptance criterion at release ensures that the FDC tablets will have a water activity of not more than 0.6, and will therefore not support microbial growth. Water content is not monitored on stability since CQAs that could potentially be impacted, including microbial limits, are tested directly.

The microbiological testing strategy for the FDC tablets follows the decision trees presented in ICH Q6A and the requirements of Ph. Eur. 5.1.4. The justification for not controlling microbial attributes on release is presented: this leverages cGMP controls, physicochemical properties of components and the final active substance, control of water content in the finished product and water activity determination, which together provide sufficient justification for the proposed approach. Microbial testing will be performed on commercial FDC tablet stability lots.

Justifications are provided for the omission of the following: physical form, chiral purity, residual solvents and elemental impurities.

The FDC tablets are comprised of crystalline elexacaftor, the most thermodynamically stable form, as well as amorphous tezacaftor and ivacaftor SDDs. Physical form for the FDC tablet is controlled via specifications on the incoming elexacaftor active substance, tezacaftor SDD, and ivacaftor SDD per ICH Q6A (decision tree #4). This is supported since it has been confirmed that physical form transformation does not occur within the manufacturing process design space nor on storage. All batches manufactured for clinical use as well as stability conform to the expected physical forms throughout storage.

In addition, physical form stability was also evaluated during forced crystallization studies of the FDC tablet. The study results demonstrate that the long-term physical form stability of the actives is maintained at the intended storage conditions.

The control of chiral purity of elexacaftor and tezacaftor have been established according to ICH Q6A (decision tree #5) by applying limits to the enantiomeric impurity in the stereogenic starting materials.

In addition, it has been demonstrated that the stereochemical integrities of elexacaftor and tezacaftor are maintained, within method variability, throughout the FDC tablet manufacturing process.

With regards to residual solvents, their levels are controlled via ICH Q3C (R7) option 1 limits for residual solvents used in the manufacturing of the elexacaftor, tezacaftor and ivacaftor active substances, and ivacaftor and tezacaftor SDD. All SDD and tablet excipients also meet ICH Q3C (R7) Option 1 limits for residual solvents.

The potential presence of elemental impurities in FDC tablets was assessed according to the ICH Q3D (R1) using a risk-based approach and taking into account the dosing regimen. The risk assessment considered the potential contributions from the three active substances, the tezacaftor and ivacaftor SDDs (including solvents, reagents, excipients), water, tablet excipients, and manufacturing equipment. The elemental impurities intentionally added in the active substances manufacturing processes are controlled in the respective active substance to levels that ensure the FDC tablets conform to ICH Q3D (R1) requirements.

The risk assessment of the content of Class 1/2A impurities in the active substances and SDDs, demonstrates that the risk of elemental impurities in these materials is low. Confirmatory testing of representative batches including nine elexacaftor active substance development batches, ten commercial tezacaftor active substance batches, eight commercial ivacaftor active substance batches, three commercial tezacaftor SDD batches, and four commercial ivacaftor SDD batches confirmed that the Class 1 and Class 2A elemental impurities is consistently below 30% of the ICH Q3D (R1) Option 1 limits. The same was shown for all tablet excipients with the exception of Opadry Orange film coating system. For Opadry Orange, the Option 2b summation approach was employed to demonstrate that the maximum daily intake of each elemental impurity is well below 30% of its respective permitted daily exposure.

Using the Option 1 and Option 2b approaches, it has been demonstrated that all Class 1/2A elemental impurities will be consistently below 30% of the established permitted daily exposures (PDEs). Confirmatory testing results on three representative development batches of FDC tablets were in alignment with the risk assessment. Therefore, no additional controls on elemental impurities in the finished product are required.

Following a major objection from the CHMP, a risk evaluation on the potential presence of nitrosamine impurities in the active substances and finished product was provided. Based on EMA guidance, a risk evaluation has been performed for the presence of nitrosamines in the three active substances and the finished product including the packaging. The applicant has deemed there is no risk for nitrosamines with respect to the main conditions for nitrosamine formation. In relation to the synthesis of the elexacaftor active substance it is agreed with the applicant that in the synthesis a nitrosating agent is not present so there is no risk. The applicant has adequately explained the introduction of nitro group in the molecule of concern and justified that there is no risk of nitrosating agents being present in the starting material (. Therefore, it is concluded that there is no risk of nitrosamine formation in the product.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH Q2(R1). Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for two commercial scale and one pilot scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

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

The proposed shelf life for tezacaftor SSD is 36 months when stored in the intended container closure system at not more than 30°C. This is the same approved for Symkevi, and the same data has been submitted in Kaftrio dossier.

With regards to the stability of the FDC tablets, stability data from one pilot and two commercial scale batches of finished product stored for up to 12 months under long term (25 ºC / 60% RH) and intermediate (30 ºC / 75% RH) conditions and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of Kaftrio are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay, degradation products, chiral purity, dissolution, water content, physical form of all active substances (XRPD), microbial limits (Ph. Eur.) and water activity (USP <1112>).

The analytical procedures used are stability indicating. All results met the acceptance criteria for the attributes evaluated. Although water content increased during real-time studies, it remained significantly below the proposed specification limit. All other parameters remained stable with either no change or changes attributable to method variability.

In accordance with EU GMP guidelines[4], any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

In addition, one commercial scale batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Samples were tested for appearance, assay, degradation products and chiral purity. No changes were observed in the exposed tablet samples as compared to the covered control, confirming that FDC tablets do not require light protective packaging.

Forced degradation studies were also conducted. FDC tablets were subjected to stress conditions, which included heat, heat/humidity, treatment under acidic, basic, and oxidative conditions, and exposure to ultraviolet (UV) and visible light. The elexacaftor, tezacaftor and ivacaftor peaks were found to be spectrally pure in all stressed samples demonstrating that the commercial HPLC methods for assay and degradation products determination of FDC tablets are stability indicating.

Based on available stability data, the proposed shelf-life of 24 months as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and

[4] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

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

Since ivacaftor and tezacaftor active substances and SDDs are common components in Kalydeco (ivacaftor) tablets and granules (EMEA/H/C/002494), Orkambi (lumacaftor/ivacaftor) tablets (EMEA/H/C/003954) and Symkevi (tezacaftor/ivacaftor) tablets (EMEA/H/C/004682), already approved in the EU, the same information on ivacaftor and tezacaftor active substances and SDDs already registered has been presented for this product.

This is the third CM application from the same applicant and the DLR equipment used for the manufacture of Kaftrio tablets is similar to that used for the manufacture of Orkambi and Symkevi tablets. However, the overall control strategy is significantly different in that the primary mechanism by which the quality of the product is assured is parametric control. This has been supported by pharmaceutical development studies and the design elements, manufacturing process description, process parameters, in-process controls and end-product testing specification described in the dossier.

Three PACMP have been included in this dossier. One to manage NIR IPC model updated, and two to manage post approval changes to tezacaftor SDD and Kaftrio FDC tablets manufacturing process design spaces, respectively.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendation for future quality development

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

1. The applicant is recommended and has committed to further perform parallel HPLC testing to demonstrate the NIR in-process control for final blend potency on all five batches in the next campaign. It will be extended to additional five batches if any of the initial five do not meet the parallel testing acceptance criteria. The Rapporteur should be informed if any criteria are not met during the parallel/confirmatory testing agreed to.

2.3. Non-clinical aspects

2.3.1. Introduction

The applicant applied for a marketing authorization for the combination of *CFTR* modulators elexacaftor, tezacaftor and ivacaftor (Kaftrio). Two correctors (elexacaftor and tezacaftor) are combined with a potentiator (ivacaftor) to facilitate the processing of mutant *CFTR* forms (correctors) and support of the chloride transport function of the mutant *CFTR* (potentiator) upon arrival at the plasma membrane.

2.3.2. Pharmacology

There is no validated animal model for CF that fully mimics the human multi organ affected disease. Furthermore, the proposed treatment is specific for mutated *CFTR* proteins. All three components bind specifically to *CFTR* aiming at increasing the levels of mutated *CFTR* on the cell membrane and improving its channel gating functionality when present at the plasma membrane. Therefore, the use of in vitro systems has been proposed to study the pharmacology of elexacaftor alone or in combination with tezacaftor and ivacaftor.

Primary pharmacodynamic studies

The applicant chose to use Primary Human Bronchial Epithelial (HBE) cells, isolated from the upper and lower bronchi of CF patient, that can be cultured for 90 days, as an *in vitro* model system. Primary cultures of fully differentiated HBE from CF lung explants exhibit many of the morphological and functional characteristics observed in CF airway epithelia in vivo, including the presence of ciliated and mucus-secreting cells, reduced salt and fluid transport, impaired cilia beating, and the formation of a thick mucus layer. As the ion channel activity and cellular function of primary CF HBE cultures are similar to *in vivo* airway tissue and as HBE cells from CF patients with a mutant *CFTR* expresses many characteristics associated with CF pathogenesis, including defective ion and fluid transport, the primary HBE cells of CF patients with known *CFTR* mutations can be regarded as relevant model system to study the pharmacological action of *CFTR* modulators.

The applicant included a graphical comparison of the amount of chloride transport in HBE cells expressing wildtype or a mutated *CFTR* variant and clinical parameters such as Δ (change in) Sweat Chloride and ppFEV1 in healthy subjects or patients expressing mutated *CFTR* variant. The plot may suggest translatability of the in vitro results towards the clinical setting however, underlying data is lacking.

For the in vitro studies, the applicant used two groups of HBE cells to study the effect of elexacaftor on top of tezacaftor and or ivacaftor. One group consisted of HBE cells from three different donors all harbouring two *F508del* alleles (F/F group). The other group consisted of HBE cells from four donors, all harbouring one *F508del* allele and one allele with a minimal function (MF) mutation (F/MF group). Among these four F/MF donors; two donors harbour a *G542X* mutation, one donor harbours a *3905insT* mutation and one donor harbours an *E585X* mutation.

In vitro binding specificity of elexacaftor and/or tezacaftor to *CFTR*

A saturation binding experiment using a thermostabilized variant of *CFTR* (TS-CFTR) reconstituted into a nanodisc was used to measure specific binding of elexacaftor and tezacaftor by Mass Spectrometry. Also, the effect of specific binding of elexacaftor to TS-CFTR upon addition of tezacaftor and vice versa was analysed to support the hypothesis that elexacaftor and tezacaftor bind TS-CFTR at different sites. The apparent Kd of elexacaftor is 72 ± 47 nM and of tezacaftor is 127 ± 59 nM for dissociation from CFTR-TS. The addition of tezacaftor at 500 nM did not change the apparent Kd of elexacaftor and the amount of bound tezacaftor remained unchanged when increasing concentrations of elexacaftor were added.

These results support the conclusion that both molecules bind simultaneously to TS-CFTR. These observations show that both molecules bind to different, non-competing binding sites on TS-CFTR. Protein binding studies with elexacaftor to *F508del-CFTR* protein is technically not feasible as this form is less stable and would not result in sufficient purified protein.

The synergistic effect of tezacaftor and elexcaftor in the chloride increase assay on double *F508del* mutants however suggested that both compounds bind also the *F508del* mutant *CFTR* on a different

region (e.g. do not compete for binding). Elexacaftor binds to both MSD1 and MSD2, which is different to tezacaftor, which binds MSD1 only.

Effect of the extra corrector (elexacaftor) on the processing of mutant *CFTR* in HBE cells

According to the applicant, elexacaftor is a *CFTR* corrector. It implies that elexacaftor can help to improve the folding process and subsequently escape to the plasma membrane of *CFTR* mutants that are not efficiently and/or correctly folded in the Endoplasmatic reticulum. To investigate the effect of elexacaftor on top of tezacaftor and/or ivacaftor, the applicant analysed on western blot the amount of *CFTR* and glycosylated *CFTR* (that has travelled through the Golgi) upon incubation of the cells with elexacaftor all or not in combination with tezacaftor and/or ivacaftor.

The results showed that elexacaftor incubation of the cells results in an increase of glycosylated *CFTR* compared to untreated, tezacaftor treated and ivacaftor treated cells. Treatment with tezacaftor and elexacaftor resulted in a synergistic effect. This effect seems to be dampened by the co-incubation with ivacaftor, but the potentiator ivacaftor is very likely needed to improve the function of the channels that have reached the membrane. Overall, the incubation with the combination of the three active compounds resulted in a higher increase in glycosylated mutant *CFTR* as compared to incubation with one corrector and one potentiator, thus with tezacaftor and ivacaftor or elexacaftor and ivacaftor.

Effect of the extra corrector (elexacaftor) on chloride transport by mutant *CFTR* in HBE cells

In addition to the effect on the processing, the effect on chloride transport of elexacaftor alone or in combination with tezacaftor and or ivacaftor was tested in F/F HBE cells or F/MF HBE cells. The plots consisted of data pooled per group, thus the F/F *CFTR* mutants together and the F/MF *CFTR* mutants together. In the report itself the data was also presented separately for each different donor. The results of this chloride transport assay showed better results for the triple combination than the combination of elexacaftor with either tezacaftor or ivacaftor alone or tezacaftor with ivacaftor when compared per donor. Thus, addition of elexacaftor yielded for HBE cells from all donors a relative increase in chloride transport.

Variation in the results was observed for the F/F group but an even larger variation was seen in the F/MF group. The variation in the F/F group may point towards the fact that CF is a multifactorial disease and that other genetic factors than the *CFTR* variant underlying the disease and may play a role in the response to treatment. The more pronounced variation in the F/MF group rather suggests that MF *CFTR* mutants are responding differently to the treatment and that MF mutants cannot be regarded as non-functional mutants or not responding to the tezacaftor/ivacaftor combination. ln addition, cells of one of the F/MF donors showed a similar increase in chloride transport compared to cells of the best performing F/F donor suggesting that in this donor the MF *CFTR* contributes to the final result in an increase of chloride transport.

Effect of the extra corrector (elexacaftor) on channel gating in FRT cells expressing *F508del CFTR*

Single-channel, patch-clamp electrophysiology is an established laboratory technique to measure ion channel gating activity.

Fischer Rat Thyroid (FRT) cells expressing one allele of the *F508del CFTR* mutant were pre-incubated with elexacaftor or elexacaftor / tezacaftor. Baseline channel gating activity was determined.

Afterwards, an acute stimulus with elexacaftor & elexacaftor plus ivacaftor or elexacaftor / tezacaftor & elexacaftor / tezacaftor plus ivacaftor were given. After spiking with the corrector(s) alone, channel opening was only very minimal. After spiking with the corrector(s) and the potentiator channel opening was achieved efficiently, supporting the use of ivacaftor in the triple combination.

In addition, it is noted that VX-445 and TEZ appear to work in an additive way based on results from the processing and trafficking and chloride transport assays; while the patch clamp assay suggests no additive effect of tezacaftor on top of elexacaftor with respect to channel gating. Although a necessary presence of both correctors is not directly clear from the patch clamp study, requirement for two correctors is justified by studies presented by the applicant. Furthermore, different concentrations of TEZ and VX-445 were used in the FRT cells and similar results were observed for VX-445 with and without TEZ. Prior to assessing gating activity, the cells were incubated with 1 μM VX-445 and 3μM TEZ in the presence of 10% foetal bovine serum (FBS). It would be assumed that considering the high protein binding of VX-445 and TEZ, nonspecific binding to serum proteins would occur, thereby reducing the effective concentration of the compounds. The applicant clarified that 25% human serum (HS) was used in the chloride transport study and 10% FBS was used in the channel gating study explaining the 2.5-fold difference in the used concentration of elexacaftor and tezacaftor in the two experiments.

Secondary pharmacodynamic studies

A-specific action of VX-445 on other mutated proteins sharing similar trafficking pathways as *CFTR* (G601S-hERG), sharing the same *CFTR* superfamily(G268V-Pgp), being endoplasmic reticulum (ER)-arrested misfolded proteins (zAAT and N370S-β-glucosidase), or being unrelated misfolded proteins presenting nuclear and cytoplasmic aggregates (mHTT Q145) was not observed. These results suggest that VX-445 is a selective corrector for *CFTR* as compared to other misfolded protein classes.

The IC50 of elexacaftor for CysLT1 receptor antagonism is 0.71 μM in a protein free condition; this value is 7-fold higher than the clinical Cmax (14.5 μM total or 101 nM protein free) suggesting a minimal risk to human safety.

Thus, elexacaftor poses only a minimal risk to human safety from potential VX-445 interaction with this receptor or other secondary, non-*CFTR* targets.

Safety pharmacology programme

In *in vivo* safety pharmacology studies, the effects of elexacaftor on the central nervous system (CNS) and the respiratory system were assessed upon single dosing in the female rat. Up to a dose of 30 mg/kg no effects on neurobehavioral endpoints, unscheduled deaths, clinical observations, or respiratory effects were observed, making 30 mg/kg the NOAEL for CNS and respiratory effects.

Effects of elexacaftor on the cardiovascular system were assessed in telemetered dogs. A single dose of elexacaftor up to a nominal dose of 30 mg/kg (24.78 mg/kg actually measured) did not result in any changes in body temperature, blood pressure, pulse pressure, heart rate, or ECGs. Therefore, the NOEL for cardiovascular effects was determined to be 24.78 mg/kg.

In vivo safety pharmacology for tezacaftor and ivacaftor was addressed in studies that were submitted with the previous MAA procedures for Kalydeco and Symkevi. Results suggested a low potential for tezacaftor and ivacaftor to elicit effects on CNS, respiratory or cardiovascular parameters at clinically relevant exposures. Effects on the gastro-intestinal (GI) system were limited to ivacaftor at higher doses (≥ 500 mg/kg), did not result in any GI motility dysfunction at lower doses in chronic rat and dog repeat-dose toxicity studies and were considered not relevant at therapeutic doses in humans.

Pharmacodynamic drug interactions

No dedicated pharmacodynamic drug interactions studies are submitted. This can be agreed since all components of Kaftrio are very specific for *CFTR* and it is not anticipated that Kaftrio will be

administered with another therapy directly affecting *CFTR*. The interaction with the three components of Kaftrio has been assessed in the in vitro pharmacology studies. Ivacaftor may interfere slightly with the increase of mature *CFTR* levels due to tezacaftor and elexacaftor incubation, however this would have minimal impact and is acceptable considering the need to add ivacaftor in order to open the chloride channels.

2.3.3. Pharmacokinetics

Introduction

The non-clinical pharmacokinetics (PK) of VX-445 were investigated in a series of *in vitro* and *in vivo* studies. The PK properties of tezacaftor, ivacaftor and the combination tezacaftor/ivacaftor were previously assessed in the registration programs for Symkevi and Kalydeco respectively and results are discussed where relevant for the triple combination.

Analytical methods

The analytical methods for the quantitation of VX-445 and the pharmacologically active metabolite M23-445 in rat, mouse and dog plasma and VX-445 in rabbit plasma were validated in GLP studies.

The validation results showed that the method for the quantitative determination of VX-455 in cynomolgus monkey plasma by HPLC followed by MS/MS detection VX-445 in plasma of monkeys has been sufficiently validated.

The metabolite M23-445 in cynomolgus monkey plasma has been measured only as part of the *in-vitro* binding study to plasma proteins, showing by LC-MS/MS analysis that VX-445 and M23-445 protein binding was high (≥99%) in mouse, rat, dog, monkey, and human plasma and that both compounds bound mainly to human serum album. The LC-MS/MS analysis method used to measure M23-445 in protein binding assays in monkey plasma has been described with sufficient detail in the study report. The analytical methods for the determination of tezacaftor, M1-TEZ, M2-TEZ, ivacaftor, M1-IVA and M6-IVA in plasma of the nonclinical species were validated to support the registration of Symdeko/Symkevi and Kalydeco and remain unchanged.

Permeability and transport

VX-445

VX-445 showed high permeability in a Caco-2 cell monolayer assay. The apparent permeability values at 5 µM were 3.08 x 10^{-6} cm/sec and 1.41 x 10^{-6} cm/sec for A>B and B>A assays, respectively. Using MDCK cells overexpressing human MDR1, it was shown that VX-445 is a substrate for Pg-P at 1 µM.

Tezacaftor and ivacaftor

TEZ and IVA showed high permeability in Caco-2 cells. The apparent permeability values at 5 µM were 3.37 x 10^{-6} cm/sec (TEZ) and 11.9 x 10^{-6} cm/sec (IVA) for the A>B assays and 1.9 x 10^{-6} cm/sec (TEZ) 36.1 x1 10^{-6} (IVA) cm/sec for the B>A assays. In the MDCK-MDR1 assay, TEZ was shown to be a substrate P-gp, but IVA not.

Single dose pharmacokinetics

VX-445

VX-445 showed good oral bioavailability in rats (84%), dogs (88%) and monkeys (68%). In the therapeutic dose range, the exposure increased as the dose increased. At higher doses, the increase in

exposure increased in a less than dose proportional manner. Sex difference was observed for VX-445 in rats (exposure in female > male), but not in dogs.
There was no apparent food effect following oral administration of VX-445 to fed and fasted beagle dogs at 10 mg/kg. The volume of distribution was 0.32 L/kg in mice, 0.62 L/kg in rats, 0.28 L/kg in dogs and 0.30 L/kg in monkeys. These values are lower than the total body water (0.5-0.7L/kg).

VX-445 showed a low plasma clearance. Values ranged from 0.22 mL/min/kg (dog) up to 1.05 mL/min/kg (mouse), 1.48 mL/min/kg (monkey) and 1.55 mL/min/kg (rats). These values correspond with values less than 1%, 3.8% and 5% of the hepatic blood flow in dogs, monkeys and rats, respectively. The values for half-life ranged from 3.1 h in mice, 4.4 up to 4.9 h in rats, 2.8 up to 3.7 h in monkeys up to 12.3 h in dogs.

The bioavailability of VX-445 in human was about 34% in the fasted state and about 80% following administration with food (Study 001, see clinical AR). The volume of distribution was 53.7 L (~ 1 L/kg), clearance was 1.18 L/h (~0.5 mL/min/kg) and half- life was 24 h.

Tezacaftor and ivacaftor

The bioavailability of tezacaftor ranged from ~40% to ~50% (rat, dog). The absorption of tezacaftor may be improved by the intake of food. Food increased absorption, as determined in dog studies. The volume of distribution ranged from 0.48-0.66 L/kg (dog, monkey) up to 1.6-1.9 L/kg (mouse, rat). The systemic clearance was lower than hepatic blood flow (mouse, rat, dog, monkey).

The bioavailability of ivacaftor ranged from ~30% to ~60% (mouse, rat, dog). Food improved the absorption at high dose levels, whereas it was similar at lower dosages in suspension formulation. The volume of distribution ranged from 0.72 L/kg (dog) up to 2.2 L/kg (monkey), 2.7 L/kg (mouse) and 3.3-3.9 L/kg (rat). Systemic clearance following intravenous administration was lower than hepatic blood flow (mouse, rat, dog, monkey).

Repeated dose pharmacokinetics

VX-445

Repeated dose PK of VX-445 was investigated in mice (28 days, 26 weeks), rats (7 days, 28 days, 26 weeks), dogs (7 days, 28 days, 39 weeks), pregnant rats (GD 6 to 17) and pregnant rabbits (GD 7 to 20).
In mice, the exposure to VX-445 (AUC, C_{max}) increased with dose in an approximately dose proportional manner, whereas the exposure to the major metabolite M23-445 (AUC, C_{max}) increased more than dose proportional. Some accumulation was observed. In the 6-month study, VX-445 exposures on Day 182 were 1.3 to 1.8-fold higher and the M23-445 exposure was 1.25 to 3.43-fold higher than on Day 1 across all doses. There were no consistent differences in exposure between males and females.
In rats, systemic exposure (AUC, C_{max}) increased with increasing dose in an approximately dose-proportional manner in males and in an approximately dose-proportional or greater than the dose-proportional manner in females. In the 6-month study, accumulation (AUC, Cmax) ratios increased 1.5 to 4-fold with dose and time from Day 14 to Day 180 in females. Accumulation ratios for males generally did not change with dose and appeared to increase 1.5 to 4-fold with time from Day 14 to Day 180. The exposures (AUC, Cmax) to the metabolite M23-445 was up to 25-fold lower in males and up to 15-fold lower in females as compared to the exposures to VX-445 at these time points.
In dogs, the exposure values for VX-445 (AUC, Cmax) increased with increasing dose in dose-proportional to greater than dose-proportional manner. In the 39-week study, VX-445 showed a 3-to 7-fold accumulation for AUC and a 3- to 5-fold accumulation was observed for C_{max}. The accumulation

ratios did not appear to change with increasing dose. The exposure values for M23-445 (AUC, C_{max}) increased with increasing dose in a greater than dose-proportional manner but remained low as compared to the exposures for VX-445. Relevant differences between males and females were not observed.
Toxicokinetic evaluations in pregnant rats on GD 6 and GD 17 and in rabbits on GD 7 to GD 20 revealed no new findings. Exposures to VX-445 (AUC, C_{max}) increased dose proportional or slightly more than dose proportional and increased with time.

Tezacaftor and ivacaftor

The non-clinical PK of tezacaftor and ivacaftor after repeated administration are known. Tezacaftor showed no apparent accumulation of tezacaftor in mice, rats and dogs. Ivacaftor showed some accumulation in plasma at the higher dose levels in mice, rats, rabbits and dogs.

VX-445 combined with tezacaftor and ivacaftor

Several combination studies of VX-445, tezacaftor and ivacaftor were conducted, including a 7-day study, a 28-day study, and a 13-week study in rats, and a 28-day study in dogs. These studies were performed with VX-445 alone, or as a triple combination with tezacaftor and ivacaftor, or in combination with tezacaftor or ivacaftor as a dual combination.
In these studies, the systemic exposures (AUC and C_{max}) to VX-445, tezacaftor and ivacaftor were generally similar to the exposures observed when these compounds were dosed individually. The exposure of VX-445, tezacaftor and ivacaftor generally increased as the dose increased. For VX-445, the increase in exposure was generally dose proportional or slightly more than dose proportional. For tezacaftor and ivacaftor, the increase in exposure was dose proportional at lower dose levels and was less than dose proportional at higher dose levels. Sex difference in pharmacokinetics was observed for VX-445 in rats (exposure in female > male), but not in dogs. No relevant differences (<2-fold) between males and females were observed for either tezacaftor or ivacaftor in rats or dogs.

Plasma protein binding

VX-445

Binding of VX-445 and its metabolite M23-445 to plasma proteins is high (>99%) in mouse, rat, dog, monkey and human plasma. At the tested concentration of 3.3 µM, human albumin was the major protein for binding, whereas the binding to alpha-1-acid glycoprotein was minimal. The high degree of protein binding suggests that variation in albumin concentrations associated with age or disease may have minimal impact on the clinical pharmacokinetics of VX-445.

Tezacaftor and ivacaftor

Tezacaftor binds for more than 98% to protein in mouse, rat, dog, and human plasma. Human serum albumin was the main component involved in the binding in human plasma, whereas alpha-1-acid glycoprotein played a minimal role. The metabolites M1-TEZ, M2-TEZ and M5-TEZ also highly bound to plasma proteins and similar across species (>97.5%), except M2-TEZ which is less protein bound in mouse plasma (93.6%).
Plasma protein binding of ivacaftor and its major metabolites (M1-IVA and M6-IVA) was greater than 98% in vitro in mouse, rat, dog, and human plasma. Protein binding of ivacaftor to human plasma components, human serum albumin, alpha-1-acid glycoprotein and human gamma globulin, was and to most proteins in human plasma components. Human serum albumin was the main plasma component involved in the binding of ivacaftor or its metabolites in human plasma.

Distribution to red blood cells

VX-445

VX-445 did not preferentially distribute into red-blood cells. In humans orally administered 200 mg VX-445, the average blood to plasma concentration ratio of radioactivity ranged from 0.581 to 0.723.

Tezacaftor and ivacaftor

Tezacaftor and ivacaftor showed no preferential partition into red-blood cells.

Tissue distribution

VX-445

The tissue distribution of VX-445 was studied in rats. Quantitative whole body autoradiography showed that orally administered ^{14}C-VX-445 was widely distributed throughout the body with the majority of tissues showing the highest concentrations at 4 h post-dose. The highest exposures were measured in the liver, bile tract and contents of the gastrointestinal tract. Lower exposures were observed in the mucosa of the gastrointestinal tract, adrenals, pancreas, heart, kidneys, harderian gland, lachrymal glands and salivary glands. VX-445-related radioactivity crossed the blood-brain barrier, but measured concentrations in the brain were about 3-fold lower relative to plasma.
A tissue distribution study in Long-Evans rats showed no significant distribution to melanin-containing tissues (skin, eyes), indicating that VX-445 did not preferentially associate with melanin. VX-445 distributes to the respiratory tract during the first 6 hours.
In a tissue distribution study with non-radiolabelled VX-445, tissue concentrations of VX-445 were determined from brain, lung, heart, kidney, liver, and plasma at T_{max} (4-6 h). The mean tissue to plasma concentration ratios were 0.185-0.219 in the brain, 0.421-0.505 in the lung, 0.971-1.13 in heart, and 1.04-1.37 in the kidney. The liver to plasma concentration ratios (2.9-5.3) for all doses was higher than the other tissues.
The exposure of the male reproductive organs was about 2-fold lower relative to plasma, whereas the exposure of the female reproductive organs was in the same range.
The distribution in pregnant animals was not significantly different from non-pregnant animals.

Tezacaftor and ivacaftor

Tezacaftor is rapidly distributed across all tissues in rats, with detectable amounts noted in all tissues at 1 hour post dose. The gastrointestinal tract and liver showed the highest levels. Ivacaftor is rapidly distributed across all tissues in rats.
Tezacaftor and ivacaftor also distribute to the respiratory tract. For tezacaftor, at T_{max} (2-8 h), the exposure of the lung was 2.5-fold greater than the exposure in plasma, indicating that the retention of M1-TEZ was somewhat higher than of tezacaftor in lung tissue and plasma. For ivacaftor, at 4 h after oral administration, the ratio of the exposure in the lung was 3.8-fold greater than in plasma.

Placental transfer and excretion in milk

VX-445

A ^{14}C radiolabel study in pregnant rats showed that after a single oral dose of 10 mg VX-445 at GD 13 and GD 18 small amounts of VX-445-related material passes the placenta and reaches the foetus. At these time points, at the Tmax of 8 h, the exposure of the foetus was 0.5–fold (at GD 13) and 0.7-fold (at GD 18) lower, relative to the exposure of blood.
In lactating rats, the exposure of VX-445 in milk at LD 6-10 was approximately 43% of the exposure in plasma.

Tezacaftor and ivacaftor

^{14}C radiolabel studies showed that placental transfer of tezacaftor in rats and ivacaftor in rats and rabbits was minimal and the exposures in foetuses were low.

Tezacaftor and ivacaftor are also excreted in the milk of lactating rats. The exposure to tezacaftor in milk was up to 3-fold greater and the exposure to ivacaftor was about 1.5-fold greater as compared to the exposures in plasma.

Metabolism

VX-445

VX-445 is primarily metabolized by oxidation, mediated by CYP3A4- and CYP3A5.
Metabolite profiling of VX-445 was performed *in vitro* (rat, dog, monkey and human liver microsomes/hepatocytes) and in vivo in rats, dogs and monkeys.
The *in-vitro* metabolite profiles were qualitatively similar across rat, dog, monkey and human. No human-specific metabolites were observed.
In hepatocytes and microsomes, the metabolites were M14 (pyrrolidine methyl oxidation), M15 (left hand side methyl oxidation), M22 (pyrazole methyl oxidation), M23 (pyrazole N-demethylation) and M24 (pyrrolidine cyclization) in microsomes, and M25 (amide hydrolysis and cyclization with the pyrrolidine) in hepatocytes.
Metabolite profiles from plasma samples of rat, dog, and monkey were qualitatively and quantitatively similar. The major observed metabolites were M15 (left hand side methyl oxidation), M23 (pyrazole N-demethylation, and M25. M22 (pyrazole methyl oxidation) was also observed.
In rats, VX-445 accounted for the majority (86.7%) of the total exposure to VX-445 and related material in plasma, followed by M15 (6.2%), M23 (4.1%) and M25 (1.7%), and unknown 16 (1.3%) in decreasing order of abundance. None of the metabolites alone accounted for more than 10% of total circulating radioactivity, indicating that none of these metabolites is considered a major metabolite in rats.
In human, VX-445 accounted for 80.7% of the total exposure to VX-445 and related material in plasma, followed by M23 (17.3%), M25 (1.6%) and unknown (0.4%). M23-445 is a major metabolite in humans.

Tezacaftor and ivacaftor

CYP3A4 and CYP3A5 are the predominant cytochrome P450 enzymes involved in the metabolism of tezacaftor, M1-TEZ, ivacaftor and M1-IVA.

Excretion

VX-445

Metabolism followed by biliary excretion of metabolites was the primary route of elimination for VX-445 in rats and dogs, and likely in humans.
The excretion balance of in bile duct cannulated rats and humans showed that the main route of excretion occurs via the faeces (82% in rats and 87.3% in human), whereas the excretion in urine plays a minor role (0.63% in rats and 0.23% in human).
In bile-duct cannulated rats, 20.18%, 61.87%, and 0.63% of the oral administrated dose was found in faeces, bile, and urine, respectively up to 72 hours. When dosed IV in the rats, there was 8.67% of the dose was recovered in faeces, potentially through intestinal secretion. This suggests that enterohepatic circulation plays a minor role.

Tezacaftor and Ivacaftor

Tezacaftor is mainly excreted into the faeces in rats (75-79%), dogs (58%) and humans (72%).

The major part of faecal excretion was due to excretion via the bile in rats (53%) and dogs (50%). Excretion via the urine was low in rats and dogs (< 10%) and humans (14%).

2.3.4. Toxicology

A comprehensive non-clinical package was submitted to evaluate the safety of elexacaftor. The rat was the pivotal rodent species in repeat dose toxicity studies with elexacaftor alone or in combination with tezacaftor or ivacaftor. The dog was the pivotal non-rodent species. One combined 5-day and 28-day repeat dose toxicity study with elexacaftor was conducted in mice.

Repeat dose toxicity

Studies in mice

Doses beyond 150 mg/kg/day with elexacaftor were poorly tolerated requiring the early termination of all animals included in these groups. A cause of death could not be attributed. At doses of 100 mg/kg/day the only notable elexacaftor related changes were an increase in total protein, albumin and globulin. In the absence of any correlates, these changes are considered not toxicologically relevant and the NOAEL in this study is 100 mg/kg/day. At this dose, animals were exposed to 27-fold of the intended clinical exposure.

Studies in rats with elexacaftor alone

Clear gender exposure differences were identified in rats, where plasma AUC was supra dose proportionally increased in females. Therefore, in the pivotal 4-week and 26-week study, female animals received approximately half the dose that males did.

In a 28 day repeat dose toxicity study in rats, only minimal changes were observed. The most notable change was a small decrease in body weight gain in all groups, but the body weight gain decrease was only significant in the high dose male group. Terminal body weight remained lower compared to control animals even though animals receiving elexacaftor continued to steadily gain weight. Reticulocytes were reduced in males receiving elexacaftor 25mg/kg/day onwards and cholesterol was reduced in males and females in the highest dose group (50mg/kg/day and 30 mg/kg/day, respectively). Reticulocytes were still slightly reduced in males receiving 50mg/kg/day elexacaftor and cholesterol remained reduced in this group. In the absence of correlating findings and the modest severity grade of the changes, these findings are not considered to be toxicologically relevant. The NOAEL in the 28 day repeat dose toxicity study in rats was the highest dose tested: 30mg/kg/day in females and 50 mg/kg/day in males. It represents 3-and 2-fold clinical exposure multiples.

In the pivotal long term (26 week) repeat dose toxicity study, all animals at 75 mg/kg/day (m) and 30 mg/kg/day (f) were terminated early (d26) due to moribundity and rapidly declining condition, which was preceded by decreased food consumption, severe body weight loss and one or more of the following observations: thin body condition, hunched posture, loss of skin elasticity, skin cold to touch, material around nose, and/or piloerection. The cause of death/moribund condition in most of these animals was erosion of the glandular mucosa of the stomach, some of which were visible as brown or black foci in the stomach at necropsy.

Among animals that survived to scheduled necropsy after 26 weeks of dosing, there were no notable changes in clinical or anatomic pathology results. Minor elexacaftor-related decreases in red blood cells (RBC), HGB and HCT at 40 mg/kg/day were noted which were not toxicologically relevant. There were no test article-related effects on urinalysis/urine chemistry parameters or ophthalmoscopic examinations. Total bilirubin was increased in males from 15 mg/kg/day onward and in females given 15 mg/kg/day (with a trend to increase in females given 7.5mg/kg/d). ALT was increased in males at

40 mg/kg/day, likely due to stress and/or reduced food intake since triglycerides and cholesterol levels were somewhat decreased in males and females (40 mg/kg/day and 15 mg/kg/day, respectively).

There were no elexacaftor related findings in gross pathology. Histopathological changes included moderate erosion of the stomach in 1 male and minimal erosion in 1 female at 40 mg/kg/day and 15 mg/kg/day, respectively. Minimal to marked degeneration of seminiferous tubules was noted in 40mg/kg/day males and correlated with minimal to severe aspermia. In females, mild to moderate increases in corpora lutea were noted in animals given 7.5mg/kg/day elexacaftor onwards. None of the observed changes were still present in the interim recovery animals. In conclusion, once daily oral gavage dosing of elexacaftor to rats for up to 26 weeks was tolerated at dose levels of 15 mg/kg/day in males and females, which is also the NOAEL. This represents a 4-fold and 13-fold clinical exposure multiple, respectively.

Differences seen in the toxicology studies are attributed to the pharmaceutical form of elexacaftor (*i.e.* jet milled vs non-jet milled, where jet milled elexacaftor improves systemic exposure). Body weight changes are primarily attributed to tezacaftor and more importantly were not seen in the clinical setting. Weight gain in rats is an indicator of general well-being, the clinical relevance of decreased weight gain is not anticipated to manifest directly in weight loss in the clinical population and may indicate uncharacterised behavioural and/or metabolic change in these animals. It is accepted this is not a new finding, as noted, decreased weight gain has been observed in studies assessing the toxicity of TEZ and VX-445 administered alone. Furthermore, it is accepted that further mechanistic studies examining this finding are not warranted.

Studies in dogs with elexacaftor

With the exception of effects on male reproductive organs and correlating clinical observations (decreased food consumption, thin appearance), none of the adverse findings seen in rats were observed in dogs. In dogs receiving up to 30 mg/kg/day for up to one month, no adverse changes in clinical observations, body weight, and food consumption, ophthalmoscopic examinations, ECG examinations, clinical pathology, and macroscopic or microscopic findings were observed that could be related to elexacaftor. The NOAEL in this study was 40mg/kg/day, which is 11 times above the intended clinical exposure. In the long term (39-week) repeat dose toxicity study, elexacaftor was relatively well tolerated at doses up to 14 mg/kg/day (approximately 19 times above the intended clinical exposure). There was no observed mortality and there were no elexacaftor related effects on macroscopic necropsy observations, urinalysis, urine chemistry, ophthalmoscopic or electrocardiographic examinations. All elexacaftor related changes were observed at 14 mg/kg/day, the highest dose tested. These included inappetence, thinning condition and animals being cold to the touch. Food consumption was reduced up to week 26. The liver was the main target organ for observed changes, likely due to enzymatic induction. In both males and females, minimal-mild hepatocellular hypertrophy was observed. In males, this was accompanied by mild vacuolation of the gallbladder epithelium due to local irritation. The liver changes were further correlated with increased absolute and relative liver weight and slightly increased ALT in males. In both males and females, total bilirubin was slightly increased. In the testes, minimal or mild, bilateral degeneration/atrophy of the seminiferous tubules was present in males administered 14 mg/kg/day that did not resolve during the recovery period. There were no noticeable changes in qualitative decreases in sperm content in the epididymides lumina, nor was there cellular debris noted. Nevertheless, the male reproductive organ is a target organ based on findings in both rat and dog.

Studies in rats with combinations of elexacaftor, tezacaftor and ivacaftor

Dosing for 28 days with high dose triple combination (TC) in male rats 40/45/30 mg/kg/day (elexacaftor/tezacaftor/ivacaftor) resulted in similar adverse microscopic gastric and bone marrow and body weight findings to those described with elexacaftor alone at 150 mg/kg/day. Adverse decreases

in body weight gains were noted in male rats administered the low dose TC 20/45/30 mg/kg/day (elexacaftor/tezacaftor/ivacaftor), which was consistent with an additive effect of elexacaftor and tezacaftor. Elexacaftor/tezacaftor/ivacaftor -related organ weight changes were present in the following organs in males only: adrenal glands, prostate gland, seminal vesicles with coagulating glands, and thyroid/parathyroid gland at 20/45/30 and 40/45/30 mg/kg/day, and epididymides and thymus at 40/45/30 mg/kg/day. Microscopic correlates consisted of cortical hypertrophy/vacuolation in the adrenal glands, atrophy in the prostate, secretory depletion in the seminal vesicles/coagulating glands, germ cell debris/oligospermia in the epididymides, and lymphoid depletion in the thymus. Male reproductive organs are considered a target organ for toxicity. The higher thyroid/parathyroid gland weights did not have any microscopic correlates. Organ weight changes noted in the thymus and adrenal gland were considered to be stress-related secondary to test article administration and not toxicologically relevant.

No new or synergistic adverse findings were observed with the triple combination after one month. However, the adverse body weight effects in males already at the lowest dose result in a NOAEL that cannot be determined for male animals. In females, the NOAEL is 7.5/45/30 mg/kg/day elexacaftor/tezacaftor/ivacaftor. However, potential synergistic effects on fertility were not investigated with the triple combination which is acceptable by CHMP since the observation in rat occurs at exposures above those reached in clinic.

A subsequent study evaluated elexacaftor alone, in combination with tezacaftor and ivacaftor or with tezacaftor and D-ivacaftor for 13 weeks. The latter group was not assessed as it does not represent the present clinical application under review. Of 13 deceased animals (early euthanasia or found dead), the unscheduled deaths of two main study males at 35/45/30 mg/kg elexacaftor/tezacaftor/ivacaftor and one male at 35/45/25 mg/kg elexacaftor/tezacaftor/D-ivacaftor were considered likely to be drug-related based on clinical signs of hunched posture and reduced body weight gains. Effects on clinical pathology parameters seen in these animals euthanized early were generally similar in nature, although of a greater magnitude, to changes seen in male and female rats at the end of the 13-week dosing period at equivalent dose levels. In addition, there were a number of effects in animals euthanized early that were indicative of stress/loss of body condition and/or inflammation and were generally consistent with the microscopic findings in these animals.

In animals surviving until the end of the study, test article-related clinical observations were noted and consisted of hunched posture, thin body condition and piloerection, which were only noted in male rats given 35mg/kg/day and in female rats given 12.5mg/kg/day elexacaftor alone.

Test article-related body weight effects were noted in males and females given the triple combination elexacaftor/tezacaftor/ivacaftor or D-ivacaftor and in females given the dual combination tezacaftor/ivacaftor. None of the body weight effects seen in males or females in this study were considered to be clinically relevant, since animals steadily gained weight over the duration of the study and the overall health of the animals was not affected. Similarly, decreased food consumption was noted in animals given the triple combination elexacaftor/tezacaftor/ivacaftor. This was not toxicologically relevant because animals steadily gained weight and there were no adverse effects on final mean body weights. Small epididymides and testes at 35/45/30 mg/kg/day elexacaftor/tezacaftor/ivacaftor was observed in 1 animal and was test article related. These findings correlated microscopically to severe seminiferous tubule atrophy in the testes and oligospermia with cellular debris in the epididymides. In other animals, reduced testes and epiydimides weight were observed in males given the triple combination elexacaftor/tezacaftor/ivacaftor. Microscopically this correlated with degeneration/atrophy in the testes, and increased germ cell debris and/or oligospermia in the epididymides.

A number of other microscopic changes were considered to be secondary to effects on body weight and/or food consumption, stress, or metabolic enzyme induction. These included effects on the liver, adrenal glands, and thymus. Except for the testicular changes, none of these findings were toxicologically relevant based on the absence of correlating observations, and/or low incidence and/or severity. In conclusion, this study did not reveal adverse synergistic effects of combining elexacaftor and ivacaftor and tezacaftor. The no-observed-adverse-effect level (NOAEL) for males given the triple combination of elexacaftor/tezacaftor/ivacaftor was considered to be 20/45/30 mg/kg/day, and the NOAEL for females given the triple combination of elexacaftor/tezacaftor/ivacaftor was considered to be 12.5/40/30 mg/kg/day. This represents an exposure multiple of 4/1/9-fold over the intended clinical exposure for males, and 7/2/16 fold for females.

Studies in dogs with elexacaftor, tezacaftor and ivacaftor

Elexacaftor was tested in combination with tezacaftor and as a triple combination of elexacaftor, tezacaftor and ivacaftor in dogs receiving either combination daily for 28 days. There were no test article related effects on mortality, clinical observations, body weight, food consumption, ophthalmoscopic and electrocardiographic examinations, haematology, clinical chemistry, coagulation, urinalysis, organ weight, or macroscopic evaluations. The only finding was minimal to mild dilated lacteals in the duodenum, ileum and jejunum of male and female dogs. This finding has already been observed in safety studies with tezacaftor and is considered tezacaftor-related. However, in the absence of correlated findings, this finding was not considered to be toxicologically relevant. The NOAEL in this study was the highest dose tested, 15/50/10 mg/kg/day elexacaftor/tezacaftor/ivacaftor. However, as this study was limited to one month in duration and did not contain a recovery period, a true dose response could not be established due to the doses selected.

Genotoxicity

Elexacaftor was not genotoxic in a bacterial and a mammalian in vitro assay in the presence or absence of S9 metabolizing mix. Elexacaftor was also not genotoxic in a chromosomal aberration assay in vivo. Similarly, ivacaftor and tezacaftor are not genotoxic, as previously established.

Carcinogenicity

A 6-month explorative study in Tg-RasH2 mice was conducted with elexacaftor with mice receiving up to 50 mg/kg/day. This study is in accordance with relevant international guidelines. There were no neoplastic lesions noted at any dose, suggesting that elexacaftor is likely not carcinogenic. However, given that the Tg RASH2 mouse data are only a rough measure of carcinogenic potential, are not fully reliable and are difficult to translate, whether elexacaftor is not carcinogenic for humans should be determined in a formal carcinogenicity study, which is currently ongoing. As previously established, tezacaftor and ivacaftor are non-carcinogenic.

Reproductive and developmental toxicity

Elexacaftor was evaluated in a rat fertility study. Males and females in the high dose group (75/35 mg/kg/day, respectively) showed decreased bodyweight which was more pronounced in males than in females. Considering bodyweight loss remained below 10% this was not adverse. There were no other notable clinical changes that could be attributed to elexacaftor.

Elexacaftor had effects on male and female reproductive parameters in the fertility and early embryonic development (FEED) study, as 6 breeding pairs in the high-dose groups for males and

females did not produce a litter. One of the females that was nongravid had prolonged diestrus, and 2 of the males that did not sire a litter showed lower sperm motility. This resulted in lower male and female fertility, male copulation, and female conception indices in the 75 mg/kg/day group males and 35 mg/kg/day group females. The changes are considered adverse, and in females likely due to alterations in estrous cycling. No embryonic toxicity was identified. The NOAEL for fertility for males is therefore 55 mg/kg/day and for females 35 mg/kg/day. The NOAEL for embryonic toxicity for males is 55 mg/kg/day and for females 35 mg/kg/day.

In an embryofetal development study with elexacaftor in rats, maternal toxicity in the form of body weight loss was noted in the highest dose group (40 mg/kg/day) and resulted in the early euthanasia of 2 females. Pathology in these animals showed enlarged, dark red discoloured adrenal glands in both females, and dark red areas in the stomach and a small spleen and thymus gland were noted in 1 female. Body weight loss was also observed in the 25 mg/kg/day group but was limited and not adverse. Nevertheless, fetal bodyweight was adversely reduced in both 25mg/kg/day and 40 mg/kg/day groups. There were no other adverse fetal findings. The maternal NOAEL in this study was 25mg/kg/day. The NOAEL for the offspring was 15 mg/kg/day.

In an embryofetal development study with elexacaftor in rabbits, maternal toxicity in the form of body weight loss was noted in the highest dose group (125 mg/kg/day) and resulted in the early euthanasia of 2 females. There were no notable pathology changes in these animals. Decreased defecation correlated to decreased food consumption was also noted in the high dose females. Decreased defecation without weight loss or decreased food consumption was noted in the 50 mg/kg/day and 100 mg/kg/day group. There were no meaningful changes on post-implantation loss, number and percentage of viable fetuses, mean fetal body weights, and fetal sex ratios. Mean numbers of corpora lutea and implantation sites and the mean litter proportions of pre-implantation loss were similar across all groups. There were no differences in fetal morphology, and skeletal, external or visceral malformations or variations compared to controls. The maternal NOAEL was 100 mg/kg/day. The fetal NOAEL was 125mg/kg/day.

A peri- and postnatal development study with elexacaftor was conducted in rats. No adverse effects on F0 maternal clinical observations, body weights, or food consumption were noted during gestation or lactation maternal clinical observations, body weights, or food consumption were noted during gestation or lactation for females at any dose level. No elexacaftor-related effects were noted on mean gestation lengths or the process of parturition for F0 females, and no elexacaftor-related macroscopic findings or effects on the mean number of former implantation sites and unaccounted-for sites were noted at any dose level. There were no elexacaftor-related effects on the mean number of F1 pups born, live litter size, percentage males at birth, postnatal survival, pup clinical observations, or necropsy findings. In the highest dose group tested (10 mg/kg/day) male and female pup body weight was reduced but were not toxicologically meaningful. Lower mean absolute body weights persisted up to PND 112. There were no other notable effects that could be attributed to elexacaftor. The NOAEL for F0 animals and F1 offspring is considered to be 10 mg/kg/day.

Elexacaftor was assessed in a juvenile toxicity study in rats. Male rats were given 7.5, 15, or 30 mg/kg/day and female rats given 5, 7.5, or 15 mg/kg/day from PND 7 through PND 70. Transient but considerable changes in body weight were noted in males given 30mg/kg/day elexacaftor. Reduced body weight was 27.4% of control values on PND24, corresponding with reduced food consumption. Over time, these changes improved and at PND70 body weight was 7.6% lower than the control group. Due to the rapid loss of weight, this change is considered adverse despite being transient. There were no other remarkable elexacaftor related changes in males apart from a minor non-adverse reduction in cholesterol levels. In females, notable changes included minor increases in total bilirubin and ALT. In females with increased ALT, creatinine kinase was increased in 4/5 animals with or without increases in AST. These changes are indicative of muscle damage, likely due to the study procedure in the absence

of correlating signs to suggest liver injury. However, no histopathology was conducted and this study is only supportive. The NOAEL in males is considered to be 15 mg/kg/day due to rapid, adverse but transient body weight loss and 15 mg/kg/day in females, the highest dose tested.

For tezacaftor, the overall conclusions from reproductive and developmental toxicity studies indicate that it is not a reproductive and/or developmental toxicant. tezacaftor did not result in toxicity to male or female reproductive systems or have effects on early embryonic development. Effects on fetal development and growth of offspring (lower F1 generation survival/lactation indices, decreased pup body weights pre- and post-weaning and lower reproductive capacity in F1 generation rats) were only noted at significantly maternally toxic dose levels. For ivacaftor, the overall conclusions from reproductive and developmental toxicity studies indicate it is not teratogenic; moreover, it has only minimal effects on female reproduction and fetal development in rats, attributable to significant maternal toxicity.

Local tolerance

A series of in vitro and in vivo studies were conducted to assess the local tolerability of elexacaftor to support limited human IV administration. Elexacaftor is well tolerated, is non-irritant to skin or eye, is not phototoxic and is compatible with human whole blood. As part of the development and registration of Symkevi and Kalydeco, both tezacaftor and ivacaftor were assessed in similar package of handler safety studies (irritation potential in dermal and ocular tissues and the potential for skin sensitization), which concluded both tezacaftor and ivacaftor to be a non-irritant and non-sensitizing in dermal studies and that tezacaftor and ivacaftor were both reported as a mild irritant in ocular irritancy. Tezacaftor did not demonstrate phototoxic potential in this assay and therefore does not appear to present any risk of phototoxicity in humans. Ivacaftor was not tested for phototoxicity however the safety profile is characterised also based on the existing post marketing experience since approval.

Other toxicity studies

Metabolites and impurities

No dedicated studies have been conducted to assess independent metabolites of elexacaftor. This is sufficiently justified. Impurities in the elexacaftor drug substance are sufficiently qualified.

2.3.5. Ecotoxicity/environmental risk assessment

The results of the ERA are presented below:

Substance (INN/Invented Name): elexacaftor			
CAS-number (if available): 2216712-66-0			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log D_{ow} 4.7 at pH 5 log D_{ow} 3.6 at pH 7 log D_{ow} 3.1 at pH 9 log K_{ow} (ion corrected) 5.15	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log D_{ow} at pH 7	3.6	not B
PBT-statement :	elexacaftor (VX-445) is not PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surface\ water}$, refined F_{pen}	0.057	µg/L	> 0.01 threshold (Y/N)

Other concerns (e.g. chemical class)	not investigated	not listed in ECHAs CL Inventory	

Substance (INN/Invented Name): tezacaftor					
CAS-number (if available): 1152311-62-0					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log K_{ow} 3.58			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	3.58			not B
	BCF	7.7 L/kg			not B
PBT-statement :	Tezacaftor (VX-661) is considered not PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surface\ water}$, refined F_{pen}	$1.25x10^{-2}$	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)	not investigated	not listed in ECHAs CL Inventory			
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: 994 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 (l/l) $DT_{50,\ system}$ = 58.1/22.3 d (l/l) % shifting to sediment 16-20% at d 14, increasing thereafter			l=lake DT_{50} values at 20°C.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*P. subcapitata*	OECD 201	NOEC	0.91	mg/L	growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	1.2	mg/L	growth
Fish, Early Life Stage Toxicity Test/*P. Promelas*	OECD 210	NOEC	1.2	mg/L	body length
Activated Sludge, Respiration Inhibition Test	OECD 209	EC10	>1000	mg/L	respiration
Phase IIb Studies					
Bioaccumulation/*C. carpio*	OECD 305	$BCF_{SS,\ L}$	7.7	L/kg	
Sediment dwelling organism/*C. riparius*	OECD 281	NOEC	310	$mg/kg_{d\ w}$	normalised to 10% o.c.

Substance (INN/Invented Name): ivacaftor					
CAS-number (if available): 873054-44-5					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log K_{ow} >4.7			Potential PBT (Y)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	>4.7			

	BCF	39.2 L/kg			not B
Persistence	DegT50	$DT_{50\ water}$ 3.6, 9.3 d (l/l) $DT_{50\ system}$ 1233, 261 d (l/l) $DT_{50\ soil}$ = 3213, 1201, 730, 1598 d			l=lake. DT_{50} values corrected to 12°C. Conclusion: vP
Toxicity	NOEC algae NOEC crustacea NOEC fish	>0.0547 mg/L 0.0031 mg/L ≥0.029 mg/L			T
	CMR	Repr 2 (notified classification)			potentially T
PBT-statement :	VX-770 is considered not PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surface\ water}$ refined F_{pen} This is a summed PEC_{sw} for 4 products containing ivacaftor: Orkambi™, Kalydeco™, Symkevi™ and Kaftrio	0.081	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)	Repr 2	notified classification			
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	$K_{oc\ sludge}$ = 11800, 10800 L/kg $K_{oc\ soil}$= 3710, 1970, 5900 L/kg			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50\ water}$ 1.7, 4.4 d (l/l) $DT_{50\ system}$ 581, 123 d (l/l) % shifting to sediment = 68-79% at d 14.			l=lake; DT_{50} values at 20°C; Significant shifting to sediment observed.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*P. subcapitata*	OECD 201	NOEC	>54.7	µg/L	growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	3.1	µg/L	reproduction
Fish, Early Life Stage Toxicity Test/*P. promelas*	OECD 210	NOEC	≥29	µg/L	hatching, surivival, growth
Activated Sludge, Respiration Inhibition Test	OECD 209	EC10	>1000	mg/L	respiration
Phase IIb Studies					
Bioaccumulation/*O. mykiss*	OECD 305	BCF_{KL}	39.2	L/kg	lipids: 5.5-7.6%
Aerobic and anaerobic transformation in soil	OECD 307	DT50	1513, 566, 344, 753	d	for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	no effect	≥1.81	mg/kg	
Terrestrial Plants, Growth Test/*A. Cepa, A. sativa, B. oleracea, D. carota, L. sativa, L. esculentum*	OECD 208	NOEC	≥1818**	mg/kg	normalised to 2% o.c.
Earthworm, Acute Toxicity Tests/*E. fetida*	OECD 207	NOEC	>417**	mg/kg	normalised to 2% o.c.
Collembola, Reproduction Test/*F. candida*	ISO 11267	NOEC	≥690**	mg/kg	normalised to 2% o.c.
Sediment dwelling organism/*C. riparius*	OECD 218	NOEC	≥7463	mg/kg	normalised to 10% o.c.

Conclusions on studies for tezacaftor

VX-661 (tezacaftor) is not PBT, nor vPvB.

Based on the prescribed use and considering the above data, VX-661 (tezacaftor) is not expected to pose a risk to the environment.

Conclusions on studies for ivacaftor

VX-770 (ivacaftor) is not PBT, nor vPvB.

Based on the prescribed use and considering the above data, VX-770 (ivacaftor) is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Pharmacology

As there is no validated animal model for CF that fully mimics the human multi organ affected disease and all three components bind specifically to *CFTR*, the use of *in vitro* systems to study the pharmacology of elexacaftor only or in combination with tezacaftor and ivacaftor can be accepted.

Use of HBE cells as model for in vitro pharmacology

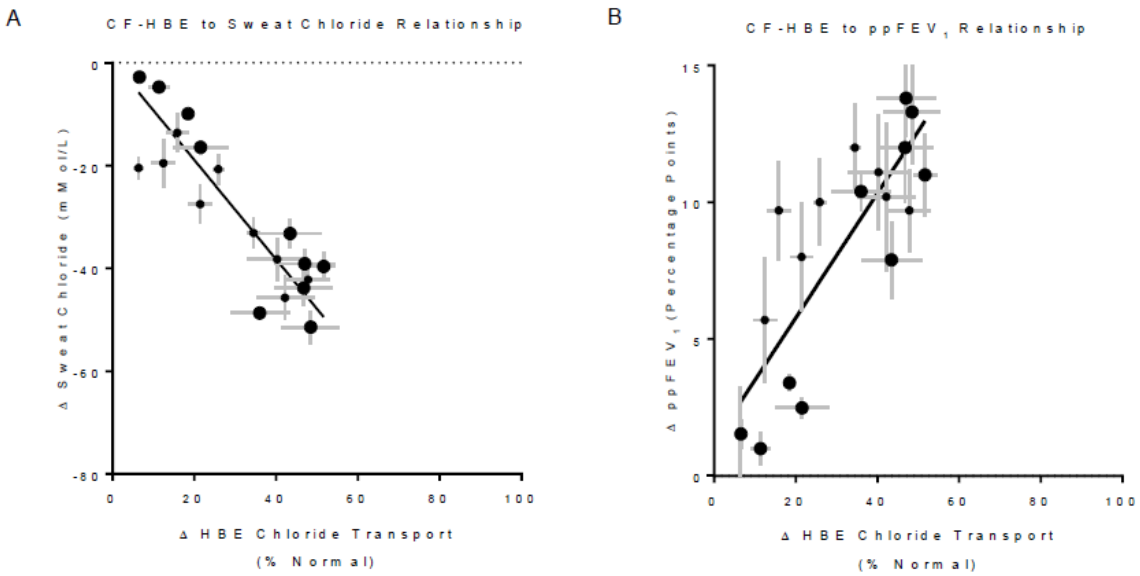
As the ion channel activity and cellular function of primary CF HBE cultures are similar to *in vivo* airway tissue and as HBE cells from CF patients with a mutant *CFTR* expresses many characteristics associated with CF pathogenesis, including defective ion and fluid transport, the primary HBE cells of CF patients with known *CFTR* mutations can as such be regarded as relevant model system to study the pharmacological action of *CFTR* modulators.

Upon request by CHMP and to further support the use of HBE cells as model for *in vitro* pharmacology analysis, the applicant included a graphical comparison of the amount of chloride transport in HBE cells expressing wildtype or a mutated *CFTR* variant and clinical parameters such as Δ (change in) Sweat Chloride and ppFEV1 in healthy subjects or patients expressing mutated *CFTR* variant. This plot (see below), shows a correlation between the *in vitro* performance of HBE cells, with regard to chloride transport and clinical performance (Δ Sweat Chloride and ppFEV1). The plot suggests translatability of the *in vitro* results towards clinical results and would thus provide further support for the use of HBE cells to study *in vitro* pharmacology, but underlying data is missing, hampering a definitive conclusion on *in vitro in vivo* correlation (IVIVC).

Assessment of the in vitro data supporting IVIVC and the Applicant F508Del only hypothesis:

In initial graphs the different *CFTR* mutations were grouped together, but the applicant was asked to derive the correlation on a per mutation basis. The applicant was furthermore requested to provide information on a non-clinical vs clinical comparison with data upon clinical treatment, including in vitro data (untreated, Symkevi & Kaftrio treated) of the different F/F (3) and F/MF (4) obtained in chloride transport assay and clinical in vivo data of these mutants in untreated fashion and in treated fashion (with Symkevi and Kaftrio), and as well plot these data, to support the use of HBE cells for the in vitro pharmacology analysis as well as the translatability of the results to the clinic (thus the in vitro in vivo correlation).

Figure 4: Relationship Between In Vitro and In Vivo Measures of CFTR function



.

The HBE cells are considered appropriate to investigate the effect on CFTR processing and conductance upon incubation with (different combinations of) the three components of Kaftrio. However, the IVIVC relationship seems disproportional for the in vitro components. Furthermore, the applicant did not attempt to provide a IVIVC on a per mutation basis. The answer falls short in that respect. In addition, combining the different MF mutants into one F/MF group is not sufficiently substantiated with in vitro data.

From HBE cells from each donor, the incubation with Kaftrio results in an increase in chloride transport as compared to DMSO, Symkevi, VX-445 alone, VX-445 & ivacaftor and VX-445 & tezacaftor. Thus, for all donors, Kaftrio seems to result in improvement in chloride transport. However, it is not clear how this can be extrapolated to other F/MF patients. Extrapolation of the results within clinical tested F/MF genotypes to other F/MF genotypes may be more relevant from the clinical data.

Upon request by CHMP, the applicant provided adequate data to demonstrate the binding of elexacaftor to both MSD1 and MSD2, which is different to TEZ, which binds to MSD1 only. In order to be functional in CF patients, the corrector should also be able to bind to mutant forms of *CFTR* resulting in CF. It can be agreed that not all mutant *CFTR* proteins leading to CF can be assessed but assessing binding of elexacaftor and/or tezacaftor to the *F508del* mutant and for example one representative of each of the 4 or 5 classes of MF *CFTR* mutants would have been informative. The applicant was asked to justify why binding of elexacaftor and/or tezacaftor was tested only on a non-mutated *CFTR* variant and not on a mutated *CFTR* variant and explain the relevance for further non-clinical and clinical assessment. The applicant explained that protein purification of the much less stable *F508del-CFTR* protein form is challenging and the yield will not be sufficient for protein binding studies. The synergistic effect of tezacaftor and elexacaftor in the Chloride increase assay on double *F508del* mutants indeed suggests that both compounds bind also the *F508del* mutant *CFTR* on a different region (e.g. do not compete for binding).

Rationale for pooling in vitro data of F/F and F/MF mutants and extrapolation to all mutations

As mentioned above, the applicant pooled the data for the three F/F mutants and the four F/MF mutants into two groups: F/F and F/MF. From the Peak Forskolin (FSK) Stimulated Cl- Transport data separated per mutant; it becomes clear that there is a substantial difference between the MF mutants

concerning the effect of elexacaftor on the improvement of Chloride transport. A conclusion on this finding cannot be drawn as it remains unclear whether this is due to the difference in the effect of ivacaftor with respect to the different MF *CFTR*s or whether this may be due to the fact that the MF mutants do not all respond to the same extent to elexacaftor. Due to these observed differences in the chloride transport for the various F/MF mutants it cannot be agreed with the applicant that the data provided are sufficient to address the effect on processing where only one F/F donor and only one F/MF mutant (*F/G542X*) are studied. The applicant was asked to provide data on the effect of tezacaftor and/or ivacaftor and/or elexacaftor on *CFTR* processing on cells of each different MF donor separately. This question was raised to gain more insight in the likeness or similarity of the different MF variants and whether one MF variant could represent a whole group of MF as stated by the applicant. However, more data was not provided by the Applicant in the answer to the LoI and the discussion of the applicant was ultimately considered not satisfactory. Further details are provided below for completeness:

In its response, the applicant explained that the G542X mutant results, due to its mutation, in a truncated variant which, together with a (mutant specific) severe reduction in the amount of mRNA will yield minimal protein levels that in the most optimal case will result in low levels of abnormal protein. The likeliness that this protein will add to the response upon Kaftrio incubation is low. From the provided data it is indeed clear that the western blot studies were only performed with cells from one donor from each of the afore set groups; F/F and F/MF (*G542X*). As one mutant is not regarded representative for the whole group, the applicant was requested by CHMP to provide clarifications, but this was not addressed. The applicant instead argued that these experiments were not designed to demonstrate differences between donors and different genotypes within the F/MF group. The CHMP is of the opinion that this information could have importantly contributed to informing on the resemblance of the different MF variants and support the grouping of these variants into a F/MF group and subsequently derive support for the requirement of the *F508del* allele only hypothesis with in vitro data. Instead, the applicant referred to clinical data to support the *F508del*-allele-only hypothesis in clinical data. This approach can be accepted by CHMP as non-clinical data are considered too limited and inconclusive to support such a hypothesis.

In addition, as a percentage of total *CFTR* in both cell lines, the effect of the combination of tezacaftor and elexacaftor is additive, resulting in approximately 70% of total *CFTR* appearing as the mature *CFTR* from. This percentage is however reduced by the addition of ivacaftor. Decrease in the mature *CFTR* form upon treatment with elexacaftor, tezacaftor and ivacaftor compared to elexacaftor and tezacaftor alone in F/F, although not a significant difference, it is also noted for tezacaftor and tezacaftor and ivacaftor implying a ivacaftor mediated reduction in improvement in processing and trafficking, and a negative pharmacodynamic relationship. The applicant was asked to comment on the consistent reduction of the amount of *CFTR* at the membrane following treatment with ivacaftor and further agreed that ivacaftor does causes a reduction in the magnitude of *CFTR* processing and trafficking by elexacaftor/tezacaftor but is required to restore the defective gating. This is regarded is an acceptable explanation and the issue was considered solved.

The results of the chloride transport assay show that the triple combination gave better results than the combination of elexacaftor with either tezacaftor or ivacaftor alone or tezacaftor with ivacaftor when compared per donor. Thus, addition of elexacaftor yielded for HBE cells from all donors a relative increase in chloride transport. However, whether this increase is substantial or not, remains a topic of discussion. It can be partially agreed with the applicant that 'In vitro evidence demonstrated *'substantially'* increased efficacy and potency of the triple combination (TC) on HBE cells from the seven tested donors with mutated *CFTRs* when compared to mono or dual therapies with these same cells. The superiority of the triple combination is thus based on the relative increase in chloride transport per donor. It has however to be noted that in vitro the improvement of Kaftrio and the

treatment with a combination of elexacaftor and ivacaftor is not very large when both are compared to untreated condition. Furthermore, as already reflected above, in vitro treatment with tezacaftor/ivacaftor gives an improvement for both the three F/F mutants (one geneotype) and the four F/MF mutants (three different genotypes), which was not observed in the clinic, at least not for the F/MF mutants. This would suggest that in vitro results cannot be directly translated to *in vivo* data. It remains unclear whether the small difference observed with Kaftrio over the combination of elexacaftor/ ivacaftor would translate to a clinical benefit and it is therefore questionable whether this difference can be considered *'substantial'* as claimed by the Applicant.

With regards to the effect of incubation with elexacaftor on chloride transport in CF HBE cells, the results are also presented per donor and show a minimal variation between results for the F/F group, but a more pronounced variation in the results from the F/MF group, suggesting that MF *CFTR* mutants are responding differently to the treatment with the triple combination. Three donors were used for the F/F group, which is limited but can be accepted considered that the variation is minimal in F/F in comparison to the F/MF group. MF mutations are variable and provide also a variation in the result (increase in chloride transport upon treatment with *CFTR* modulators), strongly suggesting that some of the MF *CFTR* will also respond to the triple combination. The final response to the triple combination may thus not be determined by the *F508del* allele only. Furthermore, in vitro data that all MF mutants respond to the combination treatment of tezacaftor with ivacaftor (Symkevi). Therefore, the CHMP concluded that based on this information, MF mutants cannot be regarded as non-functional mutants or as not responding to the tezacaftor/ivacaftor combination as defined in MF patient definition for the 102 clinical study.

In vitro evidence supporting the F508del single allele Applicant hypothesis:

According to the applicant, strong in vitro evidence supports the hypothesis that the presence of a single *F508del* allele would be sufficient to provide substantial clinical benefit to CF patients with an *F508del* on one allele and a mutant *CFTR* on the other allele resulting in either no *CFTR* protein or an allele that does not respond to IVA and TEZ/IVA in vitro (minimal function [F/MF] genotype). Currently approved *CFTR* modulators failed to show benefit in this population. The CHMP did not agree with the applicant that this has been demonstrated for all three F/MF genotypes used in the in vitro study. In vitro data is thus not regarded as supportive for the above hypothesis. The applicant was therefore asked during the assessment to further explore their hypothesis as detailed below:

A) provide data supporting the claim that the chosen mutations tested in the studies do not produce any CFTR protein and/or do not respond to TEZ or TEZ/IVA and discuss whether these three donors/ mutations are truly representative of all MF mutations.

G542X is a truncation mutant, that has a truncation in the middle of the first cytosolic domain, the NBD1 domain. *E585X* is a truncated mutant as well, but here the truncation is right after the NBD1 domain, in the linker to the R domain. Both truncation mutants have a correct first membrane spanning domain. The *3905insT* (on DNA level) -induced shift in the reading frame results in a premature termination codon (PTC) mutation after five triplets, in exon 20 (L1258X). It was observed that the PTC introduced by the mutation does neither elicit a degradation of the mRNA through NMD nor an alternative splicing through NAS, but a significantly reduced amount of *CFTR* at the apical membrane in nasal epithelial cells was observed, providing a possible molecular explanation for the more severe phenotype observed in *F508del/3905insT* compound heterozygotes compared with *F508del* homozygotes. (Sanz et al., 2009*). This suggests that PTC will not always result in decrease of mRNA by NMD.

The applicant refers to a publication that recalls that truncated variants are often accompanied by low levels of mRNA due to nonsense mediated decay (NMD) (Richards et al., Genet Med 17:404-424, 2015). In a publication from Roy et al, it was shown that CFTR G542X, when tried to be expressed in

in HEK293T cells, did not yield protein. Although the applicant did not attempt to provided experiment evidence of the absence of G542X CFTR protein in HBE cells, the referred publication provide suggestion that indeed, no protein is produced.

For E585X, NMD might occur but is not shown for this particular mutation. As the truncation leaves the first cytoplasmic NBD1 domain intact, the truncated protein may be more stable than the G542X or the R553X mutation, the latter being referred to by the applicant. For that latter mutation (R553X), for the decrease of mRNA was referred to a publication. Although NMD is a process shown to occur for proteins with a PTC, it seems not to occur for all variants with a PTC (Sanz et al., 2009). Referring to proof for NMD with another CFTR mutant (R553X) is not considered supportive for a potential decrease in mRNA for the E585X mutation.

There could be another scenario possible. The truncated form may be expressed as a protein consisting only MSD1 and NBD1 domain. This form may be can form a complex with the expressed F508del mutant that is expressed from the other allele, a process called trans complementation, which is observed and published by Liudmila Cebotaru et al. (2013** & 2014**) and Bergbower et al (2019****). The E585X and the F508del mutants may together be stabilized by the CFTR modulators as such form more function protein than one F508del allele alone. Of course, this is a hypothesis that currently also lack proof. However, lacking empirical proof, it is currently regarded not conclusive whether or not the E585X CFTR allele contributes to the increase in Chloride transport or not.

The response to Symkevi as measured in FRT cells may not be representative for the clinical situation. For the Symkevi dossier, the applicant also used FRT cells. The in vitro results with the FRT cell line did not correlate sufficiently and not for all mutants to the clinical obtained results. Thus, information on the response to Symkevi for certain genotypes should be rather derived from clinical data.

It is acknowledged that patients harbouring the three F/MF genotypes as discussed above have a comparable clinical profile with regard to sweat chloride levels and pancreatic insufficiency and suggest minimal CFTR function. Furthermore, the applicant refers to the clinical phenotype of 124 genotypes with additional MF mutations (nonsense, frameshift, and canonical splice) of which ~98% having sweat chloride levels of >86 mmol/L. However, this clinical feature is not regarded to provide proof for the potential lack protein expression of the three F/MF genotypes analysed in vitro. Also, because of this data does not take into consideration the potential for improvement upon incubation or treatment with the modulators for the three F/MF genotypes. Real data before and after treatment of several patients with F/F and several patients with the three different F/MF genotypes could have evaluated for their supportiveness for the current hypothesis.

B) Provide information on the MF mutation for each of the F/MF donors. The applicant provided the requested data as requested above.

C) to justify and explain the rationale for the combination of different F/MF mutants that react differently to the three Kaftrio components into one group.

The applicant considered the result in chloride increase upon Kaftrio for each of the F/MF genotypes comparable. It is agreed with the applicant that all genotypes profit from Kaftrio treatment relatively to their own background chloride transport value. But, the response to Kaftrio is not comparable for all genotypes. As already discussed, the F/MF carrying the E585X is standing out in its response. The statement of the applicant that all genotypes result in truncated CFTR protein is considered confusing as earlier is posited that there is no protein produced.

D) Discuss the variability in response to the triple combination of the different F/MF cell lines including relevant clinical data from patients with the corresponding MF genotypes.

The applicant was asked to explain the variability in the results for the different F/MF donors in the Chloride transport assay. The applicant noted that the observed variability is explained by the biological variability from the single F508del allele, which is also observed in F/F-HBE cells, and the inherent variability in the biological assay. However, this is not considered the case. The EC90 for the F/F donors are 74.2, 83.7 and 89.3 UA/cm2. The EC90 for the F/MF donors are 56.1, 55.3, 84 and 39.8 UA/cm2. The variance between F/F ranges from 74.2-89.3 and the variance between F/MF ranges from 39.8-84, the latter variance being much higher than the first one. The third one in the row of F/MF donors (donor carrying a F508del/E585X mutation) performed better than two of the F/F donors in the in vitro assay. Based on the observed, relatively small variation between the three F/F donors it is rather unlikely that the relatively high chloride increase obtained with cells from donor (F508del/E585X) can be explained solely by biological variation. As the SD is rather small, the relatively high increase in chloride transport is also not likely due to technical variation. It rather suggests that the E585X CFTR mutant, which has an PTC, may produce certain level of abnormal protein that could, potentially become partially functional upon treatment with Kaftrio. Furthermore, this mutant also profits in vitro from the Symkevi treatment. This MF mutant (E585X) could thus potentially produce a truncated protein, as it seems that the mutant is adding to the Cl transport result, nor is it a mutant that is not responding to Symkevi. The suggestion from the applicant that the variability is either caused by the single F508del or by the technical variation of the assay seem not likely as the technical variation of the assay is expected to be rather small (low SD) and the biological variation is not observed to be that large with two *F508del* alleles. The conclusions of the applicant that none of the MF mutants will contribute to the measured increase in chloride transport is not agreed by CHMP.

E) Elaborate on the consequence that the hypothesis (a single F508del allele will be sufficient to provide substantial clinical benefit to CF patients) is not yet agreed to be supported by in vitro data as these data show that MF allele contributes to the in vitro results.

The applicant' response suggest that the applicant is rather seeking support in clinical data for their hypothesis that *the presence of a single F508del allele would be sufficient to provide substantial clinical benefit to CF patients clinical data.* This approach is supported as non-clinical data are considered too limited and not sufficient to definitely support such hypothesis.

Overall the applicant aims at providing evidence that all three F/MF genotypes are similar in the sense that they do not produce protein because of the PTC that results in decrease mRNA levels by NMD (sub question a). But, in contradiction the applicant notes in the response to sub question c, that truncated protein is formed. Empirical analysis would have been supportive to show absence of expression of the CFTR MF variant. With regard to the absence of a response to Symkevi treatment, the use of invitro results with the FRT cell line is not supported as correlation to clinical results appeared to be rather weak and sometimes not occurring at all. Thus, information on the response to Symkevi for certain genotypes should be rather derived from clinical data. Furthermore, they argue that these genotypes result in the same clinical disease phenotypes and are comparable to 124 other MF mutations (nonsense, frameshift, and canonical splice). However, this is not of support for the question whether different F/MF genotypes respond in the same way to Kaftrio treatment. Clinical data in treated and untreated fashion as requested could have been helpful. But this attempt was not made. This and the omission of empirical supportive data for the lack protein is regarded as a limitation. The issue is not further pursued. The support for the F508del only hypothesis should be retrieved from clinical data.

* The CFTR frameshift mutation 3905insT and its effect at transcript and protein level. Sanz J1, von Känel T, Schneider M, Steiner B, Schaller A, Gallati S. Eur J Hum Genet. 2010 Feb;18(2):212-7. doi: 10.1038/ejhg.2009.140. Epub 2009 Sep 2.

** Transcomplementation by a Truncation Mutant of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Enhances ΔF508 Processing through a Biomolecular Interaction* Liudmila Cebotaru,‡§ Owen Woodward,§ Valeriu Cebotaru,¶ and William B. Guggino§,1 J Biol Chem. 2013 Apr 12; 288(15): 10505–10512.

***Correcting the Cystic Fibrosis Disease Mutant, A455E CFTR Liudmila Cebotaru, 1 , 2 Daniele Rapino, 1 , 2 Valeriu Cebotaru, 3 and William B. Guggino 2 , * Effie C. Tsilibary, Editor PLoS One. 2014; 9(1): e85183.

****Restoration of F508-del F unction by Transcomplementation: The Partners Meet in the Endoplasmic Reticulum. Bergbower EAS1, Sabirzhanova I1, Boinot C1, Guggino WB1, Cebotaru L2. Cell Physiol Biochem. 2019;52(6):1267-1279. doi: 10.33594/000000089

After spiking with the corrector(s) alone, channel opening was only very minimal. After spiking with the corrector(s) and the potentiator channel opening was achieved efficiently, supporting the use of ivacaftor in the triple combination. However, in the chloride transport assay, it appears that for one F/MF donor absolute level of chloride transport upon incubation with the triple combination is lower than the absolute level of chloride transport for two F/F donors upon incubation with the two correctors alone**,** thus lacking potentiator ivacaftor. This suggests that two correctors together may already do a good job, in case the (poor) result with the triple combination for that certain F/MF variant is regarded sufficient as an absolute result. The absolute necessity of the potentiator for channel gating activity seems to contradict with this observation in the assay measuring the chloride transport upon incubation with CFTR modulators. The applicant was asked to explain. The applicant responded that for each donor the addition of the potentiator contributed to the result and is therefore of value for each type of the donor cells.

Additionally, there is no difference in Po values in cells treated with VX-455/IVA and VX-455/TEZ/IVA, 0.89 ± 0.019 (VX-445-treated) and 0.86 ± 0.024 (VX-445/TEZ-treated). Both treatment groups increased Po to levels greater than that of normal CFTR, corresponding to 189% (VX-445-treated) and 183% (VX-445/TEZ-treated) of normal CFTR gating activity. No data was provided for TEZ alone. Although VX-445 and TEZ appear to work in an additive fashion in the processing experiment (M379) above the gating data suggests that there is no difference between VX-445 and VX-445+Tez. Based on this, the applicant was asked to justify the necessity for two correctors in combination with IVA. The applicant responded that the experimental process in patch clamp studies does not allow for the contribution of VX-445 and/or TEZ in bringing CFTR to the membrane surface to be accounted for, which is accepted. The necessity for two correctors is justified by other studies presented by the applicant. Furthermore, different concentrations of TEZ and VX-445 were used in the FRT cells and similar results were observed for VX-445 with and without TEZ. An explanation was requested. The applicant's response is not accepted as the study report states, that prior to assessing gating activity the cells were incubated with 1 µM VX-445 and 3µM TEZ in the presence of 10% FBS. It would be assumed that considering the high protein binding of VX-445 and TEZ, nonspecific binding to serum proteins would occur, thereby reducing the effective concentration of the compounds. The applicant clarified that 25% human serum (HS) was used in the chloride transport study and 10% foetal bovine serum (FBS) was used in the channel gating study explaining the 2.5-fold difference in the used concentration of elexacaftor and tezacaftor in the two experiments.

Conclusion on In vitro in vivo correlation and in vitro demonstration supporting Applicant hypothesis

HBE cells are considered appropriate to investigate the effect on *CFTR* processing and conductance upon incubation with (different combinations of) the three components of Kaftrio. The applicant submitted data underlying the IVIVC plots, however the IVIVC relationship seems disproportional for the in vitro components and this was supported by clear discussion on the translatability of the results to the clinical setting. Furthermore, as discussed above, a per mutation basis comparison has not been submitted nor an attempt has been made by the applicant to solve this issue with concrete data.

The applicant did also not provide satisfactory rationale for combining the different MF mutants, which result in variable results in the chloride transport assay, suggesting that F/MF mutants differ are not all the same.

Overall, non-clinical data are too limited and identified shortcomings were not sufficiently addressed by the Applicant to definitely support the Applicant hypothesis that *the presence of a single F508del allele would be sufficient to provide substantial clinical benefit to CF patients has not been sufficiently*

demonstrated in vitro. It is therefore concluded by CHMP that it is not possible to establish in vitro in vivo correlation and therefore clinical data are required to demonstrate the Applicant hypothesis.

Secondary pharmacology

It is agreed with the applicant that secondary pharmacology for tezacaftor and ivacaftor and M6-ivacaftor are covered with the application for Kalydeco and Symkevi.

Toxicology

In the pivotal long term (26 week) rat repeat dose toxicity study, all animals at 75 mg/kg/day (m) and 30 mg/kg/day (f) were terminated early (d26) due to moribundity and rapidly declining condition, which was preceded by decreased food consumption, severe body weight loss and one or more of the following observations: thin body condition, hunched posture, loss of skin elasticity, skin cold to touch, material around nose, and/or piloerection. The cause of death/moribund condition in most of these animals was erosion of the glandular mucosa of the stomach, some of which were visible as brown or black foci in the stomach at necropsy. This is striking considering the modest effects in females dosed at 30 mg/kg/day in the pivotal 28-day study. It should be noted that in rats, exposure multiples were low (sub 5-fold), particularly so in males. The findings are therefore potentially clinically relevant. The safety profiles of tezacaftor and ivacaftor have been established previously and are known.

Differences seen in the toxicology studies are attributed to the pharmaceutical form of elexacaftor (ie jet milled vs non-jet milled, where jet milled elexacaftor improves systemic exposure). Body weight changes are primarily attributed to tezacaftor and more importantly were not seen in the clinical setting. However, the clinical relevance of decreased weight gain may manifest directly in weight loss in the clinical population. Sporadic lower consumption was noted in this treatment group which likely was associated with the observed decrease in body weight gain. It is accepted this is not a new finding as decreased weight gain has been observed in studies assessing the toxicity of TEZ and VX-445 administered alone. Furthermore, it is accepted that further mechanistic studies examining this finding are not warranted.

The male reproductive organ is a target organ based on findings in both rat and dog. In rat, small testes and epidydimides and reduced testes and epidydimides weight has been observed in animals exposed to elexacaftor or a combination of elaxacaftor/tezacaftor and ivacaftor. This correlated with degeneration of seminiferous tubules and atrophy, to oligo/aspermia and cellular debris in epididymides. In dog testes, minimal or mild, bilateral degeneration/atrophy of the seminiferous tubules was present in males administered 14 mg/kg/day that did not resolve during the recovery period. There were no noticeable changes in qualitative decreases in sperm content in the epididymides lumina, nor was there cellular debris noted. The Applicant was requested to provide a mechanistic discussion on the findings, considering that reduced fertility was noted in the FEED study and considering the patient population, which may include more juvenile patients in the future.

No mechanistic explanation was given by the applicant in their response. The applicant suggested that despite the fact that effects on male reproductive organs were seen in 2 species, human relevance is limited because the observations occurred at 6 times higher exposures than in clinical studies. However, the CHMP considered that a 5-fold multiple is generally considered as clinically relevant. Furthermore, a definitive statement on the resolution of the adverse findings in dog cannot be made because the recovery period was not long enough. While microscopic changes themselves may not be considered adverse within the study setting, the test-article related impairment in fertility is considered clinically relevant. Nevertheless, the reduced fertility was only observed in the high dose (75 mg/kg/day in males and 35 mg/kg/day in females, respectively) with no notable findings in the low and mid dose groups. The applicant's comment that synergistic testicular toxicity was not observed in the 13-week triple combination rat study is not endorsed. No test article related microscopic changes

were noted in any animals in the elexacaftor, tezacaftor and ivacaftor or metabolites groups in this study whereas effects were noted in the TC at the same dose level. The functional effects of these findings have not been assessed considering the limited incidence and severity of the findings. The potential for synergistic toxicity on male reproduction has not been characterised and this is reflected in the SmPC.

The 2-year elexacaftor rat carcinogenicity bioassay is ongoing and will be completed in 2020 and reported out in 2021, following the initial application submission. The results should be submitted by end 2021.

ERA

VX-445 (elexacaftor) is not PBT, nor vPvB. $PEC_{surface\ water}$ is above the action limit of 0.01 µg/L and thus a phase II environmental risk assessment should be conducted as a post-marketing commitment.

The applicant is requested by CHMP to perform the following studies with VX-445 (elexacaftor) as follow-up measures according to the EMA guideline on ERA (EMEA/CHMP/SWP/4447/00 corr 2):

- Adsorption-desorption using a batch equilibrium method (OECD 106) using 3 soil types and 2 types of sewage sludge;
- Ready biodegradability test (OECD 301);
- Aerobic and anaerobic transformation in aquatic sediment systems (OECD 308);
  Algal growth inhibition test (OECD 201);
- Daphnia sp. reproduction test (OECD 211, use version 2012);
- Fish, early life stage (E.L.S.) toxicity test (OECD 210, use version 2013);
- Activated sludge, respiration inhibition test (OECD 209, use version 2010)

From all requested chronic toxicity studies and the OECD 209 test, a NOEC and/or EC10 is needed for the risk assessment. In case a limit test is performed, the OECD guidelines should be followed: if the limit test results in a statistically significant effect, a new test to determine a dose-response relationship should be performed, from which a NOEC and/or EC10 should be reported.

The applicant is also reminded to harmonise the data for the F_{pen} refinement of VX-445 and VX-661, i.e. to use the same source, preferably with the most recent data and to use the same value for both actives. This should be the value for the Member State with the highest prevalence, as per the EMA guideline EMEA/CHMP/SWP/44609/2010 (Rev. 1), in order to make the ERA protective for all MS.

2.3.7. Conclusion on non-clinical aspects

Overall, the non-clinical data suggests that elexacaftor is safe for use in patients when used in the approved indication. No novel or synergistic adverse effects have been identified in combination studies with tezacaftor and ivacaftor. A 2-year carcinogenicity study in rats is being conducted and will be submitted as a post marketing commitment by 31 December 2021. The ERA will be completed as a post marketing commitment by December 2022. A letter of commitment has been provided by the Applicant.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

Table 1 Tabular overview of clinical studies

Study Number	Study Description
Studies in Healthy Subjects	
Study 001 (Parts A, B, and C)	Single-dose and multiple-dose escalation study and BA study of VX-445 monotherapy, or VX-445/TEZ/IVA
Study 001 (Part A QT)	Cardiodynamic analysis of the effect of VX-445 on QTc interval
Study 002	DDI study of the effect of VX-445/TEZ/IVA on the PK of oral contraceptives
Study 003	Mass balance study to investigate the absorption, distribution, metabolism, and excretion of VX-445
Study 005	BA study of VX-445/TEZ/D-IVA and VX-445/TEZ/IVA FDC tablets and food effect of VX-445/TEZ/D-IVA FDC tablet
Study 006	DDI study of the effect of itraconazole on the PK of VX-445/TEZ/D-IVA
Study 009	Thorough QT/QTc study of VX-445
Studies in Subjects With CF	
Study 001 (Parts D, E, and F)	Safety and efficacy of VX-445/TEZ/IVA and VX-445/TEZ/D-IVA (F/MF and F/F subjects)
Study 102	Efficacy and safety of VX-445/TEZ/IVA (F/MF subjects)
Study 103	Efficacy and safety of VX-445/TEZ/IVA (F/F subjects)

2.4.2. Pharmacokinetics

Pharmacokinetic parameters for each active substance and PK model

Basic pharmacokinetic parameters for elexacaftor (VX-445), tezacaftor and ivacaftor at steady state in patients with cystic fibrosis (CF) aged 12 years and older are shown in Table 2 (Phase 3 studies 102 and 103).

Table 2 Mean (SD) pharmacokinetic parameters of VX-445, tezacaftor and ivacaftor in patients with CF aged 12 years and older (Phase 3 studies 102 and 103).

	Drug	C_{max} (µg/mL)	$t_{1/2, eff}$ (h)	AUC_{0-24h} or AUC_{0-12h} (µg·h/mL)*
VX-445 200 mg and tezacaftor 100 mg once daily/ivacaftor 150 mg every 12 hours	VX-445	9.15 (2.09)	27.4 (9.31)	162 (47.5)
	Tezacaftor	7.67 (1.68)	11.9 (3.79)	89.3 (23.2)
	Ivacaftor	1.24 (0.34)	10.9 (3.41)	11.7 (4.01)

*AUC_{0-24h} for elexacaftor and tezacaftor and AUC_{0-12h} for ivacaftor

VX-445 is considered a BCS class 2 (low solubility/high permeability) compound. The product has a single chiral centre, however, in light of the assumed stability of the chiral configuration, chiral interconversion *in vivo* is not expected.

The pharmacokinetics of VX-445 (and tezacaftor and ivacaftor in combination with VX-445), as well as its major metabolites were investigated both in healthy subjects and CF patients.

VX-445 as well as tezacaftor and ivacaftor were analysed in plasma and urine using liquid chromatography with MS/MS detection. Analytical methods for VX-445 and its major metabolite M23-

445 were indicated by the Applicant to be adequately validated, with accuracy, specificity and stability meeting appropriate requirements.

Physiology-based PK (PBPK) model. A PBPK model was developed to simulate the VX-445 PK profile in the presence of moderate inhibitors of CYP3A (typical inhibitors used: fluconazole, erythromycin and verapamil). For this purpose, SimCyp was used, a PBPK platform that has been shown to yield acceptable prediction of the effect of inhibition of CYP3A4 by mild, moderate and strong inhibitors of CYP3A4 for a number of known CYP3A4 substrates. For the specific purpose of this application, the VX-445 PBPK model was validated by simulating VX-445 exposure in the absence of a CYP3A4 inhibitor, and in the presence of the strong CYP3A inhibitor itraconazole, and comparing this exposure with that obtained in the actual VX-445 PK studies and in the itraconazole-VX-445 drug-drug interaction study. The baseline VX-445 PK profiles without CYP3A4 inhibitors, as well as the interaction results on VX-445 AUC and C_{max}, appeared to be mimicked adequately by the PBPK simulations, and validation of the PBPK model is considered sufficiently in line with requirements stated in the *Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation* for this High regulatory impact situation (i.e., to waive a clinical DDI study with moderate CYP3A4 inhibitors). On this basis, the VX-445 PBPK model is considered qualified for CYP3A interaction predictions related to moderate inhibitors of CYP3A based on interpolation between the validated situations without and without a potent CYP3A4 inhibitor. The same SimCyp PBPK platform was accepted for Symkevi (tezacaftor/ivacaftor) Marketing Authorisation Application for prediction of the effect of moderate CYP3A4 inhibitors on the PK of ivacaftor and tezacaftor.

Population-PK model. A two-compartment model with zero-order delivery to the absorption compartment and a first-order absorption model, including four transit compartments, provided a reasonable description of the PK for VX-445. The PK model for M23-445 was developed sequentially using the empirical Bayes estimates from the VX-445 final model, assuming that 57.4% of parent is metabolized to M23-445, although changes in the amount of drug assumed to be metabolised did not change the predicted AUC for M23 AUC-445. Although especially the M23-445 popPK model appears to underestimate especially the higher exposures to M23-445, the models appears to yield a reasonable description of the data.

The typical estimate (95% CI) of the VX-445 clearance for a reference subject (70 kg, white, CF subject receiving a triple combination of VX-445 200mg qd/TEZ 100mg qd/IVA 150mg q12h in fixed-dose combination formulation) was 1.05 (1.01, 1.09) l/h, which is in reasonable agreement with the observed clearance in healthy subjects which ranged from 1.23 to 1.97 l/h (Study 001 and 003). During the exploratory graphical analysis, it was evident that the absorption phase was different in healthy subjects and CF patients, with a mean transit time of 2.36 hours in healthy volunteers and 0.81 hour in CF patients. Consequently, adding a disease status adjustment on the transit rate improved the model fit and reduced the bias.

Absorption

Following administration of the VX-445/TEZ/IVA FDC tablet under fed conditions, maximum plasma concentrations for VX-445 were obtained after approximately 6 (4 to 12) hours. The absolute bioavailability of VX-445 under the proposed posology with food is approximately 80%. The absorption of VX-445 from a single agent tablet and the final VX-445/TEZ/IVA FDC tablet under fed conditions appears similar.

Exposure to VX-445, tezacaftor and ivacaftor in CF patients was comparable to that in healthy volunteers.

The AUC of VX-445 administered as separate tablets in the fed state increased approximately 2.5-fold relative to administration in the fasted state. Based on the MAAs for IVA (Kalydeco) and TEZ/IVA (Symkevi), it is known that the bioavailability of IVA increases approximately 2.5- to 4-fold when administered with fat-containing meals relative to fasted conditions, while food has no effect on exposures of TEZ and its metabolites. As for Kalydeco and Symkevi, it is proposed to administer VX-445/TEZ/IVA FDC tablets with a moderate-fat meal. All phase 3 studies for VX-445/TEZ/IVA FDC tablets have indeed been conducted with dosing under fed conditions.

Distribution

VX-445, tezacaftor and ivacaftor are approximately 99% bound to plasma proteins, VX-445 and tezacaftor primarily bind to albumin and ivacaftor to alpha 1-acid glycoprotein and albumin. After single oral administration of VX-445 200 mg in combination with tezacaftor 100 mg and ivacaftor 150 mg in healthy subjects under fed conditions, the mean (SD) for apparent volume of distribution of VX-445, TEZ, and IVA was 53.7 (17.7), 82.0 (22.3), and 293 (89.8) L, respectively. Neither VX-445, tezacaftor nor ivacaftor partition preferentially into human red blood cells.

Metabolism

In vitro metabolism data of VX-445 demonstrated that CYP3A4 and CYP3A5 are the CYP isozymes involved in VX-445 metabolism. Based on the provided mass-balance Study 003, M23-445 was identified as the only major metabolite circulating in plasma, which accounted for 17.3% of the total circulating radioactivity, with a mean metabolite-to-parent (M23-445/VX-445) AUC ratio in plasma of 26% after single dose administration. The mean metabolite-to-parent AUC ratio at steady-state in healthy subjects ranged from approximately 35% to 50%. M23-445 has similar potency to VX-445 in F/MF-HBE cells and is considered pharmacologically active. Overall, VX-445 is considered responsible for the major part (50-65%) of its clinical activity, however, there is a significant contribution (35-50%) of metabolite M23-445.

Elimination

The mean effective $t_{1/2}$ of VX-445, administered as monotherapy, and its major metabolite M23-445 in healthy subjects were reasonably comparable, i.e. 20 and 23 hours, respectively. Following administration of the VX-445/TEZ/IVA FDC tablets in healthy subjects, the mean (SD) effective elimination $t_{1/2}$ of VX-445 was 24.7 (4.9) hours and in the Phase 3 studies 102 and 103, this was similar, being 27.4 (9.31) hours. Apparent clearance of VX-445 in healthy subjects ranged from 1.23 to 1.97 l/h.

The majority of VX-445 related radioactivity was recovered in faeces (87.3% in 14 days), with minimal renal excretion (approximately 0.23% radioactivity in urine). The concentrations of unchanged VX-445 in urine were generally below the limit of quantification, indicating that renal excretion of VX-445 is negligible in humans. VX-445 is mainly cleared by metabolism in humans, as the mean unchanged parent recovered in faeces accounted for about 22.7% of the administered radioactive dose.

PK of metabolites. Pharmacokinetics of the active and major VX-445 metabolite M23-445 has been investigated to a reasonable extent. M23-445 has a $t_{1/2}$ that is comparable to that of VX-445. Under steady-state, exposure to M23-445 is comparable to somewhat lower than that of VX-445.

Dose proportionality, time-dependency and accumulation. Exposure to VX-445 (administered as monotherapy or in combination with TEZ and IVA) increase in an approximately dose-proportional manner with increasing doses from 60 mg to 340 mg once daily. Major metabolite M23 445 exposure increased slightly more than dose proportional from 100 to 280 mg qd.

The accumulation ratio of 2-3.7 for VX-445, when given once daily, is in line with the VX-445 $t_{1/2}$ at steady-state, ranging from 17.6 to 27.9 hours. Steady-state exposures are achieved within approximately 7 days for both VX-445 and M23-445 after the start of dosing. VX-445 exposure mean accumulation ratio, and $t_{1/2}$ were similar when VX 445 was administered in combination with TEZ and IVA relative to the administration as monotherapy.

Variability. Overall, VX-445 and M23-445 had a moderate (34%) and high (53%) intersubject variability, respectively.

Special populations

Renal impairment

In light of the minimal renal excretion observed for VX-445 (approximately 0.23% of the radioactivity in urine) the pharmacokinetic data in renally impaired patients is considered acceptable, and no dose adjustment for renal impairment in the SmPC is considered necessary.

In human pharmacokinetic studies of elexacaftor, tezacaftor, and ivacaftor, there was minimal elimination of elexacaftor, tezacaftor, and ivacaftor in urine (only 0.23%, 13.7% [0.79% as unchanged medicine], and 6.6% of total radioactivity, respectively).

Hepatic impairment

A large proportion of VX-445 related radioactivity was recovered in faeces (87.3% in 14 days), and metabolism plays an important role in the clearance of VX-445. Therefore, hepatic function is expected to have an important effect on VX-445 clearance. VX-445 pharmacokinetics has not yet been studied in subjects with hepatic impairment. The Applicant argues that an increase in exposure of VX-445 similar to TEZ and IVA is expected in patients with moderate or severe hepatic impairment, and therefore applies the dose-recommendation for subjects with hepatic impairment as is in place for tezacaftor/ivacaftor (Symkevi) also for Kaftrio.

Gender, race, weight and age

Based on popPK Study O401, in which data from 244 male subjects and 174 female subjects were included, gender did not affect VX-445 exposure. In the same popPK study, M23-445 clearance in females was 22.4% lower (95% CI 13.8-31%) compared to male CF patients. Although the exposure of the active metabolite M23-445 appears somewhat increased in females as compared to males, bearing in mind that the majority of the clinical activity (50-65%) appears to be governed by parent VX-445, it is agreed that the observed 28.9% higher M23-445 AUC in females is unlikely to be clinically relevant.

In the popPK simulations, in which data from 373 White, 30 Black or African American, 1 multiple and 14 with other ethnic backgrounds (no Asian) were included, about 22% decreased exposure to VX-445 was noted in African-American subjects as compared to White subjects. Based on PopPK/PD simulations, this ~22% decrease in VX-445 AUC in African-American subjects did not translate into differences in the pharmacodynamics endpoints of ppFEV1 and SwCl. No relevant difference in exposure in other races on VX-445 exposure was noted.

No relevant effect of weight on VX-445 exposure was observed in CF subjects >40 kg or <90 kg.

In the popPK analysis, age 12 to <18 years (n=72) or ≥18 years (n=346) did not to appear to affect VX-445 nor M23-445 exposure to a significant extent. No subjects over the age of 59 were included. Data in patients <12 years may be provided at a later stage via the paediatric development programme.

Pharmacokinetic interaction studies

Interactions in vitro

Substrate in vitro. Based on *in vitro* data, CYP3A4/5 are the main CYP isoforms involved in VX-445 metabolism. With regard to drug transporters, *in vitro*, VX-445 and M23-445 are substrate for the efflux transporter P-gp. VX-445 and M23-445 are no substrates for OATP1B1 and OATP 1B3. However, exposure to VX-445 is not expected to be affected significantly by concomitant inhibitors of P-gp due to its high intrinsic permeability and low likelihood of being excreted intact.

Inhibition/induction in vitro

Based on the outcome of the *in vitro* tests, indicating low *in vitro* inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 and lack of induction of CYP1A2, CYP2B6 or CYP3A4 by VX-445 and M23-445, no *in vivo* inhibition or induction of CYPs by VX-445 nor M23-445 is expected.

Based on in vitro data, VX-445 and M23 are substrates for (Breast cancer resistance Protein) BCRP, however, *in vivo* inhibition of BCRP is unlikely to result in relevant changes in the VX-445 or

M23-445 PK.

With regard to drug transporters, based on *in vitro* data, the potential of VX-445/M23-445 to inhibit P-gp efflux *in vivo* is predicted to be low, however, it cannot be excluded that VX-445 and M23-445 inhibit OATP1B1 and OATP1B3 *in vivo*. Further, based on in vitro data and on simulation using a mechanistic static model (for AOT3), the DDI potential of VX-445 and M23-445 through their inhibition of OAT1, OAT3, OCT1, OCT2, MATE1 and MATE2-K is predicted to be low. However, VX-445 possibly inhibits BCRP *in vivo* to such extent that an increased exposure to BCRP substrates like rosuvastatin may be expected, and this is indicated in the SmPC section 4.5.

Effect of co-administered drugs on VX-445/tezacaftor/ivacaftor in vivo

Co-administration of the strong CYP3A inhibitor itraconazole caused a substantial increase in the exposure of VX-445 (2.8-fold increase in $AUC_{0\text{-}24h}$). It was already known that co-administration of the strong CYP3A inhibitor itraconazole resulted in a 4-fold increased $AUC_{0\text{-}24h}$ for TEZ and a 16-fold increase in $AUC_{0\text{-}12h}$ for IVA.

Further, based on the results of PBPK modelling, co-administration of the moderate CYP3A inhibitors fluconazole, erythromycin, and verapamil on VX-445 exposure was predicted to yield an approximate 1.9- to 2.3-fold increase in the AUC of VX-445.

Therefore, a reduction in the dose of VX-445/TEZ/IVA combination therapy is recommended for co-administration with strong or moderate CYP3A inhibitors. The proposed dose modifications are as follows and consistent with those of TEZ/IVA combination therapy:

• When co-administered with *strong* inhibitors of CYP3A (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin), the dose should be reduced to only 2 tablets of VX-445 100 mg/TEZ 50 mg/IVA 75 mg taken approximately 3-4 days apart (i.e. 2 tablets twice a week). The evening dose of IVA should not be taken. This dose adjustment provides a 3.5-fold lower dose of VX-445 and TEZ and 7-fold lower dose of IVA and is consistent with the recommendation for TEZ/IVA and IVA during co-administration with strong CYP3A inhibitors.

• When co-administered with *moderate* inhibitors of CYP3A (e.g., fluconazole, erythromycin, verapamil), the dose should be reduced to 2 tablets of VX-445 100 mg/TEZ 50 mg/IVA 75 mg in the morning of every other day and a dose of IVA 150 mg should be taken in the morning, every other day, alternating with the VX-445/TEZ/IVA dose. The evening dose of IVA should not be taken. This

dose adjustment provides a 2-fold lower dose of VX-445, TEZ, and IVA, and is consistent with the recommendation for TEZ/IVA and IVA during co-administration with moderate CYP3A inhibitors.

Co-administration of VX-445/TEZ/IVA with grapefruit juice, which contains 1 or more components that moderately inhibit CYP3A, may increase exposure of VX-445, TEZ, and IVA. Therefore, food containing grapefruit should be avoided during treatment with VX-445/TEZ/IVA.

Based on the provided data, the dose adjustment and the recommendation against the concomitant use of CYP3A inducers are considered acceptable.

Effect of VX-445/TEZ/IVA on co-administered drugs in vivo

In light of the low *in vitro* inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 and lack of induction of CYP1A2, CYP2B6 or CYP3A4 by VX-445 or M23-445, no dose adjustment is necessary when co-administering VX-445 with any CYP substrate. However, ivacaftor may inhibit CYP2C9; therefore, monitoring of the international normalized ratio (INR) during co administration of warfarin with VX-445/TEXZ/IVA and IVA is recommended. Other medicinal products for which exposure may be increased due to this DDI include glimepiride and glipizide; these medicinal products should be used with caution.

Due to the potential inhibition of P-gp by IVA, caution and appropriate monitoring are recommended when co-administering VX-445/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 clinically significant DDI between ethinyl estradiol (EE)/ levonorgestrel (LN) and VX-445/TEZ/IVA (i.e., <33% increased exposure in EE/LN) was observed when the oral contraceptive was co-administrated with VX-445/TEZ/IVA in healthy subjects. These results indicate that co-administration with TEZ/IVA is not expected to reduce the effectiveness of hormonal contraceptives.

Overall, VX-445, as well as tezacaftor and ivacaftor pharmacokinetics have been investigated to a reasonable degree.

2.4.3. Pharmacodynamics

Primary pharmacology

Sweat chloride concentration is a direct measure of *CFTR* function in the sweat gland that is used as a PD marker of on-target activity of *CFTR* modulators. The design, methodology and results of the sweat chloride test will be described and discussed with the pivotal trials.

Secondary pharmacology

The effect of VX-445 on QT/QTc interval was investigated in a double-blind, randomized, placebo- and active-controlled, parallel with nested crossover, multiple-dose ECG study following doses of 200 and 400 mg qd. A total of 64 healthy male and female subjects were randomized 2:1:1 to 1 of 3 treatment groups. Group 1 received VX-445 200 mg qd for 7 days, followed by 400 mg qd for 7 days. A nested crossover design was utilized for moxifloxacin and placebo in Groups 2A and 2B.

Serial ECGs and matching PK samples were collected for assessment of VX-445, M23-445, and moxifloxacin plasma concentrations. Continuous ECGs were extracted in up to 10 replicates predose on Days -1, 1, 8, 15, and 16, and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, and 23.5 hours postdose (Days 2, 9, and 17). The primary analysis of ΔQTcF for therapeutic and supratherapeutic doses of VX-445 was based on C-QTc analysis of VX-445 and M23-445. Assay sensitivity was evaluated by C-QTc analysis of moxifloxacin on ΔQTcF.

VX-445 did not have an effect on the QTc interval in Study 009. Mean ΔQTcF values following VX-445 were negative at all postdose time points and mean ΔΔQTcF ranged between -2.7 and 1.4 msec on Day 8 for 200 mg qd and between -4.1 and -0.6 msec on Day 15 for 400 mg qd.

In the C-QTc analysis, a full model including both VX-445 and M23-445 and their interaction was initially fit. After the model selection procedure, the final model included M23-445 only, and this model represented the data reasonably well. The estimated slope of the C-QTc relationship was very shallow and slightly negative (-0.0004 msec per ng/mL [90% CI: -0.00080, -0.000004]), with a small, not statistically significant treatment effect-specific intercept of 0.1 msec (90% CI: -2.61, 2.86). Based on this C-QTc analysis, a QTcF effect above 10 msec for both VX-445 and M23-445 can be excluded up to VX-445 plasma concentrations of approximately 32.7 µg/mL and M23-445 plasma concentrations of approximately 14.0 µg/mL.

Assay sensitivity was demonstrated by the moxifloxacin C-QTc relationship with a statistically significant slope and by demonstrating that the predicted effect at C_{max} was above 5 msec.

VX-445 at the studied doses did not have an effect on PR and QRS intervals.

At the studied VX-445 doses of 200 and 400 mg qd, there was an increase in HR, with a largest mean placebo-corrected change from baseline HR (ΔΔHR) of 3.2 beats per minute (bpm) at 1 hour postdose on Day 8 (200 mg qd) and 7.0 bpm at 8 hours postdose on Day 15 (400 mg qd).

2.4.4. Discussion on clinical pharmacology

The pharmacokinetics of VX-445 and tezacaftor and ivacaftor in combination with VX-445, as well as its major metabolites, were investigated both in healthy subjects and CF patients.

VX-445 as well as tezacaftor and ivacaftor were analysed in plasma and urine using liquid chromatography with MS/MS detection. In general, analytical methods for VX-445 and its major metabolite M23-445 were adequately validated, with accuracy, specificity and stability meeting appropriate requirements. Adequate revalidation data for the applied analytical methods, including an additional QC covering the 30-50% range of the calibration curve, were provided.

Distribution and excretion. The volume of distribution of TEZ in Study 005 of 82 (22.3) L was much smaller than the TEZ volume of distribution observed for Symkevi, i.e. 271 (157) L. Further, based on the previous MAA for Symkevi, in CF patients, tezacaftor $t_{1/2}$ was 156 (52.7) hours, whereas in the current dossier, the mean (SD) elimination $t_{1/2}$ of TEZ following administration of the VX-445/TEZ/IVA FDC tablets in healthy subjects was 60.3 (15.7) hours, and in the currently provided Phase 3 studies 102 and 103, the effective $t_{1/2}$ of TEZ under steady state conditions in CF subjects was approximately 12 hours. The observed differences in Vd and $t_{1/2}$ reported for TEZ are most likely due to the shorter sampling period in the Kaftrio Study 005 (6 days) than in the Symkevi Study 661-101 (4 weeks). Presumably, the effective volume of distribution as well as the effective $t_{1/2}$ are better predicted using the relatively shorter sampling period, whereas the terminal $t_{1/2}$ is likely better estimated using the longer sampling period. There are no indications that the TEZ $t_{1/2}$ or Vd is affected by simultaneous administration of VX-445. To avoid confusion upon comparison of the TEZ $t_{1/2}$ for Symkevi and Kaftrio, the effective TEZ $t_{1/2}$ (11.9 h) as well as the terminal TEZ $t_{1/2}$ (156 h) is indicated in the SmPC section 5.2.

Genetic variants. VX-445 is mainly metabolised by CYP3A4. For this enzyme, a relevant and relatively abundant variant with reduced activity has been reported, i.e. CYP3A4 *22. No data are available for VX-445, however, for TEZ and IVA, also being substrates for CYP3A4, the range of exposures in heterozygous CYP3A4*22 was increased by 20% and 11%, respectively, as compared to non-CYP3A4*22 subjects and comparable results may be expected for VX-445. No data are available for

homozygous CYP3A4*22 subjects however the effects are expected to be stronger than for the heterozygous population. This has been indicated in the SmPC.

Variability. Overall, VX-445 and M23-445 had a moderate (34%) and high (53%) inter-subject variability, respectively. The actual intrasubject variability, based on repeated administrations are unknown. However, considering the relatively wide therapeutic margin for Kaftrio, no issues are expected regarding the intraindividual variability.

Hepatic impairment. A large proportion of VX-445 related radioactivity was recovered in faeces (87.3% in 14 days), and metabolism plays an important role in the clearance of VX-445. Therefore, hepatic function is expected to have an important effect on VX-445 clearance. VX-445 pharmacokinetics has not been studied in subjects with severe hepatic impairment (Child-Pugh Class C, score 10-15). In Study 007, following multiple doses of VX-445, TEZ and IVA for 10 days, subjects with moderately impaired hepatic function (Child-Pugh Class B, score 7 to 9) had an approximately 25% higher AUC and a 12% higher C_{max} for VX-445, 73% higher AUC and 70% higher C_{max} for M23-445, 20% higher AUC but similar C_{max} for tezacaftor, 22% lower AUC and 20% lower C_{max} for TEZ-M1, and a 1.5-fold higher AUC and a 10% higher C_{max} for ivacaftor compared with healthy subjects matched for demographics. Based on these data, according to the Applicant, use of VX-445/TEZ/IVA is not recommended in patients with moderate or severe hepatic impairment. However, for patients with moderate hepatic impairment, considering the high medical need for treatment of CF patients with hepatic impairment use of VX-445/TEZ/IVA could be considered when there is a clear medicinal need and the benefits are expected to outweigh the risks. If used, VX-445/TEZ/IVA should be used with caution at an approximately 25% reduced dose, as follows: two VX-445/TEZ/IVA tablets alternating with one VX-445/TEZ/IVA tablet taken in the morning, on alternate days. The evening dose of the ivacaftor tablet should not be taken.

Although the dose advice for CF patients with moderate hepatic impairment appears reasonable and can at this stage be accepted, no information has been provided by the Applicant on the effect of the proposed dose-reduction on the exposure to the active metabolite M1-TEZ. The Applicant should provide such analysis and subsequently re-discuss/refine the dose-recommendation in moderately hepatic impaired patients. This discussion is proposed to be provided at the time that the CSR from Study 007 is submitted as Post Approval Measure.

Age. No subjects over the age of 59 were included in the clinical studies supporting this application. Based on extrapolation, no indication for a pronounced difference in VX-445 PK in subjects aged >59 years was apparent.

Weight. No relevant effect of weight on VX-445 exposure was observed in CF subjects >40 kg or <90 kg. The lowest weight included in the POP-PK analyses was 29 kg but there were insufficient data in CF subjects <40 kg in the Phase 3 studies to make a conclusion about exposure at lower extremes of weight. Further data on PK in low weight patients is expected in due course from the ongoing open label PK/safety study (VX18-445-106) in children aged 6-11 years (both F/F and F/MF genotypes), where half the adult dose is being tested in patients under 30 kg.

The results of the exposure-response (PK/PD) model O401 for SwCl and ppFEV1 support the hypothesis that the exposures to VX-445 obtained upon administration of a 200mg qd dose is on the plateau region of the exposure-response curve for SwCl and ppFEV1 in both F/MF and F/F subjects. In addition, this PK/PD analysis shows that the triple VX-445/TEZ/IVA combination therapy caused a larger absolute increase in ΔppFEV1 and a larger absolute decrease in SwCl than TEZ/IVA in CF subjects with the F/F genotype.

VX-445 was assessed for QT prolongation as monotherapy. IVA and TEZ have been evaluated previously in dedicated thorough QT studies; the results showed that treatment with IVA or TEZ at

therapeutic or supratherapeutic doses did not have clinically significant effects on QTc. The assessment of the mono-component is considered acceptable based on the ICH guideline E14, that states that, in general, combinations of two or more drugs are unlikely to need a thorough QT/QTc study or intensive late stage monitoring, if the component drugs have been demonstrated to lack relevant effects in thorough QT/QTc studies.

Mean ΔQTcF values were negative at all post-dose time points in the active treatment group. For mean ΔQTcF values and mean placebo corrected ΔQTcF (ΔΔQTcF), the 90% CI did not exceed 10 ms at any timepoint. A QTcF effect (ΔΔQTcF) above 10 msec based on the upper bound of the 90% CI can be excluded up to a VX-445 plasma concentration of approximately 32.7 µg/mL and up to an M23-445 plasma concentration of approximately 14.0 µg/ml. These concentrations are approximately 3.7-fold and 4.9-fold higher, respectively, than VX-445 and M23-445 C_{max} values in subjects with CF following VX-445 200 mg qd (8.74 µg/mL and 2.88 µg/mL).

2.4.5. Conclusions on clinical pharmacology

Overall, VX-445, as well as tezacaftor and ivacaftor pharmacokinetics and pharmacodynamics have been investigated satisfactorily.

However, studies have not been conducted with severe hepatic impairment. Therefore, patients with severe hepatic impairment should not be treated with Kaftrio as indicated in section 4.2 of the SmPC.

Kaftrio is not recommended for patients with moderate hepatic impairment. In these patients, its use should only be considered if there is a clear medical need and with caution at a reduced dose as mentioned in section 4.2 of the SmPC.

The Applicant agreed to submit results of the clinical study report of study 007 in patients with moderate impairment as Post Approval Measure (PAM) by end of Q3 2020. At the same time, the Applicant should re-discuss/refine the dose-advice in moderate hepatically impaired patients, taking into account the expected exposure of the active M1-TEZ metabolite. This information is important in support of the dose advice in patients with hepatic impairment.

2.5. Clinical efficacy

The VX-445/TEZ/IVA development program was based on *in vitro* evidence demonstrating increased efficacy and potency of the triple combination (TC) regimen on the *F508del-CFTR* protein compared to previous IVA (Kalydeco) monotherapy or lumacaftor (LUM)/IVA (Orkambi) and TEZ/IVA (Symdeko, Symkevi) dual therapies. A clinical program was designed to assess whether the presence of a single *F508del* allele would be sufficient for CF patients to benefit from the TC regimen.

The core efficacy data are from 2 controlled Phase 3 main studies:

- Study 102: a 24-week study in subjects with a single *F508del* allele (F/MF)
- Study 103: a 4-week study in subjects with two *F508del* alleles (F/F)

Supportive efficacy data are from:

- Phase 1/2 Study 001 in F/MF (Part D) and F/F subjects (Part E)
- Study 105, an ongoing open-label extension (OLE) study evaluating long-term safety and efficacy for 96 weeks in subjects who participated in Studies 102 and 103.

Additionally, results of a European Medicines Agency Paediatric Committee (PDCO)-requested cross-study comparison using data from Studies 103 and 105 and Phase 3 studies of TEZ/IVA (Symkevi)

provide supportive efficacy data. This comparison is also referred to as the Meta-analysis (paediatric investigation plan [PIP] Study C9.

Table 3: Overview of the characteristics of the clinical studies

Study Identifier; Type of Study; Country; Study Status/ Location of Report	Study Design; Type of Control	Study Objectives	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Dosed With Study Drug; Population	Duration of Treatment
		TC with VX-445 in subjects with CF			
Efficacy and Safety Studies					
Controlled Clinical Studies Pertinent to the Claimed Indication					
VX17-445-102 Phase 3 Efficacy and safety Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Greece, Italy, Netherlands, Sweden, UK, US Completed Module 5.3.5.1	Randomized, double-blind, placebo-controlled, parallel-group, multicenter	Primary Objective Evaluate the efficacy of VX-445 in TC with TEZ and IVA in subjects with CF who are F/MF Secondary Objectives • Evaluate the safety of VX-445 in TC with TEZ and IVA • Evaluate the PD of VX-445 in TC with TEZ and IVA • Evaluate the PK of VX-445, TEZ, and IVA when administered in TC	• VX-445 100-mg/TEZ 50-mg/IVA 75-mg FDC tablet • IVA 150-mg tablet VX-445 200 mg qd, TEZ 100 mg qd, and IVA 150 mg q12h; or matched placebos Oral administration	403 subjects Male and female subjects with CF, 12 years of age and older, F/MF genotype	4-week IA 24 weeks VX-445/TEZ/IVA or matched placebos
VX17-445-103 Phase 3 Efficacy and safety Belgium, Netherlands, UK, US Completed Module 5.3.5.1	Randomized, double-blind, active-controlled, parallel-group, multicenter	Primary Objective Evaluate the efficacy of VX-445 in TC with TEZ and IVA in subjects with CF who are F/F Secondary Objectives • Evaluate the safety of VX-445 in TC with TEZ and IVA • Evaluate the PD of VX-445 in TC with TEZ and IVA • Evaluate the PK of VX-445, TEZ, and IVA when administered in TC	• VX-445 100-mg/TEZ 50-mg/IVA 75-mg FDC tablet • TEZ 100-mg/IVA 150-mg FDC tablet • IVA 150-mg tablet VX-445 200 mg or matched placebo qd, TEZ 100 mg qd, and IVA 150 mg q12h Oral administration	107 subjects Male and female subjects with CF, 12 years of age and older, F/F genotype	4 weeks VX-445/TEZ/IVA or TEZ/IVA (after 4-week TEZ/IVA Run-in Period)

Study Identifier; Type of Study; Country; Study Status/ Location of Report	Study Design; Type of Control	Study Objectives	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Dosed With Study Drug; Population	Duration of Treatment
Patient PD and PK/PD Studies					
VX16-445-001, Parts D, E, and F Phase 2 Safety, tolerability, efficacy, PD, PK Australia, Belgium, Netherlands, US Completed Module 5.3.4.2	Randomized, double-blind, parallel-group; placebo-controlled, TEZ/IVA-controlled	Primary Objectives **Parts D and E** • Evaluate the safety and tolerability of VX-445 in TC with TEZ and IVA in subjects with CF • Evaluate the efficacy of VX-445 in TC with TEZ and IVA in subjects with CF **Part F** • Evaluate the safety and tolerability of VX-445 in TC with TEZ and D-IVA in subjects with CF • Evaluate the efficacy of VX-445 in TC with TEZ and D-IVA in subjects with CF Secondary Objectives **Parts D and E** • Evaluate the PD effect of VX-445 in TC with TEZ and IVA on CFTR function in subjects with CF • Evaluate the PK of VX-445 when administered in TC with TEZ and IVA in subjects with CF • Evaluate the PK of TEZ, IVA, and their respective metabolites (M1-TEZ and M1-IVA) when administered in TC with VX-445 in subjects with CF **Part F** • Evaluate the PD effect of VX-445 in TC with TEZ and D-IVA on CFTR function in subjects with CF • Evaluate the PK of VX-445 when administered in TC with TEZ and D-IVA in subjects with CF • Evaluate the PK of TEZ and metabolite (M1-TEZ) and D-IVA when administered in	• VX-445 20-mg, 50-mg, and 100-mg tablets • TEZ 50-mg tablet • IVA 150-mg tablet • D-IVA 50-mg tablet • TEZ 100-mg/IVA 150-mg FDC tablet **Part D** VX-445 50, 100, or 200 mg qd, TEZ 100 mg qd, and IVA 150 mg q12h; or matched placebos **Part E** VX-445 200 mg or placebo qd with TEZ 100 mg qd and IVA 150 mg q12h **Part F** VX-445 200 mg qd, TEZ 100 mg qd, and D-IVA 150 mg qd; or matched placebos **Parts D, E, and F** Oral administration	**Part D** 65 subjects **Part E** 28 subjects **Part F** 29 subjects Male and female subjects with CF, 18 years of age and older **Parts D and F** F/MF genotypes **Part E** F/F genotypes	**Part D** 5 weeks total • 4 weeks VX-445/TEZ/IVA or matched placebos • 1 week TEZ/IVA or matched placebos **Part E** 12 weeks total • 4 weeks TEZ/IVA • 4 weeks VX-445/TEZ/IVA or TEZ/IVA • 4 weeks TEZ/IVA **Part F** 4 weeks VX-445/TEZ/D-IVA or matched placebos

Uncontrolled Clinical Studies					
VX17-445-105 Phase 3 Safety and efficacy Non-exhaustive includes: Australia, Belgium, Canada, Czech Republic, Netherlands, Sweden, US, UK Ongoing	Open-label, rollover	Primary Objective Evaluate the long-term safety and tolerability of VX-445 in TC with TEZ and IVA in subjects with CF who are homozygous or heterozygous for the *F508del* mutation Secondary Objectives • Evaluate the long-term efficacy of VX-445 in TC with TEZ and IVA • Evaluate the PD of VX-445 in TC with TEZ and IVA	• VX-445 100-mg/TEZ 50-mg/IVA 75-mg FDC tablet • IVA 150-mg tablet VX-445 200 mg qd, TEZ 100 mg qd, and IVA 150 mg q12h Oral administration	504 subjects Male and female subjects with CF, 12 years of age and older, F/MF and F/F genotypes	96 weeks VX-445/TEZ/IVA

ADME: absorption, distribution, metabolism, excretion; BA: bioavailability; CF: cystic fibrosis; CFTR: cystic fibrosis conductance regulator; DDI: drug-drug interaction; D-IVA: deuterated IVA (VX-561); EE: ethinyl estradiol; FDC: fixed-dose combination; F/F: homozygous for F508del; F/MF: heterozygous for F508del and a minimal CFTR function mutation; HR: heart rate; IA: interim analysis; IV: intravenous; IVA: ivacaftor; LN: levonorgestrel; PD: pharmacodynamic(s); PK: pharmacokinetic(s); PR: PR interval, segment; q12h: every 12 hours; qd: once daily; QRS: the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization; QT: QT interval; QTc: QT interval corrected; QTcF: QT interval corrected by Fridericia's formula; TC: triple combination; TEZ: tezacaftor; TRA: total radioactivity; UK: United Kingdom; US: United States

2.5.1. Dose-response studies

VX16-445-001, Parts D and E. Randomized, double-blind, parallel-group; placebo-controlled, TEZ/IVA-controlled

Study 001 (Parts D and E) was a Phase 1/2, randomized, double-blind, controlled, parallel group, multicentre study in F/MF and F/F subjects 18 years of age and older. The study evaluated the pharmacokinetics (PK), pharmacodynamics (PD), efficacy and safety of the VX-445/TEZ/IVA combination.

- In Part D, F/MF subjects received the triple combination (TC) of VX-445 (either 50, 100, or 200 mg once daily [qd]) with TEZ/IVA (or placebo) for 4 weeks, followed by TEZ/IVA (or placebo) only for 1 week (VX-445 Washout Period).
- In Part E, F/F subjects received TEZ/IVA for 4 weeks during the Run-in Period, followed by the TC of VX-445 200 mg qd with TEZ/IVA (or placebo + TEZ/IVA) for 4 weeks, followed by TEZ/IVA only for 4 weeks (VX-445 Washout Period).

A total of 123 subjects were enrolled in Parts D, E, and F. Part D was enrolled as 2 sequential cohorts. Subjects in Part D1 and D2 were pooled for analysis purposes and are summarized together in this report.

Key efficacy results from Study 001 are summarized in Table 4 (F/MF subjects) and Table 5. (F/F subjects).

Table 4: Key Efficacy and PD Results from Study 001 Part D (F/MF)

Statistics	Through Day 29 (MMRM) Placebo N = 12	VX-445 50 mg qd + TEZ/IVA N = 10	VX-445 100 mg qd + TEZ/IVA N = 22	VX-445 200 mg qd + TEZ/IVA N = 21
Absolute Change in $ppFEV_1$ (Percentage Points) From Baseline				
n	11	10	22	21
LS mean (95% CI)	0.0 (-3.9, 4.0)	11.1 (7.0, 15.3)	7.9 (5.1, 10.6)	13.8 (10.9, 16.6)
P value within treatment	0.9943	<0.0001	<0.0001	<0.0001
LS mean difference (95% CI)	--	11.1 (5.4, 16.8)	7.8 (3.0, 12.7)	13.8 (8.9, 18.6)
P value versus placebo	--	0.0003	0.0019	<0.0001
Absolute Change in SwCl (mmol/L) From Baseline				
n	12	10	22	21
LS mean (95% CI)	-2.2 (-9.9, 5.6)	-38.2 (-46.7, -29.8)	-33.2 (-38.9, -27.5)	-39.1 (-44.9, -33.3)
P value within treatment	0.5802	<0.0001	<0.0001	<0.0001
LS mean difference (95% CI)	--	-36.1 (-47.5, -24.7)	-31.0 (-40.6, -21.4)	-36.9 (-46.6, -27.3)
P value versus placebo	--	<0.0001	<0.0001	<0.0001

Sources: Study 001 CSR Version 2.0/Tables 11-9 and 11-12
IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; P: probability; PD: pharmacodynamics; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; q12h: every 12 hours; qd: once daily; SwCl: sweat chloride; TEZ: tezacaftor
Note: TEZ/IVA: TEZ 100 mg qd/IVA 150 mg q12h. Baseline was defined as the most recent non-missing measurement before the first dose of study drug on Day 1 of the Treatment Period.

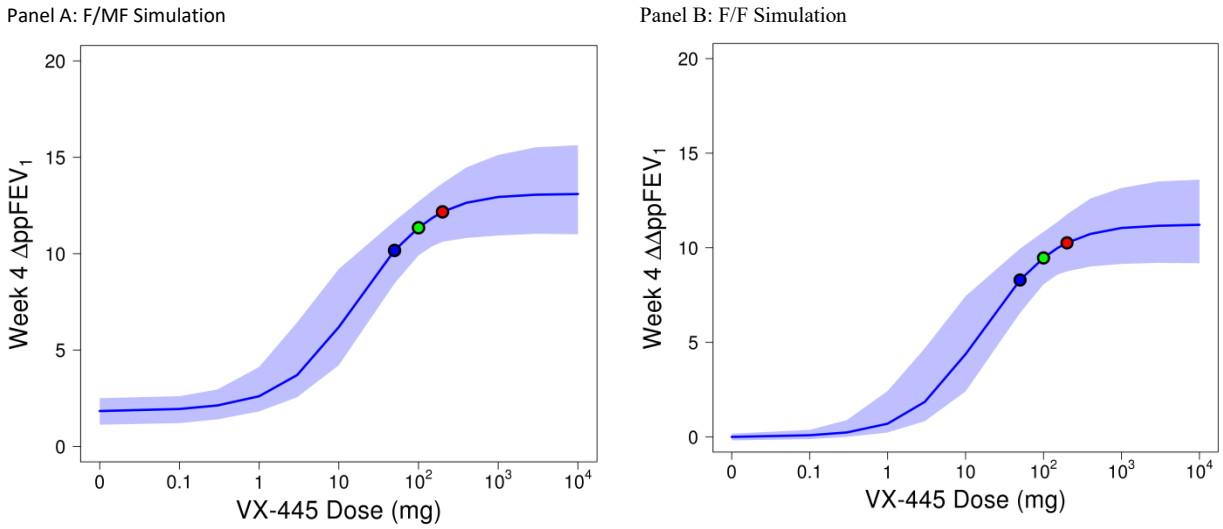
Table 5: Key Efficacy and PD Results From Study 001 Part E (F/F)

Statistics	Through Day 29 (MMRM) TEZ/IVA N = 7	VX-445 200 mg qd + TEZ/IVA N = 21
Absolute Change in $ppFEV_1$ (Percentage Points) From Baseline		
n	6	21
LS mean (95% CI)	0.4 (-5.4, 6.2)	11.0 (7.9, 14.0)
P value within treatment	0.8869	<0.0001
LS mean difference (95% CI)	--	10.6 (4.0, 17.1)
P value versus TEZ/IVA	--	0.0027
Absolute Change in SwCl (mmol/L) From Baseline		
n	7	21
LS mean (95% CI)	0.8 (-9.3, 11.0)	-39.6 (-45.3, -33.8)
P value within treatment	0.8712	<0.0001
LS mean difference (95% CI)	--	-40.4 (-52.2, -28.6)
P value versus TEZ/IVA	--	<0.0001

Sources: Study 001 CSR Version 2.0/Tables 11-10 and 11-13
IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; *P*: probability; PD: pharmacodynamics; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; q12h: every 12 hours; qd: once daily; SwCl: sweat chloride; TEZ: tezacaftor
Note: TEZ/IVA: TEZ 100 mg qd/IVA 150 mg q12h. Baseline was defined as the most recent non-missing measurement before the first dose of study drug on Day 1 of the Treatment Period, which was established after 4 weeks of TEZ/IVA Run-in treatment.

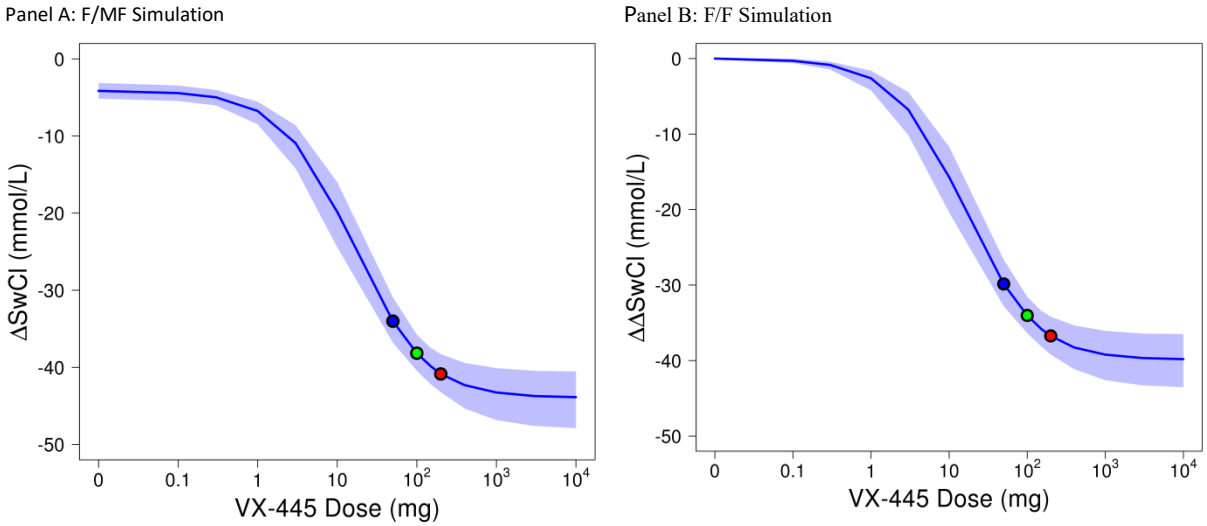
Since the dose range in the CF patients was limited (50 mg, 100 mg, and 200 mg qd), simulations were conducted to extrapolate the VX-445 dose beyond the range of 50 to 200 mg in order to visualize the effect on ppFEV1 or SwCl. Results of the simulations (for ppFEV1 and SwCL) are also displayed in Figure 6 and Figure 7, where TEZ/IVA treatment corresponds to a 0-mg dose of VX-445.

Figure 5: VX-445 Dose-response Simulations for $ppFEV_1$



IVA: ivacaftor; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; qd: once daily; TEZ: tezacaftor
Notes: The blue region denotes the 95% CI for the mean response using 1000 simulated studies. The blue line denotes the median of the 1000 simulated mean responses, and the points correspond to specific doses (the blue point is 50 mg VX-445 qd, the green point is 100 mg VX-445 qd, and the red point is 200 mg VX-445 qd). $\Delta ppFEV_1$ presents change from untreated baseline response. $\Delta\Delta ppFEV_1$ presents change from TEZ/IVA baseline response.

Figure 6: VX-445 Dose-response Simulations for SwCl



IVA: ivacaftor; qd: once daily; SwCl: sweat chloride; TEZ: tezacaftor
Notes: The blue region denotes the 95% CI for the mean response using 1000 simulated studies. The blue line denotes the median of the 1000 simulated mean responses, and the points correspond to specific doses (the blue point is 50 mg VX-445 qd, the green point is 100 mg VX-445 qd, and the red point is 200 mg VX-445 qd). ΔSwCl presents change from untreated baseline response. ΔΔSwCl presents change from TEZ/IVA baseline response.

Based on the dose-response curves, the Applicant considered there is no indication that a higher VX-445 dose than 200 mg would lead to a markedly increased PD response.

Overall, the results of study 001, the dose-response and the exposure-response analyses show that the triple VX-445/TEZ/IVA combination therapy caused a larger absolute increase in ΔppFEV1 and a larger absolute decrease in SwCl than placebo in F/MF and TEZ/IVA in F/F CF patients.

2.5.2. Main studies

Two main studies have been presented in this application as follows:

Study VX17-445-102: A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445 Combination Therapy in Subjects with Cystic Fibrosis Who Are Heterozygous for the *F508del* Mutation and a Minimal Function Mutation (F/MF).

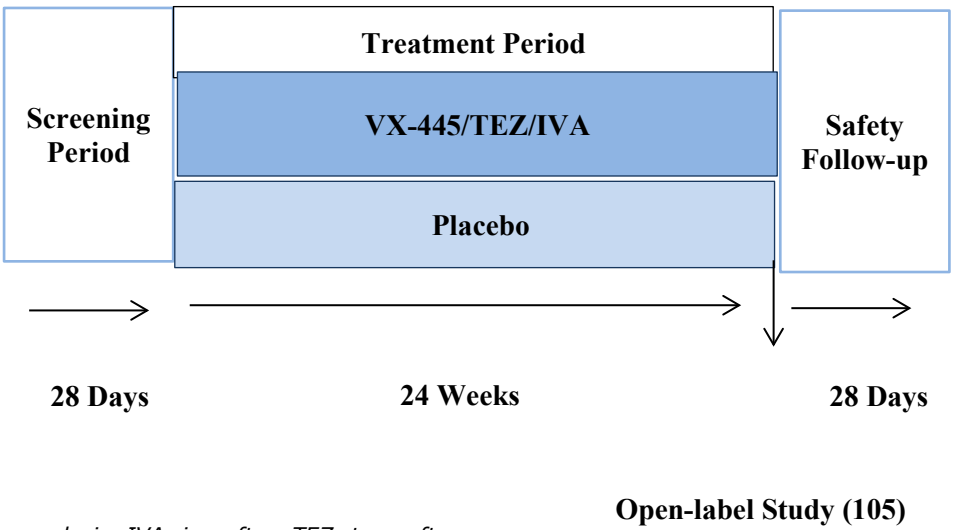
Study VX17-445-103: A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445 Combination Therapy in Subjects with Cystic Fibrosis Who Are Homozygous for the *F508del* Mutation (F/F).

Methods

Study VX17-445-102

Subjects with F/MF genotypes were randomized (1:1) to either VX-445/TEZ/IVA or placebo (Figure 7).

Figure 7:**Schematic of Study Design for Study 102**



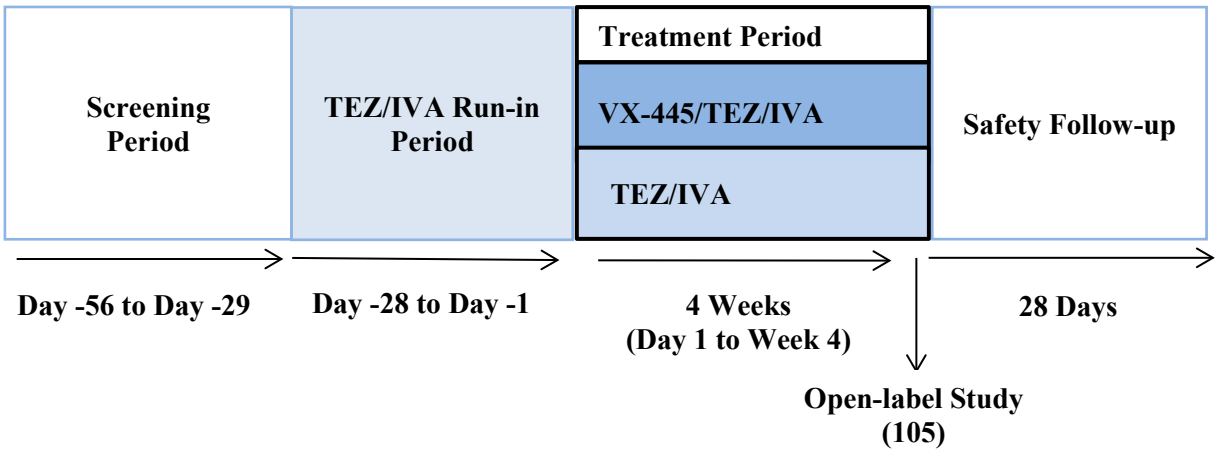
IA: interim analysis; IVA: ivacaftor; TEZ: tezacaftor

For the open label study, an IA was planned after at least 140 subjects completed the Week 4 Visit and at least 100 subjects completed the Week 12 Visit.

Study VX17-445-103

After a 4-week TEZ/IVA Run-in Period to establish an on-treatment (TEZ/IVA) baseline for comparison with the Treatment Period, subjects with the F/F genotype were randomized (1:1) to either VX-445/TEZ/IVA or TEZ/IVA (Figure 8). Randomization was stratified by $ppFEV_1$ determined during the TEZ/IVA Run-in Period (<70 versus ≥70) and by age (<18 versus ≥18 years of age) at screening.

Figure 8: Schematic of Study Design for Study 103



Study Participants

The key inclusion criteria were in both studies, aged 12 years and older, FEV1 value ⩾40% and ⩽90% of predicted mean for age, sex, and height, a confirmed diagnosis of CF by the investigator and stable CF disease as judged by the investigator.

Study 102 included patients heterozygous for *F508del* and an MF mutation (F/MF). The eligible MF mutations were pre-specified. Previous clinical studies of TEZ/IVA and LUM/IVA in F/MF patients have failed to demonstrate efficacy.

MF mutations on that list were determined by the applicant to qualify as an MF mutation if meeting one of the following 2 criteria:

(1) biological plausibility of no translated protein (genetic sequence predicts the complete absence of CFTR protein), ***or***

(2) in vitro testing that supports lack of responsiveness to TEZ, IVA, or TEZ/IVA, ***and*** *evidence of clinical severity on a population basis (as reported in large patient registries).*

Inclusion of MF Mutations Based on In Vitro Testing
Mutations that were considered to be MF mutations based on in vitro testing met the following criteria in in vitro experiments:
• baseline chloride transport that was <10% of wildtype CFTR
• an increase in chloride transport of <10% over baseline following the addition of TEZ, IVA, or TEZ/IVA in the assay

These mutations also had evidence of clinical severity on a population basis (per CFTR2 patient registry; accessed on 15 February 2016). Patients with these mutations on one allele and *F508del* on the other allele exhibited evidence of clinical severity as defined as:
• average sweat chloride >86 mmol/L, and
• prevalence of pancreatic insufficiency (PI) >50%
These clinical severity criteria do not apply to the individual subjects to be enrolled in the study but were used to categorize each mutation on a population level.

Eligible MF Mutations
The list below represents acceptable mutations, which are detectable by an FDA-cleared genotyping assay or other method (e.g., sequencing); however, this list may not include every eligible mutation, and investigators should contact the medical monitor regarding other mutations that may also meet study eligibility criteria.

Table 6 List of all eligible MF mutations defined in study 102

CFTR Mutations Eligible for VX17-445-102

MF Mutation Category	Mutation				
Nonsense mutations	Q2X	L218X	Q525X	R792X	E1104X
	S4X	Q220X	G542X	E822X	W1145X
	W19X	Y275X	G550X	W882X	R1158X
	G27X	C276X	Q552X	W846X	R1162X
	Q39X	Q290X	R553X	Y849X	S1196X
	W57X	G330X	E585X	R851X	W1204X
	E60X	W401X	G673X	Q890X	L1254X
	R75X	Q414X	Q685X	S912X	S1255X
	L88X	S434X	R709X	Y913X	W1282X
	E92X	S466X	K710X	Q1042X	Q1313X
	Q98X	S489X	Q715X	W1089X	Q1330X
	Y122X	Q493X	L732X	Y1092X	E1371X
	E193X	W496X	R764X	W1098X	Q1382X
	W216X	C524X	R785X	R1102X	Q1411X
Canonical splice mutations	185+1G→T	711+5G→A	1717-8G→A	2622+1G→A	3121-1G→A
	296+1G→A	712-1G→T	1717-1G→A	2790-1G→C	3500-2A→G
	296+1G→T	1248+1G→A	1811+1G→C	3040G→C (G970R)	3600+2insT
	405+1G→A	1249-1G→A	1811+1.6kbA→G		3850-1G→A
	405+3A→C	1341+1G→A	1811+1643G→T	3120G→A	4005+1G→A
	406-1G→A	1525-2A→G	1812-1G→A	3120+1G→A	4374+1G→T
	621+1G→T	1525-1G→A	1898+1G→A	3121-2A→G	
	711+1G→T		1898+1G→C		
Small (≤3 nucleotide) insertion/deletion (ins/del) frameshift mutations	182delT	1078delT	1677delTA	2711delT	3737delA
	306insA	1119delA	1782delA	2732insA	3791delC
	306delTAGA	1138insG	1824delA	2869insG	3821delT
	365-366insT	1154insTC	1833delT	2896insAG	3876delA
	394delTT	1161delC	2043delG	2942insT	3878delG
	442delA	1213delT	2143delT	2957delT	3905insT
	444delA	1259insA	2183AA→G[a]	3007delG	4016insT
	457TAT→G	1288insTA	2184delA	3028delA	4021dupT
	541delC	1343delG	2184insA	3171delC	4022insT
	574delA	1471delA	2307insA	3171insC	4040delA
	663delT	1497delGG	2347delG	3271delGG	4279insA
	849delG	1548delG	2585delT	3349insT	4326delTC
	935delA	1609del CA	2594delGT	3659delC	
Non-small (>3 nucleotide) insertion/deletion (ins/del) frameshift mutations	CFTRdele1	CFTRdele16-17b		1461ins4	
	CFTRdele2	CFTRdele17a,17b		1924del7	
	CFTRdele2,3	CFTRdele17a-18		2055del9→A	
	CFTRdele2-4	CFTRdele19		2105-2117del13insAGAAA	
	CFTRdele3-10,14b-16	CFTRdele19-21		2372del8	
	CFTRdele4-7	CFTRdele21		2721del11	
	CFTRdele4-11	CFTRdele22-24		2991del32	
	CFTR50kbdel	CFTRdele22,23		3121-977_3499+248del2515	
	CFTRdup6b-10	124del23bp		3667ins4	
	CFTRdele11	602del14		4010del4	
	CFTRdele13,14a	852del22		4209TGTT→AA	
	CFTRdele14b-17b	991del5			

CFTR Mutations Eligible for VX17-445-102

MF Mutation Category	Mutation			
Missense mutations that • Are not responsive in vitro to TEZ, IVA, or TEZ/IVA **and** • %PI >50% and SwCl⁻ >86 mmol/L	A46D[b]	V520F	Y569D[b]	N1303K
	G85E	A559T[b]	L1065P	
	R347P	R560T	R1066C	
	L467P[b]	R560S	L1077P[b]	
	I507del	A561E	M1101K	

CFTR: cystic fibrosis transmembrane conductance regulator; IVA: ivacaftor; SwCl: sweat chloride; TEZ: tezacaftor

Source: CFTR2.org [Internet]. Baltimore (MD): Clinical and functional translation of CFTR. The Clinical and Functional Translation of CFTR (CFTR2), US Cystic Fibrosis Foundation, Johns Hopkins University, the Hospital for Sick Children. Available at: http://www.cftr2.org/. Accessed 15 February 2016.

Notes: %PI: percentage of *F508del-CFTR* heterozygous patients in the CFTR2 patient registry who are pancreatic insufficient; SwCl: mean sweat chloride of *F508del-CFTR* heterozygous patients in the CFTR2 patient registry.

[a] Also known as 2183delAA→G.

[b] Unpublished data.

Study 103 included patients homozygous for *F508del* (F/F). Although currently approved *CFTR* modulator therapies are available for F/F patients, these patients continue to have progressive lung disease.

The main *exclusion criteria* were similar in both trials, being:

1. Any of the following abnormal laboratory values at screening:
    a. Hemoglobin <10 g/dL
    b. Total bilirubin ≥2 × upper limit of normal (ULN)
    c. Aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), or alkaline phosphatase (ALP) ≥3 × ULN
    d. 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 of age and ≤45 mL/min/1.73 m2 (calculated by the Counahan-Barratt equation) for subjects aged 12 to 17 years (inclusive)
2. An acute upper or lower respiratory infection, pulmonary exacerbation (PEx), or changes in therapy (including antibiotics) for sinopulmonary disease within 28 days before the first dose of study drug (Day 1, study 102) or before the first dose of TEZ/IVA in the Run-in Period (Day -28, Study 103)
3. Lung infection with organisms associated with a more rapid decline in pulmonary status (including, but not limited to, Burkholderia cenocepacia, Burkholderia dolosa, and Mycobacterium abscessus). For subjects who had a history of a positive culture, the investigator applied the following criteria to establish whether the subject was free of infection with such organisms:
    a. The subject did not have a respiratory tract culture positive for these organisms within the 12 months before the date of informed consent.
    b. The subject had at least 2 respiratory tract cultures negative for such organisms within the 12 months before the date of informed consent, with the first and last of these separated by at least 3 months, and the most recent one within the 6 months before the date of informed consent.

Treatments

The treatment regimens used in the Phase 3 studies are summarized in Table 7.

Table 7 Summary of Treatment Regimens in VX-445 Phase 3 Studies

	VX-445/TEZ/IVA Arm			
Study Identifier	**VX-445 Dose**	**TEZ Dose**	**IVA Dose**	**Control**
Study 102	200 mg qd	100 mg qd	150 mg q12h	Placebo
Study 103	200 mg qd	100 mg qd	150 mg q12h	TEZ/IVA[a]

IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TC: triple combination; TEZ: tezacaftor

[a]The TEZ/IVA dosages for the control group were the same as those used in the TC regimen (the commercial doses of TEZ and IVA).

Study drug was taken within 30 minutes of the start of a fat-containing meal or snack, such as a standard "CF" meal or snack or a standard meal.

For both studies use of any other *CFTR* modulator therapy for the study duration was not permitted. For **Study 102** use of *CFTR* modulators needed to be stopped at least 28 days before the first dose of study drug on Day 1.

For **Study 103** patients taking Vertex *CFTR* modulators right up to the time of screening could be recruited, and they only needed to stop these modulators at the start of the TEZ/IVA run-in period. The patients on non-Vertex *CFTR* modulators had to have a wash out period pre-screening.

Outcomes/endpoints

The primary and secondary efficacy and pharmacodynamic (PD) endpoints evaluated in Studies 102 and 103 are provided in Table 8.

In **Study 102**, the primary endpoint in the global protocol was absolute change from baseline in $ppFEV_1$ at Week 4. Subsequently, the CHMP requested a primary endpoint of absolute change from baseline in $ppFEV_1$ through Week 24, thus a Europe-specific protocol amendment was made to accommodate the request.

Table 8 Studies 102 and 103: Primary and Secondary Efficacy and PD Endpoints

	Study 102 (F/MF)	**Study 103 (F/F)**
Primary endpoint	Global protocol: Absolute change from baseline in $ppFEV_1$ at Week 4 European protocol: Absolute change from baseline in $ppFEV_1$ through Week 24	Absolute change from baseline in $ppFEV_1$ at Week 4
Key secondary endpoints	Global protocol: Absolute change from baseline in $ppFEV_1$ through Week 24 European protocol: Absolute change from baseline in $ppFEV_1$ at Week 4 Global and European Protocols Number of PEx through Week 24	Absolute change from baseline in SwCl at Week 4 Absolute change from baseline in CFQ-R RD score at Week 4

	Study 102 (F/MF)	Study 103 (F/F)
	Absolute change from baseline in SwCl through Week 24	
	Absolute change from baseline in CFQ-R RD score through Week 24	
	Absolute change from baseline in BMI at Week 24	
	Absolute change from baseline in SwCl at Week 4	
	Absolute change from baseline in CFQ-R RD score at Week 4	
Other secondary endpoints	Time-to-first PEx through Week 24	
	Absolute change from baseline in BMI z-score at Week 24	
	Absolute change from baseline in body weight at Week 24	

BMI: body mass index; CFQ-R RD: Cystic Fibrosis Questionnaire-Revised Respiratory Domain; PD: pharmacodynamic(s); PEx: pulmonary exacerbation; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride

For the F/F population, endpoints that require a longer follow-up than 4 weeks were assessed in the open-label extension of the study: study 105 (i.e., pulmonary exacerbations [PEx], body mass index [BMI], and weight).

Spirometry was performed according to the internationally recognized American Thoracic Society Guidelines/European Respiratory Society Guidelines.[5]

The Cystic Fibrosis Questionnaire-Revised (CFQ-R) was used to capture and evaluate the impact of VX-445/TEZ/IVA on patient-reported respiratory symptoms and other aspects of health-related quality of life. In children of 12 and 13 years of age (at baseline) the CFQ-R for children was used, and a CFQ-R for Parents/Caregivers version.

PEx was defined as a clinical deterioration in respiratory status necessitating a change in antibiotic therapy (intravenous [IV], inhaled, or oral) for any 4 or more of the following signs or symptoms: change in sputum; new or increased hemoptysis; 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 102 (F/MF)

Power calculations were based on 180 subjects and a 10% dropout rate in each treatment group at the final analysis and 70 subjects and a 5% dropout rate in each group at the IA.

[5] Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-38.

For the primary endpoint of mean absolute change in ppFEV1 from baseline at Week 4, assuming a within group SD of 7 percentage points, the study was estimated to have approximately 98% power at the IA and approximately 99% power at the final analysis to detect a treatment difference of 5.0 percentage points, with a 2 sided alpha of 0.044 and 0.01, respectively, at the IA and final analysis.

For the key secondary endpoint of number of PEx through Week 24, the sample size of 180 subjects per group was estimated to have approximately 80% power to detect a 40% reduction in PEx rate for the VX-445/TEZ/IVA group compared to the placebo group, assuming a PEx rate for the placebo group of 0.6 over 24 weeks.

Study 103 (F/F)

Power calculations were based on 100 subjects and a 5% dropout rate at Week 4.

For the primary endpoint of absolute change in ppFEV1 from baseline at Week 4, assuming a within-group SD of 7 percentage points, this study with 100 subjects was estimated to have approximately 93% power to detect a difference of 5.0 percentage points for the primary endpoint, with a 2-sided alpha of 0.05.

Randomisation

For **Study 102** (F/MF), subjects with F/MF genotypes were randomized (1:1) to either VX 445/TEZ/IVA or placebo. Randomization was stratified by percent predicted forced expiratory volume in 1 second (ppFEV1) determined during the Screening Period (<70 versus ≥70), age at the Screening Visit (<18 versus ≥18 years of age), and sex (male versus female).

For **Study 103** (F/F), subjects with the F/F genotype were randomized (1:1) to either VX 445/TEZ/IVA or TEZ/IVA. Randomization was stratified by ppFEV1 determined during the TEZ/IVA Run-in Period (<70 versus ≥70) and by age (<18 versus ≥18 years of age) at screening.

Blinding (masking)

For study 102 (F/MF) and study 103 (F/F), all subjects (and their parents/caregivers/companions), site personnel (including the investigator, the site monitor, and the study team), and members of the Vertex study team were blinded to the treatment codes until the final database lock, with the following main exceptions:

• Any site personnel for whom this information is important to ensure the safety of the subject in the event of a life-threatening medical emergency or to ensure the safety of the subject and her foetus in the event of a pregnancy.

• For SAE processing and reporting regulations, for preparing the final (production) randomization list and for preparing the unblinded analysis for the IDMC.

• Bioanalytical contract research organization (CRO) analysing PK samples and the Vertex Bioanalytical personnel who is not a member of the study team but reviews raw data from the Bioanalytical CRO.

For study 102 only:

• Vendor for modelling and simulations performing population PK modelling in preparation for regulatory submission(s). For the purpose of regulatory submissions in certain regions, a limited Vertex team may be unblinded to the IA results. The IA was performed by an external independent biostatistician who was not involved in and did not influence study conduct. The analyses generated by the external independent biostatistician were reviewed by the IDMC. Only after the IDMC declared that the study had crossed the prespecified efficacy boundary was the study unblinded by a limited Vertex

team to prepare a regulatory submission. Members of the limited Vertex unblinded team will not be involved in or influence the conduct of the remaining part of the study to protect the integrity of the study.

Statistical methods

For study 102, the Applicant describes two protocols: The Global protocol and the European protocol. The difference between these two protocols is that the primary efficacy endpoint for the global protocol was evaluated at 4 weeks, while for the European protocol, relevant to the current assessment, the primary endpoint was evaluated at 24 weeks. For the description of the statistical methods, the information from the global protocol will be used with any differences relevant to European assessment identified. In both studies (102 and 103), analysis of the primary efficacy endpoint of absolute change from baseline in ppFEV1 was performed using a mixed-effects model for repeated measures (MMRM). A similar MMRM was used for all key secondary endpoints with the exception of the number of PEx (in Study 102) which used a negative binomial regression model.

An underlying assumption of the MMRM method is that data are missing at random. To minimize the amount of missing data, subjects who prematurely discontinued study drug treatment were continued to be followed up for all scheduled study visits for spirometry and other efficacy assessments. To assess the impact of missing data and the assumption that data are missing at random, a multiple imputation algorithm was planned to be used if ≥10% of the subjects had missing change in ppFEV1 at Week 24 in any treatment group. In this case, missing absolute change from baseline in ppFEV1 assessments will be imputed starting from the first visit with missing values, for which all subsequent visits through Week 24 are also missing. For intermediate missing data, i.e., missing values that fall between two non-missing ones, it is reasonable to assume that they are missing at random and therefore will not be imputed. An MMRM analogous to that for the primary analysis of the primary endpoint will be applied to imputed datasets and the relevant MI estimators will be reported.

Multiple Imputation will be dependent on classification of randomized subjects into one of three categories based on the following rules:

- Non-missing category: Subjects who have a percent predicted FEV1 assessment at Week 24 (i.e., subjects who have a non-missing absolute change from baseline in percent predicted FEV1 at Week 24).
- Missing category 1: Subjects with missing absolute change from baseline in percent predicted FEV1 at Week 24, who discontinued treatment because of adverse events, non-compliance with study drug, death, or physician decision, or because the subject refused further dosing or required prohibited medication.
- Missing category 2: Subjects who discontinued treatment for any reason not listed in Category 1 and have missing absolute change from baseline in ppFEV1 at Week 24, or subjects who have completed 24 weeks treatment duration but are missing the absolute change from baseline in ppFEV1 at visit Week 24.

Control of Overall Type I Error and Testing Hierarchy

Studies 102 and 103 each included a hierarchical testing procedure to control the type I error rate for the multiple key secondary endpoints which were tested at an alpha of 0.05. For a test at any step to be considered statistically significant within the testing hierarchy, it must have been statistically significant, and all previous tests (if any) within the hierarchy must have been statistically significant at the 0.05 level.

In the global protocol of Study 102, an interim analysis (IA) was planned for the testing of absolute change from baseline in $ppFEV_1$ at Week 4. For this, a Lan and DeMets alpha spending function was applied such that an alpha of 0.01 was preserved for the final analysis. Because all subjects were included in the IA, the information fraction was 100% and thus, the primary endpoint was tested at an alpha of 0.05 during the IA. This IA was not relevant to the European protocol because the primary endpoint for the European protocol regarded change through week 24.

Results

Participant flow

In study 102 (F/MF), of the 403 subjects who received at least 1 dose of study drug, 3 (0.7%) subjects (all in the VX-445/TEZ/IVA group) prematurely discontinued treatment (2 due to an AE, 1 due to a pregnancy). A total of 13 (3.2%) had an important protocol deviation (IPD), related to prohibited medication, acute illness, safety assessment and study drug.

The following analysis sets are defined:

All Subjects Set: all subjects who were randomized or received at least 1 dose of study drug;

FAS: all randomized subjects who carry the intended *CFTR* allele mutations and received at least 1 dose of study drug;

iFAS: all subjects in the FAS whose scheduled Week 4 Visit was on or before the IA data cut-off date;

Safety Set: all subjects who received at least 1 dose of study drug

Table 9 Study 102 (F/MF): Subject Disposition

Disposition Reason	Placebo n (%)	VX-445/TEZ/IVA n (%)
All Subjects Set	204	201
iFAS[a]	203	200
FAS[b]	203	200
Safety Set	201	202
Completed treatment	203 (100)	197 (98.5)
Prematurely discontinued treatment	0	3 (1.5)
Reason for discontinuation from treatment		
AE	0	2 (1.0)
Pregnancy (self or partner)	0	1 (0.5)
Completed study	203 (100)	197 (98.5)
Prematurely discontinued study	0	3 (1.5)
Reason for discontinuation from study		
AE	0	1 (0.5)
Withdrawal of consent (not due to AE)	0	1 (0.5)
Death	0	0
Other	0	1 (0.5)

Source: Study 102 CSR/Table 10-1
AE: adverse event; FAS: Full Analysis Set; IA: interim analysis; iFAS: interim Full Analysis Set; IVA: ivacaftor; n: size of subsample; TEZ: tezacaftor

[a] The iFAS was defined as all subjects in the FAS who completed the Week 4 Visit or were randomized at least 28 days before the IA data cutoff date.

[b] The FAS was defined as all randomized subjects who carry the intended *CFTR* allele mutation and received at least 1 dose of study drug. Treatment assignment was based on the randomized treatment.

Protocol deviations

Table 10: Summary of Important Protocol Deviations

	Placebo N = 203 n (%)	VX-445/TEZ/IVA N = 200 n (%)	Total N = 403 n (%)
Subjects With any Important Protocol Deviations	10 (4.9)	3 (1.5)	13 (3.2)
– Subject took prohibited medication[a]	2 (1.0)	2 (1.0)	4 (1.0)
– Subject with acute illness[b]	1 (0.5)	0 (0)	1 (0.2)
– Safety assessment[c]	5 (2.5)	1 (0.5)	6 (1.5)
– Study drug[d]	2 (1.0)	0 (0)	2 (0.5)

[a] Subjects took itraconazole, rifampicin or clarithromycin when they were enrolled.

[b] PEx from 21 September 2018 through 05 October 2018, first dose on 30 October 2018.

[c] subjects <14 years of age who had 1 or more pregnancy tests (screening, Day 1, and/or Day 15) that were not performed, at subsequent visits test were negative.

[d] 2 subjects in placebo group received active drug. These subjects were assigned to the placebo group in the FAS (based on randomization) and assigned to VX-445/TEZ/IVA group in the Safety Set (received at least 1 dose of active study drug).

In study 103 (F/F), a total of 113 CF subjects were enrolled, of which 108 were randomized and 107 received at least 1 dose of study drug in the treatment period. No subjects discontinued study drug treatment during the Treatment Period. A total of 2 (1.9%) had an important protocol deviation (IPD) related to prohibited medication and safety assessment

All Subjects Set: all subjects who were randomized or received at least 1 dose of study drug;

FAS: all randomized subjects who carry the intended *CFTR* allele mutations and received at least 1 dose of study drug;

Safety Set for the Run-in Period: all subjects who received at least 1 dose of TEZ/IVA in the Run-in Period

Safety Set for the Treatment Period: all subjects who received at least 1 dose of study drug in the Treatment Period.

Table 11 Study 103 (F/F Subjects): Subject Disposition

Disposition Reason	TEZ/IVA n (%)	VX-445/TEZ/IVA n (%)
FAS	52	55
Completed treatment	52 (100.0)	55 (100.0)
Prematurely discontinued treatment	0	0
Completed study	52 (100.0)	55 (100.0)
Prematurely discontinued study	0	0

FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; TEZ: tezacaftor
Notes: Percentages are based on the FAS, which was defined as all randomized subjects who carry the intended *CFTR* allele mutation and received at least 1 dose of study drug in the Treatment Period. Treatment assignment was based on the randomized treatment.

Protocol deviations

Table 12 Summary of Important Protocol Deviations

	TEZ/IVA N = 52 n (%)	VX-445/TEZ/IVA N = 55 n (%)	Total N = 107 n (%)
Subjects With any Important Protocol Deviations	1 (1.9)	1 (1.8)	2 (1.9)
– Subject took prohibited medication[a]	0	1 (1.8)	1 (0.9)
– Safety assessment[b]	1 (1.9)	0	1(0.9)

[a] subject was prescrived amoxicillin during the Run-in Period. prescription was given as a prophylaxis due to close contact with a family member who was ill and was not attributed to sinopulmonary signs and symptoms, there was no safety risk associated.

[b] subject was incorrectly considered by the site to be of nonchildbearing potential; thus, the Day -28 urine pregnancy test was not performed. The pregnancy test was subsequently completed on Week 4 and was negative.

Recruitment

Study 102 (F/MF) was conducted at 110 sites in US, Canada, Europe, and Australia.

The study period was from 15 June 2018 (date first eligible subject signed the informed consent/assent form) up to 24 April 2019 (date last subject completed the last visit).

Study 103 was conducted at 44 sites in US and Europe.

Conduct of the study

Study 102 was amended 2 times. Table 13 lists the global protocol versions and global amendment dates and summarizes the major changes in study conduct specified in each protocol amendment.

Table 13 Summary of Study 102 protocol amendments

Protocol Version	Date	Key changes
1.0	01 February 2018	Original version (no subjects enrolled under v1.0)
2.0	13 April 2018	• Updated the study drug regimen to include IVA in place of VX-561 (deuterated IVA), added the dose of study drug and tablet strength, and updated guidance on missed doses to account for q12h dosing of IVA. • Added a PK assessment 2 hours after the clinic dose. • Added specific guidance for study drug interruption for rash and clarified that that no dose modifications for toxicity were allowed. • Added vendor for modelling and simulations to the list of personnel who could be unblinded. • Updated statistical analysis plan section for clarity. • Edited categories of eligible mutations to better reflect the definition provided in the appendix
3.0	19 July 2018	• Removed G6PD deficiency and history of haemolysis as exclusion criteria; updated associated study drug interruption rules. • Updated text to reflect the current regulatory status of Symdeko/Symkevi.

CFQ-R RD: Cystic Fibrosis Questionnaire – Revised respiratory domain; IVA: ivacaftor; MMRM: mixed-effects model for repeated measures; PK: pharmacokinetic; ppFEV1: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor

For both studies overall compliance was high. In Study 102, 98% of the treatment group, and 99.5% of the placebo group had a compliance rate of over 80%. In Study 103 all patients in both groups had a compliance rate of 80% or more.

Baseline data

Demographic and baseline characteristics

For study 102 and 103, the demographic and baseline characteristics are provided in Table 14 and Table 15, respectively. In general, the demographic and baseline characteristics are balanced between the two treatment groups.

Concomitant medications

The most common concomitant medications (continued and newly received) were medications typically used for management of CF.

For study 102, three antibiotic treatments were used more often in the placebo group. Tobramycin was used in 55.7% in the Placebo group and 39% in the active group. Ciprofloxacin was used in 35% in the placebo group and 16% of the active group. Sulfamethoxazole and trimethoprim were used in 26.1% of the placebo group and 17.0% of the active group.

For study 103, omeprazole seems to be used slightly more often in the TEZ/IVA group (28.8%) compared to the active treatment group (18.2%).

Table 14 Studies 102 and 103: Subject Demographics, FAS

Characteristic	Study 102 (F/MF)		Study 103 (F/F)	
	Placebo N = 203	VX-445/TEZ/IVA N = 200	TEZ/IVA N = 52	VX-445/TEZ/IVA N = 55
Age at baseline (years)				
Mean (SD)	26.8 (11.3)	25.6 (9.7)	27.9 (10.8)	28.8 (11.5)
Age groups at screening, n (%)				
≥12 to <18	60 (29.6)	56 (28.0)	14 (26.9)	16 (29.1)
≥18	143 (70.4)	144 (72.0)	38 (73.1)	39 (70.9)
Sex, n (%)				
Male	105 (51.7)	104 (52.0)	24 (46.2)	24 (43.6)
Female	98 (48.3)	96 (48.0)	28 (53.8)	31 (56.4)
Ethnicity, n (%)				
Hispanic or Latino	12 (5.9)	4 (2.0)	3 (5.8)	2 (3.6)
Not Hispanic or Latino	175 (86.2)	187 (93.5)	49 (94.2)	52 (94.5)
Not collected per local regulations	16 (7.9)	9 (4.5)	0	1 (1.8)
Race, n (%)				
White	184 (90.6)	186 (93.0)	52 (100.0)	54 (98.2)
Black or African American	2 (1.0)	4 (2.0)	0	0
Asian	1 (0.5)	0	0	0
American Indian or Alaska Native	1 (0.5)	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
Not collected per local regulations	16 (7.9)	9 (4.5)	0	1 (1.8)
Other	1 (0.5)	2 (1.0)	0	0
Geographic Region, n (%)				
North America	120 (59.1)	118 (59.0)	33 (63.5)	34 (61.8)
Europe[a]	83 (40.9)	82 (41.0)	19 (36.5)	21 (38.2)

Sources: Study 102 CSR/Table 10-2 and Table 10-3; Study 103 CSR/Table 10-3 and Table 10-4
FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; TEZ: tezacaftor
[a] In Study 102, the subgroup for Europe included subjects who were enrolled from Australia.

Table 15 Studies 102 and 103: Baseline Characteristics, FAS

Characteristic	Study 102 (F/MF)		Study 103 (F/F)	
	Placebo N = 203	VX-445/TEZ/IVA N = 200	TEZ/IVA N = 52	VX-445/TEZ/IVA N = 55
Weight (kg)				
Mean (SD)	58.3 (12.7)	59.8 (12.9)	59.8 (14.8)	59.9 (12.7)
BMI (kg/m^2)				
Mean (SD)	21.31 (3.14)	21.49 (3.07)	21.88 (4.12)	21.75 (3.19)
ppFEV$_1$ (percentage points) at baseline				
Mean (SD)	61.3 (15.5)	61.6 (15.0)	60.2 (14.4)	61.6 (15.4)
ppFEV$_1$ category at baseline, n (%)				
<40	16 (7.9)	18 (9.0)	4 (7.7)	6 (10.9)
≥40 to <70	120 (59.1)	114 (57.0)	34 (65.4)	31 (56.4)
≥70 to ≤90	62 (30.5)	66 (33.0)	14 (26.9)	18 (32.7)
>90	5 (2.5)	2 (1.0)	0	0
SwCl (mmol/L) at baseline				
Mean (SD)	102.9 (9.8)[a]	102.3 (11.9)[a]	90.0 (12.3)[b]	91.4 (11.0)[b]
CFQ-R RD (points) at baseline				
Mean (SD)	70.0 (17.8)	68.3 (16.9)	72.6 (17.9)	70.6 (16.2)

Sources: Study 102 CSR/Table 10-3; Study 103 CSR/Table 10-4

BMI: body mass index; CFQ-R: Cystic Fibrosis Questionnaire-Revised; FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; RD: respiratory domain; SwCl: sweat chloride; TEZ: tezacaftor

[a] In Study 102, 201 subjects in the placebo group and 199 subjects in the VX-445/TEZ/IVA group had SwCl measurements at baseline.

[b] In Study 103, 52 subjects in the TEZ/IVA group and 54 subjects in the VX-445/TEZ/IVA group had SwCl measurements at baseline.

In terms of the F/MF genotypes represented in Study 102, the breakdown is provided in Table 16.

Table 16: MF mutations (FAS) by treatment group (study 102)

MF Mutation Subgroup	MF Mutation Category	MF Mutation	Placebo N = 203 n (%)	VX-445/TEZ/IVA N = 200 n (%)
Class I	Nonsense Mutations	G542X	40 (19.7)	25 (12.5)
		W1282X	9 (4.4)	9 (4.5)
		R553X	11 (5.4)	8 (4.0)
		R1162X	7 (3.4)	7 (3.5)
		R1158X	0	3 (1.5)
		S489X	1 (0.5)	3 (1.5)
		Y1092X	3 (1.5)	3 (1.5)
		Q39X	0	2 (1.0)
		Q493X	3 (1.5)	2 (1.0)
		R709X	0	2 (1.0)
		W846X	1 (0.5)	2 (1.0)
		E585X	0	1 (0.5)
		E60X	5 (2.5)	1 (0.5)
		E92X	0	1 (0.5)
		G330X	0	1 (0.5)
		R851X	0	1 (0.5)
		W1204X	0	1 (0.5)
		W401X	0	1 (0.5)
		W496X	0	1 (0.5)
		E1371X	1 (0.5)	0
		K710X	2 (1.0)	0
		L88X	1 (0.5)	0
		Q1313X	1 (0.5)	0
		Q220X	1 (0.5)	0
		R1102X	1 (0.5)	0
		S466X	1 (0.5)	0
		W1089X	1 (0.5)	0
Class I	Splice Mutations	621+1G>T	13 (6.4)	14 (7.0)
		1717-1G>A	12 (5.9)	12 (6.0)
		1898+1G>A	4 (2.0)	4 (2.0)
		3120+1G>A	0	2 (1.0)
		1249-1G>A	0	1 (0.5)
		2622+1G>A	3 (1.5)	1 (0.5)
		406-1G>A	0	1 (0.5)
		406-2A>G	0	1 (0.5)
		3040G>C (G970R)	0	1 (0.5)
		1248+1G>A	1 (0.5)	0
		1525-2A>G	1 (0.5)	0
		1717-8G>A	1 (0.5)	0
		1812-1G>A	1 (0.5)	0

MF Mutation Subgroup	MF Mutation Category	MF Mutation	Placebo N = 203 n (%)	VX-445/TEZ/IVA N = 200 n (%)
		296+1G>A	1 (0.5)	0
		3121-1G>A	1 (0.5)	0
		711+1G>T	1 (0.5)	0
		712-1G>T	1 (0.5)	0
Class I	Small (≤3 nucleotide) insertion/deletion (ins/del) frameshift mutations	3659delC	3 (1.5)	7 (3.5)
		2183AA>G	0	5 (2.5)
		1154insTC	3 (1.5)	4 (2.0)
		3905insT	1 (0.5)	4 (2.0)
		394delTT	1 (0.5)	3 (1.5)
		2143delT	0	2 (1.0)
		1548delG	0	1 (0.5)
		2184delA	0	1 (0.5)
		2184insA	7 (3.4)	1 (0.5)
		3007delG	1 (0.5)	1 (0.5)
		3878delG	0	1 (0.5)
		4016insT	1 (0.5)	1 (0.5)
		908delT	0	1 (0.5)
		1078delT	4 (2.0)	0
		182delT	1 (0.5)	0
		3876delA	2 (1.0)	0
		457TAT>G	1 (0.5)	0
		663delT	1 (0.5)	0
Class I	Non-small (>3 nucleotide) ins/del frameshift mutations	CFTR dele2, 3	4 (2.0)	7 (3.5)
		4209TGTT>AA	0	1 (0.5)
		CFTRdele17a,17b	0	1 (0.5)
		CFTRdele22-24	1 (0.5)	1 (0.5)
		852del22	1 (0.5)	0
Non-Class I	Missense or in-frame deletions	N1303K	21 (10.3)	19 (9.5)
		R347P	3 (1.5)	7 (3.5)
		G85E	3 (1.5)	5 (2.5)
		I507del	5 (2.5)	4 (2.0)
		R1066C	2 (1.0)	3 (1.5)
		R560T	3 (1.5)	3 (1.5)
		V520F	1 (0.5)	2 (1.0)
		A559T	1 (0.5)	1 (0.5)
		L1077P	0	1 (0.5)
		L467P	2 (1.0)	1 (0.5)
		M1101K	0	1 (0.5)
		3199del6	1 (0.5)	0

Source: Study 102 Ad hoc Table 14.1.10

IVA: ivacaftor; TEZ: tezacaftor

Note: Only the MF allele is shown; all subjects were heterozygous for *F508del* and the listed MF mutation. Table is sorted in descending order of frequency of the VX-445/TEZ/IVA column by MF mutation for each MF mutation category.

Numbers analysed

The efficacy analyses of study 102 (n=403) and 103 (n=107) were performed on the Full Analysis Set (FAS): all randomized subjects who carry the intended *CFTR* allele mutations and have received at least 1 dose of study drug.

The modified FAS (m-FAS) excluded patients that did not meet the eligibility criteria or with significant deviations of study drug administration. In study 102, 2 patients were excluded (from placebo arm only) for the m-FAS and 8 patients (5 placebos, 3 active arm) were excluded from the mFAS analysis of SwCl (pre-dose SwCl value <60.0 mmol/L). In 103, no m-FAS analysis was performed, as all patients met the criteria.

From study 102, all 400 patients that complete dosing rolled over to the open-label study (Study 105).

From study 103, all 107 patients rolled over to the open-label study (Study 105).

Outcomes and estimation

- *Primary endpoint – Absolute change in ppFEV1*

In Study 102, treatment with VX-445/TEZ/IVA resulted in a statistically significant improvement in absolute change in ppFEV1 through Week 24 compared to placebo, with a treatment difference of 14.3 percentage points (P<0.0001). Improvements in ppFEV1 were already seen at week 4 (secondary endpoints), with a statistically significant treatment difference of 13.7 percentage points (p<0.0001) (Table 17 and Figure 9).

In Study 103, following a 4-week TEZ/IVA run-in, treatment with VX-445/TEZ/IVA resulted in a statistically significant and clinically meaningful improvement in absolute change in ppFEV1 at Week 4 compared to TEZ/IVA, with a treatment difference of 10.0 percentage points (p<0.0001) (Table 18 and Figure 10).

Table 17 Study 102 (F/MF): Absolute change from baseline in ppFEV1 through week 24

Analysis	Statistic	Placebo N = 203	VX-445/TEZ/IVA N = 200
Primary Endpoint			
European Protocol: Absolute change from baseline in ppFEV1 through Week 24 (percentage points)	n	203	196
	LS mean (SE)	-0.4 (0.5)	13.9 (0.6)
	95% CI of LS mean	(-1.5, 0.7)	(12.8, 15.0)
	LS mean difference, 95% CI	--	**14.3 (12.7, 15.8)**
	P value versus placebo	--	<0.0001

Source: Module 2.7.3/Table 9
FAS: Full Analysis Set; iFAS: Interim Full Analysis Set; IVA: ivacaftor; LS: least squares; ppFEV1: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

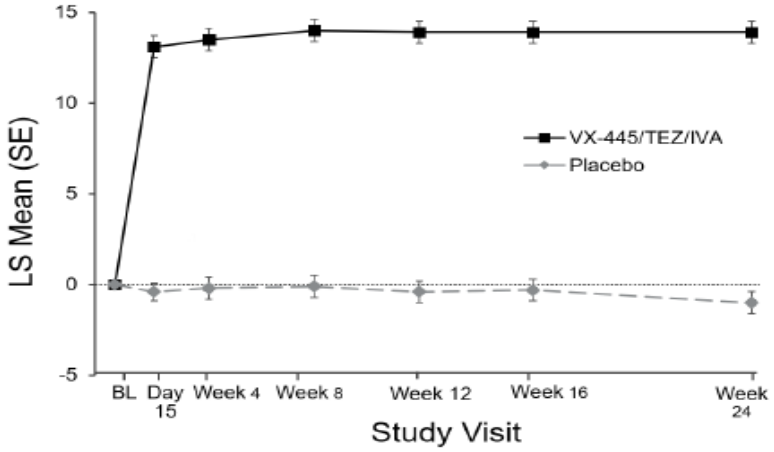
Table 18: Study 103 (F/F): Absolute change from baseline in ppFEV1 (percentage points) at week 4

Endpoint (Analysis Set)	Statistic	TEZ/IVA N = 52	VX-445/TEZ/IVA N = 55
Absolute change from baseline in $ppFEV_1$ at Week 4 (FAS)	n	49	53
	LS mean (SE)	0.4 (0.9)	10.4 (0.9)
	95% CI of LS mean	(-1.4, 2.3)	(8.6, 12.2)
	LS mean diff, 95% CI	--	**10.0 (7.4, 12.6)**
	P value vs. TEZ/IVA	--	<0.0001

Source: Module 2.7.3/Table 12

FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

Figure 9: Study 102 (F/MF): Absolute change from baseline in ppFEV1 (percentage points) by Visit

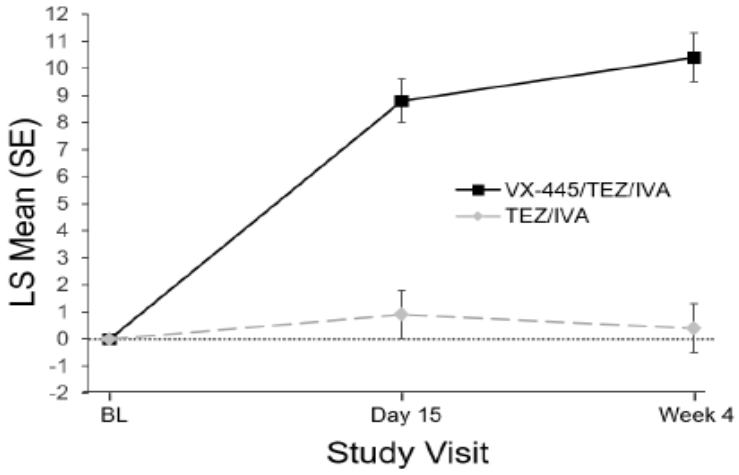


Source: Module 2.7.3/Figure 3

FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

Note: The y-axis corresponds to the LS means from the MMRM models at the final analysis.

Figure 10: Study 103 (F/F): absolute change from baseline in ppFEV1 (percentage points) by Visit



Source: Module 2.7.3/Figure 10
FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor
Note: The y-axis corresponds to the LS means from the MMRM models at the final analysis.

- *Key secondary endpoint – SwCl*

In Study 102, treatment with VX-445/TEZ/IVA resulted in a statistically significant improvement in absolute change in SwCl through Week 24 with a treatment difference of -41.8 mmol/L (p<0.0001) compared to placebo (Table 19 and Figure 11).

In Study 103, following a 4-week TEZ/IVA run-in, statistically, significant improvements were also observed at Week 4 with a treatment difference of -45.1 mmol/L for VX-445/TEZ/IVA compared to TEZ/IVA (p<0.0001) (Table 20 and Figure 12).

Table 19 Study 102 (F/MF): Absolute change from baseline in SwCl (mmol/L) through week 24

Endpoint (Analysis Set)	Statistic	Placebo N = 203	VX-445/TEZ/IVA N = 200
Absolute change from baseline in SwCl through Week 24 (FAS)	n	201	199
	LS mean (SE)	-0.4 (0.9)	-42.2 (0.9)
	95% CI of LS mean	(-2.2, 1.4)	(-44.0, -40.4)
	LS mean diff, 95% CI	--	**-41.8 (-44.4, -39.3)**
	P value vs. placebo	--	<0.0001

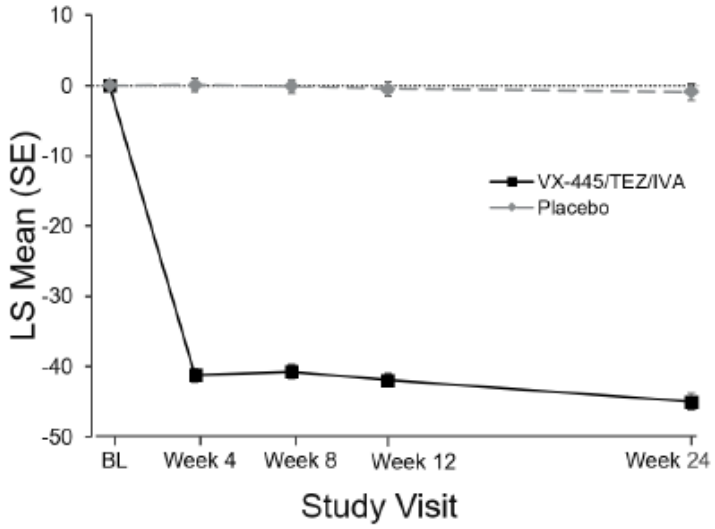
Source: Module 2.7.3/Table 9
FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; SwCl: sweat chloride; TEZ: tezacaftor

Table 20 Study 103 (F/F): Absolute change from baseline in SwCl (mmol/L) at week 4

Endpoint (Analysis Set)	Statistic	TEZ/IVA N = 52	VX-445/TEZ/IVA N = 55
Absolute change from baseline in SwCl at Week 4 (FAS)	n	48	54
	LS Mean (SE)	1.7 (1.8)	-43.4 (1.7)
	95% CI of LS Mean	(-1.9, 5.3)	(-46.9, -40.0)
	LS Mean Diff, 95% CI	--	**-45.1 (-50.1, -40.1)**
	P value vs. TEZ/IVA	--	<0.0001

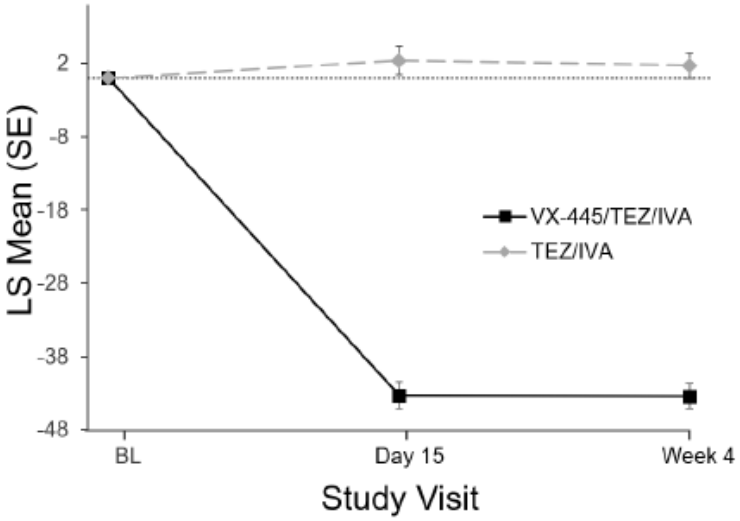
Source: Module 2.7.3/Table 12
FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; SwCl: sweat chloride; TEZ: tezacaftor

Figure 11: Study 102 (F/MF): Absolute change from baseline in SwCl (mmol/L) by Visit



Source: Module 2.7.3/Figure 5
FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; SwCl: sweat chloride; TEZ: tezacaftor
Notes: The y-axis corresponds to the LS means from the models at the final analysis.

Figure 12: Study 103 (F/F): Absolute change from baseline in SwCl (mmol/L) by Visit



Source: Module 2.7.3/Figure 11
FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; SwCl: sweat chloride; TEZ: tezacaftor
Notes: The y-axis corresponds to the LS means from the MMRM models at the final analysis.

- *Key secondary endpoint – Respiratory Symptoms*

In Study 102, treatment with VX-445/TEZ/IVA resulted in a statistically significant improvement in absolute change in CFQ-R RD score through Week 24 with a treatment difference of 20.2 points (p<0.0001) compared to placebo Table 21).

In Study 103, statistically significant improvements were also observed at Week 4 with a treatment difference of 17.4 points for VX-445/TEZ/IVA versus TEZ/IVA (p<0.0001) (Table 22).

Table 21 Study 102 (F/MF): Absolute change from baseline in CFQ-R RD Score (points) through Week 24

Endpoint (Analysis Set)	Statistic	Placebo N = 203	VX-445/TEZ/IVA N = 200
Absolute change from baseline in CFQ-R RD score through Week 24 (FAS)	n	203	200
	LS mean (SE)	-2.7 (1.0)	17.5 (1.0)
	95% CI of LS mean	(-4.6, -0.8)	(15.6, 19.5)
	LS mean diff, 95% CI	--	**20.2 (17.5, 23.0)**
	P value vs. placebo	--	<0.0001

Source: Module 2.7.3/Table 9
CFQ-R: Cystic Fibrosis Questionnaire-Revised; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; RD: respiratory domain; TEZ: tezacaftor

Table 22 Study 103 (F/F): Absolute change from baseline in CFQ-R RD Score (points) at Week 4

Endpoint (Analysis Set)	Statistic	TEZ/IVA N = 52	VX-445/TEZ/IVA N = 55
Absolute change from baseline in CFQ-R RD score at Week 4 (FAS)	n	52	55
	LS mean (SE)	-1.4 (2.0)	16.0 (2.0)
	95% CI of LS mean	(-5.4, 2.6)	(12.1, 19.9)
	LS mean diff, 95% CI	--	**17.4 (11.8, 23.0)**
	P value vs. TEZ/IVA	--	<0.0001

Source: Module 2.7.3/Table 12

CRQ-R: Cystic Fibrosis Questionnaire-Revised; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; RD: respiratory domain; TEZ: tezacaftor

- *Key secondary endpoint – Pulmonary Exacerbations (only study 102)*

In Study 102, VX-445/TEZ/IVA resulted in a statistically significant reduction in PEx through Week 24, with a PEx rate that was 63% lower in the VX-445/TEZ/IVA group than the placebo group (rate ratio = 0.37 [p<0.0001; 95% CI: 0.25, 0.55]). The annual event rate was 0.37 in the VX-445/TEZ/IVA group versus 0.98 in the placebo group.

Analysis of time-to-first PEx through Week 24 showed that a greater proportion of subjects in the VX-445/TEZ/IVA group remained free of PEx than the proportion of subjects in the placebo group. The risk of a PEx is reduced when treated with the triple combination (HR: 0.34; 95% CI 0.22, 0.52; p<0.0001).

Table 23 Negative binomial analysis of the number of pEx during the PEx analysis period (FAS)

	Placebo N = 203	VX-445/TEZ/IVA N = 200
Number of subjects with events, n (%)	76 (37.4)	31 (15.5)
Number of events	113	41
Estimated event rate per year	0.98	0.37
Rate ratio, 95% CI	--	0.37 (0.25, 0.55)
P value versus placebo	--	<0.0001

- *Key secondary endpoint – Nutritional status (only study 102)*

In Study 102, statistically significant improvements were observed for absolute change from baseline in BMI, with a treatment difference of 1.04 kg/m2 (p<0.0001) for VX-445/TEZ/IVA versus placebo at Week 24. Substantial improvements were also observed for absolute change from baseline in BMI z-score and body weight at Week 24, with a treatment difference in BMI z-score of 0.30 (nominal P<0.0001) and a treatment difference in body weight of 2.9 kg (nominal p<0.0001) for VX-445/TEZ/IVA versus placebo (Table 24).

For subject included in study 103, results on nutritional status will be displayed at study 105.

Table 24 Study 102 (F/MF): Absolute change from baseline in BMI (kg/m^2) at week 24

Endpoint (Analysis Set)	Statistic	Placebo N = 203	VX-445/TEZ/IVA N = 200
Absolute change from baseline in BMI at Week 24 (FAS)	n	202	198
	LS mean (SE)	0.09 (0.07)	1.13 (0.07)
	95% CI of LS mean	(-0.05, 0.22)	(0.99, 1.26)
	LS mean diff, 95% CI	--	**1.04 (0.85, 1.23)**
	P value vs. placebo	--	<0.0001

Source: Module 2.7.3/Table 9
BMI: body mass index; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; TEZ: tezacaftor

Ancillary analyses

Efficacy subsets (m-FAS)

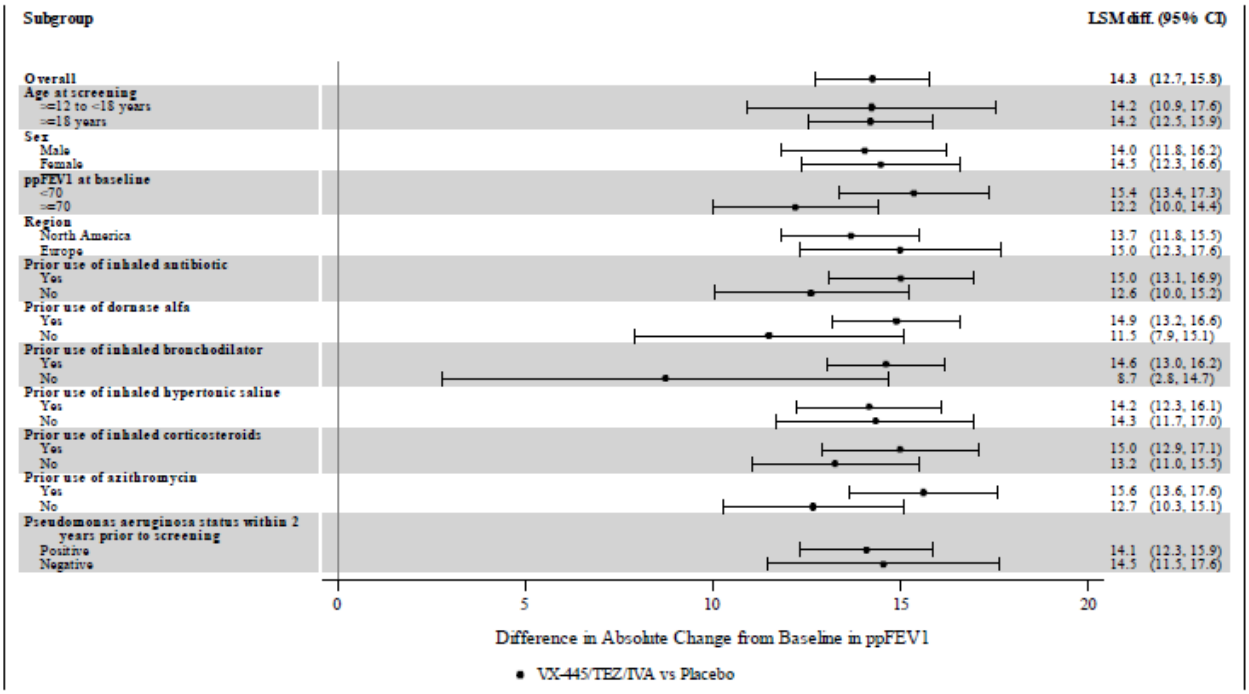
For study 102, results from the M-FAS were consistent with the analysis performed by the FAS.

For study 103, no analyses were done using subset of subjects in the FAS.

Subgroup analyses

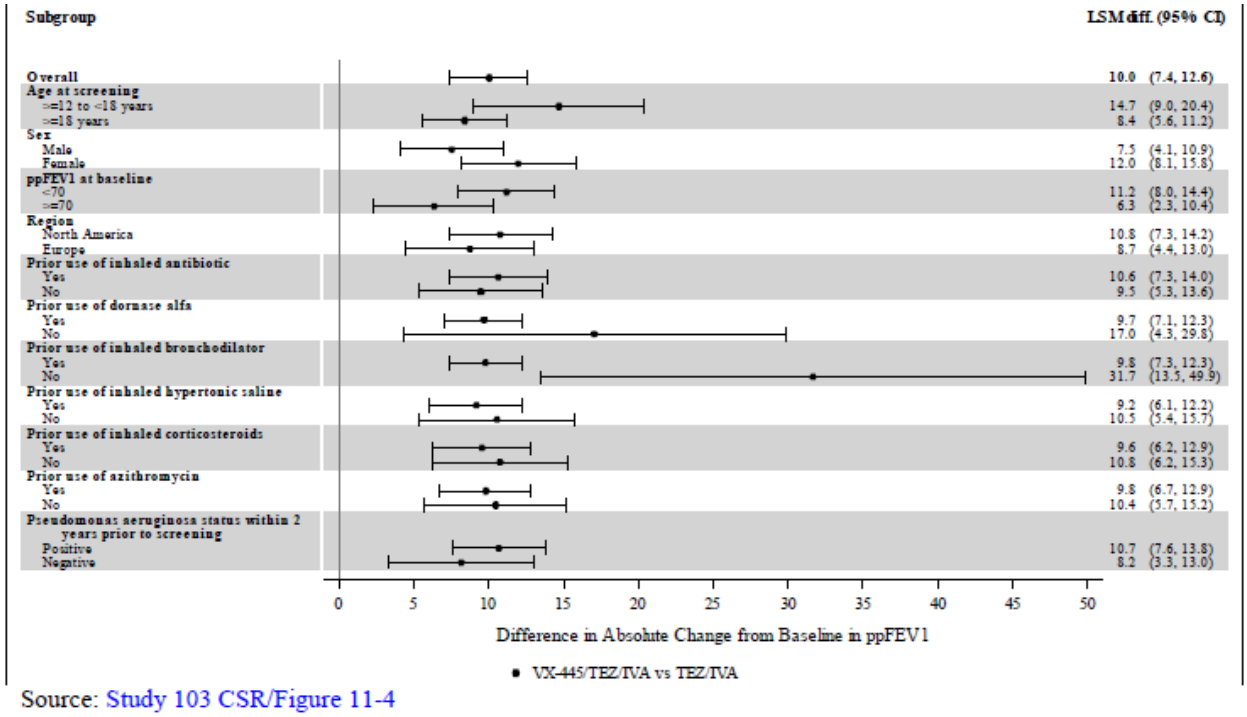
Pre-specified subgroup analyses of the absolute change in ppFEV1 from baseline were performed in a manner similar to that of the primary analysis. For both studies, the results of the subgroup analyses were consistent with the results of the primary analyses. Due to the small size of study 103, some subgroups have a limited number of subjects (Figure 13 and Figure 14).

Figure 13: Study 102 (F/MF Subjects): Subgroup analysis for absolute change from baseline in ppFEV1 Through week 24, FAS



Source: Study 102 CSR/Figure 11-8

Figure 14: Study 103 (F/F Subjects): Subgroup analysis for absolute change from baseline in ppFEV1 at week 4, FAS



Source: Study 103 CSR/Figure 11-4

To further explore the Applicant' hypothesis that a single *F508del* allele is sufficient to provide substantial clinical efficacy, an ad hoc analysis was performed to assess outcomes in F/MF subjects in Study 102 with a Class I MF mutation (n = 314, ~78% of the overall study population) (criterion 1) and patients not responding in vitro to IVA or TEZ/IVA (missense or in-frame deletion, criterion 2). Treatment of these subjects with VX-445/TEZ/IVA resulted in an absolute change from baseline in

ppFEV1 through Week 24 of 14.8 percentage points when compared to placebo for patient included based on criterion 1 and of 12.9 percentage points for patients included based on criterion 2. The outcome of this analysis was similar to the overall study outcome (14.3 percentage points) (See Table 25).

Table 25 MMRM Analysis of Absolute Change from Baseline in ppFEV1 (percentage points) through Week 24 by Genotype (FAS)

	Placebo N = 203	VX-445/TEZ/IVA N = 200
Genotype Subgroup: Missense and in-frame deletions		
n	42	47
LS mean (SE)	-0.7 (1.0)	12.2 (0.9)
95% CI of LS mean	(-2.8, 1.3)	(10.3, 14.0)
LS mean difference, 95% CI	--	12.9 (10.1, 15.7)
Genotype Subgroup: Class I		
n	161	149
LS mean (SE)	-0.3 (0.6)	14.4 (0.7)
95% CI of LS mean	(-1.6, 0.9)	(13.1, 15.8)
LS mean difference, 95% CI	--	14.8 (13.0, 16.6)

Source: Ad hoc Table 14.2.8.11

In addition, the Applicant further subdivided these subgroups, and provided post-hoc analyses in the subgroups. For the Class I (criterion 1) mutations, a subdivision was made for Nonsense mutations, Canonical splice mutations and insertions/deletions leading to a frameshift. For missense and in-frame deletions (criterion 2) a subdivision was made for mutations that were responsive or not to the triple therapy. The outcome of this analyses was similar to the overall study outcome.

Table 26 Absolute Change from Baseline in ppFEV1 (mean difference) through Week 24 by Criterion 1 subgroups

	ppFEV1	**SwCl**
Criterion 1 mutation	**14.8 (13.0, 16.6)**	**-42.1 (-44.8, -39.3)**
Nonsense	14.0 (11.5, 16.6)	-38.8 (-42.5, -35.0)
Splice	17.8 (13.7, 21.8)	-45.3 (-50.3, -40.3)
Indel-frameshift	12.9 (9.3, 16.5)	-41.6 (-47.8, -35.4)

Table 27 Absolute Change from Baseline in ppFEV1 through Week 24 by Genotype subgroups

	ppFEV1	**SwCl**
Criterion 2 mutation	**12.2 (10.3, 14.0)**	
Responsive in FRT	13.5 (9.6, 16.3)	-52.3 (-61.3, -41.3)
Non-responsive in FRT	11.0 (8.8, 13.6)	-41.8 (-46.2, -30.9)

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies (Study 102 and Study 103) supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 28 Summary of efficacy for VX17-445-102

Title: A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445 Combination Therapy in Subjects with Cystic Fibrosis Who Are Heterozygous for the F508del Mutation and a Minimal Function Mutation (F/MF).			
Study identifier	EudraCT Number: 2018-000183-28		
Design	Randomized, double-blind, placebo-controlled, parallel-group, mulicenter, 12 years and older, CF, heterozygous F/MF		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks Not applicable As extension part, patients rolled in a separate study
Hypothesis	Superiority		
Treatments groups	VX-445 + tezacaftor + ivacaftor		200mg VX-445/100 mg TEZ/150 mg IVA daily for 24 weeks + 150 mg IVA daily for 24 weeks. N=201 (randomized)
	Placebo		0 mg VX-445/0 mg TEZ/0 mg IVA daily for 24 weeks + 0 mg IVA daily for 24 weeks. N=204 (randomized)
Endpoints and definitions	Primary endpoint	ppFEV1	Absolute change in ppFEV1 from baseline through Week 24
	Key Secondary	ppFEV1	Absolute change in ppFEV1 from baseline at Week 4
	Key Secondary	PEx	Number of Pulmonary Exacerbations Through Week 24
	Key Secondary	SwCl	Absolute Change in SwCl From Baseline Through Week 24
	Key Secondary	CFQ-R	Absolute Change in CFQ-R RD Score from Baseline Through Week 24
	Key Secondary	BMI	Absolute Change in BMI From Baseline at Week 24
Database lock	24 April 2019 (date last subject completed the last visit)		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point	Full Analysis Set (FAS): all randomized subjects who carry the intended CFTR allele mutations and received at least 1 dose of study drug – 24 weeks		
Descriptive statistics and estimate variability	Treatment group	placebo	VX-445/TEZ/IVA
	Number of subjects	203	200
	LS mean ppFEV1 (week 24)	-0.4	13.9
	95% CI of LS mean	(-1.5, 0.7)	(12.8, 15.0)
	LS mean ppFEV1 (week 4)	-0.2	13.5
	95% CI of LS mean	(-1.3, 1.0)	(12.3, 14.7)

	PEx (number)	113	41
	Estimated event rate per year	0.98	0.37
	LS mean SwCl	-0.4	-42.2
	95% CI of LS mean	(-2.2, 1.4)	(-44.0, -40.4)
	LS mean CFQ-R RD	-2.7	17.5
	95% CI of LS mean	(-4.6, -0.8)	(15.6, 19.5)
	LS mean BMI	0.09	1.13
	95% CI of LS mean	(-0.05, 0.22)	(0.99, 1.26)

Effect estimates per comparison	Primary endpoint	Comparison groups	VX-445/TEZ/IVA vs placebo
		LS mean difference ppFEV1 – week 24	14.3
		95% CI	12.7, 15.8
		P-value	<0.0001
	Key secondary endpoint	Comparison groups	VX-445/TEZ/IVA vs placebo
		LS mean difference ppFEV1 – week 4	13.7
		95% CI	12.0, 15.3
		P-value	<0.0001
	Key secondary endpoint	Comparison groups	VX-445/TEZ/IVA vs placebo
		Rate reduction in PExs	0.37
		95% CI	0.25, 0.55
		P-value	<0.0001
	Key secondary endpoint	Comparison groups	VX-445/TEZ/IVA vs placebo
		LS mean difference SwCl	-41.8
		95% CI	-44.4, -39.3
		P-value	<0.0001
	Key secondary endpoint	Comparison groups	VX-445/TEZ/IVA vs placebo
		LS mean difference CFQ-R RD	20.2
		95% CI	17.5, 23.0
		P-value	<0.0001
	Key secondary endpoint	Comparison groups	VX-445/TEZ/IVA vs placebo
		LS mean difference BMI	1.04
		95% CI	0.85, 1.23
		P-value	<0.0001
Notes	All primary and key secondary endpoints were controlled for multiplicity and were statistically significant in the framework of the testing hierarchy.		

Analysis description	**Secondary analysis** As other secondary efficacy endpoints, Absolute Change in SwCl From Baseline at Week 4, Absolute Change in CFQ-R RD Score From Baseline at Week 4, Time-to-first PEx Through Week 24, Absolute Change in BMI Z-score From Baseline at Week 24 and Absolute Change in Body Weight From Baseline at Week 24 were investigated. They all showed a positive effect for VX-445/TEZ/IVA compared to placebo. **Ancillary analysis** The Forest Plot for the subgroups analysed, shows a consistent beneficial effect for VX-445/TEZ/IVA compared to placebo.

Table 29: Summary of efficacy for VX17-445-103

Title: A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445 Combination Therapy in Subjects with Cystic Fibrosis Who Are Homozygous for the F508del Mutation (F/F)			
Study identifier	EudraCT Number: 2018-000184-89		
Design	Randomized, double-blind, active-controlled, parallel-group, multicenter, 12 years and older, CF, homozygous F/F		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		4 weeks 4 weeks (on TEZ/IVA) As extension part, patients rolled in a separate study
Hypothesis	Superiority		
Treatments groups	VX-445 + tezacaftor + ivacaftor		200mg VX-445/100 mg TEZ/150 mg IVA daily for 4 weeks + 150 mg IVA daily for 4 weeks. N=56 (randomized)
	Tezacaftor + ivacator		100 mg TEZ/150 mg IVA daily for 4 weeks + 150 mg IVA daily for 24 weeks. N=52 (randomized)
Endpoints and definitions	Primary endpoint	ppFEV1	Absolute change in ppFEV1 from baseline at week 4
	Key Secondary	SwCl	Absolute Change in SwCl From Baseline at week 4
	Key Secondary	CFQ-R	Absolute Change in CFQ-R RD Score from Baseline Through at week 4
Database lock	28 December 2018 (date last subject completed the last visit)		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point	Full Analysis Set (FAS): all randomized subjects who carry the intended CFTR allele mutations and received at least 1 dose of study drug – 4 weeks		
Descriptive statistics and estimate variability	Treatment group	TEZ/IVA	VX-445/TEZ/IVA
	Number of subjects	52	55
	LS mean ppFEV1 (week 4)	0.4	10.4

	95% CI of LS mean	(-1.4, 2.3)	(8.6, 12.2)
	LS mean SwCl	1.7	-43.4
	95% CI of LS mean	(-1.9, 5.3)	(-46.9, -40.0)
	LS mean CFQ-R RD	-1.4	16.0
	95% CI of LS mean	(-5.4, -2.6)	(12.1, 19.9)

Effect estimates per comparison	Primary endpoint	Comparison groups	VX-445/TEZ/IVA vs TEZ/IVA
		LS mean difference ppFEV1 – week 4	10.0
		95% CI	7.4, 12.6
		P-value	<0.0001
	Key secondary endpoint	Comparison groups	VX-445/TEZ/IVA vs TEZ/IVA
		LS mean difference SwCl	-45.1
		95% CI	-50.1, -40.1
		P-value	<0.0001
	Key secondary endpoint	Comparison groups	VX-445/TEZ/IVA vs TEZ/IVA
		LS mean difference CFQ-R RD	17.4
		95% CI	11.8, 23.0
		P-value	<0.0001
Notes	All primary and key secondary endpoints were controlled for multiplicity and were statistically significant in the framework of the testing hierarchy.		
Analysis description	**Ancillary analysis** The Forest Plot for the subgroups analysed, shows a consistent beneficial effect for VX-445/TEZ/IVA compared to placebo.		

Analysis performed across trials (meta-analysis)

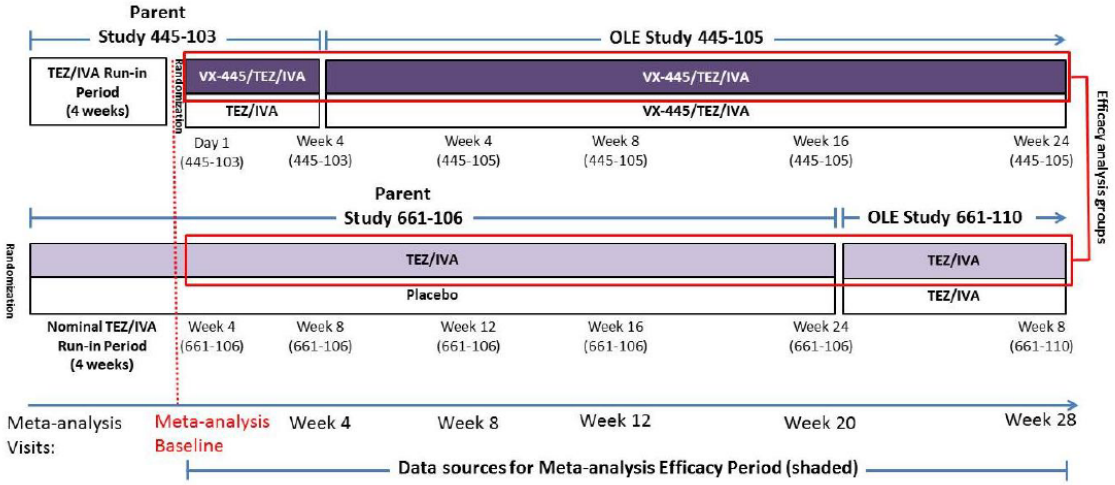
A PDCO-requested cross-study comparison (PIP Study C9 Meta-analysis) was performed to provide at least 24 weeks of comparative efficacy data for the VX-445/TEZ/IVA and TEZ/IVA regimens in F/F subjects.

This cross-study comparison included data from

- 2 studies evaluating VX-445/TEZ/IVA (Studies 103 and OLE 105) and
- 2 studies evaluating TEZ/IVA (Studies 661-106 and OLE 661-110) (used to support the MA for TEZ/IVA in F/F patients).

Baseline in Study 103 was defined after 4 weeks of treatment with TEZ/IVA (TEZ/IVA Run-in Period). In contrast, baseline in Study 661-106 was defined relative to a period without *CFTR* modulator treatment. To enable a comparison of efficacy, the first 4 weeks of TEZ/IVA treatment in Study 661-106 were considered a nominal TEZ/IVA Run-in Period to match the 4-week TEZ/IVA Run-in Period in Study 103. As a result, baseline values of efficacy endpoints for subjects in Study 661-106 were re-derived as measured at the Week 4 Visit (Figure 15).

Figure 15: Meta-analysis baseline and analysis period for efficacy endpoints



For the efficacy analysis, subjects from the VX-445/TEZ/IVA group in Study 103 and the TEZ/IVA group in Study 106 were compared; the control groups i.e. TEZ/IVA group in Study 103 and the placebo group in Study 106 were not included.

Overall the demographics and baseline characteristics of subjects in the meta-analysis were very similar between the VX-445/TEZ/IVA patients and the TEZ/IVA patients in terms of age, sex, baseline ppFEV1, and baseline SwCl. In terms of the numbers analysed for the efficacy analysis, 55 were included from the VX-445/TEZ/IVA group and 246 from the TEZ/IVA group in the FAS.

Following the 4-week TEZ/IVA run-in, treatment with VX-445/TEZ/IVA for at least 24 weeks in F/F subjects resulted in robust and clinically meaningful improvements in pulmonary and non-pulmonary endpoints. Statistically significant improvements in the VX-445/TEZ/IVA group compared to the TEZ/IVA group were observed for ppFEV1 through 28 weeks of treatment (10.7 percentage points), PEx rate (55% reduction), SwCl (-43.8 mmol/L), CFQ-R RD score (16.5 points), and BMI (1.19 kg/m2). These results provide further support for the superiority of VX 445/TEZ/IVA versus TEZ/IVA.

Responder analysis performed across trials

Analysis Methods

Responder analyses for ppFEV1 were conducted using data from 7 pivotal Phase 3 studies of VX-445/TEZ/IVA (Studies 102 and 103), TEZ/IVA (Studies 661-106 and 661-108), or IVA (Studies 770-102, 770-110, and 770-111). An individual subject in Study 102 was classified as a responder based on 2 different thresholds, either ppFEV1 ≥2.5 or ≥5.0 percentage points, if the average of Week 4, Week 8, Week 12, Week 16 and Week 24 is greater than or equal to 2.5 or 5.0, respectively.

Subjects in whom all Week 4, Week 8, Week 12, Week 16 and Week 24 ppFEV1 data were missing were classified as non-responders. An individual subject in Study 103 was classified as a responder in a similar fashion, using absolute change from base in ppFEV1 at Week 4. Because of the difference in study design, the baseline in Study 103 is defined after the 4-week TEZ/IVA run-in; thus, caution should be taken when comparing Study 103 versus other studies. The responders for TEZ/IVA or IVA studies are defined similarly to Study 102, based on the primary ppFEV1 endpoint.

The number and percentage of subjects who had improvements in ppFEV1 of ≥2.5 and ≥5.0 percentage points are summarized in Table 30. To account for differences in study populations, the placebo-adjusted proportion of subjects with improvements in ppFEV1 of ≥2.5 and ≥5.0 percentage points was calculated as the mathematical difference between the percentage of responders in the

active treatment group and the placebo group (with the exception of Study 103, which was adjusted using the TEZ/IVA comparator group as there was no placebo group in that study).

Results

These analyses show that a larger proportion of subjects responded to VX445/TEZ/IVA treatment versus placebo in Study 102 than in the pivotal studies for TEZ/IVA and IVA. This is consistent with the substantial magnitude of benefit observed with VX-445/TEZ/IVA treatment.

F/G and F/RF patients treated with VX-445/TEZ/IVA will benefit from fully leveraging both alleles. For the reasons outlined above, a greater proportion of F/G and F/RF patients will respond to VX-445/TEZ/IVA compared to TEZ/IVA and IVA, respectively.

Table 30: Responder Analyses for ppFEV1 in Pivotal VX-445/TEZ/IVA, TEZ/IVA, and IVA studies (FAS)

		Absolute Change in $ppFEV_1$	
Study Number		**≥2.5 Percentage Points**	**≥5.0 Percentage Points**
Treatment Group	**N**	**n (%)**	**n (%)**
VX-445/TEZ/IVA			
Study 102 (F/MF)[a]			
VX-445/TEZ/IVA	200	174 (87.0)	155 (77.5)
Placebo	203	46 (22.7)	30 (14.8)
VX-445/TEZ/IVA vs placebo		**64.3%**	**62.7%**
Study 103 (F/F)[b]			
VX-445/TEZ/IVA	55	47 (85.5)	37 (67.3)
TEZ/IVA	52	15 (28.8)	7 (13.5)
VX-445/TEZ/IVA vs TEZ/IVA		**56.7%**	**53.8%**
TEZ/IVA			
Study 661-106 (F/F)[a]			
TEZ/IVA	248	126 (50.8)	81 (32.7)
Placebo	256	52 (20.3)	20 (7.8)
TEZ/IVA vs placebo		**30.5%**	**24.8%**

Table 31: Continued: Responder Analyses for ppFEV1 in Pivotal VX-445/TEZ/IVA, TEZ/IVA, and IVA studies (FAS)

Study Number Treatment Group	N	Absolute Change in $ppFEV_1$ ≥2.5 Percentage Points n (%)	 ≥5.0 Percentage Points n (%)
Study 661-108 (F/RF)[c]			
TEZ/IVA	161	113 (70.2)	86 (53.4)
Placebo	161	41 (25.5)	20 (12.4)
TEZ/IVA vs placebo		**44.7%**	**41.0%**
IVA			
Study 770-102 (G551D)[a]			
IVA	83	75 (90.4)	62 (74.7)
Placebo	78	24 (30.8)	11 (14.1)
IVA vs placebo		**59.6%**	**60.6%**
Study 770-110 (R117H)[a]			
IVA	34	13 (38.2)	13 (38.2)
Placebo	35	8 (22.9)	7 (20.0)
IVA vs placebo		**15.4%**	**18.2%**
Study 770-111 (non-G551D)[d]			
IVA	38	25 (65.8)	19 (50.0)
Placebo	37	3 (8.1)	1 (2.7)
IVA vs placebo		**57.7%**	**47.3%**

Sources: Study 102 Ad hoc Table 14.2.8.49, Study 103 Ad hoc Table 14.2.5.18, Study 661-106 Ad hoc Table 1.1.1, Study 661-108 Ad hoc Table 1.2.1, Study 770-102 Ad hoc Table 2.1.1, Study 770-110 Ad hoc Table 2.1.2, Study 770-111 Ad hoc Table 2.1.3

Notes: All studies evaluated CF subjects ages 12 years and older, with the exception of Studies 770-110 and 770-111 which evaluated CF subjects ages 6 years and older.

[a] Absolute change through Week 24.

[b] Absolute change at Week 4. Baseline in Study 445-103 was established after a 4-week TEZ/IVA run-in period.

[c] Absolute change from baseline to the average of Week 4 and Week 8.

[d] Absolute change through Week 8.

Real world Data

Upon request from CHMP, the applicant provided additional information from the US Cystic Fibrosis Foundation Patient Registry (CFFPR) on F/MF, F/F, F/G and F/RF patients treated with VX-445/TEZ/IVA in the post-authorization setting.

Data collected by the CFFPR were provided to the Applicant as aggregate data report(s) only. Because the CFFPR is governed by the US Cystic Fibrosis Foundation, the applicant does not have access to patient-level data in the registry.

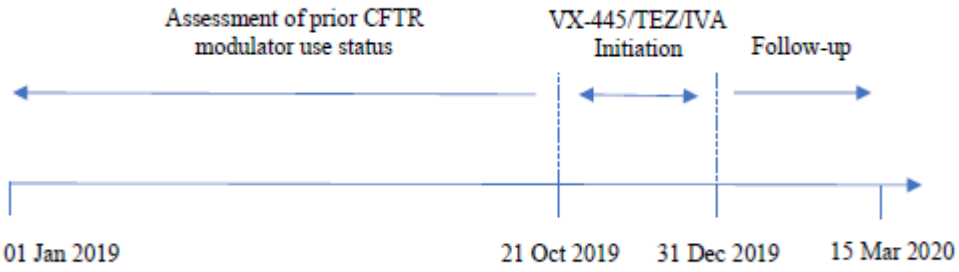
F/MF and F/F

Population

CF patients who met the following criteria were included in the analysis: (1) had a CFFPR record of initiating treatment with VX-445/TEZ/IVA between 21 October 2019 and 31 December 2019, (2) were aged 12 years and older on the date of treatment initiation, (3) had a F/MF or F/F genotype, and (4) had ppFEV1 assessments available both within 90 days before (baseline) and any time after (follow-up) treatment initiation through 15 March 2020. F/MF subjects included in this analysis had MF mutations that were defined consistently with those in Study 102.

The analysis population is summarized in Figure 16 below.

Figure 16: Patient population included in the CFFPR analyses



Individual patient-level genotype data for the analysis population were not available in this data cut.

From 21 October 2019 through 31 December 2019, a total of 1,448 F/MF and 3,178 F/F patients had a record of VX-445/TEZ/IVA treatment initiation in CFFPR; of those patients, 995 (68.7%) and 2,200 (69.2%) respectively had lung function measurements available both at baseline and follow-up and were included in these analyses.

Outcomes and Data Analysis

Improvement in lung function, as assessed by ppFEV1 (calculated using Global Lung Initiative standards [Quanjer et al 2012]), was used to determine the treatment effect with VX-445/TEZ/IVA. Other efficacy parameters (e.g., SwCl, CFQ-R) are not routinely collected in the clinical practice and/or not captured in the CFFPR and thus were not evaluated in this analysis.

The most recent measurement obtained within 90 days before VX-445/TEZ/IVA treatment initiation served as the baseline value. The last measurement available in the period following therapy initiation on or before 15 March 2020 served as the follow-up value. The change in ppFEV1 was calculated as a difference between the follow-up and baseline value for each patient, and data were summarized for F/MF and F/F subgroups using summary statistics (mean, standard deviation [SD], 95% confidence intervals [CI]).

Patients who were initiated on VX-445/TEZ/IVA treatment in 2019 were followed from the date of VX-445/TEZ/IVA treatment initiation through 15 March 2020. Treatment duration was calculated for each patient as the difference in days between the date of treatment initiation and the date of the last available post-treatment ppFEV1. Mean treatment durations were calculated for the F/MF and F/F subgroups separately.

Mean patient age at the time of VX-445/TEZ/IVA treatment initiation was summarized for the F/MF and F/F subgroups separately.

Recent use of *CFTR* modulator therapy prior to VX-445/TEZ/IVA treatment initiation was defined as any record in the registry of exposure to *CFTR* modulator therapy in 2019 prior to the VX-445/TEZ/IVA treatment initiation date; the actual CFTR modulator therapy used prior to VX-445/TEZ/IVA was not available in this data cut. Precise start and stop dates for LUM/IVA and TEZ/IVA are not available in the CFFPR and the exposure status was determined based on the presence or absence of the treatment record at each patient encounter. In 2019, in anticipation of VX-445/TEZ/IVA, CFFPR introduced a new data collection element to capture the approximate date the patient started taking therapy, which allowed more precise estimation of VX-445/TEZ/IVA initiation date in this analysis.

Results

The F/MF patients had a mean age of 26.3 years and a mean treatment duration of 65.6 days. The F/F patients had a mean age of 26.7 years and a mean treatment duration of 65.4 days.

As expected, based on the market availability of *CFTR* modulators indicated for patients with F/F genotype (LUM/IVA and TEZ/IVA), the vast majority of the F/F patients included in this analysis were receiving *CFTR* modulator therapy prior to initiating VX-445/TEZ/IVA treatment (91.5% were exposed to at least one other *CFTR* modulator in 2019). In contrast, consistent with the lack of approved *CFTR* modulator therapy for the F/MF population, only 2.9% of F/MF patients had a record of receiving *CFTR* modulator therapy prior to initiating VX-445/TEZ/IVA treatment.

Mean baseline ppFEV1 values were 65.7 for the F/MF patients and 65.8 for the F/F patients. An improvement in ppFEV1 from baseline was observed for both genotype groups: mean of 10.9 percentage points (95% CI: 10.0, 11.8) for the F/MF patients and 9.0 percentage points (95% CI: 8.6, 9.4) for the F/F patients (Table 17 and Table 18).

The data from CFFPR in F/MF and F/F patients demonstrate the transformational benefit of VX-445/TEZ/IVA in these patients. The results are consistent with results from the pivotal clinical studies in F/MF and F/F (Table 32).

Table 32: Comparison of CFFPR data with the result of the pivotal clinical studies for F/MF and F/F patients

	CFFPR Data			Pivotal Clinical Studies (Within-group Analysis)			
Genotype	Patients n	Change in $ppFEV_1$ Mean (SD)	95% CI for Change in $ppFEV_1$ [b]	Timepoint	Patients N[c]	Change in $ppFEV_1$ Mean [d]	95% CI for Change in $ppFEV_1$ [d]
F/MF	995	10.9 (15.1)	(10.0, 11.8)	Week 4	200	13.5	(12.3, 14.7)
				Week 24	200	13.9	(12.8, 15.0)
F/F	2200	9.0 (10.2)	(8.6, 9.4)	Week 4	55	10.4	(8.6, 12.2)

Source: data on file from CFFPR and Module 2.5

Note: CFFPR data are from F/MF and F/F patients who initiated treatment with VX-445/TEZ/IVA between 21 October 2019 and 31 December 2019. F/MF subjects were evaluated in Study 102. F/F subjects were evaluated in Study 103.

[a] Post-treatment $ppFEV_1$ data examined through 15 March 2020

[b] 95% CI was calculated by Vertex based on one sample t test.

[c] Number of patients represents those included in the Full Analysis Set.

[d] Model-based LS means and 95% CIs are presented.

0

F/RF and F/G

Population

CF patients who met the following criteria were included in the analysis: (1) had a CFFPR record of initiating treatment with VX-445/TEZ/IVA between 21 October 2019 and 31 December 2019, (2) were aged 12 years and older on the date of treatment initiation, (3) had a F/G or F/RF genotype, and (4) had ppFEV1 assessments available both within 90 days before (baseline) and any time after (follow-up) treatment initiation through 15 March 2020. The gating and RF mutations included were consistent with the eligible population in Study 104, and reflect the gating mutations for which Kalydeco is indicated and the RF mutations for which both Kalydeco and Symdeko (Symkevi) are indicated in the US.

Gating mutations eligible for inclusion in the analyses were G1069R, G1244E, G1349D, G178R, G551D, G551S, R1070Q, R117H, S1251N, S1255P, S549N, or S549R.

RF mutations eligible for inclusion in the analyses were 2789+5G->A, 3272-26A->G, 3849+10kbC->T, 711+3A->G, A1067T, A455E, D110E, D110H, D1152H, D1270N, D579G, E193K, E56K, E831X, F1052V, F1074L, K1060T, L206W, P67L, R1070W, R117C, R347H, R352Q, R74W, S945L, or S977F.

Individual patient-level genotype data for the analysis population were not available in this data cut. From 21 October 2019 through 31 December 2019, a total of 521 F/G or F/RF patients had a record of VX-445/TEZ/IVA treatment initiation in CFFPR. Of these patients, 297 patients (57%) had lung function measurements available both at baseline and follow-up and were included in these analyses.

Results

Their mean treatment duration was 63.4 days. Of these patients, there were 136 F/G patients who had a mean age of 32.3 years and a mean treatment duration of 62.8 days. There were 161 F/RF patients who had a mean age of 40.3 years and a mean treatment duration of 63.8 days. As expected, based on the market availability of *CFTR* modulators indicated for patients with gating (IVA) and RF (IVA, TEZ/IVA) mutations, the vast majority of the F/G and F/RF patients included in this analysis were receiving *CFTR* modulator therapy prior to initiating VX-445/TEZ/IVA treatment (97.8% of F/G patients and 89.4% F/RF patients were exposed to at least one other *CFTR* modulator in 2019).

Mean baseline ppFEV1 values were 69.0 for the F/G patients and 66.6 for the F/RF patients. An improvement in ppFEV1 from baseline was observed for both genotype groups: mean of 4.3 percentage points (95% CI: 2.7, 5.9) for the F/G patients, and 2.7 percentage points (95% CI: 1.7, 3.7) for the F/RF patients (Table 33).

Table 33: CFFPR data for F/G and F/RF patients

Subgroup	Patients n	Pre-VX-445/TEZ/IVA ppFEV$_1$ Mean (SD)	Post-VX-445/TEZ/IVA ppFEV$_1$ [a] Mean (SD)	Change in ppFEV$_1$ Mean (SD)	95% CI for Change in ppFEV$_1$ [b]
F/G	136	69.0 (26.1)	73.3 (25.2)	+4.3 (9.6)	(2.7, 5.9)
F/RF	161	66.6 (25.1)	69.3 (24.8)	+2.7 (6.6)	(1.7, 3.7)

Source: data on file from CFFPR
[a] Post-treatment ppFEV$_1$ data examined through 15 March 2020
[b] 95% CI was calculated by Vertex based on one sample t test.

Clinical studies in special populations

All trials included adolescents and adults. Subgroup analyses of the primary endpoint were performed using a model similar to that for the primary analysis. Subgroup analyses showed consistent changes in ppFEV1 regardless of age, sex, baseline lung function, geographic region, prior use of common CF medications, and P. aeruginosa colonization.

Studies 102 and 103 excluded pregnant and lactating women, and also excluded subjects with a history of any illness or condition that could confound study results or pose an additional safety risk (e.g. clinically significant hepatic cirrhosis with or without portal hypertension).

Both studies did not include any patients aged 65 years and older; thus, it is not known whether they respond differently from adults who are younger than 65 years of age.

Supportive study

VX17-445-105

Open-label extension study in subjects that completed study treatment in study 102 and 103.

Subjects who completed Studies 102 (n=400) and 103 (n=107) and met all eligibility criteria were eligible to enrol in OLE Study 105. All subjects receive the same dose of VX 445/TEZ/IVA as the VX 445/TEZ/IVA arms of Studies 102 and 103. The treatment duration in Study 105 is 96 weeks. This duration is considered sufficient for the evaluation of long-term safety and efficacy.

The primary objective of Study 105 is safety. The secondary efficacy endpoints in Study 105 are similar to Studies 102 and 103 (e.g. ppFEV1, PEx, SwCL, CFQ-R RD, BMI).

Updated Interim Analysis study data (IA2) were provided for F/MF (study 102) and F/F subjects (study 103) through the data cut-off date of 31 October 2019 from Study 105.

Results for F/MF subjects

Two subjects in each group (original arm from study 102) discontinued treatment due to an AE.

Efficacy results are provided in Table 34, Figure 17 and Figure 18.

Table 34: Study 105 IA2 (F/MF Subjects): Secondary Efficacy Analyses, OL-FAS

		OL Week 24	
Analysis	Statistic	Placebo in Study 102 N = 203	VX-445/TEZ/IVA in Study 102 N = 196
Absolute change from baseline in $ppFEV_1$ (percentage points)	n	189	180
	LS mean (SE)	14.9 (0.7)	14.3 (0.7)
	95% CI of LS mean	(13.5, 16.3)	(12.9, 15.7)
Number of PEx[a]	n	203	200
	Number of subjects with events, n (%)	35 (17.2)	55 (27.5)
	Number of events	44	84
	Estimated event rate per year (95% CI)	0.27 (0.19, 0.39)	0.32 (0.24, 0.44)
Absolute change from baseline in SwCl (mmol/L)	n	187	183
	LS mean (SE)	-50.3 (1.3)	-49.0 (1.3)
	95% CI of LS mean	(-52.9, -47.8)	(-51.6, -46.4)
Absolute change from baseline in CFQ-R RD score (points)	n	197	192
	LS mean (SE)	19.2 (1.3)	20.1 (1.3)
	95% CI of LS mean	(16.7, 21.7)	(17.6, 22.6)
Absolute change from baseline in BMI (kg/m^2)	n	196	190
	LS mean (SE)	1.21 (0.09)	1.28 (0.10)
	95% CI of LS mean	(1.03, 1.40)	(1.09, 1.46)
Absolute change from baseline in BMI z-score[b]	n	63	62
	LS mean (SE)	0.43 (0.07)	0.33 (0.07)
	95% CI of LS mean	(0.29, 0.57)	(0.19, 0.48)
Absolute change from baseline in body weight (kg)	n	196	190
	LS mean (SE)	3.9 (0.3)	4.1 (0.3)
	95% CI of LS mean	(3.4, 4.4)	(3.5, 4.6)

Sources: IA2 Tables 14.2.2.1.1, 14.2.3.2.1, 14.2.4.2.1, 14.2.5.2.1, 14.2.6.2.1, 14.2.6.4.1, and 14.2.6.6.1

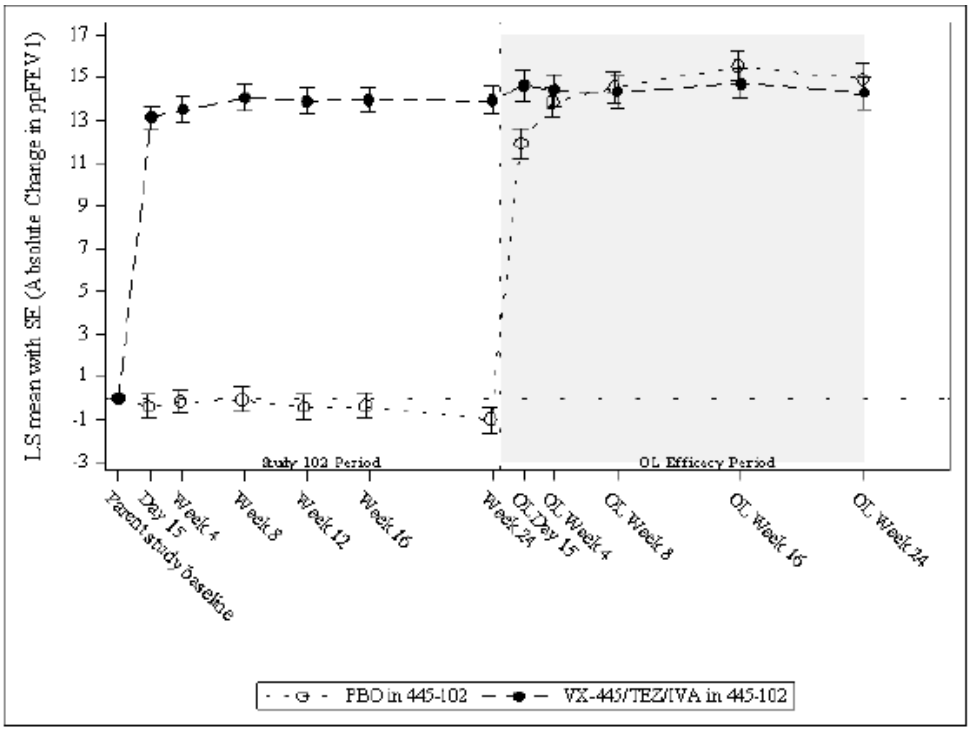
BMI: body mass index; CFQ-R RD: Cystic Fibrosis Questionnaire-Revised; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; n: size of subsample; N: total sample size; OL: open label; PEx: pulmonary exacerbation; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; RD: respiratory domain; SwCl: sweat chloride; TEZ: tezacaftor

[a] PEx was analyzed including data from the parent study.

[b] BMI z-score was analyzed for subjects ≤20 years old on the date of informed consent in the parent study.

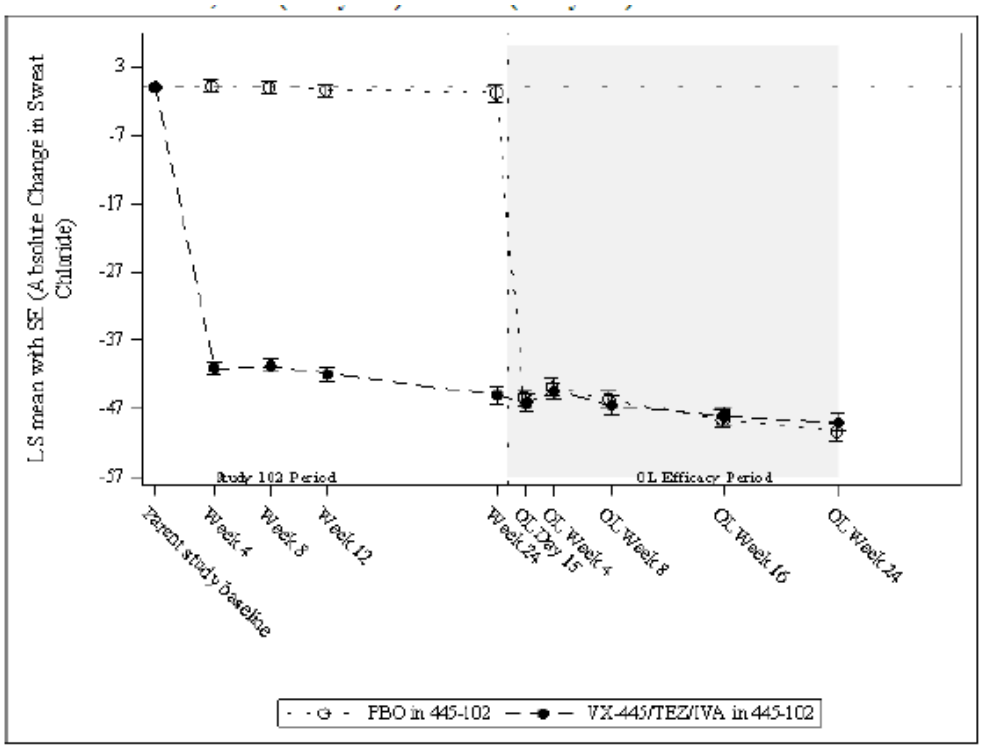
Note: Baseline is the parent study baseline, which was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study.

Figure 17: Study 105 IA2 (F/MF Subjects): Absolute Change From Baseline in $ppFEV_1$ (Percentage Points) by Visit, FAS (Study 102)/OL-FAS (Study 105)



Source: IA2 Figure 14.2.1.1
FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; OL: open label; PBO: placebo; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor
Note: The y-axis corresponds to the LS means from the MMRM models at the IA.

Figure 18: Study 105 IA2 (F/MF Subjects): Absolute Change From Baseline in SwCl (mmol/L) by Visit, FAS (Study 102)/OL-FAS (Study 105)



Source: IA2 Figure 14.2.2.1
FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; OL: open label; PBO: placebo; SwCl: sweat chloride; TEZ: tezacaftor
Note: The y-axis corresponds to the LS means from the MMRM models at the IA.

Results for F/F subjects

In the VX-445/TEZ/IVA arm 1 subjects subject and in the TEZ/IVA arm 1 subject 2 subjects (original arm from study 103) discontinued treatment due to an AE.

Efficacy results are provided in Table 35, Figure 19 and Figure 20.

Table 35: Study 105 IA2 (F/F Subjects): Secondary Efficacy Analyses, OL-FAS

Analysis	Statistic	OL Week 36	
		TEZ/IVA in Study 103 N = 52	VX-445/TEZ/IVA in Study 103 N = 55
Absolute change from baseline in ppFEV$_1$ (percentage points)	n	49	51
	LS mean (SE)	12.8 (1.3)	11.9 (1.3)
	95% CI of LS mean	(10.1, 15.4)	(9.3, 14.5)
Number of PEx[a]	N	107	
	Number of subjects with events, n (%)	27 (25.2)	
	Number of events	33	
	Estimated event rate per year (95% CI)	0.30 (0.20, 0.45)	
Absolute change from baseline in SwCl* (mmol/L)	n	48	50
	LS mean (SE)	-49.4 (2.5)	-47.2 (2.4)
	95% CI of LS mean	(-54.3, -44.5)	(-52.0, -42.5)
Absolute change from baseline in CFQ-R RD score* (points)	n	51	54
	LS mean (SE)	13.8 (2.5)	14.3 (2.4)
	95% CI of LS mean	(8.9, 18.8)	(9.5, 19.2)
Absolute change from baseline in BMI (kg/m^2)	n	51	53
	LS mean (SE)	1.18 (0.18)	1.30 (0.18)
	95% CI of LS mean	(0.82, 1.54)	(0.95, 1.65)
Absolute change from baseline in BMI z-score[b]	n	16	15
	LS mean (SE)	0.32 (0.10)	0.30 (0.10)
	95% CI of LS mean	(0.11, 0.53)	(0.09, 0.52)
Absolute change from baseline in body weight (kg)	n	51	53
	LS mean (SE)	3.6 (0.5)	4.0 (0.5)
	95% CI of LS mean	(2.6, 4.6)	(3.0, 5.0)

Sources: IA2 Tables 14.2.2.1.2, 14.2.3.2.2, 14.2.4.2.2, 14.2.5.2.2, 14.2.6.2.2, 14.2.6.4.2, and 14.2.6.6.2

BMI: body mass index; CFQ-R RD: Cystic Fibrosis Questionnaire-Revised Respiratory Domain; FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; n: size of subsample; N: total sample size; OL: open label; PEx: pulmonary exacerbation; ppFEV$_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride; TEZ: tezacaftor

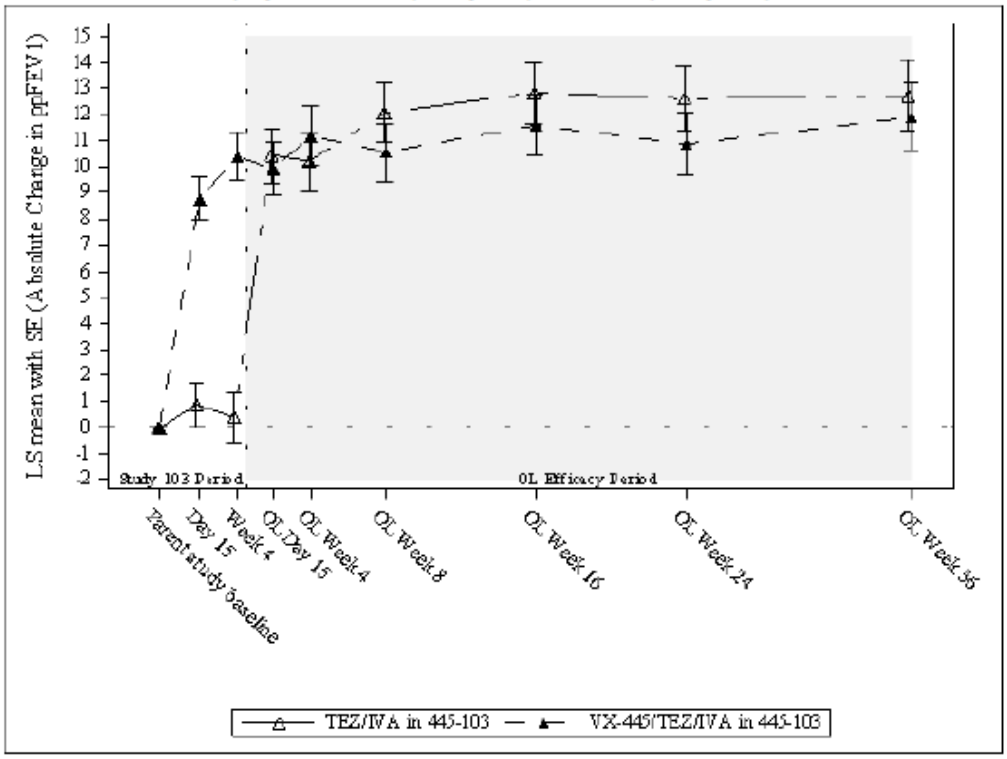
* SwCl and CFQ-R RD were not collected at OL Week 36; the results shown include data through OL Week 24.

[a] PEx was analyzed including data from the parent study and the treatment groups from Study 103 were pooled for the analysis.

[b] BMI z-score was analyzed for subjects ≤20 years old on the date of informed consent in the parent study.

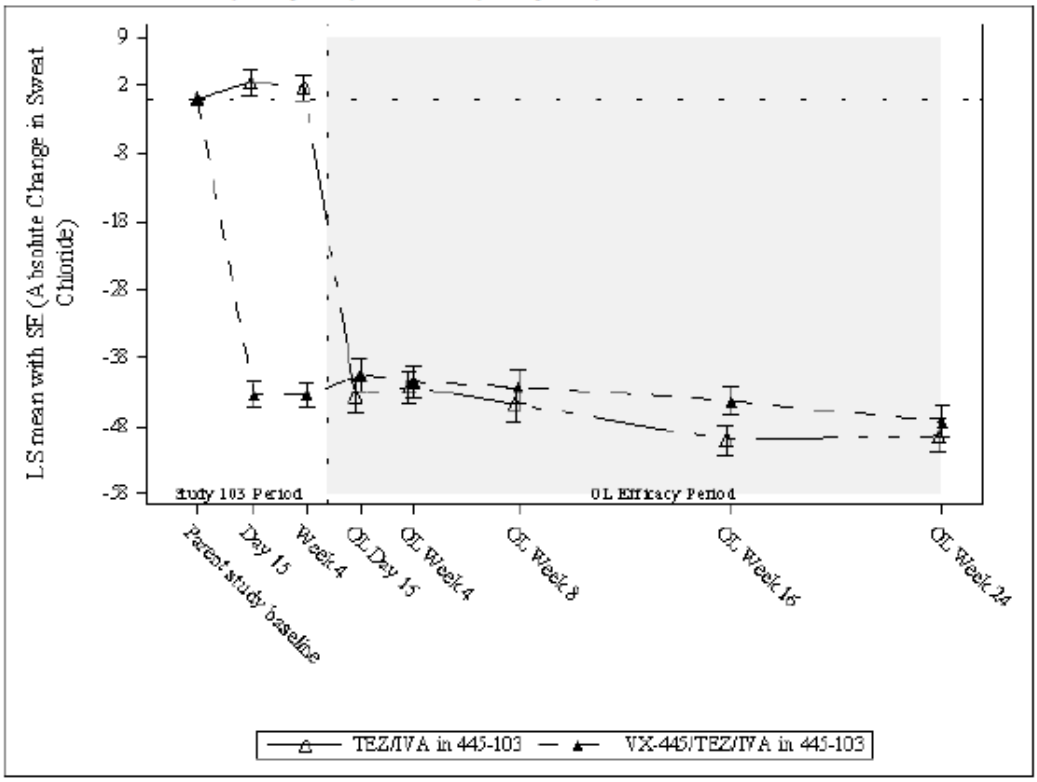
Note: Baseline is the parent study baseline, which was defined as the most recent non-missing measurement before the first dose of study drug in the Treatment Period of the parent study.

Figure 19: Study 105 IA2 (F/F Subjects): Absolute Change From Baseline in $ppFEV_1$ (Percentage Points) by Visit, FAS (Study 103)/OL-FAS (Study 105)



Source: IA2 Figure 14.2.1.2
FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; OL: open label; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor
Note: The y-axis corresponds to the LS means from the MMRM models at the IA.

Figure 20: Study 105 IA2 (F/F Subjects): Absolute Change From Baseline in SwCl (mmol/L) by Visit, FAS (Study 103)/OL-FAS (Study 105)



Source: IA2 Figure 14.2.2.2
FAS: Full Analysis Set; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; OL: open label; SwCl: sweat chloride; TEZ: tezacaftor
Note: The y-axis corresponds to the LS means from the MMRM models at the IA.

2.5.3. Discussion on clinical efficacy

VX 445 (elexacaftor) is a new-generation *CFTR* corrector, which facilitates the cellular processing and trafficking of *CFTR*. Elexacaftor has a different chemical structure and a different mechanism of action compared to the first-generation of *CFTR* correctors (TEZ, LUM) and potentiators (IVA).

The Applicant initially applied for the following indication:

Kaftrio is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

There is no other currently approved *CFTR* modulator therapy in the EU with such a broad indication requiring only the presence of one *F508del* allele, and with the potential to treat such a large percentage of the CF population (80-90%). The initially proposed indication includes patients with *F508de*l and a so called 'minimal function' mutation i.e. F/MF genotypes, a group which has not responded to the currently approved *CFTR* modulating options. It also includes patients with the F/F genotype, as well as patients with F/G (*F508del* with a gating mutation) and F/RF (*F508del* with a residual function mutation) genotypes. Essentially the argument of the applicant is that this triple drug combination targets and exerts its effect entirely by correcting the *CFTR* defect caused by the *F508del* allele, regardless of the second allele present, and sees this as a new treatment approach. This *F508del*-only hypothesis may be a plausible and clinically applicable model for treatment; however, uncertainties remain precluding definite conclusion. Details are provided below.

Design and conduct of the studies

Dosing of VX-445 was investigated in one Phase 1/2 study (Study 001). In healthy volunteers, single and multiple ascending doses were tested ranging from 20 mg – 340 mg per dose. In F/MF patients, different doses (50mg, 100mg and 200mg) daily were tested while in F/F patients, only the final 200mg dose was tested.

Efficacy and safety have been evaluated in three phase 3 studies in CF patients aged 12 years and older. Study **102** in subjects heterozygous for *F508del* and a minimal function mutation (F/MF) and study **103** in subjects homozygous for *F508del* (F/F) are the core efficacy studies. These studies were randomised double-blind, controlled multicentre studies. Study **105** was designed to support persistence of efficacy and long-term safety. Results are currently submitted as an interim analysis (IA2). The study is ongoing and further analyses will be submitted post approval.

Furthermore, upon request by PDCO, a cross-study comparison "the Meta-analysis", was performed in which the results of Studies 103 and 105 and the phase 3 studies for Symkevi (studies 106 and 110) were pooled and compared.

Upon request by CHMP, real world data (from the US Cystic Fibrosis Foundation Patient Registry, CFFPR) from a post-authorization setting were also provided.

Comparator
In the **F/MF** patient population (study 001 and 102), placebo was used as the comparator. This is considered to be an acceptable treatment arm because no other approved regimens have shown clinical efficacy in the F/MF populations, justifying the absence of TEZ/IVA or LUM/IVA arm.

In the **F/F** population (study 001 and 103), TEZ/IVA was used as the comparator, in patients already treated with TEZ/IVA. This is also considered acceptable because it is the best approved regimen in the F/F population.

The choice of only placebo in F/MF or TEZ/IVA in F/F as a comparator can be questioned. According to the applicant, the added effect of VX-445/TEZ/IVA over VX-445 monotherapy or VX-445/IVA is demonstrated by *in vitro* and mechanistic data. These data suggest that the triple combination provides additional benefit over all mono/dual therapies in both F/MF and F/F cells. The applicant also indicated that TEZ and VX-445 can bind simultaneously to the *CFTR* protein (only wild-type *CFTR* tested). Nevertheless, clinical evaluation of VX-445 monotherapy and VX-445/IVA compared with the TC, was strongly recommended in Scientific Advices (SA) given by CHMP and national authorities. This is also in line with the recommendations provided in the Guideline for Fixed Dose Combinations (EMA/CHMP/158268/2017) which states that "*clinical trials demonstrating efficacy/safety of the new active substance as monotherapy"* should be performed. While information on the safety of VX-445 can be derived from the currently provided and previously submitted clinical studies performed with placebo and TEZ/IVA; it is considered that clinical efficacy data would be required, in particular, compared to the VX-445/IVA combination. It is considered however that *in vitro* results, confirming the added benefit of the combination of two correctors (VX-445 and TEZ) over VX-445 alone provides valuable information and demonstrates that both correctors VX-445 and TEZ are required in combination with potentiator (IVA).

The HBE cells used to generate *in vitro* data can be regarded as a relevant model system to study the pharmacological action of *CFTR* modulators. Three donors with an F/F genotype were analysed and 4 donors with an F/MF genotype (2x *G452X* (non-sense); *3905InsT* (small insertion); *E585X* (non-sense). In study 102; 65, 5 and one patient with this genotype were included respectively.

The *in vitro* data demonstrate that:

- The combinations of TEZ and VX-445 (with or without IVA) results in increased processing and trafficking of *CFTR* protein to the membrane compared to monotherapy VX-445 or VX-445/IVA.

An added benefit (minimal 20% - maximal 60%) of VX-445/TEZ/IVA is seen in all donors on chloride transport for the VX-445/TEZ/IVA combination compared to dimethyl sulfoxide (DMSO), Symkevi, VX-445 alone, VX-445 & ivacaftor and VX-445 & tezacaftor in F/MF (4 donors) and F/F cells (3 donors).

- VX-445 and TEZ can bind simultaneously to a thermostabilized variant of *CFTR*.

The in vitro data suggest that the triple combination does provide a benefit over all mono and dual combination of VX-445, TEZ and IVA in all tested donors.

Uncertainties remain on the contribution of all components, as not all combination are tested in a clinical setting and the FDC guideline is not followed. Nevertheless, the *in vitro* data, the highly clinically relevant benefit and well-tolerated safety profile of the VX-445/TEZ/IVA in the F/MF and F/F population are considered relevant enough to outweigh these uncertainties on the contribution of the mono-components in a clinical setting.

Duration

The duration of the dose finding study 001 of 28 days is acceptable for the objective. The 24-week treatment period of pivotal study 102 is in line with the EMA guideline on CF and according to CHMP's SA. However, the 4-week treatment period of pivotal study 103 is not in line with guidelines and SA given, and robust conclusion cannot be drawn on the sustainability of the effect of the triple combination. In the view of the Applicant, the short duration is acceptable because a sustained benefit from day 15 towards week 24 has always been shown in clinical studies of the other *CFTR* modifiers. Although this has indeed been observed, the results from the in between time were fluctuating and not completely stable. Furthermore, important efficacy parameters such as exacerbations and BMI cannot be reliably measured in a study with a duration of 4 weeks. Therefore, a 4-week study is too short to establish a long-term clinical benefit. The open label extension phase (Study 105) provides further data on the maintenance of efficacy and long-term safety, which is considered acceptable.

Inclusion and exclusion criteria

The in-and exclusion criteria for the dose-response study 001, and pivotal studies 102 and 103 were largely similar, except for age (dose response only adult patients, pivotal also adolescents) and the genotype mutations. Patients had to have FEV1 ≥40% and ≤ 90% and stable CF. Diagnosis of CF was confirmed by the investigator. In previous trials, the CF diagnosis was confirmed by a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis, or when this 60 mmol/L was not met a patient must have had documented evidence of chronic sinopulmonary disease manifested (for milder phenotypes of CF (genotype F/RF). In the current studies, no pre-specified criteria exist for the CF diagnosis. Only a limited number of patients with a SwCl of < 60 mmol/L were included in the trial 102 (and sensitivity analysis without these patients show consistent results). No patients with a SwCl of < 60 mmol/L at baseline were included in study 103.

F/F and F/MF population

In **study 102** the definition of an MF mutation used by the applicant is considered to be unusual. The Applicant defines an MF mutation as follows:

(1) no *CFTR* protein or (2) a *CFTR* protein that is not responsive to IVA and TEZ/IVA *in vitro*. For study 102 a mutation was considered an MF mutation if it meets at least 1 of the following 2 criteria:
(1) biological plausibility of no translated protein (genetic sequence predicts the complete absence of CFTR protein). A list of eligible MF mutations was specified.

(2) *in vitro* testing that supports lack of responsiveness to TEZ, IVA, or TEZ/IVA, and evidence of clinical severity on a population basis (as reported in large patient registries).

- *In vitro* baseline chloride transport of < 10% of WT *CFTR* and increase of chloride transport <10% over baseline after TEZ, IVA or TEZ/IVA.
- Clinical severity (CFTR2 patients registry) → average sweat chloride >86 mmol/L and prevalence of pancreatic insufficiently (PI) > 50%.

With regard to (1), the pre-specified list contains mutations that are very likely to have no *CFTR* translated protein. The position of the Applicant that VX-445/TEZ/IVA only requires one *F508del* allele is based on the fact that the (included) MF mutations in study 102 have no protein and therefore the effect seen has to be caused by the *F508del* allele. Although plausible and likely, it is theoretically still possible that some of the MF mutants may have a minor contribution to the *CFTR*-mediated chloride transport upon treatment with VX-445/TEZ/IVA.

With regard to (2), the 10% cut-off seems acceptable as it has been used and justified in previous procedures. The criterion (2) mutations were tested for non-responsiveness to VX-445/TEZ/IVA. In FRT cells, 8 mutations (*3199del16, A559T, I507del, L467P, N1303K, R1066C, R560T, V520F*) did not respond to VX-445/TEZ/IVA treatment, while 4 mutations (*G85E, M1101K, L1077P and R347P*) did show responsiveness. However, the inclusion and responsiveness data are based on the assumption that *in vitro* data do correlate with *in vivo* data, while an IVIVC has not been established.

Therefore, the results from mainly the patients included based on criterion (1), which is 78% of the patients, is considered of value (provided as an ad-hoc analysis). The efficacy in this subset and in genotype subgroups could be used to draw conclusions on the acceptability of the "new paradigm" i.e. only one single *F508del* allele is required. The totality of evidence generated in the pivotal clinical studies could be considered to draw a conclusion on whether the *F508del* allele is the main target of action (see further discussion below).

In terms of F/F patients entering **Study 103** some patients may have already been on therapy at the time of screening, and indeed could continue therapy right up to the start of the TEZ/IVA run in, while others may have been naïve to Vertex *CFTR* modulators (of note, those on non-Vertex *CFTR* modulators had a wash out prior to screening). Stratification according to ppFEV1 was applied on the ppFEV1 measurements taken after at least 13 days of TEZ/IVA run-in, rather than the screening ppFEV1 values. A subgroup analysis for Vertex *CFTR* modulator naïve versus treatment-experienced patients indicates that the magnitude of the observed treatment effect (LS mean 7.8%, 95% CI (4.8,10.8)) for *CFTR* modulator experienced patients is less than that for *CFTR* modulator naïve patients (LS mean 13.2%, 95% CI (8.5,17.9)). Overall various subgroup analyses requested do not suggest a major differential treatment effect for *CFTR*-modulator naïve and *CFTR*-modulator experienced patients. However, subjects who were *CFTR* modulator naïve had a lower mean baseline ppFEV1 value (58.5 for the VX-445/TEZ/IVA group and 57.2 for the TEZ/IVA group) than subjects who were *CFTR* modulator experienced (63.8 for the VX-445/TEZ/IVA group and 61.8 for the TEZ/IVA group). Although the small sample size in these subgroups is acknowledged, comparison of the week 4 and week 8 ppFEV1 values across these four subgroups suggests that the screening period of 4 weeks may not have been sufficient for *CFTR*-modulator naïve patients randomized to TEZ/IVA to derive the full benefit of this treatment by time of baseline ppFEV1 assessment. Consequently, it is considered that the magnitude of the treatment effect of VX-445/TEZ/IVA vs TEZ/IVA in the overall study 103 population may be overestimated and that the treatment effect estimate obtained in the *CFTR*-modulator experienced patients is relevant to prescribers (LS mean 7.8%, 95% CI (4.8,10.8)). This information is considered relevant for the prescribers and is mentioned in Section 5.1 of the SmPC.

Study 105 is an extension study and enrolled subjects who participated in study 102 and 103.

Endpoints
The parameters ppFEV1 and SwCl endpoints were used in the dose response study 001. These parameters are acceptable endpoints to define the Dose-Response relationship.

For the pivotal studies 102 and 103, the primary endpoint was an absolute change in LS mean ppFEV1 (through week 24 and at week 4, for study 102 and 103 respectively). FEV1 is the advocated primary endpoint in EMA's guideline on CF (CHMP/EWP/9147/08). The key secondary efficacy endpoints in study 102 (number of pulmonary exacerbations, absolute change in SwCl, absolute change in CFQ-R RD Score and absolute change in BMI) and study 103 (absolute change in SwCl and absolute change in CFQ-R RD Score) are all accepted endpoints in clinical studies on CF.

In extension Study 105, the same endpoints were used.

Efficacy on other organs could have been explored by analysing faecal elastase-1, plasma IRT, bile acids C4 and FGF. However, such data were not collected as the included subjects are likely to have progressive damage to their exocrine pancreas that is irreversible.

Statistical Analyses

For study 102, the primary analysis was performed using a mixed-effects model for repeated measures (MMRM) with change from baseline at Week 4, Week 8, Week 12, Week 16, and Week 24 as the dependent variable. The model included treatment group, visit, and treatment by visit interaction as fixed effects, with continuous baseline ppFEV1, age at screening (<18 versus ≥18 years of age) and sex (male versus female) as covariates. Type I error was controlled through a hierarchical testing-procedure.

For study 103, a MMRM was also used, but with Day 15 and Week 4 as the dependent variable and with continuous baseline ppFEV1 and age at screening (<18 versus ≥18 years of age) as covariates. The use of a MMRM for the evaluation of the primary endpoint in both studies is acceptable. The analyses used to examine the secondary endpoints are also acceptable.

In extension study 105, a MMRM was also used to estimate the change from baseline in ppFEV1 at each time point.

A limited part of study team was unblinded following the evaluation of results from an interim analysis by the IDMC. This was only done when the efficacy boundary was crossed and the Vertex team members who were unblinded were not involved in the conduct of the remaining part of the study. It is considered that the unblinding of (senior) members of the Vertex team could still be a risk to the integrity of the study, although the approach of the applicant seems acceptable and the study was not subject to several changes after the first interim analysis (IA), this issue will remain an uncertainty.

In both studies (102 and 103), a sensitivity analysis was performed for the evaluation of the primary endpoints. This sensitivity analysis was based on the classification of patients with missing data into a number of missing categories and may not have been sufficiently sensitive to assess departures from the missing at random assumption. However, the rate of missing data is low.

Efficacy and additional analyses

Dose regimen and posology

Adults
For CF patients 18 years and older with an **F/MF** mutation, three doses (50 mg, 100 mg and 200 mg) of VX-445 were tested in combination with the approved dosage of TEZ/IVA. A difference in ppFEV1

compared to placebo was seen for all doses tested strengths (11.1, 7.8 and 13.8, for 50, 100 and 200 mg respectively). An improvement (decline) compared to placebo was also detected for SwCl (-36.1, -31.0, -36.9 mmol/Lfor 50, 100 and 200 mg, respectively). However, no clear dose response has been seen, as the 100 mg arm shows a response lower than the 50 mg and 200 mg (possibly due to pooling of D1 and D2 data which occurred in the 100 mg only).

The difference on the most sensitive and less variable parameter SwCl, between the 50 mg and 200 mg was only 0.8 mmol/L. For the ppFEV1 a difference of 2.7% was observed between the 50 mg and the 200 mg. This result could be considered as a relevant difference, but such a conclusion is hampered because the sample size (especially in the 50 mg arm) is small and the parameter therefore more variable. These results could suggest a rather flat dose-response curve. The response seen with lower doses of VX-445, could be of importance for patients with hepatic impairment as discussed in the clinical pharmacology section.

For CF patients 18 years and older with an **F/F** mutation only the 200 mg dose was investigated. A benefit with VX-445/TEZ/IVA compared to TEZ/IVA was seen, but from this population no dose-response information can be extracted. For ivacaftor and tezacaftor the approved dosing strengths were used (TEZ 100 mg qd, and IVA 150mg q12h). This is considered acceptable, as the VX-445 does not affect the TEZ or IVA PK and because steady-state exposures of TEZ and IVA are similar in the absence or presence of VX-445 in CF subjects.

When considering the efficacy data, the exposure-response models and the simulated efficacy data for ppFEV1 and SwCL, the 200-mg provides the best effect in all analyses.

Therefore, the intended dosing regimen in Adults (VX-445 200 mg qd, TEZ 100 mg qd and IVA 150 mg q12h), is considered acceptable by CHMP.

Adolescents

There were no Phase 1/2 PK adolescent data to inform the dose choice, nor was there modelling/simulation of Phase 1/2 data in advance of Phase 3. VX-445 PK in 12 to <18 years-old was predicted to be similar to the PK parameters in adults; hence, the same adult dose was used in adolescents in the pivotal studies.

The Applicant justified that the recommended dose of IVA and TEZ/IVA is the same for adults and adolescents, and like TEZ and IVA, VX-445 is a CYP3A substrate and hence the impact of CYP ontogeny is expected to be similar for all 3 drugs. CYP enzyme maturity is also similar between adults and adolescents. In addition, based on historical data on weight and age in CF subjects, body weights in the adolescent population are only slightly lower than those of adults with CF. Consequently, Pop-PK analysis of PK data from Phase 1/2 and 3 confirmed that age and weight were not significant co-variates, and clearance in adults and adolescents was similar. However, while the lowest weight included in the Pop-PK analysis was 29kg, there are a limited data in CF subjects weighting <40 kg in the Phase 3 studies. Further data on PK in low weight patients is expected in due course from the ongoing open label PK/safety study (VX18-445-106) in children aged 6-11 years (both F/F and F/MF genotypes), where half the adult dose is being tested in patients under 30 kg.

Pivotal studies

- *CF patients 12 years or older with the **F/MF** genotype (study 102)*

In pivotal study 102, the demographic and baseline characteristics were balanced between the two treatment groups. In terms of the F/MF genotypes represented in the clinical study, across the 403 F/MF subjects in the FAS, 79 different MF mutations have been represented. 314/403 patients had Class I (i.e. no *CFTR*) mutation; in total 67 Class I mutations were recruited. In terms of mutations that are not Class I, (i.e. qualified under Criterion 2), 12 MF mutation types were recruited (missense

or in frame deletion mutations) in 89 patients. Due to the genetic variability of CF as a disease, it is acknowledged by CHMP that not all genotypes will be able to be tested.

The inclusion of patients with ppFEV1 <40 (34/403) did not comply with the inclusion criteria. The inclusion criterion pertaining to screening ppFEV1 was met in all enrolled subjects in Study 102, but the ppFEV1 decreased at their baseline study visit.

Three concomitant antibiotic treatments were used more often in the placebo group (Tobramycin: 55.7% vs 39%; Ciprofloxacin: 36% vs 16%; Sulfamethoxazole and trimethoprim: 26.1% vs 17.0%). This difference can be attributed to the imbalance in the occurrence of pulmonary exacerbations (PEx) (numerically higher in the placebo group). These antibiotic usage differences are a consequence of the effectiveness of the VX-445/TEZ/IVA regimen.

Missing data for the repeated measurements data was not an issue (less than 10%).

Primary endpoint:

For the primary endpoint, the LS mean treatment difference in absolute change in ppFEV1 through week 24 between the VX-445TEZ/IVA and placebo groups was 14.3% (95% CI 12.7 – 15.8; p<0.0001) in favour of the triple combination. The obtained difference was above the predefined threshold (5.0%) and considered highly clinically relevant (Please refer to the report of the workshop on endpoints for cystic fibrosis clinical trials (EMA/769571/2012)). Approximately 80% patients treated with the TC have a benefit of ppFEV1 >5%, compared to 15% in the placebo group. The result of the sensitivity analysis, a MMRM based on multiple imputations (MIs), was consistent with the primary analysis.

Secondary endpoints:

The key secondary endpoint, absolute change in ppFEV1 in 4 weeks, was in line with the results of the primary endpoint at 24 weeks (13.7 %; P<0.0001; 95% CI: 12.0, 15.3). This suggests a stable improvement from 4 weeks on.
For the key secondary endpoints pulmonary exacerbations, the rate ratio was 0.37 (95% CI: 0.25 – 0.55, p<0.0001) in favour of VX-445/TEZ/IVA. This corresponds to a reduction of 63% of pulmonary exacerbations, which is considered clinically relevant. The reductions in pulmonary exacerbations requiring hospitalization and/or IV antibiotic treatment were also statistically and clinically significant. The hazard ratio for time-to-first pulmonary exacerbation was also in favour of the triple combination (HR: 0.34; 95% CI 0.22, 0.52; p<0.0001).
For the key secondary endpoint, changes in SwCl from baseline, the stable reduction of -41.8 mmol/L (95% CI: -44.4 to -39.3; p< 0.0001) through week 24 compared to placebo is considered clinically relevant (MCID:-10 mmol/L). Approximately 95% of the patients treated with the TC had clinically relevant benefit, compared to only 5% in the placebo group.
Also, a key secondary endpoint, change in CRQ-R RD score, improved significantly in the TC arm compared to the placebo arm (20.2 points; 95% CI 17.5,23.0; p<0.0001). With an MCID of 4 points, this increase in considered clinically relevant. All other CFQ-R domains indicated an improvement with the TC compared to placebo.
The key secondary endpoint, absolute change in BMI, presented also a benefit of the VX-445/TEZ/IVA arm over placebo. A change of 1.04 kg/m^2(95% CI: 0.85, 1.23; p<0.0001) compared to placebo was observed; considered to be clinically relevant.

At baseline, median BMI baseline was 20.80 kg/m2 (min, max: 14.42, 33.80) in the placebo group and 21.36 (15.01, 30.86) in the TC group. In total, study 102 recruited 50 overweight patients, and 17 undernourished patients. Therefore, there were an unknown number of underweight subjects as well as of overweight/obese patients. An analysis of BMI was provided for undernourished and overweight

subjects according to the WHO thresholds. Both overweight and underweight patients treated with VX-445/TEZ/IVA showed gains in BMI consistent with the overall population.

Consistent and significant benefits in ppFEV1 favouring VX-445/TEZ/IVA were observed across all prespecified subgroups: age, sex, baseline lung function, region, P. aeruginosa infection, and baseline use of common CF medications.

Additional analysis

An ad-hoc subgroup analysis was performed on patients included based on genetic criterion 1 (likely to have no CFTR protein translated) and on criterion 2 (missense not responding the TEZ and/or IVA *in vitro*). Class 1 (MF) mutant patients show an absolute change from baseline in ppFEV1 of 14.8% comparing the triple combination with placebo. The missense mutant patients showed a difference in ppFEV1 of 12.9%. Furthermore, for the criterion 1 mutations, a subdivision was made for Nonsense mutations, Canonical splice mutations and insertions/deletions leading to a frameshift. For missense and in-frame deletions (criterion 2) a subdivision was made for mutations that were responsive or not to the triple therapy. The outcomes of these analyses were similar to the overall study outcome.

Within the IA2 from study 105, the efficacy data were presented for patients from parent study 102. These data showed that the positive treatment effect continues to be maintained with continued treatment. In general, the data indicate that for MF patients from the "placebo" group, treatment with VX-445/TEZ/IVA results in a similar benefit for all efficacy parameters when compared to the group that received already the triple combination in study 102. When comparing the data from week 24 and week 48 for the patients that received already the triple combination in study 102, all the efficacy parameters still seemed to slightly improve. Subgroup analyses for FEV1 and SwCL for the different MF genotypes were also performed for the "placebo" group of study 102. The outcomes of these analyses were similar to the overall study outcome.

- *CF patients 12 years or older with the **F/F** genotype (study 103/105)*

In the pivotal study 103, the demographic and baseline characteristics were balanced between the two treatment groups. Missing data for the repeated measurements data was not an issue (less than 10%).

Primary endpoint:

For the primary endpoint, the LS mean treatment difference in absolute change in ppFEV1 at week 4 between the VX-445TEZ/IVA and TEZ/IVA groups was 10.0% (95% CI 7.4 – 12.6; p<0.0001) in favour of the triple combination. The obtained difference was above the predefined threshold (5.0%) and considered clinically relevant. Approximately 70% patients treated with the TC have a benefit of ppFEV1 >5%, compared to 13% in the TEZ/IVA group.

Secondary endpoint:

For the key secondary endpoint, change in SwCl from baseline, a positive effect is observed after treatment with VX-445/TEZ/IVA compared to TEZ/IVA. A stable reduction of -45.1 mmol/L (95% CI: -50.1 to -40.1; p< 0.0001) at week 4 is considered clinically relevant. Approximately 95% of the patients had a clinically relevant reduction in SwCl, when treated with the triple combination.
Also, key secondary endpoint, change in CRQ-R RD score, improved significantly in the TC arm compared to the TEZ/IVA arm (17.4 points; 95% CI 11.8,23.0; p<0.0001). Also, all other CFQ-R domains indicated an improvement with the TC compared to TEZ/IVA.

Although no robust conclusion can be drawn, ad-hoc analyses on BMI and weight also seem to demonstrate the beneficial effect of the TC over TEZ/IVA.

Consistent benefits in ppFEV1 favouring VX-445/TEZ/IVA were observed across all prespecified subgroups: age, sex, baseline lung function, region, P. aeruginosa infection, and baseline use of common CF medications.

- *Extension study 105*

Because of the short 4-week duration of study 103, results from the extension study 105 were also analysed to identify whether the effects seen at 4 weeks, remained stable up to 24 weeks of treatment. All patients rolled over to study 105, in which the patients from the TEZ/IVA group also received the triple combination.

The results for the change in ppFEV1, SwCl and CFQ-R RD showed a maintenance of response when treated with VX-445/TEZ/IVA. Subjects treated with the TC in the parent study continued to have a similar benefit at 4 weeks and through 24 weeks of treatment, respectively (ppFEV1: 10.4 vs 10.9 percentage points; SwCL: -43.4 vs -47.2 mmol/l; CFQ-R RD: 14.3 vs 16 points).

With a longer follow-up, data for pulmonary exacerbations (PEx) and the nutritional status also became available.

For the number of PEx, an estimated event rate per year of 0.30 (95% CI: 0.18-0.48) and a probability of event-free survival of 0.859 (95% CI: 0.777-0.912) was anticipated. For this endpoint, no control-group, or event rate at baseline was present, therefore, the benefit over TEZ/IVA is difficult to determine. When comparing the observed PEx data for study 103/105 to the data from the VX-445/TEZ/IVA group in study 102 (event rate per year 0.37 (0.25, 0.55); the probability of event-free survival 0.842 (0.783, 0.886) is considered similar. Therefore, the presented exacerbation results for F/F patients from study 105, appear supportive of the benefit observed with the TC.
With regard to the nutritional status, a benefit compared to baseline was observed for all parameters (change in BMI, BMI z-score and body weight).

Overall, the efficacy results from the F/F patients in study 105, confirmed that in this patient population a long-term benefit was observed after treatment with VX-445/TEZ/IVA. These results overcome the uncertainties that went along with the 4-week study duration of study 103. However, to ensure that these positive treatment effects continue to be maintained updated data of study 105 should be provided in the post authorization setting. Within these analyses, the applicant is also requested to perform subgroup analysis for weight, BMI, and their respective z-scores confined for adolescents.

Cross study comparison/Responder analysis

In addition, a responder analysis was performed for the 7 pivotal Phase 3 studies of VX-445/TEZ/IVA (Studies 102 and 103), TEZ/IVA (Studies 661-106 and 661-108), or IVA (Studies 770-102, 770-110, and 770-111). The comparison between the placebo controlled studies in patients with at least one *F508del* allele (study 661-108 (F/RF), study 661-106 (F/F) and study 102 (F/MF) could suggest that at least an additional 20% of patients will have a clinically relevant response to VX-445/TEZ/IVA compared to TEZ/IVA. However, this would be a useful comparison if the F/any paradigm would be well demonstrated (which currently is not), and therefore by extension that it could be accepted that all genotypes with one F can be assumed to respond sufficiently.

Moreover, the comparisons are based on cross-study comparisons with different populations, which introduces uncertainties and these comparisons cannot be considered as additional evidence for the F/any paradigm or to support extrapolation of findings in the F/MF population to the F/G and F/RF populations. The CHMP maintained that the F/any hypothesis has not been conclusively demonstrated. As such, the F/G and F/RF require their own demonstration of clinical efficacy and safety. It is

considered that these comparisons while interesting, do not obviate the need for robust, comparative, clinical data in F/G and F/RF patients from clinical trials.

Real world clinical data

Upon request by CHMP, the Applicant provided real world data from the US Cystic Fibrosis Foundation Patient Registry (CFFPR) for **F/RF** and **F/G** and also F/F and F/MF patients treated with VX-445/TEZ/IVA.

F/RF and F/G patients who started with VX-445/TEZ/IVA therapy between 21 October 2019 and 31 December 2019 (n=521), who had a lung function measurement at baseline and follow-up (n=297, 57%) were included in the analyses. Only ppFEV1 values were provided, as other efficacy parameters are not routinely measured. The registry data from the F/MF and F/F patient population showed results in line with the effects observed in studies 102 and 103.

Unfortunately, the U.S. CFFPR data presented are in itself limited and not sufficiently detailed, and as such raised several questions such as the exact modulator therapy used, the duration of use which is not known, as well as included specific genotypes and individual patient efficacy data which are not presented. Unavailability of such information is inherent to registry data but does introduce uncertainties. It can also be questioned whether the patients in the analysis set can be considered sufficiently representative of the overall F/G and F/RF populations to draw conclusions on these populations.

Based on the available data, improvements in ppFEV1 were seen in the 136 F/G and 161 F/RF populations of 4.3% and 2.7% respectively. These improvements are observed on top of approved therapies as at least 90% of the patients were exposed to at least one other *CFTR* modulator. However, it appeared that patients only needed record of exposure to *CFTR* modulators in 2019; hence it is possible that some patients may not have been current users of *CFTR* modulators at the time of starting triple therapy, and as such the 'experienced' figures presented may be an overestimation.

Bearing in mind the limitations and questions arising from the registry data, the magnitude of the additional response from treatment with VX445/TEZ/IVA over prior *CFTR* therapies is limited. It is unexpected that the F/G group had greater efficacy compared to the F/RF population. Indeed, in view of the limited efficacy observed in clinical trials for F/RFs patients treated with TEZ/IVA compared patients with G/any mutations treated with IVA, it would be considered that F/RF group should have had more potential for improvement with VX445/TEZ/IVA by treating the F allele.

It is however agreed that effect size estimates in these real-world analyses are not directly comparable to results from a clinical study in which data are collected in a controlled setting. For example, the ppFEV1 data from the pivotal clinical studies were captured and analysed after a 4-week treatment duration (Studies 102 and 103) and a 24-week treatment duration (Study 102). In contrast, ppFEV1 measurements used in this analysis of CFFPR data were captured at different time points following initiation of VX-445/TEZ/IVA treatment reflecting the real-world nature of data collection in routine clinical practice (from <28 days to over 90 days, with the mean exposure duration of 65.6 days for F/MF patients and 65.4 days for F/F patients, as noted above). Additionally, spirometry data collected in the CFFPR has greater variability because the assessment is performed at a local site using local equipment compared to the standardized equipment and protocols used in a clinical study.

An Oral Explanation was held in June 2020 CHMP meeting, in order to discuss the F/any hypothesis and efficacy data supporting the broad indication applied for F/any population.

The CHMP welcomed the registry data but considered these data inherently limited and hence subject to bias. Furthermore, the data are not complete enough to reliably demonstrate the efficacy and safety of VX445/TEZ/IVA in F/G and F/RF patients. In conclusion the CHMP was of the view that the registry

data do not obviate the need for robust, comparative, clinical efficacy and safety data in F/G and F/RF patients from randomized controlled clinical studies.In conclusion, the cross-study comparison responder analysis and the registry data on its own without the ongoing clinical trial (study 104) data in F/G and F/RF mutations do not sufficiently support the added benefit over approved modulator therapies. Therefore, the CHMP considered that the efficacy has been demonstrated only in patients with F/F and F/MF mutations where randomized clinical trial data are available.

Study 104

The data of study 104 in F/G and F/RF patients should contribute to the understanding of the efficacy in the F/RF and F/G patient populations. The Applicant was therefore encouraged to submit results of the clinical study 104 as soon as possible in a variation procedure for further assessment to which, they agreed.

There is a positive B/R identified both for F/MF patients with unmet medical need due to absence of treatment available and for (F/F) patients. Therefore, the CHMP did not agree with the request of the Applicant to wait for the data of study 104 as any further delay in CHMP opinion is considered not feasible/acceptable.

Proposed indication

Indication
The Applicant requested the following indication: "*Kaftrio (VX-445/TEZ/IVA) is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene."*

Within the current submission, the applicant only provided clinical trial data for the **F/MF** and **F/F** patient populations. Clinically relevant improvements were reached in both patient populations with the VX-445/TEZ/IVA triple combination. Considering the absence of a VX-445 monotherapy and VX-445/IVA therapy as control arms, the demonstration of efficacy of each of the components of the triple combination cannot be established in a clinical setting. Although uncertainties remain on the contribution of all components, as not all combination were tested in a clinical setting in line with the FDC guideline, the *in vitro* data, the highly relevant clinical benefit and the well-tolerated safety profile of this product were considered relevant enough to outweigh this particular uncertainty in the F/MF and F/F populations.

The Applicant introduced a new "paradigm". They consider that if a *CFTR* modulator has a large effect on the *F508del-CFTR*, then the presence of only a single *F508del* allele would be sufficient to derive a clinical benefit. The Applicant considers that "*CF patients with an F508del allele (F) and a minimal function allele (MF) that does not produce protein provide the key test for this hypothesis because any benefit can only be derived from the F508del allele.*"

Assessment of qualification under "criterion 2", required a robust validated *in vitro in vivo* correlation per mutation so that we can be confident that patients with that specific mutation will also not respond. The applicant assumed that if in the FRT cells no response is seen, also clinically the mutation will not be corrected by the triple combination. Whether such a "negative" IVIV correlation exists is not known and has not been demonstrated.

Overall, it is acknowledged that criterion 1 and criterion 2 patients both showed a relevant effect on ppFEV1 in subgroup analysis. Furthermore, significant and consistent improvements were seen in each mutation subcategory within MF Class I (splice, nonsense, and indel-frameshift). In subgroup analysis of clinical results (and even though numbers are small), in criterion 2 F/MF patients showed clinically

relevant improvement in ppFEV1 and sweat chloride, regardless of whether the MF mutation responded or didn't respond to VX-445/TEZ/IVA in FRT testing.

Theoretically, it is still possible that some of the MF mutants may make a minor contribution to the *CFTR*-mediated chloride transport upon treatment with VX-445/TEZ/IVA. The totality of evidence consists of:

- Majority of the mutations in study 102 are Class I mutations and show improved ppFEV1 and SwCl.
  - 87% of the class I mutants has a PTC before the NBD2 domain and are likely not to form a functional protein. In this subgroup the ppFEV1 improvement is 13.2% (10.4, 16.0) which is consistent with the overall study population.
  - G542X (n=65 in study 102) and R553X (used in HBE cells) do not form a protein. These alleles form half of the nonsense mutations subgroup which shows similar clinical benefit as the FAS. In a subgroup analysis for G542X specifically an ppFEV1 improvement of 13.6% (9.4, 17.7) is seen.
- CF patients with the F/MF criterion 2 show substantial clinical benefit, derived by the F508del allele.
  - Clinical results of non-responsive and responsive criterion 2 mutations suggest that effect is mediated by the F508del allele.
- Result in different studies, with specific collection of MF mutants, show consistent efficacy results.
  - Results seen in the different studies in which F/MF CF patients were participating show highly consistent efficacy results (within group).
  - The subgroups in genotypes and FRT responsiveness show highly similar results.
  - Result is consistent with effect seen in the F/F population.

Overall, based on the pre-clinical data, clinical data and the lack of evidence that all criterion 1 MF mutations do not form a protein, it is not accepted by CHMP that all MF Class I mutations are equal and that no protein is produced in each and every case. Therefore, the *F508del*-only treatment paradigm has not been adequately substantiated.
Considering the vast number of Class I mutations and the impracticality of providing empirical evidence for each case due to the nature of obtaining sufficient independent HBE cell lines from transplant donors, no further preclinical data is requested in this regard for the F/MF and F/F populations to explore the Applicant hypothesis.

The consistent results in the F/MF population subgroups, together with the magnitude of the efficacy observed indicate that extrapolation to untested MF mutations can however be accepted. Additionally, it is considered important for the prescriber to mention the list of mutations studied in section 5.1 of the SmPC and that not all mutations have been clinically tested in studies 102 and 103.

In addition, the Applicant agreed to expand the efficacy information of VX-445/TEZ/IVA (overall and per genotype subgroup) by providing registry data from a PASS.

Extrapolation to the F/RF and F/G CF patients.

The proposed indication includes all patients with at least one *F508del* allele (independent of the second allele), which is based on the above-mentioned *F508del* only paradigm. Therefore, also patients for whom already an approved modulator regimen exists will be included in the indication (F/RF and F/G). As indicated above, the Applicant hypothesis is not considered sufficiently demonstrate to allow for extrapolation in F/RF and robust, comparative clinical trial data are required. Furthermore, the additional benefit of Kaftrio over existing licensed treatments for F/G and F/RF patients has not been quantified in these populations.

2.5.4. Conclusions on clinical efficacy

Clinically relevant improvement is achieved in both the F/MF and F/F patient populations with the VX-445/TEZ/IVA triple combination compared to placebo or TEZ/IVA, respectively. Due to the absence of a VX-445 monotherapy and VX-445/IVA therapy as control arms, the requirement of demonstration of efficacy for all three compounds as required in the FDC guideline cannot be established based on clinical data. However, the *in vitro* data, the highly relevant clinical benefit and the well-tolerated safety profile could be considered relevant enough to outweigh this uncertainty in the F/MF and F/F patient populations.

It is theoretically still possible that some of the MF mutants may make a minor contribution and the *F508del*-only treatment paradigm has not been definitively substantiated. Nevertheless, the consistent results in the F/MF population subgroups indicate that extrapolation to untested MF mutations can be accepted.

Clinical data on the F/RF and F/G are limited to registry data with its inherent limitation and bias and is therefore not considered to reliably demonstrate the efficacy and safety of VX445/TEZ/IVA in F/G and F/RF patients.

Therefore, the CHMP is of the opinion that the added benefit of Kaftrio in the F/RF and F/G population over approved therapies has not been sufficiently justified. Any further delay in CHMP opinion (and awaiting the results of study 104) is not agreed in the context of patients for which there is a positive B/R identified (F/F and F/FM) and absence of treatment available (F/MF). The data of study 104 are necessary to be able to conclude on a B/R for this patient population and to support the broad *F508del*/any indication. Whether these future data are sufficient will be a matter of assessment. The applicant agreed to submit those data in the post-marketing setting (type II variation).

In conclusion, positive clinical efficacy is only considered demonstrated in the F/MF and F/F populations. The final indication granted by CHMP is as follows:

"Kaftrio is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or heterozygous for F508del in the CFTR gene with a minimal function (MF) mutation."

2.6. Clinical safety

The clinical safety database included 10 clinical studies with VX-445 as a monotherapy or as part of a TC regimen, including 5 completed Phase 1 studies (Study 002 (OC DDI), 003 (ADME), 005 (FDC BA), 006(DDI) and 009 (QT/QTc), 1 completed Phase 1/2 study (Study 001), 2 completed Phase 3 studies (102 and 103), and 2 ongoing Phase 3 studies (study 105 - long term safety and study and 106 - safety and PK).

Core Safety Analyses

The core safety analyses in CF subjects evaluated data from Study 102, Study 103, and an interim analysis (IA) of the open-label extension Study 105. A second interim analysis (IA2) was submitted with the response to the first CHMP LoQ.

Safety data from Studies 102 and 103 were not pooled in the core safety analysis because of the substantial differences in the designs of the 2 studies. These differences involve especially treatment duration, use of different comparator groups i.e. a placebo group in Study 102 and an active comparator in study 103. Because of these differences, pooling the data could confound the comparison between VX-445/TEZ/IVA and placebo in Study 102.

- The Study 102 Safety Set contains all subjects who received at least 1 dose of study drug.
- The Study 103 Safety Set for the Treatment Period (hereafter the Study 103 Safety Set) includes all subjects who received at least 1 dose of study drug in the Study 103 Treatment Period (i.e., does not include subjects who were only dosed in the TEZ/IVA Run-in Period).
- The Study 105 Safety Set includes all subjects who received at least 1 dose of study drug in Study 105.
- The Cumulative Safety Set includes all subjects who received at least 1 dose of VX-445/TEZ/IVA during the parent Studies 102 or 103 and/or during Study 105.
    - Selected safety analyses were performed for the subset of subjects in the Cumulative Safety Set who received ≥48 weeks of treatment with VX-445/TEZ/IVA.

In addition, supportive safety analyses were submitted for various doses of VX-445 and multiple treatment regimens (different TC regimens) in study 001 and ongoing Study 106 in CF subjects 6 through 11 years of age.

All data are from the second interim analysis (IA2), unless otherwise indicated.

Patient exposure

Subject demographics and baseline characteristics were similar between treatment groups in both Study 102 (VX-445/TEZ/IVA and placebo groups) and Study 103 (VX-445/TEZ/IVA and TEZ/IVA groups). The demography and baseline characteristics of these Phase 3 study populations were also representative of the CF population for the proposed indication.

Exposure data

The mean exposure duration to VX-445/TEZ/IVA was 23.6 weeks in Study 102, 4.0 weeks in Study 103 and 21.5 weeks in Study 105.

Over 700 unique subjects received at least 1 dose of VX-445 as monotherapy or as part of a TC regimen.

At the time of IA1 (study 105), in the Cumulative Safety Set (parent Studies 102 or 103 and/or during Study 105), 146 subjects had an exposure of ≤ 24 weeks, 307 subject > 24 ≤ 48 weeks, 58 subjects ≥ 48 weeks and 56 subjects > 48 weeks.

The Study 105 IA2 Safety Set included 506 subjects, who had a mean exposure duration of 37.2 weeks, representing 392.2 patient-years of exposure. The Cumulative Safety Set included 510 subjects who had a mean exposure duration of 46.7 weeks, representing 496.6 patient-years of exposure. A subset of 271 subjects received ≥48 weeks of VX-445/TEZ/IVA treatment and had a mean exposure of 57.2 weeks.

The safety profile of VX-445 in combination with TEZ/IVA was derived primarily from Study 102, a 24-week, placebo-controlled study in CF subjects, with the largest exposed population and the longest treatment duration. In addition, safety data from two interim analyses (IA1 and IA2) of the ongoing OLE Study 105 (as of the data cut-off date of 10 July 2019 and 31 October 2019, respectively) are also summarized.

Table 36: Summary of Exposure: Open Label (OL) Safety Period and Cumulative Safety and Set of Subjects with Cumulative Exposure of ⩾ 48 Weeks–

	Study 105 IA2 Safety Set	Cumulative Safety Set	Cumulative Safety Set Exposure ≥ 48 weeks
	Any VX-445/TEZ/IVA N = 506	Any VX-445/TEZ/IVA N = 510	Any VX-445/TEZ/IVA N = 271
Total exposure (patient-years)	392.2	496.6	322.7
Exposure duration (weeks)			
n	506	510	271
Mean (SD)	37.2 (8.92)	46.7 (13.31)	57.2 (6.09)
Median	36.5	49.0	55.1
Min, max	1.4, 55.4	1.0, 69.1	48.0, 69.1
Exposure duration by interval, n (%)			
≤24 weeks	13 (2.6	12 (2.4)	0
>24 to ≤48 weeks	443 (87.5)	229 (44.9)	0
>48 weeks to ≤72 weeks	50 (9.9)	269 (52.7)	271 (100.0) [a]

Sources: ISA2/Table 2.1.1.1, Table 2.1.1.2, and Ad Hoc Table 2.1.1.4
IA: interim analysis; IVA: ivacaftor; n: size of subsample; N: total sample size; NA: not applicable; OL: open label; TEZ: tezacaftor
[a]Number of subjects in the Cumulative Safety Period with exposure of ≥48 to ≤72 weeks.
Notes: Total exposure was defined as the sum total of the VX-445/TEZ/IVA exposure across all subjects in the applicable IA2 Safety Set (Study 105 or Cumulative). Duration of VX-445/TEZ/IVA exposure (weeks) = ([last dose date – first dose date] in the applicable Treatment-emergent Period + 1)/7, regardless of any interruptions in dosing. For subjects who were still on VX-445/TEZ/IVA at the IA2 data cutoff date, this date was used as the last dose date to calculate the duration of VX-445/TEZ/IVA exposure. Duration of
VX-445/TEZ/IVA exposure (years) = duration of VX-445/TEZ/IVA exposure (weeks)/48; 1 year = 48 weeks.

Adverse events

The overview of AEs in Study 102 Safety Set, and Study 105 Safety Set (OLE) is presented in Table 37. The details are provided per safety set.

Study 102 Safety Set

The incidence of subjects with at least 1 AE was 93.1% in the VX-445/TEZ/IVA group and 96.0% in the placebo group. Twenty-eight (13.9%) subjects in the VX-445/TEZ/IVA group and 42 (20.9%) subjects in the placebo group had serious AEs (SAEs). The majority of subjects had AEs that were mild or moderate in severity. Nineteen (9.4%) subjects in the VX-445/TEZ/IVA group and 10 (5.0%) subjects in the placebo group interrupted study drug due to AEs.

Two (1.0%) subjects in the VX-445/TEZ/IVA group and no subjects in the placebo group discontinued study drug due to AEs. There were no deaths, and no subjects in the VX-445/TEZ/IVA group had life-threatening AEs.

Study 103 Safety Set

The incidence of subjects with at least 1 AE was 58.2% in the VX-445/TEZ/IVA group and 63.5% in the TEZ/IVA group. Two (3.6%) subjects in the VX-445/TEZ/IVA group and 1 (1.9%) subject in the TEZ/IVA group had SAEs. The majority of subjects had AEs that were mild or moderate in severity. No subjects had AEs that led to study drug interruption or discontinuation. There were no deaths or life-threatening AEs.

Study 105

IA1

A total of 424 (84.0%) of subjects had at least 1 AE and 55 (10.9%) subjects had at least 1 SAE. The majority of subjects had AEs that were mild or moderate in severity; 2 (0.4%) subjects had life-threatening AEs. Twenty-five (5.0%) subjects interrupted study drug due to AEs, and 6 (1.2%) subjects discontinued study drug due to AEs. There were no deaths.

IA2

In the IA2, 471 (93.1%) subjects had at least 1 AE and 80 (15.8%) subjects had at least 1 serious adverse event (SAE). The majority AEs were mild or moderate in severity; 2 (0.4%) subjects had life-threatening AEs. Twenty-nine (5.7%) subjects interrupted VX-445/TEZ/IVA due to AEs, and 7 (1.4%) subjects discontinued VX-445/TEZ/IVA due to AEs. There were no deaths.

Table 37:Overview of AEs (Study 102 Safety Set and Study 105 Safety Set IA2)

	Study 102				OLS	
	PBO in 445-102 N = 201		VX-445/TEZ/IVA in 445-102 N = 202		Any VX-445/TEZ/IVA N = 506	
	n (%)	Events/100PY	n (%)	Events/100PY	n (%)	Events/100PY
Number of AEs (Total)	1287	--	1098	--	2909	--
Total duration of safety analysis period in 100 PY	--	1.00	--	1.00	--	3.93
Subjects with any AEs	193 (96.0)	1287.96	188 (93.1)	1096.01	471 (93.1)	739.87
Subjects with AEs by strongest relationship						
Not related	83 (41.3)	--	53 (26.2)	--	175 (34.6)	--
Unlikely related	58 (28.9)	--	39 (19.3)	--	127 (25.1)	--
Possibly related	46 (22.9)	--	86 (42.6)	--	146 (28.9)	--
Related	6 (3.0)	--	10 (5.0)	--	23 (4.5)	--
Subjects with AEs by maximum severity						
Mild	53 (26.4)	--	67 (33.2)	--	180 (35.6)	--
Moderate	125 (62.2)	--	102 (50.5)	--	238 (47.0)	--
Severe	14 (7.0)	--	19 (9.4)	--	51 (10.1)	--
Life-threatening	1 (0.5)	--	0	--	2 (0.4)	--
Missing	0	--	0	--	0	--
Subjects with AEs leading to VX-445/TEZ/IVA discontinuation	0	0	2 (1.0)	2.99	7 (1.4)	3.31
Subjects with AEs leading to VX-445/TEZ/IVA interruption	10 (5.0)	14.01	19 (9.4)	25.95	29 (5.7)	13.73
Subjects with Grade 3/4 AEs[a]	15 (7.5)	23.02	19 (9.4)	27.95	53 (10.5)	19.84
Subjects with related AEs[b]	52 (25.9)	140.10	96 (47.5)	210.62	169 (33.4)	97.92
Subjects with serious AEs	42 (20.9)	67.05	28 (13.9)	36.93	80 (15.8)	27.47
Subjects with related serious AEs[b]	2 (1.0)	2.00	6 (3.0)	5.99	13 (2.6)	5.09
Subjects with AEs leading to death	0	0	0	0	0	0

Source: ISA2 Table 2.3.1.1.1

AE: adverse event; IVA: ivacaftor; n: size of subsample; N: total sample size; PBO: placebo; PY: patient-year; SAE: serious adverse event; TEZ: tezacaftor

Note: A subject with multiple events within a category was counted only once in that category.

[a] Grade 3 indicates events of severe intensity; Grade 4 indicates events that were life-threatening.

[b] Related AEs and SAEs included related, possibly related, and missing categories.

Table 38: AEs With an Incidence of At Least 5% by PT (Study 102 Safety Set and Study 105 Safety Set) Treatment-emergent AEs

	Study 102				OLS	
	PBO in 445-102 N = 201		VX-445/TEZ/IVA in 445-102 N = 202		Any VX-445/TEZ/IVA N = 506	
Preferred Term	**n (%)**	**Events/100PY**	**n (%)**	**Events/100PY**	**n (%)**	**Events/100PY**
Total duration of safety analysis period in 100 PY	--	1.00	--	1.00	--	3.93
Subjects with any AEs	193 (96.0)	1287.96	188 (93.1)	1096.01	471 (93.1)	739.87
Infective PEx of CF	95 (47.3)	181.13	44 (21.8)	64.88	127 (25.1)	49.60
Cough	77 (38.3)	113.08	34 (16.8)	38.93	118 (23.3)	44.26
Oropharyngeal pain	25 (12.4)	26.02	20 (9.9)	26.95	74 (14.6)	25.69
Nasopharyngitis	26 (12.9)	34.03	22 (10.9)	29.95	69 (13.6)	21.62
Headache	30 (14.9)	42.03	35 (17.3)	48.91	66 (13.0)	24.93
Sputum increased	39 (19.4)	47.03	40 (19.8)	46.91	63 (12.5)	20.60
Upper respiratory tract infection	22 (10.9)	26.02	24 (11.9)	29.95	60 (11.9)	18.31
Fatigue	20 (10.0)	22.02	9 (4.5)	8.98	51 (10.1)	16.28
Nasal congestion	15 (7.5)	18.01	19 (9.4)	20.96	48 (9.5)	16.79
Pyrexia	19 (9.5)	25.02	17 (8.4)	17.97	44 (8.7)	12.46
Diarrhoea	14 (7.0)	23.02	26 (12.9)	31.94	38 (7.5)	10.43
Haemoptysis	28 (13.9)	42.03	11 (5.4)	11.98	36 (7.1)	15.77
Rash	9 (4.5)	12.01	19 (9.4)	24.95	35 (6.9)	11.19
Nausea	14 (7.0)	17.01	16 (7.9)	15.97	32 (6.3)	8.65
Blood creatine phosphokinase increased	9 (4.5)	9.01	19 (9.4)	19.96	31 (6.1)	8.90
Sinusitis	8 (4.0)	8.01	11 (5.4)	14.97	31 (6.1)	10.17
Sinus congestion	8 (4.0)	10.01	7 (3.5)	7.99	29 (5.7)	8.90
Abdominal pain	12 (6.0)	20.01	20 (9.9)	23.96	27 (5.3)	7.63
ALT increased	7 (3.5)	8.01	20 (9.9)	21.96	27 (5.3)	7.88
AST increased	4 (2.0)	4.00	19 (9.4)	20.96	27 (5.3)	7.88
Rhinitis	11 (5.5)	14.01	15 (7.4)	17.97	27 (5.3)	8.39
Vomiting	10 (5.0)	13.01	12 (5.9)	13.97	27 (5.3)	8.39

Source: ISA2 Table 2.3.1.3

AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; CF: cystic fibrosis; IVA: ivacaftor; n: size of subsample; N: total sample size; PBO: placebo; PEx: pulmonary exacerbation; PT: Preferred Term; PY: patient-year; TEZ: tezacaftor

Notes: MedDRA Version 22.1 was used. A subject with multiple events within a category was counted only once in that category. The table was sorted in descending order of frequency by PT.

With a sensitivity analysis with different cut-off for % of AEs, following AEs were observed (Table 39).

Table 39 AEs Occuring ≥8%, ≥5% and ≥3% of VX-445/TEZ/IVA-treated Subjects With an Incidence ≥1% Higher Compared to Placebo: Study102 Safety Set

Adverse Reaction (Preferred Term)	Placebo N = 201 n (%)	VX-445/TEZ/IVA N = 202 n (%)
Cutoff of ≥8% in VX-445/TEZ/IVA-treated Subjects		
Headache	30 (14.9)	35 (17.3)
Diarrhoea	14 (7.0)	26 (12.9)
Upper respiratory tract infection	22 (10.9)	24 (11.9)
Abdominal pain	12 (6.0)	20 (9.9)
ALT increased	7 (3.5)	20 (9.9)
AST increased	4 (2.0)	19 (9.4)
Blood creatine phosphokinase increased	9 (4.5)	19 (9.4)
Nasal congestion	15 (7.5)	19 (9.4)
Rash	9 (4.5)	18 (8.9)
Rhinorrhoea	6 (3.0)	17 (8.4)
Cutoff of ≥5% in VX-445/TEZ/IVA-treated Subjects		
Rhinitis	11 (5.5)	15 (7.4)
Influenza	3 (1.5)	14 (6.9)
Sinusitis	8 (4.0)	11 (5.4)
Blood bilirubin increased	2 (1.0)	10 (5.0)
Cutoff of ≥3% in VX-445/TEZ/IVA-treated Subjects		
Abdominal pain upper	6 (3.0)	9 (4.5)
Flatulence	3 (1.5)	9 (4.5)
Hypoglycaemia	2 (1.0)	9 (4.5)
Respiration abnormal	4 (2.0)	9 (4.5)
Viral upper respiratory tract infection	4 (2.0)	9 (4.5)
Acne	3 (1.5)	7 (3.5)
C-reactive protein increased	4 (2.0)	7 (3.5)
Dizziness	5 (2.5)	7 (3.5)
Pharyngitis	2 (1.0)	6 (3.0)
Pruritus	0	6 (3.0)
Wheezing	2 (1.0)	6 (3.0)

Source: Study 102 CSR/Table 14.3.1.3

ADR: adverse drug reaction; ALT: alanine transaminase; AST: aspartate transaminase; IVA: ivacaftor; n: size of subsample; N: total sample size; PT: Preferred Term; TEZ: tezacaftor

Notes: AEs were coded with MedDRA version 22.0. A subject with multiple events within a category was counted only once in that category. The table was sorted in descending order of frequency of the VX-445/TEZ/IVA column by PT.

Cumulative Safety Set

In IA1, a total of 470 (92.3%) subjects had at least 1 AE. The majority of subjects had AEs that were mild or moderate in severity. Two (0.4%) subjects had life-threatening AEs. SAEs were reported in 72 (14.1%) subjects. Nine (1.8%) subjects discontinued study drug due to AEs.

In IA2, the Cumulative Safety Set included safety data from all 510 subjects. A total of 488 (95.7%) subjects had at least 1 AE. The majority of subjects had AEs that were mild or moderate in severity. Two (0.4%) subjects had life-threatening AEs. SAEs were reported in 93 (18.2%) subjects. Ten (2.0%) subjects discontinued VX-445/TEZ/IVA due to AEs.

Overall, results from the Cumulative Safety Set were consistent with the safety data presented individually for Studies 102 and 103, as well as for Study 105.

Safety in Subjects Who Received VX-445/TEZ/IVA for At Least 48 Weeks

In IA1, a total of 57 (98.3%) subjects had at least 1 AE.

In IA2, a total of 265 (97.8%) subjects had at least 1 AE. The exposure-adjusted event rates for the majority of AEs were similar or lower than in the Study 102 VX-445/TEZ/IVA group. The majority of subjects had AEs that were mild or moderate in severity (63 mild (23.2%), 161 moderate (59.4%), 41 severe (15.1%)). There were no life-threatening AEs.
A total of 50 (18.5%) subjects had at least 1 SAE. The exposure-adjusted rates for SAEs were similar or lower than in the Study 102 VX-445/TEZ/IVA group.

No subjects had AEs that led to treatment discontinuation; 26 (9.6%) subjects had AEs that led to treatment interruption.

Overview of AEs in Healthy Subjects

In the pooled analysis of Phase 1 Studies in Healthy Subjects, 43 (22.5%) subjects in the Any VX-445 group and 13 (24.1%) subjects in the placebo group had at least 1 AE. In both groups, the majority of AEs were mild in severity; there were no SAEs or deaths. One (1.9%) subject in the placebo group had a severe AE.

There were 2 (1.0%) subjects in the Any VX-445 group and 1 (1.9%) subject in the placebo group who had AEs that led to treatment discontinuation. There were no AEs that led to treatment interruption in any group.

Common AEs

The AEs with an incidence of ≥5% of Study 102 Safety Set, and Study 105 Safety Set (OLE) is presented in Table 40. The details are provided per safety set.

Study 102 Safety Set

Overall, the AEs were mostly consistent with common manifestations of CF disease or with common illnesses in CF subjects 12 years of age and older.

AEs occurring in ≥8% of subjects in the VX-445/TEZ/IVA group with an incidence ≥1% higher than in the placebo group were headache, diarrhoea, upper respiratory tract infection, abdominal pain, alanine transaminase (ALT) increased, aspartate transaminase (AST) increased, blood creatine phosphokinase increased, nasal congestion, rash, and rhinorrhoea; each occurred in ≤20% of subjects in the VX-445/TEZ/IVA group.

Among the AEs with an incidence of ≥5% in any group, AEs occurring in < 8% of subjects in the VX-445/TEZ/IVA group with an incidence ≥1% higher than in the placebo group were, sinusitis, rhinitis, influenza, and blood bilirubin increased.

Blood bilirubin increased was observed with VX-445/TEZ/IVA treatment; this finding is consistent with the OATP1B1 and OATP1B3 transporter inhibition effect by VX-445.

The study was conducted through the winter season, and most of the AEs of influenza occurred during that time. In the VX-445/TEZ/IVA group, none of the AEs of influenza were considered related to study drug and all subjects continued study drug dosing, except 2 subjects who resumed treatment after an interruption.

Lastly, there was a lower rate of AEs reported in the infections and infestations SOC overall in the VX-445/TEZ/IVA group compared with the placebo group.

Study 103 Safety Set,

In the Study 103 Safety Set, Study 105 Safety Set and Cumulative Safety Set, among the AEs with an incidence of ≥5% in any group, the AEs were mostly consistent with common manifestations of CF disease or with common illnesses in CF subjects 12 years of age and older. Table 40 presents the AEs with an incidence of ≥5% in any group.

Table 40: AEs With an Incidence of At Least 5% in Any Group by PT: Study 103 Safety Set

	Treatment Period	
	TEZ/IVA N = 52	VX-445/TEZ/IVA N = 55
Preferred Term	**n (%)**	**n (%)**
Subjects with any AEs	33 (63.5)	32 (58.2)
Cough	4 (7.7)	8 (14.5)
Nasopharyngitis	2 (3.8)	4 (7.3)
Oropharyngeal pain	0	4 (7.3)
Upper respiratory tract infection	2 (3.8)	4 (7.3)
Abdominal pain	1 (1.9)	3 (5.5)
Fatigue	2 (3.8)	3 (5.5)
Headache	4 (7.7)	3 (5.5)
Nasal congestion	1 (1.9)	3 (5.5)
Respiration abnormal	0	3 (5.5)
Sputum increased	3 (5.8)	3 (5.5)
Diarrhoea	3 (5.8)	2 (3.6)
Haemoptysis	5 (9.6)	2 (3.6)
Infective PEx of CF	6 (11.5)	1 (1.8)
Nausea	3 (5.8)	1 (1.8)

Source: Study 103 CSR/Table 14.3.1.3

AE: adverse event; CF: cystic fibrosis; IVA: ivacaftor; n: size of subsample; N: total sample size; PEx: pulmonary exacerbation; PT: Preferred Term; TEZ: tezacaftor

Notes: MedDRA Version 21.1 was used. A subject with multiple events within a category was counted only once in that category. The table was sorted in descending order of frequency of the VX-445/TEZ/IVA column by PT.

Study 105 Safety Set

The exposure-adjusted event rates for the majority of AEs were similar or lower in Study 105 than in the Study 102 VX-445/TEZ/IVA group.

In IA2, 471 (93%) subjects experienced an AE. The AEs were mostly consistent with common manifestations of CF disease or with common illnesses in CF subjects 12 years of age and older.

The exposure-adjusted event rates for the majority of AEs were similar or lower in Study 105 than in the Study 102 VX-445/TEZ/IVA group. Table 41 presents the AEs with an incidence of ≥5%.

Table 41 AEs With an Incidence of At Least 5% by PT (Study 102 Safety Set and Study 105 Safety Set) Treatment-emergent AEs

	Study 102				OLS	
	PBO in 445-102 N = 201		VX-445/TEZ/IVA in 445-102 N = 202		Any VX-445/TEZ/IVA N = 506	
Preferred Term	n (%)	Events/100PY	n (%)	Events/100PY	n (%)	Events/100PY
Total duration of safety analysis period in 100 PY	--	1.00	--	1.00	--	3.93
Subjects with any AEs	193 (96.0)	1287.96	188 (93.1)	1096.01	471 (93.1)	739.87
Infective PEx of CF	95 (47.3)	181.13	44 (21.8)	64.88	127 (25.1)	49.60
Cough	77 (38.3)	113.08	34 (16.8)	38.93	118 (23.3)	44.26
Oropharyngeal pain	25 (12.4)	26.02	20 (9.9)	26.95	74 (14.6)	25.69
Nasopharyngitis	26 (12.9)	34.03	22 (10.9)	29.95	69 (13.6)	21.62
Headache	30 (14.9)	42.03	35 (17.3)	48.91	66 (13.0)	24.93
Sputum increased	39 (19.4)	47.03	40 (19.8)	46.91	63 (12.5)	20.60
Upper respiratory tract infection	22 (10.9)	26.02	24 (11.9)	29.95	60 (11.9)	18.31
Fatigue	20 (10.0)	22.02	9 (4.5)	8.98	51 (10.1)	16.28
Nasal congestion	15 (7.5)	18.01	19 (9.4)	20.96	48 (9.5)	16.79
Pyrexia	19 (9.5)	25.02	17 (8.4)	17.97	44 (8.7)	12.46
Diarrhoea	14 (7.0)	23.02	26 (12.9)	31.94	38 (7.5)	10.43
Haemoptysis	28 (13.9)	42.03	11 (5.4)	11.98	36 (7.1)	15.77
Rash	9 (4.5)	12.01	19 (9.4)	24.95	35 (6.9)	11.19
Nausea	14 (7.0)	17.01	16 (7.9)	15.97	32 (6.3)	8.65
Blood creatine phosphokinase increased	9 (4.5)	9.01	19 (9.4)	19.96	31 (6.1)	8.90
Sinusitis	8 (4.0)	8.01	11 (5.4)	14.97	31 (6.1)	10.17
Sinus congestion	8 (4.0)	10.01	7 (3.5)	7.99	29 (5.7)	8.90
Abdominal pain	12 (6.0)	20.01	20 (9.9)	23.96	27 (5.3)	7.63
ALT increased	7 (3.5)	8.01	20 (9.9)	21.96	27 (5.3)	7.88
AST increased	4 (2.0)	4.00	19 (9.4)	20.96	27 (5.3)	7.88
Rhinitis	11 (5.5)	14.01	15 (7.4)	17.97	27 (5.3)	8.39
Vomiting	10 (5.0)	13.01	12 (5.9)	13.97	27 (5.3)	8.39

Source: ISA2 Table 2.3.1.3

AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; CF: cystic fibrosis; IVA: ivacaftor; n: size of subsample; N: total sample size; PBO: placebo; PEx: pulmonary exacerbation; PT: Preferred Term; PY: patient-year; TEZ: tezacaftor

Notes: MedDRA Version 22.1 was used. A subject with multiple events within a category was counted only once in that category. The table was sorted in descending order of frequency by PT.

Cumulative Safety Set

The AEs were mostly consistent with common manifestations of CF disease or with common illnesses in CF subjects 12 years of age and older. Overall, results from the Cumulative Safety Set were consistent with the safety data from parent Studies 102 and 103, as well as for Study 105.

Subjects who received VX-445/TEZ/IVA for at least 48 weeks

In the set of subjects who received VX-445/TEZ/IVA for at least 48 weeks, 57 (98.3%) subjects had at least 1 AE. In IA2, a total of 265 (97.8%) subjects had at least 1 AE. The AEs were mostly consistent with common manifestations of CF disease or with common illnesses in CF subjects 12 years of age and older or with the safety profile for VX-445/TEZ/IVA of study 102 and study 105.

AEs that occurred in ≥5% of subjects who received VX-445/TEZ/IVA for at least 48 weeks cumulatively across studies (as of Study 105 IA2) are summarized in Table 42.

Table 42: AEs With an Incidence of At Least 5% by PT: Subjects With Cumulative TC Exposure of At Least 48 Weeks

Preferred Term	Any VX-445/TEZ/IVA N = 271 n (%)
Subjects with any AEs	256 (94.5)
Infective PEx of CF	97 (35.8)
Cough	87 (32.1)
Sputum increased	69 (25.5)
Oropharyngeal pain	68 (25.1)
Headache	60 (22.1)
Upper respiratory tract infection	59 (21.8)
Nasopharyngitis	52 (19.2)
Nasal congestion	48 (17.7)
Diarrhoea	43 (15.9)
Fatigue	40 (14.8)
Blood creatine phosphokinase increased	39 (14.4)
Pyrexia	39 (14.4)
Abdominal pain	34 (12.5)
ALT increased	33 (12.2)
Rash	33 (12.2)
Sinusitis	32 (11.8)
Rhinorrhoea	30 (11.1)
AST increased	29 (10.7)
Haemoptysis	29 (10.7)
Nausea	28 (10.3)
Vomiting	27 (10.0)
Rhinitis	26 (9.6)
Influenza	25 (9.2)
Productive cough	22 (8.1)
Respiration abnormal	22 (8.1)
Sinus congestion	22 (8.1)
Abdominal pain upper	18 (6.6)
Constipation	17 (6.3)
Dyspnoea	17 (6.3)
Hypoglycaemia	16 (5.9)
Seasonal allergy	16 (5.9)
Viral upper respiratory tract infection	16 (5.9)
Acne	15 (5.5)
Arthralgia	15 (5.5)
Blood bilirubin increased	14 (5.2)
Lower respiratory tract congestion	14 (5.2)

AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; CF: cystic fibrosis; IVA: ivacaftor; n: size of subsample; N: total sample size; PEx: pulmonary exacerbation; PT: Preferred Term; TEZ: tezacaftor
Notes: MedDRA Version 22.1 was used. A subject with multiple events within a category was counted only once in that category. The table was sorted in descending order of frequency by PT.

AEs by Relationship

Study 102 Safety Set

Ten (5.0%) subjects in the VX-445/TEZ/IVA group and 6 (3.0%) subjects in the placebo group had an AE assessed by the investigator as related; 86 (42.6%) subjects in the VX-445/TEZ/IVA group and 46 (22.9%) subjects in the placebo group had an AE assessed by the investigator as possibly related.

Related (combined related or possibly related) AEs occurring in≥5 subjects in any treatment group are presented in Table 43.

Table 43:Related AEs Occurring in ⩾5 Subjects in Any Treatment Group (Safety Set)

System Organ Class Preferred Term	Placebo N = 201 n (%)	VX-445/TEZ/IVA N = 202 n (%)
Subjects with any related AEs	52 (25.9)	96 (47.5)
Respiratory, thoracic and mediastinal disorders	25 (12.4)	29 (14.4)
Sputum increased	10 (5.0)	14 (6.9)
Cough	13 (6.5)	7 (3.5)
Productive cough	5 (2.5)	7 (3.5)
Investigations	9 (4.5)	26 (12.9)
ALT increased	1 (0.5)	12 (5.9)
AST increased	0	11 (5.4)
Blood CK increased	2 (1.0)	10 (5.0)
Blood bilirubin increased	0	6 (3.0)
Gastrointestinal disorders	12 (6.0)	22 (10.9)
Abdominal pain upper	3 (1.5)	5 (2.5)
Skin and subcutaneous tissue disorders	7 (3.5)	18 (8.9)
Rash	3 (1.5)	11 (5.4)
Nervous system disorders	10 (5.0)	11 (5.4)
Headache	8 (4.0)	9 (4.5)

Source: Table 14.3.1.6

AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; CK: creatine phosphokinase; IVA: ivacaftor; n: size of subsample; N: total sample size; PT: Preferred Term; SOC: System Organ Class; TEZ: tezacaftor

Note: AEs were coded using MedDRA version 22.0. A subject with multiple events within a category was counted only once in that category. Table was sorted in descending order of frequency of the

Study 103 Safety Set

Twelve (21.8%) subjects in the VX-445/TEZ/IVA group and 9 (17.3%) subjects in the TEZ/IVA group had at least 1 event considered related or possibly related to study drug**.** One (1.8%) subject in the VX-445/TEZ/IVA group and 1 (1.9%) subject in the TEZ/IVA group had an AE assessed by the investigator as related. Eleven (20.0%) subjects in the VX-445/TEZ/IVA group and 8 (15.4%) subjects in the TEZ/IVA group had an AE assessed by the investigator as possibly related.

The most frequent related in order of highest frequency is respiration abnormal (5.5%) while all other events were only observed in 1 or 2 patients.

In TEZ/IVA group following possibly related or related events were observed: AST increased, cough, Sputum increased, haemoptysis, rhinorrhoea, infective PEx, abdominal pain, diarrhoea, nausea, Rectal haemorrhage, fatigue, headache, rash (2).
In VX-445/TEZ/IVA group cough (2), respiration abnormal (3), oropharyngeal pain (2), sputum increase (2), haemoptysis, increased bronchial secretion, rhinorrhoea, sputum discoloured, Sputum

retention, wheezing, abdominal pain, fatigue, chest discomfort, headache (2), aphonia, lethargy, trigeminal neuralgia, rash, hyperhidrosis, ALT increased, AST increased, blood alkaline phosphatase increased, transaminases increased, muscle spasms, vaginal discharge were found as possibly related or related events.

No clear conclusion can be drawn for this data set.

Study 105 Safety Set

In Study 105, in IA1 143 (28.3%) subjects had AEs considered related or possibly related to study drug. In IA2, 169 (33.4%) subjects had AEs considered related or possibly related to VX-445/TEZ/IVA.

Related AEs that occurred in ≥5 subjects in Study 105 IA2 are summarized in Table 44. The most common related AEs were generally consistent with common manifestations and complications of CF disease or with the established safety profile for VX-445/TEZ/IVA. Related AEs of photosensitivity reaction occurred in 7 subjects.

Table 44: Related AEs Occurring in At Least 5 Subjects by PT: OL (Study 105) Safety Set

Preferred Term	Any VX-445/TEZ/IVA N = 506 n (%)
Subjects with any related AEs	129 (25.5)
ALT increased	23 (4.5)
AST increased	22 (4.3)
Blood creatine phosphokinase increased	19 (3.8)
Cough	18 (3.6)
Sputum increased	16 (3.2)
Blood bilirubin increased	14 (2.8)
Rash	12 (2.4)
Diarrhoea	9 (1.8)
Headache	8 (1.6)
Gamma-glutamyltransferase increased	8 (1.6)
Photosensitivity reaction	7 (1.4)
Abdominal pain	6 (1.2)
Hypoglycaemia	6 (1.2)
Respiration abnormal	5 (1.0)
Fatigue	5 (1.0)
Infective PEx of CF	5 (1.0)

Source: Study 105 IA2 Ad Hoc Table 2.3.1.9

AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; CF: cystic fibrosis; IVA: ivacaftor; n: size of subsample; N: total sample size; OL: open-label; PEx: pulmonary exacerbation; PT: Preferred Term; TEZ: tezacaftor

Notes: MedDRA Version 22.1 was used. A subject with multiple events within a category was counted only once in that category. When summarizing number of subjects with related AEs, AEs with relationship of related, possibly related, and missing were counted. The table was sorted in descending order of frequency by PT.

Cumulative Safety Set and Subjects who received VX-445/TEZ/IVA for at least 48 weeks

In both the overall cumulative analysis and the 48-week cumulative exposure analysis, the most common related AEs were generally consistent with common manifestations and complications of CF disease or with the established safety profile for VX-445/TEZ/IVA. In addition, exposure-adjusted analyses of event rates in Study 102 compared with Study 105 showed a decrease in the rates of the majority of related AEs with longer-term treatment.

Related AEs that occurred in ≥5 subjects who received VX-445/TEZ/IVA for at least 48 weeks cumulatively across studies (as of Study 105 IA2) are summarized in Table 45.

Table 45 Related AEs Occurring in At Least 5 Subjects by PT: Cumulative TC Safety Period (Cumulative TC Safety Set, Subjects With Cumulative TC Exposure of At Least 48 Weeks)

Preferred Term	Any VX-445/TEZ/IVA N = 271 n (%)
Subjects with any related AEs	114 (42.1)
ALT increased	23 (8.5)
Sputum increased	22 (8.1)
Blood creatine phosphokinase increased	21 (7.7)
AST increased	19 (7.0)
Cough	14 (5.2)
Rash	14 (5.2)
Headache	12 (4.4)
Respiration abnormal	10 (3.7)
Blood bilirubin increased	9 (3.3)
Haemoptysis	8 (3.0)
Diarrhoea	7 (2.6)
Fatigue	7 (2.6)
Productive cough	7 (2.6)
Abdominal pain	6 (2.2)
Hypoglycaemia	6 (2.2)
Pruritus	6 (2.2)
Rhinorrhoea	6 (2.2)
Abdominal pain upper	5 (1.8)
Blood alkaline phosphatase increased	5 (1.8)
Nausea	5 (1.8)

Source: ISA2 Ad Hoc Table 2.3.1.10

AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; CF: cystic fibrosis; IVA: ivacaftor; n: size of subsample; N: total sample size; PEx: pulmonary exacerbation; PT: Preferred Term; TEZ: tezacaftor

Notes: MedDRA Version 22.1 was used. A subject with multiple events within a category was counted only once in that category. When summarizing number of subjects with related AEs, AEs with relationship of related, possibly related, and missing were counted. The table was sorted in descending order of frequency by PT.

AEs by severity

The grade 3/4 AEs of Study 102 Safety Set, and Study 105 IA2 Safety Set (OLE) and Cumulative Safety Set are presented in Table 46. The details are provided per safety set.

Study 102 Safety Set

The majority of subjects overall had AEs that were mild (29.8%) or moderate (56.3%) in severity.

In the VX-445/TEZ/IVA group, 19 (9.4%) subjects had severe AEs and no subjects had life-threatening AEs. In the placebo group, 14 (7.0%) subjects had severe AEs and 1 (0.5%) subject had a life-threatening AE of neuroglycopenia.

Study 105 Safety Set

In IA1, 31 (6.1%) subjects had severe (Grade 3) AEs and 2 (0.4%) subjects had life-threatening (Grade 4) AEs.

In IA2, 51 (10.1%) subjects had severe (Grade 3) AEs and 2 (0.4%) subjects had life-threatening (Grade 4) AEs. The exposure-adjusted event rate for Grade 3/4 AEs was lower in Study 105 than in the Study 102 VX-445/TEZ/IVA group (19.84 versus 27.95 events/100PY).

Brief descriptions of the 2 subjects who had life-threatening AEs are provided below.

- One subject with a medical history of depression had a life-threatening AE of suicide attempt, which was considered by the investigator to be not related to VX-445/TEZ/IVA. The event resolved without change to VX-445/TEZ/IVA dosing.
- One subject with a medical history of recurrent haemoptysis had a life-threatening AE of pulmonary haemorrhage, which was considered to be possibly related to VX-445/TEZ/IVA. The event resolved with interruption of VX-445/TEZ/IVA, which has since been resumed.

Table 46: Grade 3/4 TEAEs by System Organ Class and Preferred Term - Study 102 Safety Period, OL Safety Period

	Study 102				OLS	
	PBO in 445-102 N = 201		VX-445/TEZ/IVA in 445-102 N = 202		Any VX-445/TEZ/IVA N = 506	
System Organ Class Preferred Term	n (%)	Events/100PY	n (%)	Events/100PY	n (%)	Events/100PY
Total duration of safety analysis period in 100 PY	--	1.00	--	1.00	--	3.93
Subjects with any Grade 3/4 TEAEs	15 (7.5)	23.02	19 (9.4)	27.95	53 (10.5)	19.84
Infections and infestations	9 (4.5)	12.01	3 (1.5)	3.99	23 (4.5)	6.87
Infective pulmonary exacerbation of cystic fibrosis	9 (4.5)	11.01	0	0	16 (3.2)	4.58
Influenza	0	0	0	0	3 (0.6)	1.02
Bronchopulmonary aspergillosis allergic	0	0	0	0	1 (0.2)	0.25
Chronic sinusitis	0	0	0	0	1 (0.2)	0.25
Genital herpes simplex	0	0	1 (0.5)	1.00	0	0
Infective exacerbation of bronchiectasis	1 (0.5)	1.00	0	0	1 (0.2)	0.25
Oral herpes	0	0	1 (0.5)	1.00	0	0
Pneumonia	0	0	1 (0.5)	1.00	1 (0.2)	0.25
Urinary tract infection	0	0	1 (0.5)	1.00	0	0
Vascular device infection	0	0	0	0	1 (0.2)	0.25
Investigations	0	0	6 (3.0)	8.98	10 (2.0)	4.83
Blood creatine phosphokinase increased	0	0	4 (2.0)	3.99	4 (0.8)	1.02
Aspartate aminotransferase increased	0	0	2 (1.0)	2.00	4 (0.8)	1.27
Alanine aminotransferase increased	0	0	2 (1.0)	2.00	3 (0.6)	1.02
Gamma-glutamyltransferase increased	0	0	1 (0.5)	1.00	2 (0.4)	0.76
Blood bilirubin increased	0	0	0	0	1 (0.2)	0.25
Blood immunoglobulin E increased	0	0	0	0	1 (0.2)	0.25
Influenza A virus test positive	0	0	0	0	1 (0.2)	0.25
Gastrointestinal disorders	2 (1.0)	4.00	4 (2.0)	3.99	7 (1.4)	2.29
Distal intestinal obstruction syndrome	0	0	1 (0.5)	1.00	4 (0.8)	1.27
Gastritis	0	0	0	0	2 (0.4)	0.51
Abdominal pain	0	0	1 (0.5)	1.00	0	0
Abdominal pain upper	0	0	1 (0.5)	1.00	0	0
Gastric haemorrhage	0	0	0	0	1 (0.2)	0.25
Small intestinal obstruction	1 (0.5)	2.00	1 (0.5)	1.00	0	0

Toothache	0	0	0	0	1 (0.2)	0.25
Nausea	1 (0.5)	1.00	0	0	0	0
Vomiting	1 (0.5)	1.00	0	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (0.5)	1.00	3 (1.5)	2.99	4 (0.8)	1.27
Haemoptysis	1 (0.5)	1.00	1 (0.5)	1.00	1 (0.2)	0.25
Lung infiltration	0	0	0	0	1 (0.2)	0.25
Nasal polyps	0	0	1 (0.5)	1.00	0	0
Painful respiration	0	0	0	0	1 (0.2)	0.25
Productive cough	0	0	1 (0.5)	1.00	0	0
Pulmonary haemorrhage	0	0	0	0	1 (0.2)	0.51
Hepatobiliary disorders	1 (0.5)	1.00	2 (1.0)	2.00	2 (0.4)	0.51
Cholangitis	0	0	1 (0.5)	1.00	0	0
Cholecystitis acute	0	0	0	0	1 (0.2)	0.25
Gallbladder enlargement	0	0	1 (0.5)	1.00	0	0
Hepatic steatosis	0	0	0	0	1 (0.2)	0.25
Hepatocellular injury	1 (0.5)	1.00	0	0	0	0
Psychiatric disorders	0	0	0	0	3 (0.6)	0.76
Suicide attempt	0	0	0	0	2 (0.4)	0.51
Psychotic disorder	0	0	0	0	1 (0.2)	0.25
Cardiac disorders	0	0	0	0	2 (0.4)	0.51
Arrhythmia	0	0	0	0	1 (0.2)	0.25
Pericardial effusion	0	0	0	0	1 (0.2)	0.25
General disorders and administration site conditions	0	0	2 (1.0)	2.00	0	0
Adverse drug reaction	0	0	1 (0.5)	1.00	0	0
Pyrexia	0	0	1 (0.5)	1.00	0	0
Injury, poisoning and procedural complications	0	0	1 (0.5)	1.00	1 (0.2)	0.25
Post procedural haemorrhage	0	0	1 (0.5)	1.00	0	0
Procedural pain	0	0	0	0	1 (0.2)	0.25
Musculoskeletal and connective tissue disorders	1 (0.5)	1.00	1 (0.5)	1.00	1 (0.2)	0.25
Joint stiffness	0	0	0	0	1 (0.2)	0.25
Rhabdomyolysis	0	0	1 (0.5)	1.00	0	0
Back pain	1 (0.5)	1.00	0	0	0	0
Nervous system disorders	2 (1.0)	2.00	0	0	2 (0.4)	0.51
Headache	0	0	0	0	1 (0.2)	0.25
Hepatic encephalopathy	0	0	0	0	1 (0.2)	0.25
Migraine	1 (0.5)	1.00	0	0	0	0
Neuroglycopenia	1 (0.5)	1.00	0	0	0	0
Renal and urinary disorders	0	0	0	0	2 (0.4)	0.51
Calculus urinary	0	0	0	0	1 (0.2)	0.25
Nephrolithiasis	0	0	0	0	1 (0.2)	0.25
Reproductive system and breast disorders	0	0	0	0	2 (0.4)	0.51
Ovarian cyst	0	0	0	0	1 (0.2)	0.25
Vaginal haemorrhage	0	0	0	0	1 (0.2)	0.25
Skin and subcutaneous tissue disorders	1 (0.5)	1.00	1 (0.5)	2.00	1 (0.2)	0.25
Rash	0	0	1 (0.5)	1.00	1 (0.2)	0.25
Pruritus	0	0	1 (0.5)	1.00	0	0
Hypersensitivity vasculitis	1 (0.5)	1.00	0	0	0	0
Metabolism and nutrition disorders	1 (0.5)	1.00	0	0	1 (0.2)	0.51
Hypoglycaemia	1 (0.5)	1.00	0	0	1 (0.2)	0.51

- MedDRA version 22.1.
- Events/100PY: number of events per 100 patient years (336 days = 48 weeks per year) = number of events/total duration of safety analysis period in 100PY.
- When summarizing number of events, a subject with multiple events within a category is counted multiple times in that category.
- When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category.
- A subject with missing severity levels is not counted.
- Table is sorted in descending order of frequency of the Any VX-445/TEZ/IVA column during the Cumulative TC Safety Period by System Organ Class, and by Preferred Term within each System Organ Class.

Program: VX445\ISS\ISS2\prod\tables\t-iss-ae-teae-socpt-g34.sas Creation: 31OCT2019 21:54

Study 103 Safety Set

The majority of AEs in both the VX-445/TEZ/IVA and TEZ/IVA groups were mild (41.1%) or moderate (18.7%) in severity. No subject in the VX-445/TEZ/IVA group and 1 (1.9%) subject in the TEZ/IVA group had a severe AE (musculoskeletal pain). There were no life-threatening AEs.

Cumulative Safety Set

Two (0.4%) subjects had life-threatening AEs (as in Study 105).

Subjects who received VX-445/TEZ/IVA for at least 48 weeks

The majority of subjects had AEs that were mild or moderate in severity (63 mild (23.2%), 161 moderate (59.4%).

A total of 41 (15.1%) subjects had at least 1 AE that was Grade 3 or 4 in severity. Grade 3/4 events that occurred in ≥2 subjects were infective PEx of CF (10 subjects), blood creatine phosphokinase increased (8 subjects), DIOS (4 subjects), AST increased (4 subjects), ALT increased (3 subjects), GGT increased (2 subjects), gastritis (2 subjects), and influenza (2 subjects).

There were no life-threatening AEs.

The majority of events were assessed by the investigator as unrelated (not related or unlikely related) to VX-445/TEZ/IVA treatment and generally resolved without changes to study drug dosing.

The overall exposure-adjusted rate for Grade 3/4 AEs was similar between the population who received VX-445/TEZ/IVA for at least 48 weeks as of Study 105 IA2 and the placebo group in Study 102 (21.07 and 23.02 events per 100PY, respectively.

Serious adverse events/deaths/other significant events

Deaths

There were no AEs leading to death during the clinical program.

Serious adverse events

The SAEs of at least 2 subjects in Study 102 Safety Set, and Study 105 IA2 Safety Set (OLE) are presented in Table 47. The details are provided per safety set.

Study 102 Safety Set

Twenty-eight (13.9%) subjects in the VX-445/TEZ/IVA group and 42 (20.9%) subjects in the placebo group had at least 1 SAE .

Overall, the SAEs were mostly consistent with common manifestations of CF disease or with common illnesses in CF subjects 12 years of age and older.

SAEs that occurred in ≥2 subjects in any group and were more common in the VX-445/TEZ/IVA group than the placebo group included rash and influenza. Rash events are further discussed below. The 3 SAEs of influenza in the VX-445/TEZ/IVA group were all assessed by the investigator as not related to study drug.

The majority of SAEs were assessed by the investigator as unlikely related or not related to study drug.

Study 105

In IA1, a total of 55 (10.9%) subjects had SAEs. In IA2, 80 (15.8%) subjects had SAEs. Overall, the SAEs were mostly consistent with common manifestations of CF disease or with common illnesses in CF subjects 12 years of age and older.

The exposure-adjusted event rate for SAEs was lower in Study 105 than in the Study 102 VX-445/TEZ/IVA group (27.47 versus 36.93 events/100PY).

SAEs that occurred in ≥2 subjects are summarized in Table 47.

Table 47:Serious AEs Occurring in At Least 2 Subjects by PT: Study 105 Safety Set

	Study 102				OLS	
	PBO in 445-102 N = 201		VX-445/TEZ/IVA in 445-102 N = 202		Any VX-445/TEZ/IVA N = 506	
Preferred Term	n (%)	Events/100PY	n (%)	Events/100PY	n (%)	Events/100PY
Total duration of safety analysis period in 100PY	--	1.00	--	1.00	--	3.93
Infective PEx of CF	33 (16.4)	44.03	11 (5.4)	11.98	42 (8.3)	12.21
Distal intestinal obstruction syndrome	0	0	1 (0.5)	1.00	5 (1.0)	1.53
Hemoptysis	3 (1.5)	3.00	2 (1.0)	2.00	5 (1.0)	1.53
Vascular device infection	0	0	0	0	3 (0.6)	0.76
Influenza	0	0	3 (1.5)	2.99	2 (0.4)	0.51
ALT increased	0	0	0	0	2 (0.4)	0.51
AST increased	0	0	0	0	2 (0.4)	0.51

Source: ISA2 Table 2.3.2.4.1

AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; CF: cystic fibrosis; IVA: ivacaftor; n: size of subsample; N: total sample size; PBO: placebo; PEx: pulmonary exacerbation; PT: Preferred Term; PY: patient-year; TEZ: tezacaftor

Notes: MedDRA Version 22.1 was used. A subject with multiple events within a category was counted only once in that category. The table was sorted in descending order of frequency by PT.

Study 103 Safety Set

In the VX-445/TEZ/IVA group, 2 (3.6%) subjects had SAEs: 1 subject had an SAE of infective pulmonary exacerbation (PEx) of CF and 1 subject had an SAE of rash. In the TEZ/IVA group, 1 (1.9%) subject had an SAE of infective PEx of CF.

Cumulative Safety Set

SAEs were reported in 72 (14.1%) subjects. SAEs that occurred in > 2 subjects were infective PEx of CF, distal intestinal obstruction syndrome, haemoptysis, influenza, and rash. In IA2, additionally vascular device infection, ALT increased, and AST increased occurred. All other SAEs occurred in a single subject each.

Safety in subjects who received VX-445/TEZ/IVA for at least 48 weeks

In IA2, 50 (18.5%) subjects had at least 1 SAE. SAEs that occurred in ≥2 subjects were infective PEx of CF, influenza, DIOS, haemoptysis, rash, and vascular device infection;

Related serious adverse events

Study 102 Safety Set, Study 105 IA2 Safety Set, Cumulative Safety Set

Cumulatively across the parent Studies 102 and 103 and Study 105 IA2, 20 (3.9%) subjects who received any VX-445/TEZ/IVA had related SAEs: 6 subjects with related SAEs in Study 102, and 1 subject with a related SAE in Study 103 and 13 subjects with related SAEs in Study 105.

Related SAEs that occurred in ≥2 subjects in the Cumulative TC Safety Period were haemoptysis, rash, distal intestinal obstruction syndrome (DIOS), infective PEx of CF, alanine transaminase (ALT) increased, and aspartate transaminase (AST) increased; all other related SAEs occurred in 1 subject each.

Overall, the incidence of related SAEs was low across studies. The majority of these events were consistent with common manifestations and complications of CF disease or with the established safety profile for VX-445/TEZ/IVA. Many of these events had plausible alternative aetiologies and/or confounding factors (e.g., pre-existing medical history, concurrent infections or illnesses), and most of the subjects were able to maintain or successfully resume study drug dosing.

The findings of Study 102 Safety Set, Study 105 IA2 Safety Set, Cumulative Safety Set are presented in Table 48.

Table 48:Related Serious TEAEs by System Organ Class and Preferred Term - Study 102 Safety Period, OL Safety Period IA2, and Cumulative TC Safety Period Study 102 Safety Set, OL Safety Set, and Cumulative TC Safety Set

	Study 102		Study 105 (OLS)	Cumulative TC Safety Period
Preferred Term, n (%)	Placebo in 445-102 N = 201	VX-445/TEZ/IVA in 445-102 N = 202	Any VX-445/TEZ/IVA N = 506	Any VX-445/TEZ/IVA N = 510
Subjects with any related SAEs	2 (1.0)	6 (3.0)	13 (2.6)	20 (3.9)
Haemoptysis	0	1 (0.5)	2 (0.4)	3 (0.6)
Rash	0	1 (0.5)	1 (0.2)	3 (0.6)[a]
Distal intestinal obstruction syndrome	0	0	2 (0.4)	2 (0.4)
Infective PEx of CF	0	0	2 (0.4)	2 (0.4)
ALT increased	0	0	2 (0.4)	2 (0.4)
AST increased	0	0	2 (0.4)	2 (0.4)
Abdominal pain upper	0	1 (0.5)	0	1 (0.2)
Duodenitis	0	0	1 (0.2)	1 (0.2)
Pulmonary haemorrhage	0	0	1 (0.2)	1 (0.2)
Rash pruritic	0	1 (0.5)	0	1 (0.2)
Blood bilirubin increased	0	0	1 (0.2)	1 (0.2)
Gamma-glutamyltransferase increased	0	0	1 (0.2)	1 (0.2)
Arrhythmia	0	0	1 (0.2)	1 (0.2)
Portal hypertension	0	1 (0.5)	0	1 (0.2)
Rhabdomyolysis	0	1 (0.5)	0	1 (0.2)
Hepatic encephalopathy	0	0	1 (0.2)	1 (0.2)
Psychotic disorder	0	0	1 (0.2)	1 (0.2)
Painful respiration	1 (0.5)	0	0	0
Hypersensitivity vasculitis	1 (0.5)	0	0	0

Source: ISA2 Table 2.3.2.5

AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; CF: cystic fibrosis; IVA: ivacaftor; n: size of subsample; N: total sample size; OLS: open-label study; PEx: pulmonary exacerbation; PT: Preferred Term; SAE: serious adverse event; TC: triple combination; TEZ: tezacaftor

Notes: MedDRA Version 22.1 was used. A subject with multiple events within a category was counted only once in that category. When summarizing number of subjects with related SAEs, SAEs with relationship of related, possibly related, and missing were counted. The table was sorted in descending order of frequency of the Any VX-445/TEZ/IVA column during the Cumulative TC Safety Period by PT.

[a] One related SAE of rash occurred in Study 103.

No results of related serious events were provided for subjects who received VX-445/TEZ/IVA for at least 48 weeks.

Study 103 Safety Set

The SAE of rash in VX-445/TEZ/IVA was assessed by the investigator as related.

Events of specific interest

Prespecified events of special interest are transaminase elevation events and rash events. In addition, data relevant to the assessment of blood bilirubin and creatine kinase are also discussed.

Transaminase Elevations

Liver function test (LFT) elevations have been seen in CF patients, including some receiving IVA monotherapy, TEZ/IVA, and VX-445/TEZ/IVA. Therefore, a comprehensive analysis of liver-related data in VX-445 clinical studies was performed.

The Liver function test (LFT) elevations in Study 102 Safety Set, and Study 105 IA2 Safety Set (OLE) are presented in Table 49 and Table 50. The details are provided per safety set.

Study 102 Safety Set

Twenty-two (10.9%) subjects in the VX-445/TEZ/IVA group and 8 (4.0%) subjects in the placebo group had at least 1 elevated transaminase event. The majority of events were mild or moderate in severity and were associated with ALT/AST elevations <5 × the upper limit of normal (ULN).

There were no elevated transaminase events that led to treatment discontinuation. Two (1.0%) subjects in the VX-445/TEZ/IVA group and 3 (1.5%) subjects in the placebo group had elevated transaminase events that led to treatment interruption: 1 of the subjects in the VX-445/TEZ/IVA group resumed treatment; the other subject enrolled in the open-label extension study while still on study drug interruption and eventually discontinued from the open-label extension study without resuming study drug. A narrative is provided in Study 102 CSR/Section 14.3.3.

No subjects in the VX-445/TEZ/IVA group and 1 subject (0.5%) in the placebo group had a serious elevated transaminase event.

The median time to onset of first elevated transaminase event was 57.0 days (range: 1, 176) in the VX-445/TEZ/IVA group and 58.0 days (range: 1, 169) in the placebo group. The median duration of elevated transaminase events was 17.0 days (range: 4,153) in the VX-445/TEZ/IVA group and 17.0 days (range: 5, 52) in the placebo group.

Additional relevant hepatic AEs occurred in 3 (1.5%) subjects in the VX-445/TEZ/IVA group (hepatic cirrhosis, hepatocellular injury, and portal hypertension) and 1 (0.5%) subject in the placebo group (hepatocellular injury). Events in the VX-445/TEZ/IVA group were as follows:

- The event of portal hypertension was an SAE in a subject with a medical history of hepatic cirrhosis that led to discontinuation of VX-445/TEZ/IVA treatment; it was assessed by the investigator as being of moderate severity and possibly related to study drug.
- The event of hepatocellular injury was a non-serious AE that was associated with mildly elevated transaminases (<2 × ULN) and was assessed by the investigator as being of mild severity and related to study drug. There was no change to study drug dosing.
- The event of hepatic cirrhosis was a non-serious AE that was associated with mildly elevated transaminases (<2 × ULN) and was assessed by the investigator as being of mild severity and unlikely related to study drug. There was no change to study drug dosing.

- The AE of hepatocellular injury in the placebo group was associated with transaminase elevations >8 × ULN and resulted in study drug interruption.

Mean concentrations of transaminase parameters were variable over time in both groups. In the VX-445/TEZ/IVA group, increases from baseline in mean ALT and AST were observed. The mean (SD) increases in ALT ranged from 4.8 (20.5) U/L at Week 16 to 8.2 (28.9) U/L at Week 24. The mean (SD) increases in AST ranged from 3.2 (13.5) U/L at Week 16 to 6.6 (31.6) U/L at Week 24. In the placebo group, there were no trends in ALT or AST.

An overview of subjects with ALT and/or AST elevations by predefined thresholds and of subjects with ALT and/or AST elevations >3 × ULN and total bilirubin elevation >2 × ULN is presented in Table 49. The ALT/AST and bilirubin elevations did not have to be concurrent and could occur at any time in the Treatment-emergent Period, regardless of baseline levels.

The majority of subjects had ALT and AST values that remained within the normal range. More subjects in the VX-445/TEZ/IVA group had ALT or AST >3×, 5× and 8× ULN, respectively, compared to subjects in the placebo group. No subject had elevations of ALT or AST >3 × ULN concurrent with a newly occurring elevation in total bilirubin >2 × ULN. Two subjects in the VX-445/TEZ/IVA group had ALT or AST >3 × ULN and total bilirubin >2 × ULN during the study; in 1 subject, the elevations were not concurrent (ALT and AST >3 × ULN occurred at the Day 15 Visit; total bilirubin >2 × ULN occurred at the Week 24 Visit). The other subject had a medical history of Gilbert's syndrome and an elevated total bilirubin at screening >2 × ULN that remained high throughout the study.

Table 49:Threshold Analysis of Transaminase Elevations During the Treatment-emergent Period: Study 102 Safety Set

Parameter Post-baseline Threshold Analysis Criteria	Placebo N = 201 n/N1 (%)	VX-445/TEZ/IVA N = 202 n/N1 (%)
ALT or AST (U/L), interval		
>3 × to ≤5 × ULN	8 (4.0)	11 (5.4)
>5 × to ≤8 × ULN	1 (0.5)	2 (1.0)
ALT or AST (U/L), cumulative		
>3 × ULN	11 (5.5)	16 (7.9)
>5 × ULN	3 (1.5)	5 (2.5)
>8 × ULN	2 (1.0)	3 (1.5)
ALT or AST (U/L) and total bilirubin (µmol/L)		
ALT or AST >3 × ULN and total bilirubin >2 × ULN	0	2 (1.0)[a]

Source: Study 102 CSR/Table 14.3.4.2
ALT: alanine aminotransferase; AST: aspartate aminotransferase; IVA: ivacaftor; LFT: liver function test; n: size of subsample; N: total sample size; TEZ: tezacaftor; ULN: upper limit of normal
Notes: N1 was the number of subjects with at least 1 non-missing measurement during the Treatment-emergent Period and was equal to N for all categories in this table; n was the number of subjects in the post-baseline category. Within each parameter, a subject was counted in all applicable post-baseline categories based on the worst assessment during the Treatment-emergent Period. Percentages were evaluated as n/N1. Threshold criteria involving 2 LFT parameters could be determined by assessments at different visits during the Treatment-emergent Period.
[a] In 1 subject, the transaminase and bilirubin elevations were not concurrent. The other subject had a medical history of Gilbert's syndrome and an elevated total bilirubin at screening >2 × ULN, which remained high throughout the study.

Study 103 Safety Set

Two (3.6%) subjects in the VX-445/TEZ/IVA group and 1 (1.9%) subject in the TEZ/IVA group had at least 1 elevated transaminase event. All events were mild in severity, and none were serious or led to treatment discontinuation or interruption.

Increases from baseline in mean (SD) ALT and AST were observed in the VX-445/TEZ/IVA group (9.0 (16.5) U/L for ALT and 1.6 (13.9) U/L for AST), but not in the TEZ/IVA group (-3.1 (13.1) U/L for ALT and -2.0 (8.4) for AST).

The incidences of maximum transaminase elevations (ALT or AST) >3 ×, >5 ×, or >8 × ULN in the VX-445/TEZ/IVA group were 7.3%, 3.6%, and 0%, respectively. No subjects in the TEZ/IVA group had ALT or AST elevations >3 × ULN or ALT or AST >3 × ULN with total bilirubin >2 × ULN.

Study 105 Safety Set

In IA1, a total of 23 (4.6%) subjects had at least 1 elevated transaminase event, while currently in IA2 36 (7.1%) subjects had at least 1 elevated transaminase event.

The exposure-adjusted event rate for elevated transaminase AEs was lower in Study 105 than in the Study 102 VX-445/TEZ/IVA group (16.53 versus 42.92 events/100PY).

The majority of these events were mild or moderate in severity and were associated with ALT/AST elevations <5 × ULN. Elevated transaminase events led to treatment interruption in 11 (2.2%) subjects and led to treatment discontinuation in 3 (0.6%) subjects; 2 of the discontinuations were SAEs, and no other subjects had serious elevated transaminase events.

In IA2, the incidences of subjects with maximum on-treatment transaminase elevations (ALT and/or AST) above thresholds of >3 ×, >5 ×, and >8 × ULN were 6.3%, 2.2.% and 0.6%, respectively. One subject had ALT or AST >3 × ULN and total bilirubin >2 × ULN during the study (not concurrent).

One additional subject had AST and ALT >3 × ULN concurrent with bilirubin >2 × ULN due to an SAE of acute cholecystitis, that were not captured in the clinical database nor included in the Study 105 IA tables and listings. This subject recovered quickly following a laparoscopic cholecystectomy, and ALT, AST, and bilirubin parameters returned to the subject's baseline levels (<2 × ULN).

Overall, the data related to transaminase elevations in Study 105 were consistent with those in the parent studies (refer to Table 50).

Table 50 :Summary of AESI: Treatment-emergent Elevated Transaminase Events - Study 102 Safety Period, OL Safety Period

	Study 102				OLS	
	PBO in 445-102 N = 201		VX-445/TEZ/IVA in 445-102 N = 202		Any VX-445/TEZ/IVA N = 506	
	n (%)	Events/100PY	n (%)	Events/100PY	n (%)	Events/100PY
Total duration of safety analysis period in 100 PY	--	1.00	--	1.00	--	3.93
Subjects with any events	8 (4.0)	13.01	22 (10.9)	42.92	36 (7.1)	16.53
AST/ALT ratio abnormal	0	0	0	0	0	0
Alanine aminotransferase abnormal	0	0	0	0	0	0
Alanine aminotransferase increased	7 (3.5)	8.01	20 (9.9)	21.96	27 (5.3)	7.88
Aspartate aminotransferase abnormal	0	0	0	0	0	0
Aspartate aminotransferase increased	4 (2.0)	4.00	19 (9.4)	20.96	27 (5.3)	7.88
Hepatic enzyme abnormal	0	0	0	0	0	0
Hepatic enzyme increased	0	0	0	0	0	0
Hypertransaminasaemia	1 (0.5)	1.00	0	0	0	0
Liver function test abnormal	0	0	0	0	0	0
Liver function test increased	0	0	0	0	1 (0.2)	0.51
Transaminases abnormal	0	0	0	0	0	0
Transaminases increased	0	0	0	0	1 (0.2)	0.25
Subjects with any events by maximum severity						
Mild	4 (2.0)	--	12 (5.9)	--	20 (4.0)	--
Moderate	4 (2.0)	--	8 (4.0)	--	12 (2.4)	--
Severe	0	--	2 (1.0)	--	4 (0.8)	--
Life-threatening	0	--	0	--	0	--
Missing	0	--	0	--	0	--
Subjects with events leading to treatment discontinuation	0	0	0	0	3 (0.6)	1.53
Subjects with events leading to treatment interruption	3 (1.5)	4.00	2 (1.0)	2.99	11 (2.2)	5.09
Subjects with serious events	1 (0.5)	1.00	0	0	2 (0.4)	1.02
Subjects with related serious events	0	0	0	0	2 (0.4)	1.02
Subjects with events leading to death	0	0	0	0	0	0
Duration of events (days)						
Number of events	13	--	43	--	65	--
Number of events with non-missing duration	9	--	28	--	38	--
Mean (SD)	19.6 (14.6)	--	32.8 (34.0)	--	26.0 (16.9)	--
Median	17.0	--	17.0	--	24.0	--
Min, max	5, 52	--	4, 153	--	4, 57	--
Time-to-onset of first event (days)						
Subjects with event with complete start date	8	--	22	--	36	--
Mean (SD)	61.8 (62.7)	--	78.4 (63.6)	--	103.0 (83.9)	--
Median	58.0	--	57.0	--	61.0	--
Min, max	1, 169	--	1, 176	--	10, 334	--

- Elevated transaminase events were coded using MedDRA version 22.1.
- Events/100PY: number of events per 100 patient years (336 days = 48 weeks per year) = number of events/total duration of safety analysis period in 100PY.
- When summarizing number of events, a subject with multiple events within a category is counted multiple times in that category.
- When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category.
- When summarizing number of subjects with related (serious) events, events with relationship of related, possibly related, and missing are counted.
- The duration was only calculated for the events with complete start and end dates; the time-to-onset was only calculated for the events with complete start date.
- Preferred Terms are sorted by alphabetical order.

Program: VX445\ISS\ISS2\prod\tables\t-iss-ae-teaesi-et.sas Creation: 31OCT2019 21:55

Cumulative Safety Set

Ten (2.0%) subjects discontinued VX-445/TEZ/IVA due to AEs, with 4 (0.8%) subjects discontinuing due to LFT elevations and 2 (0.4%) subjects discontinuing due to rash events.

Subjects who received VX-445/TEZ/IVA for at least 48 weeks

Elevated transaminase AEs occurred in 36 (13.3%) subjects, no events were serious.

Laboratory elevations in ALT and/or AST >3 ×, 5 ×, and >8 × ULN occurred in 30 (11.1%) subjects, 7 (2.6%) subjects, and 4 (1.5%) subjects. No subjects had elevations of ALT or AST >3 × ULN concurrent with a newly occurring elevation in total bilirubin >2 × ULN. Three (1.1%) subjects had ALT or AST >3 × ULN and total bilirubin >2 × ULN during Studies 102 or 105; in 2 subjects, the elevations were not concurrent. The third subject had a medical history of Gilbert's syndrome and an elevated total bilirubin at screening >2 × ULN that remained high throughout the study.

Pooled Analysis of Phase 1 Studies in Healthy Subjects

No subjects had transaminase elevation events. There were no trends in mean ALT or AST in the Phase 1 studies. In the Any VX-445 group, 1 (0.5%) subject had AST >3 × to ≤5 × ULN at the Safety Follow-up Visit.

Bilirubin Elevation Events

Blood bilirubin is a substrate of OATP1B1 and OATP1B3, and VX-445 is an OATP1B1 and OATP1B3 inhibitor based on *in vitro* results; as such, blood bilirubin levels could be increased with VX-445/TEZ/IVA treatment.

Study 102 Safety Set

AEs of bilirubin elevation occurred in 10 (5.0%) subjects in the VX-445/TEZ/IVA group and 2 (1.0%) subjects in the placebo group.

None of the AEs of bilirubin elevation were serious or led to treatment discontinuation. One subject in the VX-445/TEZ/IVA group had an AE of blood bilirubin increased that led to treatment interruption; the AE resolved, and study drug was resumed.

Increases from baseline in mean total bilirubin (up to 4.0 µmol/L) were observed in the VX-445/TEZ/IVA group, with a greater increase in indirect bilirubin (up to 2.7 µmol/L) than in direct bilirubin (up to 1.3 µmol/L; Study 102 CSR/Table 14.3.4.1); however, the mean values of the 3 bilirubin parameters were within normal range throughout the study. The bilirubin elevation was observed at Day 15 and remained at a similar level for the rest of the study. In the placebo group, changes from baseline in mean total bilirubin were minimal.

The majority of subjects had bilirubin values that remained within the normal range. In the VX-445/TEZ/IVA group, 8 (4.0%) subjects had elevations in total bilirubin >2 × ULN of which one subject >2 × ULN. Threshold analyses for direct bilirubin and indirect bilirubin showed a similar pattern of elevations with that observed in the mean value analyses. In the placebo group, 1 (0.5%) subject had elevations in total bilirubin >2 × ULN.

In Study 103 Safety Set, no subjects had AEs of bilirubin elevation. Increases from baseline in mean total bilirubin were observed in the VX-445/TEZ/IVA group with a greater increase in indirect bilirubin than in direct bilirubin; however, the mean values of the 3 bilirubin parameters were within normal range throughout the study. The greatest mean (SD) change in total bilirubin (3.0 (2.9) µmol/L) was observed at Week 4, compared to placebo -0.6 (2.3) µmol/L.

In Study 105 Safety Set, AEs of bilirubin elevation occurred in 23 (4.5%) subjects. Nineteen (3.8%) subjects had elevations in total bilirubin >2 × ULN. Threshold analyses for other bilirubin parameters showed a similar pattern of elevations with that observed in the VX445/TEZ/IVA group of Study 102: the incidence of >2 × ULN elevations was higher for indirect bilirubin (26 subjects [5.1%]) than direct bilirubin (1 subject [0.2%]). Overall, the bilirubin data in Study 105 were consistent with those in the parent studies (Studies 102 and 103).

In the Pooled Analysis of Phase 1 Studies in Healthy Subjects, no subjects had AEs of bilirubin elevation. Increases in mean total bilirubin were observed in 2 of the Phase 1 studies in healthy subjects, with a greater increase in indirect bilirubin than in direct bilirubin.

Rash Events

In the Phase 1 DDI study in healthy female subjects taking VX-445/TEZ/IVA and oral hormonal contraceptives (Study 002), 4 of 15 subjects (26.7%) had a rash event. Therefore, rash was considered an event of special interest in the Phase 3 studies.

Study 102 Safety Set

Twenty-two (10.9%) subjects in the VX-445/TEZ/IVA group and 13 (6.5%) subjects in the placebo group had a least 1 rash event. The majority of events were mild or moderate in severity. One (0.5%) subject in the VX-445/TEZ/IVA group had a rash event that led to treatment discontinuation. Four (2.0%) subjects in the VX-445/TEZ/IVA group and 1 (0.5%) subject in the placebo group had events that led to treatment interruption; all resumed treatment.

Serious rash events occurred in 3 (1.5%) subjects in the VX-445/TEZ/IVA group (2 SAEs of rash, 1 SAE of rash pruritic), of which 2 events were considered treatment related; all events resolved. In the placebo group, 1 (0.5%) subject had a serious rash event.

The median time to onset of first rash event was 13.5 days (range: 5, 157) in the VX-445/TEZ/IVA group and 27.0 days (range: 1, 157) in the placebo group. The median duration of rash events was 7.0 days (range: 1, 92) in the VX-445/TEZ/IVA group and 8.0 days (range: 2, 61) in the placebo group.

The incidence of rash events was higher in females than in males in both treatment groups. In the VX-445/TEZ/IVA group, 16 (16.3%) female subjects and 6 (5.8%) male subjects had rash events. In the placebo group, 8 (8.3%) female subjects and 5 (4.8%) male subjects had rash events.

In female subjects receiving VX-445/TEZ/IVA, 8 (20.5%) subjects who used hormonal therapy during the study and 8 (13.6%) subjects not using hormonal therapy had rash events. In female subjects receiving placebo, 3 (9.4%) subjects who used hormonal therapy during the study and 5 (7.8%) subjects not using hormonal therapy had rash events.

Of the 8 subjects in the VX-445/TEZ/IVA group who used hormonal therapy and had a rash event, 1 subject had a rash event before beginning hormonal therapy use; 4 subjects had no changes to study drug or hormonal therapy, and the rash resolved; 2 subjects had VX-445/TEZ/IVA treatment interruptions, discontinued hormonal therapy, and resumed study drug after the rash resolved; and 1 subject remained on hormonal therapy and discontinued VX-445/TEZ/IVA treatment, and the rash resolved.

Study 103 Safety Set

In the VX-445/TEZ/IVA group, 2 (3.6%) subjects had a rash event; both were female. One rash event occurred in a subject who had concomitant use of hormonal therapy; this event was considered serious and possibly related to study drug. The subject discontinued use of OCs and continued study drug treatment, and the rash resolved.

In the TEZ/IVA group, 2 (3.8%) subjects had a nonserious rash event; both were female, and 1 subject had concomitant use of hormonal therapy.

All rash events were mild in severity, and none led to treatment discontinuation or interruption.

Study 105 Safety Set

In Study 105, in IA1, 37 (7.3%) subjects and in IA2 50 (9.9%) had rash events. The rash events were exanthematous and mostly mild to moderate in severity. A serious rash event occurred in 1 (0.2%) subject; study drug was discontinued, and the event resolved. Five (1.0%) subjects had rash events that led to treatment interruption.

The incidence of rash events was higher in females than in males: 27 (10.8%) female subjects and 23 (9.0%) male subjects had rash events. Of the 94 female subjects taking hormonal therapy during the study, 12 (12.8%) had rash events; of the 157 female subjects not taking hormonal therapy during the study, 15 (9.6%) had rash events. Overall, the nature and severity of the rash events in Study 105 were consistent with those in the parent studies (Studies 102 and 103).

Table 51:Summary of AESI: Treatment-emergent Rash Events - Study 102 Safety Period, OL Safety Period

	Study 102				OLS	
	PBO in 445-102 N = 201		VX-445/TEZ/IVA in 445-102 N = 202		Any VX-445/TEZ/IVA N = 506	
	n (%)	Events/100PY	n (%)	Events/100PY	n (%)	Events/100PY
Total duration of safety analysis period in 100 PY	--	1.00	--	1.00	--	3.93
Subjects with any events	13 (6.5)	17.01	22 (10.9)	29.95	50 (9.9)	15.77
Subjects with any events by maximum severity						
Mild	10 (5.0)	--	17 (8.4)	--	33 (6.5)	--
Moderate	3 (1.5)	--	4 (2.0)	--	16 (3.2)	--
Severe	0	--	1 (0.5)	--	1 (0.2)	--
Life-threatening	0	--	0	--	0	--
Missing	0	--	0	--	0	--
Subjects with events leading to treatment discontinuation	0	0	1 (0.5)	1.00	1 (0.2)	0.25
Subjects with events leading to treatment interruption	1 (0.5)	1.00	4 (2.0)	3.99	5 (1.0)	1.27
Subjects with serious events	1 (0.5)	1.00	3 (1.5)	2.99	1 (0.2)	0.25
Subjects with related serious events	0	0	2 (1.0)	2.00	1 (0.2)	0.25
Subjects with events leading to death	0	0	0	0	0	0

- Rash events were coded using MedDRA version 22.1.
- Events/100PY: number of events per 100 patient years (336 days = 48 weeks per year) = number of events/total duration of safety analysis period in 100PY.
- When summarizing number of events, a subject with multiple events within a category is counted multiple times in that category.
- When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category.
- When summarizing number of subjects with related (serious) events, events with relationship of related, possibly related, and missing are counted.
- The duration was only calculated for the events with complete start and end dates; the time-to-onset was only calculated for the events with complete start date.
- Preferred Terms are sorted by alphabetical order.

Program: VX445\ISS\ISS2\prod\tables\t-iss-ae-teaesi-rash.sas Creation: 31OCT2019 21:56

Safety in subjects who received VX-445/TEZ/IVA for at least 48 weeks

In IA2, rash events occurred in 42 (15.5%) subjects; these events were generally exanthematous rashes and mostly mild (32, 11.8%) to moderate (9, 3.3%) in severity. The exposure-adjusted event rate for rash events was lower in this subset of subjects in Study 105 than in the Study 102 VX-445/TEZ/IVA group (18.90 versus 29.95 events/100PY). Three (1.1%) subjects had rash events that were serious. Four (1.5%) subjects had rash events that led to treatment interruption.

Pooled Analysis of Phase 1 Studies in Healthy Subjects

In the Any VX-445 group, 7 (3.7%) subjects had rash events, of whom 2 (1.0%) subjects discontinued study drug due to a rash event. All rash events were mild or moderate in severity and nonserious. The median time to onset of rash events was 11.0 days (range: 10 to 19 days).
Of the 7 subjects who had rash events in the Any VX-445 group, 4 were female subjects from Study 002 (OC DDI), and 3 were male subjects. The incidence of rash events in female subjects in Study 002 was 4 of 15 subjects (26.7%).

In the placebo group, 1 (1.9%) subject had 2 rash events of dermatitis. The time to onset of the first event was 9 days.

CK Elevation Events

Study 102 Safety Set

AEs of CK elevation occurred in 20 (9.9%) subjects in the VX-445/TEZ/IVA group (18 with AEs of blood creatine phosphokinase increased, 1 with an AE of rhabdomyolysis, and 1 with both AE) and 9 (4.5%) subjects in the placebo group (9 with AEs of blood creatine phosphokinase increased and 1 also with an AE of rhabdomyolysis). The majority of subjects with CK elevation events had asymptomatic laboratory elevations, many of which were preceded by exercise. The AEs were mostly mild or moderate; AEs were of severe intensity in 5 subjects in the VX-445/TEZ/IVA group and no subjects in the placebo group. One subject in the VX-445/TEZ/IVA group had an SAE of CK elevation (rhabdomyolysis).

The 2 subjects in the VX-445/TEZ/IVA group with AEs of rhabdomyolysis presented with CK elevations, and neither subject had clinical features of rhabdomyolysis (e.g., kidney involvement, myoglobinuria). Before event onset, both subjects had performed strenuous exercise (power lifting and CrossFit). Both subjects resumed treatment following interruption. The 1 subject in the placebo group with an AE of rhabdomyolysis had increased CK as well as elevated blood myoglobin. Narratives for subjects who had AEs of rhabdomyolysis are provided.
AEs of CK elevation led to study drug interruption in 3 subjects in the VX-445/TEZ/IVA group and no subjects in the placebo group. Most AEs of CK elevation in both treatment groups resolved without change to study drug dosing or after treatment interruption. No subjects discontinued treatment due to AEs of CK elevation in either treatment group.

The mean CK concentration was variable over time in both groups. In the VX-445/TEZ/IVA group, increases from baseline in mean CK were observed. The mean (SD) increases in CK ranged from 35.9 (245.6) U/L at Week 12 to 108.2 (650.2) U/L at Week 24. In the placebo group, there were no trends in CK.

The majority of subjects had CK levels that remained within the normal range. Twenty-one (10.4%) subjects in the VX-445/TEZ/IVA group had CK >5 × ULN, including 10 (5.0%) subjects with CK >10 × ULN. Ten subjects (5.0%) in the placebo group had CK >5 × ULN, including 3 subjects (1.5%) with CK >10 × ULN. The majority of subjects with elevations >10 × ULN had exercised before the elevations.

Study 103 Safety Set

No subjects had AEs of CK elevation.

Increases from baseline in mean and median CK were observed in the VX-445/TEZ/IVA group. The greatest mean (SD) change (22.6 [171.0] U/L) was observed at Day 15.

Study 105 Safety Set

In Study 105, AEs of CK elevation occurred in 31 (6.1%) subjects, none of whom had AEs of rhabdomyolysis. The exposure-adjusted event rate for AEs of CK elevation was lower in Study 105 than in the Study 102 VX-445/TEZ/IVA group (8.90 versus 19.96 events/100PY)

The AEs were mostly mild or moderate in severity. One subject had a serious CK elevation event following strenuous exercise, and the SAE resolved without changes to study drug dosing. Four (0.8%) subjects had an AE of CK elevation that led to treatment interruption, and no subjects discontinued treatment due to AEs of CK elevation.

The majority of subjects had CK levels that remained within the normal range. Forty-two (8.3%) subjects had CK >5 × ULN, including 16 (3.2%) subjects with CK >10 × ULN.

Most subjects with CK elevations had asymptomatic laboratory elevations, many of which were preceded by exercise.

Laboratory findings

Haematology and Coagulation

Mean concentrations of haematology parameters were variable over time in both groups. In the VX-445/TEZ/IVA group, decreases from baseline in mean platelets, leukocytes, and neutrophils were observed; however, mean values of all 3 parameters remained within normal limits at all assessed time points. These findings are not considered clinically adverse and may be markers of reduced systemic inflammation. There were no trends observed in other haematology parameters in the VX-445/TEZ/IVA group in study 102 or in study 103 , There were no trends in coagulation assessments in either group in both studies 102 and 103.

AEs related to haematology and coagulation were infrequent; none of the AEs were serious or led to treatment discontinuation or interruption.

Other Serum Chemistry

Selected serum chemistry laboratory assessments are discussed in events of specific interest There were no trends in other chemistry parameters. Overall, AEs related to other chemistry parameters were infrequent and had a similar overall incidence between treatment groups. None of these AEs were serious or led to treatment discontinuation, and none led to treatment interruption in the VX-445/TEZ/IVA group.

Urinalysis

There were no trends observed in the urinalysis results.

Vital Signs

In Study 102, increases from baseline in mean BP parameters were observed in the VX-445/TEZ/IVA group; increases from baseline ranged from 2.0 to 3.5 mm Hg for mean SBP and 1.1 to 1.9 mm Hg for mean DBP, without a trend of continued increase during the study. The proportion of subjects who had BP in the hypertensive range (i.e., SBP >140 mm Hg or DBP >90 mm Hg) on at least 2 occasions was similar between the treatment groups. There were few AEs of BP increase (1 subject in the VX-445/TEZ/IVA group and 2 subjects in the placebo group). Given the similar incidence of subjects in the hypertensive range between treatment groups and occurrence of few AEs, the modest increase in mean BP in this normotensive population is unlikely to be clinically relevant. There were no meaningful changes in BP in Study 103 or the Phase 1 studies in healthy subjects.

In study 105, for subjects who received VX445/TEZ/IVA in Study 102, there was no further increase in mean BP with continued VX445/TEZ/IVA treatment in Study 105. For subjects who received placebo in Study 102 and received VX445/TEZ/IVA in Study 105, the increase in mean BP was generally similar to that observed in the VX445/TEZ/IVA group in Study 102. Few subjects (5 [1.0%] subjects) in Study 105 had AEs of increased BP; all AEs were mild in severity, and none required study drug interruption or discontinuation.

In Studies 102 and 103, decreases from baseline in mean pulse rate (up to 4.3 bpm in Study 102 and up to 5.5 bpm in Study 103) were observed in the VX-445/TEZ/IVA group. No subjects had AEs of decreased HR. The decrease in mean pulse rate is not considered to be clinically relevant. There were no meaningful changes in pulse rate in the Phase 1 studies in healthy subjects.

In IA2, there were also 83 subjects that had tachycardia, and of 20 patients the tachycardia was accompanied with an increase of heartrate > 20 beats/min in subjects.

In all studies, there were no trends in temperature, respiratory rate, or pulse oximetry.

Electrocardiogram Data

In Studies 102 and 103, decreases from baseline in mean HR were observed in the VX-445/TEZ/IVA group. In study 102, the mean (SD) decreases in HR ranged from -3.7 (12.3) bpm at Week 16 to -5.8 (12.4) bpm at 2 hours post-dose on Day 15. In the placebo group, changes from baseline in mean HR were minimal. In study 103, the greatest mean (SD) change in the VX-445/TEZ/IVA group (-5.4 [8.8] bpm) was observed at Week 4 (compared to 1.9 [9.3] bpm in the TEZ/IVA group).

AEs related to ECG findings or relevant cardiac disorders were infrequent with a similar overall incidence across treatment groups. None of the AEs related to ECG findings or relevant cardiac disorders were serious or led to treatment discontinuation or interruption.

High-precision QT analysis (in Study 001) and a thorough QT/QTc study (Study 009) were conducted for VX-445 and its metabolite M23-445. Both studies showed a lack of effect of VX-445 on QTc.

In separate thorough QT studies for the TEZ and IVA clinical development programs (Studies 661-010 and 770-008, respectively), TEZ and IVA did not prolong the QT/QTc interval in healthy subjects to any clinically relevant extent at doses up to 3 times the maximum recommended dose.

Post-dose Spirometry

Post-dose spirometry was assessed in healthy subjects at approximately 6 hours post-dose on Days 1 and 9 in Study 001 (Parts B and C), and in CF subjects at 5 hours post-dose on Days 1 and 15 in Study 001 (Parts D, E, and F). There were no clinically relevant decreases in post-dose spirometry. Overall, the post-dose $ppFEV_1$ values showed no evidence of decline from the pre-dose $ppFEV_1$ at any assessment time points for both healthy and CF subjects.

Ophthalmologic Examinations

Due to nonclinical findings of cataracts/lens opacities in a study involving IVA monotherapy and the implementation of recommended ophthalmologic examinations in paediatric patients treated with IVA, ophthalmologic examinations were performed in the VX-445 clinical program in subjects <18 years of age.

In Study 102, one (0.5%) subject in the VX-445/TEZ/IVA group had AEs of cataract cortical and lenticular opacity; this subject had a history of CF-related diabetes and concomitant use of corticosteroids. One (0.5%) subject in the placebo group had an AE of cataract; this subject had concomitant use of corticosteroids. Both AEs were mild in severity, not clinically significant, and did not

require treatment or lead to interruption or discontinuation of study drug. In Study 103, follow-up ophthalmologic examinations were not required given the short study duration.

Overall, the ophthalmological examination (OE) data are consistent with previous experience with IVA and IVA-containing regimens.

Safety in special populations

A summary of the safety profile of subjects in subgroups of *F508del*-CFTR mutation with F/MF and F/F in the cumulative safety data across Studies 102, 103, and 105. Across the F/MF and F/F subgroups, the majority of AEs were mild to moderate in severity, and most were consistent with common manifestations of cystic fibrosis (CF) disease or with common illnesses in CF subjects 12 years of age and older. The most common AEs (incidence of ≥15% of subjects in any subgroup) were similar across the F/MF and F/F subgroups. Overall, the safety results were similar between the F/MF and F/F subgroups, and no new safety concerns were identified.

The safety profile is generally also similar across subgroups of patients, including sex, ppFEV1, geographic regions, and genotypes.

The safety results were generally consistent in the subgroups subjects ≥18 years of age and subjects ≥12 to <18 years of age. There were no patients > 65 year in study 102 or study 103.

Immunological events

In Study 102, 4 (2.0%) subjects in each group had an immunological event. In Study 105 IA2, 22 (4.3%) subjects had AEs in the immune system disorders SOC, mainly associated with external allergens (e.g., environmental, animal, food) and were not considered study-drug-related. One subject had a nonserious AE of anaphylactic reaction that was caused by an allergic reaction to cashews. The event resolved without change to study drug dosing and was assessed by the investigator as not related to study drug (See Table 52).

Table 52:AEs in the SOC of Immune System Disorders Occurring in At Least 1 Subject: Study 102 Safety Period, OL Safety Period, and Cumulative TC Safety Period (Study 102 Safety Set, OL Safety Set, and Cumulative TC Safety Set)

	Study 102		Study 105 (OLS)	Cumulative TC Safety Period
Preferred Term, n (%)	Placebo in 445-102 N = 201	VX-445/TEZ/IVA in 445-102 N = 202	Any VX-445/TEZ/IVA N = 506	Any VX-445/TEZ/IVA N = 510
Subjects with at least 1 AE in immune system disorders SOC	4 (2.0)	4 (2.0)	22 (4.3)	26 (5.1)
Seasonal allergy	2 (1.0)	3 (1.5)	16 (3.2)	19 (3.7)
Hypersensitivity	1 (0.5)	1 (0.5)	2 (0.4)	3 (0.6)
Drug hypersensitivity	1 (0.5)	0	2 (0.4)	2 (0.4)
Allergy to animal	0	0	1 (0.2)	1 (0.2)
Allergy to arthropod bite	0	0	1 (0.2)	1 (0.2)
Anaphylactic reaction	0	0	1 (0.2)	1 (0.2)
Food allergy	0	0	1 (0.2)	1 (0.2)

Source: ISA2 Table 2.3.1.2.1

AE: adverse event; IVA: ivacaftor; n: size of subsample; N: total sample size; OLS: open-label study; PT: Preferred Term; SOC: System Organ Class; TC: triple combination; TEZ: tezacaftor

Notes: MedDRA Version 22.1 was used. A subject with multiple events within a category was counted only once in that category. The table was sorted in descending order of frequency of the Any VX-445/TEZ/IVA column during the Cumulative TC Safety Period by PT.

Safety related to drug-drug interactions and other interactions

No information on PD interactions is provided. For PK interactions, please refer to clinical pharmacology discussion for pharmacokinetic interactions (CYP3A inducer/inhibitor interactions).

Discontinuation due to AES

In Study 102, two subjects (both in the VX-445/TEZ/IVA group) discontinued study drug due to an AE, one subject with a non-serious AE of rash and one subject with a medical history of hepatic cirrhosis because of a SAE of portal hypertension. Both events were assessed by the investigator as being of moderate severity and possibly related to study drug.

In Study 103, no subjects had AEs that led to treatment discontinuation.

In IA1 of Study 105, 6 (1.2%) subjects had AEs that led to treatment discontinuation, and 7 (1.4%) subjects in IA2. Three subjects discontinued due to AEs of transaminase elevation. The other subjects discontinued treatment due to AEs of depression (1 subject), rash (1 subject), and tinnitus and contusion (1 subject) and additionally in IA2 hepatic encephalopathy (1 subject). For the subject with non-serious AEs of tinnitus and contusion, study drug was discontinued, and the events were ongoing at time of the data cut. For the other subjects the AE were resolved after discontinuation of study drug. For the subject who discontinued VX-445/TEZ/IVA treatment due to an SAE of hepatic encephalopathy the event resolved with treatment. The subject had a history of hepatic cirrhosis, portal hypertension with gastric varices, and thrombocytopenia.

In the Cumulative Safety Set, 10 (2%) subjects discontinued study drug due to AEs, with 4 (0.8%) subjects discontinuing due to LFT elevations and 2 (0.4%) subjects discontinuing due to rash events.

In the set of subjects who received VX-445/TEZ/IVA for at least 48 weeks, none of the subjects were discontinued from study medication.

In the Healthy Subjects, in the Any VX-445 group, 2 (1.0%) subjects had AEs that led to treatment discontinuation, both of which were rash events. One subject with rash generalized who received VX-445 in Study 009, a thorough QT/QTc study and one subject with dermatitis who received VX-445/TEZ/IVA in Study 001, a single- and multiple-dose escalation first-in-human study.

AEs Leading to Interruption of Study Drug

In Study 102, 29 subjects (19 subjects [9.4%] in the VX-445/TEZ/IVA group and 10 subjects [5.0%] in the placebo group) interrupted study drug due to an AE. Of the 19 subjects in the VX-445/TEZ/IVA group, 16 subjects resumed study drug treatment in Study 102, and 3 subjects enrolled in extension Study 105 while study drug was interrupted.
In the VX-445/TEZ/IVA group, AEs that led to treatment interruption that occurred in ≥2 subjects were rash, ALT increased, infective PEx of CF, influenza, and rhabdomyolysis. In the placebo group, ALT increased led to treatment interruption in ≥2 subjects.

In Study 103, no subjects had AEs that led to treatment interruption.

In study 105, 29 (5.7%) subjects had AEs that led to treatment interruption. Events that occurred in≥2 subjects were ALT increased, AST increased, rash, blood alkaline phosphatase increased, GGT increased, and blood creatine phosphokinase increased. Other AEs that lead to interruption were pruritus generalised, abdominal pain upper, constipation, duodenitis, gastric haemorrhage, cholecystitis acute, depression, blood bilirubin increased, liver function test increased, pityriasis rosea, rash maculo-papular, infective pulmonary exacerbation of cystic fibrosis, bacterial vaginosis, hand-foot-and-mouth disease, tendonitis, pulmonary haemorrhage, pyrexia, burning sensation, haematuria.

2.6.1. Discussion on clinical safety

Patient population and exposure

The core safety analyses in CF subjects evaluated data from Studies 102 and 103, and an interim analysis (IA2) of the open-label extension Study 105 as separate sets. Study 102 provided the main safety data. In addition to the core safety analyses, a Cumulative Safety Set and a subset of subjects in the Cumulative Safety Set who received ≥ 48 weeks of treatment with VX-445/TEZ/IVA were presented. Overall, these sets together provide a sufficient overview of the safety profile of Kaftrio. Study 105 is ongoing and interim analyses (IA1 cut-off date 10 July 2019, IA2 cut-off date 31 October 2019) were submitted during this procedure. Further safety data will be provided post approval which is acceptable. This is adequately described in the RMP.

In the Phase 3 program, 510 subjects received at least 1 dose of VX-445/TEZ/IVA, with a total exposure of approximately 496.6 patient-years. In the Cumulative Safety Set (parent Studies 102 or 103 and/or during Study 105), 12 subjects had an exposure of ≤ 24 weeks, 229 subject > 24 ≤ 48 weeks, and 271 subjects ≥ 48 weeks. This is considered acceptable to assess long-term safety.

Adverse events, serious adverse events and deaths

Pivotal placebo-controlled studies, Study 102 and Study 103

Nearly all patients in both arms in study 102 experienced at least one treatment-emergent AE (93.1% of patients in the VX-445/TEZ/IVA arm and 96.0% in the placebo arm). In study 103 these numbers are much lower, 58.2% in the VX-445/TEZ/IVA group and 63.5% in the TEZ/IVA group, likely because of the shorter duration of this study.

Overall, the AEs were mostly consistent with common manifestations of CF disease or with common illnesses. In study 102, AEs occurring in ≥8% of subjects in the VX-445/TEZ/IVA group with an incidence ≥1% higher than in the placebo group were headache (17.3% versus 14.9%), diarrhoea (12.9% versus 7.0%), upper respiratory tract infection (11.9% versus 10.9%), abdominal pain (9.9% versus 6.0%), alanine transaminase (ALT) increased (9.9% versus 3.5%), aspartate transaminase (AST) increased (9.4% versus 2.0%), blood creatine phosphokinase increased (9.4% versus 4.5%), nasal congestion (9.4% versus 7.5%), rash (8.9% versus 4.5%), and rhinorrhoea (8.4% versus 3.0%). All of these are included as ADRs in section 4.8 of the SmPC.

Initially, AEs occurring in ≥8% of subjects in the VX-445/TEZ/IVA group with an incidence ≥1% higher than in the placebo group were considered an ADR. However, this margin is considered arbitrary and generous. Upon request by CHMP, additional analyses with more stringent margins were provided. Two additional ADRs occurred in ≥5% of subjects in the VX-445/TEZ/IVA group with an incidence ≥1% higher than in the placebo group compared to the cut-off level of ≥8%, i.e. rhinitis and influenza. Compared to the cut-off level of ≥5%, 8 additional ADRs occurred in ≥3% of subjects in the VX-445/TEZ/IVA group with an incidence ≥1% higher than in the placebo group, i.e. abdominal pain upper, flatulence, hypoglycaemia, acne, dizziness, pruritus, wheezing and abnormal breathing. All of these have been included in section 4.8 of the SmPC as ADRs. Blood pressure increased is also included in section 4.8 of the SmPC as an ADR.

Results in Study 103 were reasonably similar as in the study 102 Safety set. In Study 103, the incidence of subjects with at least 1 AE was lower than in Study 102 but similar in both treatment groups (58.2% in the VX-445/TEZ/IVA group and 63.5% in the TEZ/IVA group). The different duration of the studies may be likely the reason for the differences observed in incidence of AEs.

In Study 102, related AEs occurred more frequently in the VX-445/TEZ/IVA (47.5%) compared to the placebo group (25.9%). These most frequent related in order of highest frequency are sputum increased (6.9%) ALT increased (5.9%), AST increased (5.4%) and rash (5.4%). These related AEs are also more frequent than in placebo. In study 103 Safety Set, more subjects in the VX-445/TEZ/IVA group (12 (21.8%)) had related AEs compared subjects in the placebo group (9 (17.3%)). The most frequent related in order of highest frequency was respiration abnormal (5.5%) while all other events were only observed in 1 or 2 patients.

Overall the numbers of Grade 3 or 4 AEs were low. In study 102, 19 (9.4%) subjects had severe AEs and no subjects had life-threatening AEs in the VX-445/TEZ/IVA group, while 14 (7.0%) subjects had severe AEs and 1 (0.5%) subject had a life-threatening AE of neuroglycopenia in the placebo group. Blood creatine phosphokinase increased (2%) and alanine aminotransferase increased (1%) and aspartate aminotransferase increased (1%) occurred ≥ 1%. In the Study 103 Safety Set, only 1 (1.9%) subject in the TEZ/IVA group had a severe AE (musculoskeletal pain).

Eight cases of haemoptysis were classified as possibly related to study drug all in patients treated with VX-445/TEZ/IVA. Of note, an additional case of severe gastric haemorrhage (unlikely related) was reported. Two additional cases, one each of ocular retrobulbar haemorrhage (possibly related), menorrhagia (possibly related) and 3 cases of vaginal haemorrhage (not related) were reported. There were no clear markers of increased tendency to bleed. There was no evidence of increased prothrombin times, platelets decreased were reported in 6.7% of subjects but no subjects reported decreases ≥25 to <50 (10^9/L). At present it was considered premature to reflect these in the SmPC.

The event rate for influenza was 3E/100PY in the placebo arm and 16E/100PY in VX-445/TEZ/IVA arm in Study 102, while it was 4.6E/100PY and 6.9E/100PY in the long term OLS and Cumulative safety analyses respectively. The difference between placebo arm and in VX-445/TEZ/IVA arm in Study 102 was not sufficiently explained. On the basis of this analysis, and also taking into consideration the analysis of AEs occurring in ≥5%, and ≥3% of subjects, Influenza has been included as an ADR in

section 4.8 of the SmPC. The applicant committed to monitoring reporting rates of influenza in subsequent PSURs and the applicant agreed to incorporate available data on influenza in the planned PASS. As measures other than routine pharmacovigilance is being proposed to monitor this event "Susceptibility for influenza virus infections" is classified as an important identified risk in the RMP.

Analyses of the duration of a specific event were performed. There was no apparent increase in the incidence of individual AEs over time in subjects who received VX-445/TEZ/IVA, as most the most common AEs were highest during the 0- to 8-week interval.

In study 102, the incidence of SAEs was lower in VX-445/TEZ/IVA group (28 (13.9%)) than in the placebo group (42 (20.9%)). Overall, the SAEs were mostly consistent with common manifestations of CF disease or with common illnesses in CF subjects. Rash and influenza occurred in ≥2 subjects in any group and were more common in the VX-445/TEZ/IVA group than the placebo group. In study 103, 1 subject had an SAE of infective pulmonary exacerbation (PEx) of CF and 1 subject had an SAE of rash in VX-445/TEZ/IVA group while 1 (1.9%) subject had an SAE of infective PEx of CF in the TEZ/IVA group.

No deaths were reported in the VX-445/TEZ/IVA clinical development program.

Long term open-label safety study, Study 105 Safety Set, Cumulative safety Set and safety in patients who received VX-445/TEZ/IVA for at least 48 weeks

The long-term safety Study 105 Safety Set and Cumulative safety Set showed decreased incidences of (related) AEs, Grade 3-4 AEs, SAEs and AEs leading to treatment discontinuation with VX-445/TEZ/IVA compared to Study 102 Safety Set.

In the Study 105 Safety Set the (related) AEs and SAE were mostly consistent with common manifestations of CF disease or with common illnesses in CF subjects 12 years of age and older. A total of 169 (33.4%) subjects had AEs considered related or possibly related to VX-445/TEZ/IVA. In addition to already observed related AE in study 103, photosensitivity reaction was observed in 7 subjects, but all resolved with continued study drug treatment. Furthermore, the exposure-adjusted event rate for the AE of photosensitivity reaction overall was similar in Study 105 and in the placebo group of Study 102. Taking these arguments into account there is insufficient information to include photosensitivity as and ADR. Photosensitivity will be reviewed in subsequent PSURs.

The exposure-adjusted event rates for the majority of AEs were similar or lower in Study 105 than in the Study 102 VX-445/TEZ/IVA group apart from cough, fatigue, haemoptysis and sinus congestion that occurred more frequently in Study 105.

In Study 105, 51 (10.1%) subjects had severe (Grade 3) AEs and 2 (0.4%) subjects had life-threatening (Grade 4) AEs. Only pulmonary exacerbation of cystic fibrosis (3.2%) occurred >1% as Grade 3 and 4 AE. The two life-threatening AEs were an event of non-related suicide attempt and an event pulmonary haemorrhage, which was considered to be possibly related to VX-445/TEZ/IVA.

In both the overall cumulative analysis and the 48-week cumulative exposure analysis, Exposure-adjusted analyses of event rates in Study 102 showed a decrease in the rates of the majority of related AEs with longer-term treatment compared with Study 105.

In the set of subjects who receive VX-445 for at least 48 weeks, 41 (15.1%) subjects had at least 1 AE that was Grade 3 or 4 in severity. Grade 3 or 4 events that occurred in ≥2 subjects were infective PEx of CF (10 subjects), blood creatine phosphokinase increased (8 subjects), DIOS (4 subjects), AST increased (4 subjects), ALT increased (3 subjects), GGT increased (2 subjects), gastritis (2 subjects), and influenza (2 subjects).

The safety profile of subjects in subgroups of *F508del-CFTR* mutation with F/MF and F/F in the cumulative safety set was broadly comparable across the F/MF and F/F subgroups respectively.

Adverse events of special interest

Transaminase elevations are common in CF and have been observed in patients receiving IVA monotherapy, TEZ/IVA, and VX-445/TEZ/IVA. In the pivotal VX-445/TEZ/IVA, exclusion criteria for patients with pre-existing liver function impairments were more stringent compared to the Orkambi trials and Symkevi. In the VX-445/TEZ/IVA trials patients were excluded when 1 out of the defined impairments were present instead of 2 (Symkevi) or 3 (Orkambi) trial.

In Study 102, the incidence of transaminase elevation adverse events was 2-3 times higher in the VX-445/TEZ/IVA group than in the placebo group. The vast majority of the events were non-severe, non-serious and did not lead to treatment discontinuation. In addition, only one event of portal hypertension in the VX-445/TEZ/IVA was a SAE, occurring in a subject with a history of hepatic cirrhosis, that led to discontinuation of VX-445/TEZ/IVA treatment.

Results from Study 103 and Study 105 were generally consistent with those from Study 102. In addition, increases from baseline in mean total bilirubin were observed in the VX-445/TEZ/IVA group, with a greater increase in indirect bilirubin than direct bilirubin. In the placebo group, changes from baseline in mean total bilirubin were minimal. AEs associated with bilirubin elevation occurred in 10 (5.0%) subjects in the VX-445/TEZ/IVA group and 2 (1.0%) subjects in the placebo group. One subject had an AE of bilirubin elevation that was not serious and led to treatment interruption.

Consequently, a warning regarding the potential risk for elevated transaminases has been included in section 4.4 of the SmPC, similarly to Kalydeco and Orkambi, which is agreed by CHMP. As in the RMP clinical outcomes are defined for the identified elevated transaminases, hepatotoxicity is included as a potential serious risk. VX-445/TEZ/IVA is not recommended in patients with moderate hepatic impairment and should not be used in patients with severe hepatic impairment. Only in case of a clear medical need for treatment with Kaftrio and after weighing the benefits and risks of such treatment, VX-445/TEZ/IVA may be used in patients with moderate hepatic impairment applying a 25% dose reduction. Further data are awaited post marketing in patients with moderate hepatic impairment (study 007) described as category 3 in the RMP.

Rash events have been seen in subjects treated with VX-445/TEZ/IVA including in the Phase 1. In Study 102, there was a higher incidence of rash events in the VX-445/TEZ/IVA group (10.9%, 22 subjects) than in the placebo group (6.5%, 13 subjects). Most rashes occurred within the first 3 weeks of study drug treatment. Serious rash events occurred in 3 (1.5%) subjects in the VX-445/TEZ/IVA group, while in 1 (0.5%) subject in the placebo group. There was also an increase in the incidence of rash in female subjects taking hormonal therapy compared with those not taking hormonal therapy; the increase was larger in the VX-445/TEZ/IVA group than in the placebo group. Therefore, a role for hormonal therapy in the occurrence of rash cannot be excluded. This is adequately addressed in the SmPC section 4.4.

AEs of CK elevation occurred more frequently in subjects in the VX-445/TEZ/IVA group compared to the placebo group. The majority were asymptomatic laboratory elevations, many of which were preceded by exercise. Most AEs of CK elevation resolved without change to study drug dosing or after treatment interruption. Two subjects in the VX-445/TEZ/IVA group with AEs of rhabdomyolysis presented with CK elevations, and neither subject had clinical features of rhabdomyolysis (e.g., kidney involvement, myoglobinuria). Both subjects had performed strenuous exercise (power lifting and CrossFit), which was likely the cause of the CK elevations.

No clinically meaningful trends in the respiratory-related AEs or post-dose spirometry data were observed during phase I in healthy volunteers and CF patients at the proposed dose.

In Study 102, small increases from baseline in Systolic Blood Pressure (SBP) and Diatolic Blood Pressure (DBP) were observed in the VX-445/TEZ/IVA group were observed.

Safety in special populations

No patients in the Phase 3 clinical studies were aged 65 years or older at screening. This is acceptable when considering the severity of the disease and life-expectancy in the investigated CF mutations (homozygote *F508del* and heterozygote *F508del/MF*).

The safety profile is generally also similar across subgroups of patients, including sex, ppFEV1, geographic regions, and genotypes.

Assessment of paediatric data on clinical safety

No clinically relevant differences in safety profile of VX-445/TEZ/IVA between patients ≥12 to <18 years of age and ≥18 years of age have been observed.

2.6.2. Conclusions on clinical safety

With the addition of VX-445 to TEZ/IVA, an increase in hepatic toxicity, influenza and rash were identified with the addition of TEZ to IVA. These safety events can be handled in the clinical practice and have been adequately described in the SmPC and RMP. Differences in the safety profile of VX-445/TEZ/IVA across studies could be explained by the difference in exposure during the studies. Overall, VX-445/TEZ/IVA was well tolerated with low discontinuation rates due to AEs.

The results of the interim analyses of the long-term safety Study 105 are considered adequate to support approval in F/F and F/MF populations. The study is ongoing and further analyses will be submitted post approval and further characterise safety in CF patients. The ongoing study 007, in patients with moderate or severe hepatic impairment will provide further information to assess the use of Kaftrio in these populations in view of the concerns related to hepatotoxicity defined as an important potential risk in the RMP.

2.7. Risk Management Plan

Safety concerns

Safety concerns

Important identified risks	• Susceptibility for influenza virus infections
Important potential risks	• Hepatotoxicity • Cataract
Missing information	• Use in pregnant and lactating women • Long-term safety • Use in patients with moderate or severe hepatic impairment

Phamacovigilance 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)				
Not applicable				
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)				
Not applicable				
Category 3 – Required additional PV activities (by the competent authority)				
Study in patients with moderate hepatic impairment (Study 007) Ongoing	Evaluate the safety, tolerability, and PK of ELX/TEZ/IVA in subjects without CF who have moderate hepatic impairment and in matched healthy subjects	• Use in patients with moderate hepatic impairment	Final Report	Q3 2020
Open-label extension study (Study 105) Ongoing	Evaluate the long-term safety, tolerability, and efficacy and the PD of ELX/TEZ/IVA treatment for 96 weeks in subjects 12 years of age and older with CF, homozygous or heterozygous for the *F508del-CFTR* mutation	• Susceptibility for influenza virus infections • Hepatotoxicity • Cataract • Long-term safety	Final Report	31 December 2022
PASS Planned	Evaluate the safety outcomes, CF disease progression, frequency and outcome of pregnancy, and drug utilisation patterns in CF patients taking ELX/TEZ/IVA in the real-world setting	• Susceptibility for influenza virus infections • Hepatotoxicity • Use in patients with moderate or severe hepatic impairment • Use in pregnant women • Long-term safety	Annual Reports	31 December 2021/2022/ 2023/2024
			Final Report	31 December 2025

CF: cystic fibrosis; ELX/TEZ/IVA: elexacaftor in combination with tezacaftor and ivacaftor; F508del: an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type CFTR protein; LFT: liver function test; MA: market authorisation; PASS: post-authorisation safety study; PD: pharmacodynamics; PK: pharmacokinetics; PV: pharmacovigilance; Q3: Quarter 3; Study 007: VX18-445-007; Study 105: VX17-445-105

Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Susceptibility for influenza virus infections	**Routine risk minimisation measures:** SmPC Section 4.8 PL Section 4 Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** • Open-label extension study (Study 105) (Final Report: 31 December 2022) PASS (Annual Reports: 31 December 2021/2022/2023/2024; Final Report: 31 December 2025)
Hepatotoxicity	**Routine risk minimisation measures:** SmPC Sections 4.4 and 4.8 SmPC Section 4.4 where recommendations for LFT monitoring and treatment stopping rules are provided. PL Sections 2 and 4 PL Sections 2 and 4 where expectations for LFT monitoring and detection of potential signs of liver problems are discussed. Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** • Open-label extension study (Study 105) (Final Report: 31 December 2022) • PASS (Annual Reports: 31 December 2021/2022/2023/2024; Final Report: 31 December 2025)
Cataract	**Routine risk minimisation measures:** SmPC Sections 4.4 and 5.3 SmPC Section 4.4 where recommendations for baseline and follow-up ophthalmological examinations in paediatric patients are provided. PL Section 2 PL Section 2 where expectations for eye examinations are discussed. Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** • Open-label extension study (Study 105) (Final Report: 31 December 2022)

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in pregnant and lactating women	**Routine risk minimisation measures:** SmPC Sections 4.6 and 5.3 SmPC Section 4.6 where advice is given regarding use during pregnancy and breastfeeding. PL Section 2 PL Section 2 where advice is given to speak with a healthcare professional before use during pregnancy and breastfeeding. Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Pregnancy follow-up questionnaire **Additional PV activities:** • PASS (Annual Reports: 31 December 2021/2022/2023/2024; Final Report: 31 December 2025)
Long-term safety	**Routine risk minimisation measures:** SmPC Section 4.8 Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** • Open-label extension study (Study 105) (Final Report: 31 December 2022) • PASS (Annual Reports: 31 December 2021/2022/2023/2024; Final Report: 31 December 2025)
Use in patients with moderate or severe hepatic impairment	**Routine risk minimisation measure:** SmPC Sections 4.2, 4.4, and 5.2 SmPC Sections 4.2 and 4.4 where recommendations regarding use in patients with hepatic impairment are provided. PL Sections 2 and 3 PL Sections 2 and 3 where advice to speak with a healthcare professional before use in patients with liver problems is provided. Prescription only **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** None **Additional PV activities:** • Study in patients with moderate hepatic impairment (Study 007) (for evaluation of use in patients with moderate hepatic impairment only) (Final Report: Q3 2020) • PASS (Annual Reports: 31 December 2021/2022/2023/2024; Final Report: 31 December 2025)

LFT: liver function test; PASS: Post-authorisation safety study; PL: Package Leaflet; PV: pharmacovigilance; Q3: Quarter 3; SmPC: Summary of Product Characteristics; Study 007: VX18-445-007; Study 105: VX17-445-105

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.7 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 21 October 2019.

2.9. New Active Substance

The applicant compared the structure of elexacaftor with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers elexacaftor / tezacaftor / ivacaftor contained in the fixed combination medicinal product – Kaftrio to be a new active substance as this FDC is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Kaftrio (elexacaftor / tezacaftor / ivacaftor) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Cystic Fibrosis (CF) is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality for which and at present, there is no cure. Cystic fibrosis is caused by mutations in the *CFTR* gene that result in absent or deficient function of the *CFTR* protein at the cell surface. The *CFTR* protein is an epithelial chloride channel responsible for aiding in the regulation of salt and water absorption and secretion. The failure to regulate chloride transport in these organs

results in the multisystem pathology associated with CF. Lung disease is the primary cause of morbidity and mortality in people with CF. *F508del*, is the most common disease-causing mutation (84.7% of the individuals in the US and 81.1% of the individuals in Europe)[6,7].

3.1.2. Available therapies and unmet medical need

Two types of CF therapies exist. The use CF therapies that target the symptoms of the disease (such as nutritional supplements, antibiotics, and mucolytics), in combination with *CFTR* modulators (i.e. correctors and potentiators) is recommended to maintain and improve lung function, reduce the risk of infections and exacerbations; and improve quality of life.

Correctors (such as tezacaftor and VX-445), facilitate the cellular processing and trafficking of mutant *CFTR* to increase the quantity of functional *CFTR* at the cell surface, resulting in enhanced chloride transport. *CFTR* potentiators (like ivacaftor) enhance the channel gating activity of the *CFTR* which is delivered to the cell surface (by correctors).

Kalydeco (ivacaftor, IVA), Orkambi (lumacaftor/ivacaftor, LUM/IVA) and Symkevi (tezacaftor/ivacaftor, TEZ/IVA) are *CFTR* modulators approved for CF patients with specific mutations.

The claimed indication by the Applicant was as follows: *"Kaftrio (VX-445/TEZ/IVA) is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene*."

The proposed indication covers F/F genotypes, F/MF 'minimal function' genotypes, F/G 'gating' genotypes, and F/RF 'residual function' genotypes. It comprises subpopulations in which approved modulator therapies are available (*F508del* homozygous patients (F/F), patient heterozygous for *F508del* and a specific residual function mutation (F/RF) or a specific gating mutation (F/G). Nevertheless, these treatments do not cure the disease and more efficacious treatments could fulfil this gap in these patients. For the populations heterozygous for *F508del* and a minimal function mutation (F/MF) no treatment is available, which is an unmet need in this subpopulation.

3.1.3. Main clinical studies

The main evidence of efficacy and safety is obtained from three trials. All three trials investigated the triple VX-445 200 mg/tezacaftor 100mg/ivacaftor 150mg morning dose in combination with ivacaftor 150 mg as evening dose.

Study 102 in CF patients 12 years and older is a 24-week, randomized, double-blind, placebo-controlled, parallel-group study in subjects heterozygous for the *F508del-CFTR* mutation and a minimal function mutation. Patients with minimal function mutation were defined as patients with Class I mutations that predicted no CFTR protein being produced (including nonsense mutations, canonical splice mutations, and insertion/deletion frameshift mutations both small (≤3 nucleotide) and non-small (>3 nucleotide), as well as patients with missense mutations which results in CFTR protein that does not transport chloride and is not responsive to ivacaftor and tezacaftor/ ivacaftor *in vitro*.

[6] Cystic Fibrosis Foundation. Patient Registry: 2018 Annual Data Report. Bethesda, MD: CysticFibrosisFoundation; 2019.

[7] European Cystic Fibrosis Society. 2017 ECFS Patient Registry Annual Data Report. Karup, Denmark: European Cystic Fibrosis Society; 2019

A total of 403 subjects received at least one dose of study drug. Placebo was used as control treatment because no *CFTR* modulators were approved. The primary endpoint was absolute change from baseline in ppFEV1, which was accompanied by several key secondary endpoints (pulmonary exacerbations, SwCl, CFQ-R RD, BMI).

Study 103 in CF patients 12 years and older is a 4-week, randomized, double-blind, TEZ/IVA-controlled, parallel-group study in subjects homozygous for the *F508del-CFTR* mutation. A total of 107 subjects received at least one dose of study drug. TEZ/IVA (Symkevi) was used a control treatment, as this is an approved therapy in this patient population. The primary endpoint was absolute change from baseline in ppFEV1 at week 4, which was accompanied by key secondary endpoints on SwCl and CFQ-R RD score.

Study 105 is an ongoing open-label rollover study that enrolled subjects from study 102 (n=400) and 103 (n=107). This study is designed to support long-term safety (primary objective) and maintenance of efficacy (secondary objective). The Interim analysis 2 (IA2) was submitted to allow evaluation of long-term safety of F/F and F/MF patients. Efficacy data, with an additional 36 week or 24-week treatment, are submitted for F/F patients which were enrolled in study 103 and for F/MF patients enrolled in study 102, respectively.

The core safety analyses consisted of separate analyses of studies 102 and 103, and the second interim analysis (IA2) of the open-label extension Study 105. The safety profile of VX-445/TEZ/IVA was mainly derived from Study 102. Safety data from Studies 102 and 103 were not pooled because of the substantial differences in the design of the two studies. In addition, analyses of the Cumulative Safety Set and a subset of subjects in the Cumulative Safety Set who received ≥ 48 weeks of treatment with VX-445/TEZ/IVA were submitted.

The Study 102 Safety Set contains all subjects who received at least one dose of study drug. The Study 103 Safety includes all subjects who received at least one dose of study drug in the Study 103 Treatment Period (i.e., does not include subjects who were only dosed in the TEZ/IVA Run-in Period). The Study 105 Safety Set includes all subjects who received at least one dose of study drug in Study 105. The Cumulative Safety Set includes all subjects who received at least one dose of VX-445/TEZ/IVA during the parent studies 102 or 103 and/or during study 105.

3.2. Favourable effects

Rationale for the VX445 dose in the triple combination

For CF patients 18 years and older with an F/MF mutation three doses (50 mg, 100 mg and 200 mg) of VX-445 were tested in combination with the approved dosage of TEZ/IVA. ppFEV1 and SwCl changes from baseline with the TC are compared to changes from baseline with placebo. A difference in ppFEV1 compared to placebo was seen for all dose tested strengths (11.1, 7.8 and 13.8, for 50, 100 and 200mg respectively). For SwCl, an improvement (decline) compared to placebo was also detected (-36.1, -31.0, -36.9 for 50, 100 and 200mg respectively). The best efficacy results were observed with the 200 mg dose in all cases: efficacy data, exposure-response models and simulated efficacy data for FEV1 and SwCl.

For CF patients 18 years and older with an F/F mutation, only the final 200 mg dose of VX-445 was investigated. A benefit with VX-445/TEZ/IVA compared to TEZ/IVA is seen (ppFEV1:10.6%; SwCl: -40.4 mmol/L).

CF patients 12 years or older with the F/MF genotype (study 102) VX-445/TEZ/IVA showed an absolute change in ppFEV1 through week 24 between the VX-445/TEZ/IVA and placebo groups of 14.3% (CI 95%: 12.7 – 15.8; p<0.0001) in favour of the triple combination. A comparable difference was

observed at week 4 already (13.7; CI 95% 12.0 - 15.3; p<0.0001). Approximately 80% patients treated with the TC have an increase in ppFEV1 >5%, compared to 15% in the placebo group.

Several key secondary endpoints were analysed. For pulmonary exacerbations, the rate ratio was 0.37 (95% CI: 0.25 – 0.55, p<0.0001) in favour of VX-445/TEZ/IVA, corresponding to a reduction of 63%. The hazard ratio for time-to-first pulmonary exacerbations was also in favour of the triple combination (HR: 0.34; 95% CI 0.22, 0.52; p<0.0001). For changes in SwCl from baseline, a stable reduction of -41.8 mmol/L (95% CI: -44.4 to -39.3; p< 0.0001) through week 24 compared to placebo was observed. A higher CRQ-R RD score was observed in the TC arm compared to the placebo arm (20.2 points; 95% CI 17.5,23.0; p<0.0001). All other CFQ-R domains indicated an improvement with the TC compared to placebo. Last, an absolute change of 1.04 (95% CI: 0.85, 1.23; p<0.0001) compared to placebo was seen in BMI.

All other endpoints showed also a positive effect for VX-445/TEZ/IVA compared to placebo.

Consistent and significant benefits in ppFEV1 favouring VX-445/TEZ/IVA were observed across all prespecified subgroups: age, sex, baseline lung function, region, P. aeruginosa infection, and baseline use of common CF medications.

An ad-hoc subgroup analysis was performed on patients included based in genetic criterion 1 (likely no protein translated) and on criterion 2 (missense not responding the TEZ and/or IVA *in vitro*). Class 1 (MF) mutant patients showed an absolute change from baseline in ppFEV1 of 14.8% comparing the triple combination with placebo. The missense mutant patients showed a difference in ppFEV1 of 12.9%. Further subdivision of these genotypes (nonsense, splicing, and indel-frameshift) and FRT responsiveness show reasonably similar results. Subjects treated with the TC in parent study continued to show a comparable benefit at 24 weeks (study 102) and through 48 weeks (study 105) of treatment, respectively (ppFEV1: 13.9 vs 14.3; SwCl: -42.2 vs -49.0; CFQ-R RD: 17.5 vs 20.1). Patients which received placebo in the parent study showed similar benefits (ppFEV1: 14.9, SwCL: -50.3, CFQ-R: 19.2) in these parameters after 24 weeks of VX-445/TEZ/IVA treatment.

With the results from study 105, data for exacerbations and nutritional status became available. With regard to the number of PEx an estimated event rate per year of 0.32 (95% CI: 0.24-0.44) is anticipated. With regard to the nutritional status, a benefit compared to baseline is observed for all parameters (change in BMI, BMI z-score and body weight).

CF patients 12 years or older with the F/F genotype (study 103/105).
VX-445/TEZ/IVA showed an absolute change in ppFEV1 at week 4 between the VX-445/TEZ/IVA and TEZ/IVA groups of 10.0% (7.4 – 12.6; p<0.0001) in favor of the triple combination. Approximately 70% patients treated with the TC have an increase in ppFEV1 >5%, compared to 13% in the TEZ/IVA group.

For the key secondary endpoint, change in SwCl from baseline, a reduction of -45.1 mmol/L (95% CI: -50.1 to -40.1; p< 0.0001) at week 4 was observed after treatment with VX-445/TEZ/IVA compared to TEZ/IVA. Key secondary endpoint, change in CRQ-R RD score, improved significantly in the TC arm compared to the TEZ/IVA arm (17.4 points; 95% CI 11.8,23.0; p<0.0001). All other CFQ-R domains indicated an improvement with the TC compared to TEZ/IVA.

Ad hoc analyses on BMI and weight also demonstrate of beneficial effect of the TC over TEZ/IVA.

Consistent benefits in ppFEV1 favouring VX-445/TEZ/IVA were observed across all prespecified subgroups: age, sex, baseline lung function, region, P. aeruginosa infection, and baseline use of common CF medications.

Subject treated with the TC in parent study continued to have a similar benefit at 4 weeks (study 103) and through 36 (ppFEV1) or 24 weeks (SwCL and CFQ-R) (study 105) of treatment, respectively

(ppFEV1: 10.4 vs 11.9; SwCl: -43.4 vs -47.2; CFQ-R RD: 16vs 14.3). Patients which received placebo in the parent study showed comparable benefits (ppFEV1: 12.8, SwCL: -49.4, CFQ-R: 13.8) in these parameters after 36/24 weeks of VX-445/TEZ/IVA treatment.

With regard to the number of PEx an estimated event rate per year of 0.30 (95% CI: 0.20-0.45) and a probability of event-free survival of 0.859 (95% CI: 0.777-0.912) is anticipated. With regard to the nutritional status, a benefit compared to baseline is observed for all parameters (change in BMI, BMI z-score and body weight).

Real world data from the US CFFPR for F/F showed consistent results with what was seen in the clinical study 103.

CF patients 12 years or older with the F/RF and F/G genotype (real world data).

No clinical data was provided for the F/RF and F/G genotypes. Real world data from the US CFFPR for F/RF and F/G patients treated with VX-445/TEZ/IVA were however provided towards the end of the assessment. Based on the available data, improvements in ppFEV1 were seen in the F/G and F/RF populations of 4.3% and 2.7% respectively, compared to a baseline ppFEV1 measurement before the start of VX-445/TEZ/IVA therapy.

3.3. Uncertainties and limitations about favourable effects

The applicant hypothesis that if a modulator has a large effect on the *F508del-CFTR,* the presence of a single *F508del* allele would be sufficient to derive a clinical benefit (as defined by the F/any treatment paradigm) could not be demonstrated unambiguously, as it is theoretically still possible that some of the MF mutants may make a minor contribution to the *CFTR*-mediated chloride transport upon treatment with VX-445/TEZ/IVA.

With regards to the dose of VX-445 in the triple combination, no clear dose response, has been observed, most likely due to small numbers in the subgroups, as the 100 mg arm showed a lower response than the 50 mg and 200 mg arms.

The same dose is proposed for adolescents from age 12 years and older to adulthood. There were no Phase 1/2 PK adolescent data to inform the dose choice, nor was there modelling/simulation of Phase 1/2 data in advance of Phase 3. Pop-PK analysis of PK data from Phase 1/2 and 3 confirmed that age and weight were not significant co-variates and clearance in adults and adolescents was similar. However, while the lowest weight included in the Pop-PK analysis was 29kg, there were only minimal data in CF subjects <40 kg in the Phase 3 studies which prevents possibility to make a robust conclusion about exposure at lower extremes of weight**.** Further data on PK in low weight patients is expected (study 106) in due course as agreed with the applicant.

CF patients 12 years or older with the F/MF and F/F genotype (study 102 and study 103)
In the F/MF patients, placebo was used as a comparator and in F/F TEZ/IVA was used as comparator. Therefore, the added benefit over VX-445 monotherapy or VX-445/IVA has not been investigated in a clinical setting.

In study 102, the Applicant' definition of an MF mutation (1) no protein or (2) not responding to TEZ, IVA or TEZ/IVA in vitro) is different when compared to the standard MF definition (Class I, II and III mutations). An ad-hoc subgroup analysis showed a consistent benefit in the patient included based on criterion 1 (and in the nonsense, splicing and indel frameshift subgroups). However, some small uncertainties remain on whether all criterion (1) mutants do not form a protein.

Not all known MF mutations can be tested in clinical trial setting.

CF patients 12 years or older with the F/F genotype (study 103/105).

Stratification according to ppFEV1 was applied on the ppFEV1 measurements taken after at least 13 days of TEZ/IVA run-in, rather than the screening ppFEV1 values. These ppFEV1 measurements are influenced by whether the patients were Vertex *CFTR* modulator naïve or experienced. The data suggests that the screening period of 4 weeks may not have been sufficient for *CFTR*-modulator naïve patients randomized to TEZ/IVA to derive the full benefit of this treatment by time of baseline ppFEV1 assessment. Consequently, it is considered that the magnitude of the treatment effect of VX-445/TEZ/IVA vs TEZ/IVA in the overall study 102 population may be overestimated and that the treatment effect estimate obtained in the *CFTR*-modulator experienced patients is relevant to prescribers (LS mean 7.8%, 95% CI (4.8,10.8)). Therefore, this has been included in Section 5.1 of the SmPC.

There are no controlled data after 4 weeks for F/F patients due to the short study treatment duration and limited open label extension data from the 107 patients (F/F) that enrolled from parent Study 103 are provided.

Effect on number of PEx can only be determined by data from study 105, without a control group or event rate at baseline present. When comparing the observed PEx data for study 103/105 to the data from the VX-445/TEZ/IVA group in study 102 these are considered similar. Therefore, the presented exacerbation results for F/F patients from study 105, are likely to be supportive for the benefit seen with the TC.

CF patients 12 years or older with the F/RF and F/G genotype (real world data)

The registry data presented is in itself limited and not sufficiently detailed, and as such raised questions. For example, the exact modulator therapy used, the duration of use is not known, as well as included specific genotypes and individual patient efficacy data not present. Unavailability of such information is inherent to obtaining data from a registry but leads to questioning whether the patients in the analysis set can be considered sufficiently representative of the overall F/G and F/RF populations to draw conclusions on these populations. Bearing in mind the limitations and questions arising from the registry data, the magnitude of the additional response from treatment with VX445/TEZ/IVA over prior *CFTR* therapies is not overwhelming. It is unexpected that the F/G group had a greater gain than that seen in the F/RF population. Indeed, in view of the limited efficacy observed in clinical trials for F/RFs patients treated with TEZ/IVA compared those patients with G/any mutations treated with IVA, it would be considered that F/RF group should have had more potential for improvement with VX445/TEZ/IVA by treating the F allele. Overall, due to the uncertainties on the patients included and the effect size seen, these data cannot be accepted as the main data source for the F/G and F/RF populations

3.4. Unfavourable effects

As most patients were included in Study 102, the safety profile of VX-445/TEZ/IVA was mainly determined by Study 102.

Treatment-emergent AEs were reported for nearly all patients in both arms in the Study 102 Safety Set (93.1% of patients in the VX-445/TEZ/IVA arm vs. 96.0% in the placebo arm). TEAEs with an incidence of at least 8% in either treatment group and in VX-445/TEZ/IVA >1% higher than in placebo were headache, diarrhoea, upper respiratory tract infection, abdominal pain, alanine transaminase (ALT) increased, aspartate transaminase (AST) increased, blood creatine phosphokinase increased, nasal congestion, rash, and rhinorrhoea. Important AEs observed with incidence rates ≥ 3% and ≥1% more frequent than placebo are influenza, wheezing and hypoglycaemia.

The most common adverse reactions experienced by patients aged 12 years and older were headache (17.3%), diarrhoea (12.9%) and upper respiratory tract infection (11.9%).

Adverse drug reactions were mostly mild to moderate and resolved without requiring treatment discontinuation.

Related AEs occurred in 5.0% of patients treated with VX-445/TEZ/IVA and in 3.0% treated with placebo; 42.6% of the subject in the VX-445/TEZ/IVA group and 22.9% subjects in the placebo group had an AE assessed by the investigator as possibly related.

Grade 3-4 AEs were reported for 9.4% (VX-445/TEZ/IVA) vs. 7.5% (placebo) of patients; infective pulmonary exacerbation of cystic fibrosis (4.5%, placebo) and blood creatine increased (2.0%, VX-445/TEZ/IVA), ALT increased (1%, VX-445/TEZ/IVA), and AST increased (1%, VX-445/TEZ/IVA) were the only Grade 3 or 4 AEs that had an incidence of at least 1% in either treatment group.

SAEs were reported for 13.9% (VX-445/TEZ/IVA) vs. 20.9 % (placebo). The SAEs that occurred in ≥1% of patients in either treatment group were infective PEx of CF (5.4% vs. 16.4%), haemoptysis (1.0% vs. 1.5%) and rash (1.0% vs. 0.5%) and influenza (1.5% vs 0%). Related SAEs occurred in 3.0% (VX-445/TEZ/IVA) vs. 1.0% (placebo). No related SAEs occurred in 2 or more patients in either treatment group.

Transaminase elevations are common in CF patients receiving IVA monotherapy, TEZ/IVA, and VX-445/TEZ/IVA. In the pivotal VX-445/TEZ/IVA, exclusion criteria for patients with pre-existing liver function impairments were more stringent compared to the Orkambi trials and Symkevi. The incidence of transaminase elevation adverse events was 2-3 times higher in the VX-445/TEZ/IVA group than in the placebo group. The majority of the events were non-severe, non-serious and did not lead to treatment discontinuation. Increases from baseline in mean total bilirubin were also observed in the VX-445/TEZ/IVA group, with a greater increase in indirect bilirubin than direct bilirubin, while in the placebo group, changes from baseline in mean total bilirubin were minimal. AEs associated with bilirubin elevation occurred in 10 (5.0%) subjects in the VX-445/TEZ/IVA group and 2 (1.0%) subjects in the placebo group. None of the AEs of bilirubin elevation were serious or led to treatment discontinuation. This is adequately addressed in the SmPC sections 4.4 and 4.8.

Rash occurred more frequently in the VX-445/TEZ/IVA group (10.9%, 22 subjects) than in the placebo group (6.5%, 13 subjects). Most rashes occurred within the first 3 weeks of study drug treatment. Serious rash events occurred in 3 (1.5%) subjects in the VX-445/TEZ/IVA group compared to 1 (0.5%) subject in the placebo group.

AEs of CK elevation occurred more frequently in subjects in the VX-445/TEZ/IVA group compared to the placebo group. The majority were asymptomatic laboratory elevations, many of which were preceded by exercise. The 2 subjects in the VX-445/TEZ/IVA group with AEs of rhabdomyolysis presented with CK elevations, and neither subject had clinical features of rhabdomyolysis (e.g., kidney involvement, myoglobinuria). Both subjects had performed strenuous exercise.

Incidental increases from baseline in mean BP parameters were observed in the VX-445/TEZ/IVA group. Only a limited number of subjects had a blood pressure in the hypertensive range.

Discontinuations due to AEs occurred in 1.0% (VX-445/TEZ/IVA) vs. 0% (placebo). The two events leading to treatment discontinuation were rash and portal hypertension in a subject with a medical history of hepatic cirrhosis.

In Study 103 Safety set, the incidence of subjects with at least one AE was 58.2% in the VX-445/TEZ/IVA group and 63.5% in the TEZ/IVA group. In general, a similar pattern was in the TEAEs, but overall with lower frequencies.

The long-term safety data (Study 105 Safety Set, OLS) showed decreased exposure-adjusted event rate of (related AEs), Grade 3-4 AEs, SAEs with VX-445/TEZ/IVA compared to the Study 102 Safety Set. In the Cumulative Safety Set, the safety profile is quite similar to the safety profile of Study 102 Safety Set.

In Study 105 Safety Set, 7 (1.4%) subjects had AEs that led to treatment discontinuation, of whom 3 subjects discontinued due to AEs of transaminase elevation. The other subjects discontinued treatment due to AEs of depression, rash, tinnitus and contusion, and hepatic encephalopathy.

Influenza is included as an ADR in section 4.8. "Susceptibility for influenza virus infections" is classified as an important identified risk in the RMP. The applicant committed to continue the monitoring of influenza in the post marketing setting to further characterise this ADR and agreed to incorporate available data on influenza in the planned PASS.

The safety profile of subjects in subgroups of *F508del-CFTR* mutation with F/MF and F/F in the cumulative safety set was broadly comparable across the F/MF and F/F subgroups respectively. In general, the safety is broadly comparable in subgroups.

3.5. Uncertainties and limitations about unfavourable effects

In Study 105 IA2, 229 subject patients had an exposure of > 24 ≤ 48 weeks and 271 patients had an exposure ≥ 48. More information on long term safety will become available during post-marketing pharmacovigilance when final results for study 105 will be submitted.

VX-445/TEZ/IVA should not be used in patients with severe hepatic impairment. Only in case of urgent and unavoidable need for treatment with Kaftrio and after weighing the benefits and risks of such treatment, VX-445/TEZ/IVA may be used in patients with moderate hepatic impairment applying a dose reduction. This is adequately addressed in the SmPC section 4.2.

Rash occurred frequently with VX-445/TEZ/IVA treatment. There was an increase in the incidence of rash in female subjects taking hormonal therapy compared with those not taking hormonal therapy; the increase was larger in the VX-445/TEZ/IVA group than in the placebo group. Therefore, a role for hormonal therapy in the occurrence of rash cannot be excluded as mentioned in the SmPC section 4.4.

3.6. Effects Table

Table 53:**Effects Table for Kaftrio**

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	Ref. **
Favourable Effects						
CF patients with the F/MF genotype						
			VX/TEZ/IVA	**Placebo**		
ppFEV1	Change 0-24 wks LSM(95% CI)	%	13.9 (12.8, 15.0)	-0.4 (-1.5, 0.7)	**SoE**: 14.3 (12.7, 15.8) p<.0001 Highly clinically relevant	1
CFQ-R RD	Change 0-24 wks LSM(95% CI)	points	17.5 (15.6, 19.5)	-2.7 (-4.6, -0.8)	**SoE:** 20.2(17.5, 23.0) p<.0001	1
PEx	Event rate 0-24 wks	Number/yr	0.37	0.98	**SoE:** 0.37 (0.25, 0.55) p<.0001	1
BMI	Change 0-24 wks LSM(95% CI)	Kg/m^2	1.13 (0.99, 1.26)	0.09 (-0.05, 0.22)	**SoE:** 1.04 (0.85, 1.23) p<.0001	1
Sweat Chloride	Change 0-24 wks LSM(95% CI)	mmol/L	-42.2 (-44.0, -40.4)	-0.4 (-2.2, 1.4)	**SoE:** -41.8(-44.4,-39.3) p<.0001	1
CF patients with the F/F genotype						
			VX/TEZ/IVA	**TEZ/IVA**		
ppFEV1	Change 0-4 wks LSM(95% CI)	%	10.4 (8.6, 12.2)	0.4 (-1.4, 2.3)	**SoE:** 10.0 (7.4, 12.6) p<.0001 Highly clinically relevant, confirmed with LT data (24wks) **Unc:** uncontrolled LT results	2/3
CFQ-R RD	Change 0-4 wks LSM(95% CI)	Points	16.0 (12.1, 19.9)	-1.4 (-5.4, 2.6)	**SoE:** 17.4 (11.8, 23.0) p<.0001 Confirmed with LT data (24wks) **Unc:** uncontrolled LT results	2/3
Sweat Chloride	Change 0-4 wks LSM(95% CI))	mmol/L	-43.3 (-46.9, -40.0)	1.7 (-1.9, 5.3)	**SoE:** -45.1(-50.1,-40.1) p<.0001 Confirmed with LT data (24wks) **Unc:** uncontrolled results	2/3
Pulmonary exacerbations	Event rate 0-24 wks	Number/ year	0.30		**Unc**: No comparator arm	2/3

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	Ref. **
Unfavourable Effects						
Headache		%	17.3	14.9	**Unc**: Limited size of the data set **SoE**: No differences between adults and adolescents	1
Diarrhoea		%	12.9	7.0		1
Abdominal pain		%	9.9	6.0		1
ALT	ALT increased	%	9.9	3.5	Determined based on safety profile of TEZ and IVA (ALT, AST), in combination with pharmacokinetic profile (bilirubine)	1
AST	AST increased	%	9.4	2.0		1
Bilirubine	Bilirubine increased	%	5.0	1.0		1
Blood creatine phosphokinase	Blood creatine phosphokinase increase	%	9.4	4.5	**Unc**: Limited size of the data set **SoE**: No differences between adults and adolescents	
Nasal congestion		%	9.4	7.5		
Rash	Rash	%	8.9	4.5		1
Rhinorrhoea		%	8.4	3.0		
Rhinitis		%	7.4	5.5		
Influenza		%	6.9	1.5		
Sinusitis		%	5.4	4.0		
Flatulence		%	4.5	1.5		
Hypoglycaemia		%	4.5	1.0		
Respiration abnormal		%	4.5	2.0		
Viral URTI		%	4.5	2.0		
Acne		%	3.5	1.5		
Dizziness		%	3.5	2.5		
Pharyngitis		%	3.0	1.0		
Wheezing		%	3.0	1.0		
Grade 3-4 TEAEs		%	9.4	7.5		

Abbreviations: URTI upper respiratory tract infection, VX/TEZ/IVA VX-445 +Tezacaftor +Ivacaftor, PE Pulmonary Exacerbations
**1 refers to study 102, 2 refers to study 103 and 3 refers to study 105.
Notes: the safety profile in Study 102 Safety Set, and Study 103 Safety Set is generally comparable.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

According to the Applicant, if a modulator has a large effect on the *F508del-CFTR*, then the presence of a single *F508del* allele would be sufficient to derive a clinical benefit. Based on this new hypothesis and the results from studies 102 and 103, a broad indication was initially proposed to include all patients with at least one *F508del* mutation independently of the second allele. This means that efficacy for non-tested populations of F/MF, F/RF and F/G should be extrapolated. It should be noted that uncertainties remain on the value of the new paradigm proposed, as it is not accepted by CHMP that all class 1 MF mutations are equal and that no protein is produced in each and every case. Therefore, it cannot be excluded that some of the MF mutants may make a contribution to the *CFTR*-mediated chloride transport upon treatment with VX-445/TEZ/IVA.

ppFEV1 as a surrogate endpoint is a well-established endpoint and a reduction in the 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.

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

Importance of the favourable effects
The observed difference of 14.3% ($p<0.0001$) between VX-445/TEZ/IVA and placebo in absolute change of ppFEV1 is well above the predefined threshold (5%) and also above the definition of clinical relevance in the context of the natural decline in CF patients in the pivotal study 102. Approximately 80% patients treated with the TC have a benefit of ppFEV1 >5%, compared to 15% in the placebo group. The results are considered clinically and significantly relevant.

The rate ratio of 0.37 for exacerbations comparing VX-445/TEZ/IVA to placebo is relevant.

Strength of the evidence
Consistent improvements in ppFEV1 favouring VX-445/TEZ/IVA were observed across all prespecified subgroups. The results of the primary parameter are supported by all key secondary parameters. CFQ-R respiratory domain, BMI and sweat chloride all showed improvements well above the MCID.

The results were consistent across the subgroups of criterion 1 and criterion 2 mutations and upon further subdivision based on genotype or *in vitro* responsiveness. In this patient populations IVA, LUM/IVA and TEZ/IVA were not efficacious, which confirms the need for the VX-445 compound.

Impact of the uncertainties
Not all known MF mutations can be tested in a clinical trial. The clinical benefit seen in these F/MF patients has such a large effect size, that it is unlikely that uncertainties related to MF mutations not being tested, the absence of a direct in vitro in vivo comparison, inclusion criteria or chosen dose regimen will affect the data to such an extent that the benefit could be questioned.

1. CF patients with the F/"MF criterion 1" showed substantial clinical benefit, derived by the *F508del* allele, as MF mutants do not form a protein.
   - 87% of the criterion 1 mutants result in truncation that are likely not to form a functional protein. In this subgroup the ppFEV1 improvement is 13.2% (10.4, 16.0) which is consistent with the overall study population.

- It has been discussed and agreed that *G542X* (n=65 in study 102) and *R553X (*used in HBE cells) do not form a protein. These alleles form half of the nonsense mutations subgroup which showed similar clinical benefit as the FAS. In a subgroup analysis for *G542X* specifically an ppFEV1 improvement of 13.6% (9.4, 17.7) was observed.

2. CF patients with the F/"MF criterion 2" show substantial clinical benefit, derived by the *F508del* allele.
   - Clinical results of non-responsive and responsive criterion 2 mutations suggest that effect is mediated by the *F508del* allele.

3. Result in different studies, with specific collection of MF mutants, show consistent efficacy results.
   - Results seen in the different studies in which F/MF CF patients were participating show highly consistent efficacy results (within group).
   - The subgroups in genotypes and FRT responsiveness show highly similar results.
   - The result is consistent with effect seen in the F/F population.

Based on the pre-clinical data, the clinical data and the lack of evidence that all MF mutation do not form a protein, the *F508del*-only treatment paradigm has not been adequately substantiated.

The consistent results in the F/MF population subgroups, together with the magnitude of the efficacy observed indicate that extrapolation to untested MF mutations can however be accepted. Additionally, it is considered important for the prescriber to mention that not all mutations have been clinically tested in studies 102 and provide the list of mutations studied in section 5.1 of the SmPC.

In addition, the Applicant agreed to expand the efficacy information of VX-445/TEZ/IVA (overall and per genotype subgroup) by providing registry data from a PASS.

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

Importance of the favourable effects

The observed difference of 10.0% ($p<0.0001$) between VX-445/TEZ/IVA and TEZ/IVA in absolute change of ppFEV1 is well above the predefined threshold (5%) and also above the definition of clinical relevance in the context of the natural decline in CF patients in the pivotal study 103. Approximately 70% patients treated with the TC have a benefit of ppFEV1 >5%, compared to 13% in the TEZ/IVA group. The results are considered highly clinically relevant.

The results from study 105 confirm the benefit in FEV1 was maintained until 24 weeks. For pulmonary exacerbations, the estimated event rate per year was 0.30 in the F/F population of study 105.

Strength of the evidence

Consistent improvements in ppFEV1 favouring VX-445/TEZ/IVA were observed across all prespecified subgroups.

The result of the primary parameter is supported by all key secondary parameters. CFQ-R respiratory domain, BMI and sweat chloride all showed improvements well above the MCID.

Study 103 had a duration of only 4 weeks, but from study 105 it was concluded that all effect seen in primary and secondary endpoints at week 4 were maintained through week 24. The effects seen in the F/F population are in comparison to the approved TEZ/IVA (Symkevi) regimen, which confirms the need for the VX-445 compound.

Impact of the uncertainties

The clinical benefit seen in these patients has such a large effect size, that it is unlikely that

uncertainties related to for example sensitivity analyses, inclusion criteria or chosen dose regimen will affect the data in such an extent that this benefit could be questioned.

While there are no controlled data after 4 weeks for F/F patients due to the short study treatment duration, limited open label extension data from the 107 patients (F/F) that enrolled from parent Study 103 are provided. For the key parameters such as ppFEV1, Sweat Chloride, CFQ-R as well as rate of pulmonary exacerbations the improvements seen at 4 weeks appear to be sustained in all patients, and the BMI, BMI z score and weight outcomes seem to continue to improve. Therefore, the limitation of the short-controlled 4-week treatment period can be accepted.

Importantly, from a clinical setting it remains uncertain whether all three compounds are required to reach the effects seen in the F/F and F/MF patients, as VX-445 monotherapy and VX-445/IVA were not tested in a clinical setting as required according to the EU Guideline for Fixed Dose Combinations (EMA/CHMP/158268/2017). However, the in vitro data, the highly relevant clinical benefit seen and the fact that the drug is well-tolerated are considered relevant enough to outweigh this uncertainty in the F/F and F/MF population.

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

For the F/RF and F/G populations real world data form the US registry were provided, no randomised clinical data are available. The ppFEV1 results suggest improvement on top of other *CFTR* modulators, but registry data come with many uncertainties due to bias and missing information.

The cross-study comparison and responder analysis without the ongoing clinical study 104 data in F/G and F/RF mutations do not sufficiently support the added benefit of VX445/TEZ/IVA over approved modulator therapies. such F/G and F/RF populations require their own demonstration of clinical efficacy and safety by a randomized controlled trial. Therefore, the CHMP considered that the efficacy has been demonstrated only in patients with F/F and F/MF mutations where randomized clinical trial data are available.

Study 104

Study 104 data in F/G and F/RF patients are expected to contribute to the understanding of the efficacy in these patient populations where the added benefit of the triple combination over existing therapies is not clear at present. The data of study 104 cannot be awaited as any further delay in CHMP opinion (awaiting the results of study 104) is not acceptable in the context of patients for which there is a positive B/R identified (F/F and F/MF) and absence of treatment available (F/MF). The Applicant agreed to submit results of the clinical data by August 2020 in a variation procedure for further assessment.

Safety

The safety data base is considered sufficient with the submission of the second interim analysis during the assessment of this application.

VX-445/TEZ/IVA was well tolerated with low discontinuation rates due to AEs. The safety profile of the combination is similar to the already licenced *CFTR* modulators and appeared comparable across studies. However, there were more adverse events for increased ALT, AST and bilirubin indicative for hepatic involvement. Based on a PK study in subjects with moderate hepatic impairment, yielding increased exposure to VX-445, VX-445/TEZ/IVA is not recommended in patients with moderate hepatic impairment. Therefore, Kaftrio should only be used in case of urgent and unavoidable need for treatment and after weighing the benefits and risks of such treatment, VX-445/TEZ/IVA may be used in patients with moderate hepatic impairment with a dose reduction. Expected exposure in patients

with severe hepatic impairment has not been investigated but is expected to be higher than that in patients with moderate hepatic impairment, and therefore, in the absence of further data in this patient population, VX-445/TEZ/IVA should not be used in such patients.

3.7.2. Balance of benefits and risks

Efficacy

The balance of benefits and risks has to be determined in three separate populations. The patients for which preclinical and or clinical data is available (F/F and tested F/MF) and for the broader set of patients 12 years and older who have at least one *F508del* mutation in the *CFTR* gene.

For CF patients with the F/MF genotype, the placebo-controlled study provided efficacy data that demonstrate that VX-445/TEZ/IVA provides a substantial clinical benefit, both in the primary and the key secondary endpoints.

For CF patients with the F/F genotype, the active controlled study provided efficacy data demonstrating substantial clinical benefit of VX-445/TEZ/IVA both in the primary and the key secondary endpoints in comparison with TEZ/IVA.

For both populations, the results were considered sufficiently robust and highly clinically relevant.

This clinically relevant effect, in combination with in vitro data and with fact that VX-445/TEZ/IVA is well-tolerated, it is considered acceptable that no clinical data with the VX-445 monotherapy and VX-445/IVA are presented.

The absence of direct clinical data with the VX-445 monotherapy and VX-445/IVA was considered acceptable given the clinically relevant effect as well as in vitro data and well tolerated safety profile of Kaftrio.

Safety

The safety profile of VX-445/TEZ/IVA was derived primarily from Study 102, as well as study 103 and study 105 (extension study). The extensive clinical experience with CFTR modulator therapies (including IVA and TEZ/IVA) indicate that the safety profile is consistent across different genotypes for each of the individual CFTR modulator treatments. As such, the safety profile established from Study 102 in F/MF subjects is considered representative for the entire proposed indication, which is supported by the comparable safety profile observed in Study 103 in F/F subjects. Furthermore, interim analysis (IA2) of study 105 provided during the assessment provided additional long-term safety data.

Overall, VX-445/TEZ/IVA was well tolerated with low discontinuation rates due to AEs. Most important adverse events concerned the adverse events indicative for hepatic involvement (ALT, AST and bilirubin). Currently, until more data become available, VX-445/TEZ/IVA may be used in patients with moderate hepatic impairment applying a dose reduction only in case of urgent and unavoidable need for treatment with Kaftrio and after weighing the benefits and risks of such treatment. Upon request by CHMP, the Applicant will provide results of the ongoing study in moderate impairment hepatic patients by Q32020 for further assessment. At the same time, the Applicant should re-discuss/refine the dose-advice in moderate hepatically impaired patients, taking into account the expected exposure of the active M1-TEZ metabolite. This information is important in support of the dose advice in patients with hepatic impairment.

The Clinical Study Report for PASS study will be submitted as Post Approval Measure as Category 3.

This study will evaluate the safety outcomes, CF disease progression, frequency and outcome of pregnancy, and drug utilisation patterns in CF patients taking ELX/TEZ/IVA in the real-world setting. Information on CF disease progression in genotype subgroups should also be generated.

Indication

Overall, the data of clinical studies 102, 105 and 103 indicate a large clinical benefit with VX-445/TEX/IVA in F/F and F/MF patients. Although the evidence for the *F508de*l-only hypothesis is considered not definitively conclusive and some uncertainties remain, the highly clinically relevant benefit, and the consistency of these effects seen with VX-445/TEZ/IVA in studies/subgroups make the extrapolation to all patients with an F/MF genotype acceptable.

In addition, the Applicant agreed to expand the efficacy information of VX-445/TEZ/IVA (overall and per genotype subgroup) by providing data in the post approval setting from a post approval safety study as mentioned in the RMP.

For F/RF and F/G population, the evidence for the F508del-only hypothesis is considered not definitively conclusive. The registry data provided for these patients are welcome, but subject to limitations and to bias to reliably demonstrate the efficacy and safety of VX445/TEZ/IVA in F/G and F/RF patients. In conclusion the CHMP was of the view that the registry data do not obviate the need for robust, comparative, clinical data in F/G and F/RF patients from clinical trials.

Study 104 in F/G and F/RF patients

The data of study 104 in F/G and F/RF patients will meaningfully contribute to the understanding of the efficacy in the F/RF and F/G patient populations. The data of study 104 are required to show clear benefit in F/RF and F/G patients before the approval of the broad F508del/any indication requested by the Applicant can be considered.

The Applicant following the Oral explanation requested to delay the approval for at least another 3 months in order to provide the awaiting provide clinical data (Study 104) in F/G and F/RF in the procedure, but this was not agreed by CHMP. Any further delay in CHMP positive opinion is not agreed in the context of patients for which there is a positive B/R identified (F/F and F/MF) and in view of the high unmet medical need in F/MF patients where no treatment is currently available. The Applicant finally agreed to submit results of the clinical data (study 104) separately in a variation procedure as soon as possible for further assessment. The type II Variation should be submitted by September 2020.

In conclusion, a positive benefit risk is considered demonstrated in the F/MF and F/F populations and the applicant agreed to amend the claimed indication to:

"Kaftrio is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or heterozygous for F508del in the CFTR gene with a minimal function (MF) mutation (see section 5.1)."

Third party intervention during the evaluation of Kaftrio

The CHMP received, during the assessment of this application, 5 correspondences from 4 Cystic fibrosis associations (hereinafter referred to as "third parties") expressing the third parties' views about the efficacy and safety profile of Kaftrio, the unmet medical need of CF patients and their vulnerability during the Covid-19 crisis.

The CHMP considered those interventions in the context of its assessment and concluded that the observations put forward by the 4 CF associations were already known by CHMP, and as such had no impact on the CHMP assessment or its conclusions.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall B/R of Kaftrio is positive in a combination regimen with ivacaftor 150 mg tablets for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene or heterozygous for the *F508del* in the *CFTR* gene with a minimal function (MF) mutation.

4. Recommendations

Similarity with authorised orphan medicinal products

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

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Kaftrio is favourable in the following indication:

Kaftrio is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who are homozygous for the *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene or heterozygous for the *F508del* in the *CFTR* gene with a minimal function (MF) mutation.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- 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

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that ivacaftor/tezacaftor/elexacaftor is a new active substance as elexacaftor is not a constituent of a medicinal product previously authorised within the European Union and it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any EU authorised active substance.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0091/2019 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.