17 September 2020
EMA/48399/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Symkevi

International non-proprietary name: tezacaftor / ivacaftor

Procedure No. EMEA/H/C/004682/X/0015/G

Note

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

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List of abbreviations

AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
AUC	area under the concentration-time curve
BMI	body mass index
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	cystic fibrosis transmembrane conductance regulator gene
CFTR	cystic fibrosis transmembrane conductance regulator protein
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
Cl-	chloride
CQA	Critical Quality Attribute
CSR	clinical study report
DDIs	drug-drug interactions
DoE	Design of experiments
ECG	electrocardiogram
EMA	European Medicines Agency
EU	European Union
F508Del	*CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
F/F	homozygous for *F508Del*
F/RF	heterozygous for *F508Del* and a second allele that results in residual function
G551D	*CFTR* missense gene mutation that results in the replacement of a glycine residue at position 551 of *CFTR* with an aspartic acid residue
HPLC	High performance liquid chromatography
ICH	International Council for Harmonization
IPC	In-process control
IR	Infrared
KF	Karl Fischer
IVA	ivacaftor
LCI	lung clearance index
LCI2.5	number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th (2.5%) of its starting value
LCI5.0	number of lung turnovers required to reduce the end tidal inert gas concentration to 1/20th (5.0%) of its starting value
LFT	liver function test
LUM	lumacaftor
MAA	Marketing Authorization Application
NOR	Normal Operating Range
P	probability
Ph. Eur.	European Pharmacopoeia
PCTFE	Polychlorotrifluoroethylene
PDCO	European Medicines Agency Paediatric Committee
PDE	Permitted Daily Exposure

PE	physical examination
PIP	paediatric investigational plan
PK	pharmacokinetic/pharmacokinetics
ppFEV1	percent predicted forced expiratory volume in 1 second
PT	Preferred Term
PVC	Polyvinyl chloride
QbD	Quality by design
QC	Quality Control
q12h	once every 12 hours
qd	once daily
R117H	*CFTR* missense gene mutation that results in the replacement of anarginine residue at position 117 of *CFTR* with a histidine residue
RD	respiratory domain
RF	residual function
RH	Relative Humidity
SAE	serious adverse event
SAWP	Scientific Advice Working Party
SAP	statistical analysis plan
SDD	spray-dried dispersion
SD	standard deviation
SE	standard error
SmPC	Summary of Product Characteristics
SoE	Summary of Efficacy
SoS	Summary of Safety
TAMC	Total Aerobic Microbial Count
TEZ/IVA	tezacaftor/ivacaftor
TGA	Thermo-Gravimetric Analysis
TSE	Transmissible Spongiform Encephalopathy
TYMC	Total Combined Yeasts/Moulds Count
ULN	upper limit of normal
XR(P)D	X-Ray (Powder) Diffraction

Definitions of Terms

Abbreviated study numbers: In the body of the text, studies of tezacaftor/ivacaftor (TEZ/IVA) are abbreviated to the last 3 digits for Vertex Pharmaceuticals Incorporated-sponsored studies, plus the study part letter, if applicable (e.g., Study VX15-661-113 Part B is Study 113B). Studies of other Vertex products are abbreviated to the last 6 digits of the study number (e.g., Study VX14-809-109 is 809-109).

1. Background information on the procedure

1.1. Submission of the dossier

Vertex Pharmaceuticals (Ireland) Limited submitted on 11 November 2019 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension application to add a new strength of 50/75mg film-coated tablets of tezacaftor/ivacaftor to enable administration to patients aged 6 to less than 11 years. In addition the MAH applied for an extension of indication : variation C.I.6.a - To update sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.1 of the SmPC, and sections 2, 3 and 6 of the PL for the 100/150 mg film-coated tablet presentations to extend the indication for use in children aged 6 to less than 11 years old in combination with ivacaftor and to bring it in line with the new dosage form (50/75mg film-coated tablets tezacaftor/ivacaftor).
The RMP (version 2.1) is updated in accordance.
In addition, the MAH took the opportunity to implement minor updates and formatting changes in the Product Information.

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

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

The new indication, which is the subject of this application, falls within the above-mentioned orphan designation.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Symkevi as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found here <insert link>

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0193/2017 covering the application on the agreement of a paediatric investigation plan (PIP).

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

Information relating to orphan market exclusivity

Similarity

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

Protocol assistance

The MAH received Protocol assistance from the CHMP on 18 May 2017 (EMA/CHMP/SAWP/282884/2017). The Protocol assistance pertained to clinical aspects.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP: Johann Lodewijk Hillege

The application was received by the EMA on	11 November 2019
The procedure started on	28 November 2019
The Rapporteur's first Assessment Report was circulated to all CHMP members on	18 February 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	25 February 2020
The PRAC outcome	12 March 2020
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	26 March 2020
The MAH submitted the responses to the CHMP consolidated List of Questions on	23 April 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	28 May 2020
The PRAC outcome	25 February 2020
The CHMP agreed on a list of outstanding issues to be sent to the MAH on	25 June 2020
The MAH submitted the responses to the CHMP List of Outstanding Issues on	17 August 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	3 September 2020
The CHMP adopted a report on similarity on (Appendix 1)	17 September 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 Symkevi on	17 September 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Cystic Fibrosis (CF) is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality, and at present, there is no cure. 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 patients with CF, loss of chloride transport due to defects in the *CFTR* protein result in the accumulation of thick, sticky mucus in the bronchi of the lungs, loss of exocrine pancreatic function, impaired intestinal absorption, reproductive dysfunction, and elevated sweat chloride concentration.

The biochemical defect of defective chloride channel function is present from birth, with the sequelae of lung, pancreatic and other organ involvement emerging progressively throughout childhood and into adulthood.

The *CFTR* phenotype differs considerably among patients, even among patients with the same genotype. The *CFTR* genotype primarily determines the degree of pancreatic exocrine dysfunction, sweat chloride concentration and malformation of the male reproductive tract.
However, factors independent of *CFTR* are responsible for variation in lung disease, the primary cause of morbidity and mortality in CF. In lung disease, environmental factors, socio-economic factors and the presence of modifier genes play an important role. Lung disease is the primary cause of morbidity and mortality in people with CF.

2.1.2. Epidemiology

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

The most common mutation is the *F508 del* mutation. About 50% of the CF population is homozygous for the F508 del mutation, while this allele is present in at least 70% of the overall CF population.

2.1.3. Biologic features, aetiology and pathogenesis

The *CFTR* protein is an epithelial chloride ion (CL-) channel located in the epithelia of multiple organs, including lungs, pancreas, intestinal tract, liver, and vas deferens, that is responsible for aiding in the regulation of salt and water absorption and secretion. More than 1900 mutations in the *CFTR* gene have been identified; the F508 is the most frequent allele.

These mutations can be classified (a) according to the mechanisms by which they disrupt *CFTR* function or (b) by the extent of loss of chloride transport caused by the mutation.

- Classification by the disruption of the *CFTR* function

Stop codon mutations (class I) result in a truncated non-functional *CFTR*; class II mutations consist of aberrantly folded *CFTR* protein that is degraded by the cell quality control system, while class III mutations lead to defective regulation of the *CFTR* protein and, consequently, the absence of *CFTR* function. These three classes usually lead to minimal function of the *CFTR* protein and a classic CF phenotype with pancreatic insufficiency.

CFTR mutations that lead to defective chloride conductance are grouped together in class IV. Class V mutations interfere with normal transcription, thereby reducing the amount of otherwise normal *CFTR*. These mutations often lead to a reduced function of the *CFTR* protein and these patients have often a less severe form of CF.

- Classification by means of the extent of loss of chloride transport

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

The most prevalent mutation is an in-frame deletion in the *CFTR* gene resulting in a loss of phenylalanine at position 508 in the *CFTR* protein (*F508Del-CFTR*) and it is a Class II mutation: it prevents most of the *CFTR* protein from reaching the cell surface, resulting in little-to-no chloride transport. The decrease in the amount of *F508Del-CFTR* at the cell surface is due to a defect in the processing and trafficking of the *F508Del-CFTR* protein. The very small amount of *F508Del-CFTR* protein that reaches the cell surface also has defective channel gating and a decreased stability at the cell surface. Patients who are homozygous with *F508Del-CFTR* defects have little or no *CFTR* protein at the cell surface and hence suffer from a severe form of CF disease. Some patients are severely affected at birth, while others become symptomatic at a later age.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

The median predicted survival for CF patients in the United States was 39.3 years (95% CI, 37.3-41.4) according to the Cystic Fibrosis Foundation 2014 Registry Report.

The classic or typical form of CF is diagnosed if a patient demonstrates clinical disease in one or more organ systems and has elevated sweat chloride (≥60 mmol/L). Most of these patients have disease manifestations in multiple organ systems (pancreas, upper and lower respiratory tract, and male reproductive tract).

The prevalence of certain CF complications varies according to the age group. Exocrine pancreatic insufficiency is often already present from birth or develops in infancy. CF-related liver cirrhosis clinically presents most frequently between the ages of 5 to 15 years, but with a lower frequency in the third decade. CF-related pulmonary disease mostly starts in childhood. The disease manifestations are regarded as the results of the long-standings defect of the *CFTR* function. CF-related diabetes often starts to develop in patients around the age of 10 years and may progress in severity over years to insulin dependency. Lung disease is the primary cause of morbidity and mortality in CF.

The natural course of lung disease in CF is shown in Figure 1. In CF, the early lung damage starts in the peripheral, small airways due to the long-standing inflammation caused by the defect *CFTR* channel. This early deterioration of the small airways results in ventilation inhomogeneity. The ventilation inhomogeneity can be measured by the lung clearance index. Upon progression of the disease, also the larger airways will become affected. These larger airways abnormalities can be more easily measured by the FEV1.

Indeed, in children, the lung function as judged by the FEV1 is often preserved, but peripheral airways disease is shown by an abnormal Lung clearance index (LCI). The deterioration of LCI reflects disease progression. The LCI 2.5 correlates well with FEV1, although it is abnormal at an earlier stage in the disease. Therefore, the LCI can be used to measure airways disease in CF children, although the minimal clinically important difference is not known. The lung function as measured by FEV1 is often preserved until adolescence. During adolescence, the lung function also starts to decline as measured by FEV1. Most adults with CF have either moderate or severe lung disease as measured by an impaired FEV1.

Figure 1 The natural course of progression of the pulmonary CF

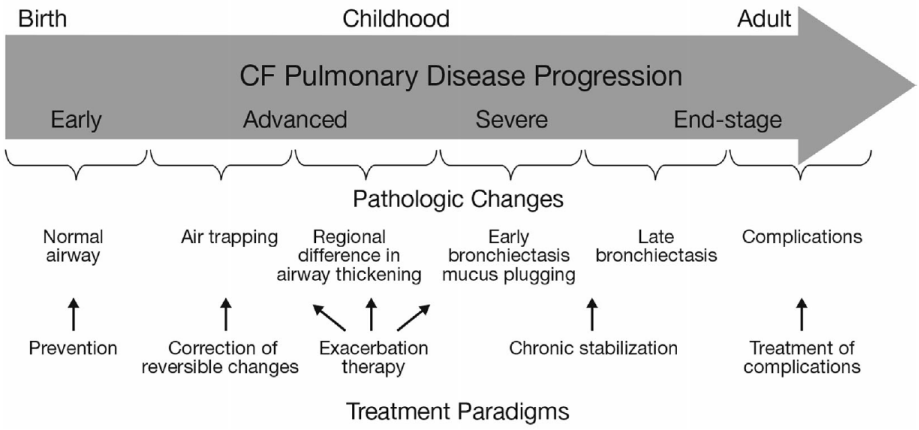


Fig. 1. Stages of disease progression and pathologic changes that occur in the airways of patients with CF as they age, along with possible treatment approaches. Reprinted with permission of the American Thoracic Society. Copyright 2014 American Thoracic Society. Ramsey BW. 2007. Use of lung imaging studies as outcome measures for development of new therapies in cystic fibrosis. Proc Am Thorac Soc;4(4):359–63. Official Journal of the American Thoracic Society.[2]

CF is included in many newborn screening programs. More than 80% of patients with CF are diagnosed by age 3. Genotyping for mutations in the *CFTR* gene is now routine practice in many countries, and 90% of patients in the EU are genotyped. During the years, the prognosis of CF has been improved, which is partly due to early recognising and early intervention.
In the 1950s, many patients died before the age of 5, while currently, many patients reach adulthood. The current life expectancy is > 30 years. The ageing of the CF population has brought a paradigm shift in outlook in the adult healthcare sector, from a focus on the care of lung disease to the management of a complex multi-system chronic illness, including the care for diabetes, renal function, osteoporosis, and hepatic function.

There is a wide spectrum of severity in CF, even among patients who harbour the same mutations. Some patients are severely affected, with symptoms already present at birth (meconium ileus). Most patients develop symptoms during childhood, while some patients may only demonstrate mild or atypical symptoms in adulthood. Usually, patients with Type I-III mutations are more severely affected than those with ≥ type 4 mutations.

2.1.5. Management

CF medications range from *CFTR* modulators and enzyme supplements to mucolytics, antibiotics, and vitamins. The treatment is aimed to reduce symptoms and prevent possible long-term detrimental side effect due to the long-standing inflammation and infections.

Most treatments are symptomatic, but the *CFTR* modulators may improve *CFTR* function, which is believed to be the primary cause of disease. Current treatment guidelines recommend *CFTR* modulator and non-modulator medications concomitantly administered to maintain and improve lung function, reduce the risk of infections and exacerbations, and improve quality of life.

CFTR protein, increasing surface expression, in class II mutation while potentiators recover the function of the *CFTR* protein at the apical surface of epithelial cells, to allow more chloride to flow through and reduce the symptoms of CF.

However, there is an inter-dependence between channel gating and cellular processing given that each depends on *CFTR* protein folding; thus a sharp distinction between a potentiator and corrector might be somewhat artificial.

Kalydeco (ivacaftor, IVA), Orkambi (lumacaftor/ivacaftor, LUM/IVA) are the only *CFTR* modulators approved for CF patients with specific mutations in children aged 6-11 years. Ivacaftor (in Kalydeco as mono-component and in Orkambi as part of a fixed-dose combination) is a potentiator; the active substance lumacaftor is a corrector (present in the fixed-dose combination Orkambi). Clinical efficacy of ivacaftor monotherapy has been established in Class III mutations that cause defects in channel gating as well as in the Class III/IV mutation *R117H*. Clinical efficacy of the combination of lumacaftor and ivacaftor has been established in patients homozygous for the *F508Del* mutation in the *CFTR* gene. However, some patients are not able to tolerate treatment with LUM/IVA due to respiratory events related to off-target effects of the lumacaftor component. In addition, lumacaftor is a strong CYP3A inducer, and some patients may not take it because of the drug-drug interaction (DDI).

Extension of the TEZ/IVA indication in combination with IVA to patients 6 through 11 years old would provide an alternative treatment option for F/F patients. Currently, there are no CFTR modulators approved in children aged 6-11 with an F/RF mutation. Symkevi would fulfil an unmet medical need for these patients.

About the product

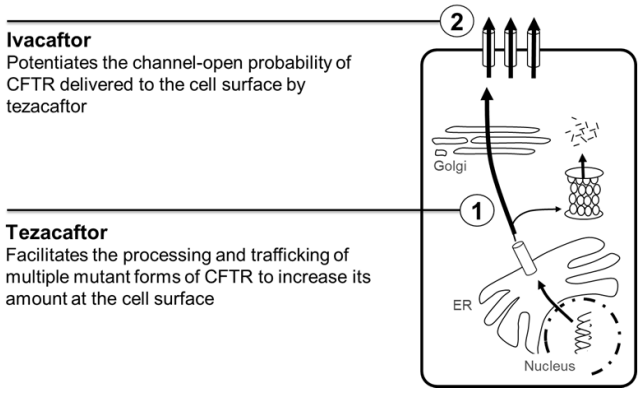
Symkevi belongs to the pharmaco-therapeutic group of 'Other respiratory system products'; ATC code: R07AX31.

Symkevi is a fixed-dose combination containing two substances, tezacaftor and ivacaftor, that work by improving activity of *CFTR* in the lungs, which is necessary to produce thin, normal mucus. Tezacaftor is a *CFTR* corrector that facilitates the cellular processing and trafficking of normal or multiple mutant forms of *CFTR* (including *F508Del-CFTR*) to increase the amount of functional *CFTR* protein delivered to the cell surface, resulting in increased chloride transport. Ivacaftor is a *CFTR* potentiator that potentiates the channel-open probability (or gating) of *CFTR* at the cell surface to increase chloride transport. Together, tezacaftor and ivacator aim to restore the basic functional defect that cause the disease manifestations of CF.

For ivacaftor to function, *CFTR* protein must be present at the cell surface. Ivacaftor can potentiate the *CFTR* protein delivered to the cell surface by tezacaftor, leading to a further enhancement of chloride transport than either agent does alone. The combined effect of tezacaftor and ivacaftor is increased quantity and function of *CFTR* at the cell surface, resulting in increases in chloride transport, airway surface liquid height, and ciliary beat frequency (

Figure **2**).

Figure 2 Mechanism of action of tezacaftor and ivacaftor



Potentiators and correctors improve lung function by improving *CFTR*-function. The relation between the improvement in *CFTR* function and lung function is complex, because in CF, the deterioration of the lung function is not only determined by the *CFTR*-function, but also by modifier genes and environmental factors. Considering that the basic pathophysiologic effect between adults and children is comparable, the proposed effect size in lung function improvement that could be attributable to the improvement in *CFTR* function might be comparable.

Previous studies showed that the potentiation of the *CFTR* function might be a predictive pharmacodynamic biomarker of lung function changes on a population bases but might be unsuitable for the prediction of treatment benefits on an individual level [FIDLER, 2017[1]].

Currently, Symkevi is indicated in a combination regimen with ivacaftor 150 mg tablets for the treatment of patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the *F508Del* mutation or who are heterozygous for the *F508Del* mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T.

The scope for the current application is to extend the above indication for children aged **≥ 6 years** i.e. *Symkevi is indicated in a combination regimen with ivacaftor tablets for the treatment of patients with cystic fibrosis (CF) aged 6 ~~12~~ years and older who are homozygous for the F508Del mutation or who are heterozygous for the F508Del mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T.*

The proposed posology is shown in Table 1.

Table 1 Dosing recommendations for patients aged 6 and older

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

1

Type of Application and aspects on development

The application consists of results from quality and clinical studies. The clinical programme for children aged 6 through 11 years is based on the partial extrapolation of efficacy from adults to children, supported by PK/safety study VX15-661-113 and pivotal phase 3 parallel-group trial VX16-661-115 in 54 patients aged 6-11 years.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a film-coated tablets containing 50 mg of tezacaftor and 75 mg of ivacaftor as active substances.

Other ingredients are:

Tablet core: hypromellose acetate succinate, sodium laurilsulfate (E487), hypromellose 2910 (E464), microcrystalline cellulose (E460(i)), croscarmellose sodium (E468), magnesium stearate (E470b),

Tablet film-coat: hypromellose 2910 (E464, hydroxypropyl cellulose (E463), titanium dioxide (E171), talc (E553b)

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

2.2.2. Active Substances

The active substances (tezacaftor and ivacaftor) are the same as for the authorised Symkevi 100 mg tezacaftor/150 mg ivacaftor film-coated tablets. No new information on the active substances has been provided within this line extension application.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is an immediate release film-coated tablet for oral administration. The tablet is a fixed dose combination (FDC) of tezacaftor and ivacaftor. The tablet contains 50 mg of tezacaftor and 75 mg of ivacaftor and has a total target weight of 304.82 mg. It is a white, capsule-shaped tablet, debossed with "V50" on one side and plain on the other (dimensions 12.70 mm x 6.78 mm). The qualitative and quantitative composition of the product is presented.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The aim of the formulation development was to manufacture an additional age-appropriate film-coated tablet strength needed for the extension of the indication to children from 6-12 years.

The formulation development was mainly based on the 100 mg/150 mg product strength. The 50 mg/75 mg tablet uses the same core tablet blend formulation as the 100 mg/150 mg tablet, and the tablet weight is adjusted to achieve the desired dose. The tablet is coated with a white, non-functional film-coat containing the same components as the film coating used for the 100 mg/150 mg tablet. The only difference is that the film coating formulation used for the 50 mg/75 mg does not contain yellow iron oxide as colourant.

The two tablet strengths are sufficiently visually distinguishable by their size, debossing and colour.

The two active substances, tezacaftor and ivacaftor, are incorporated into the FDC tablet as amorphous spray dried dispersions (SDDs). This is the same approach used for the existing 100 mg/150 mg tablet.

Comparative dissolution results using the quality control (QC) methods for ivacaftor and tezacaftor (which are identical for both product strengths) show similar release profiles for the 50 mg/75 mg clinical batches versus the 100 mg/150 mg clinical batches.

Overall, the proposed tablet formulation is considered suitable for children aged 6 years and above. An adequate general discussion on the suitability of the finished product for use in children of 6-12 years has been provided in the dossier in accordance with the Guideline on pharmaceutical development of medicines for paediatric use. The tablets need to be swallowed whole and should not be chewed, crushed or broken before swallowing as clinical data is currently not available to support these methods of administration (SmPC 4.2). The acceptability of the formulation was evaluated as part of the clinical studies where tablets were overall well accepted, and the majority of patients found the tablets easy to swallow.

The product was developed following an enhanced QbD approach as per ICH Q8. The development was largely based on pre-existing knowledge from the authorised 100 mg/150 mg strength. The manufacturing process development of the 50 mg/75 mg product and development studies performed were guided by an initial risk assessment where the potential impact of material attributes and process steps on the critical quality attributes of the product. The finished product CQAs are appearance, identification, assay, degradation products, dissolution, uniformity of dosage units, physical form, microbial limits, elemental impurities and residual solvents.

The manufacturing principles of the 50 mg/75 mg tablet are the same as for the authorised 100 mg/150 mg tablets. However, the 50 mg/75 mg tablets are manufactured using a traditional batch process, whereas the 100 mg/150 mg tablets are manufactured using a continuous manufacturing process, with different equipment types and capacities. The input materials are the same for both processes, including the tezacaftor and ivacaftor SDD components. No development data or dossier sections have been provided for the tezacaftor SDD and ivacaftor SDD components, but this is acceptable as these have already been approved for the authorised 100 mg/150 mg strength and are included in the dossier.

Due to potential interactions between material attributes of ivacaftor SDD and process parameters, these were studied inDoE.model confirmation runs were then conducted to confirm the accuracy of the resulting process models and to demonstrate process performance on commercial scale equipment. Based on the outcome of the DoE study, a design space was established for the dry granulation and compression steps. The design space is acceptable.

A second DoEwas also executed. No critical process parameters were identified, and no design space was established for the coatingprocess.

The batches used in the clinical studies were manufactured according to the finalized manufacturing process and composition and are representative for the commercial product.

The primary packaging is the same as for the existing 100 mg/150 mg tablets. It is a blister consisting of PCTFE (polychlorotrifluoroethylene)/PVC (polyvinyl chloride) with a paper backed aluminium foil lidding. The components comply with Commission Regulation (EU) No 10/2011. The choice of the container closure system is adequate for the intended use of the product.

Manufacture of the product and process controls

The 50 mg/75 mg tablets are manufactured by Vertex Pharmaceuticals Inc., United States using a batch manufacturing process which includes weighing, sieving and intragranular blending of the active SDDs with excipients, dry granulation and milling, extragranular blending and lubrication, compression, and film coating. These are the same manufacturing unit operations used for the manufacture the 100 mg/150 mg FDC tablets. The manufacturing process is a standard process.

An adequate criticality analysis was performed as part of the pharmaceutical development. Sufficient information on the control of critical steps has been provided in the dossier and the in-process acceptance limits have been justified. Compression force was identified as acritical process parameter. A design space is claimed for the compression stage of the process, which is justified. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design space.

The overall control strategy, process parameters and in-process controls seem adequate in view of the available development data and in view of the standard nature of the manufacturing process.

The manufacturing process was validated on six batches at a commercial manufacturing scale (three batches of 30 kg and three batches of 40 kg). Actual validation reports have only been provided for the three 40 kg batch, but this is considered acceptable in view of the standard nature of the manufacturing process.

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 (HPLC), dissolution (HPLC), water content (KF), physical form (XRPD) and microbiological quality (TAMC, TYMC, *E. coli*). The release and shelf-life specifications are identical, except for the test for water content, which is only performed at release.

Tezacaftor and ivacaftor are both stable molecules. No degradation products have been observed at or above the reporting threshold (0.10% w/w) in representative lots of 50 mg tezacaftor/75 mg ivacaftor FDC tablets at release or on stability.

Water content is determined at release only. Water is not a critical quality attribute (CQA) of the tezacaftor/ivacaftor FDC tablets since it has no impact on chemical and physical stability of the tablet. However, the release water specification will assure the tezacaftor/ivacaftor FDC tablets will have a water activity below 0.60, and not support microbial growth. Water content is not monitored on stability since microbial count, the only CQA that could be impacted by water, is tested directly.

Residual solvents are omitted from the FDC tablets specification since they are controlled in at the level of tezacaftor and ivacaftor active substances and SDDs, and the tablet excipients. These controls ensure the total potential residual solvent content of tezacaftor/ivacaftor FDC tablets comply with the ICH Q3C (R6) requirements.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The risk assessment of the content of Class 1 and Class 2A elemental impurities (as defined in ICH Q3D) in the tezacaftor and ivacaftor active substances and SDDs demonstrated that the risk of elemental impurities in these materials is low. Confirmatory testing of representative batches including at least three commercial batches of each active substance and SDD from each supplier confirmed that the content of Class 1 and Class 2A elemental impurities is consistently below 30% of the ICH Q3D Option 1 limits. The content of Class 1 and Class 2A elemental impurities were also shown to be below the ICH Q3D Option 1 limits for all tablet excipients except for lead (Pb) in the Opadry film coating excipient. However, using Option 2b, the maximum daily exposure of lead was shown to be significantly below 30% of its established permitted daily exposure (PDE) due to the low proportion of this component in the finished product. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

The analytical procedures for the 50 mg/75 mg product are identical to those authorised for the 100 mg/150 mg product, with only some slight differences with regards to the sample preparation, where needed, to accommodate for the difference in strength. The methods have been described in sufficient detail and were adequately validated where relevant. The reference standards are the same as used for the 100 mg/150 mg product.

Batch analysis results have been provided on three batches with a batch size of 30.0 kg (clinical batches) and three commercial batches of the maximum production scale of 40.0 kg, demonstrating consistent results and compliance with the finished product specification.

Stability of the product

Stability data from three production scale batches of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH) and intermediate conditions (30 °C/75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The stability batches of Symkevi 50 mg/75 mg tablets 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, dissolution, water content, physical form, microbiological quality and water activity (Ph. Eur). Except for a consistent increase in water content, the stability data showed no clear trends or changes in any of the tested parameters at all three storage conditions. All results were within the specification limits.

The available stability data from data from the existing 100 mg/150 mg tablets which have an approved shelf life of 4 years were used as supportive data. This was considered acceptable since, as indicated above, both tablet strengths have the same qualitative composition, with the exception of iron oxide yellow which is present only in the 100 mg /150 mg tablets film coat. In addition, both tablets strengths are manufactured using the same blend, dry granulation manufacturing process, film coating components (except for the yellow iron oxide) and use the same container closure system.

In addition, one pilot scale batch was exposed to light as per as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Samples were tested for appearance, assay and degradation products. The data showed no changes in the fully exposed test sample and the covered control, confirming that tezacaftor/ivacaftor tablets do not require light protective packaging.

Forced degradation studies have not been separately performed for the 50 mg/75 mg product, but only for the 100 mg/150 mg product. The results of these studies are considered representative by the for the 50 mg/75 mg tablets.

Based on available stability data, the proposed shelf-life of 3 years without any special storage requirements when packed in PCTFE/PVC-Al blisters as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

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

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The development of the 50 mg/75 mg tablet strength was largely based on pre-existing knowledge from the authorised 100 mg/150 mg tablets. Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the finished product and their manufacturing process. A design space has been proposed for the compression step in the manufacture of the finished product. The design space has been adequately verified.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

No non-clinical studies have been submitted in this application which is acceptable. No ERA was submitted which can be accepted taking into account the impact in the new population.

2.4. Clinical aspects

2.4.1. Introduction

The TEZ/IVA clinical package supporting the approved indication in patients ≥ 12 years (i.e. adolescents and adults) comprises 5 clinical studies in total: two 2 dose-finding studies (study VX11-661-101 and VX13-661-103), two placebo-controlled phase 3 efficacy and safety studies (Study VX14-661-106 and VX14-661-108) and one long term open-label study evaluating safety and efficacy (VX14-661-110).

The phase III Studies 106 and 108 were the key efficacy studies supporting the adult indication. Study 106 was a randomised controlled (RCT), placebo-controlled parallel study of 24 weeks duration in patients homozygous for *F508Del* (F/F); Study 108: RCT parallel-group study in patients heterozygous for *F508Del* and a residual function mutation (F/RF) [EMEA/H/C/004682/0000].

In this application, the Applicant submitted the clinical studies VX15-661-113 and Study VX16-661-115 to provide the bridge for the extrapolation of the efficacy and safety of patients ≥12 years to the children aged 6-11 years to support this extension of the indication.

Study VX15-661-113 (Study 113) is a 2-part open-label study designed to evaluate TEZ/IVA pharmacokinetics (PK) in Part A (Study 113A) and 24-week safety in Part B (Study 113B) in children 6 through 11 years of age with cystic fibrosis, homozygous or heterozygous for the *F508Del –CFTR* mutation.
Study 113 Part A is included in the TEZ/IVA EMEA-001640-PIP01-14-M04;

Study VX16-661-115 (Study 115) is phase 3, double blinded, parallel group study to evaluate the efficacy and safety of TEZ/IVA in patients 6 through 11 years of age with CF, with an F/F or F/RF genotype (8-week duration). Patients will be stratified by genotype and randomized in a 4:1 ratio to either the TEZ/IVA group or the appropriate blinding group for their genotype. The F/F blinding group received placebo and the F/RF blinding group received IVA monotherapy.
Study 115 was conducted in Europe and Australia and is included in the TEZ/IVA EMEA-001640-PIP01-14-M04; Study 12.

GCP

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

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

- Tabular overview of clinical studies

A tabular overview of the paediatric studies to support the application is provided in Table 6.

Table 2 Tabular overview of the studies conducted in children 6-11 years

Tabular overview of clinical studies									
study ID	**No study centres /location** **Start /stop date**	**Design**	**posology**	**duration Screening (S) Treatment (T) FU (follow up)**	**ob-ject-tive**	**Study enrolled (E) /dosed (D) /completed (C)**	**diagnose/ inclusion criteria genotype**	**gender M/F Genotype: F/F vs F/* Median age (range) yrs**	**Primary endpoint** other endpoints
Study VX15-661-113									
Part A	33 sites in North America (USA, Canada) Part A : 11 Nov 2016/5 Apr 2017 Part B 25 October 2017/ 11 sept 2018	open label	<25 kg TEZ 50 mg qd / IVA 75 mg q12h ≥25 kg TEZ 50 mg qd / IVA 150 mg q12h	S: 4 W T: 2W FU: 2w	PK Sec: safety	E: 13 D:13 C: 13	6-11 years CF with confirmed genotype	male/female : 6/7 Genotype: not reported Age: 8 (6-11)	**PK (TEZ, M1-TEZ, M2-TEZ, IVA, M1-IVA, M6-Iva)**
Part B		open label	<40 kg TEZ 50 mg qd / IVA 75 mg q12h ≥ 40 kg TEZ 100 mg qd / IVA 150 mg q12h	S: 4 w T: 24W FU: 4 weeks or extension study	Safety sec: PK, efficacy	E 70 D: 70 C: 67	6-11 years CF with confirmed genotype: F/F or F/RF*	male /female : 36/34 Genotype 61 F/F 9 F/RF Age: 8.0 (6-11) years	**PK (see above) and Safety** Efficacy (change from baseline at/through week 24) Spirometry, sweat chloride, Weight (Z score), height (Z-score), BMI (z score), $LCI_{2.5}$ (limited patients)
Study VX16-661-115									
	25 sites in Australia Europe Start/Stop 17 May 2018/ 21 Dec 2018	Randomised double Blinded Parallel 4:1 stratification	TEZ/IVA: see above Or blinding treatments IVA (F/RF) only <40 kg: 75 mg q12h; ≥40 kg : 150 mg q12h or placebo (F/F only)	S: 4 weeks T:8 weeks FU: 4 weeks or extension study	Efficacy	E: 69 D: 67 C :66	6-11 years CF with confirmed genotype: F/F or F/RF*	M/F: 30/37 F/F: n= 52 F/RF n=15 Age: 9.0 (6-11)	**absolute change in $LCI_{2.5}$ from baseline through week 8 for TEZ/IVA** For other efficacy and safety parameters, see above; parameters were measured at/through week 8
Study VX16-661-116*									
		open label extension	Part A see above Part B; weight-based posology cut of 30 kg.	A: 96 weeks B: additional 96 weeks	Long term safety	130	Roll over from study 113b and 115	Not provided	Safety

- E = enrolled; D = dosed C= completed F/F= homozygote F508/f508; F/RF= F508 and second allele with residual function, F/non RF= F508 and second allele non RF function *study not provided

2.4.2. Pharmacokinetics

No specific PK study was submitted. However, a phase 3 study included two parts one related to PK analysis. (Part A). This study is described below

Study VX15-661-113, a Phase 3, Open-label Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of VX-661 in Combination with Ivacaftor in Subjects 6 Through 11 Years of Age With Cystic Fibrosis, Homozygous or Heterozygous for *the F508Del-CFTR* Mutation.

Methods

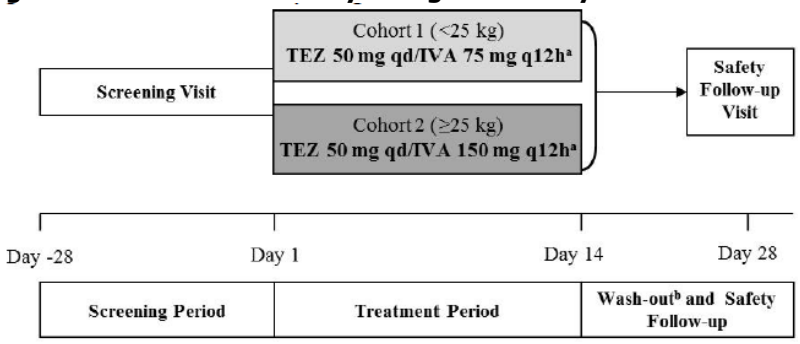
Study design

Study 113 is a 2-part (Part A and Part B), open-label, multicentre study.

Part 113A

Part 113 A included a Screening Period (28 days), Treatment Period (14 days) and a Wash-out/Safety Follow-up Period (14 days) to evaluate off-drug response. Subjects were enrolled into 2 weight-based cohorts with a cut of value of 25 kg (Figure 3).

Figure 3 Schematic of Study Design for Study 113 Part A



IVA: ivacaftor; q12h; every 12 hours; qd: daily; TEZ: tezacaftor

[a] Weight refers to weight at baseline. Study drug was administered from Day 1 through Day 14. On Day 14, only the morning dose of study drug was administered.

[b] A 2-week Washout Period (Day 14 to Day 28 [± 3 days]) was included to evaluate the off-drug response.

Part 113B included a Screening Period (28 days), Treatment Period (24 weeks [± 5 days]), and Safety Follow-up Visit (4 weeks [± 7 days]) (see Figure 15)**.**

A review of safety, tolerability, and PK data was completed by an internal Vertex team after completion of Part A to select the TEZ/IVA dose regimens for Part B. Based on this review the dosing scheme was altered. The cut of value for dosing was raised to 40 kg, and the TEZ dose of the high dosing regimen was increased. No dose adjustments were made throughout the duration of treatment of Part B

The following doses were provided during part B:

- Patients <40 kg: TEZ 50 mg qd/IVA 75 mg q12h
- Patients ≥40 kg: TEZ 100 mg qd/ IVA 150 mg q12h

Study participants

Patients aged 6-11 years with a confirmed diagnosis of CF and an eligible *CFTR* genotype. The Genotype was confirmed at the screening visit. Patients homozygous for F508/F508 were eligible for both parts of the study.

Heterozygous patients were eligible for Part A of the study if they had a second *CFTR* allele that met at least one of the following criteria:

1. mutation was predicted to have residual function
2. the mutation causes a gating defect that has been clinically demonstrated to be IVA-responsive or
3. the mutation was not likely to respond to TEZ and/or IVA therapy

For heterozygous patients with a mutation that was either predicted to have residual function or was an IVA-responsive gating mutation, the CF diagnosis was confirmed if the sweat chloride was ≥ 60 mmol/l. If the sweat chloride was < 60 mmol, the patients must have an additional chronic sinopulmonary disease and/or gastrointestinal/nutritional abnormalities associated with CF.

Patients with a history of any illness or condition that could confound study results or pose an additional safety risk (e.g., cirrhosis with portal hypertension, risk factors for Torsades de Pointes) were excluded from participation. Patients with protocol-defined laboratory values indicative of clinically significant abnormal liver or renal function were also excluded (either (a) any 2 or more of ≥ 3 x ULN for AST, ALT, GGT, ALP, or total bilirubin ≥2 × ULN; (b) ≥ 5 x ULN ALT or AST; (c) GFR ≤45 mL/min/1.73 m2 calculated by the Counahan-Barratt equation, (d) hemoglobin <10 g/dL).

The same inclusion criteria were applied for **part 113B**. However, heterozygous F508 del patient was only eligible if the second allele had a predicted residual function (see table below)

Table 3 *CFTR* mutation predicted to have a residual function and were included in the inclusion criteria of 113B

***CFTR* Mutations Predicted to Have Residual Function**			
2789+5G→A	D110E	A455E	F1074L
3849+10kbC→T	D110H	D579G	D1152H
3272-26A→G	R117C	S945L	D1270N
711+3A→G	E193K	S977F	E831X
E56K	L206W	F1052V	
P67L	A1067T	K1060T	
R74W	R352Q	R1070W	

Note: Characteristics of residual function mutations: population-level average sweat chloride <86 mmol/L (1 standard deviation from the average sweat chloride for the most common processing and trafficking mutation based on CFTR2, *F508del-CFTR*), incidence of pancreatic insufficiency ≤50% based on subjects with at least 1 copy of the mutation from epidemiologic data(CFTR2) or published literature[42-49] and in vitro response to ivacaftor, defined as an increase in percent normal chloride transport of ≥10 percentage points in transfected FRT cells expressing the CFTR form produced by the mutation.

Additional Dietary Restrictions/Prohibited Medications

Part 113A

During part A of the study, patients were asked to refrain from other investigational drugs, strenuous exercise, uncontrolled use of dietary/nutritional supplements, tobacco, juices, or other foods and medications that may affect drug-metabolizing enzymes and transporters as predefined in the protocol.

Part 113B

During part B of the study, medications and certain foods that may interfere with the CYP3A pathway were subject of certain restrictions or prohibited during the screening period and during the study.

Prior and Concomitant Medications

Subjects abstained from all restricted concomitant medications as described in the exclusion criteria. Subjects were recommended to remain on their stable CF medication regimen from 4 weeks before

Day 1 through Day 14 (Part A) or through Week 24 (Part B) or, if applicable, through the Safety Follow-up Visit.

Treatments

The test products, doses, mode of administration, and batch numbers in Part A and Part B are presented in Table 8.

Table 4 Test Product, Dose, and Mode of Administration

	Study drug	Dose	Mode of Administration
Part A			
Subjects weighing <25 kg at baseline	TEZ	50 mg	oral tablet
	IVA	75 mg	capsule containing oral granules
Subjects weighing ≥25 kg at baseline	TEZ	50 mg	oral tablet
	IVA	150 mg	oral tablet
Part B			
Subjects weighing <40 kg at baseline	TEZ/IVA	TEZ 50 mg/ IVA 75 mg	oral FDC tablet
	IVA	75 mg	oral tablet
Subjects weighing ≥40 kg at baseline	TEZ/IVA	TEZ 100 mg/ IVA 150 mg	oral FDC tablet
	IVA	150 mg	oral tablet

FDC: fixed dose combination; IVA: ivacaftor; TEZ: tezacaftor

In Part A, study drug was administered for 14 days and in Part B for 24 weeks (± 5 days).

Objectives

The primary objective was PK in Part 113A and safety in Part 113B;

In Part B, PK and efficacy were included as a secondary outcome measure.

- The PK of part B will be integrated with the description of PK of part A
- The efficacy of part B will be described as a supportive study in the section "Supportive study"
- The safety will be described in the safety part of this AR

A summary of the Study 113 objectives is outlined in Table 9.

Table 5 Study 113 Objectives

Part A	Part B
Treatment duration: 14 days	**Treatment duration:** 24 weeks
Objectives: *Primary:* • PK of TEZ and IVA after TEZ/IVA combination therapy *Secondary:* • PK of TEZ metabolites (M1-TEZ and M2-TEZ) and IVA metabolites (M1-IVA and M6-IVA) • Safety and tolerability of TEZ/IVA combination therapy	**Objectives:** *Primary:* • Safety and tolerability of TEZ/IVA combination therapy *Secondary:* • PK of TEZ, IVA and metabolites (M1-TEZ, M2-TEZ, M1-IVA, and M6-IVA) • Efficacy of TEZ/IVA combination therapy

Source: VX15-661-113 CSR/Section 8
IVA: ivacaftor; M: metabolite; PK: pharmacokinetics; TEZ: tezacaftor
Note: As described in Module 2.6.2/Section 4.3, there are 2 major circulating metabolites for both TEZ (M1-TEZ and M2-TEZ) and IVA (M1-IVA and M6-IVA). M1-TEZ is a major metabolite with similar pharmacologic activity as TEZ, while M2-TEZ is a sequential oxidation metabolite of TEZ that is 5-fold less potent than TEZ or M1-TEZ. M1-IVA is approximately 6-fold less potent than IVA and M6-IVA is considered pharmacologically inactive.

Outcomes/endpoints

Pharmacokinetic Assessments

Part A and Part B: Plasma PK parameters of TEZ, M1-TEZ, M2-TEZ, IVA, M1-IVA, and M6-IVA

Efficacy Assessments

Part B: Spirometry, weight and weight z-score, height and height z-score, BMI and BMI z-score, sweat chloride, and CFQ-R

Safety Assessments

Part A and Part B: Adverse events, clinical laboratory assessments (serum chemistry, haematology, coagulation studies, lipids, vitamins, and urinalysis), standard 12-lead ECGs, vital signs, pulse oximetry, physical examinations (PEs), and spirometry.

Part B: Ophthalmologic examinations, Lung clearance index measured by MBW (optional exploratory sub study conducted at a subset of sites).

Note: Lung clearance optional sub study to evaluate an MBW device and over-reading process that were new to the Vertex CF program. Additional analysis of LCI results is ongoing and may be presented in an additional report.

Sample size

Approximately 16 subjects (approximately 8 subjects in each cohort) were planned for enrolment in Part A.

Statistical Methods

Sample Size and Power

Part A

Sample size calculations were conducted to estimate the precision in determining TEZ clearance in paediatric subjects in the 2 weight-based cohorts. The method used non-compartmental analysis (NCA)-based PK parameters, such as clearance and volume, in adults with the assumption that there

would be similar variability in clearance in adults and paediatric subjects 6 through 11 years of age within each weight group. The calculations indicated that data from 8 subjects would allow 80% power to target a 95% CI within 60% and 140% of the geometric mean (geo mean) estimate of clearance for TEZ in each paediatric subgroup (cohort). Therefore, approximately 16 subjects (approximately 8 subjects in each cohort) were planned for enrolment in Part A.

Part B

Planned enrolment was approximately 56 subjects. Assuming a 10% dropout rate, approximately 50 subjects were expected to complete Part B. With a total sample size of 50 subjects completing the study, there would be a 92.3% chance of observing AEs in at least 1 subject if the true incidence rate were 5%, and a 99.5% chance of observing AEs in at least 1 subject if the true incidence rate were 10%. These probabilities were calculated by assuming a binomial distribution for the number of AEs.

Analysis Sets

- Part A

The following analysis sets are defined: Part A - All Subjects Set and Part A - Safety Set. Assignment of subjects to analysis sets was performed prior to the data-cut for the IA following completion of Part A.

The Part A - All Subjects Set is defined as subjects who consented to Part A of the study or received at least 1 dose of study drug in Part A of the study.

The Part A - Safety Set is defined as all subjects who received at least 1 dose of study drug in Part A of the study.

- Part B

The Part B - Safety Set was defined as all subjects who received at least 1 dose of study drug in Part B of the study.

The Part B FAS was defined as all subjects who carried the intended *CFTR* mutations and received at least 1 dose of study drug in Part B of the study. The FAS was used for all efficacy analyses except for LCI endpoints.

The Part B FAS - LCI substudy was defined as all subjects who carried the intended *CFTR* mutations and received at least 1 dose of study drug in Part B of the study and had at least 1 LCI measurement. The FAS-LCI substudy was used for efficacy analyses of exploratory LCI endpoints.

Variables

<u>Definition of Treatment-emergent Period</u>

- Part A

The treatment-emergent (TE) period for Part A corresponds to data from the first dose of study drug in Part A to the Safety Follow-up Visit in Part A, or 14 days after the last dose in Part A for subjects who did not have a Safety Follow-up Visit.

- Part B

The treatment-emergent period for Part B corresponds to data from the first dose of study drug to 28 days after the last dose of the study drug, or to the date of completion of study participation, whichever occurred first. Completion of study participation was defined as one of the following:

- For subjects who completed Part B and enrolled in the extension study within 28 days of the Week 24 Visit: the last participation date

- For subjects who completed Part B and did not enroll in the extension study within 28 days of the Week 24 Visit: the Safety Follow up Visit
- For subjects who prematurely discontinued study drug treatment, but did not withdraw consent: the latest of ETT Visit, or Safety Follow up Visit (if required)
- For subjects who withdrew consent: date of withdrawal of consent

Definition of Baseline

Part A baseline: Baseline for Part A was defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to the first dose of study drug in Part A. For ECGs, baseline values were the average of the 3 pre-treatment measurements on Day 1 of Part A.

Part B baseline: Baseline for Part B was defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to the first dose of study drug in Part B. For ECGs, baseline values were the average of the 3 pretreatment measurements on Day 1 of Part B. For sweat chloride, the baseline values were the mean of the last values on the left and the right arm prior to the first dose of the study.

Missing Data and Outliers

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

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

Pharmacokinetic Data

Samples were analysed using validated bioanalytical methods in compliance with Vertex or designee standard operating procedures (SOPs).

Calibration curves in human plasma for all 6 analytes ranged from 2.00 to 2000 ng/mL.

Pharmacokinetic Analyses

Pharmacokinetic analyses were performed upon the entire population given a dose of study drug(s), whether the subject completed all treatments or not, and if the dataset(s) supported those analyses as described in the Clinical Pharmacology Analysis Plan (CPAP).

PK parameters were determined using standard non-compartmental methods. PK parameters calculated in non-compartmental analyses included C_{max}, t_{max}, C_{trough}, t½, CLss/F, Vss/F, and AUC_T. The linear/log trapezoidal rule was used to estimate AUC with at least 4 quantifiable concentration-time points. The AUC_T calculation was based on the assumption that the drug concentration at the end of dosing interval (24 hours for TEZ and 12 hours for IVA) would be equal to the pre-dose concentration (0 hour) at steady state. PK parameters were summarized in terms of the total number of values (N), mean, and standard deviation (SD), minimum (min), median, maximum (max), coefficient of variation (CV%), geometric mean (geo mean), and CV% geo mean. For summary statistics of concentration-time series, N, total values below the limits of quantification (NBLQ), mean, SD, min, median, max, and CV%, were presented.

Results

Conduct of the study

Study initiation: 11 Nov 2016 (date first eligible subject signed the informed consent form)

Part A Completion: 5 April 2017 (date last subject completed last visit in Part A)

Part B Completion: first patient entered on 25 Oct 2017; the last subject completed the last visit on 11 Sept 2018

Changes in Conduct of Study

The Study 113 protocol was amended 2 times. Table 10 provides a list of the protocol versions, their dates, and the major changes introduced with every amendment.

Table 6 Summary of Study VX15-661-113 Protocol Amendments

Version	Date	Comments
1.2	26 May 2016	Original protocol
2.0	11 April 2017	The protocol was amended primarily to include an IDMC before the start of Part B, revise the timing restriction for the use of Orkambi (LUM/IVA), and revise the target enrollment for Part A.
3.0	19 July 2017	The protocol was revised to specify the doses selected for Part B based on the results from Part A and fasting requirements were revised to remove fasting before the lipid panel and before PK assessments.

Source: Appendix 16.1.1
IDMC: independent data monitoring committee; IVA: ivacaftor: LUM: lumacaftor; PK: pharmacokinetic

Statistical Analysis Plan

The statistical analyses plan (SAP) version 1.0 is dated 31 October 2018. The SAP has not been amended during the trial. However, the SAP was only finalised during the conduct of the trial raising concerns on how the blinding of the dataset had been maintained. It has been clarified that the clinical database was outsourced and, as such, the MAH had no access to the database. There were no unplanned unblinding events and all patients were randomised before the end date of the finalisation of the SAP. In addition, the SAP was finalised before the database lock (01 Feb 2019).

Baseline data

Subject demographics for Part A are summarized in Table 11. The majority (92.3%) of subjects were white, and all subjects were not Hispanic or Latino. A total of 46.2% of subjects were male. The median age was 8 years (range: 6 to 11 years).

Table 7 Subject Demographics, Part A Safety Set

Demographics	Cohort 1 TEZ 50 mg qd/ IVA 75 mg q12h N = 2	Cohort 2 TEZ 50 mg qd/ IVA 150 mg q12h N = 11	Total N = 13
Age at screening (years)			
n	2	11	13
Mean (SD)	7.5 (2.12)	8.2 (1.83)	8.1 (1.80)
Median	7.5	8.0	8.0
Min, Max	6, 9	6, 11	6, 11
Sex, n (%)			
Male	1 (50.0)	5 (45.5)	6 (46.2)
Female	1 (50.0)	6 (54.5)	7 (53.8)
Childbearing potential, n (%)			
Yes	0	1 (16.7)	1 (14.3)
No	1 (100.0)	5 (83.3)	6 (85.7)
Ethnicity, n (%)			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	2 (100.0)	11 (100.0)	13 (100.0)
Race, n (%)			
White	1 (50.0)	11 (100.0)	12 (92.3)
Black or African American	1 (50.0)	0	1 (7.7)

Source: Table 14.1.2

IVA: ivacaftor; max: maximum; min: minimum; n: size of subsample; N: size of sample; q12h: every 12 hours; qd: daily; SD: standard deviation; TEZ: tezacaftor

Selected baseline characteristics of subjects in Part A are summarized in Table 12.

The mean (SD) BMI was 17.09 (2.44) kg/m^2 and mean ppFEV1 was 89.1 (14.76) percent.

Table 8 Baseline Characteristics, Part A Safety Set

Demographics	Cohort 1 TEZ 50 mg qd/ IVA 75 mg q12h N = 2	Cohort 2 TEZ 50 mg qd/ IVA 150 mg q12h N = 11	Total N = 13
Weight (kg)			
n	2	11	13
Mean (SD)	23.5 (0.71)	31.7 (8.66)	30.5 (8.49)
Median	23.5	28.0	26.0
Min, Max	23, 24	25, 50	23, 50
Height (cm)			
n	2	11	13
Mean (SD)	123.0 (1.41)	134.3 (12.29)	132.5 (12.00)
Median	123.0	131.0	127.0
Min, Max	122, 124	118, 154	118, 154
BMI[a] (kg/m^2)			
n	2	11	13
Mean (SD)	15.53 (0.11)	17.37 (2.56)	17.09 (2.44)
Median	15.53	16.64	16.52
Min, Max	15.5, 15.6	13.9, 23.8	13.9, 23.8
$ppFEV_1$			
n	2	11	13
Mean (SD)	84.4 (3.32)	90.9 (15.97)	89.1 (14.76)
Median	84.4	89.9	88.9
Min, Max	82, 87	60, 116	60, 116

Source: Table 14.1.3

BMI: body mass index; IVA: ivacaftor; max: maximum; min: minimum; N: size of sample; n: size of subsample; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; q12h: every 12 hours; qd: daily; SD: standard deviation: TEZ: tezacaftor

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

[a] BMI = weight / (height*height) (kg/m^2)

Medical history in Part A was consistent with the diagnosis of CF in this age group. The most common medical history conditions (≥30% overall incidence) by PT were CF lung (100%), pancreatic insufficiency (92.3%), asthma (53.8%), constipation (46.2%), rhinitis allergic (46.2%), gastroesophageal reflux disease (38.5%), chronic sinusitis (38.5%), and cough (38.5%).

- **Part B**

Overall, most subjects were white (97.1%) and not Hispanic or Latino (95.7%). A total of 51.4% of subjects were male. The median age in Part B was 8.0 years (range: 6 to 11 years) (Table 13).

Table 9 Subject Demographics, Part B Safety Set

Demographics	Total N = 70
Age at screening (years)	
n	70
Mean (SD)	8.1 (1.8)
Median	8.0
Min, Max	6, 11
Sex, n (%)	
Male	36 (51.4)
Female	34 (48.6)
Childbearing potential, n (%)	
Yes	2 (5.9)
No	32 (94.1)
Ethnicity, n (%)	
Hispanic or Latino	3 (4.3)
Not Hispanic or Latino	67 (95.7)
Not Collected per Local Regulations	0
Race, n (%)	
White	68 (97.1)
Black or African American	0
Asian	1 (1.4)
American Indian or Alaska Native	0
Native Hawaiian or Other Pacific Islander	0
Not Collected per Local Regulations	0
Other	1 (1.4)
Country, n (%)	
USA	64 (91.4)
Canada	6 (8.6)

Source: Table 14.1.3.1b
Max: maximum value; Min: minimum value; N: size of sample; n: size of subsample; SD: standard deviation; USA: United States of America

In total, 61 subjects (87.1%) were homozygous for the *F508Del* mutation and 9 subjects (12.9%) were heterozygous for *F508Del* and a second allele that results in residual *CFTR* function. At baseline, the mean ppFEV1 was 91.1%.

Most subjects (88.6%) weighed <40 kg at baseline. The mean (SD) weight at baseline was 30.7 (10.0) kg, and the mean weight z-score was 0.20 (0.94), indicating that baseline weights were above average for subjects' age and sex. Similarly, the mean (SD) baseline BMI was 17.44 (2.69) kg/m^2 and the mean (SD) baseline BMI z-score was 0.37 (0.90). The mean (SD) baseline height was 131.0 (13.0) cm and mean (SD) baseline height z-score was -0.07 (0.98).

At baseline, the majority of subjects used an inhaled bronchodilator (98.6%), dornase alfa (88.6%), and inhaled hypertonic saline (72.9%). The majority of subjects (78.6%) were negative for Pseudomonas aeruginosa in the 2 years prior to the start of Part B (Table 14).

Table 10 Baseline Characteristics, Part B Safety Set

Demographics	Total N = 70
Type of *CFTR* Mutation, n (%)	
F508del/F508del	61 (87.1)
F508del/residual function	9 (12.9)
Weight group at enrollment, n (%)	
<40 kg	62 (88.6)
≥40 kg	8 (11.4)
Weight (kg) at baseline	
n	70
Mean (SD)	30.7 (10.0)
Median	28.6
Min, Max	19.1, 58.0
Height (cm) at baseline	
n	70
Mean (SD)	131.0 (13.0)
Median	128.6
Min, Max	110.5, 163.4
BMI[a] (kg/m^2) at baseline	
n	70
Mean (SD)	17.44 (2.69)
Median	16.58
Min, Max	13.73, 26.37
Weight *z*-score at baseline	
n	70
Mean (SD)	0.20 (0.94)
Median	0.05
Min, Max	-1.52, 2.58
Height *z*-score at baseline	
n	70
Mean (SD)	-0.07 (0.98)
Median	-0.09
Min, Max	-1.96, 2.36
BMI *z*-score at baseline	
n	70
Mean (SD)	0.37 (0.90)
Median	0.50
Min, Max	-1.44, 2.15

$ppFEV_1$(%) at baseline	
n	70
Mean (SD)	91.1 (12.3)
Median	90.4
Min, Max	63.4, 118.0
Sweat chloride (mmol/L) at baseline[b]	
n	64
Mean (SD)	99.1 (19.2)
Median	105.3
Min, Max	15.5, 120.5
CFQ-R Respiratory Domain (Child Version) at Baseline	
n	70
Mean (SD)	81.8 (13.8)
Median	83.3
Min, Max	41.7, 100.0
Use of dornase alfa[c], n (%)	62 (88.6)
Use of inhaled antibiotic[c], n (%)	10 (14.3)
Use of azithromycin[c], n (%)	16 (22.9)
Use of bronchodilator[c], n (%)	69 (98.6)
Use of inhaled bronchodilator[c], n (%)	69 (98.6)
Use of inhaled hypertonic saline[c], n (%)	51 (72.9)
Use of inhaled corticosteroids[c], n (%)	30 (42.9)
Colonization of *Pseudomonas aeruginosa*, n (%)	
Positive	15 (21.4)
Negative	55 (78.6)

Source: Table 14.1.4.1b

BMI: body mass index; CFQ-R: Cystic Fibrosis Questionnaire-Revised; *CFTR*: CF transmembrane conductance regulator gene; *F508del*: *CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein; max: maximum value; min: minimum value; N: size of sample; n: size of subsample; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SD: standard deviation

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

[a] BMI = weight / (height*height) (kg/m^2)

[b] Subjects with sweat chloride values <60 mmol/L at Screening were eligible to enroll in the study if they met alternative criteria for a diagnosis of CF as described in Section 9.3.1.

[c] Includes medication started before the first dose of study drug, regardless of when use of medication ended.

Medical history in Part B was consistent with the diagnosis of CF in this age group. The most common medical history conditions (≥30% overall incidence) were CF lung disease (92.9%), pancreatic failure (90.0%), constipation (44.3%), and gastroesophageal reflux disease (35.7%).

Subject demographics in Study 113 Part B are presented by *CFTR* mutation type (homozygous for *F508Del* [F/F] versus heterozygous for *F508Del* and a second allele that results in residual function [F/RF]) in Table 15. Baseline characteristics in Part B (including anthropometric z-scores and percentiles) are presented by mutation type in Table 16.

Table 11 Study VX15-661-113 Part B: Demographics in F/F and F/RF Subjects, Safety Set

Demographic	F/F Subjects N = 61	F/RF Subjects N = 9	Total N = 70
Age at Screening (years)			
n	61	9	70
Mean (SD)	8.0 (1.8)	9.1 (1.9)	8.1 (1.8)
Median	8.0	10.0	8.0
Min, max	6, 11	6, 11	6, 11
Sex, n (%)			
Male	31 (50.8)	5 (55.6)	36 (51.4)
Female	30 (49.2)	4 (44.4)	34 (48.6)
Childbearing potential, n (%)			
Yes	2 (6.7)	0	2 (5.9)
No	28 (93.3)	4 (100.0)	32 (94.1)
Ethnicity, n (%)			
Hispanic or Latino	3 (4.9)	0	3 (4.3)
Not Hispanic or Latino	58 (95.1)	9 (100.0)	67 (95.7)
Not collected per local regulations	0	0	0
Race, n (%)			
White	59 (96.7)	9 (100.0)	68 (97.1)
Black or African American	0	0	0
Asian	1 (1.6)	0	1 (1.4)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Not Collected per Local Regulations	0	0	0
Other[a]	1 (1.6)	0	1 (1.4)
Country, n (%)			
USA	55 (90.2)	9 (100.0)	64 (91.4)
Canada	6 (9.8)	0	6 (8.6)

Source: Study 113 CSR/Ad hoc Table 1.1b
n: size of subsample; N: Safety Set sample size
[a] Other race was listed as "Black/White" (VX15-661-113 CSR/Listing 16.2.4.1b).

Table 12 Study VX15-661-113 Part B: Baseline Characteristics in F/F and F/RF Subjects, Safety set

Characteristic	F/F Subjects N = 61	F/RF Subjects N = 9	Total N = 70
Weight Group at Enrollment, n (%)			
<40 kg	55 (90.2)	7 (77.8)	62 (88.6)
≥40 kg	6 (9.8)	2 (22.2)	8 (11.4)
Weight (kg)			
n	61	9	70
Mean (SD)	30.0 (9.6)	35.2 (11.9)	30.7 (10.0)
Median	27.4	31.7	28.6
Min, max	19.1, 58.0	24.0, 55.5	19.1, 58.0
Height (cm)			
n	61	9	70
Mean (SD)	129.8 (12.7)	139.2 (13.0)	131.0 (13.0)
Median	127.5	141.0	128.6
Min, Max	110.5, 163.4	121.1, 160.4	110.5, 163.4
BMI (kg/m²)			
n	61	9	70
Mean (SD)	17.40 (2.67)	17.71 (2.93)	17.44 (2.69)
Median	16.59	16.37	16.58
Min, Max	13.73, 26.37	15.32, 23.77	13.73, 26.37
Weight Z-score			
n	61	9	70
Mean (SD)	0.18 (0.94)	0.30 (0.98)	0.20 (0.94)
Median	0.04	0.65	0.05
Min, Max	-1.52, 2.58	-1.18, 1.72	-1.52, 2.58
Height Z-score			
n	61	9	70
Mean (SD)	-0.13 (1.00)	0.33 (0.76)	-0.07 (0.98)
Median	-0.27	0.03	-0.09
Min, Max	-1.96, 2.36	-0.81, 1.53	-1.96, 2.36
BMI Z-score			
n	61	9	70
Mean (SD)	0.39 (0.90)	0.24 (0.93)	0.37 (0.90)
Median	0.50	0.55	0.50
Min, Max	-1.44, 2.15	-0.98, 1.60	-1.44, 2.15
Weight Percentile			
n	61	9	70
Mean (SD)	54.46 (27.99)	58.36 (31.02)	54.96 (28.19)
Median	51.46	74.11	52.10
Min, Max	6.43, 99.50	11.83, 95.71	6.43, 99.50
Height Percentile			
n	61	9	70
Mean (SD)	45.26 (29.87)	59.97 (24.56)	47.15 (29.50)
Median	39.42	51.33	46.34
Min, Max	2.50, 99.10	21.03, 93.70	2.50, 99.10

BMI Percentile			
n	61	9	70
Mean (SD)	61.50 (26.82)	56.75 (30.68)	60.89 (27.15)
Median	69.05	70.77	69.16
Min, Max	7.47, 98.43	16.41, 94.55	7.47, 98.43
Percent Predicted FEV_1			
n	61	9	70
Mean (SD)	91.2 (12.4)	90.6 (12.2)	91.1 (12.3)
Median	90.9	89.9	90.4
Min, Max	63.4, 118.0	66.8, 109.2	63.4, 118.0
FEV_1 (L)			
n	61	9	70
Mean (SD)	1.53 (0.48)	1.77 (0.29)	1.56 (0.46)
Median	1.48	1.78	1.53
Min, Max	0.70, 3.36	1.29, 2.16	0.70, 3.36
Sweat Chloride (mmol/L)			
n	55	9	64
Mean (SD)	103.7 (10.6)	71.2 (33.6)	99.1 (19.2)
Median	105.5	68.0	105.3
Min, Max	59.0, 120.5	15.5, 110.5	15.5, 120.5
CFQ-R Respiratory (Child Version)			
n	61	9	70
Mean (SD)	81.7 (13.9)	82.4 (14.1)	81.8 (13.8)
Median	83.3	83.3	83.3
Min, Max	41.7, 100.0	50.0, 100.0	41.7, 100.0
Use of dornase alfa[a], n (%)	55 (90.2)	7 (77.8)	62 (88.6)
Use of inhaled antibiotic[a], n (%)	8 (13.1)	2 (22.2)	10 (14.3)
Use of azithromycin[a], n (%)	15 (24.6)	1 (11.1)	16 (22.9)
Use of bronchodilator[a], n (%)	60 (98.4)	9 (100.0)	69 (98.6)
Use of inhaled hypertonic saline[a], n (%)	45 (73.8)	6 (66.7)	51 (72.9)
Use of inhaled corticosteroids[a], n (%)	27 (44.3)	3 (33.3)	30 (42.9)
Colonization of *Pseudomonas aeruginosa*, n (%)			
Positive	15 (24.6)	0	15 (21.4)
Negative	46 (75.4)	9 (100.0)	55 (78.6)

Source: Study 113 CSR/Ad hoc Table 1.2b

BMI: body mass index; CFQ-R: Cystic Fibrosis Questionnaire – Revised; FEV_1: forced expiratory volume in 1 second; n: size of subsample; N: Safety Set sample size

Notes: Baseline is defined as the most recent non-missing measurement before the first dose of study drug in Part B.
BMI: Body Mass Index = Weight/ (Height*Height) (kg/m^2).

[a] Includes medications started before the first dose of study drug, regardless of when medication use ended.

Number analysed

- **Part A**

A total of 15 patients were screened

Screen failures

A total of two patients were screened but not enrolled. 1 subject had a scheduling conflict, and 1 subject decide to start treatment with Orkambi.

Enrolled patients

A total of 13 subjects were enrolled in Part A; 2 subjects weighed <25 kg at baseline and were enrolled in Cohort 1 and 11 subjects weighed ≥25 kg at baseline and were enrolled in Cohort 2. All subjects completed the treatment regimen in Part A. (Table 17)

Table 13 Subject Disposition – Part A

Disposition Reason	Cohort 1 TEZ 50 mg qd/ IVA 75 mg q12h (n)	Cohort 2 TEZ 50 mg qd/ IVA 150 mg q12h (n)	Total (n)
All Subjects Set	2	11	13
Safety Set	2	11	13
PK Set	2	11	13
Completed treatment regimen	2	11	13
Prematurely discontinued treatment	0	0	0
Completed Part A	2	11	13
Prematurely discontinued study during Part A	0	0	0

Source: Table 14.1.1 and Table 14.4.3
IVA: ivacaftor; PK: pharmacokinetic(s); n: size of subsample; ; q12h: every 12 hours; qd: daily; TEZ: tezacaftor

Part B

There were 70 subjects in the Safety Set and the FAS and 35 subjects in the optional LCI sub study. A total of 67 subjects (95.7%) completed TEZ/IVA treatment. A total of 3 subjects (4.3%) discontinued TEZ/IVA treatment; 1 subject (1.4%) discontinued due to an AE. (Table 18)

Table 14 Subject Disposition – Part B

Disposition Reason	Total n (%)
Safety Set	70
PK Set	69
Full Analysis Set	70
Full Analysis Set - LCI Substudy	35
Completed treatment regimen	67 (95.7)
Prematurely discontinued treatment[a]	3 (4.3)
Adverse event	1 (1.4)
Subject refused further dosing (not due to AE)	2 (2.9)
Completed Part B	67 (95.7)
Prematurely discontinued study during Part B	3 (4.3)
Adverse event	1 (1.4)
Withdrawal of consent (not due to AE)	2 (2.9)

Source: Table 14.1.1.1b and Table 14.4.7
AE: adverse event; LCI: lung clearance index; n: size of subsample; PK: pharmacokinetic(s)
[a] If a subject discontinued TEZ/IVA and IVA for different reasons, the subject was counted for both reasons, but only counted once in the total number of subjects who prematurely discontinued treatment.

No subject was excluded from the efficacy analysis

Treatment Compliance

In Part B, the mean (SD) compliance was 99.50% (2.99%). One (1.4%) subject was <80% compliant.

Protocol Deviations

- **Part A**

There were no Important protocol deviations (IPD) in Part A.

- **Part B**

In total, 3 subjects had IPDs:

- One subject (TEZ 50 mg qd/IVA 75 mg q12h) was <80% compliant with study drug.
- One subject (TEZ 50 mg qd/IVA 75 mg q12h) was enrolled in the study without review of their coagulation lab results.

- One subject
- (TEZ 50 mg qd/IVA 75 mg q12h) began the washout of physician prescribed LUM/IVA prior to signing the ICF.

Pharmacokinetic Results

- **Part A**

Geometric mean (CV%) PK parameters of TEZ, M1-TEZ, and M2-TEZ on Day 1 and Day 14 are listed in Table 19. On Day 14, the geometric mean C_{max} TEZ was 6300 ng/mL in Cohort 1(*subjects <25 kg*), and 5340 ng/mL in Cohort 2 (*subjects ≥25 kg*). The geometric mean AUC_{τ} was 66500 ng*h/mL in Cohort 1 and 71600 ng*h/mL in Cohort 2.

Table 15 Geometric mean (CV%) PK parameters of TEZ, M1-TEZ, and M2-TEZ in Part A, Part A PK set of Study VX15-661-113

Analyte	Day	Cohort	N	T_{max}[a] (h)	C_{max} (ng/mL)	C_{trough} (ng/mL)	AUC_{τ} (ng*h/mL)	CL/F (L/h)
TEZ	1	1	2	1.02 (1.00-1.03)	6630 (10.3)	NA	54300 (16.2)	NA
		2	11	3.95 (1.83-5.00)	4310 (42.6)	NA	41600 (36.2)	NA
	14	1	2	2.66 (1.00-4.32)	6300 (10.3)	1200 (47.9)	66500 (30.5)	0.752 (30.5)
		2	10	3.97 (1.88-5.17)	5340 (49.0)	1450 (78.6)	71600 (61.1)	0.698 (61.1)
M1-TEZ	1	1	2	23.1 (22.6-23.5)	1720 (3.29)	NA	36500 (5.80)	NA
		2	11	23.6 (4.92-24.7)	1530 (22.0)	NA	27400 (26.3)	NA
	14	1	2	4.16 (4.00-4.32)	8360 (22)	5480 (11.1)	160000 (15.5)	NA
		2	10	4.98 (3.92-5.17)	5930 (19.9)	4290 (14.2)	121000 (17.1)	NA
M2-TEZ	1	1	2	23.1 (22.6-23.5)	1130 (4.36)	NA	14200 (12.3)	NA
		2	11	23.9 (21.8-25.0)	922 (25.8)	NA	11100 (25.9)	NA
	14	1	2	2.59 (1.17-4.00)	6180 (27.2)	5820 (33.0)	137000 (32.7)	NA
		2	10	4.07 (0.00-5.02)	5350 (27.2)	4910 (30.7)	119000 (27.7)	NA

Source: Table 14.4.3 and Table 14.4.5

AUC_{τ}: area under the concentration-time curve during the dosing interval; CL/F: apparent clearance; C_{max}: maximum observed concentration; C_{trough}: predose concentration; CV%: coefficient of variation; N: total sample size; NA: not applicable; PK: pharmacokinetic(s); TEZ: tezacaftor; T_{max}: time of maximum concentration

[a] T_{max} is presented as median (range).

Geometric mean (CV%) PK parameters of IVA, M1-IVA and M6-IVA on Day 1 and Day 14 are listed in Table 20. On Day 14, the geometric mean C_{max} of IVA was 578 ng/mL in Cohort 1 (*subjects <25 kg*) and 1490 ng/mL in Cohort 2 (*subjects ≥25 kg*). The geometric mean AUC_{τ} of IVA was 5050 ng*h/mL in Cohort 1 and 12400 ng*h/mL in Cohort 2.

Table 16 Geometric mean (CV%) PK parameters of IVA, M1-IVA, and M6-IVA in Part A, Part A PK set of Study VX15-661-113

Analyte	Day	Cohort	N	T_{max}[a] (h)	C_{max} (ng/mL)	C_{trough} (ng/mL)	AUC_{τ} (ng*h/mL)	CL/F (L/h)
IVA	1	1	1	3.92 (NA)	656 (NA)	NA	NA	NA
		2	9	4.00 (3.50 – 5.00)	1010 (64.3)	NA	NA	NA
	14	1	2	4.12 (3.92-4.32)	578 (60.4)	409 (24)	5050 (49.1)	14.8 (49.1)
		2	10	4.10 (0.00-5.17)	1490 (105)	695 (186)	12400 (118)	12.1 (118)
M1-IVA	1	1	1	4.92 (NA)	2320 (NA)	NA	NA	NA
		2	9	4.00 (3.57, 5.05)	2430 (57.1)	NA	NA	NA
	14	1	2	2.16 (0.00-4.32)	1460 (34.6)	1370 (25.0)	13700 (52.1)	NA
		2	10	3.98 (0.00-5.05)	3420 (72.7)	2070 (113)	30300 (81.1)	NA
M6-IVA	1	1	1	4.92 (NA)	849 (NA)	NA	NA	NA
		2	9	5.00 (4.50-5.05)	1070 (55.7)	NA	NA	NA
	14	1	2	0.00 (0.00-0.00)	1090 (31.4)	1090 (31.4)	10200 (58.5)	NA
		2	10	4.05 (0.00-5.05)	2720 (59.2)	2080 (86.8)	26000 (70.6)	NA

Source: Table 14.4.4 and Table 14.4.6

AUC_{τ}: AUC during a dosing interval; CL/F: apparent clearance; C_{max}: maximum observed concentration; C_{trough}: predose concentration; CV%: coefficient of variation; IVA: ivacaftor; N: total sample size; NA: not applicable; PK: pharmacokinetic(s); T_{max}: time of maximum concentration

[a] T_{max} is presented as median (range).

- **Part B**

The adult population PK model was applied to Study 113A data (N = 13) and showed reasonable predictions of the exposures observed in Study 113A. Simulations were conducted with the assumption that clearance and volume of distribution would scale allometrically with body weight using fixed exponents. Paediatric subjects 6 through 11 years of age typically weigh between 15 and 50 kg, and population PK simulations were performed to compare exposures for subjects in this weight range to those observed in subjects ≥12 years old in Phase 3 TEZ/IVA studies.

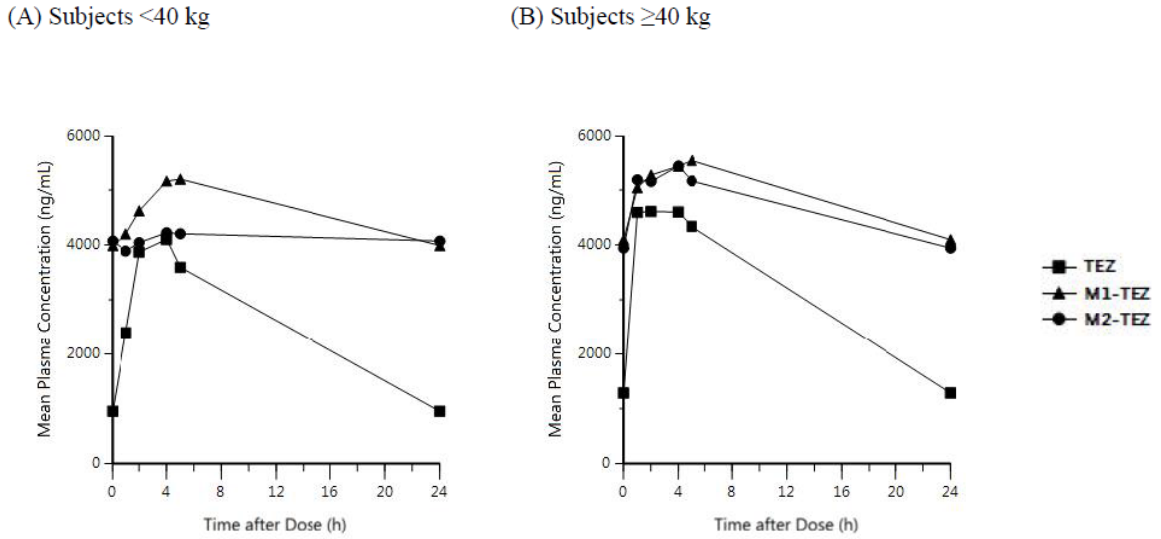
Across the weight range in 6- through 11-year-olds, simulated geometric mean ratios (Cmin, AUC, and Cmax) showed that subjects <25 kg receiving TEZ 100 mg qd/IVA 150 mg q12h would have higher exposures for parent TEZ compared to subjects ≥12 years old. The IVA weight cut-off was increased from 25 kg to 40 kg for Study 113B and Study 115 in order to (1) achieve exposures similar to subjects ≥12 years old across all of the weight ranges, (2) maintain the same TEZ:IVA dose ratio in the adult and paediatric populations, and (3) avoid exposures of TEZ that would be higher than those achieved in the ≥12-year-old population.

Therefore, for Part B, the body weight cut-off for dosing was selected to be 40 kg, because modelling and simulations predicted the potential for higher TEZ exposures in subjects receiving 100 mg qd dose of TEZ.

TEZ, M1-TEZ, and M2-TEZ

Serial PK samples of TEZ and its metabolites were collected at Week 16 visit. Mean plasma concentration-time profiles of TEZ, M1-TEZ and M2-TEZ at Week 16 are presented in Figure 4.

Figure 4 Arithmetic mean plasma concentration-time profiles of TEZ, M1-TEZ and M2-TEZ at week 16 in Part B, Part B PK set of Study VX15-661-113



Geometric mean (CV%) PK parameters of TEZ, M1-TEZ and M2-TEZ at Week 16 are listed in **Table 21**. The geometric mean C_{max} of TEZ was 4800 ng/mL for subjects <40 kg and 5870 ng/mL for subjects ≥ 40 kg. The geometric mean AUC_{τ} of TEZ was 50300 ng*h/mL for subjects <40 kg and 60900 ng*h/mL for subjects ≥40 kg.

Table 17 Geometric Mean (CV%) PK Parameters of TEZ, M1-TEZ, and M2-TEZ in Part B, Part B PK Set of Study VX15-661-113

Analyte	WK	Weight group	N	T_{max}[a] (h)	C_{max} (ng/mL)	C_{trough} (ng/mL)	AUC_{τ} (ng*h/mL)	CL/F (L/h)
TEZ	16	<40 kg	62	2.99 (0.98-5.05)	4800 (33.7)	766 (109)	50300 (36.3)[b]	0.994 (36.3)
		≥40 kg	7	3.50 (1.00-4.12)	5870 (46.5)	888 (201)[c]	60900 (50.6)[c]	1.64 (50.6)
M1-TEZ	16	<40 kg	62	4.06 (0.00-5.08)	5310 (36.0)	3520 (97.4)	104000 (44.2)[b]	NA
		≥40 kg	7	3.50 (1.03-5.03)	5440 (61.5)	3310 (128)[c]	100000 (87.2)[c]	NA
M2-TEZ	16	<40 kg	62	3.91 (0.00-5.00)	4170 (47.4)	3470 (91.4)	88400 (57.0)[b]	NA
		≥40 kg	7	3.67 (1.03-5.00)	5210 (55.0)	3700 (51.4)[c]	93600 (46.5)[c]	NA

Source: Table 14.4.7

AUC_τ: area under the concentration-time curve during the dosing interval; CL/F: apparent clearance; C_{max}: maximum observed concentration; C_{trough}: predose concentration; CV%: coefficient of variation; N: total sample size; NA: not applicable; PK: pharmacokinetic, pharmacokinetics; TEZ: tezacaftor; T_{max}: time of maximum concentration

[a] T_{max} presented as median (range).

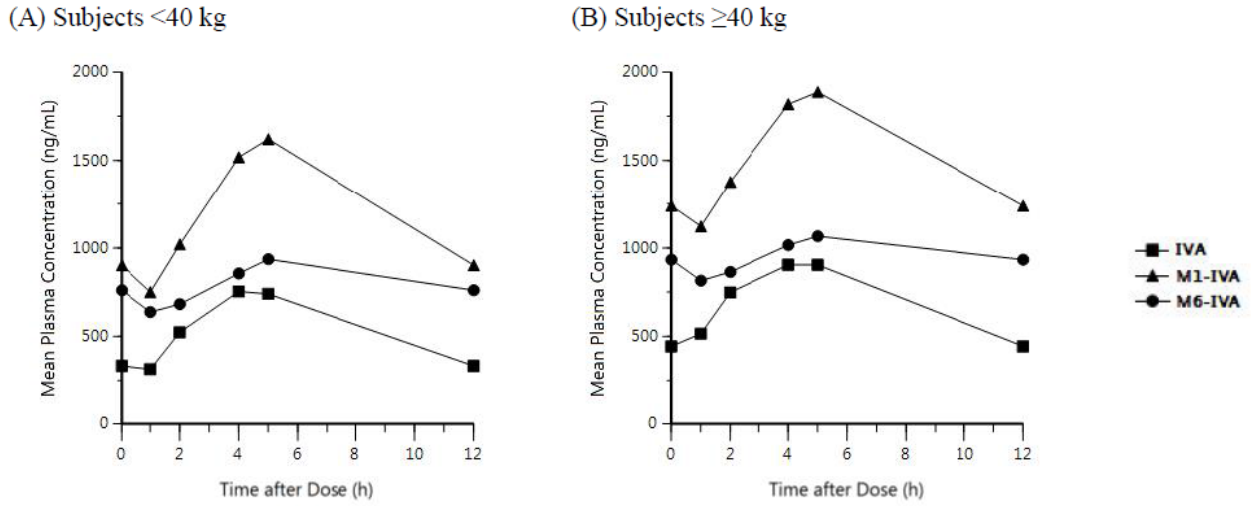
[b] N = 61

[c] N = 6

IVA, M1-IVA, and M6-IVA

Serial PK samples of IVA and its metabolites were collected at Week 16 visit. Mean plasma concentration-time profiles of IVA, M1-IVA and M6-IVA at Week 16 are presented in Figure **5**.

Figure 5 Arithmetic mean plasma concentration-time profiles of IVA, M1-IVA and M6-IVA at week 16 in Part B, Part B PK set of Study VX15-661-113



Geometric mean (CV%) PK parameters of IVA, M1-IVA, and M6-IVA at Week 16 are listed in Table 22. The geometric mean C_{max} of IVA was 725 ng/mL for subjects <40 kg, and 886 ng/mL for subjects ≥40 kg. The geometric mean AUC_τ of IVA was 5330 ng*h/mL for subjects <40 kg and 7410 ng*h/mL for subjects ≥40 kg.

Table 18 Geometric mean (CV%) PK parameters of IVA, M1-IVA, and M6-IVA in Part B, Part B PK set of Study VX15-661-113

Analyte	WK	Weight group	N	T_{max}[a] (h)	C_{max} (ng/mL)	C_{trough} (ng/mL)	AUC_τ (ng*h/mL)	CL/F (L/h)
IVA	16	<40 kg	62	4.02 (0.00-5.20)	725 (56.9)	254 (105)[b]	5330 (62.2)[c]	14.1 (62.2)
		≥40 kg	7	4.12 (2.00-4.75)	886 (58.7)	425 (43.3)[d]	7410 (53.8)[d]	20.2 (53.8)
M1-IVA	16	<40 kg	62	4.08 (0.00-5.20)	1560 (54.8)	753 (89.0)[b]	12700 (55.9)[c]	NA
		≥40 kg	7	4.50 (0.00-5.12)	1870 (50.2)	1190 (43.0)[d]	17200 (40.4)[d]	NA
M6-IVA	16	<40 kg	62	4.56 (0.00-5.32)	870 (69.2)	603 (95.8)[b]	8140 (70.2)[c]	NA
		≥40 kg	7	1.00 (0.00-5.12)	1120 (29.5)	846 (68.9)[d]	11100 (39.4)[d]	NA

Source: Table 14.4.8
AUC_τ: area under the concentration-time curve during the dosing interval; CL/F: apparent clearance; C_{max}: maximum observed concentration; C_{trough}: predose concentration; CV%: coefficient of variation; IVA: ivacaftor; N: total sample size; NA: not applicable; PK: pharmacokinetic, pharmacokinetics; T_{max}: time of maximum concentration
[a] T_{max} is presented as median (range).
[b] N = 60
[c] N = 59
[d] N = 6

Simulations of TEZ/IVA and M1-TEZ exposures with 35-kg, 30-kg and 25-kg cut-off for weight based dosing

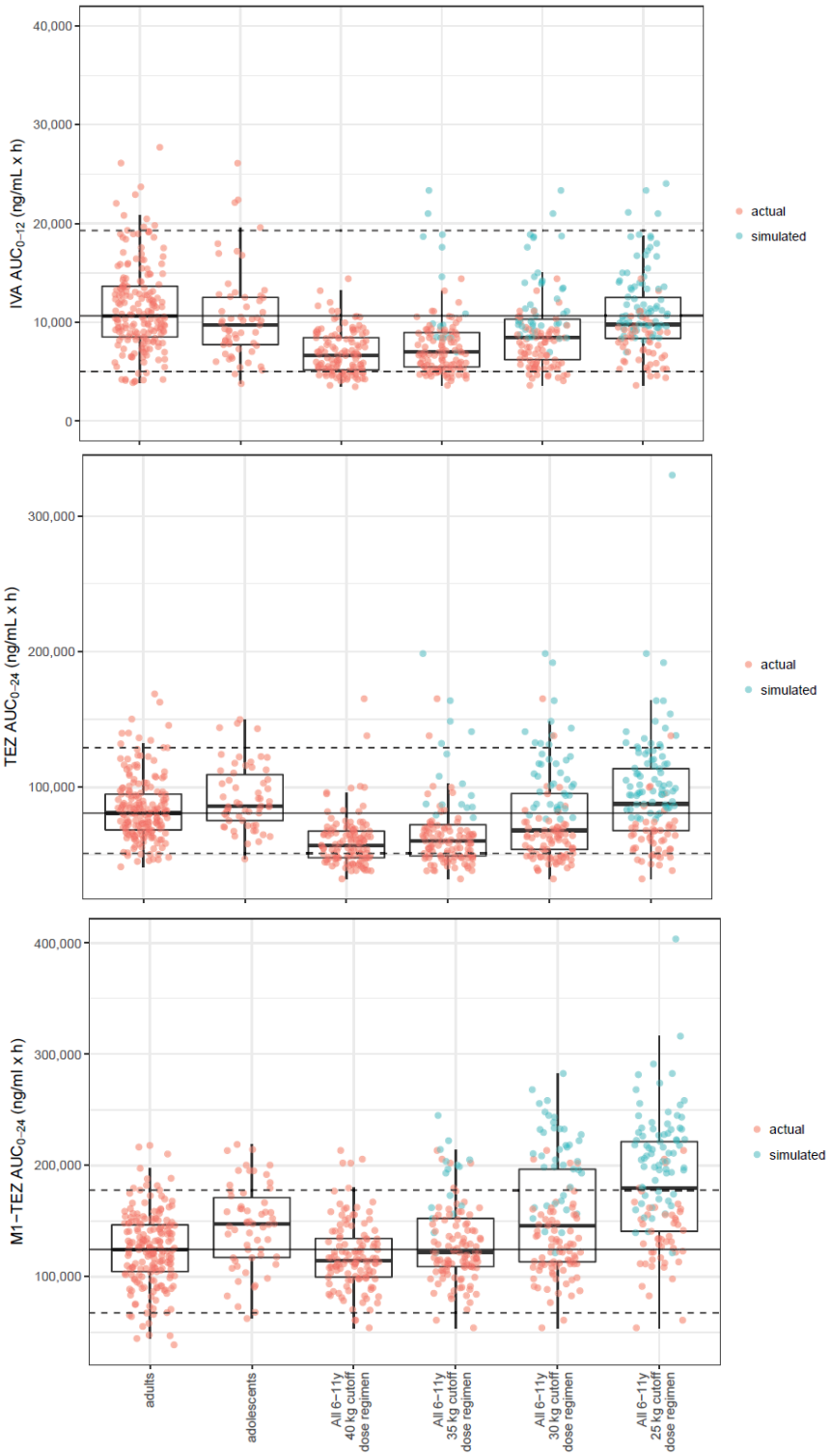
Weight cut-off-based dosing was used in Studies 113 and 115 with a weight cut-off of 40 kg. Upon review of the exposure data from these studies, an integrated popPK analysis of data was performed. The results from this integrated popPK analysis demonstrated that for subjects 6 through 11 years of age who weighed ≥40 kg and received TEZ 100 mg qd/IVA 150 mg q12h, the distribution of individual TEZ, M1-TEZ, and IVA exposures were similar to the observed range of subjects 12 years of age and older. For subjects 6 through 11 years of age who weighed <40 kg and received TEZ 50 mg qd/IVA 75 mg q12h, TEZ parent and IVA parent exposures fell within the lower range of observed exposures of subjects 12 years and older. M1-TEZ exposures were similar to those of subjects 12 years and older (Table 23).

Table 19 Summary of TEZ, M1-TEZ, and IVA observed steady-state exposures (AUCss) by age group, 40-kg weight cut-off

Age Group / Weight		TEZ $AUC_{0\text{-}24h}$ (µg·h/mL)			M1-TEZ $AUC_{0\text{-}24h}$ (µg·h/mL)			IVA $AUC_{0\text{-}12h}$ (µg·h/mL)		
		N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max
6 through 11 years	*(Both doses combined)*	121	59.8 (18.6)	32.4, 165	121	119 (30.2)	53.9, 213	122	6.94 (2.20)	3.49, 14.4
<40 kg	50 mg qd/ 75 mg q12h	112	57.8 (16.5)	32.4, 165	112	117 (28.6)	53.9, 206	113	6.74 (2.00)	3.49, 12.0
≥40 kg	100 mg qd/ 150 mg q12h	9	84.9 (25.2)	49.5, 138	9	140 (41.6)	60.7, 213	9	9.46 (3.08)	4.39, 14.4
12 through 17 years	100 mg qd/ 150 mg q12h	58	92.4 (23.7)	47, 150	58	145 (38.2)	62.2, 219	57	10.6 (4.61)	3.80, 26.1
18 years and older	100 mg qd/ 150 mg q12h	193	84.1 (23.2)	41.3, 169	193	124 (32.8)	38.6, 218	186	11.5 (4.44)	3.90, 27.7

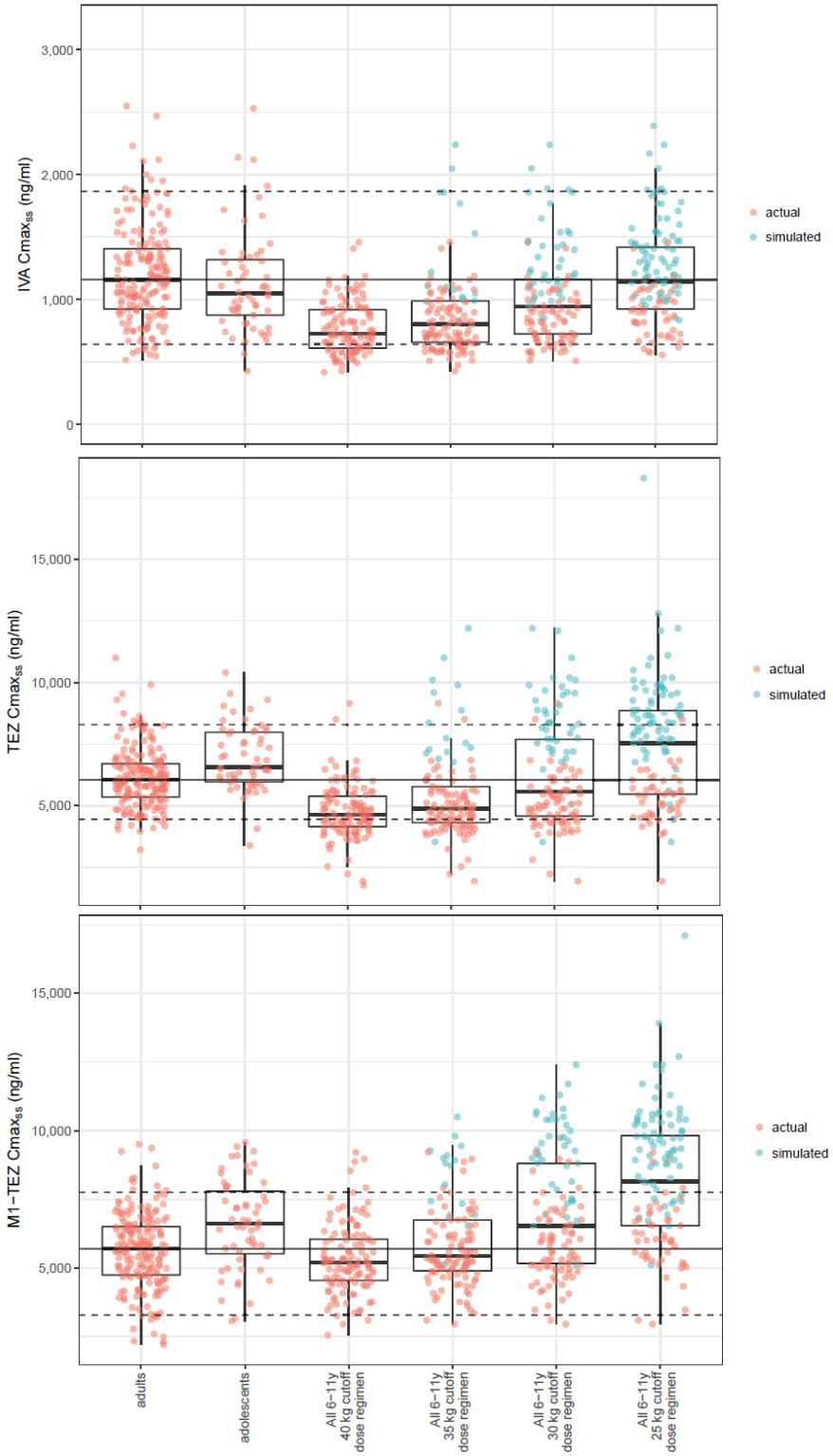
Additional simulations were performed to optimise the final proposed dosing regimen. The objective of these popPK simulations was to determine whether a different weight cut-off would achieve TEZ parent and IVA parent PK exposures that are more similar to the exposures observed in subjects 12 years and older. For this purpose, weight cut-offs of 40 kg, 35 kg, 30 kg and 25 kg were applied. Approximately one third of subjects in Studies 113 and 115 weighed ≥30 kg and <40 kg. Results for AUC, Cmax and Cmin are shown in Figure 6, Figure 7 and Figure 8.

Figure 6 Predicted steady-state IVA, TEZ and M1-TEZ exposures for children from 6 to < 12 years old (Studies 113 and 115) compared to adolescents and adults (Study 106) with different weight regimens: <u>AUC</u>



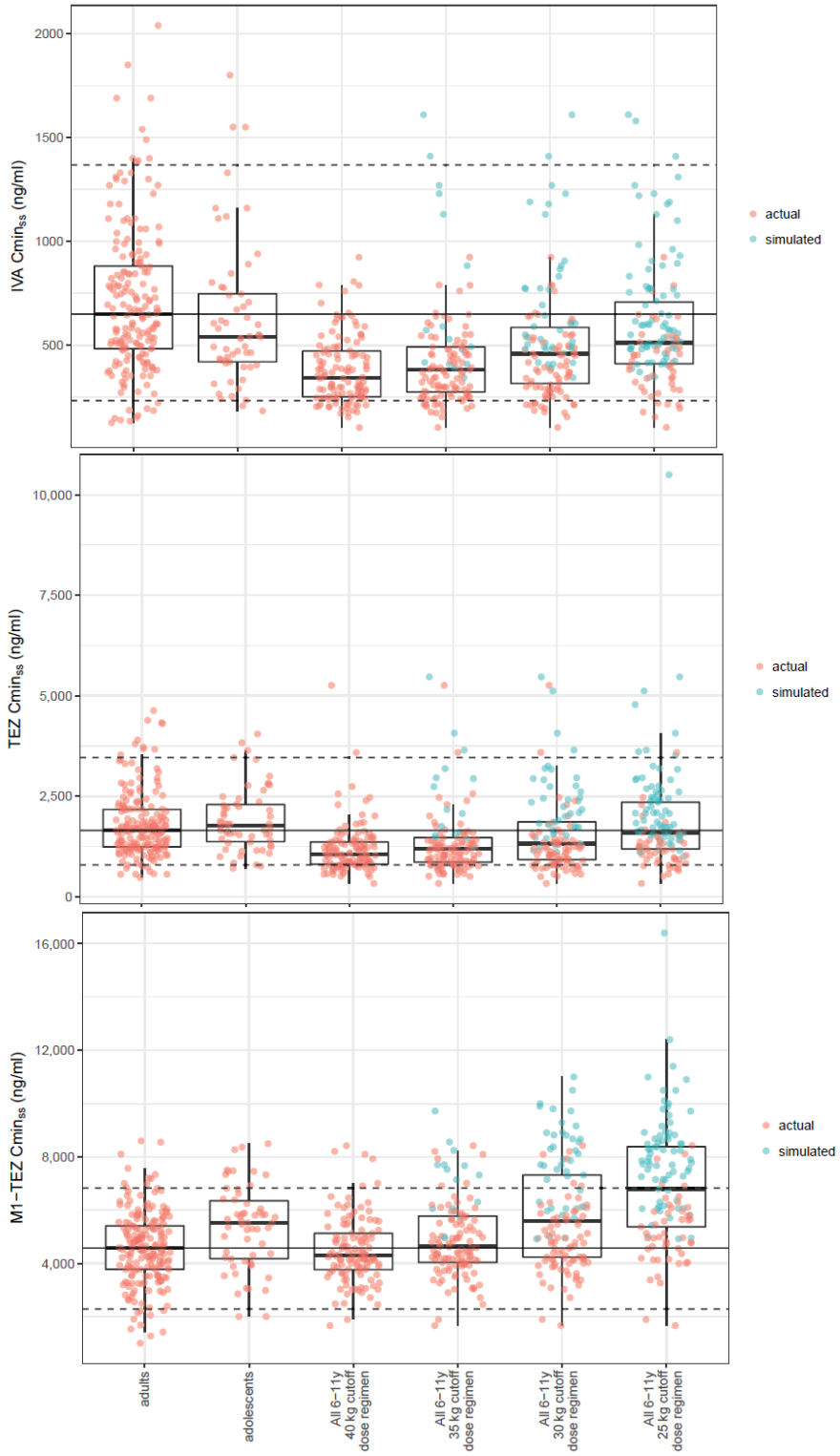
Exposure values are plotted versus age and dose group using box and whisker plots. Subjects with exposures associated with their studied dose are coloured in red. Subjects who received a different dose based on their body weight and the simulated regimen are shown in blue. Median values are designated by a black line in the centre of the box. Boxes indicate the inter-quartile range (IQR). The upper whisker extends from the hinge to the largest value no further than 1.5 * IQR from the hinge (where IQR is the inter-quartile range, or distance between the first and third quartiles). The lower whisker extends from the hinge to the smallest value at most 1.5 * IQR of the hinge. The solid reference line represents the median and the dashed lines represent the 5th and 95th percentiles for adults administered TEZ 100 mg qd and IVA 150 mg q12h.

Figure 7 Predicted steady-state IVA, TEZ and M1-TEZ exposures for children from 6 to < 12 years old (Studies 113 and 115) compared to adolescents and adults (Study 106) with different weight regimens: <u>Cmax</u>



Exposure values are plotted versus age and dose group using box and whisker plots. Subjects with exposures associated with their studied dose are coloured in red. Subjects who received a different dose based on their body weight and the simulated regimen are shown in blue. Median values are designated by a black line in the centre of the box. Boxes indicate the inter-quartile range (IQR). The upper whisker extends from the hinge to the largest value no further than 1.5 * IQR from the hinge (where IQR is the inter-quartile range, or distance between the first and third quartiles). The lower whisker extends from the hinge to the smallest value at most 1.5 * IQR of the hinge. The solid reference line represents the median and the dashed lines represent the 5th and 95th percentiles for adults administered TEZ 100 mg qd and IVA 150 mg q12h.

Figure 8 Predicted steady-state IVA, TEZ and M1-TEZ exposures for children from 6 to < 12 years old (Studies 113 and 115) compared to adolescents and adults (Study 106) with different weight regimens: Cmin



Exposure values are plotted versus age and dose group using box and whisker plots. Subjects with exposures associated with their studied dose are coloured in red. Subjects who received a different dose based on their body weight and the simulated regimen are shown in blue. Median values are designated by a black line in the centre of the box. Boxes indicate the inter-quartile range (IQR). The upper whisker extends from the hinge to the largest value no further than 1.5 * IQR from the hinge

(where IQR is the inter-quartile range, or distance between the first and third quartiles). The lower whisker extends from the hinge to the smallest value at most 1.5 * IQR of the hinge. The solid reference line represents the median and the dashed lines represent the 5th and 95th percentiles for adults administered TEZ 100 mg qd and IVA 150 mg q12h.

The results from this integrated popPK analysis demonstrated that for subjects 6 through 11 years of age who weighed ≥30 kg and received TEZ 100 mg qd/IVA 150 mg q12h, the distribution of individual TEZ, M1-TEZ, and IVA exposures were similar to the observed range of subjects 12 years of age and older. Simulated AUCss for IVA, TEZ and M1-TEZ are summarised in Table 24.

Table 20. Summary of TEZ, M1-TEZ, and IVA predicted steady-state exposures (AUCss) by age group, 30-kg weight cut-off

Age Group / Weight		TEZ $AUC_{0\text{-}24h}$ (µg·h/mL)			M1-TEZ $AUC_{0\text{-}24h}$ (µg·h/mL)			IVA $AUC_{0\text{-}12h}$ (µg·h/mL)		
		N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max	N	Mean (SD)	Min, Max
6 through 11 years	*(Both doses combined)*	121	78.7 (33.3)	32.4, 199	121	154 (50.0)	53.9, 283	122	9.05 (3.71)	3.62, 23.4
<30 kg	50 mg qd/ 75 mg q12h	71	58.9 (17.5)	32.4, 165	71	126 (30.0)	53.9, 206	71	7.1 (1.95)	3.62, 12.0
≥30 kg[a]	100 mg qd/ 150 mg q12h	50	107 (30.1)	49.5, 199	50	193 (45.8)	60.7, 283	51	11.8 (3.89)	4.39, 23.4
12 through 17 years	100 mg qd/ 150 mg q12h	58	92.4 (23.7)	47, 150	58	145 (38.2)	62.2, 219	57	10.6 (4.61)	3.80, 26.1
18 years and older	100 mg qd/ 150 mg q12h	193	84.1 (23.2)	41.3, 169	193	124 (32.8)	38.6, 218	186	11.5 (4.44)	3.90, 27.7

Source: Module 5.3.3.5/Report P133/Tables 32 and 35 (IVA); 38 and 41 (TEZ); 44 and 47 (M1-TEZ)
IVA: ivacaftor; N: total sample size; PK: pharmacokinetics; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor
[a] Exposures for subjects in ≥30-kg to <40kg weight range are predictions derived from the population PK model.

PK/PD relation

To evaluate the impact of increased TEZ exposures on efficacy, the sweat chloride PK/PD relationship in subjects 6 through 11 years of age was compared to that in subjects ≥12 years of age (Figure 9).

This figure shows that the observed sweat chloride response in subjects 6 through 11 years of age overlaps with the response observed with subjects ≥12 years of age and was reasonably predicted by the relationship in subjects ≥12 years of age. In regions where the exposures overlap between these 2 age groups, the PK/PD responses are similar with respect to shape, magnitude, and variability. The mean level sweat chloride response in subjects 6 through 11 years of ages was slightly better than the response observed in subjects ≥12 years of age, which is consistent with trends observed in the Kalydeco and Orkambi programs.

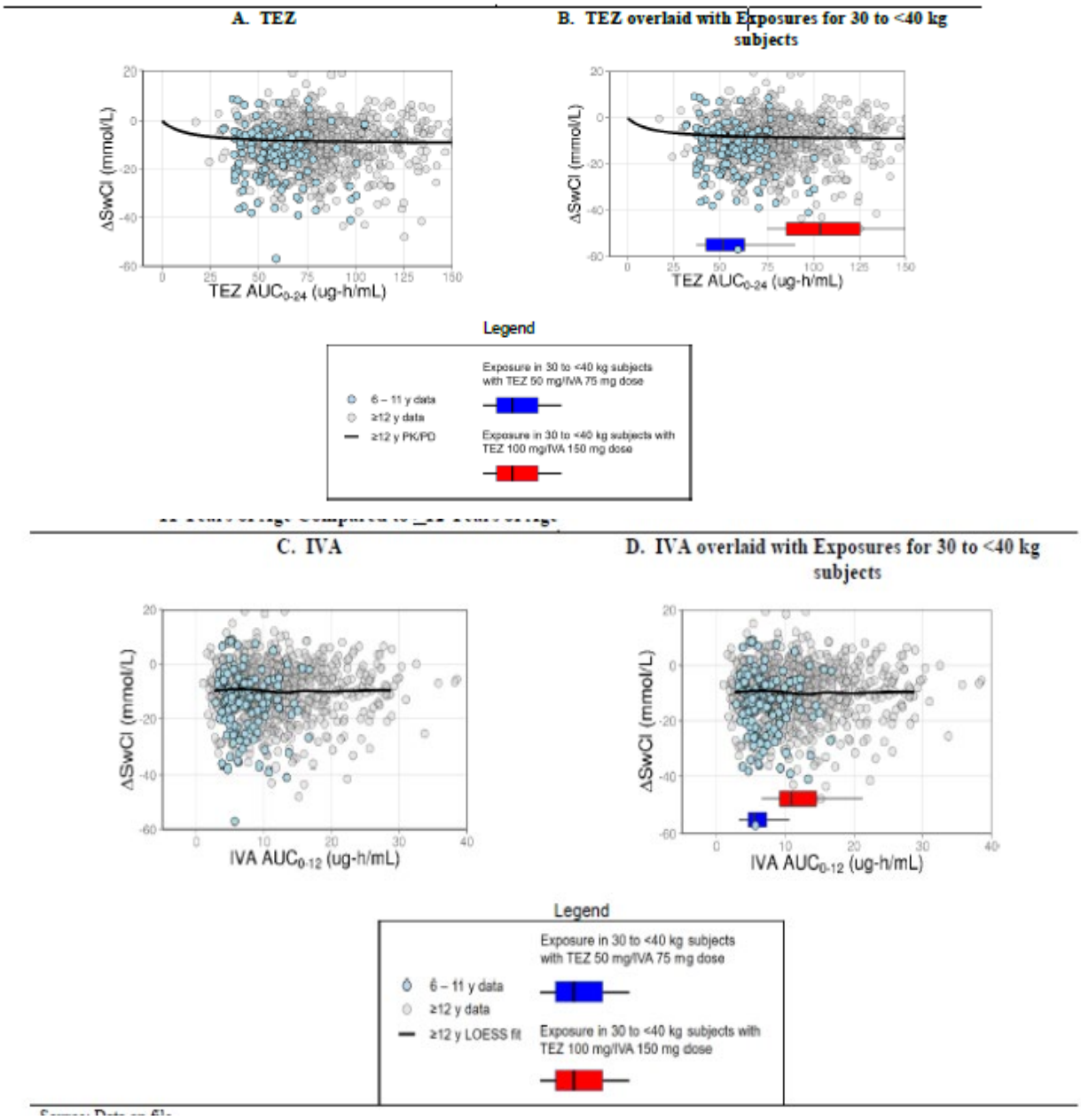
To evaluate the impact of increasing TEZ exposures for the 30 to <40 kg subjects, these PK/PD figures were overlaid with boxplots of TEZ exposures in the 30 to <40 kg subgroup under the current posology (half of the adult dose; blue boxplot in Figure 9 B) versus the proposed posology (equivalent to the adult dose; red boxplot in Figure 9 B). This display confirms that increasing the TEZ exposure improves the sweat chloride response in 30 to <40 kg subjects, when evaluated in the context of the modelled relationship for subjects ≥12 years of age (black line). Based on the change in median exposure between these 2 doses, increasing the TEZ dose in this population of subjects reduces (i.e., improves) sweat chloride by 0.8 mmol/L, as quantified using the modelled relationship.

Impact of Increased IVA Exposures

A similar approach was taken to evaluate the impact of increased IVA exposures Figure 9 C and 9D). In this figure, the relationship between IVA exposure and sweat chloride is described by the locally estimated scatterplot smoothing (LOESS) fit of the data points in subjects ≥12 years of age, because

the model did not account for the effect of continuous IVA concentration. Similar to TEZ, the PK/PD relationship in subjects 6 through 11 years of age was reasonably predicted by the relationship in subjects ≥12 years of age with respect to IVA. Increasing the IVA exposure is not expected to impact sweat chloride efficacy based on the relationship observed in subjects ≥12 years of age, as shown in Figure 9 D.

Figure 9 PK/PD relationships of Sweat Chloride Response versus TEZ or IVA Exposures in Subjects 6 Through 11 Years of Age Compared to ≥12 Years of Age



ΔSwCl: change in sweat chloride from baseline; F/F: homozygous for *F508Del-CFTR* mutation; IVA: ivacaftor; LOESS: locally estimated scatterplot smoothing; PK/PD: pharmacokinetic/ pharmacodynamic relationship; TEZ: tezacaftor; y: year

Notes: Gray points: Data from F/F subjects in Study 106 (≥12 years of age). Blue points: Data from F/F subjects in Studies 113 and 115 (6 through 11 years of age). Black line: PK/PD relationship for subjects ≥12 years of age. For TEZ, this relationship is derived from the sweat chloride PK/PD model described in Report N021. For IVA, this relationship is the LOESS of the gray points as the Report N021 model did not account for the effect of continuous IVA concentration. Blue boxplot: exposures for subjects 30 to <40 kg administered 50% of the adult dose (current posology). Red boxplot: exposures for subjects 30 to <40 kg administered 100% of the adult dose (proposed posology).

2.4.1. Discussion on clinical pharmacology

To support the extension of the indication for tezacaftor/ivacaftor in combination with IVA to patients 6 through 11 years of age, studies 113 and 115 were conducted.

Study 113 was a phase 3, 2-part, open-label study in CF subjects 6 through 11 years of age, homozygous or heterozygous for *F508del*. Study 113 Part A (Study 113A) evaluated the PK, safety, and tolerability of TEZ/IVA administered for 14 days. Safety, tolerability, and available PK data from Part A were reviewed to determine the doses and the weight cut-offs to be evaluated in Study 113 Part B (Study 113B) and Study 115. Study 113B evaluated the safety, tolerability, and PK of TEZ/IVA administered for 24 weeks; assessments related to efficacy were also evaluated. Study 115 was a randomised, double-blind, parallel-group study in CF subjects 6 through 11 years of age, homozygous or heterozygous for *F508del*. Study 115 evaluated the efficacy and safety of TEZ/IVA administered for approximately 8 weeks; assessment of TEZ/IVA pharmacokinetics was also evaluated.

Children weighing ≥ 25 kg in Study 113A were dosed with the marketed formulation of IVA tablets, but not the marketed or to-be-marketed formulation of TEZ/IVA FDC tablets. All children in Study 113B were dosed with the marketed formulations of TEZ 100mg/IVA 150 mg and IVA 150 mg or with the to-be-marketed formulations (i.e., FDC TEZ 50 mg/IVA 75 mg and IVA 75 mg tablet) depending on body weight.

Upon completion of Study 113A (N = 13), popPK simulations were performed using the allometric fixed exponents to compare exposures for subjects in the weight range from 15 to 50 kg to those observed in subjects ≥12 years old in the pivotal Phase 3 TEZ/IVA studies 106, 107, and 108. Across the weight range in 6- through 11-year-olds, simulated geometric mean ratios (Cmin, AUC, and Cmax) showed that subjects <25 kg receiving TEZ 100 mg qd/IVA 150 mg q12h would have higher exposures for parent TEZ compared to subjects ≥12 years old. The weight cut-off was thus increased from 25 kg to 40 kg for Study 113B and Study 115 in order to achieve exposures similar to subjects ≥12 years old across all of the weight ranges, to maintain the same TEZ:IVA dose ratio in the adult and paediatric populations, and to avoid exposures of TEZ that would be higher than those achieved in the ≥12-year-old population.

Upon review of the exposure data from these studies, an integrated popPK analysis of data was performed. The results from this integrated popPK analysis demonstrated that for subjects 6 through 11 years of age who weighed ≥40 kg and received TEZ 100 mg qd/IVA 150 mg q12h, the distribution of individual TEZ, M1-TEZ, and IVA exposures were similar to the observed range of subjects 12 years of age and older. For subjects 6 through 11 years of age who weighed <40 kg and received TEZ 50 mg qd/IVA 75 mg q12h, TEZ parent and IVA parent exposures fell within the lower range of observed exposures of subjects 12 years and older. M1-TEZ exposures were similar to those of subjects 12 years and older.

Additional simulations were performed to optimise the final proposed dosing regimen. The objective of these popPK simulations was to determine whether a different weight cut-off would achieve TEZ parent and IVA parent PK exposures that were more similar to the exposures observed in subjects 12 years and older. For this purpose, weight cut-offs of 40 kg, 35 kg, 30 kg and 25 kg were applied. Approximately one third of subjects in Studies 113 and 115 weighed ≥30 kg and <40 kg. The body weight cut-off of 30 kg was proposed by the MAH on the basis that in the simulations presented the majority of TEZ and IVA PK exposures were predicted to fall within the adult reference range (5th to 95th percentiles) and the median exposures will be more similar to the median adult exposure.

While it was acknowledged that the 30 kg cut-off resulted in the most comparable exposures for IVA, M1-TEZ and TEZ in children as compared to adolescents and adults as opposed to the other investigated weight cut-offs, for subjects 6 through 11 years of age who weighed <30 kg and will receive TEZ 50 mg qd/IVA 75 mg q12h, TEZ parent and IVA parent exposures still fell within the lower range of observed exposures of subjects 12 years and older. On the other hand, more than 50% of paediatric patients were predicted to show M1-TEZ exposures higher than the upper limit of the established range in adults. As a consequence, the MAH was requested to perform further model-based PK and PK-PD simulations to show that the proposed posology based on a body weight cut-off of 30 kg did not negatively impact efficacy in children weighing less than 30 kg and resulted in better efficacy outcomes (than those observed in study 115) in children weighing ≥30 to less than 40 kg. Model based simulations for 1000 virtual subjects were performed to predict TEZ, M1-TEZ, and IVA exposures using the weight-based dosing cut-offs of 40 kg, 35 kg, and 30 kg. Based on these simulations, it was confirmed that only M1-TEZ AUC was affected by the body weight cut-off at 100 mg TEZ qd, showing significant differences in the proportion of patients within the exposure of adults: ~75% (40 kg cut-off), ~50% (35 kg cut-off), and <50% (30 kg cut-off). No significant differences in M1-TEZ AUC were observed when 50 mg TEZ qd was considered, neither in TEZ and IVA AUC for both dose levels across the different body weight cut-offs.

Furthermore, the MAH has explored through a PK/PD relationship the impact in terms of sweat chloride of selecting 30 kg vs 40 kg cut-off in paediatric patients with body weights between 30 and <40 kg as compared to that in patients aged 12 years and older. The plots of the PK/PD relationship do not show a significant change in terms of sweat chloride response when 30 or 40 kg cut-off was selected, which indicates that similar response rate will be achieved irrespective of the TEZ and IVA exposures compared to patients ≥12 years of age. A slight decrease (improvement) in sweat chloride (0.8 mmol/l) is predicted in patients weighing 30 to <40 kg when receiving an increased dose compared to the actually received dose in study 115, due to the 30 kg cut-off. In children weighing less than 30 kg, the PK-PD data provided indicate that the sweat chloride reduction at the lower dose in children <30 kg, despite the somewhat lower exposures to TEZ and IVA, is within the range of sweat chloride effects in patients ≥12 years of age, even though this could have been better addressed by comparing the predicted exposure-response in these children versus those weighing more than 30 kg.

The ratio M1-TEZ/TEZ appears different for patients aged 6 through 11 years (with ratios of 2.1 and 1.8 in patients <30 and ≥30 kg, respectively) and adolescents (ratio of 1.56) and adults (ratio 1.47). This seems to indicate that relatively more M1-TEZ is formed in children aged 6 through 11 years. The MAH was requested to discuss the involvement of TEZ and M1-TEZ in efficacy and safety and the relationship between the increased exposure of TEZ + M1-TEZ versus TEZ among the efficacy and safety endpoints. In conclusion, the actual cause for the increased formation of M1-TEZ remains unclear. In terms of sweat chloride, the increased exposure does not translate into greater response, since the maximum effect is practically reached in Q1 of exposure of TEZ and TEZ+M1-TEZ. In terms of safety, the additional data provided by the MAH such as the analysis of transaminase elevations by M1-TEZ levels in subjects ≥12 years of age and children 6 through 11 years of age is reassuring although based on a limited number of patients.

No update was provided on pharmacodynamics. This is nevertheless acceptable as the mechanism of action of tezacaftor and ivacaftor is not age dependent. The reduction in sweat chloride observed in study 113B and study 115 is within the range of that observed in older patients. The PK/PD relationships provided show similar response within the range of predicted TEZ and IVA AUC exposures with the proposed dosing regimen based on a cut-off body weight of 30 kg. Overall, considering the above mentioned PK/PD relationship for sweat chloride and taking into account that similar M1-TEZ exposures have been observed in older patients with no indication of increased adverse event rates, the proposed body-weight cut-off of 30 kg is supported.

2.4.2. Conclusions on clinical pharmacology

The proposed posology for children aged 6 to less than 12 years which is based on a cut-off body weight of 30 kg is acceptable based on PopPK simulations and modelling as this dosing regimen was not investigated in studies 113B or 115 in children weighing ≥ 30 kg to less than 40 kg.

2.5. Clinical efficacy

2.5.1. Dose response study

Not applicable.

2.5.2. Main study

The main study to support the application is Study VX16-661-115 (study 115): A Phase III, Double-blind, Parallel-group Study to Evaluate the Efficacy and Safety of Tezacaftor in Combination With Ivacaftor in Patients Aged 6 Through 11 Years With Cystic Fibrosis, Homozygous or heterozygous for the *F508Del-CFTR* Mutation (see Figure 10)

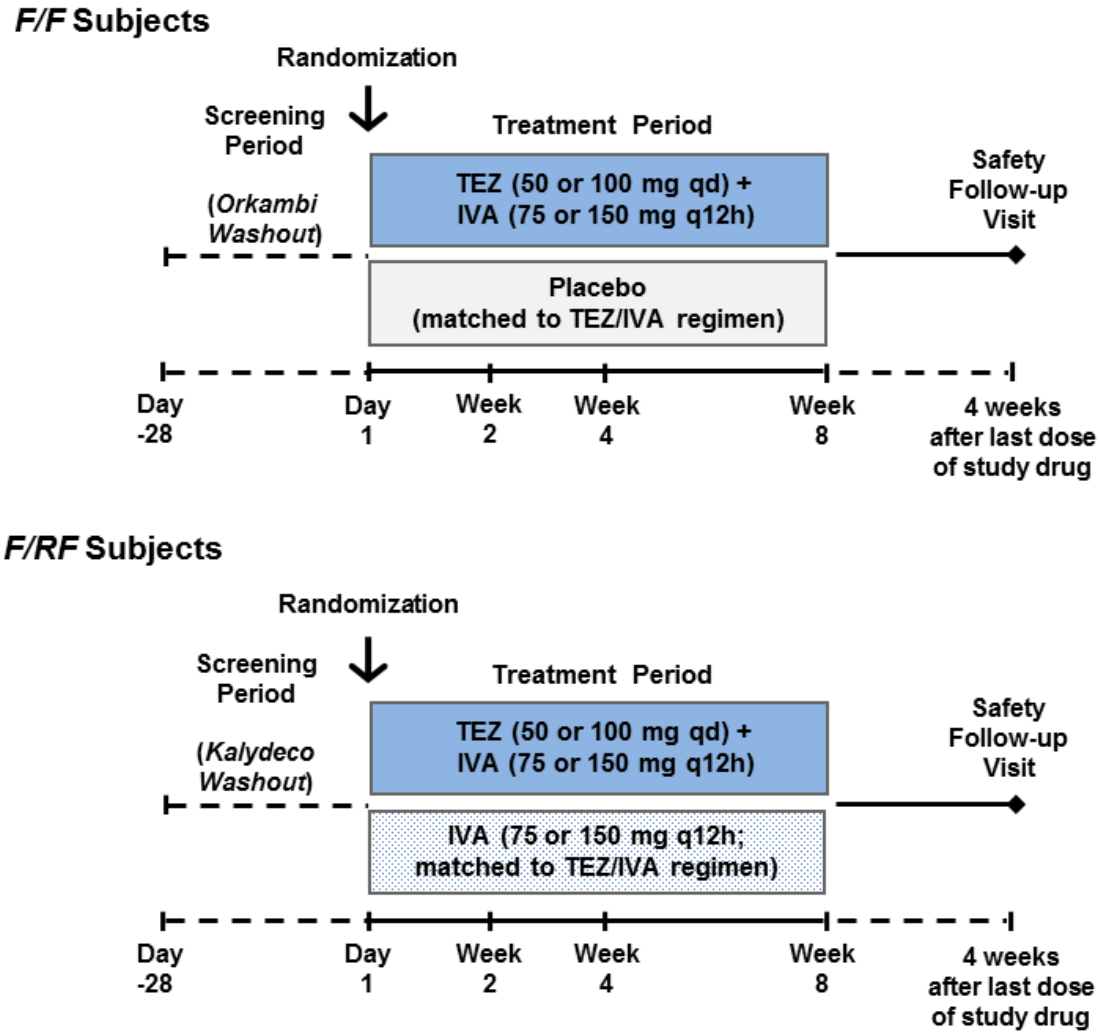
Methods

Study design

After the screening period of 4 weeks, patients were stratified by genotype before randomization so that F/F and F/RF patients would be randomized in a 4:1 ratio to either the TEZ/IVA group or the appropriate blinding group for their genotype. The F/F blinding group received placebo and the F/RF blinding group received IVA monotherapy. The placebo and IVA blinding groups' treatment regimens were visually matched to the TEZ/IVA treatment regimen to maintain the blind.

During the Screening Period, subjects who were treated with Orkambi or Kalydeco underwent a 28-day washout before the Day 1 Visit.

Figure 10 The scheme of the study VX16-661-115 design.



F/F: homozygous for *F508Del;* F/RF: heterozygous for *F508Del* and a second *CFTR* allele with residual function; IVA: ivacaftor; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor.

After completing the Week 8 Visit, patients were offered the opportunity to enrol in a 96-week open-label TEZ/IVA extension study (Study VX17-661-116). The Safety Follow-up Visit was not required for patients who enrolled in the extension study within 4 weeks after the last dose of study drug in Study VX16-661-115.

Patients who prematurely discontinued study drug treatment were asked to remain in the study and complete the efficacy assessments (LCI, CFQ-R, sweat chloride, spirometry, height, weight, BMI, and Drug Acceptability Questionnaire) from the time of discontinuation through the end of the Treatment Period.

Study Participants

Patients were 6 – 11 years old, males and females, with a confirmed diagnosis of CF. Patients were homozygous for *F508Del-CFTR* or heterozygous for *F508Del* and a second *CFTR* allele that results in residual *CFTR* function. Heterozygous patients must have a second eligible mutation that results in residual CFTR function (see table below). Genotyping was performed using a validated CF genotyping test and confirmed if the CF diagnosis was confirmed if the Sweat chloride was ≥ 60 mmol/L.

However, patients with a F/RF mutation could also be included if the sweat chloride was < 60 mmol, if these patients should have an additional chronic sino-pulmonary disease and/or gastrointestinal/nutritional abnormalities associated with CF.

Enrolment was limited to patients with $LCI_{2.5}$ result ≥7.5 at the Screening Visit, a body weight ≥ 15 kg and the ability to swallow the tablets. Spirometry at baseline (ppFEV1) could be normal (pp FEV1 ≥70%). Patients with a history of any illness or condition that could confound study results or pose an additional safety risk (e.g., cirrhosis with portal hypertension, risk factors for Torsades de Pointes) were excluded from Study 115 Patients with protocol-defined laboratory values indicative of clinically significant abnormal liver or renal function were also excluded (either (a) any 2 or more of ≥ 3 x ULN for AST, ALT, GGT, ALP, or total bilirubin ≥2 x ULN; (b) ≥ 5 x ULN ALT or AST; (c) GFR ≤45 mL/min/1.73 m^2 calculated by the Counahan-Barratt equation, (d) hemoglobin <10 g/dL). These criteria were comparable to studies 103 and 104.

Table 21 *CFTR* residual mutation, accepted for inclusion of the heterozygous F/RF patients in study VX16-661-115

CFTR Residual Function Mutations			
2789+5G→A	D110E	D579G	D1152H
3849+10kbC→T	D110H	S945L	D1270N
3272-26A→G	R117C	S977F	E831X
711+3A→G	E193K	F1052V	A1067T
E56K	L206W	K1060T	
P67L	R352Q	R1070W	
R74W	A455E	F1074L	

The boxed alleles are included in the indication of Symkevi (EMA/H/C/004682/00)

Treatments

The treatment applied in this trial was the study drug Tezacaftor/ivacaftor in combination with ivacaftor. The comparators were placebo (F508/F508) or ivacaftor (F508/RF).

Tezacaftor/Ivacaftor (F508/F508 or F/RF)

- Patients who are <40 kg at the Day 1 Visit will receive a morning dose of TEZ 50 mg/IVA 75 mg (fixed-dose combination [FDC] tablet) and an evening dose of IVA 75 mg (tablet).
- Patients who are ≥40 kg at the Day 1 Visit will receive a morning dose of TEZ 100 mg/IVA 150 mg (FDC tablet) and an evening dose of IVA 150 mg (tablet).

Ivacaftor (F/RF)

- Patients who are <40 kg at the Day 1 Visit will receive a morning dose of TEZ/IVA-matching placebo (FDC tablet), a morning dose of IVA 75 mg (tablet), and an evening dose of IVA 75 mg (tablet).
- Patients who are ≥40 kg at the Day 1 Visit will receive a morning dose of TEZ/IVA-matching placebo (FDC tablet), a morning dose of IVA 150 mg (tablet), and an evening dose of IVA 150 mg (tablet).

Placebo (F508/F508)

- Patients randomised will be given matching placebos in the morning and evening

It was recommended that patients remain on a stable CF medication regimen from 4 weeks before Day 1 through Week 8 or, if applicable, through the Safety Follow-up Visit. Information about

bronchodilator use was collected and documented. Patients who used a bronchodilator had their spirometry assessments performed according to the guidelines specified in the protocol.

Other concomitant medications were prohibited if the potential existed for untoward drug-drug interactions, such as CYP3A4 inducers and CYP3A4 inhibitors.

During the Screening Period, patients who are being treated with Orkambi or Kalydeco will undergo a 28-day washout before the Day 1 Visit.

Objectives

The primary objective was to evaluate efficacy of TEZ/IVA in combination with IVA in patients aged 6 through 11 years with CF, homozygous or heterozygous for the *F508Del-CFTR* mutation.

Secondary objectives were to evaluate the safety of TEZ/IVA in combination with IVA in patients aged 6 through 11 years with CF, homozygous or heterozygous for the *F508Del-CFTR* mutation.

Outcomes/endpoints

Primary efficacy endpoint: absolute change in lung clearance index 2.5 ($LCI_{2.5}$) from baseline through Week 8 in patients treated with TEZ/IVA for the F508/F508 and F508/RF patients randomised to TEZ/IVA.

$LCI_{2.5}$ is the number of lung turnovers required to reduce the end tidal inert gas concentration to 2.5% of its starting value). The test was conducted with results of the LCI2.5 were centrally reviewed.

Secondary efficacy endpoints:

- Absolute change from baseline in sweat chloride at Week 8
- Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from baseline through Week 8
- Safety and tolerability as measured by adverse events (AEs)
- Clinically significant changes in laboratory values (serum chemistry, haematology, coagulation studies, lipids, vitamin levels, and urinalysis), standard 12-lead ECGs, vital signs, pulse oximetry, serial lung function measurement, and ophthalmologic examinations (OEs).

Additional endpoints

- Absolute change in LCI5.0 (number of lung turnovers required to reduce the end tidal inert gas concentration to 5.0% of its starting value) from baseline through Week 8
- Absolute change in percent predicted forced expiratory volume in 1 second (ppFEV1) from baseline through Week 8
- Absolute change from baseline in body mass index (BMI) at Week 8
- Absolute change from baseline in BMI-for-age z-score at Week 8
- Absolute change from baseline in weight at Week 8
- Absolute change from baseline in weight-for-age z-score at Week 8
- Absolute change from baseline in height at Week 8
- Absolute change from baseline in height-for-age z-score at Week 8
- Drug acceptability assessment at Week 2
- Pharmacokinetic (PK) parameters of TEZ, M1-TEZ (TEZ metabolite), IVA, and M1-IVA (IVA metabolite)
- Absolute change from baseline in faecal elastase I
- Absolute change from baseline in immunoreactive trypsinogen

Randomisation and blinding (masking)

A total of n=69 patients, who met the eligibility criteria were included. Patients were stratified by genotype before randomization so that F/F and F/RF patients would be randomized in a 4:1 ratio to either the TEZ/IVA group or the appropriate blinding group for their genotype. The F/F blinding group received placebo, and the F/RF blinding group received IVA monotherapy. The placebo and IVA blinding groups treatment regimens were visually matched to the TEZ/IVA treatment regimen to maintain the blind.

Statistical methods

Sample size

The sample size of this study is driven by demonstrating that the treatment effect of TEZ/IVA is based on a within-group comparison (change from baseline in LCI2.5 in subjects on TEZ/IVA) to exclude a maximum possible placebo effect.

The placebo effect was based on study VX14-809-109, Study 809-109 evaluated treatment with LUM/IVA in F508/F508 subjects aged 6 through 11 years using change from baseline in LCI as the primary efficacy endpoint. In Study 809-109, the placebo group had a mean worsening in LCI2.5 of 0.08 units with an SD of 1.41 the one-sided 90% lower bound was -0.10 and is used as an estimate for the pre-defined maximum possible placebo effect for Study 115.

Accounting for a 10% dropout rate, approximately 40 subjects on TEZ/IVA will provide at least 90% power to exclude -0.10. The study planned to enrol approximately 50 F/F subjects and up to 15 F/RF subjects. A placebo group of F/F subjects and an IVA mono group of F/RF subjects was included in this study. The main purpose was to preserve blinding, so that subjects and investigators do not assume a subject is receiving TEZ/IVA, which could introduce bias into the results. Descriptive statistics such as mean and SD are provided for change from baseline in $LCI_{2.5}$ at each post-baseline visit for homozygous subjects in the placebo group.

The target enrolment by genotype and treatment group is provided in the Table 12-1.

Table 12-1 Target Enrollment by Genotype and Study Drug Treatment

Genotype	N	Study Drug Treatment
F/F	40	TEZ (50 or 100 mg qd) + IVA (75 or 150 mg q12h)
	10	TEZ-matching placebo (qd) + IVA-matching placebo (q12h)
F/RF	12	TEZ (50 or 100 mg qd) + IVA (75 or 150 mg q12h)
	3	TEZ-matching placebo (qd) + IVA (75 or 150 mg q12h)

Data sets

The following analysis sets were defined:

• All Subjects Set was defined as all patients who were randomised or dosed (i.e., all patients in3 the study). All patient data listings were referenced using the All Subjects Set, unless otherwise specified.

• Full Analysis Set (FAS) included all randomised patients who were exposed to at least 1 dose of study drug and had an eligible genotype. The treatment assignment for the FAS was as randomised.

• Safety Set included all patients who were exposed to at least 1 dose of study drug. The treatment assignment for the Safety Set was as treated.

Efficacy analyses were based on the Full Analysis Set (which included all patients randomized and dosed who had an eligible *CFTR* genotype) and performed as specified in the Statistical Analysis Plan (SAP; Appendix 16.1.9).

There was no adjustment for multiplicity; *P* values for secondary and additional endpoints are considered nominal.

Efficacy analyses were based on within-group changes in the TEZ/IVA treatment group (F/F and F/RF genotypes combined). No hypothesis testing was performed for the placebo or IVA blinding groups. For the placebo group, only summary statistics were presented. For the IVA group, efficacy data were presented in listings only.

Primary Endpoint- *$LCI_{2.5}$*

The primary endpoint was absolute within-group change from baseline in $LCI_{2.5}$ through Week 8. For $LCI_{2.5}$, a decrease in value reflects lung function improvement.

The $LCI_{2.5}$ was measured by the Exhalyzer D and centrally reviewed.

The objective of the primary efficacy endpoint analysis was to demonstrate that the upper bound of the 95% CI of the mean change from baseline in $LCI_{2.5}$ through Week 8 in the TEZ/IVA group excluded a pre-defined maximum possible placebo effect.

Based on the results of a previous study of $LCI_{2.5}$ in placebo-treated paediatric (6- through 11-year-old) patients with CF homozygous for *F508Del* (Study VX14-809-109), -0.10 was used as an estimate of the pre-defined maximum possible placebo effect on $LCI_{2.5}$.

The primary analysis was performed using a restricted maximum likelihood (REML)-based mixed-effect model for repeated measures (MMRM) for the patients in the TEZ/IVA treatment group. The model included absolute change from baseline in $LCI_{2.5}$ (including all measurements up to Week 8 [inclusive]) as the dependent variable, and visit (as a class variable) as a fixed effect, with adjustment for *CFTR* genotype (F/F and F/RF) and baseline $LCI_{2.5}$ (continuous) value as covariates, and patient as a random effect. An unconstructed covariance structure was used to model the within-patient errors.

The primary result obtained from the model was the estimated average treatment effect on $LCI_{2.5}$ through Week 8 for patients in the TEZ/IVA group. The corresponding within-group LS mean, SE, 95% CI, and *P* value were provided. If the upper bound of the 95% CI fell below the pre-defined maximum possible placebo effect (-0.10), the study would be considered to have achieved its primary objective.

Secondary Endpoints

Sweat Chloride

A similar MMRM model was used to analyse sweat chloride data as described for the analysis of the primary efficacy variable, with the addition of baseline sweat chloride as a covariate. The assessment of efficacy was primarily based on the estimated within-group mean change from baseline at Week 8 in the TEZ/IVA group.

CFQ-R Respiratory Domain Score

A similar MMRM model was used to analyse CFQ-R respiratory domain score, based on the Child Version of the questionnaire. Data were analysed using the same approach as described for the analysis of the primary efficacy variable, with the addition of baseline CFQ-R respiratory score as a covariate. The assessment of efficacy was primarily based on the estimated within-group mean change from baseline through Week 8.

Other endpoints

ppFEV1

A similar MMRM model was used for the FEV1 data as described for the analysis of the primary efficacy variable, with the addition of corresponding baseline values (continuous) as covariates as appropriate.

Other endpoints were the $LCI_{5.0}$, body mass index (BMI), BMI-for-age z-score, weight, weight-for-age z-score, height, height-for-age z-score, drug acceptability, faecal elastase-1 and immunoreactive trypsinogen, and pharmacokinetic parameters of TEZ, M1-TEZ, IVA, and M1-IVA.

Results

Participant flow

A total of N= 92 patients were screened.

Screen failures

A total of 23 patients were screened but not enrolled. The main reasons for screening failure was a $LCI_{2.5}$ < 7.5 (n=11), having percent predicted forced expiratory volume in 1 second (ppFEV1) <70 % at screening (n=6), having a recent acute illness (n=2), other reasons (n=2), having laboratory abnormalities deemed exclusionary (n=1), and not being able to swallow tablets (n=1)

Randomised patients

A total of 69 patients were randomized and 67 patients received at least 1 dose of study drug (54 patients in the TEZ/IVA group; 10 patients in the placebo group; 3 patients in the IVA group).

Of the 67 patients who received at least 1 dose of study drug, 66 (98.5%) completed study drug treatment. One patient prematurely discontinued treatment, because the patient's screening LCI2.5 did not meet the eligibility criteria.

Table 22 Patient disposition study VX16-661-115

Disposition Reason	Placebo n (%)	IVA n (%)	TEZ/IVA n (%)	Total n (%)
All Subjects Set[a]	11	3	55	69
Randomized	11	3	55	69
Randomized but not dosed	1	0	1	2
Safety Set[b]	10	3	54	67
Full Analysis Set[c]	10	3	54	67
Completed study drug treatment	10 (100)	3 (100)	53 (98.1)	66 (98.5)
Prematurely discontinued treatment	0	0	1 (1.9)	1 (1.5)
Adverse event	0	0	0	0
Did not meet eligibility criteria	0	0	1 (1.9)	1 (1.5)

Source: Table 14.1.1

CFTR: CF transmembrane conductance regulator gene; IVA: ivacaftor; TEZ: tezacaftor

[a] All Subjects Set includes all subjects randomized or who received at least 1 dose of study drug.

[b] Safety Set includes all subjects who received at least 1 dose of study drug.

[c] Full Analysis Set includes all randomized subjects who received at least 1 dose of study drug and had an eligible *CFTR* genotype.

Conduct of the study

The study VX16-661-115 has been conducted in 25 sites in Europe (UK, BE, DK, FR, DE, IE, PL, SW) and Australia. A total of n=53 (79.1%) were recruited in Europe and n=14 (21% in Australia).

The study was initiated on 17 May 2018 and completed on 21 December 2018.

- **Protocol and amendments**

- **Study protocol**

The final Study protocol is dated 17 November 2017. The clinical study protocol included one country-specific amendment to specify the volume of blood to be drawn at each study visit (Poland).

During the trial, the Safety and tolerability data was reviewed by an independent data monitoring committee (IDMC).

- **Important protocol deviations**

There were 2 Important Protocol Deviations in the study, both related to inclusion/exclusion criteria i.e. one patient had a LCI2.5 <7.5 (n=1) and discontinued the study. Another patient had a change in antibiotic therapy for pulmonary disease within 28 days before Day 1.

Baseline data

Demographics (FAS)

A total of 67 patients were included in the FAS. Most patients were female (n=37, 55.2%) and white (n=64, 95.5%). The mean (SD) age at screening was 8.6 (1.7) years.

The mean (SD) height was 134.1 (12.0) cm and the mean weight 29.4 (6.7) kg. Most patients (n=64, 95.5%) were below 40 kg. The mean BMI was 16.13 (1.56) kg/m2.

Comparable baseline demographics were observed in the TEZA/IVA group: the mean (SD) baseline ppFEV1 was 86.5 (12.9) and mean (SD) baseline sweat chloride was 99.2 (19.5) mmol/L. The mean (SD) baseline BMI was 16.13 (1.66) kg/m2 and mean (SD) BMI-for-age z-score was -0.25 (0.85). The mean (SD) weight was 28.9 (6.7) kg and mean (SD) weight-for-age z-score was -0.28 (0.72).

Table 23 Baseline demographics –study VX16-661-115 -FAS

	Placebo N = 10	IVA N = 3	TEZ/IVA N = 54	Total N = 67
***CFTR* Mutation, n (%)**				
F/F	10 (100)	0	42 (77.8)	52 (77.6)
F/RF	0	3 (100)	12 (22.2)	15 (22.4)
Weight group, n (%)				
<40 kg	9 (90.0)	3 (100)	52 (96.3)	64 (95.5)
≥40 kg	1 (10.0)	0	2 (3.7)	3 (4.5)
BMI (kg/m^2)[a]				
n	10	3	54	67
Mean (SD)	16.17 (1.02)	15.98 (1.58)	16.13 (1.66)	16.13 (1.56)
Median	16.03	16.11	15.91	15.92
Min, Max	14.58, 17.68	14.35, 17.50	13.18, 21.69	13.18, 21.69
BMI *z*-score				
n	10	3	54	67
Mean (SD)	-0.24 (0.37)	-0.35 (0.54)	-0.25 (0.85)	-0.26 (0.78)
Median	-0.27	-0.46	-0.05	-0.11
Min, Max	-0.87, 0.25	-0.83, 0.24	-2.58, 1.07	-2.58, 1.07
Weight (kg)				
n	10	3	54	67
Mean (SD)	30.5 (6.1)	33.5 (9.8)	28.9 (6.7)	29.4 (6.7)
Median	31.0	38.7	28.2	28.9
Min, Max	21.0, 43.0	22.2, 39.5	19.1, 51.3	19.1, 51.3
Weight *z*-score				
n	10	3	54	67
Mean (SD)	-0.19 (0.62)	0.28 (0.56)	-0.28 (0.72)	-0.24 (0.70)
Median	-0.32	0.60	-0.25	-0.26
Min, Max	-1.23, 0.61	-0.38, 0.60	-1.86, 1.42	-1.86, 1.42
Height (cm)				
n	10	3	54	67
Mean (SD)	136.7 (11.5)	143.2 (16.8)	133.1 (11.9)	134.1 (12.0)
Median	133.7	148.7	133.4	133.5
Min, Max	120.0, 158.6	124.4, 156.6	108.5, 156.0	108.5, 158.6
Height *z*-score				
n	10	3	54	67
Mean (SD)	0.11 (1.21)	1.14 (1.03)	-0.13 (0.96)	-0.03 (1.02)
Median	-0.07	1.01	0.08	0.09
Min, Max	-1.34, 1.76	0.19, 2.23	-2.44, 1.91	-2.44, 2.23

IVA: ivacaftor; max: maximum value; min: minimum value; TEZ: tezacaftor a Europe includes Switzerland. FAS full analyses set

- **Baseline disease characteristics**

Most patients had an F/F mutation (n=52, 77.6%). A total of n=15 (22.4%) had an F/RF mutation. The TEZ/IVA group included n=42 patients with an F/F mutation and n=12 with a F/RF mutation.

The mean (SD) baseline LCI2.5 was 9.54 U (1.97); the mean (SD) baseline Sweat chloride was 99.9 (17.9) mmol/L and the mean (SD) FEV1 at baseline was 87.1 (12.2) percentage of predicted (Table 28). A total of n=14 (21%) were colonised with *P. Aeruginosa*.

Table 24 Selected Baseline disease characteristics- study VX16-661-115 -FAS

	Placebo N = 10	IVA N = 3	TEZ/IVA N = 54	Total N = 67
$LCI_{2.5}$				
n	10	3	54	67
Mean (SD)	9.67 (1.65)	8.60 (1.40)	9.56 (2.06)	9.54 (1.97)
Median	9.04	8.47	8.86	8.84
Min, Max	7.66, 12.54	7.28, 10.06	6.95, 15.52	6.95, 15.52
$ppFEV_1$				
n	10	3	54	67
Mean (SD)	89.6 (10.1)	89.1 (5.7)	86.5 (12.9)	87.1 (12.2)
Median	91.5	91.4	86.0	86.2
Min, Max	74.0, 107.2	82.6, 93.4	57.9, 124.1	57.9, 124.1
Sweat chloride (mmol/L)				
n	9	3	51	63
Mean (SD)	103.8 (7.5)	100.7 (9.6)	99.2 (19.5)	99.9 (17.9)
Median	101.0	97.5	105.0	104.0
Min, Max	98.0, 121.5	93.0, 111.5	30.5, 122.0	30.5, 122.0
Colonization of *Pseudomonas aeruginosa*, n (%)				
Positive	2 (20.0)	1 (33.3)	11 (20.4)	14 (20.9)
Negative	8 (80.0)	2 (66.7)	43 (79.6)	53 (79.1)

Medical history

The most common medical history conditions (≥30% overall incidence) were CF lung disease (Preferred term (PT): CF lung; 85.1%), pancreatic insufficiency (PT: pancreatic failure; 73.1%), and constipation (31.3%).

- **Concomitant medication prior to the start of the study**

The most common concomitant medications (≥30% of total subjects) prior to the start were sodium chloride, dornase alfa, pancreatin, and salbutamol (Table 29).
A total of n=3 patients used Orkambi before the start of the study. One patient was randomised to placebo, the others to TEZ/IVA.

Table 25 Prior Medications Used by At Least 30% of Subjects in Any Treatment Group by Preferred Name – Study 115 (FAS)

Parameter	Placebo N = 10 n (%)	IVA N = 3 n (%)	TEZ/IVA N = 54 n (%)	Total N = 67 n (%)
Subjects with any prior medication occurring in ≥30% of subjects				
Sodium chloride	9 (90.0)	3 (100.0)	47 (87.0)	59 (88.1)
Dornase alfa	8 (80.0)	3 (100.0)	41 (75.9)	52 (77.6)
Pancreatin	7 (70.0)	1 (33.3)	41 (75.9)	49 (73.1)
Salbutamol	6 (60.0)	2 (66.7)	32 (59.3)	40 (59.7)
Retinol	1 (10.0)	1 (33.3)	16 (29.6)	18 (26.9)
Tocopherol	1 (10.0)	1 (33.3)	10 (18.5)	12 (17.9)
Vitamin D nos	2 (20.0)	2 (66.7)	9 (16.7)	13 (19.4)
Vitamins nos	3 (30.0)	0	9 (16.7)	12 (17.9)
Ascorbic acid/ betacarotene/ biotin/ calcium pantothenate/ colecalciferol/ cyanocobalamin/ folic acid/ nicotinamide/ phytomenadione/ pyridoxine hydrochloride/ retinol palmitate/ riboflavin/ thiamine hydrochloride/ tocopheryl acid succinate/ zinc amino acid chelate	1 (10.0)	1 (33.3)	8 (14.8)	10 (14.9)
Mometasone furoate	1 (10.0)	1 (33.3)	7 (13.0)	9 (13.4)
Ursodeoxycholic acid	5 (50.0)	0	7 (13.0)	12 (17.9)
Vitamin K nos	1 (10.0)	1 (33.3)	3 (5.6)	5 (7.5)
Montelukast	1 (10.0)	1 (33.3)	2 (3.7)	4 (6.0)
Cetirizine	0	1 (33.3)	1 (1.9)	2 (3.0)
Pancrelipase	3 (30.0)	0	1 (1.9)	4 (6.0)
Beclometasone	0	1 (33.3)	0	1 (1.5)
Hydrocortisone/ oxytetracycline hydrochloride	0	1 (33.3)	0	1 (1.5)
Lansoprazole	0	1 (33.3)	0	1 (1.5)
Nutrients nos	0	1 (33.3)	0	1 (1.5)
Ranitidine	0	1 (33.3)	0	1 (1.5)

Source: Ad Hoc Table 20.1
FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; nos: not otherwise specified; TEZ: tezacaftor; WHO-DD: World Health Organization-Drug Dictionary
Notes: Medications were coded using WHO-DD, version March 2019, format B3. Preferred Names were sorted in descending order of frequency in the TEZ/IVA column. Prior medication was defined as any medication started before the first dose of study drug regardless of its end date. A subject with multiple medications within a category (Any, or Preferred Name) was counted only once within that category.

Concomitant medication during the study

All subjects took concomitant medications during the study. The most common concomitant medications (occurring in ≥30% of subjects) were consistent with a diagnosis of CF and included sodium chloride (88.1%), dornase alfa (79.1%), pancreatin (73.1%), and salbutamol (61.2%).

Table 26 Concomitant medication –study VX16-661-115 -FAS

Preferred Name	Placebo N = 10 n (%)	IVA N = 3 n (%)	TEZ/IVA N = 54 n (%)	Total N = 67 n (%)
Subjects with any concomitant medication	10 (100.0)	3 (100.0)	54 (100.0)	67 (100.0)
SODIUM CHLORIDE	9 (90.0)	3 (100.0)	47 (87.0)	59 (88.1)
DORNASE ALFA	8 (80.0)	3 (100.0)	42 (77.8)	53 (79.1)
PANCREATIN	7 (70.0)	1 (33.3)	41 (75.9)	49 (73.1)
SALBUTAMOL	6 (60.0)	2 (66.7)	33 (61.1)	41 (61.2)
RETINOL	1 (10.0)	1 (33.3)	16 (29.6)	18 (26.9)
TOCOPHEROL	1 (10.0)	1 (33.3)	10 (18.5)	12 (17.9)
AMOXICILLIN TRIHYDRATE;CLAVULANATE POTASSIUM	3 (30.0)	0	9 (16.7)	12 (17.9)
VITAMIN D NOS	2 (20.0)	2 (66.7)	9 (16.7)	13 (19.4)
VITAMINS NOS	3 (30.0)	0	9 (16.7)	12 (17.9)
ASCORBIC ACID; BETACAROTENE; BIOTIN; CALCIUM PANTOTHENATE; COLECALCIFEROL; CYANOCOBALAMIN; FOLIC ACID; NICOTINAMIDE; PHYTOMENADIONE; PYRIDOXINE HYDROCHLORIDE; RETINOL PALMITATE; RIBOFLAVIN; THIAMINE HYDROCHLORIDE; TOCOPHERYL ACID SUCCINATE; ZINC AMINO ACID CHELATE	1 (10.0)	1 (33.3)	8 (14.8)	10 (14.9)
MOMETASONE FUROATE	1 (10.0)	1 (33.3)	8 (14.8)	10 (14.9)
URSODEOXYCHOLIC ACID	5 (50.0)	1 (33.3)	7 (13.0)	13 (19.4)
VITAMIN K NOS	1 (10.0)	1 (33.3)	3 (5.6)	5 (7.5)
MONTELUKAST	1 (10.0)	1 (33.3)	2 (3.7)	4 (6.0)
CETIRIZINE	0	1 (33.3)	1 (1.9)	2 (3.0)
MANNITOL	0	1 (33.3)	1 (1.9)	2 (3.0)
PANCRELIPASE	3 (30.0)	0	1 (1.9)	4 (6.0)
BECLOMETASONE	0	1 (33.3)	0	1 (1.5)
HYDROCORTISONE;OXYTETRACYCLINE HYDROCHLORIDE	0	1 (33.3)	0	1 (1.5)
LANSOPRAZOLE	0	1 (33.3)	0	1 (1.5)
MUPIROCIN	0	1 (33.3)	0	1 (1.5)
NUTRIENTS NOS	0	1 (33.3)	0	1 (1.5)
OXYTETRACYCLINE;POLYMYXIN B SULFATE	0	1 (33.3)	0	1 (1.5)

Numbers analysed

A total of n=69 patients were randomised. A total of n=67 received at least one study dose and were included in the FAS analyses (

Table **31**)

Table 27 Study VX16-661-115 – Analysis population

	Placebo	IVA	TEZ/IVA	Total
All Subjects Set[a]	11	3	55	69
Safety Set[b]	10	3	54	67
Full Analysis Set[c]	10	3	54	67

Source: Table 14.1.1.

IVA: ivacaftor; TEZ: tezacaftor

[a] All Subjects Set included all subjects who were randomized or received at least 1 dose of study drug.

[b] Safety Set included all subjects who had received at least 1 dose of study drug.

[c] Full Analysis Set included all subjects who were randomized, received at least 1 dose of study drug, and had an eligible genotype.

Outcomes and estimation

Primary efficacy endpoint – *absolute change in $LCI_{2.5}$ from baseline through week 8 for TEZ/IVA*

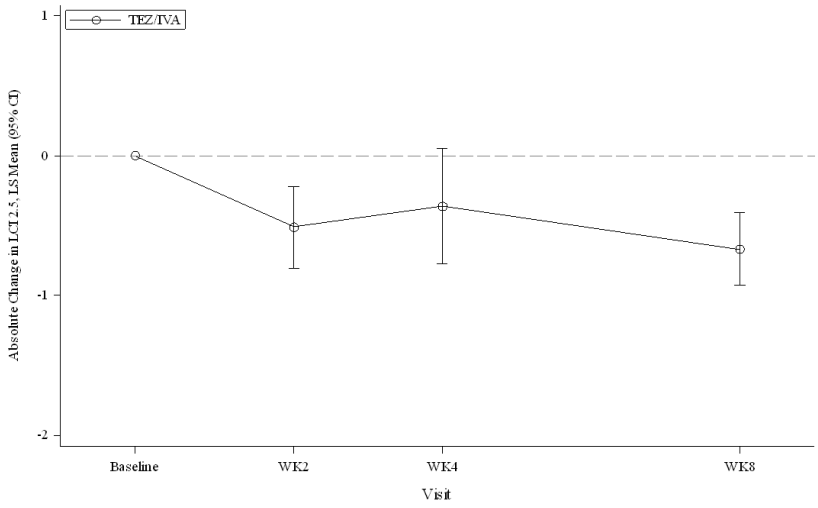
A total of n=54 patients (F508/F508 and F508/RF) were treated with TEZ/IVA. At baseline, the $LCI_{2.5}$ was mean (SD) 9.56 (2.06) and at week 8, the $LCI_{2.5}$ was mean (SD) 8.90 (1.80) for the TEZ/IVA

group. The within-group change from baseline in $LCI_{2.5}$ through Week 8 was -0.51 (95% CI: -0.74 to -0.29; P <0.0001) (see also

Figure 11). The upper bound of the 95% CI (-0.29) was below the pre-specified maximum placebo effect of -0.10.

The LS mean (SE) absolute change in $LCI_{2.5}$ at week 8 was -0.67 (0.13) (95%CI: -0.93, -0.41) for TEZ/IVA treated patients (F508/F508 and F508/RF) (n=49).

Figure 11 MMRM Analysis of Absolute Change From Baseline in LCI2.5 at Each Visit Within TEZ/IVA Group, VX16-661-115 Full Analysis Set



Source: Figure 14.2.1.

F/F: homozygous for the *F508Del-CFTR* mutation; F/RF: heterozygous for *F508Del* and a second *CFTR* allele with residual function; IVA: ivacaftor; LCI2.5: number of lung turnovers required to reduce the end tidal inert gas concentration to 2.5% of its starting value; LS mean: least squares mean; MMRM: mixed-effects model for repeated measures; TEZ: tezacaftor

Notes: The Y-axis corresponds to the LS mean from the MMRM model analysis with all measurements up to Week 8 (including on-treatment and after treatment discontinuation). Baseline is the most recent non-missing measurement before the first dose of study drug. The MMRM included visit, baseline LCI2.5, and genotype (F/F vs. F/RF) as covariates. The model used an unstructured covariance and Kenward-Roger degrees of freedom.

Secondary Endpoints

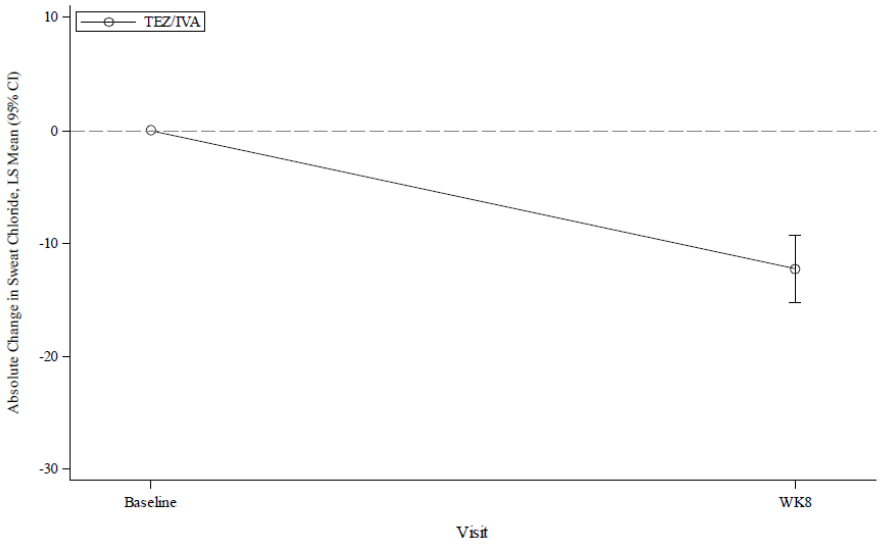
- **Sweat chloride test**

TEZ/IVA group: at baseline, the mean (SD) sweat chloride was 99.2 (19.5) mmol/l and at week 8 mean (SD) 88.4 (18.6) mmol/l.

The LS mean absolute change from baseline in sweat chloride at Week 8 was -12.3 mmol/L (95% CI: -15.3, -9.3) in the TEZ/IVA group (p<0.0001) (

Figure **12**).

Figure 12 MMRM Analysis of Absolute Change from Baseline in Sweat Chloride (mmol/L) at Each Visit within TEZ/IVA group study VX16-661-115 Full Analysis Set

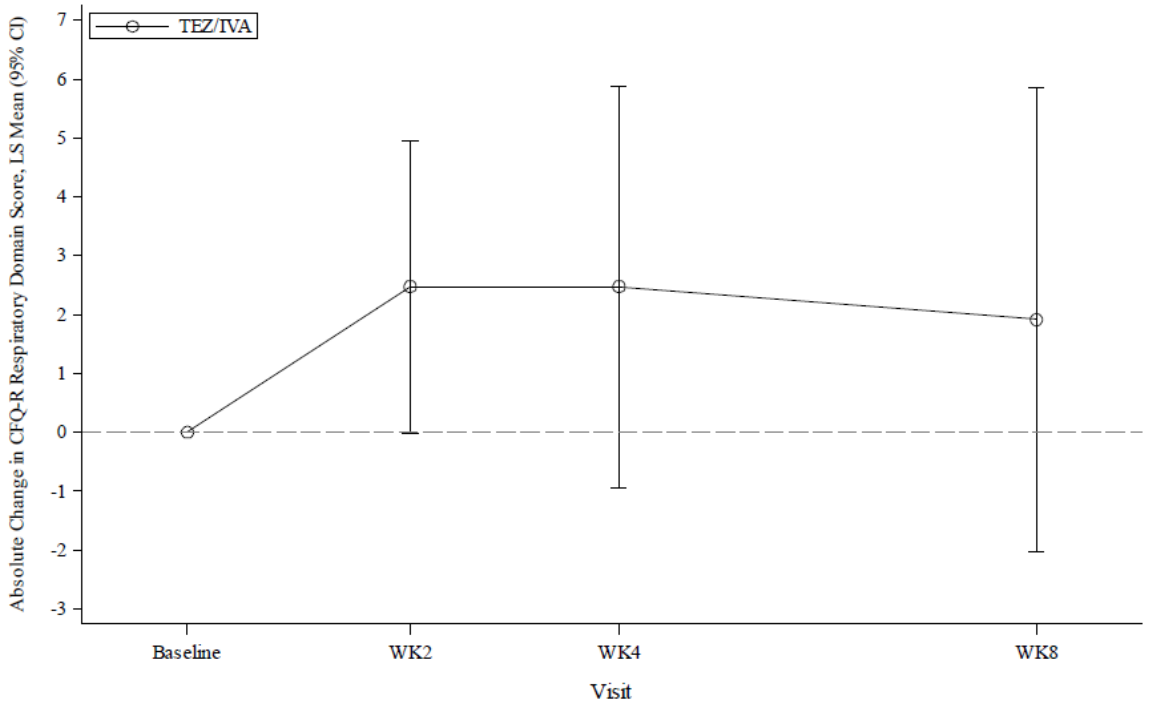


- The Y-axis corresponds to the LS Means from the MMRM model analysis with all measurements up to Week 8, including on-treatment and after treatment discontinuation.
- Baseline is the most recent non-missing measurement before the first dose of study drug.
- The mixed model for repeated measures included visit, baseline LCI2.5, baseline sweat chloride, and mutation group (F/F vs. F/RF) as covariates. Covariance structure=UN, DF=Kenward-Roger.

- **CFQ-R Respiratory domain child version.**

TEZ/IVA treatment: at baseline, the CFQ-R RD was mean (SD) 84.6 (11.4) at baseline. The LS mean absolute change from baseline in CFQ-R RD scores through Week 8 was 2.3 points (95% CI; -0.1, 4.6) in the TEZ/IVA group (Figure 13).

Figure 13 MMRM Analysis of Absolute Change from Baseline in CFQ-R Respiratory Domain Score (Child Version) at Each Visit within TEZ/IVA Group Full Analysis Set



- The Y-axis corresponds to the LS Means from the MMRM model analysis with all measurements up to Week 8, including on-treatment and after treatment discontinuation.
- Baseline is the most recent non-missing measurement before the first dose of study drug.
- The mixed model for repeated measures included visit, baseline LCI2.5, baseline CFQ-R respiratory score, and mutation group (F/F vs. F/RF) as covariates. Covariance structure=UN, DF=Kenward-Roger.

Other Endpoints

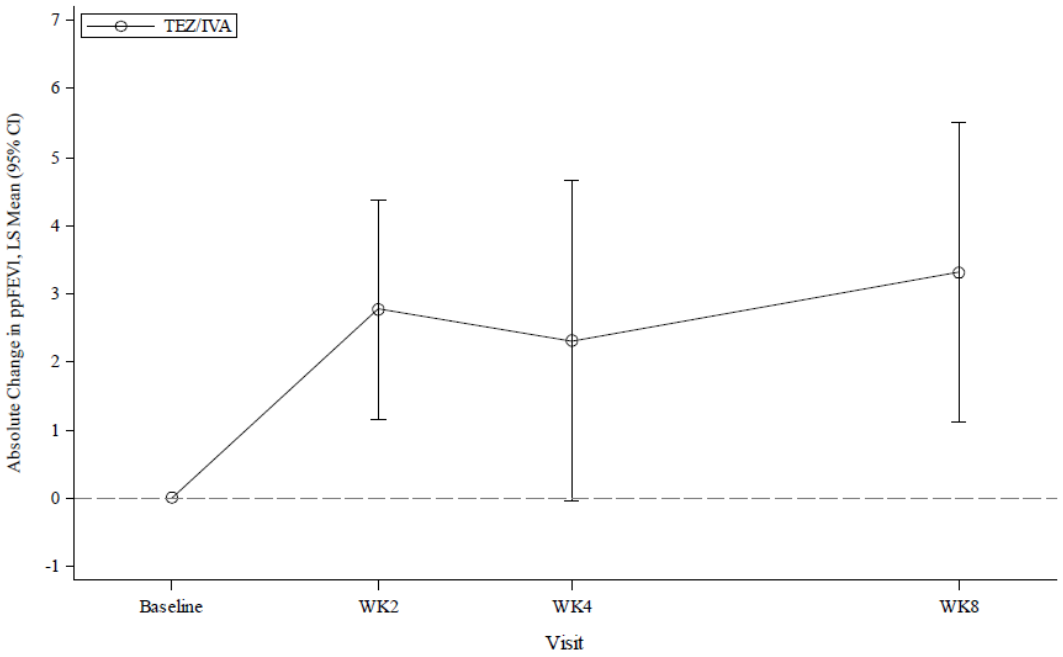
FEV1

At baseline, the mean (SD) percent predicted FEV1 (ppFEV1) of 86.5 (12.9%).

At week 8, the mean (SD) ppFEV1 was 89.9 (12.4%).

The LS mean (SE) difference in $ppFEV_1$ from baseline through week 8 was 2.8 (0.9%) (Figure 14), nominal p=0.0024.

Figure 14 MMRM Analysis of Absolute Change from Baseline in Pre-dose ppFEV1 (Percentage Points) at Each Visit within TEZ/IVA Group - VX16-661-115 Full Analysis Set



The Y-axis corresponds to the LS Means from the MMRM model analysis with all measurements up to Week 8, including on-treatment and after treatment discontinuation.
- Baseline is the most recent non-missing measurement before the first dose of study drug.
- The mixed model for repeated measures included visit, baseline LCI2.5, baseline percent predicted FEV1, and mutation group (F/F vs. F/RF) as covariates. Covariance structure=UN, DF=Kenward-Roger.

Additional Endpoints

The additional endpoints for the comparison of baseline through or at week 8 for the TEZ/IVA group are provided in Table 32.

Table 28 Results of the additional efficacy endpoints with continuous variables for the TEZ/IVA group study VX16-661-115

Statistic	TEZ/IVA within-group change N = 54
Absolute change in $LCI_{5.0}$ from baseline through Week 8 (LS mean [95% CI])	-0.30 (-0.39, -0.20)
Absolute change in $ppFEV_1$ from baseline through Week 8 (LS mean [95% CI], percentage points)	2.8 (1.0, 4.6)
Absolute change from baseline in BMI at Week 8 (Mean [SD], kg/m^2)	-0.04 (0.43)
Absolute change from baseline in BMI *z*-score at Week 8 (Mean [SD])	-0.08 (0.27)
Absolute change from baseline in weight at Week 8 (Mean [SD], kg)	0.3 (0.8)
Absolute change from baseline in weight *z*-score at Week 8 (Mean [SD])	-0.04 (0.17)
Absolute change from baseline in height at Week 8 (Mean [SD], cm)	0.9 (0.7)
Absolute change from baseline in height *z*-score at Week 8 (Mean [SD])	0.01 (0.13)

- ***Drug Acceptability Questionnaire***

Results of the Drug Acceptability Questionnaire indicated that, after taking TEZ/IVA, patients generally either "liked it very much" (40.7%) or "liked it a little" (33.3%). Ten (18.5%) patients were "not sure" and 1 (1.9%) patient "disliked it very much".

Ancillary analyses

Placebo treatment group

Demographics and baseline disease characteristics placebo group

- **Demographics**

The placebo group only include patients with F508/F508 genotype (n=10). The mean (SD) age was 9.0 (1.7) years, the mean (SD) weight was 30.5(6.1) kg and the mean (SD) BMI was 16.17 (1.02) Kg/m^2.

- **Disease characteristics**

Baseline disease characteristics mean (SD): $LCI_{2.5}$ score was 9.67 U (1.65), $ppFEV_1$ was 89.6 (10.1)% and sweat chloride was 103.8 (7.5) mmol/L.

Results placebo group

- **$LCI_{2.5}$**

In the placebo group (n=10), the absolute mean (SD) change from baseline in $LCI_{2.5}$ through Week 8 was 0.33 (0.75) U, the absolute change mean (SD) change from baseline in $LCI_{2.5}$ at Week 8 was 0.10 (1.16) unit (Table 23).

Table 29 Summary statistics for the primary outcome measure LCI 2.5 – Study VX16-661-115-FAS

	TEZ/IVA		Placebo	IVA
Genotype	F/F	F/RF	F/F	F/RF
Number of patients	n=42	n=12	n=10	n=3
LCI2.5 (U)				
baseline	9,84 (2,17)	8,6 (1,30)	9,67 (1,65)	8.60 (1.40)
absolute change at 8 week	-0,56 (1,14)	-1,12 (1,07)	0,1 (1,16)	0,61 (0,88)
absolute change through week 8	-0,39 (0,91)	-0,92 (1,08)	0,33 (0,75)	-0,81 (1,12)

Table 30 Summary statistics for the secondary outcome measures -Study VX16-661-115-FAS

	TEZ/IVA		Placebo	IVA
Genotype	F/F	F/RF	F/F	F/RF
Number of patients	n=42	n=12	n=10	n=3
Sweat chloride (mmol/L)				
baseline (mean SD)	107,1 (6,5)	73,5 (25,2)	103,8 (7,5)	100.7 (9.6)
absolute change at 8 week (mean SD)	-12,9 (9,3)	-10,9 (14,0)	-1 (12,3)	-1.0 (9,0)
min, max	-38.0, 7.0	-35, 10.0	-19.5, 12.0	-10.0, 8.0
CFQ-R Respiratory Domain- Child version				
baseline (mean SD)	85,3 (9,7)	81,9 (16,2)	80,0 (21,2)	75.0 (22,0)
absolute change at 8 week (mean SD)	2,0 (12,0)	1,5 (24,9)	9,2 (23,1)	2,8 (9,6)
absolute change through week 8 (mean SD)	1,4 (10,5)	5,6 (13,1)	7,5 (19)	2.8 (7.3)

Table 31 Summary statistics Additional outcome measures Study VX16-661-115-FAS

	TEZ/IVA		Placebo	IVA
Genotype	F/F	F/RF	F/F	F/RF
Number of patients	n=42	n=12	n=10	n=3
LCI5.0				
baseline	6,21 (1,08)	5,63 (0,58)	5,83 (0,85)	5,73 (0,73)
absolute change at 8 week	-0,26 (0,54)	-0,53 (0,64)	0,08 (0,36)	-0,48 (0,51)
absolute change through week 8	-0,28 (0,52)	-0,4 (0,55)	0,18 (0,23)	-0,47 (0,65)
FEV1 (L)				
baseline	1,5 (0,44)	1,65 (0,44)	1,7 (0,5)	1,85 (0,45)
absolute change at week 8	0,08 (0,16)	0,09(0,12)	-0,02 (0,1)	0,04 (0,13)
absolute change through week 8	0,06 (0,12)	0,1 (0,14)	-0,02 (0,09)	0,02 (0,09)
Percent Predicted FEV1 (percentage points)				
Baseline	85.1 (12.9)	91.2 (12.4)	89.6 (10.1)	89.1 (5.7)
absolute change at week 8	3.2 (8.9)	2.9 (7.1)	-3.7 (6.1)	-0.4 (6.0)
absolute change through week 8	2.6 (7.0)	3.7 (7.2)	-2.9 (5.4)	0.3 (4.7)

Outcomes are reported as mean (SD)

- **Sweat chloride**

In the placebo group, absolute change from baseline at week 8 was mean (SD) -1.0 mmol/L (12.3) (Table 34).

- **CFQ-R respiratory domain, child version**

In the placebo group, the baseline CFQ-R was 80.0 (21.2), the mean (SD) absolute change from through week 8 was 7.5 (9.0) (Table 34).

- **ppFEV1 (percentage predicted)**

In the placebo group, the baseline mean ppFEV1 was 89.6 (10.1) %. The mean (SD) change from baseline through week 8 was -2.9 (5.4) % (Table 35).

TEZ/IVA subgroups

The TEZ/IVA group consisted of a heterogeneous group of patients with F/F or F/RF *CFTR* genotypes. The placebo group consisted of F/F mutation only, while the IVA group consisted of heterozygous F/RF mutation.

Demographics

The **F508/F508** group included a total of 42 patients, n=20 (47.6%) male. The mean (SD) age was 8.5 (1.6) years, the mean (SD) weight was 28.4 (6.0) kg and the mean (SD) BMI was 15.96 (1.53) Kg/m^2.
The **F508/RF** group included a total of 12 patients, n=5 (41.7%) male. The mean (SD) age was 8.5 (1.9) years, the mean (SD) weight was 30.8 (8.5) kg and the mean (SD) BMI was 16.74 (2.00) kg/m^2.

Disease characteristics

At baseline, **F508/F508** patients' mean (SD) ppFEV1 was 85.1 (12.9), LCI2.5 was 9.84 (2.17), and sweat chloride was 107.1 (6.5) mmol/L.
In **F/RF** patients, the mean (SD) baseline ppFEV1 was 91.2 (12.4), LCI2.5 was 8.60 (1.30), and sweat chloride was 73.5 (25.2) mmol/L.

Additional post-hoc analyses as requested by the CHMP

1. MMRM analysis

a. Primary analyses

At day 120 of the assessment, requested subgroup analyses (overall, F/F and F/RF) were not provided. Instead summary statistics were provided.

These summary statistics show a larger improvement for the LCI2.5 for the F/RF compared to F/F (-0.92; 95CI% -1.65, -0.20 vs -0.39; 95 CI% -0.67, -0.10) with overlapping intervals.

In contrast: For the sweat chloride, the observed improvement in the summary statistics was larger for the F/F compared to F/RF (-12.9 mmol/L; 95% CI -16.0, -9.9 vs -10.9 mmol/L; 95% CI -20.8, -0.9).

At day 120 the subanalyses for LCI2.5 SwCl and CFQ-R respiratory domain using MMRM analysis, for subjects with F/F and F/RF mutations.

	TEZ/IVA F/F N = 42	TEZ/IVA F/RF N = 12
$LCI_{2.5}$[a]		
Baseline		
n	42	12
Mean (SD)	9.84 (2.17)	8.60 (1.30)
Absolute Change Through Week 8		
n	42	11
LS Mean (SE)	-0.33 (0.12)	-1.14 (0.22)
95% CI of LS Mean	(-0.58, -0.08)	(-1.58, -0.70)
Sweat Chloride[b]		
Baseline		
n	39	12
Mean (SD)	107.1 (6.5)	73.5 (25.2)
Absolute Change At Week 8		
n	38	10
LS Mean (SE)	-11.6 (1.9)	-14.8 (4.2)
95% CI of LS Mean	(-15.4, -7.7)	(-23.3, -6.3)

b. MMRM analyses with placebo mean imputation; within TEZ/IVA group change

The absolute change in $LCI_{2.5}$ at Week 8 and through Week 8 were re-analysed using MMRM with baseline as a covariate and placebo-mean used for imputation of missing data (Table 37).

The overall TEZ/IVA group (F/F and F/RF combined) had a change in $LCI_{2.5}$ of -0.48 U (95% CI -0.70, -0.26) through week 8. The change in the $LCI_{2.5}$ was -0.62 U (95% CI -0.86, -0.37) at week 8

The TEZ/IVA F/F group had a change in $LCI_{2.5}$ of -0.32 U (95% CI -0.56, -0.07) through week 8. The change in the $LCI_{2.5}$ was -0.45 U (95% CI -0.71, -0.18) at week 8

The TEZ/IVA F/RF had a change in $LCI_{2.5}$ of -1.07 (95% CI -1.49, -0.64) through week 8. The change in the $LCI_{2.5}$ was -1.20 (95% CI -1.64, -0.76) at week 8

Table 32 Study 115: MMRM Analysis of Absolute Change from Baseline in $LCI_{2.5}$ Using Placebo-mean Imputation: Within TEZ/IVA Group Change, 115 FAS

	TEZ/IVA F/F N = 42	TEZ/IVA F/RF N = 12	Overall TEZ/IVA N = 54
Baseline			
n	42	12	54
Mean (SD)	9.84 (2.17)	8.60 (1.30)	9.56 (2.06)
Absolute Change At Week 8			
n	42	12	54
LS Mean (SE)	-0.45 (0.13)	-1.20 (0.22)	-0.62 (0.12)
95% CI of LS Mean	(-0.71, -0.18)	(-1.64, -0.76)	(-0.86, -0.37)
Absolute Change Through Week 8			
n	42	12	54
LS Mean (SE)	-0.32 (0.12)	-1.07 (0.21)	-0.48 (0.11)
95% CI of LS Mean	(-0.56, -0.07)	(-1.49, -0.64)	(-0.70, -0.26)

Source: Ad hoc Table 29.1
CI: confidence interval; FAS: Full Analysis Set; F/F: homozygous for *F508Del*; F/RF: heterozygous for *F508Del* and a second *CFTR* allele that results in residual *CFTR* function; IVA: ivacaftor; LCI2.5: number of lung turnovers

required to reduce the end tidal inert gas concentration to 2.5% of its starting value; IVA: ivacaftor; LS Mean: least squares mean; MMRM: mixed-effects model for repeated measures; TEZ: tezacaftor; SD: standard deviation; SE: standard error
Notes: Baseline is the most recent non-missing measurement before the first dose of study drug. Analysis included all measurements up to Week 8, both on-treatment measurements and measurements after treatment discontinuation. Missing values at Week 8 are imputed with the mean of placebo subjects at the Week 8 Visit (10.05), based on summary statistics. The mixed model for repeated measures included visit, baseline LCI2.5, and mutation group (F/F vs. F/RF) as covariates. The model used an unstructured covariance and Kenward-Roger degrees of freedom.

2. Comparison with placebo

- **Overall TEZ/IVA (F/F + F/RF) group vs placebo**

As requested, the additional MMRM analyses of change from baseline at week 8 in the $LCI_{2.5}$ and sweat chloride between TEZ/IVA and placebo was provided using the placebo mean imputation.

The LS mean (SE) change in $LCI_{2.5}$ at week 8 was -0.01 (0.29) for placebo and -0.60 (0.12) for the TEZ/IVA group. The LS mean difference (SE) difference was -0.59 (032) with a 95% CI -1.22, 0.05, p=0.0699

The LS mean (SE) difference between placebo and TEZ/IVA groups for sweat chloride was -10.9 (3.8) mmol/L with a 95%CI -18.4, -3.3.

- **Comparison TEZ/IVA (FF group) vs Placebo**

As requested, the additional analyses for the comparison between TEZ/IVA (n=42) and placebo (N=10) for the F/F genotype patients were provided.

$LCI_{2.5}$

According to the primary analyses, the comparison between TEZ/IVA and placebo F/F groups, the LCI2.5 showed a LS mean difference of -0.71 U (95% CI -1.28, -0.13) through week 8. The more conservative analyses using a MMRM analyses with placebo mean imputation, showed a LS mean difference for the LCI2.5 of -0.57 (95% CI -1.23, 0.09), p=0.0916 at week 8 (Table 38)

Sweat chloride

The treatment difference for the change in sweat chloride showed similar results in both analyses.

Table 33 Study VX16-661-115 comparison between TEZ/IVA and placebo: for the F/F patients

difference from placebo	**Predefined analyses***	**MMRM analyses using placebo mean imputation**
LCI2.5 LS mean difference in the change from baseline with placebo		
through week 8	-0.71 (95% CI -1.28, -0.13)	NR
At week 8	NP	-0.57 (-1.23, 0.09) p=0.0916
Sweat chloride LS mean difference (mmol/L) in the change from baseline with placebo		
At week 8	-10.7 (-18.5, -2.9)	-10.0 (-17.0, -3.0), p=0.0063

At the request of the CHMP responder analyses were performed for LCI2.5 SwCl and CFQ-R respiratory domain in subjects with F/F

Table 34 Percentage of Subjects Reaching Specified Improvements for Selected Efficacy Endpoints – Study 115 FAS

Parameter n/N1 (%)	Placebo F/F N = 10	TEZ/IVA F/F N = 42	TEZ/IVA N = 54 n/N1 (%)
Change from baseline in $LCI_{2.5}$ through Week 8			
> -1	10/10 (100.0)	35/42 (83.3)	41/53 (77.4)
≤ -1	0/10	7/42 (16.7)	12/53 (22.6)
Change from baseline in sweat chloride at Week 8[a] (mmol/L)			
> -10	5/7 (71.4)	15/38 (39.5)	21/48 (43.8)
≤ -10	2/7 (28.6)	23/38 (60.5)	27/48 (56.3)
Change from baseline in CFQ-R respiratory domain score through Week 8			
< 4	6/10 (60.0)	27/42 (64.3)	33/54 (61.1)
≥ 4	4/10 (40.0)	15/42 (35.7)	21/54 (38.9)

Source: Ad Hoc Tables 16.2.1, 16.2.2, 16.2.3, 16.2.4, 16.2.5 and 16.2.6

CFQ-R: Cystic Fibrosis Questionnaire-Revised; F/F: homozygous for *F508del*; FAS: Full Analysis Set; $LCI_{2.5}$: number of lung turnovers required to reduce the end tidal inert gas concentration to 2.5% of its starting value; n: size of subsample; N1: number of subjects with non-missing value for change from baseline; TEZ/IVA: tezacaftor/ivacaftor

Notes: Baseline was the most recent non-missing measurement (or mean of measurements in the case of sweat chloride) before the first dose of study drug. Analyses included all measurements up to Week 8, both on-treatment measurements and measurements after treatment discontinuation.

[a] Change from baseline at Week 8 is equivalent to change from baseline through Week 8, because Week 8 was the only post-baseline sweat chloride assessment. Sweat chloride values <10 mmol/L or >160 mmol/L were excluded from the analysis.

Summary of main efficacy results

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

Table 35 Summary of efficacy for trial VX16-661-115

Study VX16-661-115, a phase III, double blind, parallel group study to evaluate the efficacy and safety of Tezacaftor in combination with ivacaftor in patients aged 6 through 11 years with cystic fibrosis, homozygous or heterozygous for the *F508Del-CFTR* mutation.			
Study identifier	VX16-661-115 (study 115) EudraCT 2016-004479-35		
Design	Double blind, randomised, parallel designed phase III study, using a 4: 1 stratification.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	8 weeks 4 weeks 4 weeks	
Hypothesis	The objective of the primary efficacy endpoint analysis is to demonstrate that the mean absolute change from baseline in LCI2.5 through Week 8 for subjects on TEZ/IVA excludes a pre-defined maximum placebo effect i.e. -0.10 U		
Treatments groups	Tezacaftor/ Ivacaftor (TEZ/IVA)	8 weeks	
	Ivacaftor (IVA) (F508/RF only)	8 weeks (included for blind only)	
	Placebo (Pla) (F508/508F only)	8 weeks (included for blind only)	
Endpoints and definition	Primary endpoint	LCI $_{2.5}$	absolute change in lung clearance index 2.5 $LCI_{2.5}$ from baseline through Week 8 in patients treated with TEZ/IVA (i.e. within group change) LCI2.5 is the number of lung turnovers required to reduce the end tidal inert gas
	Secondary endpoint	sweat chloride	Absolute change in sweat chloride from baseline **at** Week 8 for TEZ/IVA treatment group
	Secondary endpoint	CFQ -R	Average absolute change in CFQ-R respiratory domain from baseline through week 8 for TEZ/IVA
	Other endpoint	ppFEV1	Average absolute change in percentage predicted FEV1 (ppFEV1) from baseline through Week 8 for the TEZ/IVA treatment group
Database lock	01 Feb 2019		
<u>Results and Analysis</u>			
Analysis description	Primary Analysis for the efficacy is on the FAS		
Analysis population and time point description	FAS population defined as the patients randomised and exposed to at least one dose of study treatment. The observed differences (LS mean (SE) are the within treatment difference from baseline through week 8		
Descriptive statistics and	Treatment group	TEZ/IVA	
	Number of patients	n=54	

	Primary outcome	**$LCI_{2.5}$ (Units) TEZ/IVA**	
	Baseline	Mean (SD)	9.56 (2.06)
	Week 8	Mean (SD)	8.90 (1.80)
		LS mean (SE) difference	-0.51 (0.11)
		95% CI	(-0.74, -0.29)
		p value	<0.0001
	Secondary outcomes		
	sweat chloride (mmol/L) TEZ/IVA		
	Baseline	Mean (SD)	99.2 (19.5)
	Week 8	Mean (SD)	88.4 (18.6)
		LS mean (SE) difference	-12.3 (1.5)
		95% CI	(-15.3, -9.3)
		p value	<0.0001
	CFQ-R Respiratory domain child version (points) TEZ/IVA		
	Baseline	Mean (SD)	84.6 (11.4)
	week 8	Mean (SD)	86.3 (14.7)
		LS mean (SE) difference	2.3 (1.2)
		95% CI	(-0.1, 4.6)
		p-value	p=0.0546
	Other outcomes: ppFEV1 (TEZ/IVA)		
	Baseline	Mean (SD)	86.5 (12.9)
	Week 8	Mean (SD)	89.9 (12.4)
		LS mean (SE) difference	2.8 (0.9)
		95% CI	(1.0, 4.6)
		p value	0.0024
Notes	in patients weighing 30-40 kg, the current applied posology resulted in the low range of exposure compared to adult data. The applicant applies for a higher posology in this population. This posology has not been investigated in the current population. Knowledge is lacking it the higher exposure will result in improved efficacy		
Analysis description	The primary analysis of the primary efficacy endpoint will be based on a mixed-effects model for repeated measures with LCI2.5 at each time point as the outcome variable. The estimated mean change from baseline through Week 8 in $LCI_{2.5}$ for subjects treated with TEZ/IVA along with the corresponding 95% CI will be provided. If the upper bound of the 95% CI is below the pre-defined maximum placebo effect (-0.10 U), it will be interpreted as sufficient evidence to achieve the primary efficacy objective. Additional sensitivity analyses using the placebo mean imputation input are provided in Table 37.		

Supportive study

Study 113B

Study VX15-661-113, a Phase 3, Open-label Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of VX-661 in Combination with Ivacaftor in Subjects 6 Through 11 Years of Age With Cystic Fibrosis, Homozygous or Heterozygous for *the F508Del-CFTR* Mutation.

Objectives

The primary objective of study 113 B is to assess the safety and tolerability of TEZ/IVA combination therapy. Secondary objectives include PK of TEZ/IVA and metabolites (M1-TEZ, M2-TEZ, M1–IVA and M6-IVA) and the efficacy of TEZ/IVA combination therapy.

Study design

Study 113 Part B included a Screening Period (28 days), Treatment Period (24 weeks [± 5 days]), and Safety Follow-up Visit (4 weeks [± 7 days]).

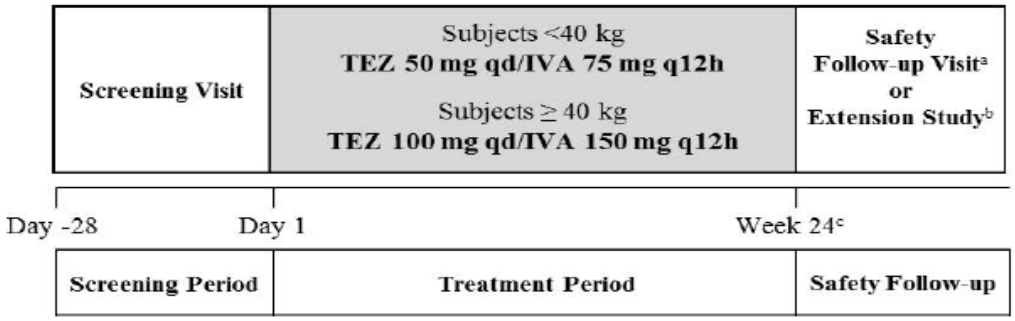
A review of safety, tolerability, and PK data was completed by an internal Vertex team after completion of Part A to select the TEZ/IVA dose regimens for Part B.

The following doses were provided during part B:

- Patients < 40 kg: TEZ 50 mg qd/IVA 75 mg q12h
- Patients ≥ 40 kg: TEZ 100 mg qd/ IVA 150 mg q12h

At the Week 24 Visit, subjects who completed study drug treatment were offered the opportunity to enrol in an extension study evaluating TEZ/IVA (enrolment was based on the eligibility criteria specified within the extension study). A Safety Follow-up Visit was scheduled to occur 4 weeks (± 7 days) after the last dose of study drug. The Safety Follow-up Visit was not required for subjects who enrolled in the extension study within 28 days after the last dose of study drug. Subjects who permanently discontinued study drug treatment before the Week 24 Visit had an Early Treatment Termination (ETT) Visit and a Safety Follow-up Visit.

Figure 15 Schematic of Study Design for Study Part 113B



IVA: ivacaftor; q12h: every 12 hours; qd: daily; TEZ: tezacaftor

[a] The Safety Follow-up Visit occurred 4 weeks [± 7 days] after the last dose of study drug and was not required for subjects who enrolled in the extension study within 28 days after the last dose of study drug.

[b] At the Week 24 Visit, subjects who completed study drug treatment were offered the opportunity to enroll in an extension study evaluating TEZ/IVA. Subjects who prematurely discontinued study drug treatment were not eligible to rollover into the extension study.

[c] The last dose of study drug was the evening dose administered the day before the Week 24 Visit.

Study population study 113B.

Study 113B included a total of n=70 patients, most patients n=68 (97.1%) were white and male n=36 (51.4%). The mean (SD) age was 8.1 (1.8) years, the mean (SD) weight was 30.7 (10.0) Kg, and mean (SD) height 131.0 (13.0) cm (Table 15, Table 16)

The study population consisted of N=61 F505/F508 and n=9 F/RF patients, all second RF mutations were approved for Symkevi. At baseline, the mean (SD) FEV1 was 1.56 (0.46) L, corresponding with a mean (SD) ppFEV1 of 91.1 (12.3) %. At baseline, the mean (SD) sweat chloride was 99.1 (19.2) $mmol.L^{-1}$. (Table 16)

The study was conducted in the USA and Canada. The number of patients weighing ≥30 kg to <40 kg at baseline was 21 (30%); the number of patients weighing ≥40 kg at baseline was 8/70 (11.4%).

Outcomes/endpoints

Efficacy Assessments (secondary outcome measure)

Part B:

The efficacy assessment for part B were Spirometry, weight and weight z-score, height and height z-score, BMI and BMI z-score, sweat chloride, and CFQ-R. Optional exploratory sub study conducted at a subset of sites: The Lung clearance index was measured by the EasyOne Pro LAB (NDD, Zurich Switzerland). These efficacy outcomes were measured as secondary outcome measures.

Safety Assessments

The safety assessment included: Adverse events, clinical laboratory assessments (serum chemistry, haematology, coagulation studies, lipids, vitamins, and urinalysis), standard 12-lead ECGs, vital signs, pulse oximetry, physical examinations (PEs), spirometry and Ophthalmologic examinations.

Statistical Methods

The planned enrolment was approximately 56 subjects. Assuming a 10% dropout rate, approximately 50 subjects were expected to complete Part B. The incidence of AEs is an important safety endpoint. With a total sample size of 50 subjects completing the study, there would be a 92.3% chance of observing AEs in at least 1 subject if the true incidence rate were 5%, and a 99.5% chance of observing AEs in at least 1 subject if the true incidence rate were 10%. These probabilities were calculated by assuming a binomial distribution for the number of AEs using SAS.

Analysis Sets

The following analysis sets were defined: Safety Set, Full Analysis Set (FAS), and FAS – LCI Substudy.

- The Safety Set was defined as all subjects who received at least 1 dose of study drug in Part B of the study.
- The FAS was defined as all subjects who carried the intended *CFTR* mutations and received at least 1 dose of study drug in Part B of the study. The FAS was used for all efficacy analyses except for LCI endpoints.
- The FAS - LCI sub study was defined as all subjects who carried the intended *CFTR* mutations and received at least 1 dose of study drug in Part B of the study and had at least 1 LCI measurement. The FAS-LCI sub study was used for efficacy analyses of exploratory LCI endpoints.

Variables

Definition of Treatment-emergent Period

The treatment-emergent period for Part B corresponds to data from the first dose of study drug to 28 days after the last dose of the study drug, or to the date of completion of study participation, whichever occurred first.

Definition of Baseline

The baseline for was defined as the most recent non-missing measurement (scheduled or unscheduled) collected prior to the first dose of study drug in Part B. For ECGs, baseline values were the average of the 3 pre-treatment measurements on Day 1 of Part B. For sweat chloride, the baseline values were the mean of the last values on the left and the right arm prior to the first dose of the study.

Missing Data and Outliers

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

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

Efficacy Analysis)

All efficacy analyses described in this section were based on the FAS, unless specified otherwise. The analysis included all available measurements through the last assessment, including measurements after treatment discontinuation.

There was no multiplicity adjustment, the p values provided for the secondary and other endpoints are considered nominal.

- *Absolute Change from Baseline in Percent Predicted FEV1 Through Week 24*

This endpoint is defined as the average of the absolute changes from baseline in ppFEV1 at each post-baseline scheduled visit.

Absolute change from baseline in ppFEV1 was analysed using a restricted maximum likelihood (REML)-based mixed effect model for repeated measures (MMRM) approach that included visit and baseline ppFEV1 (continuous) as fixed effects, and subject as a random effect. An unstructured (co)variance structure was used to model the within-subject errors. If the model failed to converge, a compound symmetry covariance structure was considered. The degrees of freedom of the denominator was approximated by the Kenward-Roger's method.

The primary result obtained from the model was the average treatment effect through Week 24. The corresponding least squares mean (LS mean), standard error (SE), the 95% CI, and P value were provided.

Other outcome measures

A similar MMRM model as described for absolute change in ppFEV1 from baseline through Week 24 was used for relative change from baseline in percentage predicted FEV1 and *Absolute Change from Baseline in CFQ-R Respiratory Domain Score*. For the outcome measures *Absolute Change from Baseline in Weight, Height, BMI, and Associated z-Scores* the similar MMRM model was used for measuring the change from baseline At Week 24.

The same slightly adjusted model was also applied for the *Absolute Change from Baseline in Sweat Chloride Through Week 4 and Through Week 24.* Because the first post-baseline assessment of sweat chloride was performed at week 4, the estimated change at week 4 was used to assess the absolute change in sweat chloride through week 4.

Safety Data

Safety was the primary objective of Part B. Safety analyses were based on the Safety Set in each study part. Only descriptive analysis of safety was performed (i.e., no statistical hypothesis testing was performed).

Conduct of the trial

See study 113A

Statistical Analysis Plan

The following changes were made in the SAP for Part B compared to the protocol:

• The All Subjects Set for Part B was removed in the SAP, due to the fact that the All Subjects Set for Part B would be the same for the Safety Set Part B, which included all subjects who received at least 1 dose of study drug in Part B. Subject data listings were presented based on the Safety Set Part B.

• The details of mixed effect model repeated measures (MMRM) approach was updated in the SAP considering the study design and study population.

Results

Efficacy results

- *Absolute Change from Baseline in ppFEV1 Through Week 24*

The LS mean absolute change in ppFEV1 from baseline through Week 24 was 0.9 percentage points (95% CI: -0.6, 2.3; nominal P value: 0.2361) (Table 41).

Table 36 MMRM Analysis of Absolute Change from Baseline in ppFEV1 Through Week 24, Part B Full Analysis Set

Statistic	Total N = 70
Baseline	
n	70
Mean (SD)	91.1 (12.3)
Absolute Change through Week 24 (percentage points)	
n	70
LS Mean (SE)	0.9 (0.7)
95% CI of LS Mean	(-0.6, 2.3)
Nominal *P* value	0.2361

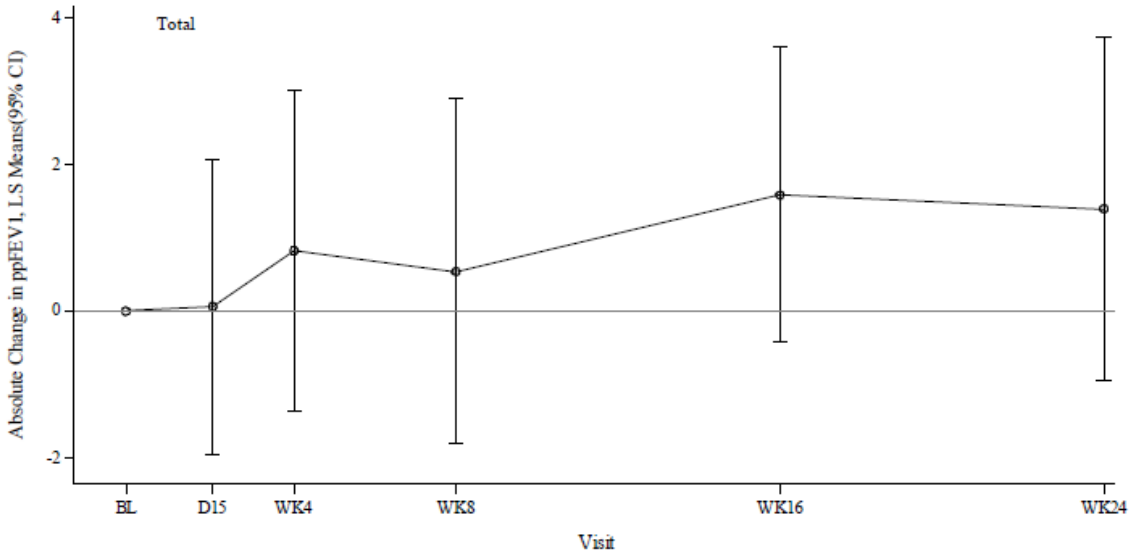
Source: Table 14.2.1.2.1b

CI: confidence interval; LS mean: least squares mean; MMRM: mixed-effects model for repeated measures; N: size of sample; n: size of subsample; *P*: probability; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SD: standard deviation; SE: standard error

Note: Analysis included all measurements up to Week 24, both on-treatment measurements and measurements after treatment discontinuation. The MMRM included baseline $ppFEV_1$ and visit as fixed effects, an unstructured covariance, and Kenward-Roger estimation of degrees of freedom.

Figure 16 illustrates the MMRM analysis of absolute change from baseline in ppFEV1 at each visit.

Figure 16 MMRM Analysis of Absolute Change from Baseline in ppFEV1 (Percentage Points) at Each Visit, Part B Full Analysis Set



Source: Figure 14.2.1b
BL: baseline; CI: confidence interval; D: day; LS Mean: least squares mean; MMRM: mixed-effects model for repeated measures; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; WK: week
Note: The Y-axis corresponds to the LS Mean from the MMRM model analysis with all measurements up to Week 24, including on-treatment and after treatment discontinuation. The MMRM analysis included baseline $ppFEV_1$ and visit as fixed effects, an unstructured covariance, and Kenward-Roger estimation of degrees of freedom.

F/F and F/RF subjects had similar absolute increases from baseline in ppFEV1 through Week 24. For F/F subjects, the mean (SD) absolute change from baseline in ppFEV1 through Week 24 was 0.9 (6.7) percentage points. For F/RF subjects, the mean (SD) absolute change from baseline in ppFEV1 through Week 24 was 0.9 (5.1) percentage points.

These data are consistent with the well-preserved baseline lung function values.

- *Relative Change from Baseline in ppFEV1 Through Week 24*

The LS mean relative change in ppFEV1 from baseline through Week 24 was 1.4% (95% CI: -0.4, 3.1; nominal P value: 0.1230).

Absolute Change from Baseline in Weight, Height, BMI, and Associated z-scores at Week 24

Table **42** presents the MMRM analysis results for BMI, weight, height, and associated z-scores.

The LS mean absolute change from baseline in weight at Week 24 was 1.7 kg (95% CI: 1.3, 2.0; nominal P value <0.0001). The LS mean absolute change from baseline in height at Week 24 was 2.7 cm (95% CI: 2.4, 2.9; nominal P value <0.0001). The LS mean absolute change from baseline in BMI at Week 24 was 0.23 kg/m2 (95% CI: 0.06, 0.4; nominal P value = 0.0081).

The LS mean absolute change from baseline in weight z-score at Week 24 was 0.0 (95% CI: -0.05, 0.05; nominal P value = 0.9490). The LS mean absolute change from baseline in height z-score at Week 24 was 0.0 (95% CI: -0.05, 0.05; nominal P value = 0.9953). The LS mean absolute change from baseline in BMI z-score at Week 24 was -0.03 (95% CI: -0.10, 0.04; nominal P value = 0.4456).

Table 37 MMRM Analysis of Absolute Change From Baseline in Weight, Height, BMI, and Associated z-scores At Week 24, Part B Full Analysis Set

Statistic	Total N = 70
Weight (kg)	
Baseline	
n	70
Mean (SD)	30.7 (10.0)
Absolute Change At Week 24	
n	67
LS Mean (SE)	1.7 (0.2)
95% CI of LS Mean	(1.3, 2.0)
Nominal *P* value	<0.0001
Weight *z*-score	
Baseline	
n	70
Mean (SD)	0.20 (0.94)
Absolute Change At Week 24	
n	67
LS Mean (SE)	0.00 (0.02)
95% CI of LS Mean	(-0.05, 0.05)
Nominal *P* value	0.9490
Height (cm)	
Baseline	
n	70
Mean (SD)	131.0 (13.0)
Absolute Change At Week 24	
n	67
LS Mean (SE)	2.7 (0.1)
95% CI of LS Mean	(2.4, 2.9)
Nominal *P* value	<0.0001
Height *z*-score	
Baseline	
n	70
Mean (SD)	-0.07 (0.98)
Absolute Change At Week 24	
n	67
LS Mean (SE)	0.00 (0.02)
95% CI of LS Mean	(-0.05, 0.05)
Nominal *P* value	0.9953

Statistic	Total N = 70
BMI (kg/m^2)	
Baseline	
n	70
Mean (SD)	17.44 (2.69)
Absolute Change At Week 24	
n	67
LS Mean (SE)	0.23 (0.09)
95% CI of LS Mean	(0.06, 0.40)
Nominal *P* value	0.0081
BMI *z*-score	
Baseline	
n	70
Mean (SD)	0.37 (0.90)
Absolute Change At Week 24	
n	67
LS Mean (SE)	-0.03 (0.04)
95% CI of LS Mean	(-0.10, 0.04)
Nominal *P* value	0.4456

Source: Table 14.2.2.2b, 14.2.3.2b, 14.2.4.2b, 14.2.5.2b, 14.2.6.2b, 14.2.7.2b

BMI: body mass index; CI: confidence interval; LS mean: least squares mean; MMRM: mixed-effects model for repeated measures; N: size of sample; n: size of subsample; *P*: probability; SD: standard deviation; SE: standard error

Note: BMI = weight / (height*height) (kg/m^2). Analysis included all measurements up to Week 24, both on-treatment measurements and measurements after treatment discontinuation. The MMRM included baseline values and visit as fixed effects, an unstructured covariance, and Kenward-Roger estimation of degrees of freedom.

Faecal elastase-1 assessments were not performed in Study 113.

- *Absolute Change from Baseline in Sweat Chloride Through Week 4 and Week 24*

The LS mean absolute change from baseline in sweat chloride through Week 4 was -13.0 mmol/L (95% CI: -16.2, -9.9; nominal P value<0.0001). The LS mean absolute change from baseline through Week 24 was -14.5 mmol/L (95% CI: -17.4, -11.6; nominal P value <0.0001).

- *Absolute Change from Baseline in CFQ-R Respiratory Domain Through Week 24*

The LS mean absolute change from baseline in CFQ-R respiratory domain score was 3.4 points (95% CI: 1.4, 5.5; nominal P value = 0.0013).

Table 38 MMRM Analysis of Absolute Change From Baseline in CFQ-R (Child Version) Respiratory Domain Score Through Week 24, Part B Full Analysis Set

Statistic	Total N = 70
Baseline	
n	70
Mean (SD)	81.8 (13.8)
Absolute Change through Week 24	
n	70
LS Mean (SE)	3.4 (1.0)
95% CI of LS Mean	(1.4, 5.5)
Nominal *P* value	0.0013

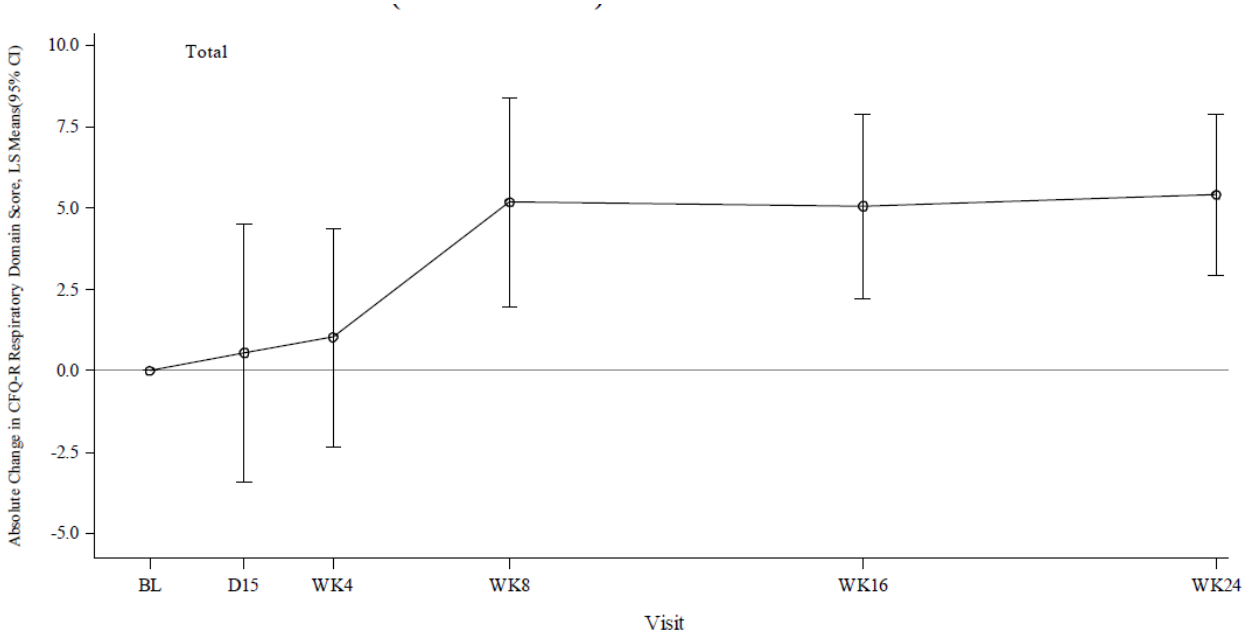
Source: Tables 14.2.9.2.1b

CFQ-R: Cystic Fibrosis Questionnaire-Revised; CI: confidence interval; LS mean: least squares mean; MMRM: mixed-effects model for repeated measures; N: size of sample; n: size of subsample; *P*: probability; SD: standard deviation; SE: standard error

Note: Analysis included all measurements up to Week 24, both on-treatment measurements and measurements after treatment discontinuation. The MMRM included baseline CFQ-R respiratory domain and visit as fixed effects, an unstructured covariance, and Kenward-Roger estimation of degrees of freedom.

At the Week 24 Visit, the LS mean absolute change from baseline in CFQ-R respiratory domain was 5.4 points (95% CI: 2.9, 7.9; nominal P value <0.0001).

Figure 17 MMRM Analysis of Absolute Change from Baseline in CFQ-R Respiratory Domain Score (Child Version) at Each Visit



- *Lung Clearance Index (Optional Exploratory Sub study)*

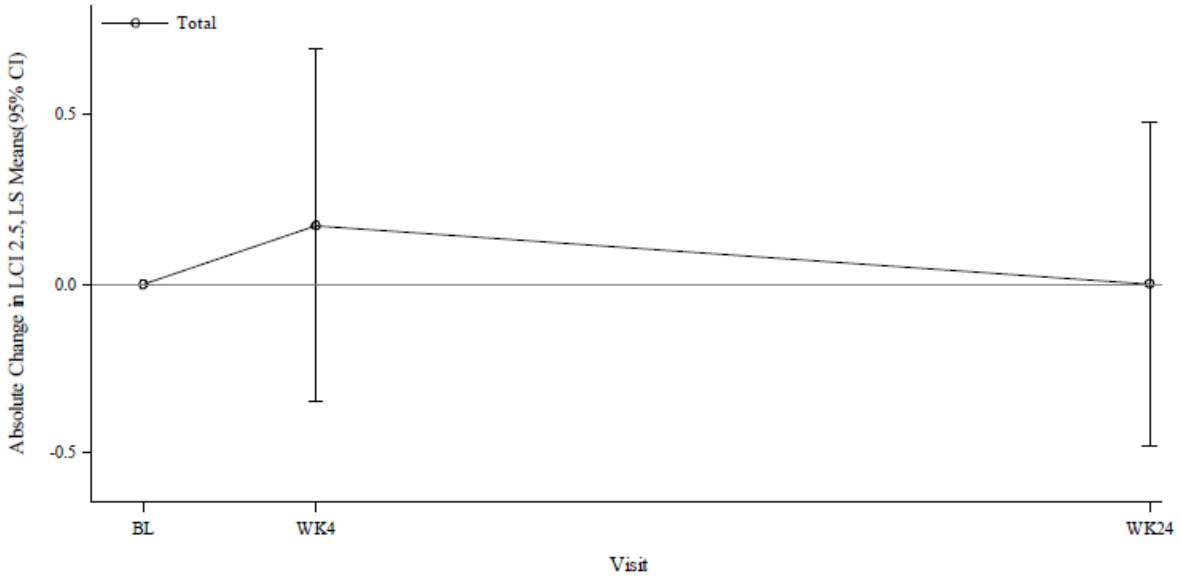
Lung clearance index was included as an exploratory endpoint in this study to evaluate an LCI device and over-reading process that were new to the Vertex CF program.

At baseline, the mean (SD) LCI2.5 was 9.39 (1.95); at week 24, the mean (SD) was 9.05 (1.91)

The LS mean (95% CI) absolute change from baseline in $LCI_{2.5}$ through Week 24 was 0.09 (-0.32, 0.49). The LS mean (95% CI) absolute change from baseline in $LCI_{5.0}$ through Week 24 was 0.05 (-0.15, 0.26).

Evaluation of $LCI_{2.5}$ data quality from the new device is ongoing. This ongoing analysis is not summarized in this report; additional information may be provided in another report**.**

Figure 18 MMRM Analysis of Absolute Change from Baseline in Lung Clearance Index 2.5 at Each Visit - Part B Full Analysis Set - LCI Sub-study



2.5.3. Discussion on clinical efficacy

The clinical programme for children aged 6 through 11 years is based on the partial extrapolation of efficacy from adults to children, supported by PK/safety study VX15-661-113 and pivotal phase 3 parallel-group trial VX16-661-115 in 67 patients aged 6-11 years.

The key studies to support the efficacy and safety in adults and adolescents aged ≥ 12 years were studies VX14-661-106 and study VX14-661-108 and VX14-661-110 (safety only). Study 106 and 108 were both randomised, double-blind, placebo-controlled phase III trials. Study 106 was a parallel designed study conducted in patients homozygous for F508/F508 of 24-week duration; study 108 was a crossover study conducted in patients heterozygous for F508 –and a residual function and had a duration of 8 weeks. Study 110 provided long-term safety data. These studies led to the approval of TEZ/IVA (Symkevi) in February 2018 for patients with CF ≥12 years old who have an indicated *CFTR* genotype (homozygote F508/F508 and certain heterogeneous patients F508 with a residual function).

The clinical development in patients 6 through 11 years of age was initiated in 2016. The initial aim of Study VX15-661-113 was to obtain similar TEZ and IVA pharmacokinetic (PK) exposures to adults and to demonstrate safety in this age group. The efficacy was included as a secondary outcome parameter. The study VX16-661-115 was designed to provide a bridge on the efficacy and safety results from patients aged 6-11 years to patients aged ≥ 12 years.

Subjects from both 113 and 115 were offered the opportunity to enrol in an open-label extension (Study VX17-661-116 [Study 116]). Study 116 is ongoing and will support long-term safety and persistence of efficacy.

Table 39 Tabular overview of the studies contributing to the extrapolation strategy by Symkevi

Study	Geno type	Adults and adolescents (≥ 12 yrs.)	Children (6-11 yrs.)	PK	PD	Efficacy	Safety	study type
VX11-661-101	F/F F/G551D	172 18		X	x	x	X	PK, dose finding
VX13-661-103	F/F							dose confirming
VX14-661-106	F/F	248[a]		X		ppFEV1	X	RCT, parallel
VX14-661-108	F/RF	161[a]		X	x	ppFEV1	X	RCT, CO,
VX14-661-110	F/F, F/RF	F/F: 459 F/RF: 222				x	X	Roll over, open label
VX15-661-113	F/F F/RF		Part A: n= 13 Part B: n=70	X		ppFEV1	X	Open label, Part A: mainly PK, part B safety and tolerability and efficacy
VX16-661-115	F/F F/RF		54[a]		X	LCI2.5	X	RCT, parallel, blinded
VX17-661-116	F/F F/RF		130				X	roll over open label long term safety

Table made by assessor. Study 106 and 108 were the key studies to support the adult indication

F/F = F508/F508, F/RF = F508 with residual function

a= number of patients treated with TEZ/IVA; NP = not provided, RCT = randomised controlled trial, CO cross over

Rationale for an extrapolation from adult to paediatric patients of Symkevi in patient homozygote for F508/F508 and certain types of F508/RF mutations.

The MAH did not consider that a Randomised Controlled Trial in children is necessary. The MAH considers that the extrapolation is appropriate, because of the similarities in the genetic, molecular and pathophysiological aetiology of CF between adults and children during the disease. The MAH also

considers that the extrapolation approach is consistent with the principles described in ICH E11 and the EMA reflection paper on paediatric extrapolation.

The MAH did not completely follow the Scientific advice adopted by CHMP on their development:

- The CHMP preferred the use of a placebo-controlled trial to show the efficacy. The primary endpoint should be a clinically relevant difference between test and placebo. However, *absolute change in $LCI_{2.5}$ from baseline through week 8 for TEZ/IVA* has been included as the primary endpoint, i.e. not compared to the placebo or IVA control arm.
- The primary endpoint is the absolute change from baseline *through* week 8 for the LCI2.5. The CHMP preferred to use the absolute change from baseline to week 8, as the former endpoint may obscure the loss of efficacy over time.

Additionally, although no explicitly recommended, the long-term extension supportive study 113B did not include the same efficacy parameter $LCI_{2.5}$ as the pivotal trial 115.

Design and conduct of clinical studies

This extension of indication for children aged 6-11 years is primarily based on the concept of partial extrapolation.

In this partial extrapolation strategy, only limited paediatric data were provided because the safety and efficacy has been shown in the adult studies. This strategy of partial extrapolation was agreed by the CHMP (EMEA/H/SA/2814/3/2017/PED/II), provided that the results of the paediatric studies would be compelling and robustly confirm the absence of a placebo effect.

Indeed, the strategy of partial extrapolation can be justified in CF for the *CFTR* therapies, because of the similar underlying genetic, and molecular aetiology of CF between children and patients ≥ 12 years. The biochemical defect of the defective chloride channels is present from birth and because of the longstanding defects, it results in sequelae in the lung, pancreas and other organs emerging progressively throughout childhood and into adulthood. These sequelae may negatively affect the course of the disease over time, e.g. like the more frequent exacerbations is adulthood compared to childhood.
The *CFTR* therapies improve the Cl transport, and as such, they can be regarded as a targeted therapy for the disease for which the extrapolation strategy is justified.

However, this partial extrapolation approach to establish the treatment in paediatric population differs from previous *CFTR*-applications like ivacaftor (Kalydeco) and lumacaftor/ivacaftor (Orkambi) that established the role of these therapies in children aged 6-11 years. These products were approved on the basis of a benefit established in a comparative placebo-controlled phase III randomised controlled trial as it was unclear at that time whether the clinical course of the disease would be different between adults and children. These studies showed efficacy results in the paediatric population that were in line with the adult population, supporting the concept of partial extrapolation. After the efficacy had been established in children aged 6-11-year, various extension of indication applications have since been approved for the younger children based on the concept of extrapolation.

The key steps for the partial extrapolation are

1. Show that the treatment is effective and safe in the adult population
2. Confirm that the adult PK is predictive for the paediatric PK
3. To show that the product has a predictive pharmacodynamic effect
4. Provide evidence for efficacy, so that the results of adults can be extrapolated to children
5. Evaluate the safety profile

Step 1: Demonstrate that the treatment is effective and safe in the adult population.

Symkevi has an established efficacy in the treatment of CF in adults and in children aged 12 years and older by showing improvement in lung function using FEV1, sweat chloride and Quality of life compared to placebo. This has led to the EU approval of Symkevi for CF patients homozygous for F508/F08 and heterozygous for specific F/RF mutations (studies 101, 103, 106 and 108, EMEA/H/C/004682/0000) in 2019.

Limited data has been submitted to support current application in children. The paediatric data set consists of 3 studies: study 113 A to support the PK, 113B to support the PK and long-term safety, and the pivotal study 115 to support the efficacy. Upon request by CHMP, the interim analysis of the long-term safety study 116 was also provided.

Step 2: Demonstrate that the adult PK is predictive for the paediatric PK.

In the concept of the partial extrapolation strategy, the dose selection is essential to provide similar exposures in the paediatric population compared to the adult population. Throughout the clinical program, PK was collected both in adults and children (Study 113 and 115). After the review of the totality of data (including study 115), it appeared that the exposure with tezacaftor 50 mg/ivacaftor 75 mg in patients weighing between 30-40 kg is below the exposure observed in adults. Therefore, the applicant proposed to lower the weight-based posology from 40 kg to 30 kg to better align with the adult exposures. This dose adjustment is considered acceptable (see PK section).

As a result of this modified posology, no clinical safety and efficacy has been provided for these patients. This adjusted posology affects about 40% of the propose EU target population and the safety and efficacy for this population must be extrapolated from the current and adult database as well.

Step 3: Demonstrate that the product has a predictive pharmacodynamic effect

The pharmacodynamic effect of Symkevi, sweat chloride transport was included as a secondary efficacy measure of efficacy in study 115. The sweat chloride transport is an important parameter in this clinical program supporting demonstration of pharmacodynamic effect. If this outcome measure shows the same improvement in paediatrics as in adults, then it will provide support for the extrapolation of the safety and efficacy from adults and children aged 12 years and older to younger children from 6 to 11 years.

Step 4: Provide evidence for efficacy, so that the results of adults can be extrapolated to children

The pivotal efficacy study is study 115. This study will be supported with longer term 24 weeks efficacy data obtained in study 113; a study primarily aimed to investigate the PK.

Both studies 113 and 115 were performed with a weight dose posology of 40 kg but not with the applied weight-based posology of 30 kg. Therefore, both studies 113 and 115 will not provide evidence for the overall proposed target population, but the results might be used for extrapolation for the proposed posology.

The pivotal study 115 included a heterogeneous CF patient population characterised by F/F and F/RF mutations. The treatments included TEZ/IVA, placebo and IVA (ivacaftor). The patients were randomised in a *4:1* randomisation to active vs the appropriate blinding group i.e. placebo (F508/F508) or ivacaftor (F508/RF). The primary efficacy endpoint was within treatment difference from baseline through week 8 for the LCI2.5 in the patient treated with TEZ/IVA.

The following additional comments are made regarding the study design of study 115 referring the design, statistics and conduct of the study.

Design

General comment
The pivotal paediatric study 115 was designed to show a statistically significant difference between baseline and week 8 of treatment for the TEZ/IVA treated patients. Therefore, the study will provide more evidence of efficacy then would be necessary according to the concept of partial extrapolation, where only supportive data may be necessary. Therefore, this study can also be seen as a stand-alone study to support the paediatric application, although in that case a randomised trial would have been preferred.

- Study 115 is effectively designed as a single trial arm

Study 115 included 3 treatments, TEZ/IVA, placebo and IVA (ivacaftor). The patients were randomised *4:1* to either active or the appropriate, blinding group, i.e. placebo (F508/F508) or ivacaftor (F508/RF).

Although the study is described as a parallel study, the study can effectively be considered an adjusted single-arm trial for several reasons:

- The overall effect size is driven by the TEZ/IVA group as this includes 80% of the population
- No *between* treatment comparisons are performed
- Each treatment included another patient population, hampering a between treatment comparison. The TEZ/IVA group included both F508/F508 and F508/RF, while the placebo group would only include a F508/F508 patient population and the IVA group a F508/RF patient population.
- The number of included patient group in the placebo group (n=10) or ivacaftor group (n=3) is too small to allow for comparisons

Therefore, by design, the study will provide insufficient comparative data with placebo. The results of this study need to be considered in light of the results obtained in adult data.
Furthermore, from a formal point of view, the CHMP considered that the placebo-treated homozygous F508/F508 patients could have been considered as being undertreated as Orkambi received a positive opinion for the extension of the indication for F506/F508 patients for children aged ≥ 6 years on 09 November 2017. The trial started in May 2018. Thus, the patients randomised to placebo should have been treated with Orkambi.

- Treatment duration is relatively short

The study has a short duration, i.e. 8 weeks, which is justified by the extrapolation strategy as previous studies have shown that the effect of *CFTR* modulator therapy is present at week 2 of treatment and maintained throughout the 24-week. Moreover, additional supportive long-term treatment data is collected in study 113.

- The primary endpoint is the within treatment difference for the LCI2.5

The primary endpoint was the within treatment difference for the LCI2.5 measurement. Although a placebo-controlled trial was preferred, this -within treatment outcome- would need a lower number of patients compared with showing a statistically significant effect from placebo outcome.

The pivotal paediatric study 115 used a different lung function measurement as primary endpoint than commonly used in the adult studies i.e. the $LCI_{2.5}$ instead of the ppFEV1. The $LCI_{2.5}$ can measure changes in the small airways, while the ppFEV1 is more associated with large airways. In CF, the small airways are earlier affected than the large airways. Therefore, the use of the $LCI_{2.5}$ as a measurement of efficacy is acceptable, given the well-preserved lung function in children.

Although, the experience with the $LCI_{2.5}$ in clinical studies is limited, it has been accepted as a primary outcome measure for example to support the paediatric application of Orkambi, based on a large,

placebo-controlled, double-blind study (Study VX14-889-109, EMEA/H/00395/X/020).

The minimal clinically important difference (MCID) for the $LCI_{2.5}$ is not known. Therefore, an effect larger than the natural variability might be regarded as clinically relevant. The natural variability for the $LCI_{2.5}$ is 1 unit[2] or 15 % of baseline[3].
Previous applications in adults and children, however, have been approved based on lung function improvements (FEV1 2-3%: Bronchitol EMEA/H/C/001252; FEV1 2-3% Orkambi EMEA H/C/003954, Symkevi (3-4%) that were smaller than the natural variability of FEV1 observed in adults i.e. 4.9% (Stanfood[4]). These products were approved considering that an improvement in lung function in CF could be regarded as clinically relevant due to the detrimental course of disease.

- Estimated effect size

The primary endpoint of the study was the within treatment difference from placebo through week 8. The lower limit of efficacy was estimated to be -0.10 U as this would be considered the maximum placebo effect. This effect was based on the placebo results of study 809-109, a study conducted in F/F patients aged 6-11 years. This estimated outcome with placebo is rather optimistic because it suggests that the lung function would improve upon placebo, while the lung function deteriorates over time. Therefore, the estimated placebo effect for the lower limit of efficacy appears to be a conservative estimate.

- Change from baseline LCI2.5 through week 8 instead of at week 8

The primary efficacy variable was the change in $LCI_{2.5}$ from baseline through week 8. The CHMP prefers the use of absolute change from baseline *at* week 8, because this endpoint is less likely to mask deteriorations over time compared to endpoint through week 8. Both endpoints were provided for the overall study population.

- Secondary and other endpoints

Secondary efficacy endpoints included analyses of sweat chloride and the Cystic Fibrosis Questionnaire-Revised [CFQ-R] for the within treatment difference in the TEZ/IVA treatment group. These outcome measures were comparable to the one that were used in the adults' program.

- Other collected endpoints

Other outcome measures were amongst others the absolute change in the percent predicted forced expiratory volume in 1 second (ppFEV1) and the drug acceptability assessment.

Study population

Study 115 enrolled a total of 69 patients of 6 – 11 years old, with a confirmed diagnosis of CF, defined as 2 CF-causing mutations in addition to either chronic sino-pulmonary disease and/or gastrointestinal/nutritional abnormalities. The inclusion criteria were generally acceptable, reflective of the proposed target population and in line with the Symkevi pivotal trials submitted for the initial authorisation.

Despite the broader inclusion criteria, the trial included only patients with a Symkevi approved RF mutation. Therefore, the results of the adult population might be extrapolated to the paediatric population.

[2] Singer F et al. Practicability of Nitrogen Multiple-Breath Washout Measurements in a Pediatric Cystic Fibrosis Outpatient Setting. Pediatric Pulmonology 2013; 48:739–746
[3] Oude Engberink et al. Inter-test reproducibility of the lung clearance index measured by multiple breath washout. Eur Respir J 2017; 50: 1700433 https://doi.org/10.1183/13993003.00433-2017
[4] Stanfoord et al, Chest 2004; 125:150-155

The enrolment was limited to subjects with LCI $_{2.5}$ ≥7.5 at the Screening Visit, reflective of uneven ventilation and small airways disease. Patients could have a normal spirometry at baseline, which is representative for the proposed target population.

Patients with a history of any illness or condition that could confound study results or pose an additional safety risk were excluded, which is agreed considering the experimental nature of the study.

Statistical considerations

Included number of patients

The study included more patients than was needed to show a statistically significant difference for the primary endpoint. The inclusion of more patients was justified to maintain the blind and to extend the indication to patients with a F/RF mutation.

Statistical analyses

The primary and secondary outcome measures were conducted according MMRM analyses that assume that patients who do not provide data at week 8 (n=5 for $LCI_{2.5}$, n = 6 for sweat chloride), continue to benefit from treatment. As a result, the treatment effect might be overestimated. At the request of the CHMP, an additional sensitivity analysis using a more conservative approach, i.e. using MMRM analyses with placebo mean imputation was submitted**.**

Efficacy data and additional analyses

Baseline and disease characteristics

The pivotal study 115 did include 67 CF patients aged 6-11 years homozygote for F508/F508 (n=52) and F508/RF (n=15). The mean (SD) age of the included patient population was 8.6 years. Slightly more females (55.2%) were included. The mean (SD) -0.26 (0.78) BMI z-score was below the normal value . Patients had evidence of uneven ventilation due to small airways disease at screening mean (SD) $LCI_{2.5}$ 9.54 U (1.97) but had a normal spirometry mean (SD) ppFEV1 87.1% (12.2).

A total of 54 patients were randomised to TEZ/IVA (42 F508/F508 and 12 F508/RF), and 10 patients to placebo (F508/F508) and 3 patients (F508/RF) to ivacaftor.

Although the included numbers are small, the patient demographics appeared to be balanced for age, weight, height, $LCI_{2.5}$ and ppFEV1. The overall disease and baseline characteristics appear to be representative for the proposed target population.

- Weight distribution

The proposed posology is weight based and has currently a different cut-off compared to the study. As the consequence, the newly proposed posology will affect the patient with a body weight ≥30 kg and <40 kg. A total of 28 (42%) of the included patients have a body weight ≥30 kg and <40 kg and were underdosed according to the currently proposed posology. As such, the included population will provide limited direct evidence for the proposed posology and results need to be extrapolated.

Results:

Primary efficacy analyses: LCI 2.5

Overall TEZ/IVA population treated population

The primary efficacy endpoint was the absolute change from baseline in LCI $_{2.5}$ from baseline through week 8 for TEZ/IVA. Note that an improvement in ventilation inhomogeneity measured by $LCI_{2.5}$ is shown by a numerical decrease from baseline.

The primary endpoint was met in demonstrating a statistically significant within treatment difference of LCI2.5 of -0.51 U (95% CI: -0.74 to -0.29; P <0.0001). The upper bound of the 95% CI (-0.29) was below the pre-specified maximum placebo effect of -0.10.

Additional sensitivity analyses using the placebo mean imputation showed comparable effects for the overall population.

F508/F508 and F508/RF – TEZ/IVA treated patients
Both the included subgroup of patients with F508/F508 and F508/RF showed both improvements from baseline. The effect was larger in the subgroup F508/RF compared with the homozygote group: summary statistics LS mean SD -0.92 U (1.08) vs -0.39 U (0.91).

The additional sensitivity analyses using mean placebo mean imputation showed that in both subgroups, the point estimate exceeded the predefined -0.10 Units. The observed efficacy was larger for the F/RF (-1.07 U; 95% CI -1.49, -0.64) group compared to F/F (-0.32 U; 95%CI -0.56, -0.07). For the F/F group, the lower bound of the 95% CI crossed the predefined boundary of -0.07 at the endpoint through week 8, but not at week 8, thus exceeding the pre-specified maximum placebo effect of -0.10.
Though, the results might be regarded as relevant. The predefined margin for placebo was a conservative estimate and the observed improvements in lung function were supported with a relevant improvement in the sweat chloride, an effect that was comparable as observed in adults. In adults, the observed improvement in sweat chloride resulted in a clinically relevant improvement in lung function supporting the clinical benefit in the paediatric population.

Supportive study 113

The supportive study 113 shows a small initial deterioration in $LCI_{2.5}$, but at the end of treatment, the $LCI_{2.5}$ is almost returned to the baseline value. CF is a progressive disease, and a deterioration compared with baseline would have been expected. As no deterioration is seen compared to baseline, these results suggest that the improvement is maintained over time. However, no strong conclusion can be made by the lack of placebo comparison and the small number of included patients.

Secondary outcome measures

Sweat chloride

The primary efficacy outcome in study 115 was supported with statistically significant within treatment improvements in sweat chloride and ppFEV1 for patients treated with TEZ/IVA.

The observed within treatment improvement in the pharmacodynamic parameter sweat chloride was comparable to the one observed in the adult population i.e. LS mean (SD) -12.3 (1.5) mmol/L and -9.9 (0.5) mmol/L in children and adults, respectively. The study showed within treatment improvements in the sweat chloride transport for both subgroups F508/F508 and F508/RF in line with the results observed in adults.

This observed effect in the sweat chloride shows that TEZ/IVA modulated the *CFTR* function in the paediatric population to the same extent as in adults. It provides the bridge to the adult data to extrapolate the efficacy and safety obtained in adults to paediatrics and supports the effect of the partial extrapolation.

The reduction in sweat chloride is consistent with at least partial restoration of the *CFTR* dysfunction and with the combined corrector/potentiator action of TEZ/IVA. As expected, no improvement in sweat chloride was observed in the placebo group (mean (SD) change at week 8: -1.0 (12.3) mmol/L.

Other outcome measures

ppFEV1 and CFQ-R

The ppFEV1 showed a small, but statistically improvement with baseline through week 8, supporting the improvements in the LCI 2.5. The observed improvement in the ppFEV1 in this paediatric population has a smaller effect size is smaller (LS mean (SE): 2.8 (0.9%), p=0.0024), than observed in the adult population (LS mean (SE): 3.4 (0.3) %). This smaller effect size is not an unexpected finding, as in children the lung function is often preserved, leaving less room for improvement. Though, the observed improvement exceeds the annual rate of decline in both F/RF subjects (-0.80 percentage points) and F/F subjects (-1.32 percentage points) 6 to 12 years of age, supporting the efficacy of TEZ/IVA in this population.

Study 113 showed a small mean (SD) improvement from baseline in ppFEV1 through Week 24, which may support the finding that the treatment effects in lung function are maintained over time.

The CFQ-R showed a numerical improvement from baseline. Unlike adults, no statistically significant difference was observed.

Growth outcome parameters

During treatment Weight, z-score, Height z-score and BMI z-score remained stable, without improvement. An extra-pulmonary effect in weight, the height of BMI is therefore not established.

Cross study comparison with LUM/IVA

Symkevi is proposed for the homozygous F/F population. This population overlaps with the target population of lumacaftor/ivacaftor. Therefore, a cross-study comparison was made with the pivotal study VX14-809-109, the study leading to the approval of lumacaftor/ivacator.

Although conclusions from cross-study comparisons have undoubted limitations, the comparisons show that the observed improvement in LCI2.5 compared to placebo is smaller with Symkevi (LS mean difference -0.71 U; 95% CI -1.28, -0.13) than with Orkambi (-1.07 U; 95% CI -1.42, -0.71). Also, a smaller difference in the sweat chloride is observed with Symkevi (LS mean difference -10.7 mmol/L; 95%CI -18.5, -2.9) vs Orkambi (-25.6 mmol/L; 95% CI -28.6, -22.5). These cross-study comparisons suggest that Orkambi might be of more value in the treatment of paediatric CF homozygous patients than Symkevi. However, head to head comparisons are missing to allow firm conclusions.

Symkevi fulfils an unmet medical need for F/F patients who cannot tolerate Orkambi due to respiratory adverse events or who cannot take it due to drug-drug interactions. However, once the extension of the indication is approved, the use will likely not be limited to these patients. Therefore, the CHMP considered that the results of the F/F subgroup should be mentioned in the SmPC in order to provide careful consideration of the potential benefit/risk ratio on an individual basis in comparison with Orkambi SmPC.

2.5.4. Conclusions on clinical efficacy

The current application is based on partial extrapolation. The pivotal study 115 was a parallel designed study but effectively a single-arm trial investigating the within treatment improvement of TEZ/IVA in CF patients harbouring an F/F mutation or a certain F/RF mutation. The study met its primary endpoint by showing a clinically relevant improvement in the LCI2.5 from baseline through week 8. Also, a relevant improvement in ppFEV1 was shown. These improvements were supported with an increase in sweat chloride transport, an improvement in line with adult data. The paediatric data show that TEZ/IVA modulates the *CFTR* function, which leads to improvements in lung function. The observed

lung functions improvements in paediatrics are supported with data obtained in the adult population. Thus, the trial provided the evidence to support the partial extrapolation from the adult efficacy data to the paediatric population.

The study was conducted with a lower posology in patients weighing 30-40 kg than the currently proposed posology. The proposed adapted higher posology will affect about 40% of the EU population. Additional PD/PK modelling showed that new posology increases sweat chloride transport, further supporting the efficacy for the proposed posology.

However, cross-study comparisons raised the concern that the reported efficacy measured by the LCI and sweat chloride might be somewhat lower than observed with lumacaftor/ivacaftor. Therefore, the results of the subgroups should be reported in the SmPC, to provide a careful consideration of the benefit-risk ratio on an individual basis in comparison with Orkambi.

2.6. Clinical safety

Introduction

The patients that entered study 113B and 115 are the main datasets to support the safety of the applied application. Additional long-term safety was provided by the **interim analyses for safety** (data cut-off date 18 December 2019) of VX17-661-116 when all patients had completed the week 48 visit of part A of the study.

Study 116 is a phase 3, open-label, rollover study to evaluate the safety of long-term treatment with Tezacaftor in combination with ivacaftor in patients with CF aged 6 years and older homozygous or heterozygous for the *F508DelCFTR* mutation. The study enrolled patients who completed the study VX15-661-113B and VX16-661-115. Patients who permanently stopped treatment because of elevated transaminases were not allowed to participate. Those who temporarily stopped treatment due to elevated transaminase could participate after 4-week negative rechallenge.

The study included a total of 130 patients, while up to 133 patients could be included.

The study consisted of two parts, part A and part B. In part A, the patients received treatment for up to 96 weeks according to the same posology as applied in the clinical studies.
After completing part, A, patients could be entered in part B. Part B was added following an amendment (data 8 Nov 2019) to collect additional long-term safety data according to the new proposed posology using the 30 Kg weight cut off.

The interim safety analyses of study 116 was conducted before the implementation of the amendment. Therefore, the currently provided safety data will not provide clinical safety data according to the currently applied posology.

Safety data set

The main data safety database set for TEZ/IVA treated children age 6-11yrs is defined by the parent studies, i.e. study 113B (n=70) and study 115 (n=54) and consists of 124 patients. Additional long-term safety data is provided n=130 patient that rolled over to the long-term safety study 116. The additional cumulative exposure set combined the exposure of TEZ/IVA received in the parent studies 113B or 115 and study 116 (n=129 subjects with >48 weeks cumulative TEZ/IVA exposure).

The comparison with placebo is limited to the 10 F/F patients that were treated for 8 weeks during the study 115.

Patient exposure

Table 45 summarizes the exposure to TEZ/IVA in the parent studies (i.e. study 113B and 115), Study 116 and cumulatively TEZ/IVA exposure across the parent studies and Study 116.

The median exposure in the parent studies was 23.3 weeks (n=125), 68.1 weeks in study 116 (n=130) and 75.9 weeks in the cumulative exposure safety set (n=137).

In the cumulative analyses a total of 129 patients had an exposure > 48 weeks, and 37 had an exposure > 96 weeks (Table 45).

Table 40 Summary of Exposure (TEZ/IVA Safety Set in Parent Studies; 116 Safety Set in Study 116; Cumulative TEZ/IVA Safety Set in Cumulative Group)

	TEZ/IVA in Parent Studies N = 124	Study 116 N = 130	Cumulative TEZ/IVA N = 137
Total exposure (patient years)	39.8	162.7	202.6
Exposure duration (weeks)			
N	124	130	137
Mean (SD)	16.8 (8.1)	65.3 (10.9)	77.2 (23.0)
Median	23.3	68.1	75.9
Min, Max	1, 26	24, 86	1, 110
Exposure duration category (weeks), n (%)			
> 0 and ≤ 4	2 (1.6)	0	2 (1.5)
> 4 and ≤ 8	35 (28.2)	0	0
> 8 and ≤ 12	18 (14.5)	0	0
> 12 and ≤ 24	41 (33.1)	1 (0.8)	4 (2.9)
> 24 and ≤ 36	28 (22.6)	0	1 (0.7)
> 36 and ≤ 48	0	0	1 (0.7)
> 48 and ≤ 72	0	93 (71.5)	55 (40.1)
> 72 and ≤ 96	0	36 (27.7)	37 (27.0)
> 96 and ≤ 120	0	0	37 (27.0)
> 120	0	0	0

Source: Ad Hoc Table 14.1.2
IVA: ivacaftor; n: size of subsample; N: total sample size; TEZ: tezacaftor
Notes: Analyses represent data as of the data cut of 18 December 2019. The duration of study drug exposure in weeks is calculated as (the last dose date in the corresponding study period – the first dose date in the corresponding study period + 1)/7, regardless of any study drug interruption.

Adverse events

On overview of the adverse events of the main safety data sets is provided in Table 46. For comparison, also the placebo arm of study 115 is included.

The overall incidence of AE or treatment related AE's was generally comparable. However, the incidence of SAE'S was higher in study 116 (n=27; 20.8%) and the cumulative exposure (n=31; 22.6%) compared to the parent studies 115 and 113b (n=6; 4.8%) (Table 46).

Table 41 Safety data set of the placebo group of study 115, the parent studies study 113B, and study 115, 116 and cumulative Tez/IVA group

	115 Placebo n=10	Parent studies N=124	116 TEZ/IVA N=130	cumulative Tez/IVA N=137
Number of AEs (total)	19	441	1045	1486
Subjects with any AEs	8 (80.0)	106 (85.5)	129 (99.2)	134 (97.8)

	115 Placebo n=10	Parent studies N=124	116 TEZ/IVA N=130	cumulative Tez/IVA N=137
AE by relationship				
Not related	1 (10.0)	42 (33.9)	45 (34.6)	30 (21.9)
Unlikely related	6 (60.0)	35 (28.2)	53(40.8)	55 (40.1)
Possibly related	1 (10.0)	28 (22.6)	28 (21.5)	45 (32.8)
Related	0	1 (0.8)	3 (2.3)	4 (2.9)
AE by severity				
Mild	4 (40.0)	63 (50.8)	50 (38.5)	47 (34.3)
Moderate	4 (40.0)	38 (30.6)	60 (46.2)	65 (47.4)
Severe	0	5 (4.0)	19 (14.6)	22 (16.1)
Life-threatening	0	0	0	0
Subjects with AE leading to treatment discontinuation	0	1 (0.8)	2 (1.5)	3 (2.2)
Subjects with AE leading to treatment interruption	0	4 (3.2)	8 (6.2)	13 (9.5)
Subjects with Grade 3 or Grade 4	0	5 (4.0)	19 (14.6)	22 (16.1)
Subjects with SAEs	0	6 (4.8)	27 (20.8)	31 (22.6)
Related serious AE	0	0	2 (1.5)	2 (1.5)
Subjects with AE leading to death	0	0	0	0

AE: adverse event; IVA: ivacaftor; N: total sample size; n: size of subsample; SAE: serious adverse event; TEZ: *tezacaftor ; table made by assessor, source table 3 and 4 SoS.*
Notes: For number of events summaries, a subject with multiple events within a category was counted multiple times in that category. For summaries of number and percentage of subjects with events, a subject with multiple events within a category was counted only once in that category.
a Related = study drug regimen-related, which includes related, possibly related, and missing categories.
b All the AEs were Grade 3 and no subjects had Grade 4 AEs.
Analyse represent data as of the data cut of 18 Dec 2019. When summarizing the number of events, a subject with multiple event within a category is counted number lies in that category. When summarizing number and percentage of subjects, a subject with multiple events within a category is counted only once in that category (the event of worse severity or greater relatedness is counted, if applicable

Common treatment-emergent AE's

TEAEs were defined as any AE that increased in severity or that developed upon or after the initial dosing of study drug to 28 days after the last dose of study drug (referred to as AEs), regardless of relationship. Most patients experienced at least one TEAE, in all safety data sets.

Table 47 presents TEAEs with an incidence of ≥5% in any group by Preferred Term (PT) and SOC cross the different trials and Soc.

- Parent studies 113 and 115

The most frequently reported TEAEs by (PT) were cough (26.6%), infective pulmonary exacerbation of CF (15.3%), and pyrexia (12.1%).

- Long-term safety study 116

3The most frequently reported TEAS (PT) were cough (52.6%), infective pulmonary exacerbation of CF (40.0%), and upper respiratory tract infection (21.5%).

- Cumulative safety data set

The most frequently reported TEAS (PT) were cough (58.4%), infective pulmonary exacerbation of CF (43.8%), and pyrexia (24.1%).

Table 42 AEs With an Incidence of ≥5% by SOC and PT (TEZ/IVA Safety Set in Parent Studies; 116 Safety Set in Study 116; Cumulative TEZ/IVA Safety Set in Cumulative Group)

	Parent Studies TEZ/IVA N = 124		Study 116 N = 130		Cumulative TEZ/IVA N = 137	
System Organ Class Preferred Term	n (%)	Events/100PY	n (%)	Events/100PY	n (%)	Events/100PY
Total duration of TE period in 100 PY	--	0.41	--	1.63	--	2.03
Any TEAEs	106 (85.5)	1088.20	129 (99.2)	641.35	134 (97.8)	731.10
Infections and infestations	57 (46.0)	236.89	110 (84.6)	208.05	114 (83.2)	214.51
Infective pulmonary exacerbation of cystic fibrosis	19 (15.3)	61.69	52 (40.0)	55.85	60 (43.8)	57.07
Upper respiratory tract infection	8 (6.5)	27.14	28 (21.5)	26.39	31 (22.6)	26.57
Nasopharyngitis	11 (8.9)	29.61	23 (17.7)	22.71	28 (20.4)	24.60
Viral upper respiratory tract infection	6 (4.8)	17.27	9 (6.9)	10.43	13 (9.5)	11.81
Ear infection	5 (4.0)	12.34	6 (4.6)	3.68	11 (8.0)	5.41
Gastroenteritis	4 (3.2)	12.34	9 (6.9)	7.36	11 (8.0)	8.36
Influenza	5 (4.0)	12.34	7 (5.4)	4.30	11 (8.0)	5.90
Rhinitis	0	0.00	11 (8.5)	8.59	11 (8.0)	6.89
Otitis media	4 (3.2)	9.87	7 (5.4)	6.75	10 (7.3)	7.38
Pharyngitis streptococcal	3 (2.4)	7.40	8 (6.2)	4.91	10 (7.3)	5.41
Sinusitis	2 (1.6)	7.40	7 (5.4)	5.52	7 (5.1)	5.90
Respiratory, thoracic and mediastinal disorders	59 (47.6)	303.51	95 (73.1)	167.55	106 (77.4)	194.34
Cough	33 (26.6)	113.51	68 (52.3)	72.42	80 (58.4)	80.69
Nasal congestion	13 (10.5)	37.01	21 (16.2)	20.87	29 (21.2)	23.62
Oropharyngeal pain	8 (6.5)	19.74	20 (15.4)	16.57	26 (19.0)	17.22
Productive cough	13 (10.5)	39.48	17 (13.1)	12.89	24 (17.5)	18.20
Rhinorrhoea	10 (8.1)	27.14	11 (8.5)	7.98	18 (13.1)	11.81
Gastrointestinal disorders	38 (30.6)	152.99	52 (40.0)	58.92	78 (56.9)	77.73
Abdominal pain	13 (10.5)	34.55	18 (13.8)	16.57	29 (21.2)	20.17
Vomiting	11 (8.9)	29.61	15 (11.5)	11.66	25 (18.2)	15.25
Constipation	4 (3.2)	9.87	9 (6.9)	6.75	13 (9.5)	7.38
Abdominal pain upper	6 (4.8)	14.81	6 (4.6)	5.52	12 (8.8)	7.38
Diarrhoea	5 (4.0)	12.34	6 (4.6)	4.30	11 (8.0)	5.90
Nausea	4 (3.2)	12.34	7 (5.4)	4.91	11 (8.0)	6.40
Investigations	24 (19.4)	123.38	43 (33.1)	64.44	52 (38.0)	76.26
Alanine aminotransferase increased	7 (5.6)	19.74	9 (6.9)	6.75	14 (10.2)	9.35
Bacterial test positive	4 (3.2)	17.27	11 (8.5)	7.36	13 (9.5)	9.35
Pseudomonas test positive	1 (0.8)	2.47	10 (7.7)	7.36	11 (8.0)	6.40
Aspartate aminotransferase increased	2 (1.6)	4.94	9 (6.9)	6.14	10 (7.3)	5.90
Forced expiratory volume decreased	3 (2.4)	7.40	4 (3.1)	3.07	7 (5.1)	3.94
General disorders and administration site conditions	20 (16.1)	61.69	36 (27.7)	34.98	48 (35.0)	40.34
Pyrexia	15 (12.1)	39.48	24 (18.5)	23.94	33 (24.1)	27.06
Fatigue	5 (4.0)	12.34	6 (4.6)	3.68	10 (7.3)	5.41
Nervous system disorders	17 (13.7)	59.22	23 (17.7)	23.94	33 (24.1)	31.00
Headache	14 (11.3)	51.82	18 (13.8)	18.41	26 (19.0)	25.09
Injury, poisoning and procedural complications	11 (8.9)	39.48	22 (16.9)	17.80	29 (21.2)	22.14
Skin and subcutaneous tissue disorders	12 (9.7)	37.01	17 (13.1)	16.57	25 (18.2)	20.66
Rash	4 (3.2)	9.87	6 (4.6)	4.30	9 (6.6)	5.41
Musculoskeletal and connective tissue disorders	4 (3.2)	17.27	13 (10.0)	11.05	16 (11.7)	12.30
Ear and labyrinth disorders	5 (4.0)	14.81	10 (7.7)	6.14	14 (10.2)	7.87
Ear pain	2 (1.6)	4.94	7 (5.4)	4.30	9 (6.6)	4.43
Eye disorders	4 (3.2)	9.87	9 (6.9)	5.52	13 (9.5)	6.40
Psychiatric disorders	4 (3.2)	9.87	9 (6.9)	7.36	12 (8.8)	7.87
Metabolism and nutrition disorders	4 (3.2)	14.81	5 (3.8)	3.68	9 (6.6)	5.90
Immune system disorders	1 (0.8)	2.47	6 (4.6)	4.30	7 (5.1)	3.94

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; PY: patient-year TE: treatment-emergent; TEZ: tezacaftor

Notes: Analyses represent data as of the data cut off 18 December 2019. MedDRA Version 22.1 was used. When summarizing the number of events, a subject with multiple events within a category is counted multiple times in that category. When summarizing number and percentage of subjects, a subject with multiple events within a category is counted only once in that category. The table was sorted in descending order of frequency by PT in the cumulative TEZ/IVA group.

Possibly related AEs

On overview of the related TEAE is provided by Table 48.

- Parent studies 113 and 115

In the parent studies, a total of n=29 (23.4%) reported a related TEAE. The most commonly reported TEAE's by preferred term were alanine aminotransferase increased (ALT) (n=4; 3.2%), headache (n=4; 3.2%), and infective pulmonary exacerbation of CF (n=3, 2.4%).

- Long term safety study 116

In the long-term safety study, the most frequently reported related TEAE by preferred term was aspartate amino transferase (AST) increased (n=6; 4.6%), ALT increased (n=5; 3.8%) and abdominal pain (n=5; 3.8%)

- Cumulative safety group

In the cumulative treatment group, the most frequently related TEAE event was ALT increased (n=9, 6.6%), AST increased (n=7, 5.1%) and headache (n=8, 5.8%).

For comparison, a total of n=1 (10%) of the placebo-treated patients in study 115 reported a possible related TEA's the reported AE were headache, rash and sputum increased (table 14.3.1.4 study report)

Table 43 Treatment-related AE's with an incidence ≥5% in the Cumulative Group by SOC and PT (TEZ/IVA Safety Set in Parent Studies; 116 Safety Set in Study 116; Cumulative TEZ/IVA Safety Set in Cumulative Group)

	Parent Studies TEZ/IVA N = 124		Study 116 N = 130		Cumulative TEZ/IVA N = 137	
System Organ Class Preferred Term	n (%)	Events/100PY	n (%)	Events/100PY	n (%)	Events/100PY
Total duration of TE period in 100 PY	--	0.41	--	1.63	--	2.03
Any related TEAEs	29 (23.4)	130.78	31 (23.8)	46.03	49 (35.8)	62.48
Gastrointestinal disorders	12 (9.7)	32.08	9 (6.9)	7.98	19 (13.9)	12.79
Abdominal pain	3 (2.4)	7.40	5 (3.8)	3.07	7 (5.1)	3.94
Investigations	7 (5.6)	34.55	12 (9.2)	17.18	19 (13.9)	20.66
Alanine aminotransferase increased	4 (3.2)	12.34	5 (3.8)	4.30	9 (6.6)	5.90
Aspartate aminotransferase increased	1 (0.8)	2.47	6 (4.6)	3.68	7 (5.1)	3.44
Respiratory, thoracic and mediastinal disorders	8 (6.5)	27.14	4 (3.1)	4.30	11 (8.0)	8.36
Nervous system disorders	5 (4.0)	14.81	6 (4.6)	5.52	10 (7.3)	7.38
Headache	4 (3.2)	12.34	5 (3.8)	4.91	8 (5.8)	6.40
Infections and infestations	3 (2.4)	7.40	5 (3.8)	3.07	7 (5.1)	3.94

Serious adverse events and deaths

- Parent studies 113 and 115

In the parent studies, a total of n=6 (4.8%) subjects had SAEs, but none of the SAEs were related to study drug.

The Reported Serious AE's were Infective pulmonary exacerbations of CF (n=2, 1.6%), breath odour (n=1, 0.8%), constipation (n=1, 0.8%), failure to thrive (n=1, 0.8%) sinusitis (n=1, 0.8%) and snoring (n=1, 0.8%).

- Long term safety study 116

In study 116, a total of n=27 (20.8%) had a SAE. SAE's that occurred in ≥ 2 subjects were infective PX of CF (n=15), abdominal pain (n= 2), and bacterial test positive (n=2) (Table 49).

A total of N=2 SAE were considered related or possibly related to TEZ/IVA i.e. abdominal pain with increased AST, ALT, LDH and Y-GT and infective Px of CF.

No SAE led to treatment discontinuation. A total of N=5 led to treatment interruption. These SAE resolved, and patients resumed dosing with TEZ/IVA.

The exposure-adjusted event rate for SAEs was higher in Study 116 (33.76 events per 100PY) than in the parent studies TEZ/IVA groups (17.27 events per 100PY).

Table 44 Serious adverse events with Incidence n≥2 in Any Group by SOC and PT (TEZ/IVA Safety Set in Parent Studies; 116 Safety Set in Study 116; Cumulative TEZ/IVA Safety Set in Cumulative Group)

	Parent Studies TEZ/IVA N = 124		Study 116 N = 130		Cumulative TEZ/IVA N = 137	
System Organ Class Preferred Term	n (%)	Events/100PY	n (%)	Events/100PY	n (%)	Events/100PY
Total duration of TE period in 100 PY	--	0.41	--	1.63	--	2.03
Any serious TEAEs	6 (4.8)	17.27	27 (20.8)	33.76	31 (22.6)	30.50
Infections and infestations	3 (2.4)	7.40	20 (15.4)	17.18	21 (15.3)	15.25
Infective pulmonary exacerbation of cystic fibrosis	2 (1.6)	4.94	15 (11.5)	12.27	16 (11.7)	10.82
Sinusitis	1 (0.8)	2.47	1 (0.8)	0.61	2 (1.5)	0.98
Gastrointestinal disorders	2 (1.6)	4.94	5 (3.8)	4.30	7 (5.1)	4.43
Abdominal pain	0	0.00	2 (1.5)	1.23	2 (1.5)	0.98
Constipation	1 (0.8)	2.47	1 (0.8)	0.61	2 (1.5)	0.98
Investigations	0	0.00	6 (4.6)	6.14	6 (4.4)	4.92
Bacterial test positive	0	0.00	2 (1.5)	1.84	2 (1.5)	1.48
Respiratory, thoracic and mediastinal disorders	1 (0.8)	2.47	4 (3.1)	3.07	5 (3.6)	2.95

Deaths

No deaths were reported in any of the studies.

Laboratory findings

During the study, liver function tests, lipid panels, vitamin levels, chemistry, haematology and coagulation were measured at regular intervals.

- **Liver function tests**

The mean values for LFT parameters were generally within normal ranges at all visits during the Treatment Period during study 113 and 115.

- Parent studies 113 and 115

A total of n=7 patients had elevated transaminases in the parent studies. All the AEs associated with elevated transaminases were mild in severity, and none of them were serious or led to discontinuation of study drug.

Among the 7 subjects with TEAEs of elevated transaminases, the median (range) time-to-onset of the first AESI was 57 (1 to 120) days

For comparison, one patient in the placebo group of study 115 had an AE associated with elevated transaminase.

- Long term safety Study 116

In study 116, a total of n=10 (7.7%) had at least 1 elevated transaminase event. In 3 cases they were of severe intensity. In one patient, it resulted in a serious related adverse event. In n=1 case led to a treatment interruption and n=2 cases this led to a treatment discontinuation (1.5%) (table 50).

The two subjects that discontinued treatment had elevated transaminase before dosing in the parent study. Both subjects experienced nonserious transaminase elevation that led to discontinuation of study treatment. They did not receive treatments for these events.

Among the 10 subjects with AESIs of elevated transaminases, the median (range) time-to-onset of the first AESI was 209.5 (16 to 420) days.

The exposure-adjusted event rate for elevated transaminase AEs was lower in Study 116 than in the parent studies TEZ/IVA groups (12.89 versus 24.68 events per 100PY).

Table 45 Summary of Treatment-Emergent Elevated Transaminases Events (TEZ/IVA Safety Set in Parent Studies; 116 Safety Set in Study 116; Cumulative TEZ/IVA Safety Set in Cumulative Group)

	Parent Studies TEZ/IVA N = 124		Study 116 N = 130		Cumulative TEZ/IVA N = 137	
	n (%)	Events/100PY	n (%)	Events/100PY	n (%)	Events/100PY
Total duration of TE period in 100 PY	--	0.41	--	1.63	--	2.03
Any events, n (%)	7 (5.6)	24.68	10 (7.7)	12.89	14 (10.2)	15.25
Alanine aminotransferase abnormal	0	0.00	0	0.00	0	0.00
Alanine aminotransferase increased	7 (5.6)	19.74	9 (6.9)	6.75	14 (10.2)	9.35
Aspartate aminotransferase abnormal	0	0.00	0	0.00	0	0.00
Aspartate aminotransferase increased	2 (1.6)	4.94	9 (6.9)	6.14	10 (7.3)	5.90
Transaminases abnormal	0	0.00	0	0.00	0	0.00
Transaminases increased	0	0.00	0	0.00	0	0.00
Liver function test abnormal	0	0.00	0	0.00	0	0.00
Liver function test increased	0	0.00	0	0.00	0	0.00
Hypertransaminasaemia	0	0.00	0	0.00	0	0.00
Hepatic enzyme increased	0	0.00	0	0.00	0	0.00
Hepatic enzyme abnormal	0	0.00	0	0.00	0	0.00
Any events by severity, n (%)						
Mild	7 (5.6)	24.68	7 (5.4)	10.43	10 (7.3)	12.79
Moderate	0	0.00	0	0.00	1 (0.7)	0.49
Severe	0	0.00	3 (2.3)	2.45	3 (2.2)	1.97
Events leading to treatment discontinuation, n (%)	0	0.00	2 (1.5)	1.23	2 (1.5)	1.48
Events leading to treatment interruption, n (%)	1 (0.8)	4.94	1 (0.8)	0.61	2 (1.5)	1.48
Serious events, n (%)	0	0.00	1 (0.8)	1.23	1 (0.7)	0.98
Related serious events, n (%)	0	0.00	1 (0.8)	1.23	1 (0.7)	0.98
Events leading to death, n (%)	0	0.00	0	0.00	0	0.00

Table 51 provides the incidences of the subjects with maximum on treatment elevation (ALT or AST) above thresholds >1 ×, >3 ×, >5 ×, and >8 × ULN.
The incidence of ALT/AST > 1 to ≤3ULN was comparable between the parent studies (58.1%) and study 116 (52.3%) and cumulative period (59.9%)
In study 116, the incidence of ALT or AST >3 × ULN is n=12 (9.2%) compared with n=10 in the parent studies (8.1%).

Table 46 Threshold Analysis of LFT Chemistry Parameters (TEZ/IVA Safety Set in Parent Studies; 116 Safety Set in Study 116; Cumulative TEZ/IVA Safety Set in Cumulative Group)

Parameter Threshold Analysis Criteria n/N1 (%)	Parent Studies TEZ/IVA N = 124	Study 116 N = 130	Cumulative TEZ/IVA N = 137
ALT or AST (U/L)			
>1 to ≤3 x ULN	72/124 (58.1)	68/130 (52.3)	82/137 (59.9)
>3 to ≤5 x ULN	7/124 (5.6)	6/130 (4.6)	11/137 (8.0)
>5 to ≤8 x ULN	2/124 (1.6)	5/130 (3.8)	6/137 (4.4)
>8 to ≤20 x ULN	1/124 (0.8)	1/130 (0.8)	2/137 (1.5)
>20 x ULN	0/124	0/130	0/137
Bilirubin (umol/L)			
>1 to ≤1.5 x ULN	6/124 (4.8)	3/130 (2.3)	4/137 (2.9)
>1.5 to ≤2 x ULN	0/124	4/130 (3.1)	4/137 (2.9)
>2 to ≤3 x ULN	0/124	0/130	0/137
>3 to ≤10 x ULN	0/124	0/130	0/137
>10 x ULN	0/124	0/130	0/137

Lipid panels/ vitamin level/ other serum chemistry parameters.

During the study 113B, 115 and 116, serum lipid levels, vitamin levels, serum chemistry and haematology parameters were monitored. No clinically meaningful trends were observed.

Ophthalmologic Evaluations

In the parent studies, no cases of cataract possible related to study medication were reported.

In the long-term study 116, a total of 2 patients experienced cataracts, possibly related with study medication.

Electrocardiogram results

In the parent studies (Study 113B and Study 115), no male subjects had QTcF >450 msec, and no female subjects had QTcF >470 msec. No subject had a maximum QTcF change >60 msec. In Study 116, 2 subjects met the criterion of QTcF >450 msec for a male, or QTcF >470 for a female.

Safety in special populations

The proposed posology is not evaluated in the current study. Weight cutoff-based dosing was used in Studies 113 and 115 with a weight cutoff **of 40 kg**. Upon review of the exposure data from these studies, an integrated analysis of data was performed. Following review of available data, a **30 kg** weight cut-off was proposed for CF patients 6 through 11 years of age in order to have the best matched TEZ and IVA exposures to the exposures in subjects 12 years and older.

For subjects 6 through 11 years of age who weighed <40 kg and received low dose TEZ 50 mg qd/IVA 75 mg q12h, TEZ parent and IVA parent exposures fell within the lower range of observed exposures of subjects 12 years and older. M1-TEZ exposures were similar to those of subjects 12 years and older.

Based on additional simulations, using a **30 kg** weight cutoff, the majority of PK exposures are predicted to be within the adult reference range (5^{th} to 95^{th} percentiles) for TEZ, M1-TEZ, and IVA, with the median TEZ parent and IVA parent exposures more similar to the median exposures seen in subjects 12 years of age and older than upon applying a 40-kg cut-off.

To further support the proposed dosing regimen, the following safety data were also reviewed:

1. Bodyweight: Safety data from **patients 12 to <18 years old who weighed ≤40 kg** in Phase 3 studies of TEZ/IVA and received the approved dose of TEZ/IVA (TEZ 100 mg qd/IVA 150 mg q12h), which is the same dose patients ≥30 kg will receive with the proposed dosing regimen.
2. Exposure: Safety data for subjects from Study 106 and Studies 113B and 115 who had M1-TEZ exposure ≥95th percentile of M1-TEZ exposures in Study 106 (Section 4.2).

Bodyweight of patients 12 to <18 years old who weighed ≤40 kg

The safety data of the placebo-controlled integrated summary of safety (Studies 106, 107 and 108) were pooled for this analysis. A total of n= 199 patients aged 12 to < 18 years were included.
The post hoc analysis included a total of n=30 patients with a body weight < 40 Kg: A total of N=13 placebo and N=17 tezacaftor (Table 52); data from the same patients in the open-label extension study (study 110) through 96 weeks were also evaluated.

A total of N=30 patients 12 to <18 years old weighed ≤40 kg and received TEZ 100 mg qd/IVA 150 mg q12h. TEZ/IVA was generally safe and well-tolerated in these subjects, and the safety outcomes were consistent with the established safety profile of TEZ/IVA. No specific safety concerns were identified.

Table 47 Overview of Treatment-Emergent Adverse Events by Weight Group (⩽40kg or >40kg) Placebo-Controlled Safety Set

	Baseline weight ≤40		Baseline weight > 40	
	Placebo n=13 n (%)	TEZ/IVA n=17 n (%)	Placebo n=88 n (%)	TEZ/IVA n=81 n (%)
Number of TEAEs (Total)	108	64	380	314
Subjects with any TEAEs	11 (84.6)	16 (94.1)	73 (83.0)	68 (84.0)
Subjects with TEAEs by strongest relationship				
Related	0	0	1 (1.1)	1 (1.2)
Possibly related	4 (30.8)	4 (23.5)	16 (18.2)	14 (17.3)
Unlikely related	1 (7.7)	3 (17.6)	19 (21.6)	12 (14.8)
Not related	6 (46.2)	9 (52.9)	37 (42.0)	41 (50.6)
Subjects with related TEAEs	4 (30.8)	4 (23.5)	17 (19.3)	15 (18.5)
Subjects with TEAEs by maximum severity				
Mild	5 (38.5)	9 (52.9)	35 (39.8)	37 (45.7)
Moderate	4 (30.8)	6 (35.3)	35 (39.8)	26 (32.1)
Severe	2 (15.4)	1 (5.9)	3 (3.4)	5 (6.2)
Life-threatening	0	0	0	0
Missing	0	0	0	0
Subjects with grade 3-4 TEAEs	2 (15.4)	1 (5.9)	3 (3.4)	5 (6.2)
Subjects with serious TEAEs	1 (7.7)	3 (17.6)	17 (19.3)	10 (12.3)
Subjects with related serious TEAEs	0	0	3 (3.4)	2 (2.5)
Subjects with TEAE leading to treatment	0	0	2 (2.3)	2 (2.5)
Subjects with TEAE leading to treatment	1 (7.7)	0	2 (2.3)	2 (2.5)
Subjects with TEAE leading to death	0	0	0	0

MedDRA version 19.1.
- TEAE: Treatment-emergent adverse event.
- When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category.
- An AE with relationship missing is counted as Related.
- Related TEAEs include related, possibly related and missing categories.
- The Placebo-Controlled Safety Set includes all subjects who received at least one dose of TEZ/IVA or Placebo in Studies 106/107/108.
- Only subjects aged 12 to <18 years of age at Screening are included.
- Subjects from Study 108 may receive two periods of treatment due to the cross-over design and therefore may be double counted in two columns.
- Baseline is the most recent measurement prior to first dose of study drug.

Table 48 Overview of Treatment-Emergent Adverse Events in the 96 Weeks of Open-Label Extension Study by Weight Group (⩽40kg or >40kg) Safety Set

	Baseline weight≤40 kg	Baseline weight > 40 kg
	TEZ/IVA N=30 n (%)	TEZ/IVA N=146 n (%)
Number of TEAEs (Total)	265	1508
Subjects with any TEAEs	30 (100.0)	142 (97.3)
Subjects with TEAEs by strongest relationship		
Related	0	2 (1.4)
Possibly related	2 (6.7)	30 (20.5)
Unlikely related	8 (26.7)	36 (24.7)
Not related	20 (66.7)	74 (50.7)
Subjects with related TEAEs	2 (6.7)	32 (21.9)
Subjects with TEAEs by maximum severity		
Mild	13 (43.3)	42 (28.8)
Moderate	17 (56.7)	76 (52.1)
Severe	0	23 (15.8)
Life-threatening	0	1 (0.7)
Missing	0	0
Subjects with grade 3-4 TEAEs	0	24 (16.4)
Subjects with serious TEAEs	10 (33.3)	54 (37.0)
Subjects with related serious TEAEs	1 (3.3)	3 (2.1)
Subjects with TEAE leading to treatment	0	3 (2.1)
Subjects with TEAE leading to treatment	0	11 (7.5)
Subjects with TEAE leading to death	0	0

MedDRA version 22.0.
- TEAE: Treatment-emergent adverse event.
- When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category.
- An AE with relationship missing is counted as Related.
- Related TEAEs include related, possibly related and missing categories.
- The Safety Set includes all subjects who received at least one dose of TEZ/IVA in Study 661-110.
- Only subjects aged 12 to <18 years of age at Screening in Study 106/107/108 are included.
- Baseline is the most recent measurement prior to first dose of study drug in Study 106/107/108
Table made by assessor

Exposure to M1-TEZ ≥ 95% percentile.

With the proposed body weight cut off of 30 kg, M1-TEZ exposures are predicted to be in the higher range of clinical experience in subjects 12 years and older. Therefore, the safety of TEZ/IVA was reviewed for subjects with M1-TEZ exposures ≥95th percentile of M1-TEZexposures in Study 106.

- In Study **106**, there were **10 subjects** with M1-TEZ exposures ≥95th percentile who had AEs.

  Of the 10 subjects, 3 had SAEs (2 subjects with SAEs of infective PEx of CF and 1 subject with an SAE of musculoskeletal chest pain; both assessed not related to study drug), none had Grade 3/4 AEs, or AEs leading to treatment discontinuation or interruption. The AEs profile of these 10 subjects was generally consistent with the overall population of Study 106.

- In Studies 113 and 115, there were **4 subjects** (3 in Study 113B and 1 subject in Study 115) who had M1-TEZ exposures ≥95th percentile of M1-TEZ exposures in Study 106. None of these subjects had SAEs, Grade 3/4 AEs, or AEs leading to treatment discontinuation or interruption. The AEs profile of these 4 subjects was generally consistent with the overall population of Studies 113 and 115.

Time and dose dependency of observed liver function test abnormalities of the N=10 patients in the parent studies

In Study 113B and 115, there were 10 subjects who received TEZ/IVA with ALT or AST elevations >3 × ULN. Post hoc, the elevations in ALT, AST and bilirubin were summarized by TEZ and combined TEZ and M1-TEZ according to the exposure quartiles defined by the adult population.

Among the 10 subjects with ALT or AST elevations > 3 x ULN, a total of n=8 of patients had combined M1-TEZ+TEZ exposure below the median exposure (as defined by the exposure in adults populations), while none of the patients with exposure ≥ 5 x ULN had an exposure > the adult median.

Discontinuation due to AES

- Parent studies 113 and study 115

One patient in study 113B prematurely left the trial because of constipation. The constipation was not likely to be related to treatment.

- Long term safety 116

A total of n=2 (1.5%) of patients had AE that leaded to treatment discontinuation. The patients discontinued treatment because of transaminase elevation, which were considered by the investigator to be possibly related to study drug. Both subjects had elevated transaminase levels prior to dosing in the parent study.

The exposure-adjusted event rate for AEs leading to TEZ/IVA discontinuation was similar between Study 116 (2.45 events per 100PY) and the parent studies (2.47 events per 100PY).

Adverse events leading to interruption of the drug

- Parent studies 113 and 115

In study 113, a total of 4 subjects had AEs that led to treatment interruption. A total of 2 patients had AEs that were considered related or possibly related to study drug (1 subject with an AE of blood creatinine phosphokinase increased and 1 subject with AEs of ALT, AST, ALP, and GGT increased). No related AE that led to treatment interruption was serious. All related AEs that led to interruption resolved without any treatment.

No AE that led to treatment interruption occurred in ≥2 subjects. No treatment interruptions occurred in study 115.

- Long term safety 116

In study 116, 8 (6.2) patients experience AE's that led to treatment interruption. All treatment interruptions occurred by PT in n=1 patient. In one patient, the treatment was interrupted because of ALT increased. No AEs leading to interruption occurred in ≥2 subjects.

The exposure-adjusted event rate for AEs that led to treatment interruption was lower in Study 116 (9.21 events per 100 PY) than in the parent studies (19.74 events per 100PY).

Cumulative safety

In the cumulative safety database, a total of 13 patients (9.5%) interrupted therapy. TEAES that resulted to treatment interruption observed in 2 patients was ALT increased, and blood CK increased. All other AE were mentioned in one patient.

Post-marketing experience

Post-marketing surveillance of 6- through 11-year-old patients taking TEZ/IVA with the proposed posology has been ongoing in the US since approval on 21 June 2019 for patients ≥6 years of age. Over 600 patients 6 through 11 years of age have initiated treatment with TEZ/IVA in the US. The results of post-marketing surveillance are consistent with clinical studies, and no new safety concerns have been identified.

2.6.1. Discussion on clinical safety

The main safety database for TEZ/IVA treated children aged 6-11 years is defined by the parent studies 113B (n=70) and study 115 (n=54) and consists of a total of 124 patients. In the long-term safety 116 a total of 129 subjects are exposed for > 48 weeks while in the cumulative set a total of 37 subjects are exposed for > 96 weeks.

The provided safety sets provide enough patients with a treatment duration of >48 (n=129) to support the application. However, the safety data set has also some limitations i.e. it will not provide clinical data for the applied posology for children weighing 30-40 kg. This affects about 40% of the EU target population. Furthermore, the comparison with placebo is limited to the 10 F/F patients that were treated for 8 weeks during the study 115. The safety data set mainly exists of data collected in an uncontrolled, open label study period which is biased by the longer disease duration.

As no clinical safety data has been provided to support the proposed posology, the safety assessment will be based on the data of the currently provided safety data base, the data obtained in adults, other provided data and additional measurements that can be taken to mitigate the risk.

The provided safety data sets show that the treatments were generally well-tolerated, and the reported adverse events appear to be in line with the adult's safety database. Most of the adverse events were of mild intensity.

The exposure-adjusted event rate for SAEs was higher in Study 116 (33.76 events per 100PY) and cumulative safety set (n=31 (30.50 event/100 PY) than in the parent studies TEZ/IVA groups (17.27 events per 100PY). According to the applicant, this might be adjusted to the unusually low rate of SAE in the parent studies when comparing the data with the reported exposure adjusted SAE rate of 42.77 event per 100 PY reported in the placebo group in study 809-109 that led to the approval of lumacaftor/ivacaftor in the same age group. The observed exposure adjusted event rate of study 116 (33.76 event/100 PY) remains below this rate (42.77 events/100 PY).

The number of treatments related adverse events appeared to be consistent for the parent studies and the long-term safety study (23.8%). Additionally, the treatment appeared to be well tolerated as the number of patients that discontinued over time was low (n=3, 2.2%). A total of 2 patients discontinued because of non-serious elevations of transaminases in the long-term safety study. These patients had also elevated transaminases before the start of the parent study.

The most frequently reported AE related to medication was elevated transaminases (occurring in 10% of subjects in the cumulative treatment-emergent period [median exposure duration: 76 weeks]), an incidence being higher than that observed in subjects 12 years of age and older (3.2%). These observations are consistent available in the published literature that indicates transaminase elevations are more common in younger patients with CF than in adults and are in line with the observed frequency in the placebo arm of study VX14-809-109 of shorter treatment duration of 26 weeks.

Various additional a post-hoc analyses were provided to show the correlation between treatment exposure and adverse events, including the transaminase elevations. These analyses were conducted because of the request for a higher posology and the possible correlation with treatment. These additional analyses failed to show a correlation, indicating that such correlating might not be strong. However, the analyses were hampered by the fact that they were conducted in a limited number of patients. Therefore, the concern remains that with a higher exposure, this AE of transaminase elevation will occur more frequently.

Nevertheless, as a possible association between transaminase elevation and treatment cannot be excluded for *CFTR* correctors/potentiators. Recommendations for liver test monitoring at initiation and periodically during treatment, with recommendations to discontinue or interrupt treatment in the presence of abnormal liver function are included in section 4.4 of the SmPC.

The applicant proposes to collect additional safety data for the proposed posology in study 116B, and the post-marketing study, study 117.
In study 116B, the included study population is collected from part A of the study i.e. the patients who have already received treatment for 96 weeks and are willing to give informed consent. Patients who permanently discontinued treatment because of elevated transaminases or a positive re-challenge could not be included.
Study 117 is not designed to collect adverse events. It will provide limited safety data for major adverse event and may probably not register the number of patients that discontinue or interrupt treatment because of modest transaminase elevations.

2.6.2. Conclusions on clinical safety

Overall, the use of TEZ/IVA in subjects 6 through 11 years of age with CF, homozygous for *F508Del* was generally well tolerated. The safety outcomes were generally consistent with the background profile in patients with CF and the established safety profile of TEZ/IVA.

No clinical data has been provided to support the proposed weight-based posology in children weighing 30-40 kg which will results in a higher exposure in these children compared to the clinical studies. This should affect about 40% of the target population.

In line with previous applications in paediatric CF, more paediatric patients showed elevations in transaminases compared to adults.

Additional post-hoc analyses failed to show a correlation between exposure and elevated transaminases, but these additional analyses are hampered by the limited number of patients included.

Considering that a treatment-related effect of transaminase elevations could not be excluded, the SmPC includes recommendations that for liver test monitoring at initiation and periodically during treatment, with recommendations to discontinue or interrupt treatment in the presence of abnormal liver function.

2.7. Risk Management Plan

Safety concerns

Important identified risks	• None
Important potential risks	• Hepatotoxicity • Concomitant use of TEZ/IVA with strong CYP3A inhibitors or inducers • Cataract
Missing information	• Use in pregnant and lactating women • Long-term safety • Patients with moderate or severe hepatic impairment • Patients with $ppFEV_1$ <40

CYP: cytochrome P450; $ppFEV_1$: forced expiratory volume in 1 second; TEZ/IVA: tezacaftor in combination with ivacaftor

Pharmacovigilance plan

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional PV activities which are Conditions of the MA (key to benefit risk)				
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)				
VX17-661-117 (Study 117) (PASS) Ongoing	To evaluate • the safety outcome in the real-world setting, • CF disease progression in patients treated with TEZ/IVA in the real-world setting, as measured by changes over time in lung function and nutritional status, • frequency and outcome of pregnancy in female patients • drug utilisation and to characterise potential off-label use	• Hepatotoxicity • Use in pregnant and lactating women • Long-term safety • Patients with hepatic impairment • Patients with $ppFEV_1$ <40	Annual reports/ Final Report	Annual Reports: December 2019 December 2020 December 2021 December 2022 Final Report: December 2023

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
VX17-661-116 (Study 116) ongoing	To evaluate the safety and efficacy of long-term treatment with TEZ/IVA in subjects with CF aged 6 years and older, homozygous or heterozygous for the *F508Del-CFTR* mutation	• Hepatotoxicity • Concomitant use of TEZ/IVA with strong CYP3A inhibitors or inducers • Cataract • Long-term safety	Final Report	October 2022

CF: Cystic Fibrosis; *CFTR*: cystic fibrosis transmembrane conductance regulator gene; CYP: cytochrome P450, MA: market authorisation; $ppFEV_1$: forced expiratory volume in 1 second , PASS: post-authorisation safety study; PV: pharmacovigilance; TEZ/IVA: tezacaftor in combination with ivacaftor

With respect to study 117, the study duration is currently defined for the 5 year-period from 2018 through to 2022 with the final report due for submission in 2023. The applicant confirmed that at the time of the planned analysis of the study, they intend on having 3 years of post-marketing data from the US and 2 years of post-marketing data from European patients. This would therefore mean that paediatric patients recruited within the registry study following approval of this extension of indication would only be followed for a much more limited duration (no longer than 2 years for the majority of the European cohorts) which would not be considered sufficient.

Consequently, the Applicant agreed to discuss in consultation with the EMA/PRAC Rapporteur the need for a longer follow-up at the time of the planned final analysis of study 117.

Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Hepatotoxicity	**Routine risk minimisation measure:** SmPC Sections 4.4 and 4.8 SmPC Section 4.4 and PL Sections 2 and 4 where advice is given on monitoring LFTs. PL Sections 2 and 4. **Additional risk minimisation measures:** No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** • Study 117 (PASS) • Study 116

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Concomitant use of TEZ/IVA with strong CYP3A inhibitors or inducers	**Routine risk minimisation measure:** SmPC Sections 4.2, 4.4, and 4.5 SmPC Sections 4.2 and 4.5 where dose reductions are recommended when TEZ/IVA is co-administered with a strong inhibitor of CYP3A. PL Section 2. **Additional risk minimisation measures:** No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** • Study 116
Cataract	**Routine risk minimisation measure:** SmPC Sections 4.4 and 5.3 SmPC Section 4.4 where advice is given on recommended ophthalmological examinations. PL Section 2 **Additional risk minimisation measures:** No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** • Study 116
Use in pregnant and lactating women	**Routine risk minimisation measure:** SmPC Sections 4.6 and 5.3 SmPC Section 4.6 and PL Section 2 where advice is given to avoid the use of Symkevi during pregnancy and to determine the use during breastfeeding after taking into account the benefit of breastfeeding the child and the benefit of therapy for the woman. PL Section 2. **Additional risk minimisation measures:** No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only Pregnancy follow-up form **Additional PV activities:** • Study 117 (PASS)
Long-term safety	**Routine risk minimisation measure:** SmPC Sections 4.8 and 5.1 SmPC Sections 4.8 and 5.1 describe the available clinical evidence, including the number and extent of exposure in clinical studies. **Additional risk minimisation measures:** No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** • Study 117 (PASS) • Study 116

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Patients with moderate or severe hepatic impairment	**Routine risk minimisation measure:** SmPC Sections 4.2, 4.4, and 5.2. SmPC Section 4.2 where advice is given on dose adjustment based on severity of hepatic impairment. PL Section 3. **Additional risk minimisation measures:** No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** • Study 117 (PASS)
Patients with ppFEV$_1$ <40	**Routine risk minimisation measure:** SmPC Section 5.1 **Additional risk minimisation measures:** No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** • Study 117 (PASS)

CYP: cytochrome P450; LFT: liver function test; PASS: Post-authorisation safety study; PL: Package Leaflet; ppFEV$_1$: forced expiratory volume in 1 second; PV: pharmacovigilance; SmPC: Summary of Product Characteristics; TEZ/IVA: tezacaftor in combination with ivacaftor

Conclusion

The CHMP and PRAC considered that the risk management plan version 3.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

Based on the approval of the new population of children from the age of 6 years, the CHMP is of the opinion that the already existing entry in the EURD list for tezacaftor/ ivacaftor needs to be amended as follows: the PSUR cycle for the medicinal product should follow a half-yearly cycle. The next data lock point will be 11 February 2021.

2.9. Product information

2.9.1. User consultation

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

This procedure is to extend the indication to include patients of 6 years to less than 12 years. The MAH confirms that updates as a result of this procedure do not impact the readability of the package leaflet and that further readability testing is not considered necessary. Readability testing was previously conducted for the Symkevi 100 mg/150 mg film-coated tablets package leaflet and reviewed during the initial application, procedure EMEA/H/C/004682. According to the applicant updates made to the package leaflets are minimal, and the structure and guidance for caregivers remains aligned to the principles agreed on in procedure EMEA/H/C/004682.

2.9.2. Amendments to the Product information

This application introduced changes in the PI as follows:

- Update of SmPC and PI to add the new strength (TEZ 50 mg/IVA 75 mg) and the corresponding extension of indication in children from the age of 6 years.

Therefore, amendments to annex I, II, IIIA, IIIB are introduced.

- Update of SmPC and PI for the existing strength ((TEZ 100 mg/IVA 150 mg) to add an extension of the existing patient population to include children from the age of 6years.

Therefore, amendments to annex I, and IIIB are introduced.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication of the present application is as follows: (changes in bold and underlined)

Symkevi tablets are indicated in a combination regimen with ivacaftor tablets for the treatment of patients with cystic fibrosis (CF) aged **6** years and older who are homozygous for the *F508Del* mutation or who are heterozygous for the *F508Del* mutation and have one of the following mutations in the *CFTR* gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T.

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 the absent or deficient function of the *CFTR* protein at the cell surface that regulates salt and water absorption and secretion. The failure to regulate chloride transport results in the accumulation of thick, sticky mucus in the bronchi of the lungs, loss of exocrine pancreatic function, impaired intestinal absorption, reproductive dysfunction, and elevated sweat chloride concentration. Lung disease is the primary cause of morbidity and mortality in people with CF. At very young ages clinically apparent lung disease may be absent although lung structural changes may be already present and progressing.

3.1.2. Available therapies and unmet medical need

Most CF therapies target the symptoms of the disease, such as nutritional supplements, antibiotics, and mucolytics. A few years ago, *CFTR* modulators became available which have the potency to modify

the progress of the disease as they improve the underlying pathophysiological caused, the defective *CFTR*- function. Two *CFTR* modulators are approved for the treatment of CF in the EU in children aged ≥ 6 years, Kalydeco (ivacaftor) and Orkambi (lumacaftor/ivacaftor).
Symkevi is approved for adolescents and children aged ≥ 12 years. Kaftrio is approved for adolescents and adult patients with homozygous F508del mutations and heterozygous patients with minimal function mutations.

The current application applies for an extension of the indication for Symkevi in children aged ≥ 6 years in CF patients homozygous for F508/F508 and for heterozygous for F508/ and certain residual mutations.

Homozygous F508/F508

The currently applied indication for Symkevi (TEZ/IVA) partly overlaps with the approved indication of Orkambi referring to homozygous *F508Del* patients. However, the extension of the TEZ/IVA indication to patients 6 through 11 years old would provide an alternative treatment option for the homozygous F/F patients because not all patients tolerate Orkambi well due to adverse events (e.g. bronchoconstriction, liver function impairment). Orkambi is also a strong CYP3A inducer which may lead to unwanted drug-drug interactions with commonly prescribed medications whereas Symkevi is a less strong inducer.

Heterozygous F508/RF

The extension of the applied indication may fill an unmet medication need for patients with F/RF mutation aged 6-11 years old. This patient group represents about 9% of the CF population for whom no other *CFTR* modulators have been approved. These patients are characterised by slower disease progression than the homozygous F508 population, but they will eventually experience the clinical consequences of CF, including a reduced lifespan.

The applied posology for Symkevi is:

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

3.1.3. Main clinical studies

The pivotal efficacy study is study VX16-661-115 (study 115), and the safety study is study VX15-661-113 (study 113). Study 115 was a randomised, double-blind, parallel-group study to evaluate the efficacy and safety of tezacaftor/ivacaftor in paediatric patients aged 6-11 years. The included CF patients were confirmed to be homozygous for *F508Del-CFTR* or F508/residual function.

This application is based on partial extrapolation considering the similarities in the genetic, molecular and pathophysiological aetiology of CF between adults and children during the disease as outlined in the principles described in ICH E11 and the EMA reflection paper on paediatric extrapolation.

Indeed, this strategy of partial extrapolation can be justified in CF for the *CFTR* therapies, because of the similar underlying genetic, and molecular aetiology of CF between children and patients ≥ 12 years. The biochemical defect of the defective chloride channels is present from birth and because of the longstanding defects, it results in sequelae in the lung, pancreas and other organs emerging progressively throughout childhood and into adulthood. These sequelae may negatively affect the

course of the disease over time, e.g. like the more frequent exacerbations is adulthood compared to childhood. The *CFTR* therapies improve the Cl transport, and as such, they can be regarded as a targeted therapy for the disease for which the extrapolation strategy is justified.

Additionally, experience with previous *CFTR*-applications like ivacaftor((Kalydeco) and lumacaftor/ivacaftor (Orkambi) established the role of these therapies in children aged 6-11 years in a comparative placebo-controlled phase III randomised trial. It was unknown whether the clinical course of the disease might be different between adults and children at that time. These studies showed efficacy results that were in line with the adult population, supporting the concept of partial extrapolation.

In summary, the partial extrapolation approach to establish the treatment in paediatric population for Symkevi is therefore acceptable considering the existing scientific knowledge in paediatric patients with CF and with other *CFTR* modulators.

The table below summarises the main studies included in the extrapolation strategy.

Study	**Adults and adolescents (≥ 12 yrs) (n)**	**Children (6-11 yrs) (n)**	**PK**	**PD**	**Efficacy**	**Safety**	**primary aim study**
VX11-661-101	31		X	x	X	X	Dose finding PK
VX13-661- 103	39					X	Dose finding
VX14-661-106	248*		X		$ppFEV_1$	X	Phase III efficacy safety, PK
VX14-661-108	161*		X	x	$ppFEV_1$	X	Phase III efficacy and safety, PK
VX14-661-110	459				x	X	Phase III, long term safety, efficacy
VX15-661-113		70	X		ppFEV1	X	Phase III, dose finding, PK, safety
VX16-661-115		54*		X	$LCI_{2.5}$	X	Phase III, dose confirmation, efficacy, safety
VX17-661-116		130			X	x	Phase III, Long term safety and efficacy

*patients exposed to TEZ/IVA

Patients had evidence of uneven ventilation due to small airways disease at screening (LCI 2.5 ≥7.5) but could have normal spirometry (pp FEV1 >70). This is characteristic of this age population of this patient population.

The proposed posology in patients aged 6 to less than 12 years is as follows:

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

6 to <12 years weighing ≥ 30 kg	tezacaftor 100 mg/ivacaftor 150 mg	ivacaftor 150 mg

3.2. Favourable effects

In study VX16-661-115 the primary efficacy outcome, the within-group (TEZ/IVA group) change in $LCI_{2.5}$ from baseline through Week 8, was LS mean (SE) -0.51 (0.11) (95% CI: -0.74 to -0.29; P <0.0001).
The upper bound of the 95% CI (-0.29) was below the pre-specified maximum placebo effect of -0.10.

The key secondary outcomes and other outcomes (ppFEV1 and CFQR) show within treatment (TEZ/IVA) improvements from baseline through week 8 as well:

- Sweat chloride: LS mean (SE) -12.3 (1.5) (95% CI -15.3, -9.3) mmol. L^{-1}, p<0.0001.
- CFQ-R Respiratory domain: LS mean (SE) 2.3 (1.2) (95% CI -0.1, 4.6); p=0.0546
- Percentage predicted FEV1 ($ppFEV_1$): LS mean (SE) 2.8 (0.9) (95% CI 1.0, 4.6); p=0.0024.

Improvements in primary and secondary outcome measures were observed in both populations of F508/F508 and F508/RF.

The additional sensitivity analyses for the LCI 2.5 (MMRM with placebo mean imputation) showed LCI 2.5 baseline through week 8 for F/F: LS mean (SE) -0.32 (0.12) (95% CI -0.56, -0.07); for the F/RF: -1.07 (0.21) (95% CI -1.49, -0.64)

The long-term supportive study 113B showed an improvement in ppFEV1 and $LCI_{2.5}$ from baseline through week 24 without signs of deterioration over time.

3.3. Uncertainties and limitations about favourable effects

No dedicated dose-finding Phase II trial has been conducted in the paediatric population. The applicant applied for a higher posology for patients weighing >30 and < 40 kg than currently investigated in trial 115. No clinical data has been provided for this posology adjustment which will impact about 40% of the proposed EU target population. Upon request from CHMP, additional PK/PD relationships were provided showing that under the new applied posology, the sweat chloride transport will increase by 0.8 mmol/L. This likely also improves the $LCI_{2.5}$, but the actual effect size remains uncertain.

The treatment duration of the pivotal study 115 is relatively short (8 weeks). The duration is justified as previous efficacy studies with *CFTR* modulator/potentiator showed that the improvement observed in children at week 8 was maintained during long term follow-up to 24 weeks.

The paediatric population included a different patient population (F508/F508 and F508/RF) compared to the two adult pivotal trials (two trials, one for each population). These difference in the trial population may hinder the extrapolation because the clinical course might be different in these two populations. On the other hand, Symkevi modulates the *CFTR* receptor in both populations to the same extent as shown in the adult data for sweat chloride.

The observed LS mean (SE) improvement in sweat chloride is small -12.3 (1.5) mmol.L^{-1} but above the identified MCID of -10 mmol/L, and in line with the adult's data (F/F -10.1 mmol/L and F/RF -9.5 mmol/l).

The MMRM analyses assume that patients who do not provide data (n= 6) at week 8 continue to benefit from treatment. Additional analyses using the placebo-mean imputation showed smaller effects, but the point estimate still pointed towards a beneficial effect.

For the F/F population the cross-study comparisons with placebo show a smaller effect in terms of sweat chloride and $LCI_{2.5}$ with TEZ/IVA when indirectly compared with LUM/IVA.
Cross study comparison:

- Mean (SD) $LCI_{2.5:}$ -1.07 (95% CI -1.42, -0.71) vs. -0.71 (95% CI -1.28, -0.13) U in LUM/IVA and TEZ/IVA, respectively
- Mean (SD) sweat chloride: -25.6 (95% CI -28.6, -22.5) vs -10.7 (95% CI -18.5, -2.9) $mmol.L^{-1}$ in LUM/IVA and TEZ/IVA, respectively

In terms of the ppFEV1, the results with TEZ/IVA showed a better effect compared with LUM/IVA, i.e., 2.6 (7.0) versus 0.5 (8.1) percentage points respectively.

The results of the open-label study 113 are hard to interpret, as patients show initially, a small, clinically irrelevant deterioration of $LCI_{2.5}$. At the end of the study, the $LCI_{2.5}$ has returned to baseline. The absolute change from baseline in $LCI_{2.5}$ through Week 24 was (LS mean (95% CI) 0.09 (-0.32, 0.49). Nevertheless, the study does not show a deterioration of efficacy over time.

The patients were selected on the availability to swallow the tablet. This may have biased the drug acceptability results towards a more favourable outcome.

3.4. Unfavourable effects

The main safety data set included 137 patients, among them 129 patients with an exposure ≥ 48 weeks. Most frequently reported AEs are cough (58.4%), followed by infective pulmonary exacerbation of CF (43.8%), and pyrexia (24.1%).

The most frequently treatment-related reported AE was transaminase elevation. The observed incidence of ALT and AST elevations appeared to be higher (7.7%) in this paediatric population than in subjects 12 years of age and older (3.2%).

A higher number of SAE's /100 patient-years were reported in the long-term safety study 116 (n=27, 20.8%) compared to the parent studies 115 and 113 (n=6, 4.8%).

A total of 8 (6.2%) patients interrupted treatment over time; 2 (1.5%) patients interrupted because of transaminase elevations.

Two patients (1.5%) discontinued treatment and both were because of nonserious transaminase elevations.

3.5. Uncertainties and limitations about unfavourable effects

The safety data set mainly consist of data collected in an uncontrolled, open label study period in which the contribution from the longer disease duration versus the longer drug exposure is hard to distinguish.

Cross study comparisons with the placebo arm of study 809-109 in the same F/F target population showed that the incidence of transaminase elevations is in the range of 10% and SAE's were comparable as the one observed in the current study.

The applied posology will result in a higher exposure in patients weighting between 30- 40 kg. No

clinical data for the proposed posology for patients weighing 30-40 kg is available. This lack of data affects about 40% of the EU target population.

Additional post hoc analyses failed to show a correlation between exposure and elevated transaminases, but the data is obtained in only a small number of patients, therefore no conclusion can be reached.

An association between the Symkevi and drug-induced liver function test cannot be excluded. Therefore, section 4.4. of the SmPC includes recommendations for liver test monitoring at initiation and periodically during treatment, with recommendations to discontinue or interrupt treatment in the presence of abnormal liver function**.**

3.6. Effects Table

Table 49 Effects Table for Symkevi of patients with cystic fibrosis (CF) aged 6 years and older who are homozygous for the *F508Del* mutation or who are heterozygous for the *F508Del* mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T.

Effect	Short Description	Unit	TEZ/IVA	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
$LCI_{2.5}$	absolute change baseline through wk8	LCI unit	LS mean (95%CI) -0.51 (-0.74, -0.29	No direct control	**Unc:** within treatment effect MCID not established, the measured effect is within the natural variability of the parameter/ p<0.0001	Pediatric pulmonology 2013: 48:739-46 Eur Respir J 2017; 50: 1700433
Sweat chloride	absolute change baseline through wk8	mmol/L	LS Mean (95% CI) -12.3 (-15.3, -9.3)	idem	**Unc:** within treatment effect, Pharmacodynamic biomarker MCID is -10 mmol/L, p<0.0001	CHMP consensus
ppFEV1	absolute change baseline through wk8	%	LS Mean (95% CI) 2.8 (1.0, 4.6)	idem	**Unc:** within treatment effect, ppFEV1 insensitive endpoint for this patient population because of preserved lung function, p=0.0024	
CFR-Q child version	absolute change baseline through wk8	Points	LS Mean (95% CI) 2.3 (-0.1, 4.6)	idem	**Unc:** within treatment effect, an insensitive endpoint in patients with a relatively well-preserved disease, p=0.0546	
Unfavourable Effects*						
Cough	All events	n (%)	25 (35.7%)	idem	**Unc:** Limited safety set results obtained from open label study 113B, which include n=70 patients; the patient exposure > 24 weeks is N=28	
Transaminase elevation	possibly related	n (%)	6 (8.6%)	idem	**SoE:** Recognised in older patients as well – Additional risk minimisation in place. Cross study comparisons show a similar incidence in the placebo arm (study VX14-809-109)	EMEA/H/C/ 003954/X/0020

Abbreviations: n= number; wk = week
*Notes: The results are obtained from open label study 113B, which included n=70 patients with exposure of max 24 weeks

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Symkevi is a *CFTR* modulator which specifically targets *CFTR* dysfunction, the basic pathophysiological defect in CF. This defective dysfunction has the same genetic and molecular aetiology in both paediatrics and adults. These similarities in disease might justify the use of a partial extrapolation strategy to establish the efficacy and safety of Symkevi in paediatric CF patients. Therefore, limited efficacy and safety data in the paediatric population could be accepted, and the main efficacy and safety data can be extrapolated from the adult's data. Also, the reduced clinical program decreases the number of children participating in clinical studies.

Symkevi is regarded as targeted therapy. As such, it has the potential to improve the natural course of the disease over time. Therefore, early initiation of treatment might be important, as it may prevent irreversible changes of disease.

Symkevi is approved for CF patients ≥ 12 years harbouring a homozygous for F508/F508 and heterozygous for F508/ certain residual functions.

Upon approval in the paediatric population (i.e. from 6 to 11 years old), Symkevi would be the second *CFTR* modulator for younger patients with F508/F508. It provides an alternative for those patients who cannot tolerate Orkambi because of respiratory side effects or because of certain drug/drug interactions. Symkevi will be the first *CFTR* modulator for paediatric patients who harbour certain F/RF mutations.

The clinical program to support the paediatric application is based on partial extrapolation of the adult data to the paediatric population. The concept of partial extrapolation is based on the fact that the Symkevi PK in adults is predictive of the PK in paediatric data and the drug has a predictive, similar pharmacodynamic effect in both populations. In addition, paediatric clinical data were gathered to support the extrapolated adult efficacy and safety data.

Throughout the clinical program, PK data was collected. After reviewing the totality of data, it appeared that for children weighing 30-40 kg, the TEZ parent and IVA parent exposures fell within the lower range of observed exposures of subjects 12 years and older. Therefore, the applicant adjusted the proposed posology (weight cut-off of 30kg), to align with the adult exposure. This adjustment affects about 40% of the target EU population. The clinical package does not contain clinical data to provide evidence for this posology however PK/PD simulation data provided during assessment supports the proposed posology which is agreed.

Despite the lower exposure in patients 30-40 kg in the studies, the conducted paediatric studies showed a pharmacodynamic effect, i.e. an improvement in the sweat chloride that was similar to the effect observed in adults. In addition, the additional PK/PD modelling showed that the applied posology will likely improve the Cl transport with 0.8 mmol/L, further support the efficacy for the higher posology.

Based on the similar PK and pharmacodynamics effects in both populations, extrapolation of the efficacy and safety in the approved adult indication to the paediatric population is considered acceptable. Moreover, extrapolation is supported by limited paediatric data available.

The pivotal study 115, met its primary endpoint by showing a within treatment difference in the LCI2.5 from baseline through week 8 that was highly statistically significant, while the 95% CI did not cross the predefined boundary with placebo. The effect was supported with an improvement in the FEV1.

Additional sensitivity analyses supported the observed improvement as the point estimate showed a favourable effect. These data show that, like in adults, TEZ/IVA modulates the *CFTR* function in paediatrics. This modulation will result in improved lung function.

The observed improvement in the LCI2.5 is within the normal variability of the disease. Nevertheless, this improvement can be regarded as clinically relevant as it is supported with data in the older population ≥ 12 years obtained with Symkevi. Previous adult applications (Bronchitol (EMEA/H/C 001251), Orkambi (EMEA/H/C/003954) and Symkevi (EMEA/H/C/004682) also showed lung function improvements that were within the normal variability of FEV1.These improvements were regarded as clinically relevant, considering the detrimental course of the disease. Statistically significant effects in ppFEV1 and sweat chloride supported the clinical relevance of Symkevi treatment in the paediatric population.

Relevant clinical effects were observed for both the F/F group and F/RF group, although the overall treatment effect in the LCI2.5 appeared to be driven by the F/RF population. The cross-study comparisons showed that the observed treatment effects for the F/F population were somewhat smaller compared to the treatment effect observed with lumacaftor/ivacaftor in this homozygous population.

The effect on LCI can be regarded as relevant as it was supported with improvements in FEV1 and sweat chloride transport and clinical data obtained in adults (study VX-116 -106).
However, cross study comparisons with lumacaftor/ivacaftor in the same target population showed larger improvements. Therefore, the CHMP recommended reporting the results of both subgroups in section 5.1 of the SmPC in order to provide information on each population RF and F/F which would be relevant for the prescriber.

In the clinical program, Symkevi appeared to be well-tolerated, both in the short term and in the long-term safety studies. The most frequently reported related adverse event was transaminase elevation. However, as the safety database mainly consisted of open, label uncontrolled data, it is not possible to draw definite conclusions due to the lack of placebo-controlled arm and the bias in the results due to the contribution to the disease. Cross study comparisons showed that the observed frequency of elevated transaminase (~ 10%) of the long-term safety database of 75-week duration was in line with the placebo arm of a comparative trial of 24-week duration (VX14-809-109). Although a correlation with treatment cannot be excluded, this comparison suggests that this adverse event can also be attributed to CF, as elevated transaminases are frequently observed in paediatric CF.

No clinical data has been provided to support the safety for the higher, proposed posology. This proposed posology may affect about 40% of the proposed EU target population. Concerns were raised, if the higher exposure would increase the risk of transaminase elevations. Various post hoc analyses were conducted but failed to show such a correlation. Although these analyses included a limited number of patients, together with the long-term safety database they provided enough support for the higher applied posology. Additionally, recommendations to monitor the liver function prior and during treatment are included in the SmPC section 4.4.

Balance of benefits and risks

In the paediatric clinical program, Symkevi showed a similar improvement in the sweat chloride in paediatrics compared to adults. The observed pharmacodynamic improvement was associated with statistically significant and relevant improvement in lung functions in both the F/F and F/RF population, improvements that are supported with the lung function improvements obtained in the adult's population. The treatment appeared well tolerated. Overall the data support extension of indication in children above 6 years and approval of the new strength (TEZ 50mg/ IVA 75mg) of Symkevi tablets.

From the PK point of view, the posology investigated in studies 113B and study 115 resulted in TEZ and IVA exposures at the lower end of that seen in older patients i.e. children weighting 30 to less than 40 kg. Therefore, the MAH proposed to shift the body weight cut-off for dosing from 40 kg to 30 kg, i.e., children weighing ≥30 kg will be treated with the adult dose of TEZ 100mg qd/IVA 150 mg q12h which is expected to result in a more comparable systemic exposure. This proposed posology which has not been tested in the paediatric clinical studies (i.e., in children weighing at least 30 kg to less than 40 kg) is supported with additional PK/PD analyses as well with the longer-term safety and post-hoc analyses that contribute to alleviate the concerns regarding the potential for increased systemic exposure and risk of transaminase elevations.

3.8. Conclusions

The overall B/R of Symkevi is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Symkevi is not similar to Bronchitol, TobiPodhaler, Kalydeco, Kaftrio within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Symkevi 50/75 mg is favourable in the following indication:

Symkevi is indicated in a combination regimen with ivacaftor tablets for the treatment of patients with cystic fibrosis (CF) aged 6 years and older who are homozygous for the *F508Del* mutation or who are heterozygous for the *F508Del* mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene: *P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G,* and *3849+10kbC→T*.

The CHMP therefore recommends the extension of the marketing authorisation for Symkevi 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).

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.

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0193/2017 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation, to update the indication for the Symkevi tablets currently authorised (100mg /150 mg) to the paediatric patients from 6 years and above.

Overall the application relates to the following changes:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIB
X.02.III	Annex I_2. (c) Change or addition of a new strength/potency	Line Extension	I, II, IIIA, IIIB and A

Extension application to add a new strength of 50/75mg film-coated tablets of tezacaftor/ivacaftor and extend the indication to patients aged 6 to less than 11 years for this strength.
C.II.6.a - update of sections 4.1, 4.2, 4.4, 4,5, 4.8, 5.1, 5.2, 6.1 and 6.3 of the SmPC for the 100/150 mg film-coated tablet presentations and corresponding sections of the PL to extend the indication for use in children aged 6 to less than 11 years old in combination with ivacaftor and to bring it in line with the new dosage form (50/75mg film-coated tablets tezacaftor/ivacaftor).

Annex II is updated as a consequence of the above new strength.

The RMP (version 3.0) is updated in accordance.
In addition, the MAH took the opportunity to implement minor updates and formatting QRD related changes in the Product Information.