17 September 2020
EMA/628136/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kalydeco

International non-proprietary name: ivacaftor

Procedure No. EMEA/H/C/002494/X/0083/G

Note

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

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Table of contents

List of abbreviations

ADR	adverse drug reaction
AE	adverse event
ALT	alanine transaminase
AUC	area under the concentration versus time curve
AUC0-∞	AUC from the time of dosing extrapolated to infinity
AUCss	AUC at steady-state
AUC0-tlast	AUC from the time of dosing to the last measurable concentration
BA	bioavailability
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	CF transmembrane conductance regulator gene
CFTR	CF transmembrane conductance regulator protein
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	clearance
CL/F	apparent clearance
Cmax	maximum observed concentration
Cmin	minimum observed concentration
Cmin,ss	Cmin at steady-state
CPP	Critical process parameter
CQAs	Critical Quality Attributes
CYP	cytochrome P450
DDI	drug-drug interaction
DSL	Design Space Limits
DoE	Design of experiments
ECG	electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FE-1	fecal elastase-1
FEF25%-75%	forced expiratory flow 25%-75%
FEV0.5	forced expiratory volume in 0.5 seconds
FRC	functional residual capacity
FVC	forced vital capacity
GLSMR	geometric least squares means ratio
GMP	Good Manufacturing Practices
HPLC	High performance liquid chromatography
IA2R	Interim Analysis 2 Report
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IPC	In-Process Control
IPFT	infant pulmonary function tests
IQR	interquartile range
IRT	immunoreactive trypsin and/or trypsinogen

IVA	ivacaftor
KF	Karl Fischer titration
LCI	lung clearance index
MIAH	Manufacturer and Importer Authorisation Holder
Max	maximum
Min	minimum
n	size of subsample
N	total sample size
ND	not determined
NMT	Not more than
NOR	Normal Operating Range
OE	ophthalmologic examination
P	probability
PCTFE	Polychlorotrifluoroethylene
PD	pharmacodynamic, pharmacodynamics
PDCO	European Medicines Agency Pediatric Committee
PEx	pulmonary exacerbation
Ph.Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PK	pharmacokinetic, pharmacokinetics
ppFEV1	percent predicted forced expiratory volume in 1 second
PT	Preferred Term
PVC	Polyvinyl chloride
q12h	every 12 hours
QC	Quality Control
qd	daily
Q/F	apparent inter-compartmental clearance
QbD	Quality by Design
QP	Qualified Person
QTPP	Quality target product profile
QWP	Quality Working Party
RH	Relative Humidity
RSD	Relative standard deviation
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDD	Spray Dried Dispersion
SLS	Sodium Lauryl Sulfate
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SwCl	Sweat chloride
TAMC	Total Aerobic Microbial Count
TEZ	tezacaftor
TSE	Transmissible Spongiform Encephalopathy
TYMC	Total Combined Yeasts/Moulds Count
UK	United Kingdom
ULN	upper limit of normal
US	United States
Vc/F	apparent central volume
Vp/F	apparent peripheral volume
WR	written request
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

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

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 75 mg film-coated tablets of ivacaftor to enable administration to patients aged 6 to less than 11 years grouped with an extension of indication - C.I.6.a - To update sections 4.1, 4.2 and 6.5 of the SmPC, and sections 1 and 2 of the PL for the 150 mg film-coated tablet presentations to extend the indication for use in children aged 6 to less than 12 years old in combination with tezacaftor/ivacaftor and to bring it in line with the new dosage form (75 mg film-coated tablets of ivacaftor). The RMP (version 8.6) is updated in accordance.
In addition, the MAH took the opportunity to implement minor updates 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

Kalydeco, was designated as an orphan medicinal product EU/3/08/556 on 25 July 2012 in the following condition: Treatment of cystic fibrosis.

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 Kalydeco 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/0353/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0353/2018 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 (Symkevi - EMEA/H/SA/2814/3/2017/PED/II). The Protocol assistance pertained to clinical aspects.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Maria Concepcion Prieto Yerro Co-Rapporteur: N/A

The application was received by the EMA on	11 November 2019
The procedure started on	28 November 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	26 February 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	4 March 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 PRAC Rapporteur's Assessment Report was circulated to all PRAC members on	29 May 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	11 June 2020
The Rapporteur's Assessment Report was circulated to all CHMP members on	21 June 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	08 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 Kalydeco on	17 September 2020
The CHMP adopted a report on similarity on	17 September 2020

2. Scientific discussion

2.1. Problem statement

The MAH applied for a new strength (75mg tablets) to be used in a new indication in combination with Symkevi in children from 6 to less than 12 years.

The MAH did not apply for the use of this new strength (75 mg tablets) in the other indication (as monotherapy) of Kalydeco for children weighing at least 14 kg to less than 25 kg.

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 CF patients, 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 disease 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 the *CFTR* genotype 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 also the presence of modifier genes play an important role. Lung disease is the primary cause of morbidity and mortality in people with CF. However, CF is a systemic disease and complications such as cystic fibrosis-related diabetes and cystic fibrosis-related liver disease have emerged as important causes of morbid-mortality which are usually present in the paediatric age.

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 *F508del* mutation. About 50% of the CF population is homozygous for the *F508del* mutation, while this allele is present in at least 70% of the overall CF population.

2.1.3. Aetiology and pathogenesis

The *CFTR* protein is an epithelial chloride ion (CL-) channel located in the epithelia of multiple organs, including lungs, pancreas, intestinal tract, liver, and vas deferens, that is responsible for aiding in the

regulation of salt and water absorption and secretion. More than 1900 mutations in the *CFTR* gene have been identified.

CFTR mutations can be classified according to the mechanisms by which they disrupt *CFTR* function. Stop codon mutations (class I) result in a truncated non-functional *CFTR*, class II mutations consist of aberrantly folded *CFTR* protein that is degraded by the cell quality control system, while class III mutations lead to defective regulation of the *CFTR* protein and, consequently, the absence of *CFTR* function. These three classes usually lead to a classic CF phenotype with pancreatic insufficiency. *CFTR* mutations that lead to defective chloride conductance are grouped together in class IV. Class V mutations interfere with normal transcription, thereby reducing the amount of otherwise normal *CFTR*. These latter two classes are mostly associated with a milder expression of the disease.

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

2.1.4. Clinical presentation, diagnosis

The median predicted survival for CF patients in the US 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. 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 which 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.

Figure 1 The natural course of progression of the pulmonary CF

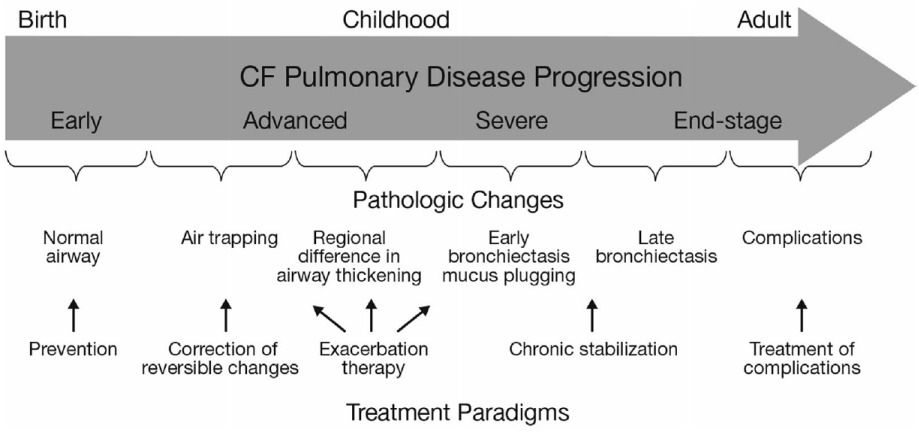


Fig. 1. Stages of disease progression and pathologic changes that occur in the airways of patients with CF as they age, along with possible treatment approaches. Reprinted with permission of the American Thoracic Society. Copyright 2014 American Thoracic Society. Ramsey BW. 2007. Use of lung imaging 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]

Indeed, in children, the lung function as judged by FEV1 is often preserved, but peripheral airways disease is shown by an abnormal Lung clearance index (LCI). The deterioration of LCI reflects disease progression. Lung Clearance Index 2.5 ($LCI_{2.5}$) correlates well with FEV1, although it is abnormal at an earlier stage in the disease course. 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.

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, prognosis of CF has been improved which is partly due to early recognising and early intervention.

In the 1950, 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

Data in the literature suggest that early therapeutic intervention is beneficial to young children with CF; studies have demonstrated benefits such as improved measures of growth, nutrition, and lung disease through early intervention in children diagnosed by newborn screening.

Most treatments available for the treatment of CF 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 symptomatic medications concomitantly administered to maintain and improve lung function, reduce the risk of infections and exacerbations, and improve quality of life.

Symkevi is a *CFTR* modulator, a product that affects the underlying defect in the CF transmembrane conductance regulator (*CFTR*) protein. *CFTR* modulators can be classified as potentiators and/or correctors. Symkevi is a fixed dose combination consisting of the *CFTR* corrector tezacaftor and the *CFTR* potentiator ivacaftor. Correctors improve intracellular processing of the *CFTR* protein, increasing surface expression, in class II mutations 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 IV mutation *R117H* which also produces a gating defect. 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 potential to cause clinically relevant drug-drug interactions.

Extension of the IVA in combination with TEZ/IVA indication to patients 6 through 11 years old would provide an alternative treatment option for patients homozygous for *F508del* (F/F). Currently, there are no *CFTR* modulators approved in children aged 6-11 heterozygous for *F508del* and *CFTR* mutations of residual function (F/RF). Symkevi would fulfil an unmet medical need for these patients.

2.2. About the product

In the EU, Kalydeco is indicated in monotherapy for patients with certain pre-specified gating (class III) mutations as well as for those with the *R117H-CFTR* mutation. Kalydeco is also indicated in a combination regimen with tezacaftor 100 mg/ivacaftor 150 mg tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) 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*.

The scope for the current application is to apply for an extension of the above indication for children aged ≥ 6 years, i.e. Kalydeco tablets are also indicated in a combination regimen with tezacaftor/ ivacaftor tablets for the treatment of patients with cystic fibrosis (CF) aged 6 years and older with cystic fibrosis (CF) 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.*

The proposed posology 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
≥ 12 years	tezacaftor 100 mg/ivacaftor 150 mg	ivacaftor 150 mg

2.3. The development programme/compliance with CHMP guidance/scientific advice

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 VX661-115 in 54 patients aged 6-11 years.

In clinical studies of patients ≥12 years old, TEZ/IVA demonstrated clinically meaningful improvements in lung function and improvements in pulmonary exacerbations, Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain (RD) score, and other important CF outcomes (EMEA/H/C/004682/0000 and EMEA/H/C/002494/II/63).

The key studies to support the efficacy and safety in adults and adolescents aged ≥ 12 years were study VX14-661-106 and study VX14-661-108. Study 106 and 108 were both randomised, double blind, placebo-controlled phase III trials. Study 106 was a parallel study conducted in patients homozygous for *F508del* of 24-week duration; study 108 was a crossover study conducted in patients heterozygous for *F508del* and an *CFTR* mutation of residual function of 8-week duration. Study VX14-661-110 (open label extension) provided evidence of safety (primary endpoint) and efficacy outcomes beyond the duration of study 106 and study 108.

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 achieve at the selected doses of tezacaftor and ivacaftor similar systemic exposures to those of older patients as well as to assess the safety of the treatment in this age group. Efficacy was included as a secondary endpoint. 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.

Children from both studies 113 and 115 were offered to roll over 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.

Tabular overview of the studies contributing to the extrapolation strategy from patients aged 12 years and older to children aged 6 to less than 12 years old

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		LCI2.5	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 = *F508del/F508del*, F/RF = *F508del/CFTR* mutation with residual function
[a] number of patients treated with TEZ/IVA; NP = not provided, RCT = randomised controlled trial, CO = cross-over

Given the similarities in the genetic, molecular and pathophysiological aetiology of CF across different age groups, the MAH considered that the principles of extrapolation could be applied in line with the principles described in the ICH E11 guideline, the EMA Reflection Paper on Paediatric Extrapolation and the FDA paediatric guidance.

The initial paediatric investigational plan (PIP) was agreed in May 2015 and included Studies 113 and 115.

Scientific advice

The MAH sought CHMP scientific advice for Study 115 after the Phase 3 data in subjects ≥12 years old became available in 2017 (EMEA/H/SA/2814/3/2017/PED/II). Study 115 was designed to provide supportive efficacy data that could bridge to the efficacy data observed in adults.

2.4. Quality aspects

2.4.1. Introduction

The finished product introduced within this line extension application is presented as film-coated tablets containing 75 mg of ivacaftor as active substance. This is to be added to the existing 150 mg film-coated tablets and 25 mg, 50mg and 75 mg granules.

150 mg tablets 25, 50 and 75 mg granules

Other ingredients are:

Tablet core: hypromellose acetate succinate, microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, sodium laurylsulfate (E487), colloidal anhydrous silica and magnesium stearate

Tablet film coat: polyvinyl alcohol, titanium dioxide (E171), macrogol (PEG 3350), talc, indigo carmine aluminum lake (E132), carnauba wax

Printing ink: shellac, iron oxide black (E172), propylene glycol (E1520), ammonium hydroxide

The product is available in a thermoform (PolyChloroTriFluoroEthylene [PCTFE]/foil) blister.

2.4.2. Active Substance

This is a line extension application where no new information on the active substance has been provided.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The new strength introduced with this line extension application is Kalydeco 75mg immediate-release film-coated tablets for oral administration. Specifically, this new tablet strength has been co-developed to be used as the evening dose for the combination treatment with fixed dose combination tablets of Symkevi (tezacaftor /ivacaftor) (50mg/75mg) in children from 6 through 11 years of age and body weight below 30 kg as part of a mismatched regimen.

These tablets are 12.70 mm x 6.78 mm light blue capsule-shaped, printed with V 75 in black ink on one face and plain on the other. The acceptability and palatability of the paediatric tablet has been demonstrated in the paediatric population as part of the clinical studies. There were no reported product complaints attributed to difficulty swallowing tablets. Because the product was only administered as a tablet in these studies, there are no clinical data currently available to support other methods of administration besides swallowing whole; chewing or crushing the tablet is not recommended and a warning has been added in section 4.2 of the SmPC and section 5 of the package leaflet.

The absence of studies on possible modification of the tablets is justified by the presence of alternative age appropriate formulations (Kalydeco granules), in line with the guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2) and the approved PIP.

As for the marketed Kalydeco 150 mg tablets and granules presentations, ivacaftor active substance is provided as an amorphous spray dried dispersion (SDD) intermediate.

Opadry II (Blue) is an excipient used for non-functional film-coating of the core tablet.

Opacode Black, is the ink used for printing the film-coated tablet. The printing ink components are listed in section 6.1. of the SmPC.

The excipients used for the manufacture of Kalydeco 75 mg tablets are qualitatively the same as those used for Kalydeco 150 mg tablets. They are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards, with the exception of: methyl ethyl ketone (MEK), which is a process solvent used for the manufacture of the SDD and is removed during processing, Opadry II (Blue) (coating excipient) and Opacode Black, (printing ink). Opadry II (Blue) and Opacode Black, consist of mixtures of excipients wherein their individual components meet appropriate Ph. Eur. or international 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 and in the introduction of the quality section of this report.

The pharmaceutical development of this new tablet strength relies on the development of Kalydeco 150 mg film-coated tablets and Kalydeco granules and is aligned with the approved PIP 001640-PIP01-14-M05.

The ivacaftor 75mg tablet uses the same core tablet blend formulation as that contained in the ivacaftor 150mg tablet and the tablet weight is adjusted to achieve the desired dose. The quantitative composition of the two strengths is dose proportional with the exception the concentration of blue pigment (FD&C Blue #2), which is used at a lower concentration to achieve a lighter blue colour for the tablet. This difference is accounted for by adjusting the level of titanium dioxide in the film coating composition.

Due to its poor aqueous solubility the crystalline ivacaftor active substance is converted into an amorphous SDD intermediate for use in the tablet formulation as described above.

The quality target product profile (QTPP) is provided in the table below.

Quality Target Product Profile

Safe and efficacious
Bioavailable
Oral administration
Immediate release tablet of 75 mg ivacaftor
At least 48 month shelf life at room temperature packaged in blister

Critical quality attributes (CQAs) for ivacaftor SDD and ivacaftor 75 mg tablets and their impact on quality, safety, and/or efficacy of the product have been described. These include appearance, identification, assay, degradation products, dissolution, uniformity of dosage units, physical form, water content, microbial attributes, elemental impurities and residual solvents.

Once the tablet CQAs were identified, initial risk assessments of the incoming materials and manufacturing process were performed. The in-vitro dissolution method for quality control (QC) testing of ivacaftor 75 mg tablets was developed based on the approved method for Kalydeco 150 mg tablets and Kalydeco granules. It uses the same conditions as those used for the ivacaftor 150 mg tablets; the only difference is the surfactant level as less surfactant is required to achieve sink conditions. The same approach was employed for the ivacaftor 50 mg and 75 mg granules, resulting in better discriminatory power.

The ivacaftor 75 mg dissolution method was shown to be able to discriminate against material attributes and tablet properties that could affect product performance, namely tablet hardness, SDD bulk density and presence of crystalline ivacaftor. The dissolution method is considered suitable for its intended use as the primary QC method for testing the dissolution performance of the ivacaftor 75 mg tablets during release and stability studies.

The 75 mg tablets are manufactured using the same direct compression batch manufacturing process as the ivacaftor 150 mg tablets, comprising preparation of the SDD, blending of the active SDD with excipients, compression, film coating and printing.

The manufacturing process development of ivacaftor 75 mg tablets followed a Quality by Design (QbD) approach. Risk assessment, prior knowledge and screening experiments were used to design multivariate experiments to evaluate main effects and interactions. Specifically, a design of experiments (DOE) was performed to evaluate the potential impact of incoming material attributes and compression process parameters on finished product CQAs and define a design space. These experiments considered the desired manufacturing ranges (DMR) as well as incoming material specifications and equipment capability. Any differences in scale or equipment between the experiments conducted and the commercial equipment have been considered (scale-up and engineering risk assessment) to ensure results are representative of the commercial process and are documented as appropriate. Four model confirmation runs were also conducted to confirm the accuracy of the resulting process models and to demonstrate process performance on commercial scale equipment.

The compression unit operation was assessed as having a medium risk of impacting the tablet appearance. Appearance of the core tablet was not noticeably impacted across the entire evaluated experimental manufacturing range.

A DOE was performed to evaluate the potential impact of the film coating process parameters on drug product CQAs. Four confirmation runs were also conducted on commercial scale equipment to confirm the accuracy of the process models as well as assess the impact of compressing tablets at both the high and low ends of the compression DMR on the CQAs of appearance and water content.

All the DOE runs met the appearance specification.

The impact of the film coating process parameters on the tablet water content CQA was assessed the highest observed coated tablet water content was below the specification of in the final coated tablet put in place to control both the physical form and microbial attributes of the ivacaftor 75mg tablets. The three lots of coated and waxed tablets from the film coating confirmation runs were utilized for the printing experiments. All the printed tablets met the appearance specification.

After the criticality assessment, the design space was defined. A summary of the design space and IPC limits has been provided In-process controls (IPCs) are in place for core tablet weight, thickness and hardness during compression, tablet weight gain during the film coating and visual inspection at the end of the printing process.

The formulation used during clinical studies is the same as that intended for marketing.

Bulk tablets are packaged in double low-density polyethylene bags inside a heat-sealed foil laminated bag. The finished product is packaged in a thermoform blister consisting of clear Aclar (PCTFE – polychlorotrifluoroethylene) film laminated to PVC (polyvinyl chloride) film and sealed with a blister foil lidding. The Aclar/foil blister configuration will be sealed in a weekly blister card. All packaging components comply with Commission Regulation (EU) No 10/2011. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of six main steps: manufacturing of ivacaftor SDD (which in turn comprised mixture preparation, spray drying and secondary drying); blending of the SDD with tablet excipients microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, colloidal silicon dioxide, and sodium lauryl sulfate; blending of the resulting mixture magnesium stearate, direct compression, film-coating and printing. The process is considered to be a standard manufacturing process.

As described above, a design space has been proposed for compression and film-coating. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design space.

The proposed hold time of 24 months for the bulk tablets has been justified with stability data from a bulk batch of 75 mg tablets stored for 24 months at 25 ºC / 60% RH in the bulk tablet packaging configuration and supplemented with data from three batches of 150 mg tablets stored in the bulk packaging configuration for 36 months. No significant change was observed. Since both tablet strengths are manufactured from a common blend and have the same bulk packaging configurations this is acceptable.

It has also been confirmed that the product shelf life is calculated from the start of the finished product manufacturing process in line with the CHMP Guideline on manufacture of the finished dosage form (EMA/CHMP/QWP/245074/2015).

Process validation was performed in accordance with the EMA Guideline on Process Validation for Finished Products – Information and Data to be Provided in Regulatory Submissions (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1,Corr.1) on three commercial scale batches to demonstrate that the tablet manufacturing process is capable of reproducible commercial manufacture. The in-process controls are adequate for this type of manufacturing process.

Product specification

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

The organic impurities in the ivacaftor 75mg tablet are the same as those in ivacaftor active substance and SDD (also used to manufacture the existing Kalydeco 150 mg tablets and Kalydeco granules) and ivacaftor 150 mg tablets. No additional degradants have been identified for the ivacaftor 75 mg tablets.

No additional potential risk of nitrosamines formation has been identified; hence, it is agreed that it does not need to be resubmitted with this line extension. During development, physical form of tablets was monitored at both release and on stability by XRPD. No crystalline content was observed for any lot of uncoated or coated tablets at release, including testing of QbD study samples during process

development, clinical, and primary campaigns utilizing the process representative of commercial production.

Since the 75 mg tablets have the same core tablet composition and coating components as the 150 mg tablets, and use a similar manufacturing process, the same justification of specification is applicable for the two strengths.

The same water content specification at release has been defined to ensure physical stability, as supported by crystallization and moisture uptake modelling indicating that tablets will remain physically stable for at least 48 months when stored in the intended container and closure system at the intended storage conditions. The defined release water specification limit will also assure a water activity below 0.60, which does not support microbial growth. The limit is also supported by development stability data. Additionally, crystallization and moisture uptake modelling for ivacaftor 75 mg tablets provide justification that tablets containing water up to the acceptable limit at release will remain physically stable for at least 48 months when stored in the intended container and closure system at the intended storage conditions.

All CQAs that can potentially be impacted by water content (physical form, microbial limits, and dissolution) will be tested on stability. Therefore, water content is measured only at release.

Microbiological purity is not included in the release specification, this is acceptable since the proposed release water specification limit does not support microbial, as also supported by stability data. Although the data indicate that ivacaftor tablets possess very low risk of microbial contamination, the applicant will perform microbial limits testing on commercial stability lots to verify that the risk remains low.

Physical form of the active substance (by XRPD) for the ivacaftor 75 mg tablets are not included in the release specification, as it is ensured by process and material controls: control of the incoming ivacaftor SDD, which has a specification of absence of crystalline ivacaftor; control of the manufacturing process and excipients (i.e. microcrystalline cellulose and croscarmellose sodium) to ensure tablet water content is at an acceptable level at release; confirmation that an acceptable level of tablet water content has been achieved by testing tablet water content at release. Additionally, during development, the physical form was monitored both at release and on stability. For any lot of uncoated or coated tablets used in the QbD study, process development, clinical, and primary campaigns, which have all being manufactured using a manufacturing process representative of commercial production, no crystalline content was observed at release. During development, physical form of tablets was monitored at both release and on stability by XRPD. No crystalline content was observed for any lot of uncoated or coated tablets at release, including testing of QbD study samples during process development, clinical, and primary campaigns utilising the process representative of commercial production. Given the existing controls of the incoming materials and the manufacturing process, the physical form of the tablet will be confirmed by XRPD during stability only.

The potential presence of elemental impurities in ivacaftor 75 mg tablets was assessed according to the ICH Q3D Guideline for Elemental Impurities using a risk-based approach. The risk assessment considered the potential contributions from the ivacaftor active substance and SDD (including solvents, reagents, excipients, and equipment), water, tablet excipients, and manufacturing equipment to determine the overall contribution of elemental impurities to the ivacaftor tablets. The elemental impurities intentionally added in the ivacaftor active substance manufacturing process are controlled according to ICH Q3D requirements. The risk assessment of the content of Class 1 and Class 2A elemental impurities (as defined in ICH Q3D) in the ivacaftor active substance and SDD demonstrated that the risk of elemental impurities in these materials is low. All tablet excipients were also shown to comply with ICH Q3D requirements in the tablet. Batch analysis data, using a validated ICP-MS method, of representative batches, including nine commercial batches of active substance, four

commercial batches of SDD and three primary stability batches of 75 mg tablets confirmed that the contents of Class 1 and Class 2A elemental impurities are consistently below 30% of the ICH Q3D Option 1 limits.

This risk assessment and confirmatory testing demonstrates that the risk of elemental impurities in the ivacaftor 75 mg tablets is low and the product will consistently meet the ICH Q3D requirements. Therefore, no additional controls on elemental impurities are required. The information on the control of elemental impurities is satisfactory.

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

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

Stability of the product

Stability data from three pilot scale batches of Kalydeco 75 mg tablets stored for up to 24 months under long term conditions (25 ºC / 60% RH) and intermediate conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of Kalydeco 75 mg are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Additional supportive stability data from Kalydeco 150 mg tablets which are part of Kalydeco MA dossier and have an approved shelf-life of 4 years were taken into consideration. These are considered representative, since as discussed above, both tablet strengths are manufactured using the same blend, direct compression manufacturing process, film coating components, and container closure system.

Samples were tested for appearance, assay, degradation products, dissolution, physical form (XRPD). Although not part of the proposed stability specification water content (KF) was also included in the initial stability program. In addition, microbial limits (TAMC, TYMC, *E. coli*) and water activity were tested the initial time point. The analytical procedures used are stability indicating.

All results met the acceptance criteria for the attributes evaluated.

No trends in the assay data were observed after storage for up to 18 months at 25°C/60% RH and 6 months at 40°C/75% RH for the primary stability lots. A slight upward trend in assay was observed after storage for up to 18 months at 30°C/75% RH. However, all results obtained were well within specification limits and the small increase in assay values is within the expected analytical variability.

For all stability studies, the X-ray powder diffraction data show absence of crystalline ivacaftor at all test points under all storage conditions.

The water content data from the primary stability lots showed a modest increase in water content under the long-term and accelerated storage conditions with values above 4.0% at 18 months at 30°C/75% RH and 6 months at 40°C/75% RH. However, all parameters that can potentially be impacted by water content (physical form, microbial limits and dissolution) are tested on stability with no out of specification results.

In accordance with EU GMP guidelines1, any confirmed out-of-specification result, or significant negative trend, should be reported to the Rapporteur and EMA.

In addition, one pilot scale batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products ICH Q1B Option 2. Samples were tested for appearance, assay, and degradation products. The data, showing no changes in the fully exposed test sample and the covered control, confirms that Kalydeco 75 mg tablets do not require light protective packaging.

The data from the primary stability lots of Kalydeco 75 mg tablets remain well within the commercial specification acceptance limits at 25°C/60% RH, 30°C/75% RH and 40°C/75% RH and are consistent with the stability results obtained for the weight multiple Kalydeco 150 mg tablets, and therefore, the proposed shelf-life of 4 years when stored in the container closure system and no special storage condition as stated in the SmPC (section 6.3) is acceptable.

It has been confirmed that the product shelf-life is calculated in accordance with the CHMP NfG on the Start of shelf-life of the finished dosage form (CPMP/QWP/072/96).

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of Kalydeco 75 mg film-coated tablets has been presented in a satisfactory manner. As discussed above, most of the pharmaceutical development relevant for Kalydeco 75 mg film-coated tablets was performed for Kalydeco 150 mg film-coated tablets. Both tablet strengths are manufactured from the same blend and using the same manufacturing process.

QbD principles were applied in the development of the tablets and their manufacturing process. A design space has been proposed for the compression and film-coating steps. This has been adequately verified. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. 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. Data has been presented to give reassurance on TSE safety.

[1] 26.32 of Vol. 4 Part I of the Rules Governing Medicinal products in the European Union

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

No new clinical data have been submitted in this application, which is considered acceptable.

2.5.1. Ecotoxicity/environmental risk assessment

Even though this submission encompasses a proposed extension of the indication for Kalydeco to support the combination regimen with Symkevi for fixed dose combination tablet in patients age 6 to 11 years old who have an indicated *CFTR* genotype, the addition of the 6-11 years patient age group is covered by the prevalence data used for Kalydeco environmental risk assessment (procedure EMEA/H/C/002494/IB/WS/1595). Therefore, there will be no increase in environmental risk to ivacaftor from the addition of the 6-11 years patient age group.

2.5.2. Discussion and conclusion on non-clinical aspects

The data submitted in the non-clinical part of the dossier are acceptable for this type of application. The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of ivacaftor. Considering the above data, ivacaftor is not expected to pose a risk to the environment.

2.6. Clinical aspects

2.6.1. Introduction

In order to support this extension of indication application, the MAH 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 children aged 6 to less than 12 years old.

- **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 CF, homozygous or heterozygous for the *F508del–CFTR* mutation.
  Study 113 Part A is included in the TEZ/IVA EMEA-001640-PIP01-14-M04; Study 11 (Study C, Part A).
- **Study VX16-661-115 (Study 115)** is a 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

- **Tabular overview of clinical studies**

Study ID	**Study centres/ location** **Initiation/completion dates**	**Design**	**Posology**	**Duration Treatment (T) Follow up (FU)**	**Objectives (pri: primary; sec: secondary)**	**Number of patients Enrolled (E), Dosed (D), Completed (C)**	**Study population** **Sex Genotype Median age (range) yrs**	**Primary endpoint (PE) Secondary endpoints (SE)**
Study VX15-661-113								
Part A	33 sites in North America (USA, Canada) Part A 11 Nov 2016/5 Apr 2017 Part B 25 Oct 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	T: 2W FU: 2w	pri: PK sec: safety	E: 13 D:13 C: 13	6-11 years with CF Male/female: 6/7 Genotype: F/F (5), F/RF (4), F/other (4) Age: 8 (6-11)	PE: PK (parent), SE: PK (metabolites), safety
Part B		open label	<40 kg TEZ 50 mg qd / IVA 75 mg q12h ⩾ 40 kg TEZ 100 mg qd / IVA 150 mg q12h	T: 24W FU: 4 weeks or extension study	pri: safety sec: PK, efficacy	E 70 D: 70 C: 67	6-11 years with CF Male /female: 36/34 Genotype: 61 F/F 9 F/RF Age: 8.0 (6-11) years	**PE: PK and safety** SE: Efficacy (change from baseline at/through week 24) Spirometry, sweat chloride, weight (z score) height, (z score), BMI (z score)
Study VX16-661-115								
	25 sites in Australia Europe 17 May 2018/ 21 Dec 2018	Randomised (4:1 to either TEZ/IVA or the appropriate blinding group for their genotype)	TEZ/IVA: see study 113B OR blinding treatment according to genotype (placebo or	T:8 weeks FU: 4 weeks or extension study	pri: Efficacy sec: safety	E: 69 D: 67 C :66	6-11 years with CF M/F: 30/37 Genotype: F/F (52); F/RF (15) Age: 9.0 (6-11)	PE: within TEZ/IVA group absolute change in $LCI_{2.5}$ from baseline through week 8 SE: within-TEZ/IVA group absolute

		double blind, and parallel	ivacaftor). IVA (F/RF) only <40 kg: 75 mg q12h; ≥40 kg: 150 mg q12h or placebo (F/F only)					change from baseline in sweat chloride at week 8 and the absolute change from baseline through Week 8 respiratory domain score of CFQ-R. Safety and tolerability assessments Pharmacokinetcis (additional endpoint)
Study VX17-661-116*								
		open label extension	Part A: as in study 113B and study 115 Part B: weight-based dosing using the 30 kg cut-off.	A: 96 weeks B: additional 96 weeks	pri: Long term safety sec: efficacy	130	Roll over from study 113B and study 115 Not provided	PE: Safety SE: Part A: Absolute change from baseline in lung clearance index2.5 (LCI2.5; for subjects from Study 115 and the Study 113B LCI Substudy only) Absolute change from baseline in sweat chloride Absolute change from baseline in Cystic Fibrosis Questionnaire –Revised (CFQ-R) respiratory domain score Absolute change from baseline in body mass index (BMI) Part B: AEs Serum liver function tests (LFTs) Ophthalmologic examinations

F/F= homozygous *F508del*; F/RF= heterozygous *F508del* and second *CFTR* allele with residual function;*study not provided

2.6.2. Pharmacokinetics

Dose selection for the pivotal efficacy and safety study 115 in children aged 6 to less than 12 years was derived principally from Phase III study 113 Parts A and B (Part A evaluated PK, safety and tolerability for 14 days as a PK lead-in to Study 113B, which evaluated PK, efficacy, safety and tolerability for 24 weeks). Evaluation of PK was included as an additional objective in study 115. Population PK models for TEZ and IVA were used for evaluation of PK results obtained in both studies. The objective of the population PK analysis was to characterize TEZ and IVA exposures in subjects 6 through 11 years of age for comparison with exposures from subjects 12 years and older.

The test products, doses, and mode of administration in Study 113 Part A and Part B are presented in the table below.

Table 1 Test Product, Dose, and Mode of Administration in Study 113

	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 study 113A, in children weighing less than 25 kg, tezacaftor 50 mg was administered as a 50-mg tablet using 500 mg/g of a spray-dried dispersion while ivacaftor 75 mg was administered as a capsule containing ivacaftor 75 mg granules spray-dried dispersion. None of these correspond to the formulations to be marketed, i.e., the TEZ 50-mg/IVA 75-mg FDC and IVA 75-mg tablet. Children weighing ≥ 25 kg in Study 113A received the marketed IVA 150-mg tablet in combination with a 50-mg tablet of TEZ not intended for marketing. All children in Study 113B were dosed with the marketed formulations of TEZ/IVA and IVA or with the to-be-marketed formulations (i.e., FDC TEZ 50 mg/IVA 75 mg tablet and IVA 75 mg tablet) depending on body weight.

The pharmacokinetic (PK) Set was defined as subjects who received at least 1 dose of study drug and for whom the primary PK data were considered to be sufficient and interpretable. The initial target enrolment in Part A was 16 subjects but this number was amended and finally a total of 13 subjects were enrolled and integrated the PK dataset; 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 14-day treatment regimen in Part A. Tezacaftor PK data were available in the 13 subjects in the PK dataset at Day 1 and in 12 subjects at Day 14. For ivacaftor, PK data were available for 10 subjects at Day 1 and for 12 subjects at day 14. Three subjects were receiving IVA monotherapy before receiving TEZ/IVA at the start of study 113, and for these subjects, IVA

concentration data from Day 1, Day 21, and the Safety Follow-up Visit were excluded from the data analysis. One subject had difficulties with venepuncture at Day 14; therefore, blood collections were not collected for TEZ and IVA PK analyses.

In Part B, the planned enrolment was approximately 56 subjects but finally 70 subjects were enrolled and 69 integrated the PK dataset. Out of these, 62 subjects weighed less than 40 kg and were dosed with TEZ 50 mg qd/IVA 75 mg q12h and 7 subjects weighed ≥ 40 kg and received TEZ 100 mg qd/IVA 150 mg q12h.

Pharmacokinetic parameters were determined using standard non-compartmental methods. PK parameters calculated in non-compartmental analysis included Cmax, tmax, Ctrough, t½, CLss/F, Vss/F, and AUCτ.

In part A, PK blood samples were collected on Day 1 at 1, 2, 4, 5, and 24 hours (i.e., pre-dose on Day 2) after the morning dose of study drugs, before the morning dose of study drug on Day 14 and at 1, 2, 4, and 5 hours after the morning dose of study drugs on Day 14. A PK blood sample was also collected at 168 hours (i.e., Day 21) after the morning dose of study drugs on Day 14 and at the Safety Follow-up Visit.

In part B, a single PK blood sample was collected within 60 minutes before dosing at the Week 4 and Week 8 visits. At the Week 16 visit, PK blood samples were collected before the morning dose and at 1, 2, 4, and 5 hours after the morning dose. If study drug was not administered on the day of the visit (i.e., study drug interruption or permanent discontinuation of study drug), only 1 PK blood sample was collected.

Geometric mean (CV%) PK parameters of TEZ, M1-TEZ, and M2-TEZ on Day 1 and Day 14 are listed in Table 2. On Day 14, the geometric mean Cmax TEZ was 6300 ng/mL in Cohort 1 (subjects <25 kg; n=2), and 5340 ng/mL in Cohort 2 (subjects ≥25 kg; n=10). The geometric mean AUCτ was 66500 ng*h/mL in Cohort 1 and 71600 ng*h/mL in Cohort 2.

Table 2 Geometric Mean (CV%) PK Parameters of TEZ, M1-TEZ, and M2-TEZ, Part A PK Set

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

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 the table below. On Day 14, the geometric mean Cmax 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 AUCτ of IVA was 5050 ng*h/mL in Cohort 1 and 12400 ng*h/mL in Cohort 2.

Table 3 Geometric Mean (CV%) PK Parameters of IVA, M1-IVA, and M6-IVA, Part A PK Set

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).

The adult popPK model was applied to Study 113A data and 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 popPK 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.

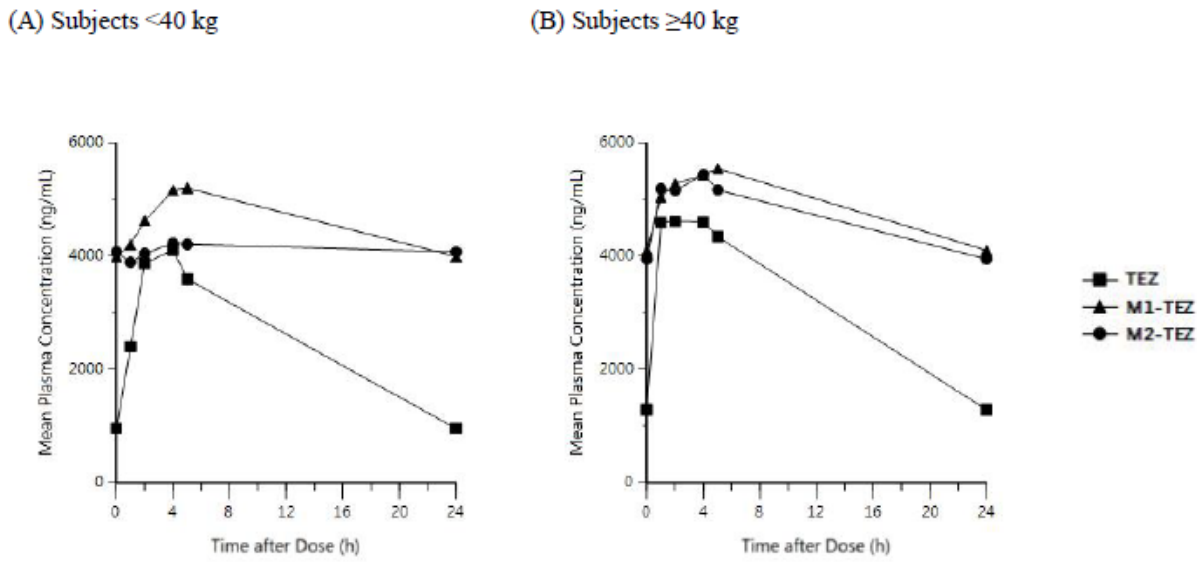
Across the weight range in 6- through 11-year-olds, simulated geometric mean ratios (Cmin, AUC, and Cmax) showed that subjects <25 kg receiving TEZ 100 mg qd/IVA 150 mg q12h would have higher exposures for parent TEZ compared to subjects ≥12 years old. The weight cut-off was increased from 25 kg to 40 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. Therefore, for Part B, the body weight cut-off for dosing was shifted from 25 kg to 40 kg, because modelling and simulations predicted the potential for higher TEZ exposures in subjects receiving 100 mg qd dose of TEZ.

In Part B, 70 subjects were enrolled and a total of 67 subjects (95.7%) completed TEZ/IVA treatment, i.e., 62 who weighed less than 40 kg and received TEZ 50 mg QD/IVA 75 mg BID and 8 who weighed ≥ 40 kg and received TEZ 100 mg QD/IVA 150mg BID.

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 1.

Figure 1 Arithmetic mean plasma concentration-time profiles of TEZ, M1-TEZ and M2-TEZ at week 16, Part B PK Set



Geometric mean (CV%) PK parameters of TEZ, M1-TEZ and M2-TEZ at Week 16 are listed in Table 4. 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 4 Geometric Mean (CV%) PK Parameters of TEZ, M1-TEZ, and M2-TEZ, Part B PK Set

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

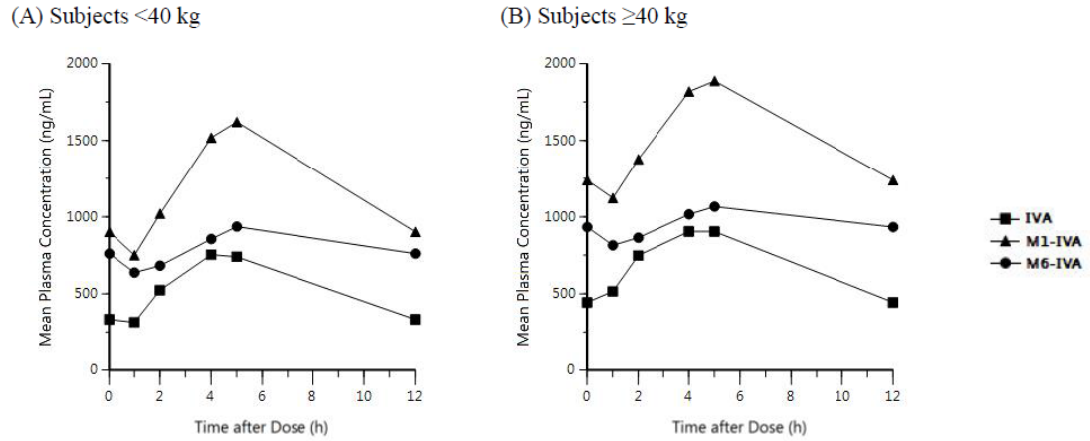
AUC_{τ}: area under the concentration-time curve during the dosing interval; CL/F: apparent clearance; C_{max}: maximum observed concentration; C_{trough}: predose concentration; CV%: coefficient of variation; N: total sample size; NA: not applicable; PK: pharmacokinetic, pharmacokinetics; TEZ: tezacaftor; 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 2.

Figure 2 Arithmetic mean plasma concentration-time profiles of IVA, M1-IVA and M6-IVA at week 16, Part B PK Set



Geometric mean (CV%) PK parameters of IVA, M1-IVA, and M6-IVA at Week 16 are listed in Table 5. 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 5 Geometric mean (CV%) PK parameters of IVA, M1-IVA, and M6-IVA, Part B PK Set

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 113B 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 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 6).

Table 6 Summary of TEZ, M1-TEZ, and IVA observed steady-state exposures (AUCss) by age group, 40-kg weight cut-off (popPK analyses P133, including paediatric PK data from Study 113 and 115)

Age Group / Weight		TEZ AUC_{0-24h} (µg·h/mL) N	TEZ AUC_{0-24h} (µg·h/mL) Mean (SD)	TEZ AUC_{0-24h} (µg·h/mL) Min, Max	M1-TEZ AUC_{0-24h} (µg·h/mL) N	M1-TEZ AUC_{0-24h} (µg·h/mL) Mean (SD)	M1-TEZ AUC_{0-24h} (µg·h/mL) Min, Max	IVA AUC_{0-12h} (µg·h/mL) N	IVA AUC_{0-12h} (µg·h/mL) Mean (SD)	IVA AUC_{0-12h} (µg·h/mL) 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

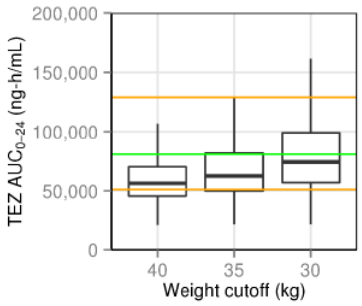
Source: Module 5.3.3.5/Report P133/Tables 32 and 35 (IVA); 38 and 41 (TEZ); 44 and 47 (M1-TEZ)
IVA: ivacaftor; N: total sample size; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor

Additional simulations were performed 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. Upon request from CHMP, the MAH provided graphs and tables of the simulated (expected) exposure levels given the 40 kg, 35 kg, and 30 kg weight cut-offs based on a minimum of 500 simulations per scenario and including only simulated data and the reference ranges. Predicted TEZ, M1-TEZ, and IVA exposures were therefore simulated for 1000 virtual subjects using the popPK model at the requested weight-based dosing cut-offs. Predicted AUC for TEZ, M1-TEZ and IVA are shown in Figure 3. Panels A and C show the results of the new simulations for 1000 virtual subjects and Panels B and D the simulations which were initially submitted based on post hoc PK parameters (empirical Bayes estimates) from individual subjects in Phase 3 studies whose PK were measured. In these graphs, red data points correspond to exposures for subjects who would receive the same dose under the proposed posology as they did in the study, whereas blue data points correspond to exposures for subjects who would receive a different dose under the proposed posology than they did in the study.

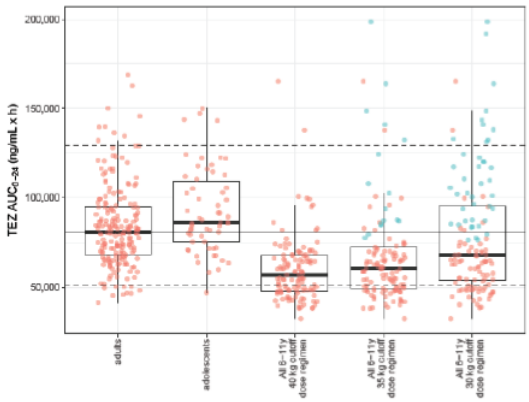
Figure 3 Comparison of Simulated TEZ, M1-TEZ, and IVA Exposures (AUC_T) in 1,000 Virtual Subjects (Left Column) to Simulation of Subjects Enrolled in Phase 3 Studies Using Post-hoc (Empirical Bayes Estimates) PK Parameters (Right Column)

Tezacaftor

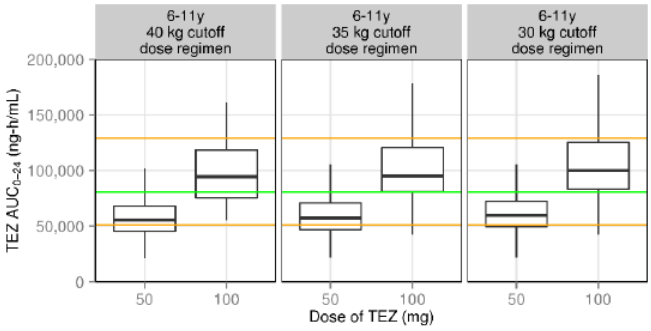
A. Simulation of 1,000 virtual subjects using the popPK model
Doses Combined



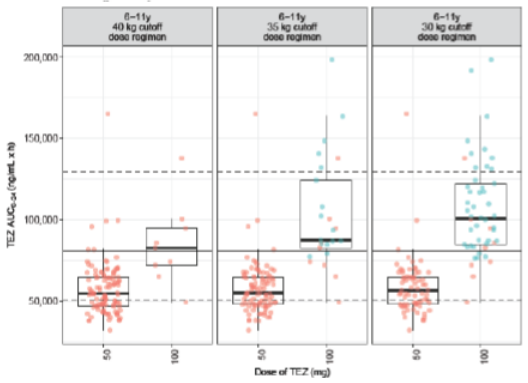
B. Simulation of subjects enrolled in Phase 3 studies using post hoc (empirical Bayes estimates) PK parameters
Doses Combined



C. Simulation of 1,000 virtual subjects using the popPK model
By Dose



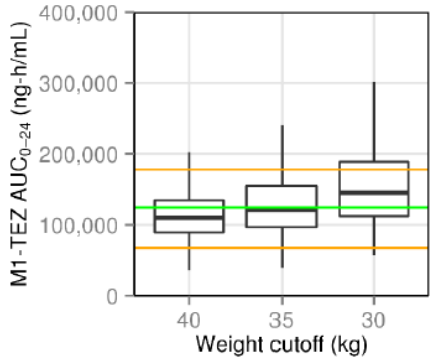
D. Simulation of subjects enrolled in Phase 3 studies using post hoc (empirical Bayes estimates) PK parameters
By Dose



M1-tezacaftor

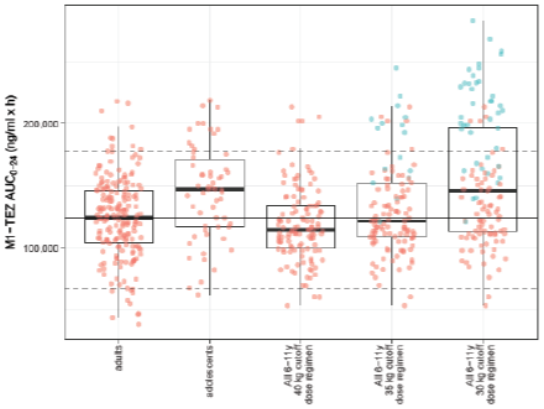
A. Simulation of 1,000 virtual subjects using the popPK model

Doses Combined



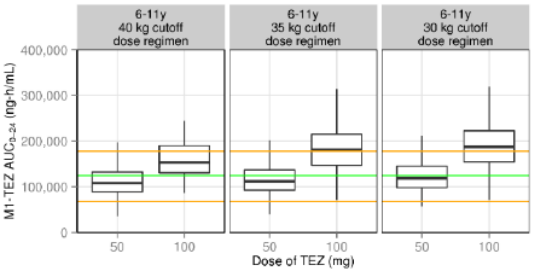
B. Simulation of subjects enrolled in Phase 3 studies using post hoc (empirical Bayes estimates) PK parameters

Doses Combined



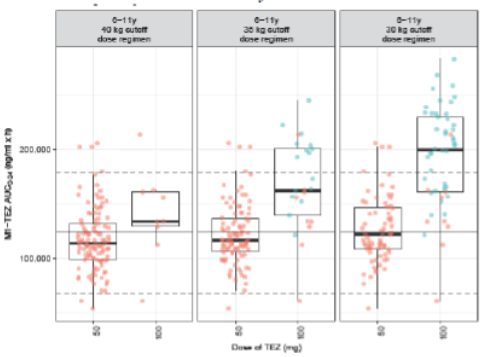
C. Simulation of 1,000 virtual subjects using the popPK model

By Dose



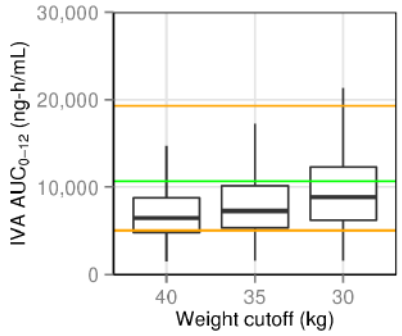
D. Simulation of subjects enrolled in Phase 3 studies using post hoc (empirical Bayes estimates) PK parameters

By Dose

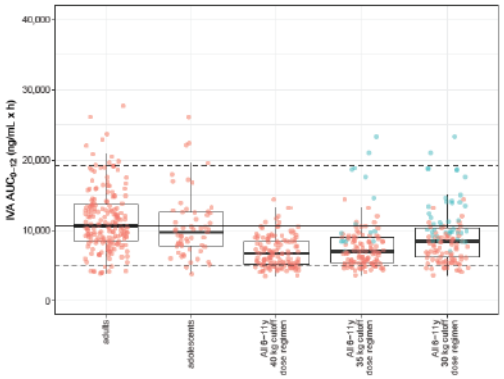


Ivacaftor

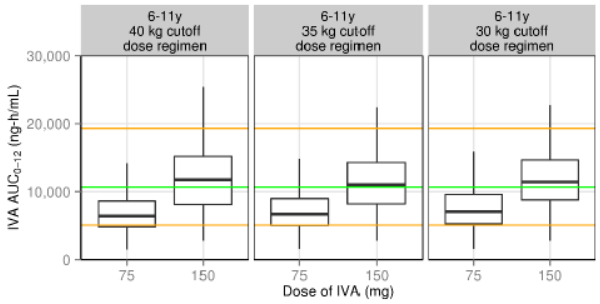
A. Simulation of 1,000 virtual subjects using the popPK model
Doses Combined



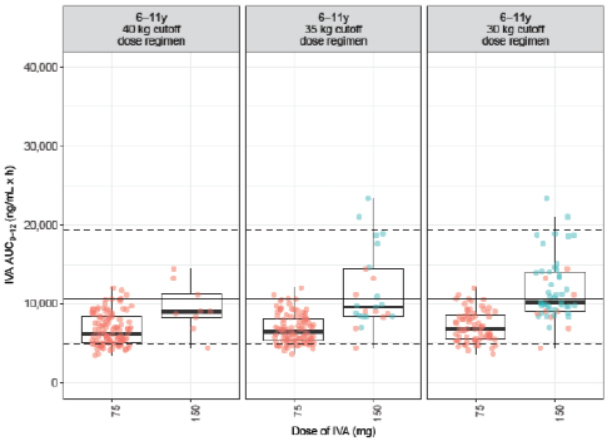
B. Simulation of subjects enrolled in Phase 3 studies using post hoc (empirical Bayes estimates) PK parameters
Doses Combined

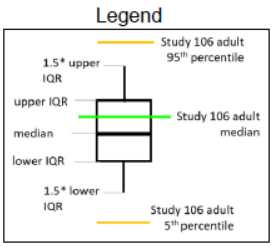


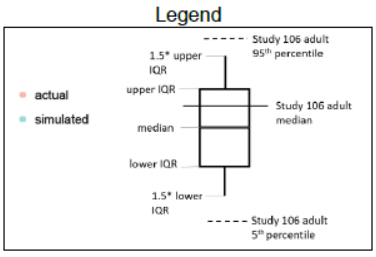
C. Simulation of 1,000 virtual subjects using the popPK model
By Dose



D. Simulation of subjects enrolled in Phase 3 studies using post hoc (empirical Bayes estimates) PK parameters
By Dose





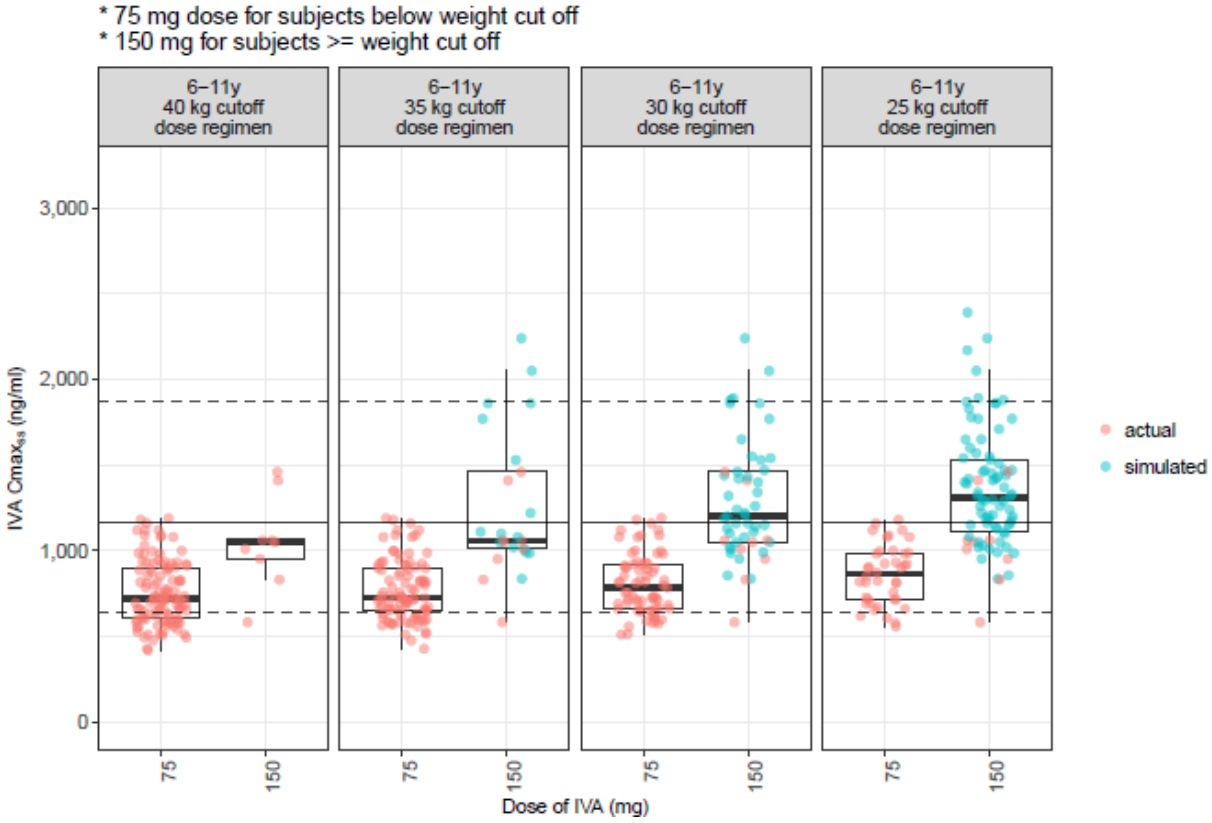


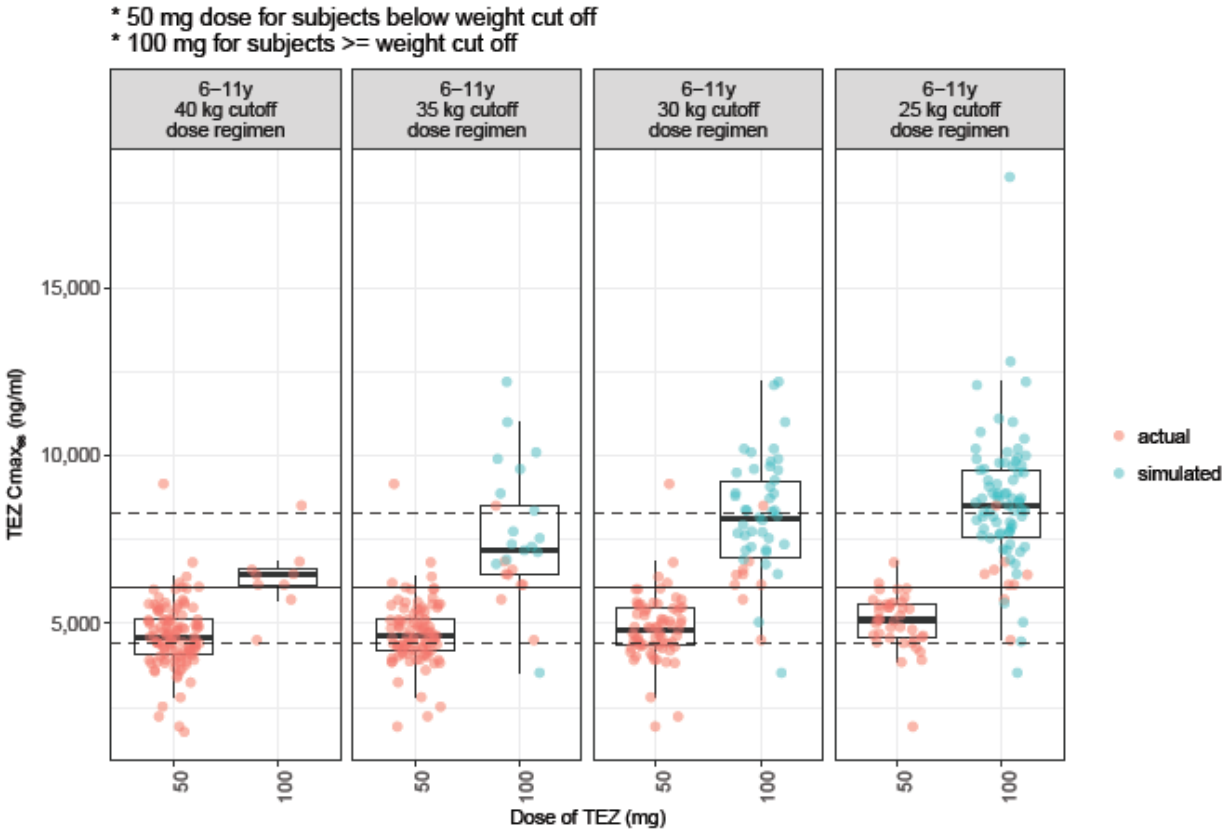
Sources: Panel A and C: Data on file; Panel B and Panel D: Report P133
IVA: ivacaftor; IQR: interquartile range; N: total sample size; PK: pharmacokinetic; popPK: population PK; q12h: every 12 hours; TEZ: tezcaftor
Notes: Subjects below the weight cutoff received TEZ 50 mg qd/IVA 75 mg q12h and subjects at or above the cutoff received TEZ 100 mg qd/IVA 150 mg q12h. Whiskers on box plots show the largest and smallest values within 1.5 × upper and lower IQR, respectively. Reference lines are included to show median (green line), 5th and 95th percentile for exposures in adult F/F subjects in Study 661-106. Panel A and C: Each boxplot represents simulated exposures from the population PK model for N=1,000 virtual F/F subjects who are 6- through 11-years of age.

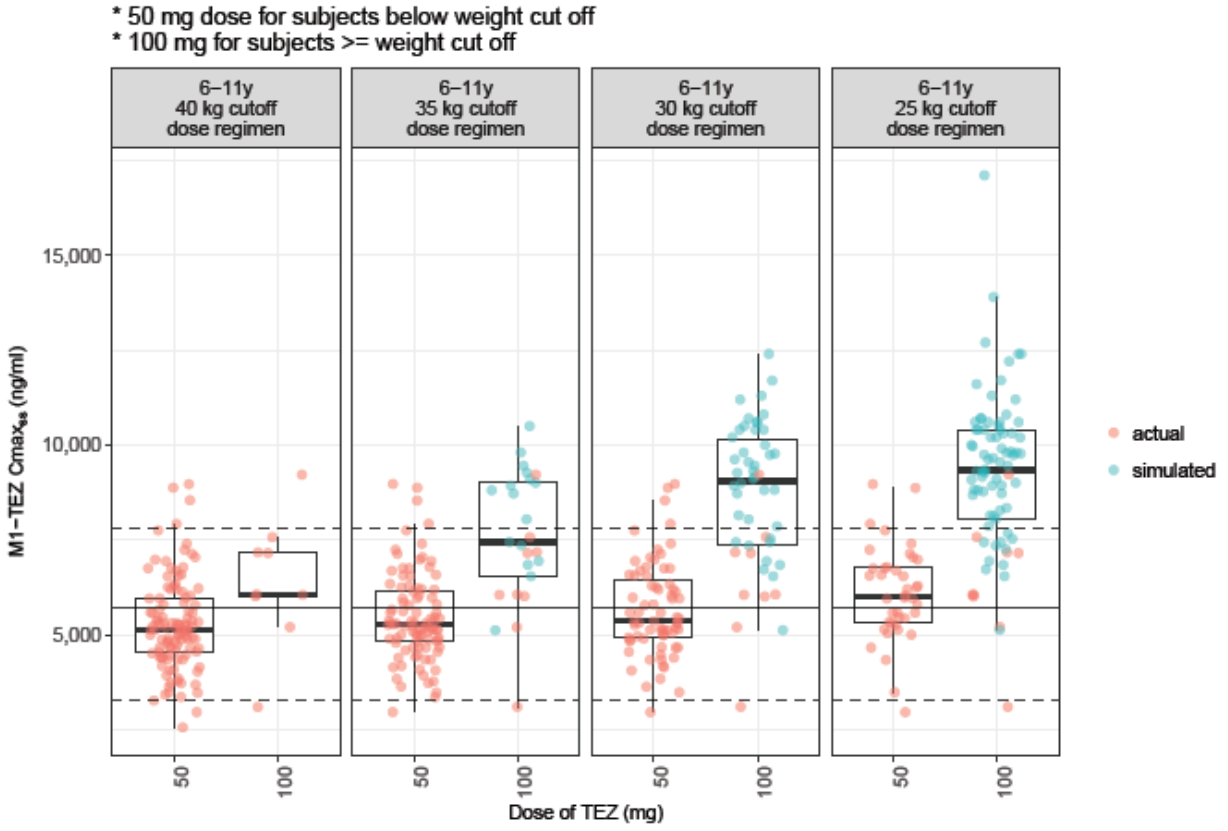
Results of the new simulations (Panels A and C) were consistent with the predicted exposures that were originally submitted (Panels B and D). Both approaches to exposure simulation demonstrate better matching of TEZ and IVA parent exposures with the 30-kg cut-off and therefore this weight cut-off was selected for dosing recommendations.

Paediatric results stratified by dosing regimen are presented in Figures 4 and 5 for C_{max}, and C_{min} respectively based on the pop-PK model initially submitted. In these graphs, all exposures were simulated using post hoc PK parameters (empirical Bayes estimates) from individual subjects in Phase 3 studies whose PK were measured given that in terms of AUC_T it has been shown that no major differences exist in the simulations when empirical Bayes estimates or population parameters are used.

Figure 4 Predicted Steady-State IVA, TEZ, M1-TEZ Exposures for Children from Six to Less Than Twelve Years Old (Studies 113 and115) with Different Weight Regimens: Cmax (pop-PK report p266).



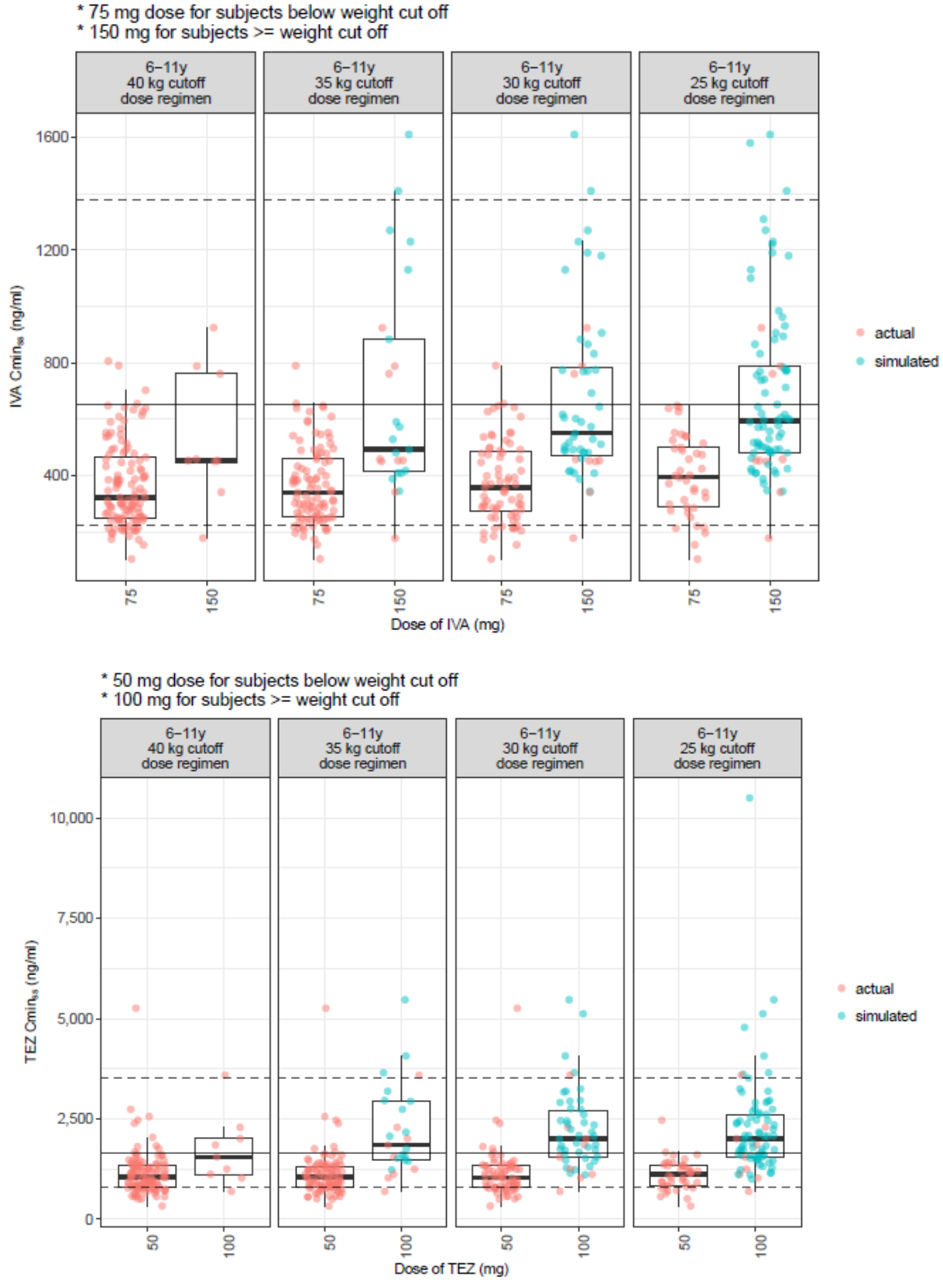


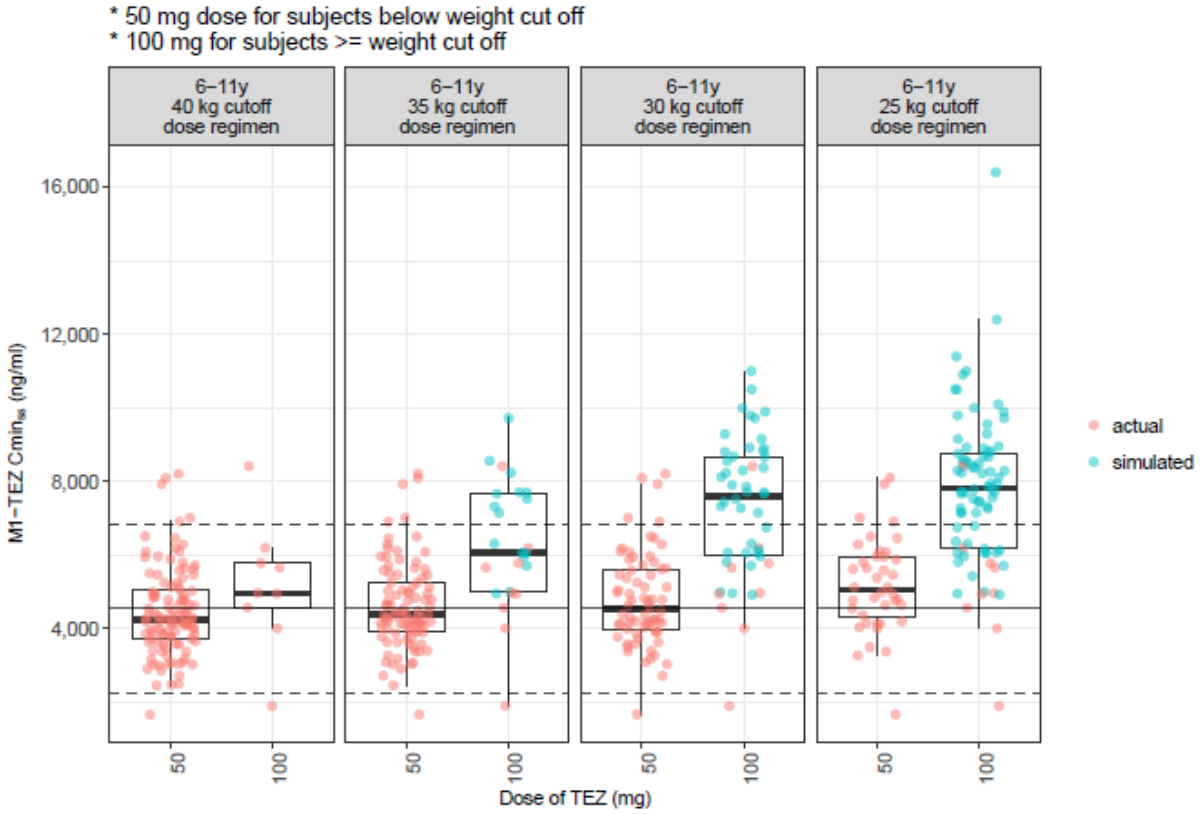


Exposure values are plotted for each dose for each dose regimen using box and whisker plots. Subjects with exposures associated with their studied dose are colored in red. Subjects who received a different dose based on their body weight and the simulated regimen are shown in blue. Median values are designated by a black line in the center 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 tezacaftor 100 mg QD (for TEZ and M1-TEZ) or IVA 150 mg bid (for IVA).

Figure 5 Predicted Steady-State IVA Exposures for Children from Six to Less Than Twelve Years Old (Studies 113 and 115) with Different Weight Regimens: Cmin (pop-PK report p266).





Exposure values are plotted for each dose for each dose regimen using box and whisker plots. Subjects with exposures associated with their studied dose are colored 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 center 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 tezacaftor 100 mg QD (for TEZ and M1-TEZ) or IVA 150 mg bid (for IVA).

A tabulated summary of the predicted TEZ, M1-TEZ, and IVA exposures with a 30-kg cut-off is presented in Table 7, with observed adult and adolescent exposures provided for reference.

Table 7 Summary of TEZ, M1-TEZ, and IVA predicted steady-state exposures (AUCss) by age group, 30-kg weight cut-off (popPK study P133)

Age Group / Weight		TEZ $AUC_{0\text{-}24h}$ (µg·h/mL) N	TEZ Mean (SD)	TEZ Min, Max	M1-TEZ $AUC_{0\text{-}24h}$ (µg·h/mL) N	M1-TEZ Mean (SD)	M1-TEZ Min, Max	IVA $AUC_{0\text{-}12h}$ (µg·h/mL) N	IVA Mean (SD)	IVA 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.

The ratio of M1-TEZ to TEZ was higher in subjects 6 through 11 years of age in studies 113 and 115 compared to adolescents and adults. However, the cause and significance of this difference remains unknown.

2.6.3. Pharmacodynamics

Tezacaftor is presumed to partially overcome the folding defect in *F508del-CFTR*, facilitating its correct cellular processing and trafficking, allowing the protein to reach the cell surface, where it exhibits improved chloride channel function compared to uncorrected *F508del-CFTR*. The channel gating activity of *F508del-CFTR* delivered to the cell surface by tezacaftor can be potentiated by ivacaftor to further enhance chloride transport. In vitro, 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.

Primary pharmacodynamics

Sweat chloride (SwCl) was assessed in patients aged 12 years and older in the Phase 2 studies, Study 101 and 103, and in the Phase 3 studies, Study 106 (F/F) and Study 108 (F/RF), as a biomarker of *CFTR* activity.

In study 101, randomized, double-blind, placebo-controlled study, TEZ and TEZ/IVA at multiple dose levels in adult subjects with the F/F genotype and in adult and adolescent subjects with F/G551D were investigated. TEZ was evaluated as a monotherapy and as a combination therapy with IVA 150 mg or IVA 50 mg every 12 hours (q12h) to evaluate the contributions of TEZ and IVA and to evaluate dosing schedule. Four regimens of TEZ monotherapy and 8 regimens of TEZ/IVA combination therapy were planned for evaluation in subjects homozygous for *F508del*. A single regimen (TEZ 100 mg qd/IVA 150 mg q12h) was assessed in F/G551D subjects.

In F/F patients, monotherapy with tezacaftor 100 mg qd and 150 mg qd resulted in a mean treatment difference vs. placebo in the absolute change from baseline through day 28 in SwCl vs. placebo of -19.6 and -9.6 mmol/l respectively. The mean treatment difference of the combination of tezacaftor 100 mg qd and ivacaftor 150 mg q12h was -5.2 mmol/l. In F/G551D subjects, the mean treatment difference vs. placebo was -17.2 mmol/l.

The inferior effect of TEZ/IVA compared with TEZ on SwCl in the phase 2 study 101 is not fully understood. There appears to be no sufficient reasons to exclude the possibility that TEZ as monotherapy may have clinically relevant pharmacodynamic activity, particularly when there are also discrepancies within the *in vitro* data and there is evident complexity in the mechanisms involved in correcting the *CFTR* function. The results of exposure-response modelling, submitted at the time of initial MAA to support clinical superiority of TEZ/IVA over TEZ are limited, since the model appears to be more accurate for FEV1 than for SwCl, but there are limitations for interpretation because of the very wide confidence intervals around the predicted responses.

In the pivotal study 106 (F/F), the LS mean treatment difference between the TEZ/IVA and placebo groups for the absolute change from baseline in SwCl was -9.1 mmol/L (95% CI: -10.7, -7.5) at week 4. Through Week 24, the LS mean treatment difference was -10.1 mmol/L (95% CI: -11.4, -8.8). Within group, the LS mean change in SwCl from baseline through Week 24 was -9.9 mmol/L in the TEZ/IVA group and 0.2 mmol/L in the placebo group.

In study 108 (F/RF), the LS mean treatment difference versus placebo for the absolute change in SwCl from study baseline to the average of Week 4 and Week 8 was -9.5 mmol/L (95% CI: -11.7, -7.3) for TEZ/IVA and -4.5 mmol/L (95% CI: -6.7, -2.3) for IVA. The reduction in SwCl levels was greater in TEZ/IVA group than in the IVA group. The LS mean treatment difference for the absolute change in SwCl from study baseline to the average of Week 4 and Week 8 was -5.1 mmol/L in favour of TEZ/IVA (95% CI: -7.0, -3.1; P<0.0001)

Sweat chloride responses were also determined in study 113B and study 115 in children ages 6 to less than 12 years. In study 115, the LS mean absolute change from baseline in SwCl at Week 8 was -12.3

mmol/L (95% CI: -15.3, -9.3) in the TEZ/IVA group. In study 113B, the LS mean absolute change from baseline through Week 24 was -14.5 mmol/l (95% CI: -17.4, -11.6).

Given the shift proposed in the body weight cut-off for dosing recommendations in children aged 6 to less than 12 years, the MAH was requested to discuss and demonstrate that the predicted increased exposure in children weighing ≥30 to less than 40 kg will likely result in improved efficacy outcomes than those observed in study 115 while efficacy is not negatively affected in children weighing less than 30 kg of body weight as the predicted systemic exposure is at the lower end of that of older patients. To that end PK/PD analyses of sweat chloride were provided. 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 6 and 7).

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

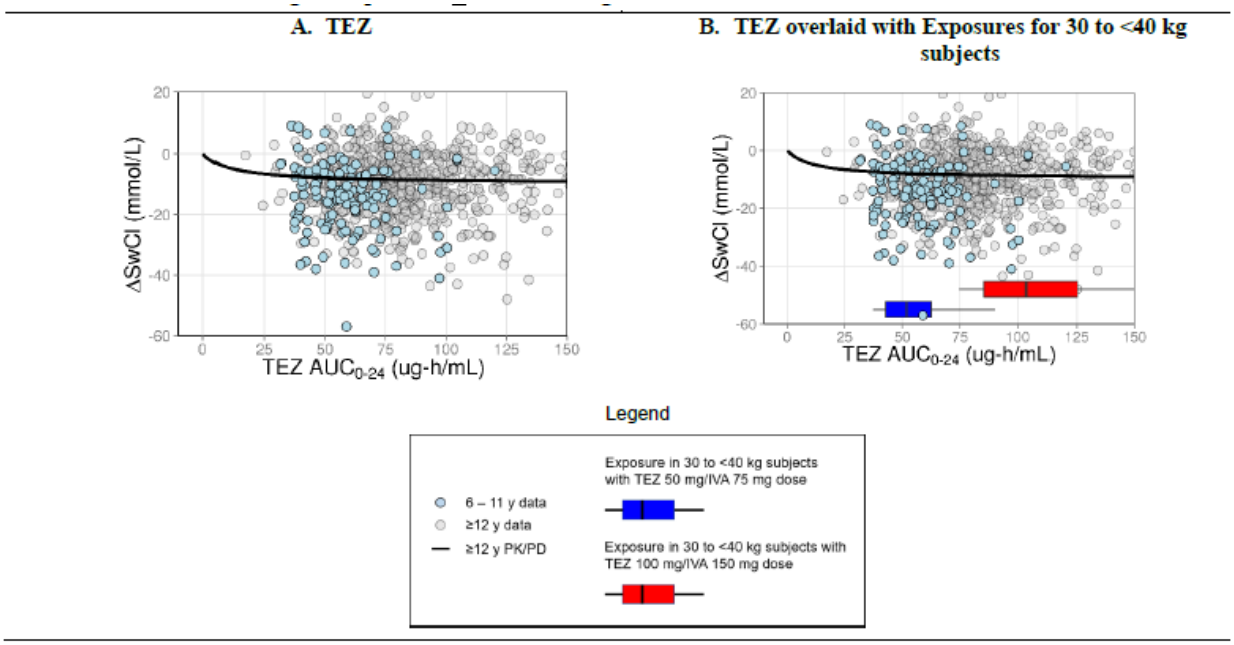
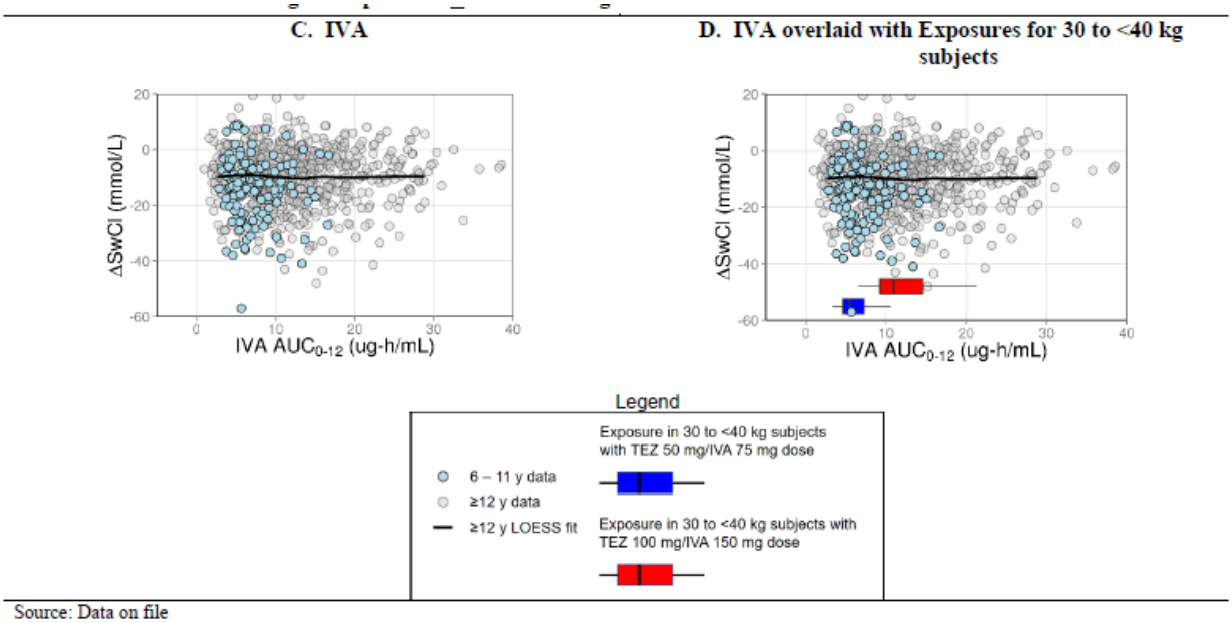


Figure 7 PK/PD relationships of Sweat Chloride Response versus IVA Exposures in Subjects 6 Through 11 Years of Age Compared to ≥12 Years of Age



Source: Data on file

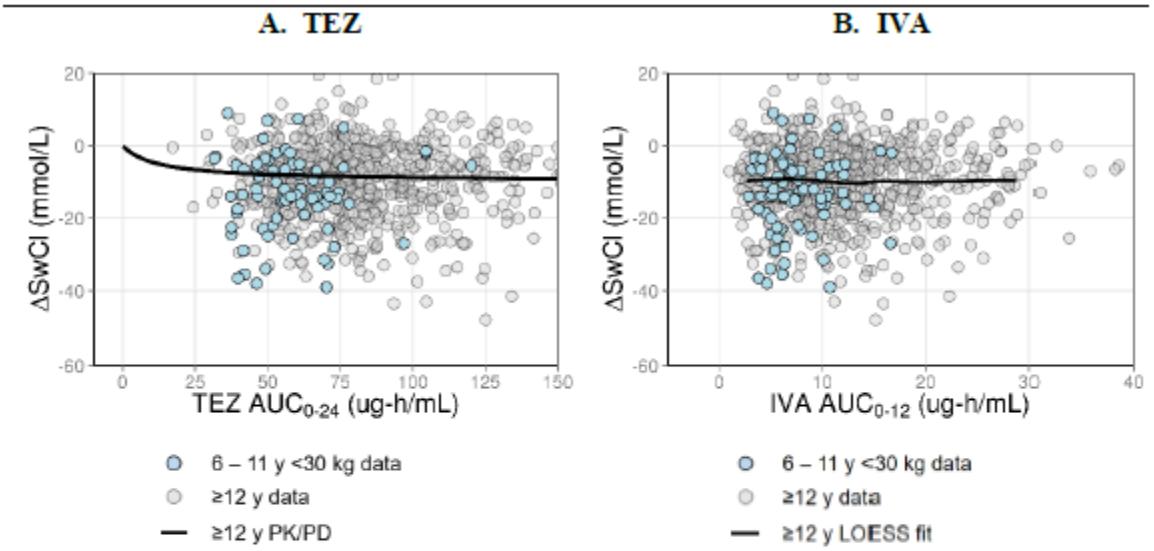
ΔSwCl: change in sweat chloride from baseline; F/F: homozygous for *F508del-CFTR* mutation; IVA: ivacaftor; LOESS: locally estimated scatterplot smoothing; PK/PD: pharmacokinetic/ pharmacodynamic relationship; TEZ: tezacaftor; y: year

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).

The observed sweat chloride response in subjects 6 through 11 years of age overlaps with the response observed in 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.

Sweat chloride PK/PD responses in subjects 6 through 11 years of age weighing <30 kg are shown in Figure 8.

Figure 8 PK/PD relationships of Sweat Chloride Response versus TEZ or IVA Exposures in Subjects 6 Through 11 Years of Age Weighing <30 kg Compared to ≥12 Years of Age



Source: Data on file
ΔSwCl: change in sweat chloride from baseline; F/F: homozygous for the *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, <30 kg only). 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.

Decreases in sweat chloride observed in subjects <30 kg were similar to the overall decrease observed in the TEZ/IVA group of study 115 and similar to that of subjects ≥12 years of age. TEZ/IVA-treated subjects who weighed <30 kg had a mean (SD) decrease in sweat chloride of -12.8 (10.6) mmol/L at Week 8, similar to the overall TEZ/IVA treatment group (mean [SD] change in sweat chloride at Week 8: -12.5 [10.3] mmol/L). This improvement was also similar in magnitude to the within-group -9.9 mmol/L decrease in sweat chloride observed in subjects ≥12 years of age in Study 106.

Secondary pharmacodynamics

The potential QTc prolongation of tezacaftor has been evaluated in a dedicated study in 116 healthy volunteers. It was concluded that tezacaftor at supratherapeutic dose did not prolong the QTcF interval in healthy subjects. The conduct of a dedicated QTc study with only TEZ is considered justified because tezacaftor has only a modest effect on the exposure of IVA. Since IVA has been shown not to prolong the QTc interval at supratherapeutic doses of 450 mg q12h, the increased IVA exposure in combination with TEZ is not considered relevant with respect to the probability to influence the QTc.

2.6.4. Discussion on clinical pharmacology

The main goal of the clinical pharmacology programme was to select a dosing regimen that would achieve TEZ and IVA parental exposures in children 6 through 11 years of age that were comparable to those shown to be safe and efficacious in the pivotal studies of subjects ≥12 years old with F/F and F/RF genotype.

This line extension proposes an additional lower strength tablet of Kalydeco (75 mg) to be administered in combination with Symkevi (TEZ/IVA) at a dose of 50 mg qd/75 mg q 12h for children weighing less than 30 kg or at 100 mg qd/150 mg q12 h for children weighing ≥ 30 kg. The lack of demonstration of bioequivalence between the new strength of 75 mg vs. the marketed 150-mg tablet of Kalydeco is considered acceptable based on the general requirements described in section 4.1.6 of the Guideline on Investigation of Bioequivalence, i.e., same manufacturing process, linear pharmacokinetics over the therapeutic range, same qualitative composition, same ratio between active substance and excipients, and similar dissolution profile under identical conditions between both strengths.

To support the extension of the indication for ivacaftor in combination with TEZ/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.

In study 113, tezacaftor and its metabolites as well as IVA and its metabolites in plasma were assayed according to previously reported analytical methods.

In study 113A, in children weighing less than 25 kg, tezacaftor 50 mg was administered as a 50-mg tablet using 500 mg/g of a spray-dried dispersion while ivacaftor 75 mg was administered as a capsule containing ivacaftor 75 mg granules spray-dried dispersion. None of these correspond to the formulations to be marketed, i.e., the TEZ 50-mg/IVA 75-mg FDC and IVA 75-mg tablet. However, the granule formulation of ivacaftor was tested in bioavailability and food effect study (study 770-015) and considered comparable to the film-coated tablet formulation under fed conditions. Children weighing ≥ 25 kg in Study 113A were dosed with the marketed formulation of IVA 150 mg and with a TEZ 50-mg monotherapy tablet not intended for marketing. 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 who 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 weighing at least 30 kg 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 of body weight 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 predicted 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. In addition, the MAH 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 appears 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. The actual cause for the increased formation of M1-TEZ remains unclear, but the relationship between the increased exposure of TEZ + M1-TEZ versus TEZ among the efficacy and safety endpoints have been explored by the MAH. 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 (e.g.) 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 albeit based on a limited number of patients.

No update was provided on pharmacodynamics which is 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.

The CHMP recommended the MAH to submit a new application to register the ivacaftor 75 mg granules formulation for the use in combination with Symkevi in order to provide paediatric patients who are not able to swallow tablets with an appropriate formulation. However, the MAH did not agree with this recommendation. It is therefore not expected that the MAH will submit a new application for the 75 mg granules formulation to allow its use in combination with Symkevi for patients not able to swallow tablets.

2.6.5. 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 agreeable even though the regimen TEZ 100mg qd/IVA 150 mg q12h has not been investigated in studies 113B or 115 in children weighing ≥ 30 kg to less than 40 kg. This is reflected in section 5.2 of the SmPC of Kalydeco tablets where it is stated that exposures in children aged 6 to less than 12 years old weighing ≥ 30 kg to less than 40 kg are predictions derived from the population PK model.

he CHMP recommended the MAH to submit an application for the 75 mg granules formulation to allow its use in combination with Symkevi for patients not able to swallow tablets. This was not agreed by the MAH.

2.7. Clinical efficacy

2.7.1. Dose response study

The proposed posology for children aged 6 to less than 12 years is based on the principle of exposure matching between this population and a reference population (adults/adolescents). A model-based analysis of the systemic exposure of TEZ, IVA, and M1-TEZ led the MAH to shift the body weight cut-off from 40 kg to 30 kg (please refer to Section 3.2.6. Discussion on clinical pharmacology).

2.7.2. 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.

Methods

Study design

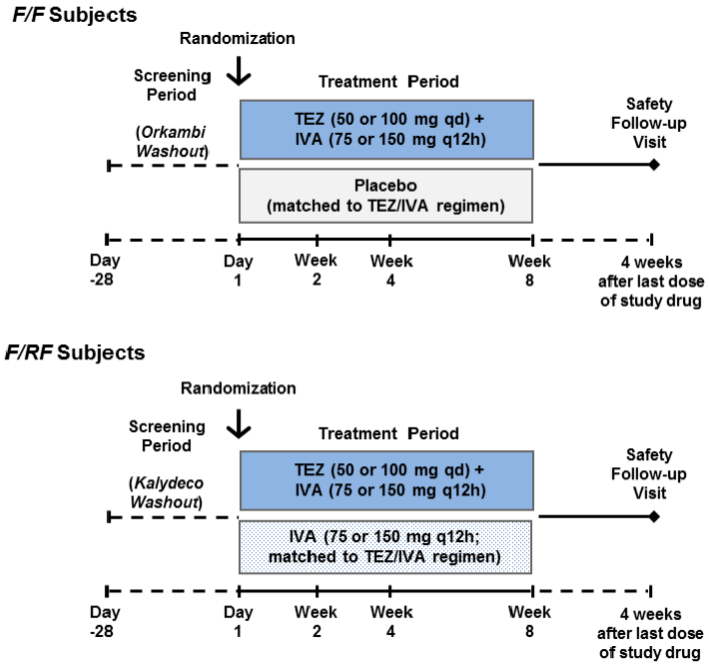
After the screening period of 4 weeks, patients were stratified by genotype before randomization so that F/F and F/RF patients would be randomized in a 4:1 ratio to either the TEZ/IVA group or the appropriate blinding group for their genotype. The F/F blinding group received placebo and the F/RF blinding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

Subjects who were taking commercially available *CFTR* modulators (Orkambi or Kalydeco) were required to washout for 28 days before the Day 1 Visit. Study drug dose was determined based on weight on Day 1 (<40 kg or ≥40 kg).

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 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.

Figure 9. 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.

Study Participants

Patients were children aged 6 to 11 years (inclusive) with a confirmed diagnosis of CF. Patients were homozygous for *F508del-CFTR* or heterozygous for *F508del*. Heterozygous patients must have a second eligible mutation within the ones listed in Table 9. Genotyping was performed using a validated CF genotyping test and the diagnosis of CF confirmed if sweat chloride value was ≥60 mmol/l.

Heterozygous patients with sweat chloride less than 60 mmol/L could be enrolled if they had documented evidence of chronic sinopulmonary disease and/or gastrointestinal disease consistent with a diagnosis of CF.

Table 9 CFTR residual function mutation, accepted for inclusion of the heterozygous F/RF patients in study VX16-661-115- FAS

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 labelling of Kalydeco in combination with Symkevi.

Enrolment was limited to patients with $LCI_{2.5}$ result ≥7.5 at the Screening Visit, a body weight ≥ 15 kg, percent predicted FEV1 ≥70 percentage points and the ability to swallow the tablets. 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 two 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; or (d) hemoglobin <10 g/dL).

Treatments

The treatments applied in this study was the study drug tezacaftor/ivacaftor. The comparators were placebo (*F508del/F508del,* F/F) or ivacaftor (*F508/CFTR* mutation of residual function*,* F/RF).

Tezacaftor/ivacaftor (F/F or F/RF)

- Patients who were <40 kg at the Day 1 Visit received 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 were ≥40 kg at the Day 1 Visit received 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 were <40 kg at the Day 1 Visit received 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 were ≥40 kg at the Day 1 Visit received 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 (*F/F*)

- Patients randomised to placebo were given matching placebos in the morning and evening

Study drug was administered within 30 minutes of the consumption of fat-containing food such as a standard CF high-fat, high-calorie meal or snack by the subject.

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 there was potential for untoward drug-drug interactions, such as CYP3A4 inducers and CYP3A4 inhibitors.

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

Objectives

The primary objective was to evaluate efficacy of TEZ/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 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 F/F and F/FR 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 LCI assessment device used in Study 115 was the Exhalyzer D (Ecomedics, Duernten, Switzerland). Central review of $LCI_{2.5}$ measurements was conducted.

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 $LCI_{5.0}$ (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), weight, and height and associated z-scores 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-1
- Absolute change from baseline in immunoreactive trypsinogen

Randomisation and blinding (masking)

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.

The main purpose of these two groups (i.e. placebo and IVA monotherapy) is 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 were provided for change from baseline in LCI2.5 at each post-baseline visit for homozygous subjects in the placebo group.

Statistical methods

Sample size

The study planned to enrol approximately 65 subjects, of which up to 15 subjects should be heterozygous for RF.

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 $LCI_{2.5}$ in subjects on TEZ/IVA) to exclude a maximum possible placebo effect. The size of the placebo effect was based on study VX14-809-109 (study 109) in which treatment with LUM/IVA in homozygous *F508del* subjects aged 6 through 11 years was assessed using the between-group difference in absolute change from baseline through week 24 in $LCI_{2.5}$ as the primary efficacy endpoint. In Study 109, the placebo group had a mean worsening in $LCI_{2.5}$ 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.

Per the protocol and SAP, 40 subjects with the F/F genotype were specified receive TEZ/IVA to provide at least 90% power to exclude the predefined placebo effect. Power calculations were not performed for subjects with the F/RF genotype because this genotype is rarer compared to the F/F genotype; therefore, less historical data were available for this population to help ascertain how many of these subjects should be enrolled in Study 115. Per the protocol and SAP, 9 subjects with the F/RF genotype were specified to receive TEZ/IVA.

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 in 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.

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 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.

Sweat Chloride (secondary endpoint)

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 (secondary endpoint)

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

A similar MMRM model will be used for the FEV1 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 for age, weight, weight-for-age-z-score, height, height for age score, drug acceptability, faecal elastase-1 and immunoreactive trypsinogen, and pharmacokinetic endpoints like TEZ, M1-TEZ, IVA, M1-IVA. For these endpoints, only summary tables were to be provided.

Placebo group

The main purpose of the placebo group was to preserve blinding. Therefore, only summary statistics such as mean and SD were provided for change from baseline in $LCI_{2.5}$ at each post-baseline visit for homozygous subjects in the placebo group.

Safety analyses

All safety analyses were based on the Safety Set (which included all subjects who received at least 1 dose of study drug). Only descriptive summaries were presented, and no hypothesis testing was performed.

Results

Participant flow

Twenty-three screened subjects were not enrolled. The main reasons for screening failure was $LCI_{2.5}$ < 7.5 (n=11), having ppFEV1 <70 percentage points 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).

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). A total of 52 F/F subjects received at least 1 dose of study drug (42 subjects in the TEZ/IVA group and 10 subjects in the placebo group). Fifteen F/RF subjects received at least 1 dose of study drug (12 subjects in the TEZ/IVA group and 3 in the IVA group).

Two subjects were randomized but not dosed in Study 115 for the following reasons, i.e., in the placebo group, 1 subject had an acute upper and lower respiratory infection on the planned first day of dosing and in the TEZ/IV group, 1 subject had an AE of lower respiratory tract infection subjects on the day of randomization. Both subjects met Exclusion Criterion 4 and were no longer eligible to participate in the study.

Of the 67 patients who received at least 1 dose of study drug, 66 (98.5%) completed study drug treatment. One patient in the TEZ/IVA group prematurely discontinued treatment, because the patient's screening $LCI_{2.5}$ did not meet the eligibility criteria.

Table 10 Subject Disposition, All Subjects Set

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 study drug 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)
Completed study[d]	10 (100)	3 (100)	53 (98.1)	66 (98.5)
Prematurely discontinued the study	0	0	1 (1.9)	1 (1.5)
Adverse event	0	0	0	0
Other	0	0	1 (1.9)	1 (1.5)

Source: Table 14.1.1
IVA: ivacaftor; TEZ: tezacaftor
Note: If a subject discontinued treatment for multiple reasons, the subject was counted in each category but counted only once in the total number of subjects who prematurely discontinued treatment.
[a] All subjects who were randomized or received at least 1 dose of study drug
[b] All subjects who received at least 1 dose of study drug
[c] All subjects who were randomized, received at least 1 dose of study drug, and had an eligible *CFTR* genotype
[d] A subject was considered to have completed the study if they completed all the scheduled visits and either completed the Safety Follow-up Visit or enrolled in the extension study.

The FAS included all subjects who were randomized, received at least 1 dose of study drug, and had an eligible *CFTR* genotype. The Safety Set included all subjects who received at least 1 dose of study drug. In this study the FAS and the Safety Set were the same and included 67 subjects.

Recruitment

Study 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.

Conduct of the study

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).

Safety and tolerability data were reviewed by an independent data monitoring committee (IDMC).

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).

There were two Important Protocol Deviations in the study, both related to inclusion/exclusion criteria. One randomised patient did not meet the inclusion criteria for the $LCI_{2.5}$ value at screening. This patient discontinued the study. Another patient had a change in antibiotic therapy for pulmonary disease within 28 days before Day 1.

Baseline data

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. Comparable baseline demographics were observed in the TEZ/IVA group with respect to the overall FAS population of study 115.

Table 11 Subject Demographics, Study 115 FAS

	Placebo N = 10	IVA N = 3	TEZ/IVA N = 54	Total N = 67
Sex, n (%)				
Male	4 (40.0)	1 (33.3)	25 (46.3)	30 (44.8)
Female	6 (60.0)	2 (66.7)	29 (53.7)	37 (55.2)
Childbearing potential, n (%)				
Yes	0	0	0	0
No	6 (100)	2 (100)	29 (100)	37 (100)
Age at screening (years)				
n	10	3	54	67
Mean (SD)	9.0 (1.7)	9.0 (1.7)	8.5 (1.7)	8.6 (1.7)
Median	9.5	10.0	8.5	9.0
Min, max	6, 11	7, 10	6, 11	6, 11
Ethnicity, n (%)				
Hispanic or Latino	0	0	1 (1.9)	1 (1.5)
Not Hispanic or Latino	10 (100)	3 (100)	46 (85.2)	59 (88.1)
Not collected per local regulations	0	0	7 (13.0)	7 (10.4)
Race, n (%)				
White	10 (100)	3 (100)	51 (94.4)	64 (95.5)
Black or African American	0	0	1 (1.9)	1 (1.5)
Asian	0	0	0	0
American Indian or Alaska Native	0	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0	0
Not collected per local regulations	0	0	2 (3.7)	2 (3.0)
Other	0	0	0	0
Geographical region, n (%)				
Europe[a]	9 (90.0)	2 (66.7)	42 (77.8)	53 (79.1)
Australia	1 (10.0)	1 (33.3)	12 (22.2)	14 (20.9)

Source: Study 115 CSR/Table 14.1.3
FAS: Full Analysis Set; IVA: ivacaftor; N: total sample size; n: size of subsample; TEZ: tezacaftor
[a] Includes Switzerland

Selected baseline characteristics are summarized in Table 12.

Table 12 Selected Baseline Characteristics, Study 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[a] (kg/m^2)				
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
$LCI_{2.5}$				
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
CFQ-R respiratory domain				
n	10	3	54	67
Mean (SD)	80.0 (21.2)	75.0 (22.0)	84.6 (11.4)	83.5 (13.6)
Median	83.3	83.3	83.3	83.3
Min, max	33.3, 100.0	50.0, 91.7	50.0, 100.0	33.3, 100.0

	Placebo N = 10	IVA N = 3	TEZ/IVA N = 54	Total N = 67
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
Use of dornase alfa[b], n (%)	8 (80.0)	3 (100)	41 (75.9)	52 (77.6)
Use of inhaled antibiotic[b], n (%)	2 (20.0)	0	8 (14.8)	10 (14.9)
Use of azithromycin[b], n (%)	1 (10.0)	0	4 (7.4)	5 (7.5)
Use of inhaled bronchodilator[b], n (%)	9 (90.0)	2 (66.7)	37 (68.5)	48 (71.6)
Use of inhaled hypertonic saline[b], n (%)	7 (70.0)	2 (66.7)	34 (63.0)	43 (64.2)
Use of inhaled corticosteroids[b], n (%)	5 (50.0)	1 (33.3)	11 (20.4)	17 (25.4)
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)

Source: Study 115 CSR/Table 14.1.4

BMI: body mass index; CFQ-R: Cystic Fibrosis Questionnaire-Revised; FAS: Full Analysis Set; F/F: homozygous for the *F508del-CFTR* mutation; F/RF: heterozygous for *F508del* and a second *CFTR* allele with residual function; IVA: ivacaftor; $LCI_{2.5}$: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value; N: total sample size; n: size of subsample; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

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

[a] BMI = weight / (height × height)

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

In total, 52 (77.6%) subjects had the F/F genotype and 15 (22.4%) subjects had F/RF genotypes. The TEZ/IVA group included 42 patients with an F/F mutation and 12 with an F/RF mutation. All patients with a F/RF genotype harboured a mutation of residual function included in the adult indication. The included RF mutations were *2789+5G>A* (n=3); *3849+10kbC>T* (n=5); *A455E* (n=2); *3272-26A>G* (n=3); *R117C* (n=1); and *P67L* (n=1).

The mean (SD) $LCI_{2.5}$ at baseline was 9.54 (1.97) and mean (SD) at baseline was ppFEV1 87.1 (12.2) percentage points.

Most subjects (n=64, 95.5%) weighed <40 kg at baseline. A total of 28 patients weighted ≥30 to less than 40 kg.

The mean (SD) weight at baseline was 29.4 (6.7) kg, and the mean (SD) baseline weight z-score was -0.24 (0.70), i.e., within the ±2SD of the population of reference indicative of normal weight. Similarly, the mean (SD) baseline BMI was 16.13 (1.56) kg/m2 and the mean (SD) baseline BMI z-score was -0.26 (0.78). The mean (SD) baseline height was 134.1 (12.0) cm and the mean (SD) baseline height z-score was -0.03 (1.02).

The majority of subjects (79.1%) were negative for *Pseudomonas aeruginosa* in the 2 years before study start. Although not shown in Table 11, all homozygous *F508del* subjects had exocrine pancreatic insufficiency as the maximum value of faecal elastase-1 at baseline was 94 µg/g. All F/RF subjects were pancreatic sufficient.

Baseline characteristics have also been provided by genotype within the TEZ/IVA group. Among F/F subjects (n=42), 47.6% (20/42) were males and the mean (SD) age was 8.5 (1.6) years. Forty-one (97.6%) weighed less than 40 kg and the median (min, max) weight-for-age z-score was -0.31 (-1.86, 1.42). Mean (SD) ppFEV1 was 85.1 percentage points (12.9) with a minimum value of 57.9. Mean (SD) LCI2.5 was 9.84 (2.17) and mean (SD) sweat chloride was 107.1 mmol/l (6.5). In the subgroup of F/RF subjects (n=12), 41.7% were males and the mean (SD) age was 8.5 (1.9) years. Almost 92% of them weighed less than 40 kg with a median (min, max) weight-for-age z-score of -0.01 (-1.01, 0.93), a mean (SD) ppFEV1 of 91.2 percentage points (12.4), a mean (SD) LCI2.5 of 8.60 (1.30) and

a mean sweat chloride of 73.5 (25.2) mmol/l. Overall, these baseline data show that disease severity is higher in homozygous *F508del* subjects than in heterozygous *F508del/RF* subjects.

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%).

Prior and concomitant medications

The most common medications (≥30% of total subjects) prior to the start of the study were sodium chloride (88.1%), dornase alfa (77.6%), pancreatin (73.1%), and salbutamol (59.7%). A total of 3 patients were being treated with Orkambi prior to study start. One patient was randomised to placebo, the other two to TEZ/IVA.

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%).

Numbers analysed

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

Table 13 Populations of analysis, Study 115

	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

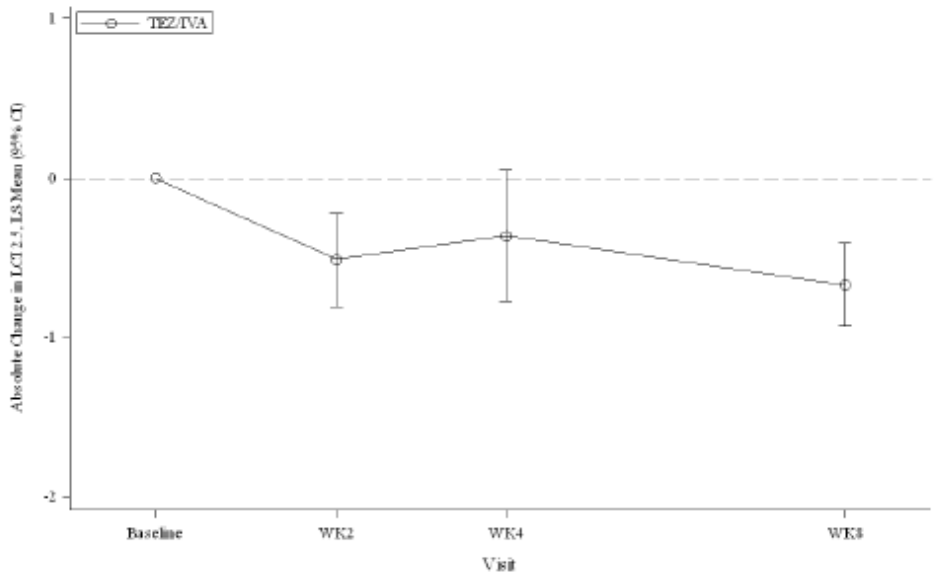
Source: Table 14.1.1.
IVA: ivacaftor; TEZ: tezacaftor
[a] All Subjects Set included all subjects who were randomized or received at least 1 dose of study drug.
[b] Safety Set included all subjects who had received at least 1 dose of study drug.
[c] Full Analysis Set included all subjects who were randomized, received at least 1 dose of study drug, and had an eligible genotype.

Outcomes and estimation

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

The mean (SD) $LCI_{2.5}$ at baseline was 9.56 (2.06) and 8.90 (1.80) at week 8 for the TEZ/IVA group. The within-group LS mean (SE) absolute change from baseline in $LCI_{2.5}$ through Week 8 was -0.51 (0.11) (95% CI: -0.74 to -0.29; P <0.0001) (see also Figure 10). The upper bound of the 95% CI (-0.29) was below the pre-specified maximum placebo effect of -0.10.

Figure 10 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; $LCI_{2.5}$: 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 $LCI_{2.5}$, and genotype (F/F vs. F/RF) as covariates. The model used an unstructured covariance and Kenward-Roger degrees of freedom.

The MMRM analysis makes use of all available data but at week 8, data were only available for 49 patients out of the 54 in the TEZ/IVA FAS which represents nearly 10% of missing data. Similarly, the analysis through week 8 takes the risk of mitigating deleterious effects over time compared to the change from baseline at week 8. Therefore, additional analyses were requested by CHMP. First, the MAH was requested to provide an analysis of the between-treatment difference versus placebo at Week 8 using placebo mean imputation for all patients with data not recorded at that week. This has been performed using an MMRM analysis. At baseline, the mean (SD) $LCI_{2.5}$ values were 9.67 (1.65) and 9.56 (2.06) in the placebo and the TEZ/IVA groups respectively. The LS mean difference vs. placebo at week 8 was -0.59 (95% CI: -1.22, 0.05). The same analysis restricted to F/F subjects resulted in a LS mean treatment difference vs. placebo of -0.57 (95% CI: -1.23, 0.09). Then, a reanalysis of the TEZ/IVA within-group absolute change in LCI2.5 at Week 8 and through Week 8 using MMRM with baseline as a covariate and placebo-mean used for imputation of missing data. This analysis was performed for the overall TEZ/IVA group, F/F subjects, and F/RF subjects (Table 14).

Table 14 MMRM Analysis of Absolute Change From Baseline in LCI2.5 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)

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.

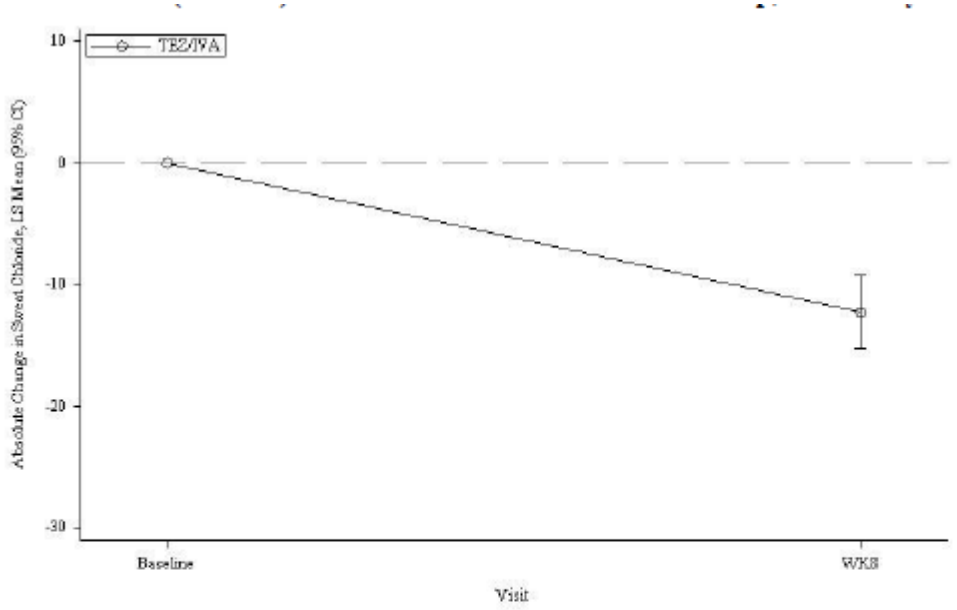
The overall TEZ/IVA group (F/F and F/RF combined) had a within-group change in $LCI_{2.5}$ of -0.48, with a 95% CI that excludes the predefined placebo effect of -0.10. Analysis of change in $LCI_{2.5}$ by genotype was consistent with subgroup analysis based on summary statistics in which the mean absolute change in $LCI_{2.5}$ from baseline through week 8 was -0.39 (95% CI: -0.67, -0.10) in F/F patients and -0.92 (95%CI: -1.65, -0.20) in F/RF patients based on data from 42 F/F patients and 12 F/RF patients (see Table 16 further below).

Secondary Endpoints

- **Sweat chloride test**

In the TEZ/IVA group, the mean (SD) sweat chloride at baseline was 99.2 (19.5) mmol/l and at week 8 (n=49) it was 88.4 (18.6) mmol/l. The LS mean (SE) absolute change from baseline in sweat chloride at Week 8 was -12.3 (1.5) mmol/L (95% CI: -15.3, -9.3) in the TEZ/IVA group (p<0.0001), (Figure 11).

Figure 11 MMRM Analysis of Absolute Change from Baseline in Sweat Chloride (mmol/L) at Each Visit within TEZ/IVA study VX16-661-115 Group Full Analysis Set



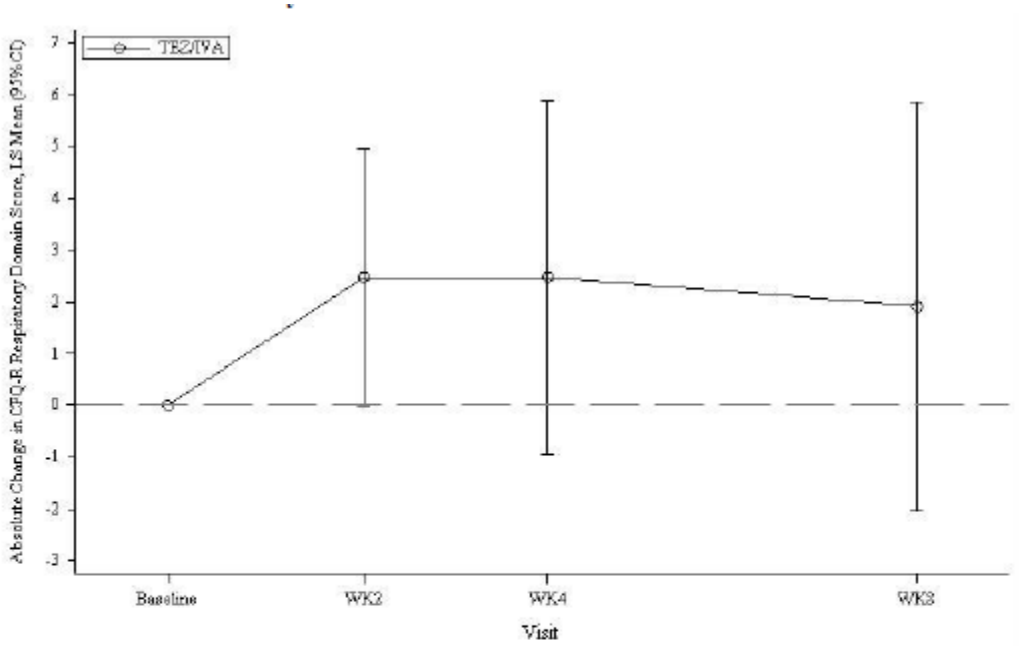
Source: Figure 14.2.2
IVA: ivacaftor; LS mean: least squares mean; MMRM: mixed-effects model for repeated measures; TEZ: tezacaftor
Notes: The *Y*-axis corresponds to the LS mean from the MMRM model analysis with all measurements up to Week 8 (including on-treatment and after treatment discontinuation). Baseline is the most recent non-missing measurement before the first dose of study drug. The MMRM included visit, baseline $LCI_{2.5}$, baseline sweat chloride, and genotype (F/F vs. F/RF) as covariates. The model used an unstructured covariance and Kenward-Roger degrees of freedom.

Similarly to the primary endpoint, an analysis of the absolute change from baseline at Week 8 using placebo mean imputation for all patients with data not recorded at Week 8 was requested by CHMP. The MMRM analysis of the absolute change from baseline at week 8 in sweat chloride using placebo-mean imputation yielded a LS mean difference vs. placebo of -10.9 mmol/l (95% CI: -18.4, -3.3). The same analysis restricted to F/F subjects resulted in a LS mean treatment difference vs. placebo of -10.0 mmol/l (95% CI: -17.0, -3.0).

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

In the TEZ/IVA treatment group, the mean (SD) respiratory domain score of the CFQ-R was 84.6 (11.4) points at baseline. The LS mean (SE) absolute change from baseline in the CFQ-R respiratory domain score through Week 8 was 2.3 (1.2) points (95% CI; -0.1, 4.6), (Figure 12).

Figure 12 MMRM Analysis of Absolute Change from Baseline in CFQ-R Respiratory Domain Score (Child Version) at Each Visit within TEZ/IVA VX16-661-115 Group Full Analysis Set



Source: Figure 14.2.3
CFQ-R: Cystic Fibrosis Questionnaire Revised; IVA: ivacaftor; 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 $LCI_{2.5}$, baseline CFQ-R respiratory domain score, and genotype (F/F vs. F/RF) as covariates. The model used an unstructured covariance and Kenward-Roger degrees of freedom.

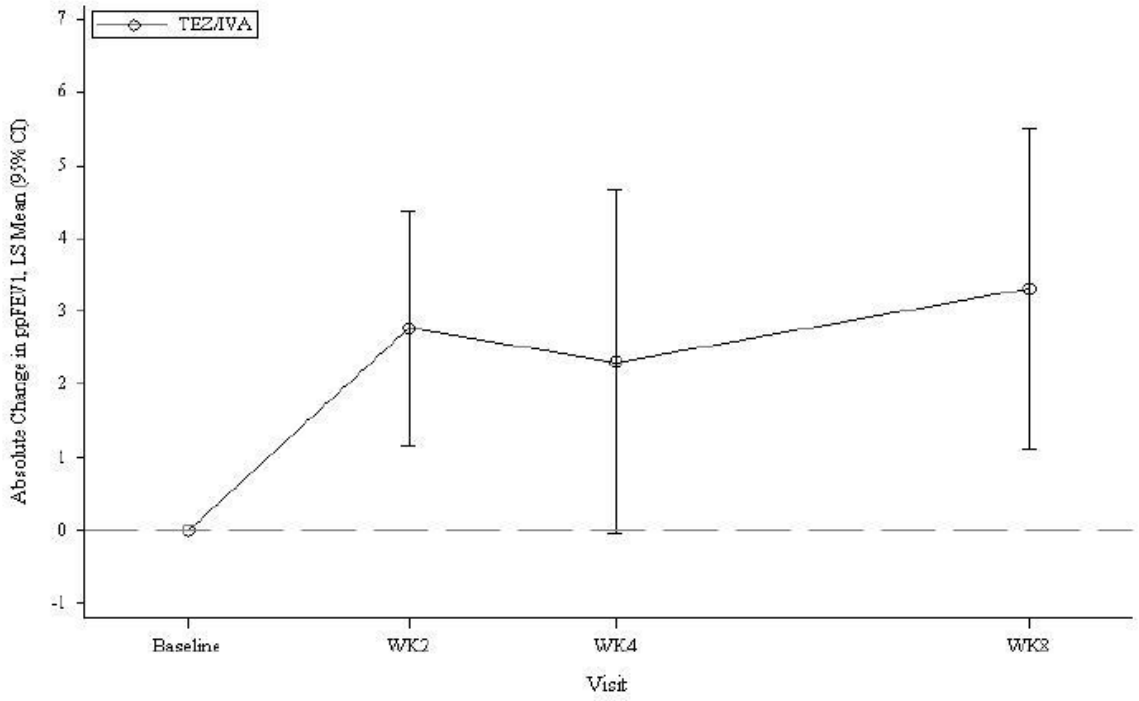
Other Endpoints

- **Percent predicted FEV1**

In the TEZ/IVA group, the mean (SD) ppFEV1 at baseline was of 86.5 (12.9) percentage ooints. At week 8, the mean (SD) ppFEV1 was 89.9 (12.4) percentage points. The LS mean (SE) difference in FEV_1 from baseline through week 8 was 2.8 (0.9) percentage points (95% CI: 1.0, 4.6) (Figure 13).

Summary statistics of the change from baseline at week 8 and through week 8 for ppFEV1 are provided by genotype for the TEZ/IVA group. The mean (SD) absolute change absolute change through week 8 was 2.6 (7.0) percentage points in F/F patients (n=41) and 3.7 (7.2) percentage points in F/RF patients (n=12).

Figure 13 MMRM Analysis of Absolute Change from Baseline in Pre-dose ppFEV1 (Percentage Points) at Each Visit within TEZ/IVA - VX16-661-115-Group Full Analysis Set



Source: Figure 14.2.5

IVA: ivacaftor; LS mean: least squared mean; MMRM: mixed model of repeated measures; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

Note: 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 $LCI_{2.5}$, $ppFEV_1$, and genotype (F/F vs. F/RF) as covariates. The model used an unstructured covariance and Kenward-Roger degrees of freedom.

- **Additional endpoints**

The additional endpoints for the comparison of baseline through week 8 for the TEZ-IVA group are provided in Table 15.

Table 15 Results of 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)

Sources: Table 14.2.1.3, Table 14.2.4.2, and Table 14.2.5.1
BMI: body mass index; IVA: ivacaftor; $LCI_{5.0}$: number of lung turnovers required to reduce the end tidal inert gas concentration to 5.0% of its starting value; LS mean: least squares mean; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

An analysis of the absolute change from baseline at Week 8 using placebo mean imputation for all patients with data not recorded at Week 8 was requested by CHMP for $LCI_{5.0}$. For F/F subjects, the MMRM analysis of the absolute change from baseline at week 8 in $LCI_{5.0}$ using placebo-mean imputation yielded a LS mean difference vs. placebo of -0.19 (95% CI: -0.46, 0.09).

- **Exocrine pancreatic function**

In the TEZ/IVA group, baseline values of faecal elastse-1 (FE-1) and immunoreactive trypsinogen (IRT) differed between F/F subjects and F/RF subjects. All 40 F/F subjects with baseline data had FE-1 levels ≤200 µg/g, consistent with pancreatic insufficiency whereas all F/RF subjects had baseline FE-1 levels ≥500 µg/g, consistent with normal pancreatic function.

No subject with a baseline FE-1 level ≤200 µg/g became pancreatic sufficient (i.e., had an FE-1 level >200 µg/g) after TEZ/IVA treatment. The mean (SD) change from baseline in FE-1 at Week 8 among pancreatic-insufficient subjects in the TEZ/IVA group was 1.6 (16.9) µg/g. All of the 10 subjects with baseline data in the placebo group were pancreatic insufficient at both baseline and Week 8.

The normal range levels for IRT were 140 to 400 ng/mL; values below the LLQ were imputed with half the LLQ value, or 7.0 ng/mL. At baseline, pancreatic-insufficient subjects had a median IRT value of 7.0 ng/mL (i.e., >50% of subjects' IRT levels were below the LLQ of the assay) and a mean (SD) IRT value of 48.3 (102.2) ng/mL. After 8 weeks of TEZ/IVA treatment, the median IRT value remained 7.0 ng/mL and the mean IRT value decreased with a mean (SD) change from baseline of -20.4 (53.4) ng/mL. For pancreatic-sufficient subjects, the mean (SD) baseline IRT level was 544.2 (308.6) ng/mL. After 8 weeks of TEZ/IVA treatment, the mean (SD) change in IRT was -235.4 (246.2) ng/mL.

A comparison of the change from baseline in faecal elastase-1 and immunoreactive trypsinogen by baseline FE-1 values (≤200 µg/g vs. > 200 µg/g) observed in the studies of lumacaftor/ivacaftor and ivacaftor alone in children of the same age range was requested. In response, it has been clarified that the assays used to assess FE-1 were the same in study 115 and study 809-109 (lumacaftor/ivacaftor) but differed in case of IRT. The MAH stated that direct comparisons of these parameters across these studies are hampered given the differences in treatment duration (8 weeks in study 115 vs. 24 weeks in study 109), subject genotype, assay collection, and statistical methodology. Nevertheless, data were

provided for study 109 (homozygous *F508del* children treated for 24 weeks with lumacaftor/ivacaftor) which showed similar results to those of study 115 in F/F patients.

In the IVA program, FE-1 and IRT were evaluated in study 770-110, which enrolled subjects 6 years of age and older with the *R117H* mutation; these data are not comparable to those in the TEZ/IVA program due to the different age range (including mostly adult subjects) and different genotype (usually associated to exocrine pancreatic sufficiency at young ages).

- **Drug Acceptability Questionnaire**

Results of the Drug Acceptability Questionnaire indicated that, after taking TEZ/I.VA, 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 group

Demographics and baseline disease characteristics

The placebo group only include patients with *F508del/F508del* 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 16.07 (1.02) Kg/m^2. The corresponding mean (SD) z-scores were -0.19 (0.62) and -0.24 (0.37) respectively.

Selected baseline disease characteristics were as follows: mean (SD) $LCI_{2.5}$ was 9.67 (1.65), $ppFEV_1$ was 89.6 (10.1) percentage points, and sweat chloride 103.8 (7.5) mmol/L.

Results

- **$LCI_{2.5}$**

The mean (SD) absolute change from baseline in $LCI_{2.5}$ through Week 8 was 0.33 (0.75); the mean (SD) absolute change from baseline in $LCI_{2.5}$ at Week 8 was 0.10 (1.16) (Table 16).

- **Sweat chloride**

The mean (SD) absolute change from baseline at week 8 (n=7) was -1.0 (12.3) mmol/L (Table 17).

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

The mean (SD) baseline CFQ-R was 80 (21.2) points. The mean (SD) absolute change from baseline through week 8 was 7.5 (19.0) points while at week 8 it was 9.2 (23.1) points (Table 17).

- **ppFEV1 (percentage predicted)**

The mean (SD) pppFEV1 at baseline was 89.6 (10.6) percentage points. The mean (SD) change from baseline through week 8 was -2.9 (5.4) percentage points while at week 8 it was -3.7 (6.1) percentage points (Table 17).

TEZ/IVA group

The TEZ/IVA group consisted of a heterogeneous group of patients with F/F or F/RF mutation.

Demographics and baseline disease characteristics

The TEZ/IVA group included a total of 54 patients, with 42 of them homozygous for *F508del*. Of the F/F patients, 20 (47.6%) were 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 corresponding mean (SD) z-scores were -0.37 (0.73) and -0.34 (0.88) points.

The *F508del/RF* group included a total of 12 patients. Five (41.7%) were 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. The corresponding mean (SD) z-scores were 0.03 (0.62) and 0.02 (0.70), respectively

At baseline, ***F508del/F508del*** patients' mean (SD) ppFEV1 was 85.1 (12.9) percentage points, $LCI_{2.5}$ was 9.84 (2.17), and sweat chloride was 107.1 (6.5) mmol/L.
In ***F508del/RF*** patients, the mean (SD) baseline ppFEV1 was 91.2 (12.4) percentage points, $LCI_{2.5}$ was 8.60 (1.30), and sweat chloride was 73.5 (25.2) mmol/L.

In Table 16, Table 17, and Table 18 the summary of results according to the 2 subgroups of the TEZ/IVA group is provided (i.e. F/F and R/F). The results of the placebo and ivacaftor groups are included for comparison.

Table 16 Summary statistics for the primary outcome measure ($LCI_{2.5}$) - Study 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, mean (SD)				
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)	0.10 (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 17 Summary statistics for the secondary outcome measures - Study 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)	-1.0 (12.3)	-1.0 (9.0)
min, max	-38.0, 7.0	-35.0, 10.0	-19.5 (12.0)	-10.0, 8.0
CFQ R- Child version (respiratory domain)				
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 (19.0)	2.8 (7.3)

Table 18 Summary statistics for the additional outcome measures - Study 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**
$LCI_{5.0}$				
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)	-0.40 (0.55)	0.18 (0.23)	-0.47 (0.65)
FEV1 (L)				

	TEZ/IVA		Placebo	IVA
Genotype	**F/F**	**F/RF**	**F/F**	**F/RF**
Number of patients	**n=42**	**n=12**	**n=10**	**n=3**
baseline	1.50 (0.44)	1.65 (0.44)	1.7 (0.50)	1.85 (0.45)
absolute change at week 8	0.08 (0.16)	0.09 (0.12)	-0.02 (0.10)	0.04 (0.13)
absolute change through week 8	0.06 (0.12)	0.10 (0.14)	-0.02 (0.09)	
FEV1 (% predicted)				
Baseline	85.1 (12.9)	91.2 (12.9)	89.6 (10.6)	89.1 (5.7)
absolute change at week 8	3.2 (8.9)	2.9 (7.8)	-3.7 (6.1)	NP
absolute change trough week 8	2.6 (7.0)	3.7 (7.2)	-2.9 (5.4)	NP

Outcomes are reported as mean (SD)

Additional post-hoc analyses (as requested by the CHMP)

Responder analysis for $LCI_{2.5}$, sweat chloride, and the respiratory domain of CFQ-R for F/F subjects treated with placebo and TEZ/IVA in Study 115 are shown in Table 19.

Table 19 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
Change from baseline in $LCI_{2.5}$ through Week 8		
> -1	10/10 (100.0)	35/42 (83.3)
≤ -1	0/10	7/42 (16.7)
Change from baseline in sweat chloride at Week 8[a] (mmol/L)		
> -10	5/7 (71.4)	15/38 (39.5)
≤ -10	2/7 (28.6)	23/38 (60.5)
Change from baseline in CFQ-R respiratory domain score through Week 8		
< 4	6/10 (60.0)	27/42 (64.3)
≥ 4	4/10 (40.0)	15/42 (35.7)

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.

In the overall TEZ/IVA group, the percentage of subjects with improvement from baseline in $LCI_{2.5}$ (i.e., change from baseline through week 8 of ≤ -1) was 22.6% in Study 115 as compared to 16.7% in the F/F subgroup. As for sweat chloride, in the overall TEZ/IVA group, the percentage of subjects showing an improvement from baseline (i.e., change from baseline at week 8 of ≤-10 mmol/L) was 56.3% versus 60.5% in the F/F subgroup. A change from baseline in the respiratory domain score of CFQ-R ≥ 4 points was achieved by 38.9% of subjects in the overall TEZ/IVA group versus 35.7% in the F/F subgroup.

Summary of main study

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

Table 20 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 randomisation to either TEZ/IVA or a blinding group. Blinding group differ by genotype, i.e., placebo for F/F subjects and IVA monotherapy for F/RF subjects.		
	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) (n=54; 42 F/F and 12 F/RF)		8 weeks
	Ivacaftor (*F508del/RF* only) (n=3)		8 weeks (included for blinding purposes only)
	Placebo (*F508del/F508del* only) (n=10)		8 weeks (included for blinding purposes only)
Endpoints and definition	Primary endpoint	$LCI_{2.5}$	TEZ/IVA within-group absolute change in lung clearance index $_{2.5}$ ($LCI_{2.5}$) from baseline through Week 8. $LCI_{2.5}$ is the number of lung turnovers required to reduce the end tidal inert gas concentration to 2.5% of its starting value
	Secondary endpoint	sweat chloride	TEZ/IVA within-group absolute change in sweat chloride from baseline at Week 8.
	Secondary endpoint	CFQ -R	TEZ/IVA within-group absolute change in CFQ-R respiratory domain score from baseline through week 8
	Other endpoint	ppFEV1	TEZ/IVA within-group absolute change in ppFEV1 from baseline through Week 8
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. TEZ/IVA within-group change from baseline through or at week 8 expressed as the LS mean (SE) absolute change.		
Descriptive statistics and estimate variability, outcome measurements	Treatment group	TEZ/IVA	
	Number of patients	n=54	
	Primary outcome	LCI2.5	
	Baseline	Mean (SD) (n=54)	9.56 (2.06)
	Week 8	Mean (SD) (n=49)	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)		
	Baseline	Mean (SD) (n=51)	99.2 (19.5)
	Week 8	Mean (SD) (n=49)	88.4 (18.6)
		LS mean (SE) difference	-12.3 (1.5)
		95% CI	(-15.3, -9.3)
		p value*	<0.0001
	Respiratory domain CFQ-R child version (points)		
	Baseline	Mean (SD) (n=54)	84.6 (11.4)
	week 8	Mean (SD) (n=53)	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 (percentage points)		
	Baseline	Mean (SD) (n=54)	86.5 (12.9)
	Week 8	Mean (SD) (n=49)	89.9 (12.4)
		LS mean (SE) difference	2.8 (0.9)
		95% CI	(1.0, 4.6)
		p value*	0.0024
Notes: A shift in the body weight cut-off for dosing recommendations is proposed, i.e., from ≥ 40 kg to ≥ 30 kg based on model-based analysis of systemic exposure of TEZ, M1-TEZ, and IVA in children versus older patients. TEZ 100 mg qd/IVA 150 mg q12h has not been investigated in children weighing ≥30 to less than 40 kg in study 115. Primary analysis: data are missing on the primary endpoint at week 8 for 5 children out of the 54 in the FAS.			

Analysis description: The primary analysis of the primary efficacy endpoint is based on a mixed-effects model for repeated measures with $LCI_{2.5}$ 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 is provided. If the upper bound of the 95% CI is below the pre-defined maximum placebo effect of -0.10, it will be interpreted as sufficient evidence to achieve the primary efficacy objective.

Additional analyses were requested between the TEZ/IVA and the placebo groups using placebo-mean imputation for patients with data not available at week 8 for $LCI_{2.5}$, sweat chloride, and $LCI_{5.0}$. The results of these additional analyses are reflected in the corresponding sections of the report.

*No multiplicity adjustment was performed for hypothesis testing. P values provided for the secondary and other endpoints are considered nominal.

Supportive study

Study VX15-661-113 (study 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.

Study 113 has been previously assessed in procedure EMEA/H/C/004682/P46/006 and EMEA/H/C/002494/P46/0027. The PK results of both parts of the study are discussed in section 2.6.2. Pharmacokinetics.

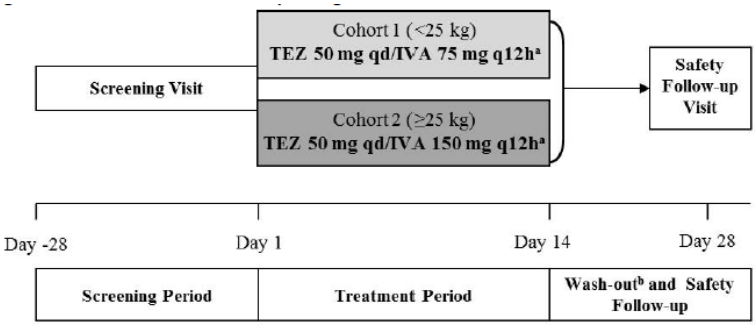
Methods

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

Study 113, Part A (Study 113A)

Study 113A 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 (see Figure 14). Subjects were enrolled into 2 weight-based cohorts with a cut-off value of 25 kg.

Figure 14 Schematic of Study Design for Study 113A

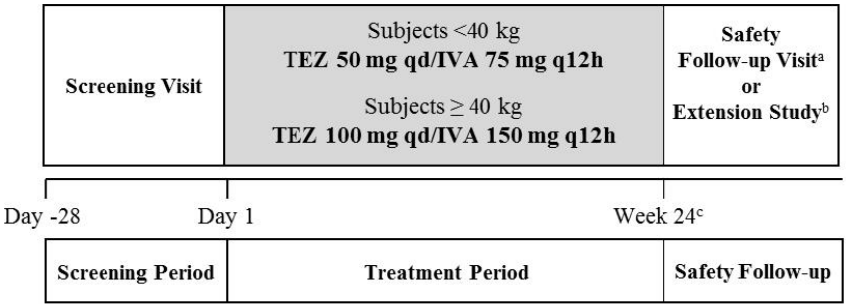


IVA: ivacaftor; q12h; every 12 hours; qd: daily; TEZ: tezacaftor
[a] Weight refers to weight at baseline. Study drug was administered from Day 1 through Day 14. On Day 14, only the morning dose of study drug was administered.
[b] A 2-week Washout Period (Day 14 to Day 28 [± 3 days]) was included to evaluate the off-drug response.

Study 113, Part B (Study 113B)

Study 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**).

Figure 15 Schematic of Study Design for Study 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 Participants

Patients aged 6 through 11 years and weighing >15 kg at the screening visit with a confirmed diagnosis of CF and an eligible *CFTR* genotype were eligible for enrolment. The genotype was confirmed at the screening visit. Patients homozygous for *F508del/F508del* were eligible for both parts of the study.

In study 113A, heterozygous *F508del* were eligible for enrolment if they had a second *CFTR* allele that met at least 1 of the following criteria: (1) the 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. In study 113B, only heterozygous *F508del* subjects with a second allele with a *CFTR* mutation predicted to have residual function were eligible for enrolment.

The lists below represent acceptable mutations for the second *CFTR* allele for heterozygous subjects.

***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.

The CF diagnosis was confirmed if sweat chloride was ≥60 mmol/l for all subjects. If sweat chloride was less than 60 mmol/l for heterozygous patients with a mutation that was either predicted to have residual function or was an IVA-responsve gating mutation, the patients were required to have documented evidence of chronic sinopulmonary disease and/or gastrointestinal disease consistent with a diagnosis of CF as judged by the principal investigator.

In addition, subjects must have predicted forced expiratory volume in 1 second (ppFEV1) ≥40 percentage points adjusted for age, sex, height, and ethnicity using the Global Lung Function Initiative (GLI) equation at the Screening Visit and stable CF disease at the Screening Visit.

Key exclusion criteria for both parts of the study were as follows:

- History of any comorbidity reviewed at the Screening Visit such as history of cirrhosis with portal hypertension or history of risk factors for Torsades de Pointes.
- Any of the following abnormal laboratory values at the Screening Visit:
    - Hemoglobin <10 g/dL
    - Abnormal liver function defined as any 2 or more of the following: ≥3 × upper limit of normal (ULN) aspartate aminotransferase (AST), ≥3 × ULN alanine aminotransferase (ALT), ≥3 × ULN gamma-glutamyl transpeptidase (GGT), ≥3 × ULN alkaline phosphatase (ALP), ≥2 × ULN total bilirubin
    - Abnormal liver function, defined as any increase of ≥5 × ULN ALT or AST
    - Abnormal renal function, defined as glomerular filtration rate ≤45 mL/min/1.73 m2 (calculated by the Counahan-Barratt equation)

Treatments

The following doses were administered during Part A:

- Patients < 25 kg: TEZ 50 mg qd/IVA 75 mg q12h
- Patients ≥ 25 kg: TEZ 50 mg qd/ IVA 150 mg q12h

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 (from 50 mg to 100 mg). 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

Additional Dietary Restrictions/Prohibited Medications

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.

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.

Objective(s)

The primary objective was PK in Study 113A and safety in Study 113B. PK and efficacy were included as secondary outcome measures in study 113B. A summary of the objectives of Study 113 objectives is outlined in Table 21.

Table 21 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

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.

Other outcome measures

A similar MMRM model as described for absolute change in ppFEV1 from baseline through Week 24 was used for the absolute change in FEV1 (L), relative change form baseline in ppFEV1, 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 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.

Lung clearance index measured by MBW was part of an optional exploratory substudy conducted at a subset of sites. The LCI substudy was used 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.

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.

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).

Part B: Ophthalmologic examinations,

Randomisation and blinding (masking)

Not applicable (single arm study).

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 using SAS®.

Analysis Sets

The following analysis sets were established:

- Safety Set (Part A and Part B) defined as all subjects who received at least 1 dose of study drug.
- All Subjects Set (Part A) defined as subjects who are eligible for study enrolment and received a subject identification number or were dosed. Subject data listings were presented based on the Safety Set Part B.
- PK Set (Part A and Part B) defined as subjects who received at least 1 dose of study drug and for whom the primary PK data are considered to be sufficient and interpretable.
- Full Analysis Set (Part B Only) defined as subjects who carry the intended *CFTR* mutations and received at least 1 dose of study drug. All efficacy analyses are based on the FAS, except for LCI endpoints. Incomplete/Missing data were not imputed, unless specified otherwise. No formal statistical analyses were performed to detect or remedy the presence of statistical outliers, unless specified otherwise.

Variables

The treatment emergent (TE) period for Part B will correspond to data from first dose of study drug in Part B through the Safety Follow-up Visit or 28 days after the last dose in Part B for subjects who do not have an Safety Follow-up Visit.

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. Baseline for Part B was similarly defined.

The absolute change from baseline in percent predicted FEV1 through week 24 was 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 analyzed 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.

The change from baseline in weight, height, BMI, and associated z-scores at week 24, the absolute change from baseline in sweat chloride through week 4 and through week 24, and the absolute change from baseline in CFQ-R respiratory domain score through week 24 were calculated using a similar MMRM model.

Results

Participant flow/Numbers analysed

Study 113A

A total of 13 subjects were enrolled instead of the 16 initially targeted; 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 22)

Table 22 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

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

Study 113B

There were 70 subjects in the Safety Set and the FAS and 35 subjects in the optional LCI substudy. 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 23)

Table 23 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 Full Analysis Set.

Baseline data

Study 113A

Subject demographics for Part A are summarized in Table 24. 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 24 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 25.

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

Table 25 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)

The MAH has clarified that in Part A, 5 children were homozygous for *F508del*, 4 had an F/RF mutation and 4 remaining children were heterozygous *F508del/A559T* (n=1) and *F508del/G551D* (n=3). The last four were not allowed to enrol in Part B due to the emerging data about the potential lack of efficacy of TEZ/IVA for heterozygous *F508del/G551D;* the other genotype was not eligible for Part B.

Median BMI-for-age z-score was 0.43 (min, max: -2.37, 1.78), median weight-for-age z-score was 0.37 (-1.52, 1.82) and median height-for-age z-score was 0.46 (-1.92, 1.11) for the 13 children enrolled in Part A.

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%).

All subjects took concomitant medications during Part A. The most common concomitant medications (≥ 30% overall incidence) were salbutamol (84.6%), pancreatin (76.9%), dornase alfa (69.2%), sodium chloride (69.2%), fluticasone propionate (53.8%), colecalciferol (38.5%), aquadeks/07679501 (30.8%), and loratadine (30.8%).

Study 113B

Baseline subject demographics in Study 113B are presented by *CFTR* mutation type (homozygous *F508del* [F/F] versus heterozygous *F508del* and a second allele that results in residual function [F/RF]) in Table 26.

The majority of 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 26 Baseline demographics in F/F and F/RF Subjects, Study 113 B, 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).

Baseline characteristics in Part B (including anthropometric z-scores and percentiles) are presented by mutation type in Table 27. 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. All included children with heterozygous F/RF had mutations as allowed in the label.

At baseline, the mean ppFEV1 was 91.1 percentage points. Most subjects (88.6%) weighed <40 kg at baseline. The number of patients with a body weight ≥ 30 kg to less than 40 kg was n=21 (30%); the number of patients weighing ≥ 40 kg was 8/70 (11.4%). The mean (SD) weight at baseline was 30.7 (10.0) kg, and the mean weight z-score was 0.20 (0.94), indicative of normal weight. 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

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%).

Table 27 Baseline disease characteristics in F/F and F/RF Subjects, Study 113B, 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/m^2)			
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.

Overall, the baseline data provided by genotype show the highest severity of the disease in homozygous *F508del* subjects as expected even at this young age. Homozygous *F508del* subjects had a median (min, max) weight-for-age percentile of 51.46 (6.43, 99.50) as compared to heterozygous patients (i.e., 74.11 [11.83, 95.71]). Similarly, median (min, max) height-for-age percentile is 39.42 (2.50, 99.10) as compared to 51.33 (21.03, 93.70). This results in median (min, max) BMI percentile of 69.05 (7.47, 98.43) vs. 70.77 (16.41, 94.55) in heterozygous patients. In subjects with cystic fibrosis aged 2 to 18 years the target is 0 SD (50th percentile) of BMI for a healthy, same-age population. This is considered as indicative of adequate nutritional status. However, when assessing BMI the change in height percentile/SD score should be considered, as stunted (low height-for-age) children can have a normal BMI (Turck et al 2016). This seems to be the case in the population of homozygous *F508del* children for whom the height percentile is well below the 50th percentile in spite of which the BMI percentile is above 50.

Conduct of the study

The final study protocol of study 113 is Version 3.0, dated 19 July 2017. 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: 11 Sept 2018 (date last subject completed the last visit).

The date of first subject entry for Study 113B was 25 October 2017.

The study protocol was amended 2 times. Table 28 provides a list of the protocol versions, their dates, and the major changes introduced with every amendment.

Table 28 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

Planned methods of analyses were provided in the interim analysis (IA) statistical analysis plan (SAP) for Part A (SAP IA1 Part A Version 1.0, dated 11 January 2017), the Part B SAP for Part B (SAP Part B Version 1.0, dated 22 June 2018) and the clinical pharmacology analysis plan (CPAP, CPAP Version 1.0).

Changes were also made in the SAP for Part B compared to the protocol. One of the amendments was to clarify the details of the mixed effect model repeated measures (MMRM) approach considering the study design and study population. The protocol for Study 113 was amended to create Version 3.0, dated 19 July 2017. This version of the protocol states that "treatment" and "treatment-by-visit" would be included as fixed effects in the MMRM. The SAP for Study 113 Part B removed "treatment" and "treatment-by-visit" as fixed effects for the MMRM model and further clarified that "subject" is included as a random effect in the analyses. These changes to the SAP were made because a difference in "treatment" effect by dose was not expected, as the weight-based dosing regimen was intended to match study drug exposures for subjects receiving different doses. Therefore, per the SAP, only the overall TEZ/IVA treatment effect was analyzed in the MMRM model.

There were no important protocol deviations in Part A, and three important protocol deviations in Part B. In Part B, the mean (SD) compliance was 99.50% (2.99%). One subject (TEZ 50 mg qd/IVA 75 mg q12h) was <80% compliant, one subject (TEZ 50 mg qd/IVA 75 mg q12h) was enrolled in the study without review of their coagulation lab results and one subject (TEZ 50 mg qd/IVA 75 mg q12h) began the washout of physician prescribed LUM/IVA prior to signing the ICF.

Outcomes and estimation

All efficacy endpoints were secondary outcome measures. The 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 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 29).

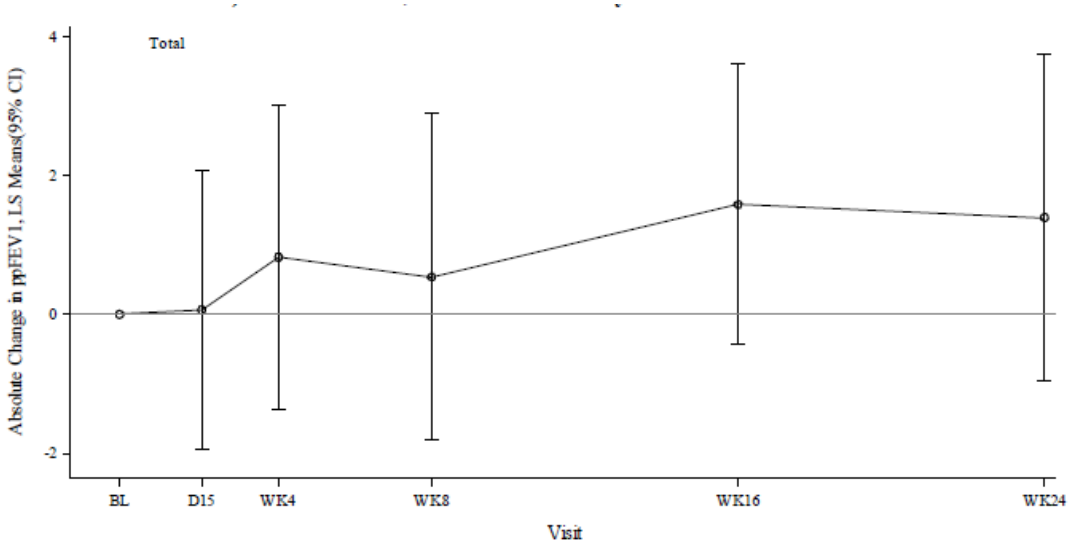
Table 29 MMRM Analysis of Absolute Change From Baseline in ppFEV1 Through Week 24, Part B Full Analysis Set

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.

No sensitivity analysis for missing data was performed. This is acceptable for two reasons: premature discontinuation was small (4.3%) and efficacy is a secondary objective and no statistical conclusion can be drawn.

- ***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).

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

Table 30 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). The LS mean absolute change from baseline in height at Week 24 was 2.7 cm (95% CI: 2.4, 2.9). The LS mean absolute change from baseline in BMI at Week 24 was 0.23 kg/m2 (95% CI: 0.06, 0.4).

The LS mean absolute change from baseline in weight z-score at Week 24 was 0.0 (95% CI: -0.05, 0.05). The LS mean absolute change from baseline in height z-score at Week 24 was 0.0 (95% CI: -0.05, 0.05). The LS mean absolute change from baseline in BMI z-score at Week 24 was -0.03 (95% CI: -0.10, 0.04).

Table 30 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
BMI (kg/m^2)	
Baseline	
n	70
Mean (SD)	17.44 (2.69)

Statistic	Total N = 70
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). The LS mean absolute change from baseline through Week 24 was -14.5 mmol/L (95% CI: -17.4, -11.6).

- ***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 from baseline though week 24 was 3.4 points (95% CI: 1.4, 5.5), (Table 31).

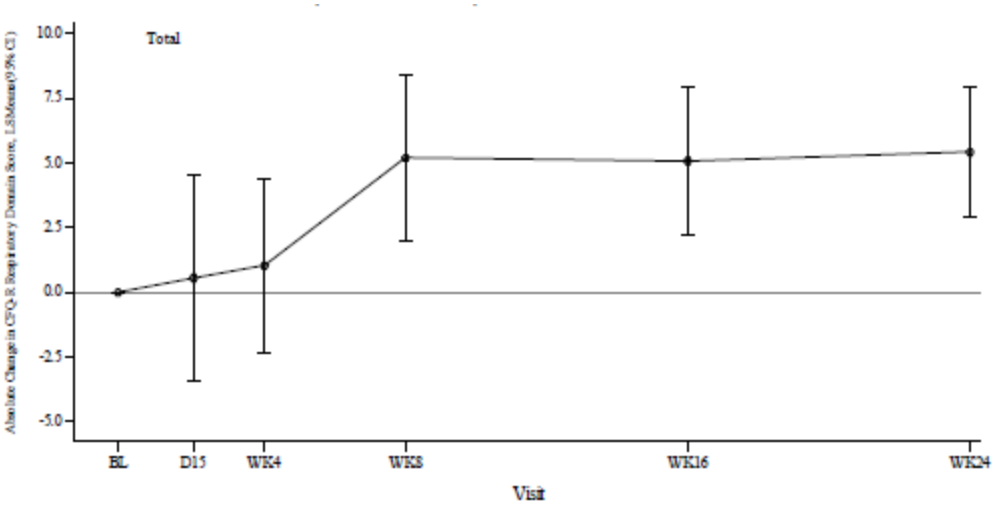
Table 31 MMRM Analysis of Absolute Change From Baseline in CFQ-R (Child Version) Respiratory Domain Score Through Week 24, Part B Full Analysis Set

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.

Figure 17 illustrates the MMRM analysis of absolute change from baseline in the respiratory domain score of CFQ-R.

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



Source: Figure 14.2.10.1b
BL: baseline; CI: confidence interval; CFQ-R: Cystic Fibrosis Questionnaire – Revised; D: day; LS Means: least squares means; MMRM: mixed effect model of repeated measures; WK: week
Note: The *Y*-axis corresponds to the LS means from the MMRM model analysis with all measurements up to Week 24, including on-treatment measurements and measurements after treatment discontinuation. The MMRM analysis included baseline CFQ-R and visit as fixed effects, an unstructured covariance, and Kenward-Roger estimation of degrees of freedom.

- *Lung Clearance Index (Optional Exploratory Substudy)*

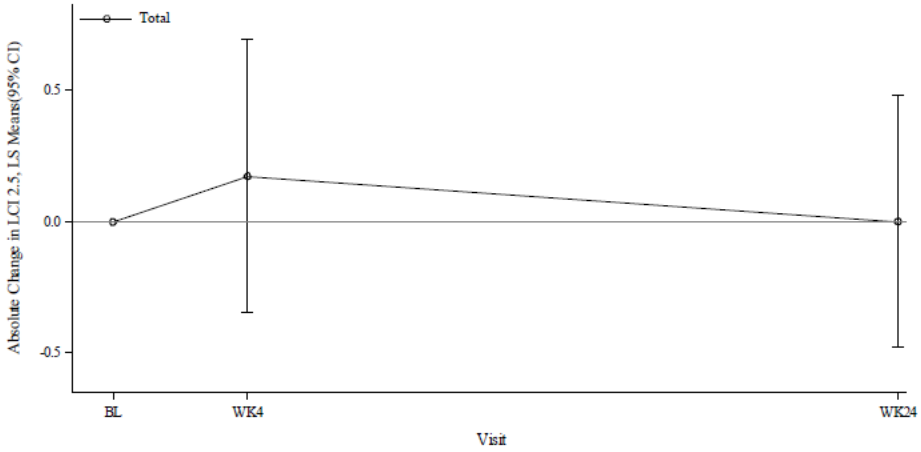
Lung clearance index was included as an exploratory endpoint in this study to evaluate a LCI device and over-reading process that were new to the MAH CF team.

At baseline, the mean (SD) $LCI_{2.5}$ was 9.39 (1.95); at week 24, the mean (SD) value 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



2.7.3. Discussion on clinical efficacy

In the EU, Kalydeco 150 mg tablets, is currently approved in a combination regimen with Symkevi tablets, for the treatment of patients with CF 12 years of age and older who are homozygous for the *F508del-CFTR* mutation or who are heterozygous for the *F508del-CFTR* mutation and have 1 of the following mutations in the *CFTR* gene*: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G*, and *3849+10kbC→T*.

The current application is to add a new strength (Kalydeco 75 mg tablets) for the use in combination use with Symkevi to children aged aged 6 to less than 12 years old. This age range is based on the partial extrapolation of efficacy from adults and adolescents to children, supported by the PK and safety study 113 and the pivotal phase 3 study 115.

The extrapolation strategy is justified as the underlying genetic and molecular aetiology of CF is similar across age ranges and no age-dependency in the mechanism of action of the *CFTR* modulators has been observed. In addition, the pathogenesis of the disease is also comparable across paediatric and older populations although there may be a significant age-dependency for the presence of certain symptoms and signs of the disease with younger children generally less affected than older patients or with a different pattern of organ damage. However, the biochemical defect of the defective chloride channels is present from birth and because of the longstanding defect, 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 as shown by the prevalence of chronic lung infection by *Pseudomonas aeruginosa* and of pulmonary exacerbations in adulthood compared to childhood.

Thus, paediatric studies aimed at investigating the PK and safety of the study drug are considered acceptable to demonstrate efficacy based on extrapolation from adults to younger patients. There is a need for a good understanding of the PK of the candidate drug in the different paediatric age groups affected by the disease. Furthermore, the safety profile should be established in the paediatric studies performed so that a bridge between the adult and paediatric population can be made. The efficacy of ivacaftor in a combination regimen with Symkevi has been established in phase 3 studies in patients aged 12 years and older by showing improvement in lung function using FEV1, sweat chloride and quality of life compared to placebo. This led to the EU approval of Symkevi for CF patients homozygous for *F508del/F508del* and heterozygous for specific F/RF mutations. Bridging the efficacy from older patients (source population) to children aged 6 to less than 12 years of age is based on matching the systemic exposure which has been shown efficacious and safe in the source population.

Overall, the approach proposed by the MAH was considered to be in line with the principles described in ICH E11 and the EMA reflection paper on the use of extrapolation in the development of medicines for paediatrics. The MAH sought CHMP scientific advice for Study 115 after the Phase 3 data in subjects ≥12 years old became available. Overall, CHMP agreed that from a mechanistic point of view, the therapeutic rationale in the older population could, in principle, equally apply to younger populations. The proposed 8-week treatment duration and the use of $LCI_{2.5}$ as primary endpoint were also acknowledged provided that the open label extension study includes periodic efficacy evaluations. Regarding the primary endpoint, CHMP clearly expressed a clear preference for a formal comparison versus placebo in the absolute change in $LCI_{2.5}$ from baseline at week 8 rather than the proposed TEZ/IVA within-group change through week 8.

Design and conduct of clinical studies

To support this extension of indication, two paediatric studies have been conducted, i.e., the pivotal study 115 and the supportive study 113. Upon request by CHMP, interim results of an open-label extension study (study 116) have been provided.

Study 113 is a 2-part (Part A and Part B), open-label study to assess the pharmacokinetics, safety, and tolerability of tezacaftor in combination with ivacaftor in subjects 6 through 11 years of age with CF, homozygous or heterozygous for the *F508del-CFTR* mutation. The primary objectives were PK in part A (14 days) and safety in part B (24 weeks); PK and efficacy were included as secondary outcome measures in study 113B.

Based on the PK data of study 113A and model-based simulations, the weight cut-off was 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 two studies, an integrated popPK analysis of data was performed. The results 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 adult subjects. As a consequence, the weight-based posology was shifted from 40 kg to 30 kg to better align with the adult exposures. The 30kg cut off is based on the PopPK results previously described and is appropriately demonstrated (see section 2.6.2 pharmacokinetics).

Changes in sweat chloride were assessed in the paediatric studies 113 and 115 as a secondary endpoint. The comparison of the sweat chloride changes versus those estimated in the pivotal studies 106 and 108 in the Symkevi clinical programme shows that the magnitude of the mean reduction in sweat chloride is comparable in older patients and in children, thus further supporting extrapolation of efficacy to children (see section 2.6.2 pharmacokinetics).

Study 115 is a 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 were stratified by genotype and randomized in a 4:1 ratio to either the TEZ/IVA group or an appropriate blinding group for their genotype, i.e., the F/F blinding group received placebo (although lumacaftor/ivacaftor was available for homozygous *F508del* subjects) and the F/RF blinding group received IVA monotherapy.

This study although designed as a randomised, placebo and active comparator-controlled study, can be effectively considered as a single arm study due to the following:

- The overall effect size is driven by the TEZ/IVA group as this includes 80% of the population.
- No between-treatments comparisons were pre-specified but within-TEZ/IVA group changes.
- Each treatment group included different genotypes, i.e., the TEZ/IVA group included both F/F and F/RF patients, while the placebo and IVA groups included F/F and F/RF patients respectively, hampering a between-treatment comparison.
- The number of patients in the placebo group (n=10) or in the IVA group (n=3) is too small to allow sound comparisons between treatment groups.

Patients who weighed <40 kg received 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 were ≥40 kg received a morning dose of TEZ 100 mg/IVA 150 mg (FDC tablet) and an evening dose of IVA 150 mg (tablet). The study is of short duration, i.e. 8 weeks, which was justified on the basis that prior studies showed that the effect of CFTR modulator therapy is apparent at week 2 and maintained throughout the 24-week duration treatments. Moreover, additional supportive long-term treatment data was collected in study 113B.

The primary endpoint was the TEZ/IVA within-group absolute change from baseline through week 8 in $LCI_{2.5}$, i.e., different from ppFEV1 which is the usual measurement of lung function in older patients. This is considered acceptable given that children tend to have a well-preserved lung function as measured by spirometry which does not detect the disease in the small airways. The results of the test were centrally reviewed which is endorsed.

The minimal clinically important difference (MCID) for the $LCI_{2.5}$ has not been determined. The natural variability for the $LCI_{2.5}$ is 1 unit[2] or 15% of baseline[3]. An effect larger than the natural variability might be regarded as clinically relevant.

Secondary efficacy endpoints included the TEZ/IV within-group absolute change in sweat chloride and in the respiratory domain score of the Cystic Fibrosis Questionnaire-Revised [CFQ-R]. Sweat chloride is a pharmacodynamic endpoint and shows the effect of the CFTR modulator therapy on the chloride transport. The (respiratory domain of) the CFQ-R (Child and Parent Versions) was used to capture and evaluate the impact of TEZ/IVA on patient-reported respiratory symptoms and other aspects of health-related quality of life.

Other outcome measures included the absolute change in ppFEV1 as well as in anthropometric parameters. Acceptability of the study drugs formulations was also assessed.

CFTR modulator therapy is a systemic therapy. Therefore, it is expected that it may also have additional systemic effects like improvement of the pancreatic function (faecal elastase-1 and immunoreactive trypsinogen) and improvement in anthropometric parameters. These effects were included for descriptive purposes only.

The sample size of study 115 is driven by demonstrating that the treatment effect of TEZ/IVA is based on a within-group comparison (change from baseline in $LCI_{2.5}$ in subjects on TEZ/IVA) to exclude a maximum possible placebo effect. The size of the placebo effect was based on study 809-109 in which treatment with LUM/IVA in homozygous *F508del* subjects aged 6 through 11 years was assessed. In this study, the treatment difference was -1.09 (95% CI: -1.43, -0.75) in favour of LUM/IVA, a treatment effect which was considered modest. The placebo group had a mean worsening in $LCI_{2.5}$ of 0.08 units with an SD of 1.41; the one-sided 90% lower bound was -0.10 which is used as an estimate for the pre-defined maximum possible placebo effect for study 115, i.e., if the upper bound of the 95% CI is below the pre-defined maximum placebo effect of -0.10, it will be interpreted as sufficient evidence to achieve the primary efficacy objective. However, the magnitude of the maximum placebo effect estimated via one-sided 90% lower bound seems not sufficiently conservative.

The analysis of the primary and of the secondary endpoints 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 MMRM analysis assumes that patients who do not provide data at Week 8 continue to benefit from the treatment. As a result, the treatment effect might be

[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

overestimated. Upon request by CHMP, additional sensitivity analyses using placebo mean imputation data for all patients with data not recorded at Week 8 were provided which included a formal statistical analysis for the difference between the combination therapy and placebo in terms of the absolute difference at week 8 (rather than through week 8 as this takes the risk of masking deleterious effects over time).

Efficacy data and additional analyses

Study 115 enrolled a total of 69 children with an eligible genotype and with a confirmed diagnosis of CF defined as sweat chloride value ≥60 mmol/l (homozygous *F508del*) or, if the sweat chloride was below 60 mmol/l (heterozygous F/RF subjects), the presence of chronic sino-pulmonary disease and/or gastrointestinal disease consistent with CF diagnosis was required. Enrolment was limited to patients with LCI2.5 result ≥7.5 at the Screening Visit, a body weigh≥ 15 kg, ppFEV1 ≥70 percentage points and the ability to swallow the tablets (given the dimensions of the higher-strength TEZ/IVA tablet which are 15.9 mm x 8.5 mm). This exclusion criterion may limit the conclusions on the acceptability of the study drug formulations. Patients with protocol-defined laboratory values indicative of clinically significant abnormal liver function were excluded (either (a) and two 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-Barratee equation; or (3) hemoglobin <10 g/dL). Given that moderate transaminase increases are frequent in children with CF this exclusion criterion seems unnecessarily restrictive and limits the generalisation of the study results in terms of safety (in particular liver safety).

Out of the 69 patients enrolled, 67 integrated the Full Analysis Set (FAS), the primary population for all efficacy analyses. 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.

In total, 52 (77.6%) subjects had the F/F genotype and 15 (22.4%) subjects had F/RF genotypes. The TEZ/IVA group included 42 patients with an F/F mutation and 12 with an F/RF mutation. All subjects in the placebo group were homozygous for *F508del* and 3 subjects with an F/RF genotype were enrolled in the IVA group. Only patients with a Symkevi approved RF mutation were enrolled.

The mean (SD) $LCI_{2.5}$ was 9.54 (1.97) (normal value: <7.5) and mean (SD) ppFEV1 87.1 (12.2) percentage points.

Most subjects (n=64, 95.5%) weighed <40 kg at baseline. The BMI-, weight-, and height-for age z-scores were all close to 0 and within ±2SD of the population of reference indicative of normal growth which is not unexpected in this age group. The majority of subjects (79.1%) were negative for *Pseudomonas aeruginosa* in the 2 years before study start. All homozygous *F508del* subjects had exocrine pancreatic insufficiency while all F/RF subjects pancreatic sufficient.

Overall, the patient demographics appeared to be balanced for age, weight, height, $LCI_{2.5}$ and ppFEV1. The overall disease and baseline characteristics are considered representative for the proposed target population of homozygous *F508del* subjects and heterozygous *F508del* and a *CFTR* mutation of residual function.

Results

Primary efficacy endpoint

The primary efficacy endpoint in study 115 was the TEZ/IVA within-group absolute change in $LCI_{2.5}$ from baseline through week 8 which was -0.51 (95% CI: -0.74 to -0.29; P <0.0001). As the upper bound of the 95% CI (-0.29) was below the pre-specified maximum placebo effect of -0.10, it is

concluded that the primary endpoint met the pre-defined criterion for success. A larger effect was seen in the heterozygous F/RF population of the TEZ/IVA group based on subgroup analyses which were consistent in both descriptive statistics analyses based on patients with non-missing data as well as in MMRM analysis using placebo-mean imputation data at week 8. The latter resulted in LS mean (95% CI) within-group changes in $LCI_{2.5}$ at week 8 of -0.45 (-0.71, -0.18) in homozygous *F508del* patients and -1.20 (-1.64, -0.76) in heterozygous F/RF patients. The LS mean (95% CI) treatment difference of TEZ/IVA vs. placebo at week 8 was -0.59 (95% CI: -1.22, 0.05) and -0.57 (95% CI: -1.23, 0.09) when this analysis is restricted to the F/F population.

All point estimates exceeded the predefined placebo effect of -0.10. In all additional analyses presented of within-group changes, the upper limit of the 95% CI interval was below the pre-specified threshold with the exception of the upper limit of the 95% CI of the TEZ/IVA within-group change through week 8 restricted to F/F subjects which was -0.07. Study 115 was not powered for between-treatment comparisons vs. placebo. The LS mean change in $LCI_{2.5}$ in the placebo group at week 8 was -0.01 (-0.59, 0.57) while in the TEZ/IVA group this was -0.60 (-0.84, -0.35).

Overall, the size of the treatment effect appears small, particularly in homozygous *F508del* subjects which is not unexpected. However, there are limited data from trials using this endpoint and a MCID has not yet been defined. Effect sizes in studies have ranged from -1 to -2 depending on the type of intervention and the duration of treatment. Limited longitudinal data from the placebo group of interventional trials are available to define whether an intervention exceeds the intrinsic variability of the test. Nevertheless, this endpoint is considered sufficiently established for trials in CF patients 6 through 11 years of age.

It cannot be excluded that longer (than 8 weeks) treatment duration may have resulted in additional decreases in $LCI_{2.5}$ values (reflecting improvement in ventilation inhomogeneity). However, the pattern of decrease seen in the lumacaftor/ivacaftor studies suggests that the greatest change from baseline is seen in the first 4 weeks of treatment.

In the supportive study 113B, LCI was included as an exploratory endpoint given that the main aim of the study was to evaluate the LCI device that had not been used in any prior trials conducted by the MAH.

Thirty-five subjects participated in the LCI exploratory sub-study of study 113B but only 30 of them contributed at baseline with $LCI_{2.5}$ data. The LS mean (95% CI) absolute change from baseline in $LCI_{2.5}$ through Week 24 was 0.09 (-0.32, 0.49). An initial slight deterioration (increase in the $LCI_{2.5}$ score) was seen at week 4 which returned to the baseline value by the end of treatment at week 24. However, no strong conclusion can be made by the lack of placebo comparison and the small number of included patients.

Secondary endpoints

The primary efficacy outcome in study 115 was supported by the TEZ/IVA within-group change in sweat chloride. The LS mean absolute change from baseline at Week 8 in sweat chloride was -12.3 mmol/L (95% CI: -15.3, -9.3) in the TEZ/IVA group which is comparable to the one observed in the older population, as shown by a LS mean (SE) in older patients of -9.9 (0.5) mmol/l. Reduction in sweat chloride was observed for both genotypes in the TEZ/IVA group of study 115. The mean reduction at week 8 was slightly higher in the F/F subgroup (-12.9 mmol/, 95% CI: (-16.0, -9.9) than in the F/RF subgroup (-10.9 mmol/l, 95%CI: -20.8, -0.9). In the context of prior demonstration of efficacy for a TEZ/IVA combination in *F508del-CFTR* homozygous F/F and heterozygous F/RF patients 12 years and older, and considering PK support for comparable exposure to TEZ and IVA, in the 6 through 11 years age group, the result on sweat chloride, although indicative of partial functional correction only, can be considered likely to predict a slowing of disease rate progression.

The reduction in sweat chloride is consistent with at least partial restoration of the biochemical defect and with the combined corrector/potentiator action of TEZ/IVA. As expected, no improvement in sweat chloride was observed in the placebo group as shown by a LS mean (SE) absolute change at week 8 of -0.9 (3.5) mmol/l (additional MMRM analysis of between-treatment differences requested by CHMP).

The analysis of the change in the respiratory domain score of CFQ-R showed a numerical improvement from baseline in the TEZ/IVA treated group as shown by a LS mean (SE) within-group change from baseline through week 8 of 2.3 (1.2) points. The magnitude of this change was smaller compared to the older population which is not unexpected given that the school-age children enrolled in study 115 were at a relatively early stage of disease, and therefore patient reported outcome would be relatively insensitive to detect a treatment benefit. In addition, the MAH claims that the results obtained in children are not directly comparable to that of adults and adolescents because of the lack of published data comparing the Child version of the CFQ-R questionnaire to the Adolescents and Adults version. The MAH was asked to provide a responder analysis, i.e., percentage of children who reached an increase ≥ 4 points after 24 weeks of treatment in study 113B or after 8 weeks of treatment in study 115. In study 113B, this analysis showed that the percentage of F/RF and F/F patients in the TEZ/IVA group who reached the predefined improvement through Week 24 was 33.3% and 42.6% respectively. In the overall population of the TEZ/IVA group this percentage was 41.4%. In study 115, the percentage of subjects who reached a change ≥ 4 through week 8 in the overall population of the TEZ/IVA group was 38.9% while in the F/F subgroup this percentage was 35.7%.

Other endpoints

Treatment with TEZ/IVA resulted in a within-group mean absolute change in ppFEV1 from baseline through week 8 of 2.8 percentage points (95% CI: 1.0, 4.6). The magnitude of this change in ppFEV1 is lower than the change observed in the older population, i.e., 3.4 (0.3) percentage points (homozygous *F508del* subjects). This is not an unexpected finding, as in children 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) in children aged 6 to 12 years of age, supporting the efficacy of TEZ/IVA in this population.

Improvements in ppFEV1 were observed in both genotypes (mean change of 2.6 and 3.7 percentage points for the homozygous and heterozygous subgroups respectively) with TEZ/IVA treatment in Study 115. In study 113B, the LS mean (SE) change in ppFEV1 was smaller than in study 115, i.e., 0.9 (0.7) percentage points.

During treatment with TEZ/IVA, weight, height, BMI, and the associated z-scores remained stable, without improvement in study 115, this can be partially explained by the short treatment duration and also because of the mean z-scores of the anthropometric parameters that were close to 0 at baseline and therefore indicative of normal growth. In study 113B where treatment duration was for 24 weeks there was no evidence either of a gain in weight-, height-, and BMI z-scores. As most of the population were homozygous *F508del* patients, the results can be considered mainly indicative for this population. In the pivotal study 106 in subjects with the same genotype similar results were seen, i.e., the mean within-group change in BMI after 24 weeks of treatment with TEZ/IVA was 0.18 kg/m2. An extra-pulmonary effect in weight, height and BMI is therefore not (yet) established but it is acknowledged that this may be consistent with the stable and normal mean values for these parameters at baseline.

In study 113B, faecal elastase-1 values were not collected. In study 115, in the TEZ/IVA group, baseline values of faecal elastse-1 (FE-1) and immunoreactive trypsinogen (IRT) differed between F/F subjects and F/RF subjects. All 40 F/F subjects with baseline data had FE-1 levels ≤200 µg/g, consistent with pancreatic insufficiency whereas all F/RF subjects had baseline FE-1 levels ≥500 µg/g, consistent with normal pancreatic function. No subject with a baseline FE-1 level ≤200 µg/g became pancreatic sufficient (i.e., had an FE-1 level >200 µg/g) after TEZ/IVA treatment.

A comparison of the change from baseline in faecal elastase-1 and immunoreactive trypsinogen by baseline FE-1 values (≤200 µg/g vs. > 200 µg/g) observed in the studies of lumacaftor/ivacaftor and ivacaftor alone in children of the same age range was requested. In response, it has been clarified that the assays used to assess FE-1 were the same in study 115 and study 809-109 (lumacaftor/ivacaftor) but differed in case of IRT. The MAH stated that direct comparisons of these parameters across these studies are hampered by the differences in treatment duration (8 weeks in study 115 vs. 24 weeks in study 109), subject genotype, assay collection, and statistical methodology. Nevertheless, data were provided for study 109 (homozygous *F508del* children treated for 24 weeks with lumacaftor/ivacaftor) which showed similar results to those of study 115 in F/F patients. At the age of 6 years exocrine pancreatic insufficiency is usually well established in patients homozygous for *F508del* and therefore earlier treatment would be needed to modify the course of this CF complication. In the IVA program, FE-1 and IRT were evaluated in Study 770-110, which enrolled subjects 6 years of age and older with the *R117H* mutation; these data are not comparable to those in the TEZ/IVA program due to the different age range (including mostly adult subjects) and different genotype (usually associated to exocrine pancreatic sufficiency at least in young ages).

Cross study comparison with LUM/IVA

Symkevi is proposed for the homozygous F/F population which overlaps with the target population of Orkambi (lumacaftor/ivacaftor). Therefore, a cross-study comparison was made with the pivotal study VX14-809-109 which was the pivotal study leading to the approval of lumacaftor/ivacator in this paediatric age group.

In this cross study comparison, TEZ/IVA showed smaller within-group effects in the LS mean (SE) change in sweat chloride compared to LUM/IVA, (i.e., -12.3 [1.5] vs. -20.0 [1.0] mmol/l and $LCI_{2.5}$ (i.e., -0.51 [0.11] vs. -1.01 [0.13]); both for the overall TEZ/IVA-treated population as well as for the subgroup of homozygous *F508del* subjects. However, TEZ/IVA showed a numerically larger effect on ppFEV1 (i.e., 2.8 [0.9] vs. 1.1 [0.8] percentage points). However, final conclusions cannot be made due to undoubted limitations of cross-study comparisons.

Kalydeco in combination with Symkevi may fulfil an unmet medical need for patients homozygous for *F508del* who cannot tolerate Orkambi due to (e.g.) respiratory adverse events or cannot take it due to drug-drug interactions. However, once approved, the use will likely not be limited to these patients. Therefore, as both medicinal products are indicated for homozygous *F508del* children aged 6 to less than 12 years, the CHMP considered that the results observed in these children should be presented in section 5.1 of the SmPC of Symkevi so that prescribers are aware of the results fully acknowledging that study 115 was not powered for subgroup analysis. This may allow them to make informed decisions for individual patients taking into consideration the potential risks and benefits of Symkevi and Orkambi.

2.7.4. Conclusions on the clinical efficacy

The current application is based on extrapolation of efficacy. The pivotal study 115 was a randomised, parallel designed study but effectively a single-arm trial investigating the TEZ/IVA within-group changes in CF patients harbouring an F/F or certain F/RF mutations in patients aged 6 to less than 12 years. The study met its primary endpoint by showing a statistically significant improvement in $LCI_{2.5}$ from baseline through week 8, the pre-specified primary endpoint. The size of the effect is small but considered sufficient in the context of prior demonstration of efficacy for a TEZ/IVA combination in *F508del-CFTR* homozygous and heterozygous F/RF patients 12 years and older. In addition, supportive evidence of efficacy was shown in terms of ppFEV1 and sweat chloride. The result on sweat chloride, although indicative of partial functional correction only, can be considered likely to predict a slowing of

rate of disease progression. Thus, the trial provided the evidence to support the partial extrapolation from the adult efficacy data to the paediatric population.

Children enrolled in studies 113B and study 115 received a weight-based dosing regimen of TEZ 50 mg qd/IVA 75 mg q12h for those weighing less than 40 kg. After model-based simulations and analysis of systemic exposure, a shift in the body weight cut-off was proposed from 40 kg to 30 kg. As a consequence, no clinical data have been generated in the proposed studies in children weighing ≥30 kg to less than 40 kg who will receive according to current dosing recommendations TEZ 100 mg qd/IVA 150 mg q12h. Additional PD/PK modelling showed that this dosing results in more similar systemic exposure to that of older patients. In addition, the reduction in sweat chloride observed in study 113B and study 115 is within the range of that observed in the adult study 106. 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.

Cross study comparisons between study 115 and study 109 (Orkambi) raised the concern that the treatment effect in terms of $LCI_{2.5}$ and sweat chloride might be somewhat lower than those observed with lumacaftor/ivacaftor. Therefore, it is considered that the results of the subgroups (homozygous *F508del* patients and F/RF patients) should be reported in the SmPC of Symkevi, so that prescribers are aware of the results for each subpopulations and may make informed decisions for individual patients taking into consideration the potential risks and benefits of Symkevi and Orkambi.

2.8. Clinical safety

Patient exposure

Study 113B and 115 are the main datasets which support the safety of the combination of tezacaftor and ivacaftor for the treatment of children aged 6 to less than 12 years old. Upon request, an interim analysis of the open-label extension VX17-661-116 (study 116) has been provided after all subjects completed the week 48 Visit (data cutoff date: 18 December 2019).

Study 116 is an ongoing open-label extension study for subjects who completed either of the parent studies (Study 113B or 115) to evaluate longer-term safety of TEZ/IVA treatment. 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 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 parent studies. After completing part A, patients could be entered in part B. Part B was added following a recent amendment (data 8 Nov 2019) to collect additional safety data according the new proposed posology using the 30 Kg weight cut off. As the interim analyses of study 116 was conducted before the implementation of the amendment, the safety data provided correspond to the posology used in the parent studies 113B and 115.

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

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 N=124 patients. Additional long-term safety data is provided for n=130 patients who rolled over to the long-term safety study 116. The Cumulative TEZ/IVA Safety Set combines the exposure of TEZ/IVA in the parent studies and in study 116 (n=137).

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

Patient exposure

Table 32 summarizes the exposure to TEZ/IVA in Study 116 and cumulatively across the parent studies and Study 116.

The median exposure in the parent studies, in study 116, and in the cumulative TEZ/IVA dataset was 23.3 weeks (n=124), 68.1 weeks (n=130), and 75.9 weeks (n=137) respectively. In the cumulative TEZ/IVA dataset a total of n=129 patients had an exposure > 48 weeks, and n=37 had an exposure > 96 weeks.

Table 32 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 33. 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 in the cumulative TEZ/IVA dataset (n=31; 22.6%) compared to the parent studies 115 and 113b (n=6; 4.8%).

Table 33 Overview of AE (Placebo group of study 115, Parent studies, Study 116 and Cumulative TEZ/IVA Safety Set), (n, %)

	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)
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 34 presents TEAEs with an incidence of ≥5% in any group by System Organ Class (SOC) and Preferred Term (PT).

- 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%).

- Study 116

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

- Cumulative IVA/TEZ 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 34 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 of 18 December 2019. MedDRA Version 22.1 was used. When summarizing 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 SOC and PT in the cumulative TEZ/IVA group.

Possibly related AEs

On overview of the related TEAE is provided in Table 35.

- 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%)

- Open-label extension 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 TEZ/IVA safety set

In the cumulative treatment group, the most frequently related TEAE events were 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 AEs.

Table 35 Treatment related AE' s with an incidence ≥5% in the cumulative group report (TEZ/IVA safety set in Parent studies, 116 safety set and in the 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 event/deaths/other significant events

An overview of SAEs is provided in Table 36. No deaths were reported.

- 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%).

- Open-label extension 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).

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

No SAE led to treatment discontinuation but a total of 5 SAEs led to treatment interruption. These SAE were 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 36 SAEs Occurring in >1 Subject in the Cumulative TEZ/IVA Group by SOC and PT (Parent Studies TEZ/IVA Safety Set - Parent Studies TE Period; 116 Safety Set - 116 TE Period; Cumulative TEZ/IVA Safety Set - Cumulative TEZ/IVA TE Period)

	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

Laboratory findings

Liver function tests, lipid panels, vitamin levels, chemistry, haematology and coagulation were collected at regular intervals in the clinical studies.

- **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.

A summary of treatment-emergent elevated transaminases events is provided in Table 37.

- 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 transaminases.

- Open-label extension study 116

In study 116, a total of n=10 (7.7%) had at least an event of transaminase increase, 3 of which were considered severe in intensity.

Two (1.5%) subjects had AEs related to transaminase elevation which led to treatment discontinuation. Both subjects had experienced elevated transaminases prior to TEZ/IVA dosing in the parent study. In study 116, they both experienced nonserious increases of hepatic enzymes. They did not receive treatments for these events. It should be clarified if these elevations normalise over time.

An additional subject in study 116 had SAEs related to increases in hepatic enzymes which led to treatment interruption. The SAEs resolved and TEZ/IVA was resumed.

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 37 Summary of Treatment-Emergent Elevated Transaminases Events (Parent Studies TEZ/IVA Safety Set - Parent Studies TE Period; 116 Safety Set - 116 TE Period; Cumulative TEZ/IVA Safety Set - Cumulative TEZ/IVA TE Period)

	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
Life-threatening	0	0.00	0	0.00	0	0.00
Missing	0	0.00	0	0.00	0	0.00
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
Duration of events (days)						
Number of events	10	--	21	--	31	--
Number of events with duration	7	--	12	--	21	--
Mean (SD)	53.9 (56.3)	--	48.8 (70.2)	--	82.0 (122.7)	--
Median	57.0	--	19.5	--	23.0	--
Min, Max	7, 169	--	2, 245	--	2, 505	--
Time-to-onset of first event (days)						
Subjects with event with complete start date	7	--	10	--	14	--
Mean (SD)	54.3 (47.7)	--	226.8 (130.1)	--	189.5 (175.3)	--
Median	57.0	--	209.5	--	114.5	--
Min, Max	1, 120	--	16, 420	--	1, 519	--

- Elevated Transaminase events were coded using MedDRA version 22.1.
- PY: patient years; Events/100PY: number of events per 100 patient years = number of events/(total duration of TE period in days/(365.25 * 100)).
- When summarizing number of events, a subject with multiple events within a category is counted multiple times in that category.
- When summarizing number and % of subjects, a subject with multiple events within a category is counted only once in that category (the worst event is counted, if applicable).
- Related serious events = Study drug regimen-related serious events, which includes Related, Possibly Related, and missing categories.
- The duration is only calculated for the events with complete start and end dates.
- Parent studies: Study 113B and 115.

Table 38 provides the incidences of the subjects with maximum on treatment elevation (ALT or AST) above thresholds >1 x, >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 the TEZ/IVA Cumulative safety set.
In study 116, the incidence of ALT or AST >3 x ULN was n=12 (9%) compared with n=10 in the parent studies (8%).

Table 38 Threshold Analysis of LFT Chemistry Parameters

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

Ophthalmologic evaluations

In study 113B, subjects had an Ophthalmologic Evaluation at baseline (Screening) and at Week 24. At Screening, 5 subjects had cataracts or lens opacities, which were all considered not clinically significant. Of these 5 subjects, 3 subjects had ophthalmologic evaluation at Week 24. Among these 3 subjects, 1 subject continued to have cataracts at Week 24, and 2 subjects did not have cataracts detected at the Week 24 Ophthalmologic Evaluation.

At Week 24, 2 subjects had non-cataract lens opacities that were not noted at Screening. In 1 subject, the finding was reported as a mild AE of slit-lamp test abnormal (non-cataract); in the other subject, the lens opacity (non-cataract) was not considered an AE. These 2 subjects had prior steroid use and the lens opacities were not considered clinically significant.

In study 115, subjects had an ophthalmic evaluation at baseline (Screening), and no follow-up exam at Week 8, according to the protocol.

In study 116, 4 subjects had cataract AEs: 3 had AEs of cataract and 1 had an AE of lenticular opacities. All four AEs were considered non-serious, mild or moderate in severity, and did not lead to change in study drug dosing.

Cataracts/lens opacities are not included in section 4.8 of the SmPC of Kalydeco given that a clear relationship with the study medication could not be established. However, the need for ophthalmological examinations is included in section 4.4 of the SmPC.

Electrocardiogram

Prolongation of the QTc interval (i.e., QTcF >450 msec for males or QTcF >470 msec for females) was not reported in Studies 113 and 115. Similarly, no subject had a maximum QTcF change >60 msec.

Safety in special populations

The proposed posology has not been fully assessed in study 115 or in study 113B, i.e., in both studies weight cutoff-based dosing was used 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 is 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 children aged 6-11 years and weighing less than 30 kg who will receive the (lower) TEZ 50 mg qd/IVA 75 mg q12h dose, TEZ and IVA systemic exposure are predicted to be at the lower end of the systemic exposure seen in older patients, while M1-TEZ systemic exposure is predicted to be similar to that of older subjects. At the adult dose of TEZ 100 mg qd/IVA 150 mg q12h for children weighing ≥ 30 kg, the exposure to TEZ-M1 is predicted to be increased with respect to that of older patients.

Therefore, no safety have been generated in study 113B, study 115, or study 116 at the time of the interim analysis in children weighing ≥30 kg to less than 40 kg at the proposed adult dose of TEZ 100 mg qd/IVA 150 mg q12h.

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).

<u>Safety data in subjects 12 to <18 years old who weighed ≤40 kg</u>

The safety data of the placebo-controlled integrated summary of safety (Studies 106, 107 and 108) were pooled for this analysis. A total of 199 patients aged 12 to less than 18 years were included. The post hoc analysis included a total of n=30 adolescent patients with a body weight < 40 Kg, i.e., 13 placebo-treated patients and 17 TEZ/IVA-treated patients (Table 39).

Table 39 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.

Data from the same patients in the open label extension study (study 110) through 96 weeks were also evaluated (Table 40). Thirty subjects 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 40 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

Safety data based on M1-TEZ exposure ≥ 95% percentile

With the proposed body weight cut off of 30 kg, M1-TEZ exposures are predicted to be (also) 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-TEZ exposures in the pivotal study 106 (adult and adolescents homozygous for *F508del*).

- 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 in the parent studies

Transaminase elevations in study 113B and study 115 were analysed by each subject's total active TEZ (TEZ+M1-TEZ) exposure or M1-TEZ exposure, as compared to the exposure quartiles and 95th percentile for study 106 (the pivotal Phase 3 study in F/F subjects ≥12 years of age).

Of the 10 subjects with ALT or AST >3 × ULN in the parent studies, 8 had TEZ and M1-TEZ exposure below the study 106 median. There were 3 subjects with AST or ALT elevations >5 × ULN; all had total active TEZ and M1-TEZ exposures below the study 106 median. No trend towards increased liver function test (LFT) elevations was observed in subjects with higher total active TEZ or M1-TEZ exposures.

Safety related to drug-drug interactions and other interactions

Dose adjustment is recommended for children aged 6 to less than 12 years of age receiving concomitant treatment with strong or moderate CYP3A inhibitors that is expected to match the systemic exposure of patients not receiving these drugs. Safety data in these patients have not been generated in study 113B or study 115 given that the use of known inducers and inhibitors of CYP3A was restricted in both studies.

Discontinuation due to adverse events

- Parent studies 113 and 115

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

- Open-label extension study 116

A total of n=2 (1.5%) of patients had AE of transaminase elevations that led to treatment discontinuation. The patients discontinued treatment because of nonserious transaminase elevations. Both subjects had elevated transaminases 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 n=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, a total of n=8 (6.2) patients experience AE's that leaded to treatment interruption. All treatment interruptions occurred by PT in n=1 patient. In n=1 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).

- TEZ/IVA Cumulative safety set

In the cumulative safety database, a total of n=13 (9.5%) interrupted therapy. TEAEs that resulted in treatment interruption were reported by 2 patients and were ALT increased and blood CK increased. All other AEs were reported by single patients.

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. 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.

2.8.1. Discussion on clinical safety

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 N=124 patients. Additional long-term safety data is provided for n=130 patients who rolled over to the ongoing open-label extension study 116. The cumulative TEZ/IVA Safety Set combines the exposure of TEZ/IVA in the parent studies and in study 116 (n=137).

The median exposure in the parent studies, in study 116, and in the cumulative TEZ/IVA dataset was 23.3 weeks (n=124), 68.1 weeks (n=130), and 75.9 weeks (n=137) respectively. In the cumulative TEZ/IVA dataset a total of n=129 patients had an exposure > 48 weeks, and n=37 had an exposure > 96 weeks.

The additional safety data discussed in response to the Request for Supplementary Information which are based on 129 patients who have been exposed to TEZ/IVA for more than 48 weeks further support the present extension of indication. Nevertheless, some limitations have been identified. There is a lack of direct safety data in children dosed with IVA in combination with TEZ/IVA at the adult doses in the weight band from ≥ 30 kg to less than 40 kg.

This will affect about 40% of the EU target population. As no safety data are available for the subset of children aged 6 to less than 12 years old, the safety assessment is extrapolated from indirect safety data from adolescents in the same weight band (≥30 to less than 40 kg) who were treated in the pivotal studies and in the extension study 110 with the adult doses of TEZ and IVA. In addition, comparative safety data vs. placebo is limited due to the small number of subjects enrolled in the placebo group of study 115 (n=10) who were treated for 8 weeks. Therefore, the safety dataset mainly consisted of data collected in an uncontrolled, open-label study period in which the contribution from the longer disease duration versus the longer drug exposure may be hard to distinguish.

Overall the safety data set assessed showed that treatment with IVA in combination with TEZ/IVA is well tolerated, and the reported adverse events appear to be in line with the adult's and older paediatric patients safety database. Most of the adverse events were of mild intensity.

The exposure-adjusted event rate for serious adverse events (SAE) was higher in study 116 (33.76 events per 100 patient years) and the TEZ/IVA cumulative safety set (n=31 [30.50 event/100 patient years]) than in the TEZ/IVA groups of parent studies (17.27 events per 100PY). The MAH state that 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 100PY reported in the placebo group of 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 remains below this rate (33.76 event/100 PY) vs 42.77 events/100 PY.

The number of treatments related adverse events appeared to be consistently reported in both the parent studies and the long-term safety study (23.8%). 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 n=2 patients discontinued because of non-serious elevations of transaminases in the long-term safety study. These patients had experienced elevated transaminases prior to being dosing with TEZ/IVA in 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: after 75.9 weeks]), an incidence being higher than that observed in subjects 12 years of age and older (3.2%). These observations are consistent with published data that indicate that (moderate) transaminase elevations are more common in younger patients with CF than in older patients and are in line with the observed frequency in the placebo arm of study VX14-809-109 with a treatment duration of 24 weeks.

As no safety data are available for a subset of children aged 6 to less than 12 years old due to the proposed shift in the body weight cut-off from 40 kg to 30 kg for dosing recommendations, the safety assessment needs to be based on indirect safety data from adolescents in the same weight band (≥30 to less than 40 kg) who were treated in the pivotal studies and in the extension study 110 with the adult doses of TEZ and IVA. This approach is endorsed since from a pharmacokinetic point of view maturation processes that may affect systemic exposure are completed in children 6 to 11 years old. Other safety data have been discussed to justify that the expected higher M1-TEZ levels in these children are not associated to an increase of adverse events, in particular increased in liver functions tests. All these analyses have been conducted post-hoc and even though they are supportive of the lack of dose-response (safety) relationship, this conclusion is based on a limited number of subjects. Additional safety data at the proposed posology is being collected in part B of the ongoing open-label extension study 116.

Transaminase elevations are listed as an adverse reaction in the SOC "Hepatobiliary disorders" of section 4.8 of the SmPC of Kalydeco tablets and granules. Recommendations for liver function test monitoring at initiation and periodically during treatment, with recommendations to discontinue or interrupt treatment in the presence of abnormal liver function tests are already included in section 4.4 of the SmPC and are relevant for the use in combination with Symkevi in patients from 6 to less than 12 years of age.

Additional safety data post marketing will be needed to further characterise the safety profile in the patient population. In study 116B, additional safety data is being collected at the proposed posology for children aged 6 to less than 12 years. Patients who permanently discontinued treatment or temporarily stopped treatment because of elevated transaminases and had a positive rechallenge could not be included. In addition, a post-marketing study 117 is being conducted. However, collection of safety data in study 117 will be very limited as the study is not designed to collect adverse events. Therefore, it may probably not register the number of patients that discontinue or interrupt treatment because of modest transaminase elevations.

2.8.2. Conclusions on the clinical safety

Overall, treatment with IVA in combination with TEZ/IVA in children 6 through 11 years of age with CF who are homozygous for F508del or heterozygous F508del/CFTR mutation with residual function was well tolerated. The safety outcomes were generally consistent with the background profile of IVA in combination with TEZ/IVA in older patients with CF. In line with previous applications in paediatric CF, more paediatric patients showed elevations in transaminases compared to adults.

No clinical data have been provided to support the proposed weight-based posology which is predicted to result in a higher M1-TEZ exposure in children weighing ≥30 to less than 40 kg. Additional post-hoc analyses failed to show a correlation between exposure and elevated transaminases, however these additional analyses are hampered by the limited number of patients included.

There is however a need for monitoring of liver function prior and during treatment. The current recommendations in place in the Kalydeco SmPC sections 4.4 and 4.8 are adequate to monitor the hepatic function for the use in combination with Symkevi and remain unchanged.

2.9. Risk Management Plan

Safety concerns

Important identified risks	• None
Important potential risks	• Hepatotoxicity • Cataract • Concomitant use of IVA with strong CYP3A inhibitors or inducers
Missing information	• Use in pregnant and lactating women • Indicated use in children aged less than 6 years

Pharmacovigilance plan

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 – Imposed mandatory additional PV activities which are Conditions of the MA (key to benefit risk)				
None				
Category 2 – Imposed mandatory additional PV activities which are Specific Obligations in the context of a conditional MA under exceptional circumstances (key to benefit risk)				
None				
Category 3 – Required additional PV activities (by the competent authority)				
Study 126 Ongoing	IVA Arm In subjects with CF who are <24 months of age at treatment initiation and have an approved IVA-responsive mutation:	• Hepatotoxicity • Cataract • Use in children aged 12 to <24 months old at initiation	Final Report	March 2022

Study/Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
	• To evaluate the safety of long-term IVA treatment • To evaluate the PD of long-term IVA treatment • To evaluate the efficacy of long-term IVA treatment <u>Observational Arm</u> To evaluate long-term safety after discontinuation of IVA treatment in subjects with CF who were <24 months of age at treatment initiation and have an approved IVA-responsive mutation			
Study 122 Ongoing	• To confirm the long-term safety and effectiveness of Kalydeco (IVA) in US CF patients with the *R117H-CFTR* mutation <18 years of age • To describe the long-term safety and effectiveness of Kalydeco in CF patients with the *R117H-CFTR* mutation overall and in patients ≥18 years of age	• Indicated use in children aged <6 years (with the *R117H* mutation)	Final Report	December 2020

CF: cystic fibrosis; IVA: ivacaftor; PD: pharmacodynamics
Note: Study 126 addresses a subpopulation of the Missing Information of "Indicated use in children aged less than 6 years."

Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Hepatotoxicity	**Routine risk minimisation measure:** SmPC Section 4.4 where advice is given on monitoring LFTs. SmPC Section 4.8 PL Section 4 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** Study 126
Cataract	**Routine risk minimisation measure:** SmPC Section 4.4 where advice is given on recommended ophthalmological examinations SmPC Section 5.3 PL Section 2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** Study 126

Concomitant use of IVA with strong CYP3A inhibitors or inducers	**Routine risk minimisation measure:** SmPC Section 4.2 where dose reductions are recommended when co-administered with a strong inhibitor of CYP3A. SmPC Section 4.4 PL Section 2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** None
Use in pregnant and lactating women	**Routine risk minimisation measure:** SmPC Section 4.6 where advice is given on to use Kalydeco during pregnancy only if clearly needed and during breastfeeding if the potential benefit outweighs the potential risks. PL Section 2 **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only Pregnancy follow-up form **Additional PV activities:** None
Indicated use in children aged less than 6 years	**Routine risk minimisation measure:** SmPC Section 4.2 where the posology is described SmPC Sections 4.8 and 5.2 PL Section 2 **Additional risk minimisation measures:** No risk minimisation measures	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection** Prescription only **Additional PV activities:** Study 126 Study 122

CYP: cytochrome P450, PL: Patient Leaflet; SmPC: Summary of Product Characteristics Note: Study 126 addresses a subpopulation of the Missing Information of "Indicated use in children aged less than 6 years."

Conclusion

The CHMP and PRAC considered that the risk management plan version 10.0 is acceptable.

2.10. 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

The requirements for submission of periodic safety update reports for this medicinal product are set

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

2.11. Product information

2.11.1. 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:

The updates as a result of this procedure do not impact the readability of the package leaflet. Readability testing was previously conducted for the Kalydeco 150 mg film-coated tablets package leaflet and reviewed during the initial application, procedure EMEA/H/C/002494, and bridging conducted during the initial indication extension for Kalydeco tablets in a combination regimen with tezacaftor /ivacaftor, procedure EMEA/H/C/002494/II/0063/G. Updates made to the package leaflet are minimal, and the structure and guidance for caregivers remains aligned to the principles agreed on in previous procedures.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This application corresponds to a new strength for Kalydeco (75 mg tablets) to be used for a new indication in younger patients in combination with Symkevi as follows:

Kalydeco tablets are indicated in a combination regimen with tezacaftor/ivacaftor tablets for the treatment of adults, adolescents, and children aged **6** years and older with cystic fibrosis (CF) 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.

In children with CF, pancreatic insufficiency and poor nutritional status are the most significant clinical manifestations of the disease. Published studies have demonstrated benefits such as improved growth and nutrition through early intervention in children diagnosed following newborn screening. Other complications of the disease such as liver disease and cystic fibrosis-related diabetes occur more frequently in the paediatric population.

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. Instead, CFTR modulators target the mutated CFTR protein and improve its function and, as such, they could modify the progress of the disease which is expected to translate into prolonged survival. This would be the ultimate goal of the CFTR modulators.

Two CFTR modulators are approved for the treatment of CF in the EU in children aged 6 years and older, Kalydeco (ivacaftor) and Orkambi (lumacaftor/ivacaftor). Symkevi is approved for adolescents and adults aged 12 years and older. Kaftrio is approved for adolescents and adult patients who are homozygous for the *F508del-CFTR* mutation and heterozygous *F508del* patients with a second *CFTR* mutation of minimal function.

The current application applies for an extension of the indication for Kalydeco in combination use with Symkevi for the treatment of children aged ≥ 6 years with CF who are homozygous for the *F508del-CFTR* mutation as well for those who are heterozygous *F508del* and have certain other mutations of residual function in the second allele of the *CFTR* gene.

Homozygous *F508del* subjects

The claimed indication for Kalydeco in combination with Symkevi (TEZ/IVA) partly overlaps with the approved indication of Orkambi. However, the extension of the IVA in combination with TEZ/IVA indication to patients 6 through 11 years old would provide an alternative treatment option for these patients considering that Orkambi is not tolerated by a number of subjects due to adverse events (e.g. bronchoconstriction, liver function impairment). In addition, lumacaftor is a strong CYP3A inducer which may lead to unwanted drug-drug interactions with commonly prescribed medications, while tezacaftor/ivacaftor is less prone to cause clinically relevant drug-drug interactions.

Heterozygous *F508del/RF* subjects

The claimed indication may cover an unmet need for children aged 6 to less than 12 years of age with cystic fibrosis who are heterozygous *F508del*/*CFTR* mutation of residual function. This patient group represents about 9% of the CF population. These patients are characterised by slower disease progression than the homozygous *F508del* population, but they will eventually experience the clinical consequences of CF including a reduced lifespan.

Proposed posology

The proposed posology for Kalydeco in a combination regimen with 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 for the current application is study VX16-661-115 (study 115), and the safety study is study VX15-661-113, part B (study 113B). 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. Children homozygous for *F508del* and heterozygous *F508del/CFTR*-mutations of residual function were enrolled.

This application is based on extrapolation of efficacy considering the similarities in the genetic, molecular and pathophysiological aetiology of CF between adults and paediatric patients as outlined in the principles described in ICH E11 and the EMA reflection paper on the use of extrapolation for in the development of medicines for paediatrics.

Additionally, the role of CFTR modulators such as ivacaftor (Kalydeco) and lumacaftor/ivacaftor (Orkambi) has been established in children aged 6-11 years in a comparative placebo-controlled phase III randomised trial.

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	PK, PD and dose finding
VX13-661- 103						X	Dose finding
VX14-661-106	248*		X		$ppFEV_1$	X	Pivotal efficacy and safety study (F/F)
VX14-661-108	161*		X	x	$ppFEV_1$	X	Pivotal efficacy and safety study (F/RF)
VX16-661-110	459					X	Open-label safety extension study
VX15-661-113		70	X	X	$LCI_{2.5}$	X	PK and dose finding, safety
VX16-661-115		54*		X	$LCI_{2.5}$	X	Dose confirmation and efficacy (F/F and F/RF)
VX17-661-116		130				x	Open-label safety extension study (ongoing)

*patients exposed to TEZ/IVA

In study 115, paediatric patients had evidence of uneven ventilation due to small airways disease at screening ($LCI_{2.5}$ ≥7.5) but could have preserved lung function (as shown by ppFEV1). This is characteristic of children in the age range from 6 to less than 12 years old.

3.2. Favourable effects

The primary efficacy outcome of the pivotal study 115, i.e., the LS mean (SE) within-group change in $LCI_{2.5}$ from baseline through Week 8 in the TEZ/IVA group was -0.51 (0.11) (95% CI: -0.74, -0.29; P <0.0001). As the upper bound of the 95% CI (-0.29) was below the pre-specified maximum placebo effect of -0.10 (based on the 1-sided 90% lower bound of the within-group change of the placebo arm of study 109 in the clinical programme of Orkambi in children aged 6 to less than 12 years), it is concluded that the primary endpoint met the pre-defined criterion for success.

The additional sensitivity analyses for $LCI_{2.5}$ (MMRM with placebo mean imputation) showed the following outcomes in $LCI_{2.5}$ from baseline through week 8, i.e., the within-group LS mean absolute change was -0.32 (95% CI -0.56, -0.07) for homozygous *F508del* children; for the heterozygous population these figures were -1.07 (-1.49, -0.64). The upper bound of the 95% CI interval exceeded the pre-defined maximum placebo effect of -0.10 only in the analysis of homozygous *F508del* subjects (-0.07). In all other analyses presented (included the between-treatment difference vs. placebo) the point estimates exceed the predefined placebo effect and the upper limit of the 95% CI was below the predefined placebo effect (IVA/TEZ within-group comparisons).

The key secondary outcomes and other outcomes (ppFEV1) showed favourable TEZ/IVA within-group changes from baseline trough/at week 8 as well:

- Sweat chloride: LS mean (SE) -12.3 (1.5) (95% CI: -15.3,-9.3) mmol/l, p<0.0001..
- Respiratory domain of CFQ-R: LS mean (SE) 2.3 (1.2) (95% CI: -0.1, 4.6) points, p=0.0546.
- Percent predicted FEV1 ($ppFEV_1$): LS mean (SE) 2.8 (0.9) (95% CI: 1.0, 4.6) percentage points, p=0.0024.

The reduction in sweat chloride, albeit of limited magnitude, is in the range of that observed in the adult trials. Improvements in primary and secondary outcome measures were observed in both subgroups of subjects enrolled in the study, i.e., homozygous *F508del* and heterozygous *F508del*/mutation of residual function.

In the supportive study 113B an improvement in mean sweat chloride and in the mean score of the respiratory domain of the CFQ-R was observed.

The drug was well tolerated by most of the patients.

3.3. Uncertainties and limitations about favourable effects

Dosing recommendations in the pivotal study 115 were based on pop PK model-based simulations and analysis of systemic exposure which included PK data from study 113. The aim of the paediatric development programme was to match in children aged 6 to 11 years TEZ and IVA systemic exposures which have been shown to be efficacious and safe in patients aged 12 years and older. Based on various pop-PK analyses, model-based simulations led to the choice of a body weight cut off of 30 kg, i.e., children aged 6 to less than 12 years and weighing less than 30 kg will receive TEZ 50 mg qd/ IVA 75 mg every 12 hours while those weighing ≥ 30 kg will receive the adult dose of TEZ 100 mg qd/ IVA 150 mg every 12 hours. While it may be agreed that based on the modelling and simulations provided, the cut-off of 30 kg likely represents the best choice to match the systemic exposure of adult and adolescents subjects, overall the simulations showed that for children below 30 kg, TEZ and IVA systemic exposure were at the lower end of the systemic exposure in older patients, while for children weighing ≥ 30 kg higher M1-TEZ levels were predicted. These raised concerns in terms of efficacy and safety. Upon request by CHMP, additional pop-PK and pop PK/PD modelling and simulation were provided and confirmed, that only M1-TEZ exposure is predicted to be affected by the shift in the body weight cut-off at 100 mg TEZ qd, and that a similar response in terms of sweat chloride is to be expected irrespective of the predicted TEZ, IVA, and M1-TEZ exposures in children weighing ≥ 30 kg to less than 40 kg as well as in children weighing less than 30 kg when dosed according to the above proposed posology.

Although study 115 is a randomised, double-blind, parallel study, within-group group changes in the TEZ/IVA arm were predefined as the primary analysis for all continuous variables. No between-treatment differences were planned in the statistical analysis plan. Consequently, a formal statistical

analysis for the difference from baseline at week 8 between the TEZ/IVA and the placebo groups was requested for $LCI_{2.5}$, $LCI_{5.0}$ and sweat chloride using placebo-mean imputation data for subjects with missing data at week 8. The LS mean difference (SE) vs. placebo in $LCI_{2.5}$ was -0.59 (95% CI: -1.22, 0.05).

Overall, the size of the treatment effect appears small, particularly in homozygous *F508del* subjects. However, there are limited data from trials using this endpoint and a MCID has not yet been defined. Effect sizes in studies have ranged from -1 to -2 depending on the type of intervention and the duration of treatment. Limited longitudinal data from the placebo group of interventional trials are available to define whether an intervention exceeds the intrinsic variability of the test. Nevertheless, this endpoint is considered sufficiently established for trials in CF patients 6 – 11 years of age.

Treatment duration of study 115 is relatively short (8 weeks). It cannot be excluded that longer (than 8 weeks) treatment duration may have resulted in an additional decrease in the $LCI_{2.5}$ value (reflecting improvement in ventilation inhomogeneity). However, the pattern of decrease seen in the lumacaftor/ivacaftor study 109 suggests that the greatest change from baseline is seen in the first 4 weeks of treatment. This is also the case for endpoints such as sweat chloride and ppFEV1 for which an effect under CFTR modulator therapy is usually observed quite early and maintained for 24 weeks.

In the supportive study 113B, LCI was included as an exploratory endpoint given that the main aim of the study in this respect was to evaluate the LCI device that had not been used in any prior trials conducted by the MAH. Children show initially a small, clinically irrelevant deterioration of $LCI_{2.5}$. At the end of the study, the $LCI_{2.5}$ has returned to the baseline value. The LS mean absolute change in $LCI_{2.5}$ from baseline through Week 24 was 0.09 (95% CI: -0.32, 0.49).

Cross-study comparisons with study 109 show a smaller effect of TEZ/IVA in terms of sweat chloride and $LCI_{2.5}$ when compared with LUM/IVA as shown by within-group LS mean (SE) absolute change in sweat chloride of -12.3 (1.5) vs. -20.0 (1.0) mmol/l and in $LCI_{2.5}$ of -0.51 (0.11) vs. -1.01 (0.13). However, TEZ/IVA showed a numerically larger effect on ppFEV1 as shown by a mean (SE) within-group change of 2.8 (0.9) vs. a mean (SE) within-group change of 1.1 (0.8) percentage points in the LUM/IVA arm of study 109.

The study drugs appeared to be well accepted, but patients were selected based on their ability to swallow the tablet. This may have biased the results of the acceptability testing towards a more favourable outcome.

3.4. Unfavourable effects

The main safety data set included 137 patients, among them 129 patients who have been exposed for more than 48 weeks. Most frequently reported adverse events were cough (58.4%), followed by infective pulmonary exacerbation of CF (43.8%), and pyrexia (24.1%).

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

A higher incidence of serious adverse events per 100 patient-years was reported in the open-label extension study 116 (n=27, 20.8%) compared with the parent studies (n=6, 4.8%).

A total of 8 patients interrupted treatment due to adverse events which include two who had transaminase elevations. A total of 3 patients (2.2%) discontinued treatment, two of them due to because of nonserious transaminase elevations.

3.5. Uncertainties and limitations about unfavourable effects

The safety dataset mainly consists of data collected in an uncontrolled study period in which the contribution from the longer disease duration versus the longer drug exposure may be hard to distinguish. Comparative safety data vs. placebo is limited due to the small number of subjects enrolled in the placebo group of study 115 (n=10) who were treated for 8 weeks.

In addition, as no safety data are available for a subset of children aged 6 to less than 12 years old, the safety assessment needs to be based on indirect safety data such as that of adolescents in the same weight band (≥30 to less than 40 kg) who were treated in the pivotal studies and in the extension study 110 with the adult doses of TEZ and IVA. This and other post-hoc safety analyses failed to show a correlation between increased exposure and elevated transaminases, but this conclusion is based on a limited number of patients.

Cross study comparisons with the placebo arm of study 809-109 in the same F/F target population show that the incidence of transaminase elevations ~10% and SAE's is 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.

Transaminase elevations were already included as adverse reactions in section 4.8 of the SmPC of Kalydeco and section 4.4 includes recommendations for liver function test monitoring at initiation and periodically during treatment, with recommendations to discontinue or interrupt treatment in the presence of significantly abnormal liver function tests.

3.6. Effects Table

Table 1. Effects Table for Kalydeco in patients with cystic fibrosis (CF) aged 6 years to less than 12 years and 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 from baseline through wk8	-	LS mean (95%CI) -0.51 (-0.74,-0.29)	Comparison vs. placebo not planned	TEZ/IVA within-group change, MCID not established, measured effect is within the natural variability of the parameter/indicates improvement and reached highly statistical significance in the predefined analysis	Pediatric pulmonology 2013: 48:739-46 Eur Respir J 2017; 50: 1700433

Effect	Short Description	Unit	TEZ/IVA	Control	Uncertainties / Strength of evidence	References
Sweat chloride	absolute change from baseline at wk8	mmol/L	LS Mean (95% CI) -12.3 (-15.3, -9.3)	idem	TEZ/IVA within-group change/reduction of similar magnitude of that seen in older patients	Accepted by CHMP as indicative of partial restoration of the biochemical defect of the mutated CFTR protein.
Respiratory domain CFR-Q	absolute change from baseline through wk8	Points	LS Mean (95% CI) 2.3 (-0.1, 4.6)	idem	TEZ/IVA within-group change, relatively insensitive endpoint in patients with relatively well preserved lung function/indicates improvement	
ppFEV1	absolute change from baseline through wk8	Percentage points	LS Mean (95% CI) 2.8 (1.0, 4.6)	idem	TEZ/IVA within-group change, ppFEV1 insensitive endpoint for this patient population because of preserved lung function/indicates improvement	
BMI z-score	absolute change from baseline at wk 8	points	Mean (SD) -0.08 (0.27)	idem	Within-TEZ/IVA group change, treatment period is short, improvement not shown likely due to the normal baseline value.	
Unfavourable Effects*						
Cough	All events	n (%)	25 (35.7%)	idem	Limited safety dataset from open label study 113B (n=70); the patient exposure > 24 weeks is n=28	
Transaminase elevation	possibly related	n (%)	6 (8.6%)	idem	Recognised as an adverse reaction for older patients (included in section 4.8 of the SmPC) – Additional risk minimisation measures in place.	

*Notes: The results are obtained from the open label study 113B, which include 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

Ivacaftor and tezacaftor are *CFTR* modulators targeting the defect of the mutated CFTR protein which is the basis of the pathophysiological features in CF. This dysfunction of the CFTR protein has the same underlying genetic and molecular aetiology across age groups and there is no age-dependency in the mechanism of action of the drugs considered either. In addition, the pathogenesis of the disease is also comparable across paediatric and adult populations although there may be a significant age-

dependency for the presence of certain symptoms and signs of the disease with younger children generally less affected than older patients or with a different pattern of organ damage. These similarities in disease justify the use of an approach based on extrapolation to establish the efficacy of TEZ/IVA in paediatric patients with CF. Paediatric studies investigating the PK and safety of the drug are considered an acceptable way to establish the role of CFTR modulators for the treatment of children with CF.

The efficacy of ivacaftor in a combination regimen with Symkevi has been established in phase 3 studies in patients aged 12 years and older by showing improvement in lung function using FEV1, sweat chloride and quality of life compared to placebo. This led to the EU approval of Symkevi for CF patients homozygous for *F508del/F508del* and heterozygous for *F508del*/certain *CFTR* mutations of residual function. Bridging the efficacy from older patients (source population) to children aged 6 to less than 12 years of age is based on matching the systemic exposure which has been shown efficacious and safe in the source population.

In order to support this paediatric indication, PK data was collected in children aged 6 to less than 12 years. Based on the data submitted to support this application, it appeared that for children weighing ≥30 to less than 40 kg, TEZ parent and IVA parent systemic exposures fell within the lower range of observed exposures in subjects 12 years and older. Therefore, the weight cut-off for dosing recommendations was shifted from 40 kg to 30 kg to better match the exposure of older patients. This adjustment affects about 40% of the target EU population. The clinical package does not contain clinical data to provide evidence for this posology in children weighing at least 30 kg to less than 40 kg. However, this was accepted by CHMP since the additional data provided sufficiently support the proposed posology.

A pharmacodynamic effect was shown in the paediatric studies 113B and 115, i.e., a reduction in sweat chloride of 12 mmol/l was shown in the TEZ/IVA group of study 115 (and also in the additional analysis vs. placebo) that was similar to the effect observed in older patients.

Based on the similar systemic exposure and pharmacodynamic effect in both populations, extrapolation of efficacy in the approved indication in patients aged 12 years and older to the children aged 6 to 11 years old (inclusive) is considered acceptable.

The pivotal study 115 met its primary endpoint according to the pre-defined statistical analysis. The result was highly statistically significant but of small magnitude, in particular for homozygous *F508del* children. For the heterozygous population, the within-group LS mean absolute change was -1.07 (as compared to -0.32 in F/F patients). Nevertheless, this is considered sufficient in the context of prior demonstration of efficacy for a TEZ/IVA combination in F/F and F/RF patients aged 12 years and older. In addition, supportive evidence of efficacy was also shown in terms of ppFEV1 (with a mean within-group change of 2.8 percentage points) and sweat chloride. The result on sweat chloride, although indicative of partial functional correction only, can be considered likely to predict a slowing of rate of disease progression.

In cross-study comparisons of study 115 with study 109 (pivotal study for the approval of lumacaftor/ivacaftor in children aged 6 to less than 12 years homozygous for *F508del*), the effect of TEZ/IVA lag behind that of LUM/IVA in terms of $LCI_{2.5}$ and sweat chloride. Given that once approved in children aged 6 to less than 12 years of age both will be available for homozygous *F508del* subjects, it is considered that the SmPC of Symkevi should include in section 5.1 the results of study 115 for both F/F and F/RF subjects to allow healthcare professionals to take informed decisions about treating individual F/F patients with Orkambi or with Symkevi even acknowledging that study 115 was not powered for subgroup analysis. If approved, Symkevi will provide an alternative for homozygous *F508del* 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 children who are heterozygous

F/certain *CFTR* mutations of residual function. These patients are characterised by slower disease progression, but they will eventually experience the clinical consequences of CF including a reduced lifespan.

In the clinical program, IVA in combination with TEZ/IVA appeared to be well-tolerated, both after short and longer term treatment. The most frequently reported related adverse event was transaminase elevation. However, the safety data base mainly consists of uncontrolled data, which makes it hard to distinguish the contribution from the longer disease duration versus the longer drug exposure as a comparison with placebo is lacking. Cross study comparisons showed that the observed frequency of elevated transaminase (~ 10%) of the long-term safety data base of 75-week duration was in line with the placebo arm of a comparative trial of 24-week duration (study 109 in the Orkambi programme).

Transaminase elevations are already included as adverse reactions in section 4.8 of the SmPC of Kalydeco and section 4.4 includes recommendations for monitoring of liver function at initiation and periodically during treatment, with recommendations to discontinue or interrupt treatment in the presence of significantly abnormal liver function tests. No additional information is needed to mitigate the risk of hepatotoxicity when Kalydeco will be used in combination with Symkevi in patients from 6 to 11 years of age.

No clinical data has been provided to support the safety for the higher proposed posology which may affect about 40% of the proposed EU target population. Concerns were raised, if the higher (M1-TEZ) 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 data base they provide enough support to the proposed posology.

The CHMP recommended the MAH to submit an application for the 75 mg granules formulation to allow its use in combination with Symkevi for patients not able to swallow tablets. This was not agreed by the MAH.

3.7.2. Balance of benefits and risks

In the paediatric studies 113B and 115, IVA in combination with TEZ/IVA showed a similar improvement in sweat chloride in children with CF as compared to older patients. The observed pharmacodynamic improvement was associated with an improvement in $LCI_{2.5}$ of limited magnitude in particular in children homozygous for the *F508del-CFTR* mutation but still sufficient in the context of prior demonstration of efficacy for a TEZ/IVA combination in F/F and F/RF patients aged 12 years and older. The treatment appeared overall well tolerated.

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. 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 as with longer-term safety data and post-hoc analyses that contribute to alleviate the concerns regarding the potential for increased systemic exposure and risk of transaminase elevations. In section 5.2 of the Kalydeco tablets SmPC, a footnote in table 9 showing the ivacaftor systemic exposure when combined with tezacaftor/ivacaftor, indicates that exposures in children aged 6 to less than 12 years and weighing ≥30 kg to <40 kg are predictions derived from the population PK model.

Overall, the data support the extension of the indication to children aged 6 years and older and the approval of the new 75 mg strength of Kalydeco tablets.

3.8. Conclusions

The overall B/R of Kalydeco is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

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

Outcome

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

Kalydeco tablets are indicated in a combination regimen with tezacaftor/ivacaftor tablets for the treatment of adults, adolescents, and children aged 6 years and older with cystic fibrosis (CF) 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.*

The CHMP therefore recommends the extension of the marketing authorisation for Kalydeco 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.

Obligation to conduct post-authorisation measures

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

Description	Due date
Long-term effectiveness study to compare disease progression among children with CF who have a specified CFTR gating mutation and are aged 2 through 5 years at the time of Kalydeco treatment initiation versus disease progression among concurrent matched cohort of children with CF who have never received Kalydeco treatment.	Interim analysis 1: December 2017 Interim analysis 2: December 2019 Interim analysis 3: December 2021 Final report: December 2023

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0353/2018 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, concerning the following change(s):

Variations requested		Type	Annexes affected
X.02.III	Annex I_2.(c) Change or addition of a new strength/potency	Line Extension	I, IIIA, IIIB and A
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, IIIA, IIIB and A

Extension application to add a new strength of 75 mg film-coated tablets of ivacaftor to enable administration to patients aged 6 to less than 11 years
C.II.6.a - To update sections 4.1, 4.2 and 6.5 the SmPC, and sections 1 and 2 of the PL for the 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 tezacaftor/ivacaftor and to bring it in line with the new dosage form (75 mg film-coated tablets of ivacaftor).
The submitted RMP (version 10.0) is accepted.
In addition, the MAH took the opportunity to implement minor updates in the Product Information.