22 August 2019
EMA/CHMP/411016/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Symkevi

International non-proprietary name: TEZACAFTOR/IVACAFTOR

Procedure no.: EMEA/H/C/004682/P46/006 and EMEA/H/C/002494/P46/0027

Marketing authorisation holder (MAH): Vertex Pharmaceuticals (Ireland) Limited

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LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC_T	AUC during a dosing interval
BL	baseline
BLQ	below the limits of quantification
BMI	body mass index
BP	blood pressure
BQL	below the quantifiable limit
CF	cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFTR	CF transmembrane conductance regulator protein
CFTR	CF transmembrane conductance regulator gene
CI	confidence interval
Cl^-	chloride ion
CL	clearance
CL/F	apparent clearance
CLSS/F	apparent clearance at steady-state
Cmax	maximum observed concentration
CPAP	clinical pharmacology analysis plan
CRF	case report form
CSR	clinical study report
Ctrough	predose concentration
CV%	coefficient of variation
D	day
DBP	diastolic blood pressure
ECG	electrocardiogram
EDC	electronic data capture
ETT	Early Treatment Termination
F	bioavailability

F508del	CFTR gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDC	fixed-dose combination
$FEF_{25\%-75\%}$	forced expiratory flow, midexpiratory phase
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practice
geo mean	geometric mean
GGT	gamma-glutamyl transpeptidase
GLI	Global Lung Function Initiative
h	hour
HR	heart rate
IA	interim analysis
ICF	informed consent form
ICH	International Council for Harmonization
IDMC	independent data monitoring committee
IEC	independent ethics committee
IPD	important protocol deviation
IRB	institutional review board
IVA	ivacaftor
LCI	lung clearance index
$LCI_{2.5}$	number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value
$LCI_{5.0}$	number of lung turnovers required to reduce the end tidal inert gas concentration to 1/20th of its starting value
LFT	liver function test
LLOQ	lower limit of quantification
LS	least squares
LS mean	least squares mean
LUM	lumacaftor
max	maximum value
MBW	multiple-breath washout

MedDRA	Medical Dictionary for Regulatory Activities
min	minimum value
MMRM	mixed-effects model for repeated measures
MRT	mean residence time
N	total sample size
n	size of subsample
NA	not applicable
NBLQ	total values below the limits of quantification
NCA	noncompartmental analysis
OE	ophthalmological examination
P	probability
PE	physical examination
PK	pharmacokinetic, pharmacokinetics
ppFEV1	percent predicted forced expiratory volume in 1 second
PT	Preferred Term
q12h	every 12 hours
QC	quality control
qd	daily
QT	QT interval
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia's formula
REML	restricted maximum likelihood
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SI	SI units (International System of Units)
SOC	System Organ Class
SOP	standard operating procedure
t½	terminal phase half-life
TE	treatment-emergent
TEAE	treatment-emergent adverse event

TEZ	tezacaftor
tmax	time of maximum concentration
ULN	upper limit of normal
Vss	volume of distribution at steady-state
WK	week

1. Introduction

On 06 March 2019, the MAH submitted a completed paediatric study, Study VX16-661-113 for Symkevi (tezacaftor/ivacaftor) 100 mg/150 mg film coated tablets in a combination regimen with ivacaftor 150 mg tablets, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

Study VX16-661-113 involved the use of two authorised medicinal products held by Vertex Pharmaceuticals (Ireland) Limited:

- Symkevi (tezacaftor/ivacaftor) 100 mg/150 mg film coated tablets.

- Kalydeco (ivacaftor) 150 mg film-coated tablets

The same Article 46 submission has therefore been submitted in parallel for Kalydeco (EMEA/H/C/002494).

These data are also submitted as part of the post-authorisation measure(s).

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Study VX16-661-113 is 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.

In the EU, TEZ/IVA is approved as a combination regimen of Symkevi® with IVA 150-mg tablets (Kalydeco®) 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*.

In 2016, Vertex initiated clinical development in subjects 6 through 11 years of age with CF. Currently, there are 3 studies that have been completed or are ongoing in this population. A brief description of these studies is provided below.

• Study VX16-661-113 (completed): A Phase 3, open-label study to evaluate the pharmacokinetics (PK), safety, and tolerability of TEZ/IVA combination therapy in subjects 6 through 11 years of age with CF, homozygous or heterozygous for the F508del-CFTR mutation. Study 113 was conducted in the US and Canada to support the indication extension of the US label to the 6 through 11-year-old age group. In Study 113 Part A, 13 subjects received at least 1 dose of TEZ/IVA for 14 days. In Study 113 Part B, 70 subjects received at least 1 dose of TEZ/IVA for 24 weeks. 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; study conduct completed, data analysis ongoing): A Phase 3, double-blind, parallel-group study to evaluate the efficacy and safety of TEZ/IVA in subjects 6 through 11 years of age with CF, homozygous or heterozygous for the F508del-CFTR mutation. Subjects were administered TEZ/IVA for approximately 8 weeks. Study 115 was conducted in Europe and Australia and is included in the TEZ/IVA EMEA-001640-PIP01-14-M04; Study 12.

• Study VX17-661-116 (Study 116; ongoing): A Phase 3, open-label, rollover study to evaluate the safety and efficacy of long-term treatment with TEZ/IVA in subjects 6 years of age and older with CF, homozygous or heterozygous for the F508del-CFTR mutation.

The MAH stated that study VX16-661-113 is part of a clinical development program. Vertex plans to submit a Line Extension grouped with a Type II variation to extend the indications of Symkevi and Kalydeco to children aged 6 through 11 years. The planned submission date is in the second half of 2019.

A line listing of all the concerned studies is annexed.

Part A of the study VX16-661-113 is part of paediatric investigation plan, study 11 (EMEA-001640-PIP01-14-M05). Clinical efficacy and safety will be studied in Study 12 (Study C, part B; VX16-661-115).

2.2. Information on the pharmaceutical formulation used in the study

A 50 mg/75 mg fixed-dose combination (FDC) tablet dosage was developed for this paediatric population. A summary of the TEZ/IVA and IVA formulations and dose regimen used in Studies 113, 115, and 116 are provided in

Table 1. No specific paediatric pharmaceutical form was required for this study. PK results from Study 113 Part A were used to select the weight cut-off and dose regimens evaluated in Part B. A new lower dose strength of the TEZ/IVA tablet has been introduced for patients <40 kg to achieve target exposures in lighter weight patients.

Table 1 Formulations and Dose Regimen in Studies 113, 115, and 116

Weight	Formulation	Dose Regimen
Study 113 Part A		
Subjects 6 through 11 years of age		
Subjects <25 kg at baseline	TEZ 50-mg tablet AND capsule containing IVA 75-mg granules	TEZ 50 mg qd/IVA 75 mg q12h
Subjects ≥25 kg at baseline	TEZ 50-mg tablet AND IVA 150-mg tablet	TEZ 50 mg qd/IVA 150 mg q12h
Study 113 Part B, Study 115, and Study 116		
Subjects 6 through 11 years of age		
Subjects <40 kg at baseline[a]	FDC tablet of TEZ 50-mg/IVA 75-mg AND IVA 75-mg tablet	TEZ 50 mg qd/IVA 75 mg q12h
Subjects ≥40 kg at baseline	FDC tablet of TEZ 100-mg/IVA 150-mg AND IVA 150-mg tablet	TEZ 100 mg qd/IVA 150 mg q12h
Subjects 12 years of age and older[a,b]		
NA	FDC tablet of TEZ 100-mg/IVA 150-mg AND IVA 150-mg tablet	TEZ 100 mg qd/IVA 150 mg q12h

FDC: fixed-dose combination; IVA: ivacaftor; NA: not applicable; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor

[a] In Study 116, doses may be adjusted for weight (i.e., subject who is 6 through 11 years of age weighs <40 kg at enrollment and subsequently weighs ≥40 kg at 2 consecutive visits) and age (i.e., following enrollment subject turns 12 years of age).

[b] Study 116 includes subjects 6 through 11 years of age as well as subjects 12 years of age and older.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report(s) for:

- Study VX16-661-113, a Phase 3, Open-label Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of VX-661 in Combination with Ivacaftor in Subjects 6 Through 11 Years of Age With Cystic Fibrosis, Homozygous or Heterozygous for *the F508del-CFTR* Mutation

2.3.2. Clinical study

Clinical study number and title

Study VX16-661-113, a Phase 3, Open-label Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of VX-661 in Combination with Ivacaftor in Subjects 6 Through 11 Years of Age With Cystic Fibrosis, Homozygous or Heterozygous for *the F508del-CFTR* Mutation

Description

Methods

Objective(s)

A summary of the Study 113 objectives is outlined in Table 2.

Table 2 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.

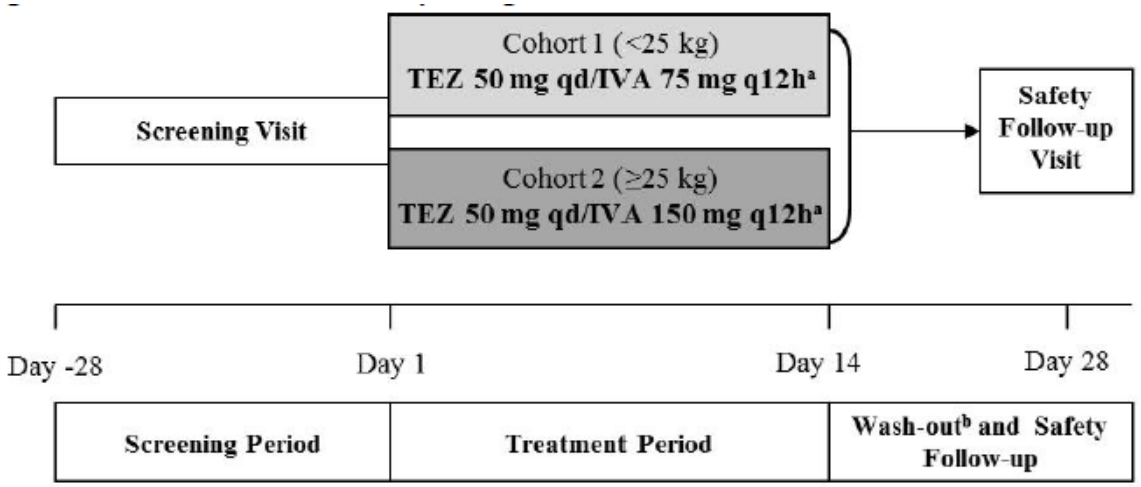
Study design

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

Part A

Part A included a Screening Period (28 days), Treatment Period (14 days) and a Wash-out/Safety Follow-up Period (14 days) to evaluate off-drug response. Subjects were enrolled into 2 weight-based cohorts and dosed as shown in Figure 1

Figure 1 Schematic of Study Design for Study 113 Part A



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

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

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

Part B

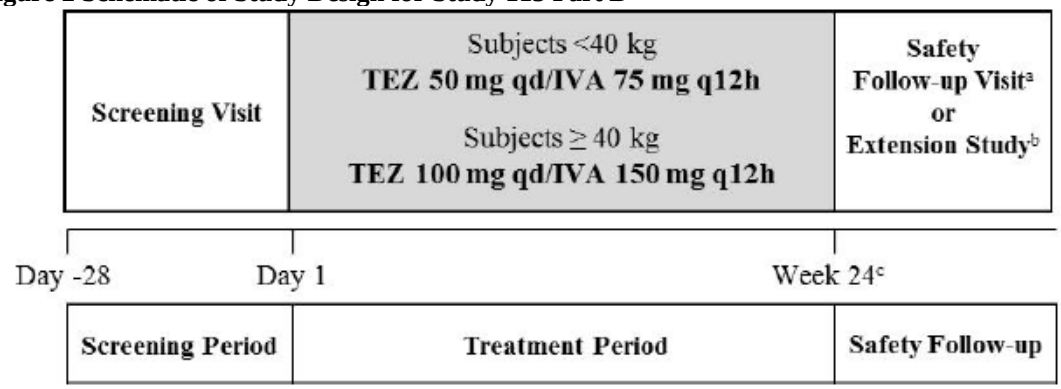
Part B included a Screening Period (28 days), Treatment Period (24 weeks [± 5 days]), and Safety Follow-up Visit (4 weeks [± 7 days]).

A review of safety, tolerability, and PK data was completed by an internal Vertex team after completion of Part A to select the TEZ/IVA dose regimens for Part B. Based on this review, subjects were dosed by weight as shown in

Figure 2. No dose adjustments were made throughout the duration of treatment of Part B.

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

Figure 2 Schematic of Study Design for Study 113 Part B



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.

Rapporteurs' comments

The dosing differs between Part A and Part B for tezacaftor compound as well as for ivacaftor compound.

For ivacaftor component, the dosing is 75 mg q12 h and 150 mg q12h in both parts, but the cut-off in weight is different i.e. 25 kg in Part A and 40 kg in Part B. For tezacaftor compound the dosing is 50 mg qd in part A, while there is a cut-off in weight of 40 kg with either 50 or 100 mg qd in Part B.

Study population /Sample size

Eligibility Criteria

Subjects who met all of the following main inclusion criteria were eligible for Part A and Part B. Subjects who participated in Part A may have participated in Part B, if the subject met all Part B eligibility criteria.

1. Subjects (male and female) were between the ages of 6 and 11 years, inclusive, on the date(s) of informed consent (and assent, if applicable) for each relevant part of the study (Part A and/or Part B, as applicable).
2. Subjects weighed >15 kg without shoes at the Screening Visit.
3. Subject had a confirmed diagnosis of CF and an eligible CFTR genotype. Subject genotype was confirmed at the Screening Visit. If the CFTR screening genotype result was not received before enrolment, a previous CFTR genotype lab report may have been used to establish eligibility. If a subject had enrolled, but their screening genotype did not confirm study eligibility, the subject would have been discontinued from the study.
4. F508del homozygous subjects were eligible for both Part A and Part B.

   Different populations of F508del heterozygous subjects were eligible for Part A and Part B:

- For Part A, subjects who were heterozygous for 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 (Truncation mutations: %PI >50% and/or SwCl >86 mmol/L, no full-length protein; Canonical splice mutations: %PI >50% and/or SwCl >86 mmol/L, no or little mature mRNA; Frameshift mutations %PI >50% and/or SwCl >86 mmol/L, garbled or truncated protein; Class II, III, IV mutations not responsive to ivacaftor or VX-661, %PI >50% and/or SwCl >86 mmol/L, OR not responsive in vitro to ivacaftor and VX-661) (Refer to Appendix 16.1.1/Protocol Version 3.0/Appendix A of the CTR for a list of eligible mutations in each category)
- For Part B, F508del heterozygous subjects were only eligible if clinical efficacy of TEZ/IVA had been demonstrated in a corresponding adult population. At the time of Part B enrolment, clinical studies had demonstrated efficacy for F508del heterozygous subjects with a second CFTR allele predicted to have residual function (evaluated in Study VX14-661-108), but not for the other heterozygous genotypes eligible for Part A (evaluated in Studies VX14-661-107 and 109). Therefore, only heterozygous subjects who had a residual function mutation on the second CFTR allele were eligible for Part B.

  Appendix 16.1.1/Protocol Version 3.0/Appendix A of the CTR:

  Encodes a mutation predicted to have residual function

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.

  - Encodes a mutation with a gating defect clinically demonstrated to be ivacaftor-responsive (subjects may be eligible if clinical benefit has been demonstrated in the corresponding adult population): *R117H , G178R, S549N, S549R, G551D, G551S, G1244E, S1251N, S1255P, G1349D* (Source: CFTR2.org [Internet]. Baltimore (MD): Clinical and functional translation of CFTR. The Clinical and Functional Translation of CFTR (CFTR2), US Cystic Fibrosis Foundation, Johns Hopkins University, the Hospital for Sick Children. Available at: http://www.cftr2.org/. Accessed 15 September 2014.)

Criteria for the diagnosis of CF varied depending on genotype as follows:

a. For subjects who were homozygous for the F508del-CFTR mutation (eligible for Part A and Part B):

    - Confirmed diagnosis of CF defined as a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis (as documented in the subject's medical record or from the sweat chloride test result obtained at the Screening Visit).

b. For subjects who were heterozygous for the F508del-CFTR mutation with a second allele with a CFTR mutation predicted to have residual function (eligible for Part A and Part B):

    - Confirmed diagnosis of CF defined as a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis (as documented in the subject's medical record or from the sweat chloride test result obtained at the Screening Visit).
    - If the sweat chloride value was <60 mmol/L, the subject was 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, manifested by at least 1 of the following:
        - Persistent colonization/infection, defined as ≥2 positive respiratory cultures within a 6 month period, with 1 or more typical CF pathogens (e.g., Staphylococcus aureus, Haemophilus influenzae, mucoid and nonmucoid Pseudomonas aeruginosa)
        - Chronic cough and sputum production
        - Persistent chest radiograph abnormalities consistent with CF pulmonary disease (e.g., bronchiectasis, atelectasis, infiltrates, hyperinflation)
        - Nasal polyps or chronic sinusitis as manifested by radiographic or computed tomographic abnormalities of the paranasal sinuses
        - Evidence of gastrointestinal disease consistent with the diagnosis of CF
        - Significant delays in growth and/or weight gain consistent with the diagnosis of CF

c. For subjects who were heterozygous for the F508del-CFTR mutation with a second CFTR mutation that was not likely to respond to TEZ and/or IVA therapy (only eligible for Part A).

    - Confirmed diagnosis of CF defined as a sweat chloride value ≥60 mmol/L by quantitative pilocarpine iontophoresis (as documented in the subject's medical record or from the sweat chloride test result obtained at the Screening Visit).

d. For subjects who were heterozygous for the F508del-CFTR mutation with a second CFTR allele with a gating defect that has been clinically demonstrated to be IVA responsive (only eligible for Part A)

    - Confirmed diagnosis of CF defined as a sweat chloride value ≥ 60 mmol/L by quantitative pilocarpine iontophoresis (as documented in the subject's medical record or from the sweat chloride test result obtained at the Screening Visit).
    - If the sweat chloride value was <60 mmol/L, subject was 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, manifest by at least 1 of the following:

- Persistent colonization/infection, defined as ≥2 positive respiratory cultures within a 6 month period, with 1 or more typical CF pathogens (e.g., Staphylococcus aureus, Haemophilus influenzae, mucoid and nonmucoid Pseudomonas aeruginosa)
- Chronic cough and sputum production
- Persistent chest radiograph abnormalities consistent with CF pulmonary disease (e.g., bronchiectasis, atelectasis, infiltrates, hyperinflation)
- Nasal polyps or chronic sinusitis as manifested by radiographic or computed tomographic abnormalities of the paranasal sinuses
- Evidence of gastrointestinal disease consistent with the diagnosis of CF
- Significant delays in growth and/or weight gain consistent with the diagnosis of CF

5. Subjects had a percent 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.
6. Subjects with stable CF disease, as deemed by the investigator, at the Screening Visit.
7. Subjects were willing to remain on their stable CF medication regimen through Day 14 (Part A) or through Week 24 (Part B) or, if applicable, through the Safety Follow-up Visit.
8. Female subjects of childbearing potential had a negative serum pregnancy test at the Screening Visit and a negative urine pregnancy test at the Day 1 Visit before receiving the first dose of study drug.
9. Subjects of childbearing potential who were sexually active met the contraception requirements outlined in the Protocol
10. As deemed by the by the investigator, the subject or their legally appointed and authorized representative (e.g., parent or legal guardian) was able to understand protocol requirements, restrictions, and instructions. The subject or their legally appointed and authorized representative could ensure that the subject would comply with study restrictions and would be likely to complete the study as planned.

Subjects who met any of the following exclusion criteria were not eligible for Part A or Part B.

1. History of any comorbidity reviewed at the Screening Visit that, in the opinion of the investigator, might have confounded the results of the study or posed an additional risk in administering study drug to the subject. For example:
   - history of cirrhosis with portal hypertension
   - history of risk factors for Torsades de Pointes
     - e.g., familial long QT syndrome, hypokalemia, heart failure, left ventricular hypertrophy, bradycardia, myocardial infarction, cardiomyopathy, history of arrhythmia (ventricular and atrial fibrillation), obesity, acute neurologic events (subarachnoid hemorrhage, intracranial hemorrhage, cerebrovascular accident, intracranial trauma), and autonomic neuropathy
2. Any clinically significant laboratory abnormalities at the Screening Visit that could have interfered with the study assessments or posed an undue risk for the subject (as deemed by the investigator).

3. 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)23
4. An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1 (first dose of study drug).
5. Colonization with organisms associated with a more rapid decline in pulmonary status (e.g., Burkholderia cenocepacia, Burkholderia dolosa, and Mycobacterium abscessus) at the Screening Visit. The investigator was guided by the following suggested criteria to determine if a subject was considered free of colonization:
    - The subject had at least 2 respiratory tract cultures negative for these organisms within the past 12 months, with no subsequent positive cultures.
    - These 2 negative respiratory tract cultures were separated by at least 3 months.
    - One of these 2 negative respiratory tract cultures was obtained within the past 6 months.
6. A standard 12-lead ECG demonstrating QTc >450 msec at the Screening Visit. If QTc exceeded 450 msec at the Screening Visit, the ECG was repeated 2 more times during the Screening Period, and the average of the 3 QTc values was used to determine the subject's eligibility.
7. History of solid organ or hematological transplantation at the Screening Visit.
8. Ongoing or prior participation in an investigational drug study or use of commercially available CFTR modulator that failed to meet the following requirements:
    - A washout period of 30 days or 5 terminal half-lives of the previous investigational study drug, whichever is longer, must have elapsed before screening.
        - The duration of the elapsed time may have been longer if required by local regulations.
    - A washout period of 28 days for investigational lumacaftor (LUM)/IVA or physician-prescribed Orkambi™ must have elapsed before the Day 1 Visit.
    - Investigational IVA or physician-prescribed Kalydeco could not be taken until the Day 1 Visit, at which time IVA was dispensed from the investigational study drug supply.

Note: Ongoing participation in a noninterventional study (including observational studies) was permitted.

9. Use of restricted medication or food within a specified duration before the Screening Visit or first dose of study drug and/or unwillingness to maintain the restrictions as defined in (Part A) or Table 4 (Part B).

10. History or evidence of cataract, lens opacity, Y-suture, or lamellar rings determined to be clinically significant by the ophthalmologist during the ophthalmologic examination at the Screening Visit. Refer to Section 9.5.8.6 for details.

11. Pregnant and nursing females.

12. The subject or a close relative of the subject is the investigator or a sub-investigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study.

Rapporteurs' comments

In Part A, patients with different classes and therefore different severities of CF were allowed to be included. Overall, this is not expected to impact PK.

In Part B, in and exclusion are quite similar compared to the registration trials Study VX14-661-106 (F508del homozygous subjects) and Study VX14-661-108 (F508del heterozygous subjects). The main difference concerns the included mutation of F508del heterozygous subjects. According to the MAH, F508del heterozygous subjects with a second CFTR allele predicted to have residual function for which efficacy have been demonstrated in clinical studies could be included in Part B. However, during the MAA not all of the above mentioned mutations were accepted. The following mutations are registered for Symkevi: *P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G*, and *3849+10kbC→T*. Furthermore, compared to the MAA pivotal trial 108, currently patients with documented evidence of chronic gastrointestinal disease consistent with a diagnosis of CF were allowed if the sweat chloride value was <60 mmol/L. Overall, this difference is not expected to impact PK or safety. However, for efficacy a difference in results cannot be excluded. Therefore, the efficacy results should be interpreted with caution.

Additional Dietary Restrictions/Prohibited Medications

Part A

To avoid variable PK results due to uncontrolled use of dietary/nutritional supplements, tobacco, juices, or other foods and medications that may affect drug-metabolizing enzymes and transporters, subjects were required to comply with study restrictions summarized in Table 3.

Table 3 Lifestyle Guidelines and Study Restrictions (Part A)

Restricted Medication/Food/ Activity	Timing of Restriction	
	From (Minimum)	To
Investigational (from another study) or physician-prescribed Kalydeco	Day 1	Until last dose of study drug
Investigational or physician-prescribed Orkambi (LUM/IVA)	None allowed within 28 days before the Day 1 Visit	Completion of Safety Follow-up assessments
Other investigational drugs or devices	30 days or 5 half-lives before screening, or time determined by local requirements; whichever is longer	Completion of Safety Follow-up assessments
Moderate and strong CYP3A inducers	None allowed within 14 days before the first dose of the study drug	Until last PK sample is taken
Strong and moderate CYP3A inhibitors (except Ciprofloxacin)	None allowed within 14 days before the first dose of the study drug	Until last PK sample is taken
Nonprescription medications	14 days or 5 half-lives (whichever is longer) before first study drug dose Occasional, limited ibuprofen (≤1200 mg/day) and acetaminophen at doses of ≤2 g/day was allowed for pain.	Completion of Safety Follow-up assessments
Herbal and dietary supplements	14 days before first study drug dose	Completion of Safety Follow-up assessments
Tobacco or nicotine-containing product	45 days before first study drug dose	Until last PK sample is taken
Grapefruit or grapefruit juice, pomelos, star fruit, Seville oranges or Seville orange juice	7 days before first study drug dose	Until last PK sample is taken
Orange juice, vegetables from the mustard green family (e.g., kale, broccoli, watercress, collard greens, kohlrabi, brussels sprouts, mustard), and charbroiled meats	7 days before first study drug dose	Until last PK sample is taken
Alcohol	Not more than 2 drinks[a]/day before screening AND none 48 hours before first study drug dose	Completion of Safety Follow-Up assessments
Caffeine	An average of no more than five 240 mL servings per day of coffee or other caffeinated beverages per day beginning at screening AND none 24 hours before first study drug dose	Until last PK sample is taken
Strenuous exercise (e.g., heavy lifting, weight training, and aerobics)[b]	24 hours before the Screening Visit 24 hours before Day 1 24 hours before Day 7 24 hours before Day 14 24 hours before Safety Follow-up Visit	Not applicable After end of the Day 2 Visit After end of the Day 7 Visit After end of the Day 14 Visit After the Safety Follow-up Visit

CYP: cytochrome P450; IVA: ivacaftor; LUM: lumacaftor; PK: pharmacokinetic.
Note: The use of restricted medication in subjects with a medical need was addressed on a case-by-case basis with the medical monitor or authorized designee.
[a] One drink equals 5 ounces/150 mL of wine, 12 ounces/360 mL of beer, or 1.5 ounces/45 mL of hard liquor.
[b] Walking at a normal pace was permitted.

Part B

Prohibited medications and certain foods were not allowed in Part B (Screening Period through Week 24) as summarized in Table 4. Both TEZ and IVA are metabolized predominantly via the hepatic enzymatic pathway using CYP3A4. Inducers and inhibitors of CYP3A have the potential to significantly alter the exposure of TEZ and IVA; therefore, the use of known CYP3A inducers and inhibitors was restricted in this study.

Table 4 Lifestyle Guidelines and Study Restrictions (Part B)

	Study Period	
Restricted Medication/Food	**Screening Period**	**Treatment Period**
Certain fruits and fruit juices (Grapefruit, grapefruit juice, Seville oranges, marmalade)	None allowed within 14 days before the first dose of the study drug	None allowed through the Safety Follow-up Visit
Moderate and strong CYP3A inducers	None allowed within 14 days before the first dose of the study drug	None allowed through the Safety Follow-up Visit
Strong and moderate CYP3A inhibitors (except Ciprofloxacin)	None allowed within 14 days before the first dose of the study drug	None allowed through the Safety Follow-up Visit
Investigational (from another study) or physician-prescribed Kalydeco	None allowed after the first dose of the study drug (no restriction during the Screening Period)	Last dose of study drug
Investigational or physician-prescribed Orkambi (LUM/IVA)	None allowed within 28 days before the Day 1 Visit	None allowed through the Safety Follow-up Visit
Other investigational drugs or devices	None allowed within 30 days or 5 half-lives before screening, or time determined by local requirements; whichever was longer	None allowed through the Safety Follow-up Visit

CYP: cytochrome P450; IVA: ivacaftor; LUM: lumacaftor.
Note: The use of restricted medication in subjects with a medical need was addressed on a case-by-case basis with the medical monitor or authorized designee.

Rapporteurs' comments

Restrictions are similar to the pivotal trials and acceptable. Study restrictions which were applied, e.g. to avoid inhibitors and inducers of CYP3A4, are expected to reduce variability in PK response in the study population. CYP3A4 is fully mature at an age of 6, so no different effects of inhibition of CYP3A4 as compared to older patients are expected. The advice regarding CYP3A4 inhibitors and inducers as stated in the SmPC for patients 12 years of age and older is expected to be applicable also for the 6-11 years patient population.

Prior and Concomitant Medications

Subjects abstained from all restricted concomitant medications as described in the exclusion criteria.

Information regarding all prior and concomitant medications (including the subject's CF medications, other medications, and herbal and naturopathic remedies) administered from 4 weeks before the Screening Period through the Safety Follow-up Visit were recorded in each subject's source documents and electronic case report form.

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. Stable medication regimen was defined as the current medication regimen for CF (except for commercially available CFTR modulators) that subjects had been following for at least 4 weeks before Day 1. Subjects were prohibited from initiating long-term treatment with new medication

from 28 days before Day 1 through the Safety Follow-up Visit, unless discussed and approved by the Vertex medical monitor. Guidelines for stable medication regimens for CF are as follows:

- Subjects who took daily inhaled tobramycin or other chronically inhaled antibiotics were advised to remain on that regimen throughout the study.
- Subjects who took inhaled cycling antibiotics were advised to continue on their prior schedule. The timing of the first dose of study drug was synchronized as closely as possible to the first day of inhaled cycling antibiotics in the cycle.
- Subjects who alternated 2 different antibiotics monthly were advised to remain on the same schedule during the study. The timing of the first dose of study drug was synchronized as closely as possible to the first day of 1 of the inhaled alternating antibiotics.
- Subjects were permitted to receive doses of prednisone (or prednisolone) of up to 10 mg qd (chronically), or prednisone (or prednisolone) 60 mg qd for up to 5 days with tapering down to 10 mg qd within 2 weeks, without prior approval of the medical monitor.
    - Information about bronchodilator use during the study was collected and documented. Subjects who used a bronchodilator had their spirometry assessments performed according to the guidelines.
    - Subjects were permitted to use concomitant medications known to prolong the QT interval with caution during the study, even though the effect of TEZ/IVA on the QT interval had been evaluated in a thorough QT study, which demonstrated no prolongation of the QT interval. Consideration was given to obtaining an ECG when concomitant medication known to prolong the QT interval was administered

Rapporteurs' comments

Prior and Concomitant Medications are considered acceptable.

Treatments

The test products, doses, and mode of administration in Part A and Part B are presented in Table 5.

Table 5 Test Product, Dose, and Mode of Administration

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

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

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

Rapporteurs' comments

The dosing differs between Part A and Part B for tezacaftor compound as well as for ivacaftor compound. For more details refer to comments at study design.

Outcomes/endpoints

Pharmacokinetic Assessments

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

Efficacy Assessments

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

Safety Assessments

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

Part B: Ophthalmologic examinations

Exploratory Assessments

Part B: Lung clearance index measured by MBW (optional exploratory substudy conducted at a subset of sites).

Note: Lung clearance index (LCI) derived from multiple-breath washout (MBW) assessments was assessed in an exploratory optional substudy 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.

Rapporteurs' comments

Efficacy parameters are the usual parameters for measuring efficacy in CF in a 24 weeks study. Exacerbations were measured as safety events.

Safety parameters are sufficient to capture relevant safety issues.

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

Rapporteurs' comments

Part A

Assuming variability in PK in adults and patients 6-11 years of age is comparable, the samples size calculation is agreed. The target of 8 patients per cohort was not fully met in Part A, however, PK data were also obtained in Part B of the study, confirming PK in patients 6-11 years of age.

Part B

The sample size calculation indicates that AEs with true incidence rate of 5% or more will be very likely picked up. However, such a small sample size hampers the interpretation of the safety data for AES with lower incidence rates. Therefore, it will be difficult to draw safety conclusions based on this small sample size.

Analysis Sets

Part A

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

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

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

Part B

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

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

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

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

Variables

Definition of Treatment-emergent Period

Part A

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

Part B

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

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

Definition of Baseline

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

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

Absolute change from baseline was calculated as post-baseline value – baseline value.

Relative change from baseline was calculated and expressed in percentage as 100 × (post-baseline value – baseline value)/ baseline value.

Missing Data and Outliers

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

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

Rapporteurs' comments

No removal of outliers is considered acceptable.

Pharmacokinetic Data

Samples were analysed using validated bioanalytical methods in compliance with Vertex or designee standard operating procedures (SOPs). Descriptions of the assay and validation data are provided in separate reports:

For the determination of TEZ, M1-TEZ, M2-TEZ in human plasma:

• Method validation Report L105

• Bioanalytical Report O283

For the determination of IVA, M1-IVA, M6-IVA in human plasma:

• Method validation Report L114

• Bioanalytical Report O284

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

Rapporteurs' comments

TEZ and its metabolites as well as IVA and its metabolites in plasma were assayed according to previously reported methods. Calibration curves were in agreement with requirements as stated in the EMA bioanalytical guidance

Pharmacokinetic Analyses

Pharmacokinetic analyses were performed upon the entire population given a dose of study drug(s), whether the subject completed all treatments or not, and if the dataset(s) supported those analyses as described in the Clinical Pharmacology Analysis Plan (CPAP). Phoenix WinNonlin Professional Edition v. 7.0 was used to evaluate drug concentration - time profiles and generate pharmacokinetic parameters.

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

Efficacy Analysis (Part B Only)

There was no multiplicity adjustment in this study; P values provided for the secondary and other endpoints are considered nominal.

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

Absolute Change from Baseline in Percent Predicted FEV1 Through Week 24

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

Percent predicted FEV1 is the ratio of FEV1 (L) to the predicted FEV1 (L), expressed as a percentage. The predicted FEV1 was calculated using the Quanjer GLI-2012 Regression Equations and Lookup Tables, adjusting for age, height, sex and ethnicity.

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

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

Furthermore, absolute change from baseline in ppFEV1 at each post-baseline scheduled visit was estimated from the main model above. The LS mean at Week 24, with the corresponding 2-sided 95% CIs and P values, were provided; LS mean and the corresponding 2-sided 95% CIs were provided for other post-baseline scheduled visits.

Rapporteur's comments

The repeated measurements analysis, including the choice for random effects, covariance matrix and degrees of freedom, is considered standard and agreed. However, if drop-out would be substantial, then the estimated effect by this analysis is rather the hypothetical effect as if no patients would have drop-out assuming that trajectories for drop-out patients would have been as the trajectories of similar patients that did not drop-out.

Relative Change from Baseline in Percent Predicted FEV1 Through Week 24

A similar MMRM model as described for absolute change in ppFEV1 from baseline through Week 24 was used for this variable using the same approach as described for the absolute change in ppFEV1 from baseline.

Absolute Change from Baseline in Weight, Height, BMI, and Associated z-Scores At Week 24

Weight, height, and BMI z-scores were calculated using the CDC growth charts as described in the SAP.

A similar MMRM model was used for the above variables using the same approach as described for the absolute change in ppFEV1 from baseline through Week 24. The MMRM included corresponding baseline values (continuous) as covariates instead of baseline ppFEV1. For these variables, the assessment of efficacy was primarily based on the estimated mean change from baseline at Week 24.

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

A similar MMRM model was used for this variable, using the same approach as described for the absolute change in ppFEV1 from baseline. The MMRM included baseline sweat chloride value as a covariate instead of baseline ppFEV1. Because the first post-baseline assessment of sweat chloride was performed at Week 4, the estimated mean change at Week 4 was used to assess the absolute change in sweat chloride from baseline through Week 4.

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

A similar MMRM model was used for this variable, using the same approach as described for the absolute change in ppFEV1 from baseline. The MMRM included the baseline CFQ-R respiratory domain score as a covariate instead of baseline ppFEV1.

Safety Data

Safety was the primary objective of Part B and a secondary objective of Part A.

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). Safety endpoints are summarized using descriptive summary statistics. The primary analysis of safety is based on the total subjects in the Safety Set, and a by-dose level summary is also provided. Due to the small sample sizes in the dosage level subgroups, the by-dose level summary should be interpreted with caution.

Throughout this section, “change” refers to absolute change from baseline.

Adverse Events

Adverse events were coded according to MedDRA and categorized as pretreatment AEs, TEAEs, or post-treatment AEs for each study part as follows:

- Pretreatment AE: any AE that started before the first dose of study drug in Part A.
- TEAE: any AE that increased in severity or that was newly developed during the TE period for Part A.
- Post-treatment AE: any AE that increased in severity or that was newly developed beyond the TE period for Part A. For subjects from Part A who enrolled in Part B, an AE that increased in severity on or after the first dose of study drug in Part B will not be considered as a post-treatment AE.
- For AEs with missing or partial start dates, if there was no clear evidence that the AEs started before or after study treatment for Part A, then the AEs were classified as TEAEs.

  For Part B , as an intermediate step for programming purposes, imputation rules for missing or partially missing AE start/end dates are defined in Appendix 16.1.9/SAP Part B Version 1.0/Section 12.5 of CTR.

For all AEs, the action taken on the CRF for TEZ/IVA FDC tablet (AM dose) was collected separately from the AE action taken for the IVA tablet (PM dose).

Respiratory Events and Symptoms (Part B only)

Respiratory symptoms were defined as any TEAEs for the following 3 PTs: Chest discomfort, Dyspnoea, Respiration abnormal

Respiratory events were defined as any of the previously mentioned respiratory symptoms, or any TEAEs for the following 4 additional PTs: Asthma, Bronchial hyperreactivity, Bronchospasm, Wheezing.

Rapporteurs' comments

Overall, the analyses and definitions are in agreement with usual requirements. Important to note is that there was no multiplicity adjustment in this study and that testing was not planned to be confirmatory (efficacy was a secondary objective); P values provided for the secondary and other endpoints are thus considered descriptive.

Changes in Conduct of Study

The Study 113 protocol was amended 2 times. Table 6 provides a list of the protocol versions, their dates, and the major changes introduced with every amendment.

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

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

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

Statistical Analysis Plan

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

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

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

No changes were made to the analysis planned in Version 1.0 of the IA SAP for Part A or Version 1.0 of the SAP for Part B.

Rapporteurs' comments

The protocols only specify to use an unstructured (co)variance structure to model the within-subject errors and no random effect for subject, while the SAP does specify (additionally) a random effect for subject. Because the within-subject errors are modelled with an unstructured (co)variance structure, this is not expected to affect the estimated effect and precision: it will only mean that the total covariance structure is split differently. Therefore, this change is considered acceptable.

Thus, the changes in the conduct of the study are acceptable and not considered of major influence.

Results

Recruitment / Number analysed

Part A

A total of 13 subjects were enrolled in Part A; 2 subjects weighed <25 kg at baseline and were enrolled in Cohort 1 and 11 subjects weighed ≥25 kg at baseline and were enrolled in Cohort 2. All subjects completed the treatment regimen in Part A. (Table 7)

Table 7 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 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 8)

Table 8 Subject Disposition – Part B

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

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

No subject was excluded from the efficacy analysis

Rapporteurs' comments

Prematurely discontinuation of the study was low (4.3%).

Baseline data

Subject demographics for Part A are summarized in table 9. 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 9 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	[redacted]	6, 11	6, 11
Sex, n (%)			
Male	[redacted]	5 (45.5)	6 (46.2)
Female	[redacted]	6 (54.5)	7 (53.8)
Childbearing potential, n (%)			
Yes	[redacted]	1 (16.7)	1 (14.3)
No	[redacted]	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	[redacted]	11 (100.0)	12 (92.3)
Black or African American	[redacted]	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 10.

The mean (SD) BMI was 17.09 (2.44) kg/m2 and mean ppFEV1 was 89.1 (14.76) percent.

Table 10 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	[redacted]	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	[redacted]	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	[redacted]	13.9, 23.8	13.9, 23.8
$ppFEV_1$			
n	2	11	13
Mean (SD)	84.4 (3.32)	90.9 (15.97)	89.1 (14.76)
Median	84.4	89.9	88.9
Min, Max	82, 87	60, 116	60, 116

Source: Table 14.1.3

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

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

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

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

Part B

Overall, 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 11)

Table 11 Subject Demographics, Part B Safety Set

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

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

In total, 61 subjects (87.1%) were homozygous for the F508del mutation and 9 subjects (12.9%) were heterozygous for F508del and a second allele that results in residual CFTR function. At baseline, the mean ppFEV1 was 91.1%.

Most subjects (88.6%) weighed <40 kg at baseline. The mean (SD) weight at baseline was 30.7 (10.0) kg, and the mean weight z-score was 0.20 (0.94), indicating that baseline weights were above average for subjects' age and sex. Similarly, the mean (SD) baseline BMI was 17.44 (2.69) kg/m2 and the mean (SD) baseline BMI z-score was 0.37 (0.90). The mean (SD) baseline height was 131.0 (13.0) cm and mean (SD) baseline height z-score was -0.07 (0.98).

At baseline, the majority of subjects used an inhaled bronchodilator (98.6%), dornase alfa (88.6%), and inhaled hypertonic saline (72.9%). The majority of subjects (78.6%) were negative for Pseudomonas aeruginosa in the 2 years prior to the start of Part B. (Table 12)

Table 12 Baseline Characteristics, Part B Safety Set

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

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

Source: Table 14.1.4.1b

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

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

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

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

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

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

Subject demographics in Study 113 Part B are presented by CFTR mutation type (homozygous for F508del [F/F] versus heterozygous for F508del and a second allele that results in residual function [F/RF]) in Table 13. Baseline characteristics in Part B (including anthropometric z-scores and percentiles) are presented by mutation type in Table 14.

Table 13 Study 113 Part B: Demographics in F/F and F/RF Subjects, Safety Set

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

Source: Study 113 CSR/Ad hoc Table 1.1b
n: size of subsample; N: Safety Set sample size

[a] Other race was listed as "Black/White" (VX15-661-113 CSR/Listing 16.2.4.1b).

Table 14 Study 113 Part B: Baseline Characteristics in F/F and F/RF Subjects, Safety Set

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

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

Source: Study 113 CSR/Ad hoc Table 1.2b

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

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

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

Rapporteurs' comments

Most patients (87.1%) were homozygous for the F508del mutation. The median age in Part B was 8.0 years covering the full age range 6 to 11 years. Mean baseline ppFEV1 was 91.1% indication FEV1 was still well preserved, but the range (63.4-188.0%) indicated that subjects could already have impaired FEV1. Most subjects (88.6%) weighed <40 kg at baseline. The mean (SD) weight z-score (0.20 (0.94)) and mean (SD) BMI z-score (0.37 (0.90)) indicated that baseline weights and BMI were above average for subjects' age and sex. While the mean (SD) weight Z-score at baseline was 0.20 (0.94), the median (range) was 0.05 (-1.52, 2.58) which indicates that some children were obese. Comparing the mean and median weight Z-scores shows that the distribution is somehow skewed.

Overall, the baseline data provided show the highest severity of the disease in homozygous *F508del* subjects as expected even at this young age. Homozygopus *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.

Mean sweat chloride was higher in children homozygous for F508 CFTR. This difference in sweat chloride is considered a characteristic of the difference in disease genotype.
Small, irrelevant differences were seen in the use of medication.

Treatment Compliance

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

Protocol Deviations

Part A: There were no IPDs in Part A

Part B

In total, 3 subjects had IPDs:

- One subject (TEZ 50 mg qd/IVA 75 mg q12h) was <80% compliant with study drug.
- One subject (TEZ 50 mg qd/IVA 75 mg q12h) was enrolled in the study without review of their coagulation lab results.
- One subject (TEZ 50 mg qd/IVA 75 mg q12h) began the washout of physician-prescribed LUM/IVA prior to signing the ICF.

Rapporteurs' comments

The compliance with therapy was high (99.5%).

Protocol deviations are not considered to be of major influence on the efficacy, except for the early beginning of the washout of physician-prescribed LUM/IVA in one subject, because baseline values e.g. FEV1 value could be affected.

Pharmacokinetic Results

Part A

Geometric mean (CV%) PK parameters of TEZ, M1-TEZ, and M2-TEZ on Day 1 and Day 14 are listed in Table 15. On Day 14, the geometric mean C_{max} TEZ was 6300 ng/mL in Cohort 1(*subjects <25 kg*), and 5340 ng/mL in Cohort 2 (*subjects ≥25 kg*). The geometric mean AUC_{τ} was 66500 ng*h/mL in Cohort 1 and 71600 ng*h/mL in Cohort 2.

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

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

Geometric mean (CV%) PK parameters of IVA, M1-IVA and M6-IVA on Day 1 and Day 14 are listed in Table 16. On Day 14, the geometric mean C_{max} of IVA was 578 ng/mL in Cohort 1 (*subjects <25 kg*) and 1490 ng/mL in Cohort 2 (*subjects ≥25 kg*). The geometric mean AUC_{τ} of IVA was 5050 ng*h/mL in Cohort 1 and 12400 ng*h/mL in Cohort 2.

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

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

Part B

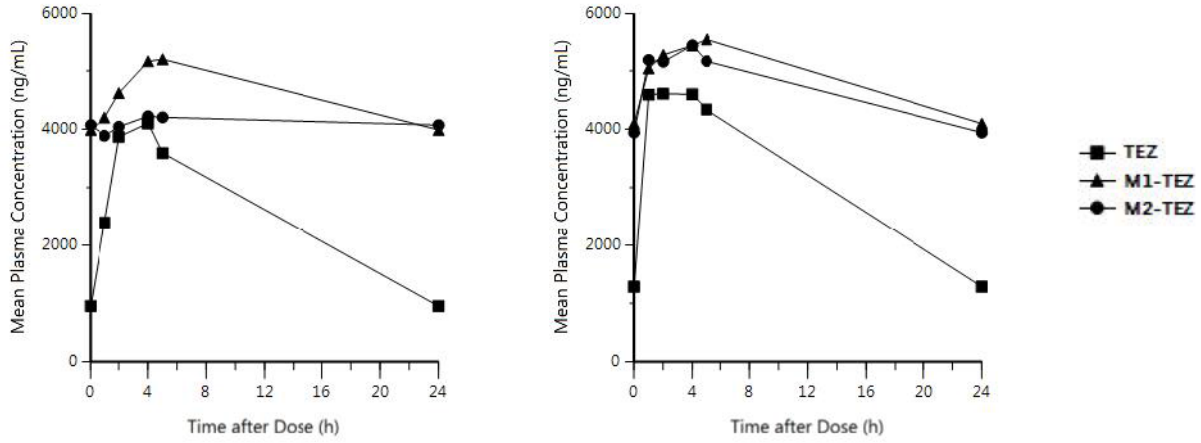
For Part B, the body weight cut-off for dosing was shifted from 25 kg to 40 kg, because modelling and simulations predicted the potential for higher TEZ exposures in subjects receiving 100 mg qd dose of TEZ.

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 3.

Figure 3 Arithmetic mean plasma concentration-time profiles of TEZ, M1-TEZ and M2-TEZ at week 16 in Part B, Part B PK set of Study 113

(A) Subjects <40 kg (B) Subjects ≥40 kg



Geometric mean (CV%) PK parameters of TEZ, M1-TEZ and M2-TEZ at Week 16 are listed in Table 17. The geometric mean C_{max} of TEZ was 4800 ng/mL for subjects <40 kg and 5870 ng/mL for subjects ≥ 40 kg. The geometric mean AUC_{τ} of TEZ was 50300 ng*h/mL for subjects <40 kg and 60900 ng*h/mL for subjects ≥40 kg.

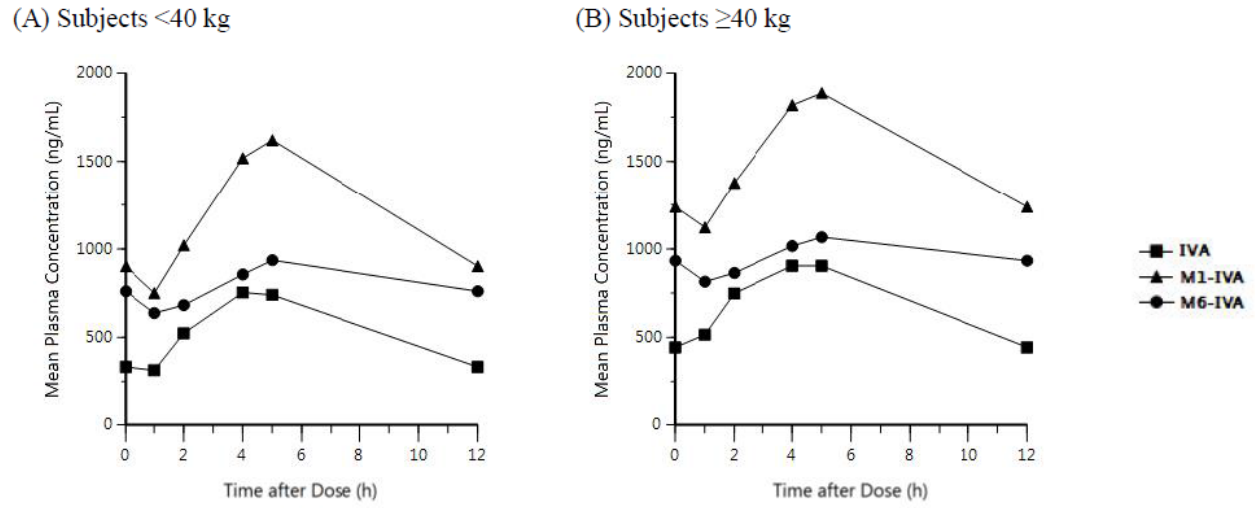
Table 17 Geometric Mean (CV%) PK Parameters of TEZ, M1-TEZ, and M2-TEZ in Part B, Part B PK Set of Study 113

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

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 4.

Figure 4 Arithmetic mean plasma concentration-time profiles of IVA, M1-IVA and M6-IVA at week 16 in Part B, Part B PK set of Study 113



Geometric mean (CV%) PK parameters of IVA, M1-IVA, and M6-IVA at Week 16 are listed in Table 18. The geometric mean C_{max} of IVA was 725 ng/mL for subjects <40 kg, and 886 ng/mL for subjects ≥40 kg. The geometric mean AUC_{τ} of IVA was 5330 ng*h/mL for subjects <40 kg and 7410 ng*h/mL for subjects ≥40 kg.

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

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

Rapporteurs' comments

Although details on the applied modelling and simulations were not provided, the actual PK outcome of part B appears to conform that exposure to TEZ and IVA in paediatric patients 6-11 years of age <40 kg and ≥40 kg is comparable.

Further, in Part A and Part B, TEZ and IVA exposures in subjects 6 through 11 years of age appear within the range of exposures in subjects 12 years of age and older (PK data from EPAR) when given in combination, though mean exposure to TEZ and IVA appear at the lower end of the exposure ranges

observed in older patients. An overview of steady-state exposures in adults, adolescents and children 6-11 years is provided in the table below.

	Tezacaftor		Ivacafor	
	C_{max} (ng/ml) (CV) or ± SD	AUC_T (ng.h/ml) (CV) or ± SD	C_{max} (ng/ml) (CV) or ± SD	AUC_T (ng.h/ml) (CV) or ± SD
6-11 years < 40 kg	4800 (33.7%)	50300 (36.3%)	725 (56.9%)	5330 (62.2%)
6–11 years > 40 kg	5870 (46.5%)	60900 (50.6%)	886 (58.7%)	7410 (53.8%)
12-17 years		97100 ± 35.8%		11400 ± 5500
adults	6520 ± 1830	82700 ± 23300	1280 ± 440	10900 ± 3890

Efficacy results

Absolute Change from Baseline in ppFEV1 Through Week 24

The LS mean absolute change in ppFEV1 from baseline through Week 24 was 0.9 percentage points (95% CI: -0.6, 2.3; nominal P value: 0.2361). (Table 19)

Table 19 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

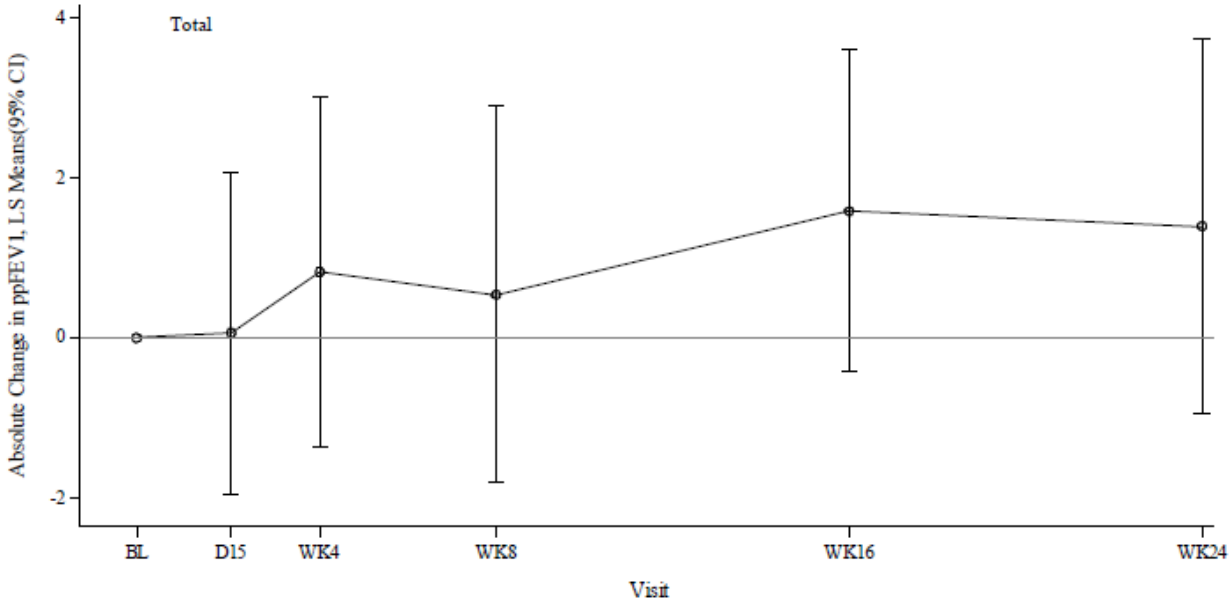
Source: Table 14.2.1.2.1b

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

Figure 5 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.

Rapporteurs' comments

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). This change in ppFEV1 from baseline through Week 24 is lower compared to the MAA in adults and adolescents with homozygous F508del mutation (3.4, 95% CI: 2.7, 4.0). The less impaired lung function in this younger population may be of influence for this difference, but also the number of patients is low (n=70), making it more difficult to draw final conclusions.

Furthermore, the population was mixed consisting of homozygous F508del mutation patients and heterozygous F508del mutation patients. Patients heterozygous for F508del mutation + residual function mutation are less severely affected than homozygous F508del mutation patients. As the vast majority of patients was homozygous for the F508del mutation (87.1%), the results are driven by this group. Within the limitations of performing a subanalysis, patients with F/F and F/RF mutations had similar mean (SD) absolute increases from baseline in ppFEV1 through Week 24, i.e. 0.9 (6.7) percentage points in F/F subjects and 0.9 (5.1) percentage in F/RF subjects. In the adult/adolescents studies, study VX14-661-106 and study VX14-661-108, absolute change from baseline in ppFEV1

through Week 24 was 3.4 and 6.5 in respectively F/F subjects and F/RF subjects. The well-preserved baseline lung function values may be the reason for the small increase in mean ppFEV1.

All included children with heterozygous F/RF had mutation as allowed in the label.

No missing data sensitivity analysis 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, because no multiplicity correction was applied.

Unfortunately, the subanalysis by gender for the homozygous patients was not included in the question. At the moment, this issue is not pursued further, because the applicant will submit a variation for a line extension in children aged 6 through 11 years. It is expected that more results will become available through Study VX16-661-115. At that time, the results will be assessed together.

Relative Change from Baseline in ppFEV1 Through Week 24

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

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

Table 20 presents the MMRM analysis results for BMI, weight, height, and associated z-scores.

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

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

Table 20 MMRM Analysis of Absolute Change From Baseline in Weight, Height, BMI, and Associated z-scores At Week 24, Part B Full Analysis Set

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

Statistic	Total N = 70

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

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

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

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

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

Rapporteurs' comments

There was no evidence of a gain in Weight z-score, Height z-score and BMI z-score. An extra-pulmonary effect in weight, height of BMI is therefore not (yet) established, although interpretation of the data is hampered by the limited number of patients included.

No responder analysis was performed for these endpoints despite a request by the CHMP. As the vast majority of the population were patient with F/F mutation, the results can be considered as indicative for this population. In the pivotal study 106 in subjects homozygous *F508del* 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/m^2 which suggests that the effect of TEZ/IVA on anthropometric parameters is limited for the homozygous *F508del* population.

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

Because the first post-baseline assessment of sweat chloride was performed at Week 4, the estimated mean change at Week 4 was used to assess the absolute change in sweat chloride from baseline through Week 4.

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

Rapporteurs' comments

The change from baseline in sweat chloride through Week 4 (-13.0 mmol/L) or through Week 24 (-14.5 mmol/L) is considered relevant for the establishment of the mode of action.

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

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

Table 21 MMRM Analysis of Absolute Change From Baseline in CFQ-R (Child Version) Respiratory Domain Score Through Week 24, Part B Full Analysis Set

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

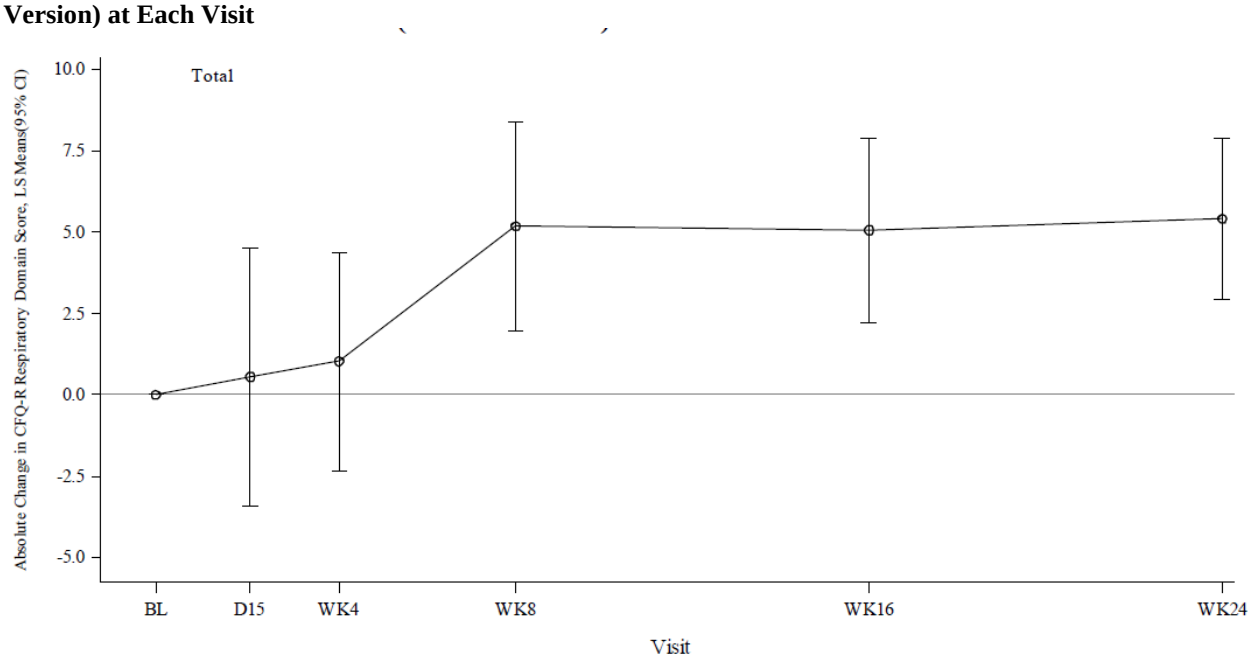
Source: Tables 14.2.9.2.1b

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

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

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

Figure 6 MMRM Analysis of Absolute Change from Baseline in CFQ-R Respiratory Domain Score (Child Version) at Each Visit



Rapporteurs' comments

Using the MMRM analysis as defined in the SAP, the LS mean absolute change from baseline through week 24 in CFQ-R respiratory domain score of 3.4 points (95% CI: 1.4, 5.5; nominal P value = 0.0013) being below the minimal clinically important difference (MCID) of 4 points. Additional information about the responder rate, i.e. the percentage of homozygous *F508del* patients who achieved a change from baseline through week 24 ≥ 4, was considered needed for insight how many patients experience a benefit in quality of life. The MAH argues that there is no consensus MCID for the Child Version of the questionnaire. For these reasons, no analysis of change from baseline in CFQ-R ≥4 points is presented. However, in previous procedures the MAH accepted the minimal clinically important difference (MCID) of 4 points and this instrument has been used as a primary endpoint for regulatory approval. Although the general arguments against the subanalysis are acknowledged, consistency is expected across procedures unless the scientific evidence leads to change of opinion on this issue.

When using the posthoc LS mean absolute change from baseline at week 24 in CFQ-R respiratory domain score (5.4 points) was above the MCID. This ad-hoc analysis is not further motived by the MAH, but it may be motived by the course of the scores.

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 Vertex CF program.

The LS mean (95% CI) absolute change from baseline in LCI2.5 through Week 24 was 0.09 (-0.32, 0.49). The LS mean (95% CI) absolute change from baseline in LCI5.0 through Week 24 was 0.05 (-0.15, 0.26).

Evaluation of LCI 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.

Rapporteurs' comments

Lung clearance index is considered an acceptable alternative for traditional pulmonary function test (PFT) using FEV1. Lung clearance index is capable to detect abnormalities in mild and moderate stages of disease early and reflect changes in disease severity directly. However, there is limited experience of this as an outcome measure, and an established clinically relevant magnitude of benefit is not established yet.

In this exploratory substudy no benefit could be established, as LS mean (95% CI) absolute change from baseline in LCI2.5 through Week 24 increased (0.09 (-0.32, 0.49)), reflecting worsening.

Safety results

Extent of Exposure

Part A

A total of 13 subjects received at least one dose of study drug in Part A. The mean exposure duration was 14.2 days (range: 14 to 15 days).

Part B

A total of 70 subjects received at least one dose of study drug in Part B. The mean exposure was 23.6 weeks. A total of 69 (98.6%) subjects received >16 weeks of treatment. (Table 22)

Table 22 Summary of Exposure, Part B Safety Set

	Total N = 70
Total exposure (patient years)	31.6
Exposure duration (weeks)	
n	70
Mean (SD)	23.6 (2.7)
Median	24.0
Min, Max	4, 26
Exposure duration by interval, n (%)	
≤2 weeks	0
>2 to ≤4 weeks	1 (1.4)
>4 to ≤8 weeks	0
>8 to ≤16 weeks	0
>16 to ≤24 weeks	41 (58.6)
>24 weeks	28 (40.0)

Source: Table 14.1.7.1b
N: size of sample; n: size of subsample; max: maximum; min: minimum; SD: standard deviation
Note: Duration of study drug exposure in weeks = (last dose date - first dose date + 1)/7, regardless of any interruption in dosing. Patient years = (total duration of exposure of all patients)/365.25.

Adverse events

Treatment-emergent adverse events were defined as any AE that increased in severity or that was newly developed at or after the first dose of study drug through the end of the treatment-emergent period. TEAEs will hereafter be referred to as AEs.

Part A

In total, 12 subjects (92.3%) had AEs during the treatment-emergent period. There were no deaths, serious, severe or life-threatening AEs. No subject had an AE that led to study drug interruption or discontinuation. All AEs were either mild (9 subjects [69.2%]) or moderate (3 subjects [23.1%]) in severity. Most subjects had AEs that were not related (5 subjects [38.5%]) or unlikely related (3 subjects [23.1%]) to study drug.

Part B

A total of 65 (92.9%) subjects had at least 1 AE in Part B. Overall, the majority of subjects had AEs that were either mild (48.6%) or moderate (40.0%) in severity; no deaths and no life-threatening AEs occurred in Part B.

A total of 19 (27.1%) subjects had an AE considered to be related or possibly related to study drug.

A total of 6 (8.6%) subjects had SAEs, but none of the SAEs were considered to be related to study drug. By severity, 3 (4.3%) subjects had Grade 3/4 AEs. Among the subjects with Grade 3/4 AEs, 3 subjects had severe (Grade 3) AEs, and no subject had a life-threatening (Grade 4) AE. One (1.4%) subject had an AE that led to treatment discontinuation and 4 (5.7%) subjects had AEs that led to treatment interruption.

Table 23 Overview of Adverse Events, Part B Safety Set

Table 24 presents an overview of treatment-emergent adverse event (AE) for subjects <40 kg and ≥ 40 kg.

Table 24 Study 113 Part B: Overview of Adverse Events, Safety Set

	Subjects <40 kg TEZ 50 mg qd/ IVA 75 mg q12h N = 62 n (%)	Subjects ≥40 kg TEZ 100 mg qd/ IVA 150 mg q12h N = 8 n (%)	Total N = 70 n (%)
Number of AEs (total)	294	34	328
Subjects with any AEs	59 (95.2)	6 (75.0)	65 (92.9)
Subjects with related AEs[a]	15 (24.2)	4 (50.0)	19 (27.1)
Subjects with AEs by strongest relationship			
Related	1 (1.6)	0	1 (1.4)
Possibly related	14 (22.6)	4 (50.0)	18 (25.7)
Unlikely related	24 (38.7)	1 (12.5)	25 (35.7)
Not related	20 (32.3)	1 (12.5)	21 (30.0)
Subjects with AEs by maximum severity			
Mild	32 (51.6)	2 (25.0)	34 (48.6)
Moderate	24 (38.7)	4 (50.0)	28 (40.0)
Severe	3 (4.8)	0	3 (4.3)
Life-threatening	0	0	0
Subjects with Grade 3/4 AEs	3 (4.8)	0	3 (4.3)
Subjects with SAEs	5 (8.1)	1 (12.5)	6 (8.6)
Subjects with related SAEs	0	0	0
Subjects with AEs leading to treatment discontinuation	0	1 (12.5)	1 (1.4)
Subjects with AEs leading to treatment interruption	4 (6.5)	0	4 (5.7)
Subjects with AEs leading to death	0	0	0

Source: Study 113 CSR/Table 14.3.1.1b
AE: adverse event; n: size of subsample; N: total sample size; SAE: serious adverse event
Notes: Adverse events were coded using MedDRA Version 19.1. For number of subjects and percent of subjects, a subject with multiple events within a category was counted only once in that category. When summarizing number of events, a subject with multiple events within a category is counted multiple times in that category.
[a] Related includes the related, possibly related, and missing categories.

Rapporteurs' comments

The primary objective of Part B is to investigate the safety and tolerability. In this part, the dosing was for subjects ≥ 40 kg identical to the dosing in adults in adolescents. For children with a weight < 40 kg at baseline the dosing was adapted.

In the total group, overall, distribution of AEs is within normal expectation; 3 patients with severe events, no life- threatening events and no deaths, 6 patients with SAE of which no related. For more detailed assessments see below.

More AEs were severe Grade 3/4 in subjects <40 kg versus ≥40 kg. However, the number of patients in ≥40 kg group is low i.e. N = 8, and the results should be interpreted with caution. With the submission of the variation to extend the indications of Symkevi and Kalydeco to children aged 6 through 11 years, more studies will be submitted and this issue will be further analysed during the variation.

Display of Adverse Events

Part A

Adverse events that occurred in at least 2 subjects in Part A are presented in Table 25. The most common AEs included cough (23.1%), headache (23.1%), and nasal congestion (15.4%).

Table 25 Adverse Events Occurring in At Least 2 Subjects by System Organ Class and Preferred Term, Part A Safety Set

System Organ Class Preferred Term[a]	Overall N = 13 n (%)
Any adverse event	12 (92.3)
Respiratory, thoracic, and mediastinal disorders	4 (30.8)
Cough	3 (23.1)
Nasal congestion	2 (15.4)
Nervous system disorders	3 (23.1)
Headache	3 (23.1)

Source: Table 14.3.1.2.1
MedDRA: Medical Dictionary for Regulatory Activities; n: size of subsample; N: total sample size
Note: Adverse events were coded using MedDRA Version 19.1.
[a] Preferred terms were provided only for adverse events that occurred in at least 2 subjects. A subject with multiple events within a system organ class or preferred term was counted only once within the system organ class or preferred term.

Part B

AEs occurring in at least 5% of subjects in Part B by SOC and PT are summarised in Table 26. The most common AEs by SOC (occurring in ≥30% of subjects) were respiratory, thoracic, and mediastinal disorders (58.6%), infections and infestations (54.3%), and gastrointestinal disorders (35.7%). The most common AEs by PT (occurring in ≥10% of subjects) were consistent with the clinical manifestations of CF in the pediatric population and included cough (35.7%), infective pulmonary exacerbation of CF (22.9%), pyrexia (18.6%), nasal congestion (14.3%), abdominal pain (14.3%), rhinorrhea (10.0%), and vomiting (10.0%).

Table 26 Adverse Events Occurring in At Least 5% of Subjects by System Organ Class and Preferred Term, Part B Safety Set

System Organ Class[a] Preferred Term	Overall N = 70 n (%)
Subjects with any adverse event	65 (92.9)
Respiratory, thoracic and mediastinal disorders	41 (58.6)
Cough	25 (35.7)
Nasal congestion	10 (14.3)
Rhinorrhea	7 (10.0)
Oropharyngeal pain	6 (8.6)
Productive cough	6 (8.6)
Infections and infestations	38 (54.3)
Infective pulmonary exacerbation of cystic fibrosis	16 (22.9)
Nasopharyngitis	6 (8.6)
Upper respiratory tract infection	6 (8.6)
Ear infection	5 (7.1)
Influenza	5 (7.1)
Viral upper respiratory tract infection	4 (5.7)
Gastrointestinal disorders	25 (35.7)
Abdominal pain	10 (14.3)
Vomiting	7 (10.0)
Abdominal pain upper	5 (7.1)
Investigations	17 (24.3)
Alanine aminotransferase increased	6 (8.6)
General disorders and administration site conditions	15 (21.4)
Pyrexia	13 (18.6)
Nervous system disorders	8 (11.4)
Headache	6 (8.6)

Source: Table 14.3.1.2.1b
MedDRA: Medical Dictionary for Regulatory Activities; n: size of subsample; N: total sample size
Note: adverse events were coded using MedDRA Version 19.1.
[a] Preferred terms were provided only for adverse events that occurred in ≥5% of subjects. A subject with multiple events within a system organ class or preferred term was counted only once within the system organ class or preferred term.

Rapporteurs' comments

Overall, the types of AEs are similar to the adult and adolescent population.

Severity of Adverse Events

Overall, all AEs were either mild (9 subjects [69.2%]) or moderate (3 subjects [23.1%]) in severity. No subject had a severe or a life-threatening AE in Part A.

Part B

Overall, most AEs in Part B were mild (48.6%) or moderate (40.0%) in severity. A total of 3 subjects (4.3%) had severe AEs. There were no life-threatening AEs in Part B.

Table 27 Incidence and Severity of Adverse Events, Part B Safety Set

Severity	Overall N = 70 n (%)
Mild	34 (48.6)
Moderate	28 (40.0)
Severe	3 (4.3)
Life-threatening	0

Source: Table 14.3.1.1b
n: size of subsample; N: total sample size
Note: A subject with multiple severities for the same adverse event was counted only under the adverse event with the maximum severity (in order of increasing severity from mild to life-threatening).

No subject had a Grade 4 (life-threatening) AE. There were 3 (4.3%) subjects with Grade 3 (severe) AEs. No Grade 3 AE occurred in >1 subject. Grade 3 AEs included infective pulmonary exacerbation of CF, sinusitis, breath odor, and snoring.

Rapporteurs' comments

No life-threating SAE were observed. The SAE observed, infective pulmonary exacerbation of CF, and sinusitis, are common events in CF population.

Relationship of Adverse Events

Part A

The incidence of AEs in Part A and their relationship to study drug is summarized in Table 28. Most of the subjects had AEs that were considered not related (i.e. not related or unlikely related) to study drug. A total of 4 (30.8%) subjects had AEs that were considered by the investigator to be related to study drug (i.e. related or possibly related).

The most common related or possibly related AE (occurring in >1 subject) was cough, which occurred in 2 subjects (15.4%).

Table 28 Subjects With Related Adverse Events by System Organ Class and Preferred Term, Part A Safety Set

System Organ Class Preferred Term[a]	Overall N = 13 n (%)
Subjects with any related[b] AEs	4 (30.8)
Respiratory, thoracic, and mediastinal disorders	2 (15.4)
Cough	2 (15.4)
Sputum increased	1 (7.7)
Gastrointestinal disorders	1 (7.7)
Constipation	1 (7.7)
Nervous system disorders	1 (7.7)
Headache	1 (7.7)
Skin and subcutaneous tissue disorders	1 (7.7)
Rash erythematous	1 (7.7)

Source: Table 14.3.1.2.2
AEs: adverse events; n: size of subsample; N: total sample size
Note: AEs were coded using MedDRA version 19.1
[a] If a subject had multiple events within a system organ class or preferred term, the subject was counted once.
[b] Related includes either related, possibly related, or missing study drug categories.

Part B

Overall, most AEs were considered to be either not related (30.0%) or unlikely related (35.7%) to study drug. In total, 19 (27.1%) subjects had AEs that were considered related to study drug (i.e. related or possibly related).

Table 29 summarizes related AEs (i.e. related and possibly related) by SOC and PT. Overall, 19 subjects (27.1%) had related AEs. The most common related AEs by PT (occurring in >1 subject) were ALT increased (4.3%), infective pulmonary exacerbation of CF (4.3%), nausea (2.9%), cough (2.9%), productive cough (2.9%), and rhinorrhea (2.9%), and blood ALP increased (2.9%).

Table 29 Related Adverse Events Occurring in At Least 2 Subjects by System Organ Class and Preferred Term, Part B Safety Set

System Organ Class [a] Preferred Term	Overall N = 70 n (%)
Subjects with any related[b] adverse events	19 (27.1)
Gastrointestinal disorders	6 (8.6)
Nausea	2 (2.9)
Respiratory, thoracic and mediastinal disorders	6 (8.6)
Cough	2 (2.9)
Productive cough	2 (2.9)
Rhinorrhea	2 (2.9)
Investigations	5 (7.1)
Alanine aminotransferase increased	3 (4.3)
Blood alkaline phosphatase increased	2 (2.9)
Infections and infestations	3 (4.3)
Infective pulmonary exacerbation of cystic fibrosis	3 (4.3)

Source: Table 14.3.1.2.3b
n: size of subsample; N: total sample size
[a] If a subject had multiple events within a system organ class or preferred term, the subject was counted once.
[b] Related included either related possibly or related study drug categories.

Rapporteurs' comments

Related AEs are known AEs already observed in the adult and adolescent population.

Adverse Events Associated With Elevated Transaminases

An AE associated with elevated transaminases was pre-defined as one of the following PTs:

- Alanine aminotransferase abnormal, Alanine aminotransferase increased
- Aspartate aminotransferase abnormal, Aspartate aminotransferase increased
- Hepatic enzyme abnormal, Hepatic enzyme increased
- Hypertransaminasaemia
- Liver function test abnormal, Liver function test increased
- Transaminases abnormal, Transaminases increased

In total, 6 subjects (8.6%) had an AE associated with elevated transaminases. All of these subjects had an AE of ALT increased, and 2 subjects had an AE of AST increased as well. All of the AEs associated with elevated transaminases were mild. None of the AEs associated with elevated

transaminases led to discontinuation of study drug or death. None of the AEs associated with transaminase elevations were serious.

Table 30 Summary of Treatment-emergent Elevated Transaminase Events, Part B Safety Set

	Total N = 70 n (%)
Subjects with any AEs of elevated transaminases	6 (8.6)
Alanine aminotransferase increased	6 (8.6)
Aspartate aminotransferase increased	2 (2.9)
Subjects with any elevated transaminases by severity	
Mild	6 (8.6)
Moderate	0
Severe	0
Life-threatening	0
Subjects with events leading to treatment discontinuation	0
Subjects with serious events	0
Subjects with related serious events	0
Subjects with events leading to death	0

Source: Table 14.3.1.8b

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; N: total sample size; n: size of subsample

Note: A subject with multiple events is counted only once in that category. Related serious events refers to study-drug related serious adverse events, and includes the categories of related, possibly related, and missing. Elevated transaminase events were coded using MedDRA Version 21.0.

Rapporteurs' comments

In total, 6 subjects (8.6%) had an AE associated with elevated transaminases i.e. ALT either or not in combination with AST. All of the AEs associated with elevated transaminases were mild. Elevated transaminases were observed before in ivacaftor, but not in Symkevi. Moreover, the shift table of transaminases below showed that the incidence of maximum transaminase (ALT or AST) in adult and adolescent population were somewhat lower.

Adverse Events Associated With Respiratory Symptoms and Respiratory Events

Respiratory AEs and symptoms are a group of PTs pre-defined to explore select AEs within the respiratory system. These PTs included in this group were used to assess and characterize the respiratory symptoms/events of LUM/IVA, as included in the product labels.

Respiratory symptoms were defined as AEs with any of the following PTs: Chest discomfort, Dyspnea, Respiration abnormal.

Respiratory events were defined as AEs with any of the following PTs: Asthma, Bronchial hyperreactivity, Bronchospasm, Wheezing, Chest discomfort, Dyspnea, Respiration abnormal.

In total, 2 subjects had a respiratory symptom and/or respiratory event. Two subjects (2.9%) had AEs of respiration abnormal (considered a respiratory symptom and an event). One of these 2 subjects had a mild AE of respiration abnormal, and the other subject had a moderate AE of respiration abnormal. No subject had an AE of chest discomfort, dyspnea, asthma, bronchial hyperreactivity, bronchospasm, or wheezing. No subject had a respiratory symptom or event that led to treatment discontinuation or interruption or was considered serious.

Rapporteurs' comments

The number of patients is low, thus conclusions need to be drawn with caution. Within this limitation, Symkevi in combination with ivacaftor appears to have a low incidence of adverse events associated with respiratory symptoms, and respiratory events (2.9%).

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Deaths

There were no deaths in Part A or Part B.

Other Serious Adverse Events

Part A

There were no SAEs in Part A.

Part B

In total, 6 subjects (8.6%) had a SAE. Only 1 SAE occurred in >1 subject: infective pulmonary exacerbation of CF (occurring in 2 [2.9%] subjects). None of these SAEs were considered related to study drug by the investigator.

Table 31 Serious Adverse Events by Preferred Term, Part B Safety Set

	Total N = 70 n (%)
Subjects with any adverse event	6 (8.6%)
Infective pulmonary exacerbation of cystic fibrosis	2 (2.9)
Breath odor[a]	1 (1.4)
Constipation	1 (1.4)
Failure to thrive	1 (1.4)
Sinusitis	1 (1.4)
Snoring[a]	1 (1.4)

Source: Table 14.3.1.7.1b
MedDRA: Medical Dictionary for Regulatory Activities; N: total sample size; n: size of subsample
Note: Adverse events were coded using MedDRA version 21.0. A subject with multiple events within a category is counted only once in that category.
[a] [redacted]

Rapporteurs' comments

Six patients had a SAE. All SAEs were considered unrelated to study drug by the investigator. Therefore, these SAE are not considered as a new safety signal.

Adverse Events That Led to Discontinuation or Interruption of Study Drug

Part A

No AE led to study drug discontinuation or interruption.

Part B

Adverse Events That Led to Discontinuation of Study Drug

One subject discontinued study drug due to an SAE of constipation, which was considered moderate in severity, and unlikely related to study drug.

Adverse Events That Led to Interruption of Study Drug

In total, 4 subjects had AEs that led to treatment interruption. No AE that led to treatment interruption occurred in >1 subject. Among the subjects with AEs that led to treatment interruption, 2 subjects had AEs that were considered related or possibly related to study drug (1 subject with an AE of blood creatine phosphokinase increased and 1 subject with AEs of liver laboratory parameters increased). No related AE that led to treatment interruption was serious. All related AEs that led to interruption resolved without any treatment.

Rapporteurs' comment

Two subjects with interruption of study drug had AEs related to study drug. The AEs resolved without any treatment. The AEs are known and are not considered as a new safety signal.

Liver Function Tests

Part A

There were no AEs related to LFTs during Part A. Overall, no clinically meaningful trend in LFT results was identified.

Part B

The mean values for LFT parameters were generally within normal ranges at all visits during the TE Period. No clinically meaningful trends were observed. Adverse events associated with elevated transaminases are discussed above.

Liver function test results that met threshold criteria are summarized in Table 32. Overall, the incidence of ALT or AST >3, >5, and >8 × ULN was 10.0%, 4.3%, and 1.4%, respectively. No subject had an elevated ALT or AST level >3 x ULN associated with elevated total bilirubin >2 × ULN.

There were 3 (4.3%) subjects with AEs of blood ALP increased and 2 (2.9%) subjects with AEs of GGT increased. One subject had AEs of liver enzymes increased that led to study drug interruption. For the 2 other subjects with ALP increased, the AE was not serious, mild, and did not result in interruption or discontinuation of study drug. For the other subject with an AE of GGT increased, the AE was considered not serious, mild, not related to study drug, and did not require treatment or study drug interruption.

Overall, the LFT data were consistent with the expected outcomes in paediatric patients with CF, who are known to have background LFT abnormalities.

Table 32 Threshold Analysis of Liver Function Tests during the Treatment-emergent Period, Part B Safety Set

Parameter Threshold Analysis Criteria n/N1 (%)	Total N = 70
ALT	
>ULN to ≤3 × ULN	45/70 (64.3)
>3 to ≤5 × ULN	4/70 (5.7)
>5 to ≤8 × ULN	2/70 (2.9)
>8 to ≤20 × ULN	1/70 (1.4)
>20 × ULN	0/70
AST	
>ULN to ≤3 × ULN	20/70 (28.6)
>3 to ≤5 × ULN	0/70
>5 to ≤8 × ULN	0/70
>8 to ≤20 × ULN	1/70 (1.4)
>20 × ULN	0/70
ALT or AST	
>ULN to ≤3 × ULN	45/70 (64.3)
>3 to ≤5 × ULN	4/70 (5.7)
>5 to ≤8 × ULN	2/70 (2.9)
>8 to ≤20 × ULN	1/70 (1.4)
>20 × ULN	0/70
ALP	
>ULN to ≤1.5 × ULN	16/70 (22.9)
>1.5 to ≤2.5 × ULN	0/70
>2.5 to ≤5 × ULN	0/70
>5 to ≤20 × ULN	0/70
>20 × ULN	0/70
Total bilirubin	
>ULN to ≤1.5 × ULN	4/70 (5.7)
>1.5 to ≤2 × ULN	0/70
>2 to ≤3 × ULN	0/70
>3 to ≤10 × ULN	0/70
>10 × ULN	0/70
ALT and total bilirubin	
ALT >3 × ULN and total bilirubin >2 × ULN	0/70
AST and total bilirubin	
AST >3 × ULN and total bilirubin >2 × ULN	0/70
ALT or AST and total bilirubin	
AST or AST >3 × ULN and total bilirubin >2 × ULN	0/70

Source: Table 14.3.4.1.2b

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; LFT: liver function test; n: size of subsample; N: total sample size; N1: number of subjects with at least 1 non-missing measurement during the TE period; TE: treatment-emergent; ULN: upper limit of normal

Note: If multiple LFT assessments were performed at a visit, the assessment with the highest LFT values was reported in the threshold analysis. Assessments from multiple visits were combined when assessing criteria involving two LFT parameters.

Rapporteurs' comments

In the adult and adolescent population, during the placebo-controlled Phase 3 studies the incidence of maximum transaminase (ALT or AST) >8, >5, or >3 x ULN were in Symkevi in combination with ivacaftor 0.2%, 1.0%, and 3.4%. The increases in LFT are in children are somewhat higher compared to the outcomes in the adult and adolescent population. In ivacaftor and lumacaftor/ivacaftor combination, also ALT and AST elevations appeared to be higher than that observed in subjects 12 years of age and older. These observations are consistent with information available in the published

literature that indicates transaminase elevations are more common in younger patients with CF than in adults.

Vitamin Levels

Part A

There were no AEs related to vitamin levels during Part A and no clinically meaningful change in vitamin levels was observed.

Part B

No clinically meaningful trends that could be attributed to TEZ/IVA were observed. There were 2 subjects with AEs related to vitamin panels; 1 subject had elevated vitamin E levels and 1 subject had elevated vitamin B12 levels. Both vitamin-related AEs were mild, considered unrelated or unlikely related to study drug, and did not result in study drug interruption or discontinuation.

Lipid Panels

Part A

There were no AEs in Part A associated with lipid panels.

Part B

No subject had an AE related to lipid panels in Part B. There were no identifiable trends in lipid panels that could be attributed to TEZ/IVA.

Other Serum Chemistry

Part B

Serum chemistry lab results were generally within the normal range. No trends in serum chemistry labs that could be attributed to TEZ/IVA were identified.

In total, 3 subjects had AEs related to serum chemistry tests. One subject had an AE of creatine phosphokinase increased that was moderate in severity, non-serious, and considered related to study drug. This event resolved without any treatment, after study drug interruption. One subject had an AE of lipase increased that was mild and considered not related to study drug. One subject had an AE of GGT increased that was mild and considered not related to study drug.

Haematology

Part B

Haematology lab results were generally within the normal range in Part B. No trends in haematology lab results that could be attributed to TEZ/IVA were observed.

In total, 2 subjects had AEs related to haematology results. Both subjects had 2 AEs related to haematology results, which were the same for both subjects: neutrophil count decreased and white blood cell count decreased. One subject's AEs were mild and considered possibly related to study drug. The other subject's AEs were mild and considered unlikely related to study drug.

Coagulation

Part A

One subject had 3 AEs related to laboratory parameters. These AEs were considered mild and not related to study drug.

Part B

Overall there were no clinically meaningful trends in coagulation results and no subjects had AEs related to coagulation in Part B.

Rapporteurs' comments

Overall, the vitamin Levels, lipid panels, serum chemistry data were consistent with the expected outcomes in paediatric patients with CF, who are known to have background LFT abnormalities.

Haematology showed unexpected AEs; 2 subjects had 2 AEs of neutrophil count decreased and white blood cell count decreased. One subject's AEs were considered possibly related to study drug.

Overall, no conclusions can be drawn based on 1 patient.

Vital Signs

Part A

No subject had an AE related to vital signs. No clinically meaningful trend in vital signs was observed.

Part B

No clinically meaningful trends in vital signs were identified in Part B. No subject had an SAE related to vital signs.

No subject had an AE related to increased BP, 1 subject (1.4%) had an AE of syncope, 1 subject (1.4%) had an AE of poor weight gain, and 13 subjects (18.6%) had an AE of pyrexia . The AE of syncope was moderate in severity, non-serious, not related to study drug, and resolved without treatment or study drug discontinuation or interruption. The AE of poor weight increased was mild in severity, non-serious, considered unlikely related, did not require study drug discontinuation or interruption, and was not resolved at the end of the study. All AEs of pyrexia were mild or moderate in severity, none were considered serious, all were considered not related or unlikely related, none led to study drug interruption or discontinuation, and all resolved (7 of them requiring treatment).

Electrocardiograms

Part A

No subjects had QTcF >450 msec, or a maximum QTcF change >60 msec. Overall, no clinically meaningful trend in ECG results was observed during Part A. There was no AE related to ECG findings.

Part B

No male subjects had QTcF >450 msec and no female subjects had QTcF >470 msec. No subject had a maximum QTcF change >60 msec. No clinically meaningful trends in ECGs were observed and there were no AEs associated with ECG findings in Part B.

Rapporteurs' comments

No specific findings were observed in ECG.

Pulse Oximetry

Part B

Overall, no clinically meaningful trends were identified from pulse oximetry results. No subjects had AEs related to pulse oximetry in Part B.

Rapporteurs' comments

No specific finding were observed in pulse oximetry.

Ophthalmological Examinations (Part B only)

Subjects had ophthalmologic examinations at baseline (Screening) and Week 24. Overall, no clinically meaningful trends attributable to TEZ/IVA were identified from ophthalmological exams.

At Screening, 5 subjects had cataracts or lens opacities, which were all considered not clinically significant. Of these 5 subjects, 4 subjects had ophthalmological exams at Week 24. Among these 4 subjects, 1 subject continued to have cataracts at Week 24.

At Week 24, 2 subjects had lens opacities that were not present at Screening. These lens opacities occurred in 2 subjects with prior steroid use and were not deemed to be cataracts or clinically significant. Overall, no new cataracts were detected at Week 24 that were not present at Screening.

For 1 of the 2 subjects with lens opacities that were present at Week 24 but not at Screening, the ophthalmological exam findings were reported as an AE of slit lamp test abnormal. This AE was mild, not serious, and occurred in a subject with a family history of. There was no other AE relevant to ophthalmological exam findings.

Rapporteurs' comments

No specific finding were observed in ophthalmological examinations .

2.3.3. Discussion on clinical aspects

In the EU, Symkevi is approved as a combination regimen with ivacaftor 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*.

Design and conduct of clinical studies

Study VX16-661-113 is a phase 3, open-label study to evaluate the pharmacokinetics, safety, and tolerability of Symkevi in combination with ivacaftor in patients 6 through 11 years of age with cystic fibrosis, homozygous or heterozygous for *the F508del-CFTR* mutation.

Study 113 is a, 2-part (Part A and Part B), open-label, multicenter study. A new lower dose strength of the TEZ/IVA tablet has been introduced for lighter weigh patients to achieve target exposures.
Part A included a Screening Period (28 days), Treatment Period (14 days) and a Wash-out/Safety Follow-up Period (14 days) to evaluate off-drug response.
Part B included a Screening Period (28 days), Treatment Period (24 weeks [± 5 days]), and Safety Follow-up Visit (4 weeks [± 7 days]). A Safety Follow-up Visit was scheduled to occur 4 weeks (± 7 days) after the last dose of study drug.
The dosing differs between Part A and Part B. For ivacaftor component, the dosing is 75 mg q12 h and 150 mg q12h in both parts, but the cut-off in weight is different i.e. 25 kg in Part A and 40 kg in Part B. For tezacaftor compound the dosing is 50 mg qd in part A, while there is a cut-off in weight of 40 kg with either 50 or 100 mg qd in Part B.

The inclusion criteria were acceptable and generally in line with the Symkevi authorisation trials. The inclusion criteria were identical for Part A and part B with the exception of the allowed mutations. In part A, all different classes and therefore different severities of CF mutations were allowed to be included (mutation with residual function, the mutation with a gating defect that has been clinically demonstrated to be IVA-responsive or the mutation was not likely to respond to TEZ and/or IVA therapy). Overall, this is not expected to impact PK.

In Part B, F508del homozygous subjects were eligible as well as F508del heterozygous subjects if clinical efficacy of TEZ/IVA had been demonstrated in a corresponding adult population. Furthermore, subjects had a percent predicted ppFEV1 ≥40 percentage points. These criteria are quite similar compared to the registration trials Study VX14-661-106 (F508del homozygous subjects) and Study VX14-661-108 (F508del heterozygous subjects). The main difference concerns the included mutation of F508del heterozygous subjects as more mutations were allowed than registered for Symkevi. Furthermore, in this study patients with documented evidence of chronic gastrointestinal disease consistent with a diagnosis of CF were allowed if the sweat chloride value was <60 mmol/L. Overall, this difference is not expected to impact PK or safety. However, for efficacy a difference in results cannot be excluded. Therefore, the efficacy results should be interpreted with caution.

Important exclusion criterion concerned existing abnormal liver function.

Pharmacokinetic assessments consisted from measuring plasma PK parameters of TEZ, M1-TEZ, M2-TEZ, IVA, M1-IVA, and M6-IVA.
For efficacy evaluation, spirometry, weight and weight z-score, height and height z-score, BMI and BMI z-score, sweat chloride, and CFQ-R were assessed. These are all relevant parameters.
Safety parameters were the usual measurements.

Statistics were adequate, but only descriptive for efficacy parameters.

Demographics and patient characteristics

In part A, 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).

The mean (SD) weight was 30.5 (8.49) kg, the mean (SD) height 132.5 (12.00) cm and the mean (SD) BMI was 17.09 (2.44) kg/m2. Mean ppFEV1 was 89.1 (14.76) percent.

In Part B, the vast majority of the patients (87.1%) were homozygous for the F508del mutation. Most subjects (88.6%) weighed <40 kg at baseline. The mean (SD) weight at baseline was 30.7 (10.0) kg, and the mean weight z-score was 0.20 (0.94), indicating that baseline weights were above average for subjects' age and sex. Furthermore, the median (range) was 0.05 (-1.52, 2.58), indicating the distribution was somewhat skewed and that some children were obese (z-score > +2).
The mean baseline BMI z-score was 0.37 (0.90) and mean (SD) baseline height z-score was -0.07 (0.98). Mean baseline ppFEV1 was 91.1% indication FEV1 was still well preserved, but the range (63.4-188.0%) indicated that subjects could already have impaired FEV1. Because there are differences between homozygous and heterozygous patients, demographics and baseline characteristics for both populations separately were requested. Overall, the baseline data provided in relation to the anthropmetreic parameters showed the highest severity of the disease in homozygous *F508del* subjects as expected even at this young age. This is particularly the case for weight-for-age and height-for-age z-scores and percentiles. Differences were also seen in sweat chloride. Mean sweat chloride was higher in children homozygous for F508 CFTR. This difference in sweat chloride is considered a characteristic of the difference in disease genotype.

Discussion on pharmacokinetics

A total of 13 patients were enrolled in Part A and 70 patients in in Part B. In Part A, PK data are not available for all patients. However, though TEZ-related PK data are described for 13 patients at D1 (TEZ, M1-TEZ, M2-TEZ), at Day 14 data are only available for 12 patients. In case of IVA and metabolites the numbers are 10 (at Day 1) or 12 (at Day 14) (See Tables 13 and 14). The MAH clarified why TEZ and IVA PK data is not available for all patients, i.e., because patients received IVA monotherapy just prior to day 1, and the fact that no samples could be obtained in one patient at day 14.PK assessment of TEZ/IVA in Part A was conducted in a small number of subjects (N = 13) to evaluate TEZ/IVA regimens and determine the TEZ/IVA dose for Part B. In part A, patients <25 kg were dosed with TEZ 50 mg QD/IVA 75 mg q12h, and patients ≥ 25 kg TEZ 50 mg QD/IVA 150 mg q12h.

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. Based on the TEZ exposures in adult subjects, the TEZ dose for subjects weighing ≥ 40 kg in Part B was increased to the adult dose of 100 mg qd to be comparable to the exposures in adult subjects. Thus, paediatric patients 6-11 years <40 kg were dosed with TEZ 50 mg QD/IVA 75 mg q12h, and patients ≥40 kg TEZ 100 mg QD/IVA 150 mg q12h. In Part B, 62 subjects weighing <40 kg and 7 subjects weighing ≥40 kg were included in PK analyses.

Although details on the applied modelling and simulations were not provided, the actual PK outcome of part B appears to conform that exposure to TEZ and IVA in paediatric patients 6-11 years <40 kg and ≥40 kg is within the range of exposures obtained in older patients, though mean exposure to TEZ and IVA appear at the lower end of the exposure ranges observed in older patients. See table below for a rough comparison of the exposure data in patients 6-11 years of age (Cohort B Study 113) and older patients (EPAR):

	Tezacaftor		Ivacafor	
	C_{max} (ng/ml) (CV) or ± SD	AUC_T (ng.h/ml) (CV) or ± SD	C_{max} (ng/ml) (CV) or ± SD	AUC_T (ng.h/ml) (CV) or ± SD
6-11 years < 40 kg	4800 (33.7%)	50300 (36.3%)	725 (56.9%)	5330 (62.2%)
6–11 years > 40 kg	5870 (46.5%)	60900 (50.6%)	886 (58.7%)	7410 (53.8%)
12-17 years		97100 ± 35.8%		11400 ± 5500
adults	6520 ± 1830	82700 ± 23300	1280 ± 440	10900 ± 3890

In this respect, it is noted that for IVA given as single agent, the dose of IVA for children aged 6 years and older and weighing 25 kg or more is 150 mg BID while those below 25 kg are dosed with 75 mg BID. Therefore, patients weighing 25 to 40 kg in Study 113 Cohort B treated with TEZ/IVA received a lower IVA dose (75 mg BID) than when given as single agent (150 mg BID). Further PK comparison data, i.e., a direct comparison of exposures between children, adolescents, and adults at the proposed doses for both TEZ and IVA based on pop-PK modeling and simulation were provided. The popPK data support the view that exposure to TEZ, TEZ-M1, and IVA in children 6-12 years <40 kg are within the range of exposures obtained in adolescent and adult patients receiving Symkevi, to a reasonable extent. It is further acknowledged that dose-selection for Kalydeco and Symkevi were independently conducted. Moreover, the use of a single weight cut-off both for the TEZ and IVA component of Symkevi is considered beneficial with regard to usability/simplicity of the dose regimen. However,

further discussion of the posology at the time of submission of the type II variation, including all available data at that time, is awaited.

Discussion on clinical efficacy

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), was lower compared to the MAA in adults and adolescents with homozygous F508del mutation (3.4, 95% CI: 2.7, 4.0). The less impaired lung function in this younger population may be of influence for this difference. Alternatively, the lower IVA dose may also have been of influence although the PK results showed similar exposure as in adults.

Furthermore, the population was mixed consisting of homozygous F508del mutation patients and heterozygous F508del mutation patients. Patients heterozygous for F508del mutation + residual function mutation are less severely affected than homozygous F508del mutation patients. As the vast majority of patients was homozygous for the F508del mutation (87.1%), the results are driven by this group. Despite the acknowledgment of the limitations of the subanalyses because of the small group of children with heterozygous F/RF and efficacy was a secondary parameter, a subanalysis was requested because disease progression is different in the two population. Moreover, the results of Symkevi in the adults and adolescents population were also different for the two populations. In study 113, the mean (SD) absolute change from baseline in ppFEV1 through Week 24 was 0.9 (6.7) percentage points for F/F subjects, and the mean (SD) absolute change from baseline in ppFEV1 through Week 24 was 0.9 (5.1) percentage points for F/RF subjects.
In addition, subanalyses are requested for the homozygous patients by gender because differences in disease progress. It is expected that more results will soon become available through Study VX16-661-115 with the submission of the variation for a line extension in children aged 6 through 11 years. At that time the results will be assessed together. The range of BMI Z-scores at baseline indicated that some children are below 0 while other are obese. The EU consensus guidelines for nutrition in patients with cystic fibrosis (Turck D. et al. 2016) state that the target for children 2 to 18 years is 0 SD (50th percentile) of BMI for a healthy, same-age population. Given that TEZ/IVA is a systemic therapy, it has the potential to improve extrapulmonary manifestations of CF, including gastrointestinal symptoms. During treatment Weight z-score, Height z-score and BMI z-score remained stable, without improvement. An extra pulmonary effect in weight, height of BMI is therefore not established. The MAH was requested to provide the percentage of homozygous F508del patients with a BMI at baseline below 0 who at week 24 reached a BMI Z-score ≥0 together with the corresponding change in height Z-score as stunted children can have a normal BMI. No responder analysis was performed for these endpoints despite a request by the CHMP. As the vast majority of the population were patients with F/F mutation, the results can be considered as indicative for this population. Overall, the (lack of) effect in anthopometric parameters is similar to that observed in the pivotal study 106 (adult and adolescents homozygous *F508del* subjects) although children are expected to have a more preserved nutritional status than older patients.

~~If~~ Faecal elastase-1 levels have not been collected. This would have been of interest as an increase of FE-1 values (above 100 or 200 µg/g) in combination with a decrease in serum immune reactive trypsinogen (IRT) would be indicative of a decrease in the stress that exocrine pancreatic cells undergo under disease circumstances.

When using the predefined MMRM analysis, the LS mean absolute change from baseline <u>through</u> week 24 in CFQ-R respiratory domain score was 3.4 points (95% CI: 1.4, 5.5; nominal P value = 0.0013). This was below the minimal clinically important difference (MCID) of 4 points. When using a post-hoc analysis, the LS mean absolute change from baseline <u>at</u> Week 24 was above MCID of 4 points, indicating symptomatic improvement. This ad-hoc analysis may be motived by the course of the scores. The MAH did not provide an analysis of the percentage of patients homozygous for *F508del*

who reached a change from baseline through week 24 ≥ 4 points. In the current view of the MAH there is no consensus MCID for the Child Version of the questionnaire. This view is inconsistent with previous claims. Consistency is expected across procedures unless the scientific evidence leads to a change of opinion.

Lung clearance index was included as an exploratory endpoint in this study. Lung clearance index is considered an acceptable alternative for traditional PFT using FEV1. Lung clearance index is capable to detect abnormalities in mild and moderate stages of disease early and reflect changes in disease severity directly. However, there is a limited experience of this as an outcome measure, and an established the clinically relevant magnitude of benefit is not established yet. In this exploratory substudy, no benefit could be established as LS mean (95% CI) absolute change from baseline in LCI2.5 through Week 24 increased (0.09 (-0.32, 0.49)) reflecting worsening.

Sweat chloride is a biomarker of CFTR function; improvements in CFTR function result in reduced sweat chloride. In this study, reductions in sweat chloride concentration were observed during the treatment period. 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; nominal P value <0.0001).

Discussion on Safety

In Part A, 13 subjects received at least one dose of study drug. The mean exposure duration was 14.2 days (range: 14 to 15 days). In Part B, 70 subjects received at least one dose of study drug in Part B. The mean exposure was 23.6 weeks. A total of 69 (98.6%) subjects received >16 weeks of treatment.

In Part A, 12 subjects (92.3%) had AEs during the treatment-emergent period. There were no deaths, serious, severe or life-threatening AEs. All AEs were either mild (9 subjects [69.2%]) or moderate (3 subjects [23.1%]) in severity.
The most common AEs included cough (23.1%), headache (23.1%), and nasal congestion (15.4%), while in Part B the most common AEs included cough (35.7%), infective pulmonary exacerbation of CF (22.9%), pyrexia (18.6%), nasal congestion (14.3%), abdominal pain (14.3%), rhinorrhea (10.0%), and vomiting (10.0%) consistent with paediatric population with CF. Overall, the type of AEs are similar to the adult and adolescent population.
Most subjects had AEs that were not related (5 subjects [38.5%]) or unlikely related (3 subjects [23.1%]) to study drug. The most common related or possibly related AE (occurring in >1 subject) was cough, which occurred in 2 subjects (15.4%).
No subject had an AE that led to study drug interruption or discontinuation.

In Part B, In the total group, overall, distribution of AEs is within normal expectation; 3 patients with severe events, no life- threatening events and no deaths, 6 patients with SAE of which no related. For more detailed assessments see below. No major differences were seen between subjects <40 kg versus ≥40 kg. Only, more AEs were severe Grade ¾ were seen in subjects <40 kg. However, the number of patients in ≥40 kg group is too low to draw conclusions.

In the total group, 65 (92.9%) subjects had at least 1 AE in Part B. Overall, the majority of subjects had AEs that were either mild (48.6%) or moderate (40.0%) in severity.
A total of 19 (27.1%) subjects had an AE considered to be related or possibly related to study drug. The most common related AEs by PT (occurring in >1 subject) were ALT increased (4.3%), infective pulmonary exacerbation of CF (4.3%), nausea (2.9%), cough (2.9%), productive cough (2.9%), and rhinorrhea (2.9%), and blood ALP increased (2.9%).
A total of 6 (8.6%) subjects had SAEs, but none of the SAEs were considered to be related to study drug. Only infective pulmonary exacerbation of CF (2 [2.9%] subjects) occurred in >1 subject.

In total, 4 subjects had AEs that led to treatment interruption. Among the subjects with AEs that led to treatment interruption. Two subjects had AEs that were considered related or possibly related to study drug (1 subject with an AE of blood creatine phosphokinase increased and 1 subject with AEs liver enzymes increased). All resolved without any treatment.
No deaths and no life-threatening AEs occurred in Part B.

The incidence of ALT or AST >3, >5, and >8 × ULN was 10.0%, 4.3%, and 1.4%, respectively. In the adult and adolescent population, during the placebo-controlled Phase 3 studies the incidence of maximum transaminase (ALT or AST) >8, >5, or >3 x ULN were in Symkevi in combination with ivacaftor 0.2%, 1.0%, and 3.4%. The increases in LFT are in children somewhat higher compared to the outcomes in the adult and adolescent population. This was also observed in ivacaftor and lumacaftor/ivacaftor combination, and are also observed in the published literature that indicates transaminase elevations are more common in younger patients with CF than in adults.

General

The Company indicated plans to submit a line extension to extend the indications of Symkevi and Kalydeco to children aged 6 through 11 years in the second half of 2019. Therefore, a proposal for an updated SmPC is not necessary at the moment. The SmPC can be updated when all data are available.

3. Rapporteur's overall conclusion and recommendation

In Study 113 Part B, 69 paediatric patients aged 6-11 years and <40 kg were dosed with TEZ 50 mg QD/IVA 75 mg q12h, while patients ≥40 kg were dosed TEZ 100 mg QD/IVA 150 mg q12h. Applying this posology, TEZ and IVA exposures in subjects 6-11 years of age weighing <40 kg or ≥40 kg were comparable, and were within the range of exposures in subjects 12 years of age and older obtained with the adult dosing regimen of TEZ 100 mg QD/IVA 150 mg q12h. Although mean exposure to TEZ and IVA in subjects 6-11 years appears to be at the lower end of the exposure ranges observed in older patients, further PK comparison data, i.e., a direct comparison of exposures between children, adolescents, and adults at the proposed doses for both TEZ and IVA based on pop-PK modelling and simulation support the view that exposure to TEZ, TEZ-M1 and IVA in children 6-12 years <40 kg are within the range of exposures obtained in adolescent and adult patients with Symkevi to a reasonable extent. It is further acknowledged that dose-selection for Kalydeco and Symkevi were independently conducted. Moreover, the use of a single weight cut-off both for the TEZ and IVA component of Symkevi is considered beneficial with regard to usability/simplicity of the dose regimen. However, further discussion of the posology in patients aged 6-11 years is awaited at the time of submission of the type II variation, including all available data at that time.

Common AEs were mostly expected manifestations of underlying CF disease. The incidence of treatment discontinuation due to AEs was low. Most AEs were mild or moderate in severity and were considered not related to study drug.

Treatment with TEZ/IVA resulted in improvements in sweat chloride concentration that sustained for 24 weeks of treatment. Treatment with TEZ/IVA also improved CFQ-R respiratory domain scores from baseline. Lung function (ppFEV1 and LCI) and growth parameters (weight, height, and BMI z-scores) remained stable over 24 weeks of treatment with TEZ/IVA. There are only results of FEV1 presented for the subpopulation. As the vast majority of the population were patients with F/F mutation, the results can be considered as indicative for this population.

☒ **Fulfilled:**

Vertex plans to submit a Line Extension grouped with a Type II variation to extend the indications of Symkevi and Kalydeco to children aged 6 through 11 years. The submission is planned for the second half of 2019.

4. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. A total of 13 patients were enrolled in Part A of Study 113. However, though TEZ-related PK data are described for 13 patients at Day 1 (TEZ, M1-TEZ, M2-TEZ), at Day 14 data are only available for 12 patients. The number of patients analysed for PK of IVA and metabolites is 10 (at Day 1) or 12 (at Day 14). The Applicant should clarify why TEZ and IVA PK data is not available for all subjects and clarify at which dose these excluded subjects were treated (TEZ 50 mg QD/IVA 75 mg q12h or TEZ 50 mg QD/IVA 150 mg).
2. Applying the TEZ 50 mg QD/IVA 75 mg q12h and TEZ 100 mg QD/IVA 150 mg q12h posology in patients 6-11 years <40 and > 40 kg, respectively, TEZ and IVA exposures in subjects 6-11 years of age weighing <40 kg or ≥40 kg were within the range of exposures in subjects 12 years of age and older obtained with the recommended dosing regimen. However, mean exposure to TEZ and IVA in patients 6-11 years appear at the lower end of the exposure ranges as observed in older patients. Therefore, further comparative PK data should be provided, i.e., a direct comparison of exposures between children, adolescents, and adults at the proposed doses for both TEZ and IVA based on pop-PK modelling and simulation. Based on this direct comparison, the optimal dose should be discussed further. In this respect, the lower IVA dose applied in combination with TEZ (75 mg BID) as compared to the IVA dose given as single agent (150 mg BID) in patients 6-11 years weighing between 25 and 40 kg should be included in this discussion.
3. The MAH is requested to indicate when a variation including data from other studies as well will be submitted. If no variation will be submitted, the MAH should include tezacaftor and ivacaftor PK data (including information based on the requested popPK and simulation comparison of the exposure) in paediatric patients aged 6-11 years from Study 113 in the SmPC.
4. As Part A of the study VX16-661-113 is part of paediatric investigation plan, the MAH is requested to submit the most recent version of the PIP.
5. The patient population was mixed consisting of homozygous F508del mutation patients and heterozygous F508del mutation patients. Patients heterozygous for F508del mutation + residual function mutation are less severely affected than homozygous F508del mutation patients. As the vast majority of patients was homozygous for the F508del mutation (87.1%), the results are driven by this group. The MAH is requested to provide the demographics and baseline characteristics for both populations separately. In addition to the baseline characteristics, faecal elastase-1 levels should be provided as well. For both Part A and Part B, anthropometric measures should be provided as Z-scores and percentiles.
6. For completeness, the MAH is requested to provide the results for both homozygous F508del mutation patients and heterozygous F508del mutation patients separately, including the mutation of the heterozygous patients.

7. The MAH is requested to present the percentage of homozygous F508del patients with a BMI at baseline below 0 who at week 24 reached a BMI Z-score ≥0 with the corresponding change in height Z-score.
8. If collected, the MAH is requested to provide the change from baseline at week 24 for homozygous *F508del* patients who have exocrine pancreatic insufficiency (based on FE-1 levels < 100 µg/g stool) as well as the percentage of patients who at week 24 achieved a level ≥ 200 µg/g.
9. The MAH is requested to present the percentage of patients homozygous for F508del who reached a change from baseline through week 24 in the respiratory domain of the CFQ-R ≥ 4 should be presented.
10. The primary objective of Part B is to investigate the safety and tolerability. In this part, the dosing was for subjects ≥ 40 kg identical to the dosing in adults in adolescents. For children with a weight < 40 kg at baseline the dosing was adapted. Although most subjects (88.6%) weighed <40 kg at baseline, it is considered of interest to have the results for the two groups separately provided. This request concerns the overview of adverse events, subjects with any and with related AEs, subjects with SAE, and subjects with AEs leading to treatment discontinuation/interruption.
11. The incidence of ALT or AST >3, >5, and >8 × ULN was 10.0%, 4.3%, and 1.4%, respectively. The increases in LFT are in children somewhat higher compared to the outcomes in the adult and adolescent population. Especially the group >5 and ≤ 8 ULN and the group >8 × ULN are of interest and needs further detailed (e.g. values) discussion.

The timetable is a 30 day response timetable with clock stop.

MAH responses to Request for supplementary information

Pharmacokinetics

1. **A total of 13 patients were enrolled in Part A of Study 113. However, though TEZ-related PK data are described for 13 patients at Day 1 (TEZ, M1-TEZ, M2-TEZ), at Day 14 data are only available for 12 patients. The number of patients analysed for PK of IVA and metabolites is 10 (at Day 1) or 12 (at Day 14). The Applicant should clarify why TEZ and IVA PK data is not available for all subjects and clarify at which dose these excluded subjects were treated (TEZ 50 mg QD/IVA 75 mg q12h or TEZ 50 mg QD/IVA 150 mg).**

Company's response

In Study 113 Part A, pharmacokinetic (PK) data were missing for the following reasons:

Day 1: Ivacaftor (IVA) PK data from 3 subjects were excluded from analysis because these subjects received IVA monotherapy before the first dose of tezacaftor/ivacaftor (TEZ/IVA).

Day 14: One subject had difficulties with venipuncture; therefore, blood collections were not collected for TEZ and IVA PK analyses.

Table 1 summarizes the number of subjects with missing PK results in each cohort in Study 113 Part A, including the doses of TEZ and IVA each of these subjects received.

Table 1 **Study 113 Part A: Number of Subjects With Missing PK Data, All Subjects Set**

Study Visit	Analyte	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)
Day 1	TEZ	0	0	0
	IVA	1	2	3
Day 14	TEZ	0	1	1
	IVA	0	1	1

Source: Study 113 CSR/Table 11-1 and Table 11-2
IVA: ivacaftor; N: size of sample; PK: pharmacokinetic; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor

Assessment of the response:

The Applicants response is acceptable. IVA was not measured in 3 patients at day 1 (single dose day) since they received IVA monotherapy before this day, and for one patient at day 14 no samples could be taken, and therefore no analysis for TEZ and IVA was possible.

Issue resolved

2. **Applying the TEZ 50 mg QD/IVA 75 mg q12h and TEZ 100 mg QD/IVA 150 mg q12h posology in patients 6-11 years <40 and > 40 kg, respectively, TEZ and IVA exposures in subjects 6-11 years of age weighing <40 kg or ≥40 kg were within the range of exposures in subjects 12 years of age and older obtained with the recommended dosing regimen. However, mean exposure to TEZ and IVA in patients 6-11 years appear at the lower end of the exposure ranges as observed in older patients. Therefore, further comparative PK data should be provided, i.e., a direct comparison of exposures between children, adolescents, and adults at the proposed doses for both TEZ and IVA based on pop-PK modelling and simulation. Based on this direct comparison, the optimal dose should be discussed further. In this respect, the lower IVA dose applied in combination with TEZ (75 mg BID) as compared to the IVA dose given as single agent (150 mg BID) in patients 6-11 years weighing between 25 and 40 kg should be included in this discussion.**

Company's response

Comparison of TEZ and IVA Exposures in Children, Adolescents, and Adults

To evaluate the dosing regimen in Study 113 Part B, data from this study was used to update population PK models for TEZ, M1-TEZ, and IVA. M1-TEZ is an active metabolite of TEZ that has similar pharmacologic activity to TEZ.

Population PK modelling results from the updated models are presented for children (6 through 11 years of age), adolescents (12 through 17 years of age), and adults (18 years of age and older) in Table 2 (exposures at steady-state by age group), Figure 1 through Figure 3 (boxplots of steady-state exposures by age group), and Figure 4 (exposures at steady-state versus weight). Area under the concentration versus time curve at steady state (AUCss) was assessed as AUC0-24h for TEZ and M1-TEZ and as AUC0-12h for IVA.

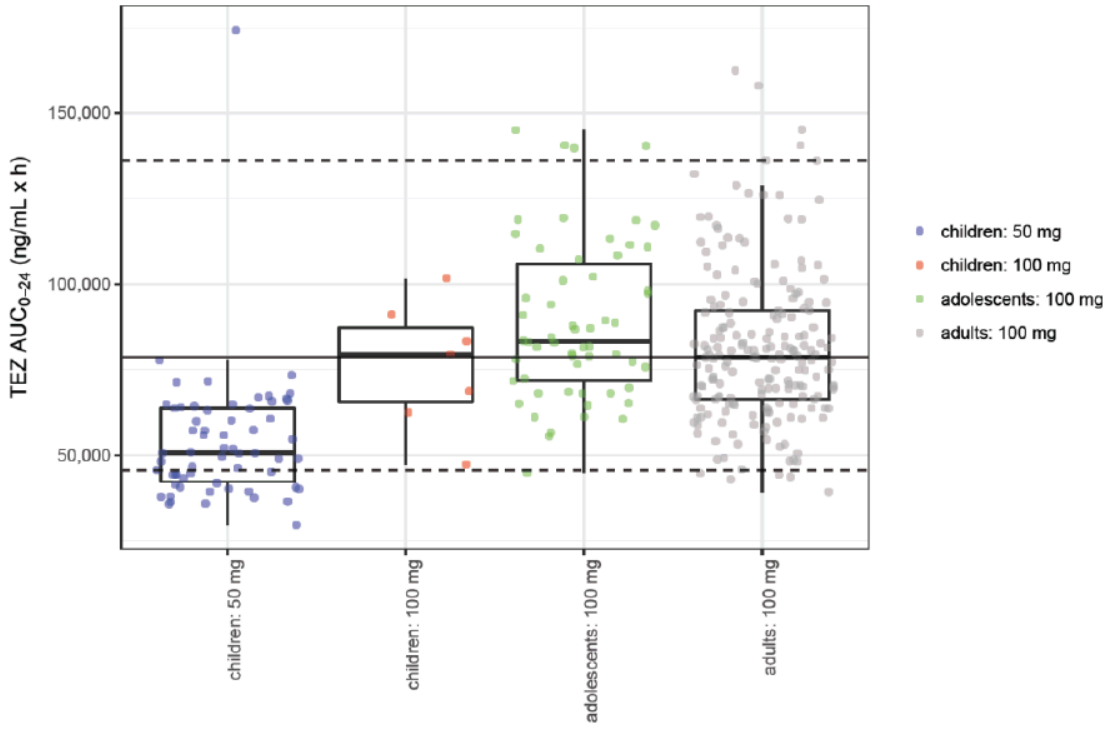
Overall, the population PK models indicate that individual exposures for all 3 analytes in Study 113 were within the ranges observed for subjects 12 years of age and older.

Table 2 **Summary of TEZ, M1-TEZ, and IVA Steady-state Exposures (AUC_{ss}) by Age Group**

Age Group	N	TEZ (ug·h/mL) Mean (SD)	M1-TEZ (ug·h/mL) Mean (SD)	IVA (ug·h/mL) Mean (SD)
6 through 11 years (<40 kg)	62	54.1 (19.4)	117 (34.9)	7.12 (2.24)
6 through 11 years (≥40 kg)	7	76.4 (18.3)	131 (36.2)	9.16 (2.83)
12 through 17 years	97	97.1 (35.8)	145 (38.1)	11.4 (5.50)
18 years and older	389	85.9 (28.0)	124 (32.7)	11.4 (4.14)

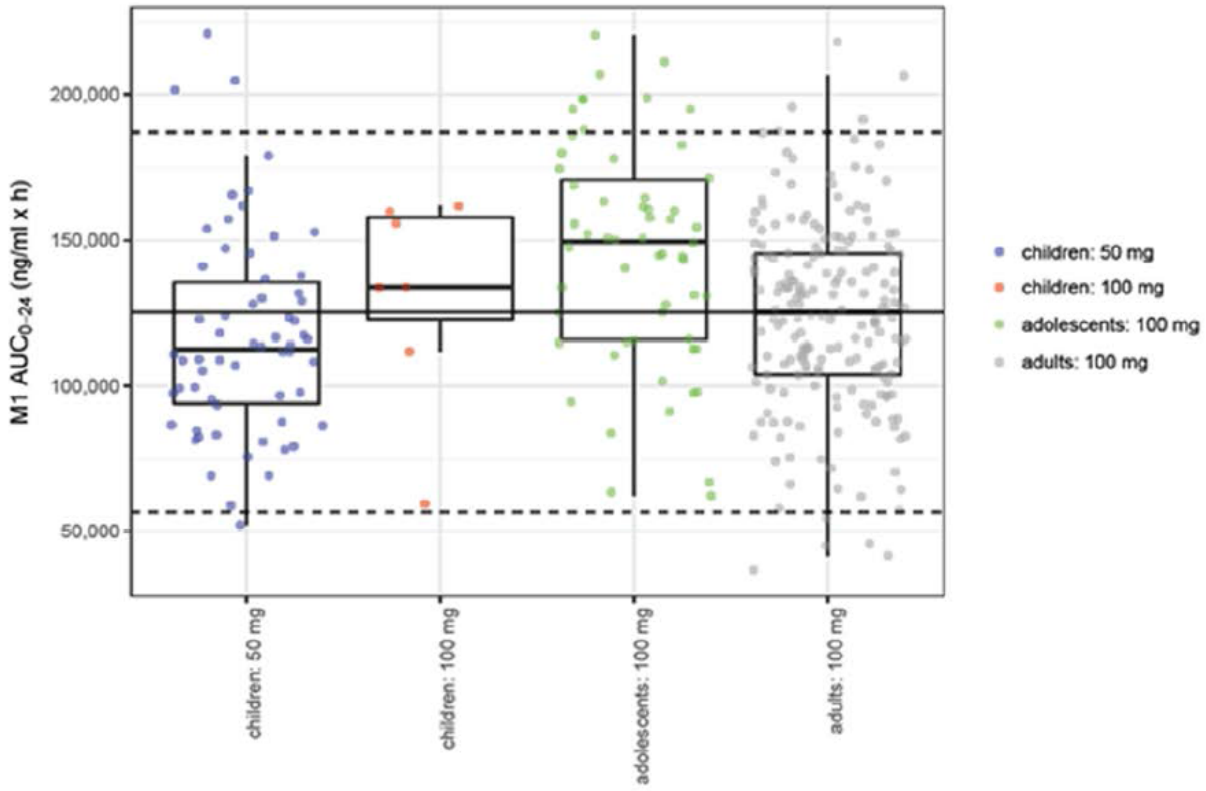
Sources: Report O350 and Report O394
IVA: ivacaftor; M1-TEZ: metabolite of TEZ; TEZ: tezacaftor
Note: $AUC_{0\text{-}24h}$ was assessed for TEZ and M1-TEZ; $AUC_{0\text{-}12h}$ was assessed for IVA.

Figure 1 **TEZ $AUC_{0\text{-}24h}$ in Children, Adolescents, and Adults**



Source: Report O350/Figure 146
IQR: interquartile range; PK: pharmacokinetics; TEZ: tezacaftor
Notes: PK data are from Study 113 Part B (children: subjects 6 through 11 years of age) and Study 106 (adolescents: 12 through 17 years of age; adults: 18 years of age and older). Dash lines indicate 2.5th and 97.5th percentiles of the adult values. The boxplots show the median (horizontal line) and IQRs (box). The whiskers represent the largest and smallest values within 1.5 × IQR.

Figure 2 M1-TEZ AUC_{0-24h} in Children, Adolescents, and Adults

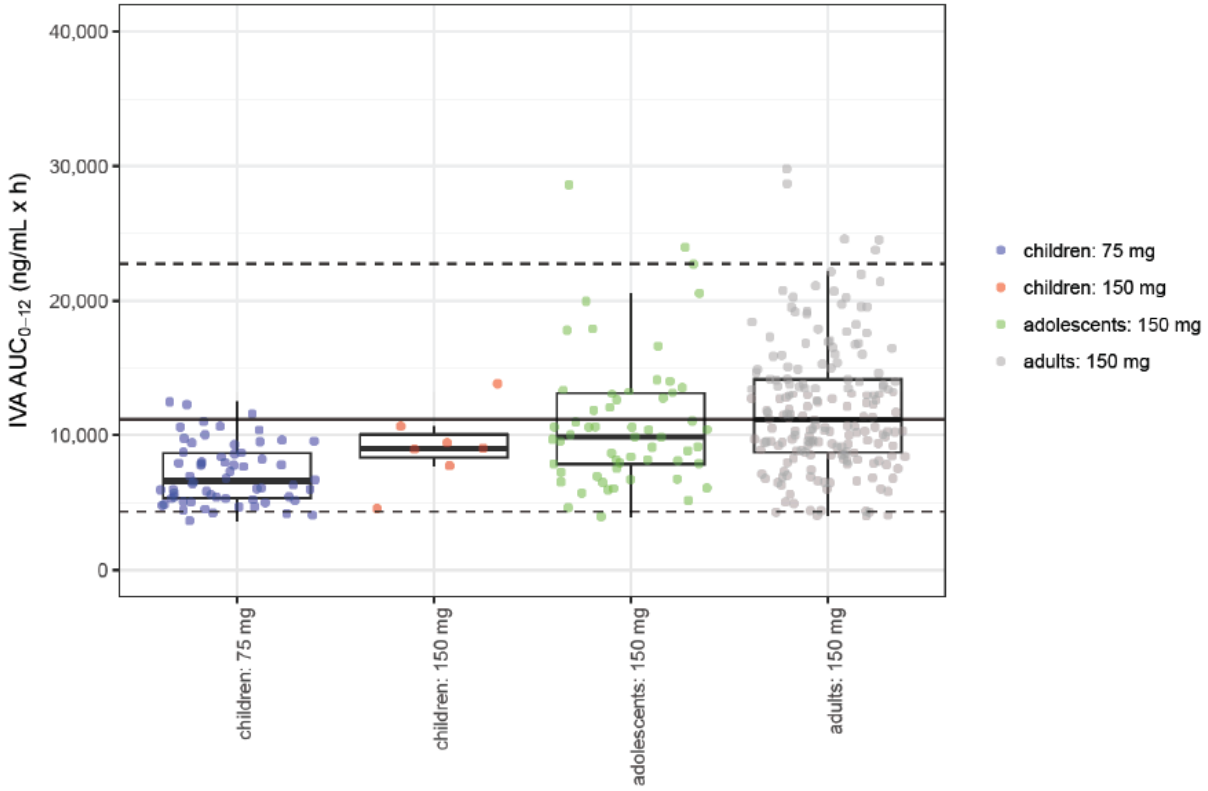


Source: Report O350/Figure 149

IQR: interquartile range; M1-TEZ: metabolite of TEZ; PK: pharmacokinetics; TEZ: tezacaftor

Notes: PK data are from Study 113 Part B (children: subjects 6 through 11 years of age) and Study 106 (adolescents: 12 through 17 years of age; adults: 18 years of age and older). Dash lines indicate 2.5th and 97.5th percentiles of the adult values. Boxplots show the median (horizontal line) and IQRs (box). The whiskers represent the largest and smallest values within 1.5 × IQR.

Figure 3 IVA AUC_{0-12h} in Children, Adolescents, and Adults



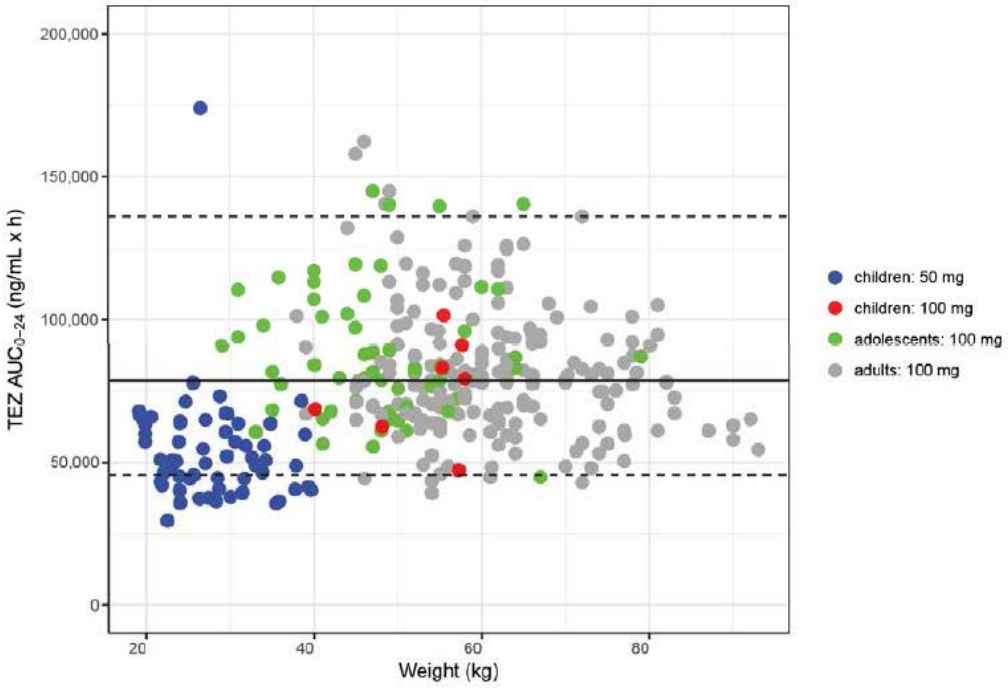
Source: Report O350/Figure 152

IQR: interquartile range; IVA: ivacaftor; PK: pharmacokinetics

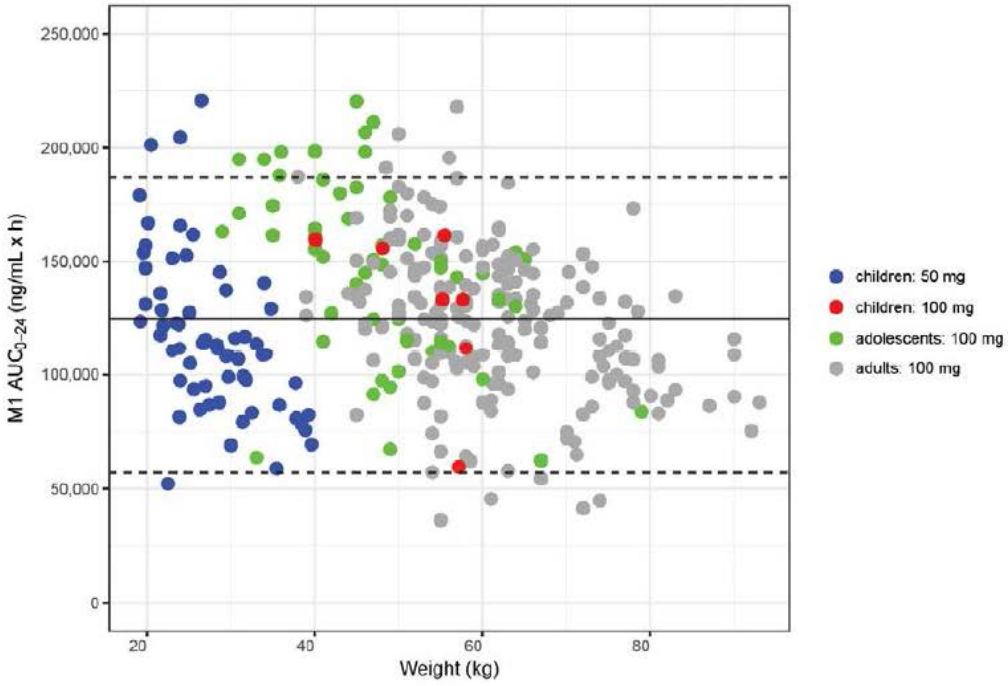
Notes: PK data are from Study 113 Part B (children: subjects 6 through 11 years of age) and Study 106 (adolescents: 12 through 17 years of age; adults: 18 years of age and older). Dash lines indicate 2.5th and 97.5th percentiles of the adult values. Boxplots show the median (horizontal line) and IQRs (box). The whiskers represent the largest and smallest values within 1.5 × IQR.

Figure 4 **TEZ, M1-TEZ, and IVA AUC Versus Weight for Children, Adolescents, and Adults**

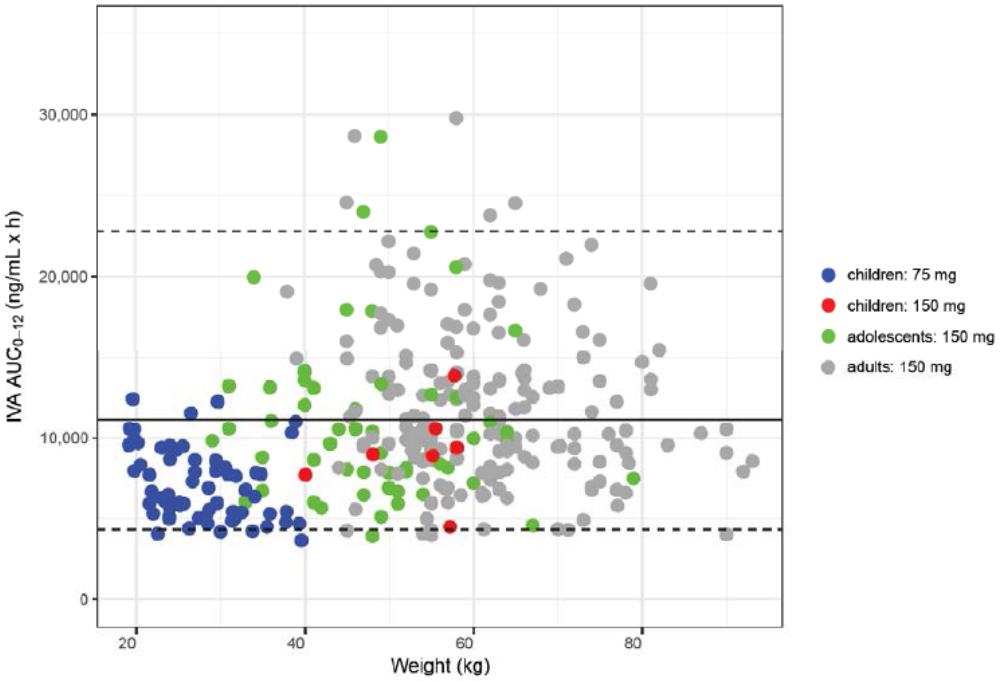
TEZ



M1-TEZ



IVA



Source: Report O394/Figures 1, 2, and 3
IVA: ivacaftor; M1-TEZ: metabolite of TEZ; PK: pharmacokinetics; TEZ: tezacaftor
Note: PK data are from Study 113 Part B (children: subjects 6 through 11 years of age) and Study 106 (adolescents: 12 through 17 years of age; adults: 18 years of age and older). Solid line represents median of the adult values and dash lines indicate 2.5th and 97.5th percentiles of the adult values.

TEZ/IVA Versus IVA Monotherapy Dose and Optimal TEZ/IVA Dose

Dose selections and weight cut-offs are optimized independently for the Kalydeco™ (IVA monotherapy) and Symkevi™ (TEZ/IVA) programs. For the Kalydeco program, doses were selected based on data derived from the population PK modeling of IVA only, whereas both TEZ and IVA were evaluated for the Symkevi program.

In Study 113 Part B, a different weight cut-off (40 kg) was selected for the lower dose of TEZ/IVA treatment (TEZ 50 mg once daily [qd]/IVA 75 mg every 12 hours [q12h]) compared to the weight cut-off (25 kg) that is approved to treat children 6 years of age and older with the 75-mg dose of Kalydeco. The 40-kg weight cut-off was chosen for evaluation in Study 113 for the following reasons:

- Population PK modeling predicted that a 40-kg weight cut-off for dosing with TEZ/IVA in 6- through 11-year-old subjects with cystic fibrosis (CF) would yield exposures of TEZ and IVA that would be within the adult ranges.
- IVA has a wide therapeutic window. Predicted exposures of IVA were expected to fall within the well-characterized, wide therapeutic window.
- Using the same weight cut-off for both TEZ and IVA simplifies the dose regimen.

As described in response to Question 3, Vertex plans to submit a Line Extension grouped with a Type II variation to extend the indications of Symkevi and Kalydeco to children 6 to 11 years of age. Additional discussion of the proposed commercial doses of TEZ and IVA will be provided in this submission.

Assessment of the response

The provided discussion and data is appreciated. It is acknowledged that dose-selection for Kalydeco and Symkevi were independently conducted. Further, the use of a single weight cut-off both for the TEZ and IVA component of Symkevi is considered beneficial with regard to usability/simplicity of the dose regimen. Finally, the popPK data provided, support the view that exposure to TEZ, TEZ-M1, and IVA in children 6-12 years <40 kg are within the range of exposures obtained with Symkevi in adolescent and adult patients to a reasonable extent.

Further discussion at the time of submission of the type II variation (See OC3), including all available data at that time, is awaited.

Issue resolved.

Regulatory

3. **The MAH is requested to indicate when a variation including data from other studies as well will be submitted. If no variation will be submitted, the MAH should include tezacaftor and ivacaftor PK data (including information based on the requested popPK and simulation comparison of the exposure) in paediatric patients aged 6-11 years from Study 113 in the SmPC.**

Company's response

Vertex plans to submit a Line Extension grouped with a Type II variation to extend the indications of Symkevi and Kalydeco to children aged 6 through 11 years. The submission is planned for the second half of 2019.

Assessment of the response

Because the Company plans to submit a line extension to extend the indications of Symkevi and Kalydeco to children aged 6 through 11 years in the second half of 2019, a proposal for an updated SmPC is not necessary at the moment. The SmPC can be updated when all data are available.

Issue resolved.

Clinical

4. **As Part A of the study VX16-661-113 is part of paediatric investigation plan, the MAH is requested to submit the most recent version of the PIP.**

Company's response

The most recent PIP Decision is provided in Module 1.10.

Assessment of the response

The applicant submitted the most recent version of the PIP, EMEA-001640-PIP01-14-M05. According to the PIP, Part A of the study VX16-661-113 is part of paediatric investigation plan, study 11 (EMEA-001640-PIP01-14-M05). Clinical efficacy and safety will be studied in Study 12 (Study C, part B; VX16-661-115). It is assumed that study VX16-661-115 will be submitted with the variation.

5. **The patient population was mixed consisting of homozygous F508del mutation patients and heterozygous F508del mutation patients. Patients heterozygous for**

F508del mutation + residual function mutation are less severely affected than homozygous F508del mutation patients. As the vast majority of patients was homozygous for the F508del mutation (87.1%), the results are driven by this group. The MAH is requested to provide the demographics and baseline characteristics for both populations separately. In addition to the baseline characteristics, faecal elastase-1 levels should be provided as well. For both Part A and Part B, anthropometric measures should be provided as Z-scores and percentiles.

Company's response

Subject demographics in Study 113 Part B are presented by CFTR mutation type (homozygous for F508del [F/F] versus heterozygous for F508del and a second allele that results in residual function [F/RF]) in Table 3. Baseline characteristics in Part B (including anthropometric z-scores and percentiles) are presented by mutation type in Table 4. Study 113 Part A baseline anthropometric measures (including z-scores and percentiles) are presented by mutation type in Table 5.

Fecal elastase-1 assessments were not performed in Study 113; therefore, these data are not available.

Table 3 Study 113 Part B: Demographics in F/F and F/RF Subjects, Safety Set

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

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

Table 4 Study 113 Part B: Baseline Characteristics in F/F and F/RF Subjects, Safety Set

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

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

Source: Study 113 CSR/Ad hoc Table 1.2b

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

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

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

Table 5 Study 113 Part A: Baseline Anthropometric Measures in F/F and F/RF Subjects, Full Analysis Set

Characteristic	F/F Subjects N = 5	F/RF Subjects N = 4	Total[a] N = 9
Weight (kg)			
n	5	4	9
Mean (SD)	26.0 (1.2)	35.8 (10.1)	30.3 (8.1)
Median	26.0	33.5	26.0
Min, Max	25.0, 28.0	26.0, 50.0	25.0, 50.0
Height (cm)			
n	5	4	9
Mean (SD)	125.6 (5.9)	141.3 (12.1)	132.6 (11.8)
Median	126.0	143.0	127.0
Min, Max	118.0, 134.0	125.0, 154.0	118.0, 154.0
BMI (kg/m^2)			
n	5	4	9
Mean (SD)	16.51 (0.88)	17.86 (4.19)	17.11 (2.73)
Median	16.38	16.87	16.52
Min, Max	15.59, 17.95	13.91, 23.78	13.91, 23.78
Weight Z-score			
n	5	4	9
Mean (SD)	0.54 (0.43)	0.45 (1.08)	0.50 (0.73)
Median	0.35	0.37	0.35
Min, Max	0.07, 1.15	-0.77, 1.82	-0.77, 1.82
Height Z-score			
n	5	4	9
Mean (SD)	0.39 (0.42)	0.66 (0.51)	0.51 (0.45)
Median	0.46	0.72	0.46
Min, Max	-0.06, 1.01	0.08, 1.11	-0.06, 1.11
BMI Z-score			
n	5	4	9
Mean (SD)	0.49 (0.58)	0.03 (1.75)	0.29 (1.17)
Median	0.43	0.36	0.43
Min, Max	-0.27, 1.35	-2.37, 1.78	-2.37, 1.78
Weight Percentile			
n	5	4	9
Mean (SD)	69.14 (13.76)	61.61 (31.50)	65.80 (21.97)
Median	63.84	63.85	63.84
Min, Max	52.64, 87.52	22.16, 96.58	22.16, 96.58
Height Percentile			
n	5	4	9
Mean (SD)	64.19 (14.64)	72.59 (16.28)	67.92 (15.04)
Median	67.66	75.27	67.66
Min, Max	47.49, 84.48	53.26, 86.55	47.49, 86.55
BMI Percentile			
n	5	4	9
Mean (SD)	66.55 (18.38)	56.18 (40.53)	61.94 (28.55)
Median	66.64	63.79	66.64
Min, Max	39.42, 91.13	0.88, 96.27	0.88, 96.27

Source: Study 113 CSR/Ad hoc Table 2.1a

BMI: body mass index; n: size of subsample; N: Full Analysis Set sample size

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

[a] Total refers to all subjects who were F/F or F/RF. As allowed per protocol, Part A enrolled 4 subjects who were neither F/F nor F/RF (3 subjects had an *F508del/G551D* genotype; 1 subject had an *F508del/A559T* genotype).

Assessment of the response

In part B, out of the 70 patients, 61 children were homozygous for F508del mutation. The remaining 9 children were heterozygous for F508del mutation and a residual function mutation.

Overall, the two populations were comparable in baseline demographics and baseline characteristics with some exceptions. The baseline data provided show the highest severity of the disease in homozygous *F508del* subjects as expected even at this young age. Homozygopus *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. The difference in sweat chloride is a characteristic of the difference in disease genotype.

In part A, the groups are small i.e. 5 children with homozygous F/F mutations and 4 children with heterozygous F/RF. Overall Children with homozygous F/F mutations were heavier and children with heterozygous F/RF were taller resulting in a higher BMI in children with homozygous F/F mutations.

Conclusion: The applicant provided the requested tables. Issue solved.

6. **For completeness, the MAH is requested to provide the results for both homozygous F508del mutation patients and heterozygous F508del mutation patients separately, including the mutation of the heterozygous patients.**

Company's response

Study 113 had primary objectives of PK (Part A) and safety and tolerability (Part B).

With the exception of spirometry endpoints, efficacy endpoints were not analysed separately for F/F and F/RF subjects because:

1. Efficacy was a secondary objective of the study (Part B only).

2. This study was not powered for subgroup analysis of efficacy endpoints in F/F and F/RF subjects.

3. Given the small sample size for the F/RF group (N = 9), statistically robust conclusions cannot be drawn from a subgroup analysis of subjects with F/RF genotypes.

Descriptive summary statistics for change in percent predicted forced expiratory volume in 1 second (ppFEV1; secondary endpoint, Part B only) were provided separately for F/F and F/RF subjects in Study 113 CSR/Table 14.2.1.1.1b.

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. Given the small number of F/RF subjects, the high baseline ppFEV1 values in Study 113, and that similar increases in ppFEV1 were observed in F/F and F/RF subjects, further analyses in F/RF and F/F subgroups are not considered to provide further insight.

No subgroup analysis was performed for the individual residual function (RF) mutations, because no RF mutation was carried by >2 subjects. The RF mutations enrolled in Study 113 Part B are summarized below:

CFTR Mutation	Number of Subjects Enrolled
3849+10kbC>T	2
2789+5G>A	2
R352Q	1
3272-26A>G	1
D1152H	1
L206W	1
D579G	1

Assessment of the response

The applicant provided the subanalysis only for the efficacy parameter percent predicted forced expiratory volume in 1 second (ppFEV1).

The applicant did not provide other subanalyses based on the facts that efficacy was a secondary objective of Study 113, the study was not powered for subgroup analysis and the vast majority of the patients were carrying F/F mutation (refer also to response to question 7).

The Rapporteurs are well aware of the limitations of the subanalyses and the small group of children with heterozygous F/RF and these results are considered with caution. However, because the populations are different for disease progression but also for response to Symkevi as been seen in the adults and adolescents (refer to initial marketing application), in the view of the rapporteurs, these two populations should be distinguished from each other. Thus, the requested analyses should have been provided.

The mean (SD) absolute change from baseline in ppFEV1 through Week 24 is similar in the two populations, i.e. 0.9 (6.7) percentage points in F/F subjects and 0.9 (5.1) percentage in F/RF subjects. In the adult/adolescents studies, study VX14-661-106 and study VX14-661-108, absolute change from baseline in ppFEV1 through Week 24 was 3.4 and 6.5 in respectively F/F subjects and F/RF subjects. It is agreed with the applicant that the well-preserved baseline lung function values may be the reasons for the small increase in children.

The included children with heterozygous F/RF had mutation as allowed in the label for the use in adults and adolescents.

In the assessment report in the comment box and discussion, subanalyses were requested for the homozygous patients by gender because differences in disease progress were requested. Unfortunately, this was not included in the question.

At the moment, this issue is rested, because the applicant will submit a variation for a line extension in children aged 6 through 11 years. It is expected that more results will be become available through Study VX16-661-115. At that time, the results will be assessed together.

Conclusion: issue is considered resolved within this procedure.

7. **The MAH is requested to present the percentage of homozygous F508del patients with a BMI at baseline below 0 who at week 24 reached a BMI Z-score ≥0 with the corresponding change in height Z-score.**

Company's response

As described in response to Question 6, efficacy was a secondary objective of Study 113. The study was not powered for subgroup analysis for efficacy, including subgroups defined by CFTR mutation or baseline z-scores above/below 0.

Overall, body mass index (BMI) and height Z-scores were stable across 24 weeks of TEZ/IVA treatment in Part B. No subgroup analysis was performed for these endpoints, given that the overall LS mean (SE) absolute change in BMI z-score was -0.03 (0.04) and the overall LS mean (SE) absolute change in height z-score was 0.00 (0.02). The F/F subgroup would be expected to have similar results to the overall study population, given that 87.1% of the Study 113 population had an F/F genotype.

Assessment of the response

The information requested has not been provided. The Rapporteurs are well aware of the limitations of the subanalyses (refer to question 6). The requested analyses should have been provided.

In the pivotal study 106 in subjects homozygous *F508del* 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/m^2 which suggests that the effect of TEZ/IVA on anthropometric parameters is limited for the homozygous *F508del* population. In study 108 (heterozygous *F508del*/CFTR mutation of residual function), the mean within-group change in the TEZ/IVA group after 8 weeks of treatment was 0.34 kg/m^2. The baseline data for part B provided in response to Question 5 show that based on the anthropometric parameters for each population (homo- and heterozygous), the latter have a better preserved nutritional status as expected.

Given that in response to Question 3, the MAH states that a Line Extension grouped with a type II variation is planned to extend the indications of Symkevi and Kalydeco to children aged 6 through 11 years no further questions in this respect are raised. In study 115 anthropometric parameters have been analysed and compared vs. placebo even though just for 8 weeks of treatment (according to opinion on EMEA-001640-PIP01-14-M05). At that time, the results will be assessed together.

Conclusion: issue is considered resolved within this procedure.

8. **If collected, the MAH is requested to provide the change from baseline at week 24 for homozygous *F508del* patients who have exocrine pancreatic insufficiency (based on FE-1 levels < 100 µg/g stool) as well as the percentage of patients who at week 24 achieved a level ≥ 200 µg/g.**

Company's response

Faecal elastase-1 assessments were not performed in Study 113; therefore, Vertex is not able to provide these data.

Assessment of the response

As faecal elastase-1 (FE-1) was not collected, data are not available. It is assumed that at the age of 6 years most homozygous *F508del* subjects are (exocrine) pancreatic insufficient as the disease is usually established very early in life and FE-1 values expected to be below 50 µg/g. It would have been of interest to assess whether treatment with TEZ/IVA results in FE-1 increases above the cut-off of 100 or 200 µg/g. In combination with a decrease in IRT, this would be indicative of a decrease of the stress that pancreatic exocrine cells undergo (with increases in FE-1 reflecting some recovery of CFTR

function at the gastrointestinal tract and reduction in IRT levels interpreted as a decreased leakage into the bloodstream under disease circumstances).

Conclusion: Faecal elastase-1 data was not collected. Therefore, no assessment can be made. Issue resolved.

9. **The MAH is requested to present the percentage of patients homozygous for F508del who reached a change from baseline through week 24 in the respiratory domain of the CFQ-R ≥ 4 should be presented.**

Company's response

The primary objectives of Study 113 were to evaluate TEZ/IVA PK (Part A) and safety and tolerability (Part B); efficacy was a secondary objective (Part B only). While the minimal clinically important difference (MCID) for the Adult and Adolescent Versions of the Cystic Fibrosis Questionnaire- Revised (CFQ-R) respiratory domain score is 4 points, there is no consensus MCID for the Child Version of the questionnaire. For these reasons, no analysis of change from baseline in CFQ-R ≥4 points is presented.

Assessment of the response

The MAH argues that there is no consensus MCID for the Child Version of the questionnaire. For these reasons, no analysis of change from baseline in CFQ-R ≥4 points is presented. However, in previous procedures, the MAH accepted the minimal clinically important difference (MCID) of 4 points and this instrument has been used as a primary endpoint for regulatory approval. The difference of ≥4 points as the MCID is based on the results of the study performed by Quittner et al (2009) which included children aged 6 to less than 13 years old.

Although the arguments against the subanalysis may be acknowledged, the inconsistency in the opinion of the MAH regarding the MCID of 4 points for the CFQ-R in children 6 to less than 12 years old would need further justification. At the moment, this issue is rested, because variation will be submitted for a line extension in children aged 6 through 11 years. Consistency is expected across procedures unless the scientific evidence leads to change of opinion on this issue.

Conclusion: issue is considered resolved within this procedure.

10. **The primary objective of Part B is to investigate the safety and tolerability. In this part, the dosing was for subjects ≥ 40 kg identical to the dosing in adults in adolescents. For children with a weight < 40 kg at baseline the dosing was adapted. Although most subjects (88.6%) weighed <40 kg at baseline, it is considered of interest to have the results for the two groups separately provided. This request concerns the overview of adverse events, subjects with any and with related AEs, subjects with SAE, and subjects with AEs leading to treatment discontinuation/interruption.**

Company's response

All safety results are presented separately for subjects weighing ≥40 kg (TEZ 100 mg qd/IVA 150 mg q12h) and subjects weighing <40 kg (TEZ 50 mg qd/IVA 75 mg q12h) in Study 113/CSR/Section 14.

Table 6 presents an overview of treatment-emergent adverse event (AE) for subjects <40 kg and ≥ 40 kg. Additional information about AEs in subjects <40 kg and ≥40 kg can be found in Study 113/CSR/Section 14.3.1.

Although there are no clinically significant differences between subjects <40 kg versus ≥40 kg, results in the ≥40 kg group (N = 8) should be interpreted with caution due to the small number of subjects.

Table 6 Study 113 Part B: Overview of Adverse Events, Safety Set

	Subjects <40 kg TEZ 50 mg qd/ IVA 75 mg q12h N = 62 n (%)	Subjects ≥40 kg TEZ 100 mg qd/ IVA 150 mg q12h N = 8 n (%)	Total N = 70 n (%)
Number of AEs (total)	294	34	328
Subjects with any AEs	59 (95.2)	6 (75.0)	65 (92.9)
Subjects with related AEs[a]	15 (24.2)	4 (50.0)	19 (27.1)
Subjects with AEs by strongest relationship			
Related	1 (1.6)	0	1 (1.4)
Possibly related	14 (22.6)	4 (50.0)	18 (25.7)
Unlikely related	24 (38.7)	1 (12.5)	25 (35.7)
Not related	20 (32.3)	1 (12.5)	21 (30.0)
Subjects with AEs by maximum severity			
Mild	32 (51.6)	2 (25.0)	34 (48.6)
Moderate	24 (38.7)	4 (50.0)	28 (40.0)
Severe	3 (4.8)	0	3 (4.3)
Life-threatening	0	0	0
Subjects with Grade 3/4 AEs	3 (4.8)	0	3 (4.3)
Subjects with SAEs	5 (8.1)	1 (12.5)	6 (8.6)
Subjects with related SAEs	0	0	0
Subjects with AEs leading to treatment discontinuation	0	1 (12.5)	1 (1.4)
Subjects with AEs leading to treatment interruption	4 (6.5)	0	4 (5.7)
Subjects with AEs leading to death	0	0	0

Source: Study 113 CSR/Table 14.3.1.1b
AE: adverse event; n: size of subsample; N: total sample size; SAE: serious adverse event
Notes: Adverse events were coded using MedDRA Version 19.1. For number of subjects and percent of subjects, a subject with multiple events within a category was counted only once in that category. When summarizing number of events, a subject with multiple events within a category is counted multiple times in that category.
[a] Related includes the related, possibly related, and missing categories.

Assessment of the response

The number of patients in ≥40 kg group is low i.e. N = 8. Therefore, results should be interpreted with caution making it difficult to draw conclusions. However, still an impression, more AEs were severe Grade ¾ in subjects <40 kg versus ≥40 kg. These Grade ¾ concern infective pulmonary exacerbation of cystic fibrosis, sinusitis, breath odour and snoring. SAEs were absent.
With the submission of the variation to extend the indications of Symkevi and Kalydeco to children aged 6 through 11 years, more studies will be submitted and this issue will be further analysed during the variation.

Conclusion: Issue resolved.

11. The incidence of ALT or AST >3, >5, and >8 × ULN was 10.0%, 4.3%, and 1.4%, respectively. The increases in LFT are in children somewhat higher compared to the outcomes in the adult and adolescent population. Especially the group >5 and ≤ 8

ULN and the group >8 × ULN are of interest and needs further detailed (e.g. values) discussion.

Company's response

The incidence of transaminase elevations observed in Study 113 is consistent with expectations of patients with CF in this age group. Published literature indicates that transaminase elevations are more common in younger patients with CF than in adults.[1]

The results are also consistent with Vertex's previous paediatric studies of IVA monotherapy and lumacaftor (LUM)/IVA therapy. In a 48-week study of IVA monotherapy treatment in 6- to 11-year-old subjects, the percent of subjects with alanine transaminase (ALT) and/or aspartate transaminase (AST) >3, >5, and >8 × upper limit of normal (ULN) were 19%, 4%, and 0%, respectively, in the placebo group and 19%, 4%, and 4%, respectively, in the IVA monotherapy group (Study 770-103 CSR). Similarly, in a 24-week study of LUM/IVA treatment in 6- to 11-year-old subjects, placebo-treated subjects had a rate of ALT or AST >3, >5, and >8 × ULN of 8%, 3%, and 2%, respectively.[2] Together, these results suggest that the rates of liver function test (LFT) elevation observed after TEZ/IVA treatment in Study 113 (1) were similar to background levels in patients with CF in this age range and (2) were not increased compared to treatment with IVA alone.

Given the sample size in Study 113 Part B (N = 70), a difference of just 1 subject with a transaminase elevation would yield a 1.4% difference in rate, so apparent differences in rates in Study 113 compared to adult data could be due to the effects of small sample size.

In Study 113, 3 subjects had ALT or AST >5 × ULN; 1 of these subjects also met the criterion of ALT or AST >8 × ULN. A summary of these subjects' baseline, maximum, and Week 24 Visit ALT and AST values is presented in Table 7. More detailed LFT values for these subjects, along with additional relevant clinical details, are provided in subject narratives in Study 113 CSR/ Section 14.3.3.3.

Analysis of transaminase elevations for all 3 subjects with ALT or AST >5 × ULN was confounded by high baseline ALT values and/or alternative aetiologies for the elevations. No subject discontinued TEZ/IVA due to elevated transaminases. For the 2 subjects with ALT >5 × ULN and <8 × ULN, the elevations did not result in study drug interruption. The subject with ALT and AST >8 × ULN was treated with antibiotics before the elevations. After this subject interrupted treatment, the subject successfully resumed dosing with TEZ/IVA and completed the study.

Table 7 Study 113 Part B: Summary of Subjects With ALT or AST Values >5 × ULN

	Baseline		Maximum		Week 24		
Subject No.	ALT (U/L)	AST (U/L)	ALT (U/L)	AST (U/L)	ALT (U/L)	AST (U/L)	Notes
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	TEZ/IVA dosing interrupted. After interruption, subject resumed treatment and completed the study.
[redacted]	59[a]	41	188[c]	100[a]	67[a]	47[a]	TEZ/IVA dosing not interrupted. No AE associated with elevation.
[redacted]	79[d]	31	103[c]	55[a]	64[d]	43[a]	TEZ/IVA dosing not interrupted. No AE associated with elevation.

Source: Study 113 CSR/Listing 16.2.8.1.2b and Table 14.3.2.4b

AE: adverse event; ALT: alanine transaminase; AST: aspartate transaminase; IVA: ivacaftor; TEZ: tezacaftor; ULN: upper limit of normal

[a] Value >ULN and <3 × ULN.
[b] Value >8 × ULN.
[c] Value >5 × ULN and ≤8 × ULN.
[d] Value ≥3 × ULN and ≤5 × ULN.

1 Bhardwaj S, Canlas K, Kahi C, Temkit M, Molleston J, Ober M, et al. Hepatobiliary abnormalities and disease in cystic fibrosis. J Clin Gastroenterol. 2009;43(9):858-64.

2 Ratjen F, Hug C, Marigowda G, Tian S, Huang X, Stanojevic S, et al. Efficacy and safety of lumacaftor and ivacaftor in patients aged 6-11 years with cystic fibrosis homozygous for F508del-CFTR: a randomised, placebo-controlled phase 3 trial. Lancet Respir Med. 2017;5(7):557-67.

Assessment of the response

ALT and AST elevations appeared to be higher than that observed in subjects 12 years of age and older but similar tot the frequencies found in ivacaftor and lumacaftor/ivacaftor combination. These observations are consistent with information available in the published literature that indicates transaminase elevations are more common in younger patients with CF than in adults. At the time of the line variation, this issue will be further assessed.

Conclusion: issue resolved.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Clinical studies

Clinical studies Product Name: Symkevi in combination with ivacaftor (Kalydeco) Active substance: tezacaftor/ivacaftor and ivacaftor

Study title	Study number	Date of completion (Last Subject Last Visit)	Date of submission of final study report
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	VX15-661-113	11 Sep 2018	07 March 2019
A Phase 3, Double-blind, Parallel-group Study to Evaluate the Efficacy and Safety of Tezacaftor in Combination With Ivacaftor in Subjects Aged 6 Through 11 Years With Cystic Fibrosis, Homozygous or Heterozygous for the F508del-CFTR Mutation	VX16-661-115	21 Dec 2018	Pending
A Phase 3, Open-label, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment With Tezacaftor in Combination With Ivacaftor in Subjects With Cystic Fibrosis Aged 6 Years and Older, Homozygous or Heterozygous for the F508del-CFTR Mutation	VX17-661-116	Study ongoing	Pending