11 November 2021
EMA/714293/2021
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Kalydeco

International non-proprietary name: ivacaftor

Procedure No. EMEA/H/C/002494/II/0096

## Note

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

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# List of abbreviations

| Abbreviation | Term |
|---|---|
| ADRs | adverse drug reactions |
| AEs | adverse events |
| AESI | adverse event of special interest |
| ALT | alanine transaminase |
| AST | aspartate transaminase |
| AUC | area under the concentration versus time curve |
| $AUC_{0-\infty}$ | AUC from the time of dosing extrapolated to infinity |
| $AUC_{0-\tau}$ | AUC over the dosing interval |
| BA | bioavailability |
| BMI | body mass index |
| CF | cystic fibrosis |
| CFQ-R | Cystic Fibrosis Questionnaire-Revised |
| *CFTR* | CF transmembrane conductance regulator gene |
| CI | confidence interval |
| CK | creatine kinase |
| CL | clearance |
| $C_{max}$ | maximum observed concentration |
| CSR | clinical study report |
| EBE | empirical Bayes estimate |
| ECG | electrocardiogram |
| ELX | elexacaftor |
| EU | European Union |
| F/F | *F508del* on both alleles |
| F/G | heterozygous for *F508del* and a gating mutation |
| *F508del* | *CFTR* gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein |
| FAS | Full Analysis Set |
| FDC | fixed-dose combination |
| IA | interim analysis |
| ICH | International Council for Harmonization |
| IQR | interquartile range |
| IVA | ivacaftor |
| $LCI_{2.5}$ | number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value |
| LS | least squares |
| LUM | lumacaftor |
| max | maximum value |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MF | minimal function |
| min | minimum value |
| MMRM | mixed-effects model for repeated measures |
| N | total sample size |
| *P* | probability |
| PE | physical examination |
| PEx | pulmonary exacerbations |

| Abbreviation | Term |
|---|---|
| PK | pharmacokinetic |
| popPK | population PK |
| $ppFEV_1$ | percent predicted forced expiratory volume in 1 second |
| PT | Preferred Term |
| q12h | every 12 hours |
| qd | once daily |
| RD | respiratory domain |
| RF | residual function |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SDD | spray-dried dispersion |
| SE | standard error |
| SwCl | sweat chloride |
| TEAEs | treatment-emergent adverse events |
| TEZ | tezacaftor |
| ULN | upper limit of normal |
| US | United States |

# 1. Background information on the procedure

## *1.1. Type II variation*

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Vertex Pharmaceuticals (Ireland) Limited submitted to the European Medicines Agency on 1 April 2021 an application for a variation.

The following variation was requested:

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

Extension of indication for Kalydeco tablets in combination regiment with Kaftrio to include the treatment of adults, adolescents and children aged 6 years and older with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene or heterozygous for F508del and have a minimal function (MF) mutation in the CFTR gene. This application is based on the results of study VX18-445-106, a phase 3, open-label, multicentre study in subjects 6 through 11 years of age, with F/MF and F/F genotypes. As a consequence, sections 4.1, 4.2, 5.1, and 5.2 of the SmPC are updated. The Packaged Leaflet is updated in accordance. Version 12.0 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

## *Information relating to orphan designation*

Kalydeco, was designated as an orphan medicinal product EU/3/08/556 on 8 July 2008.

Kalydeco was designated as an orphan medicinal product in the following indication: treatment of cystic fibrosis (CF).

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

## *Information on paediatric requirements*

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0163/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0163/2020 was not yet completed as some measures were deferred.

### *Information relating to orphan market exclusivity*

### Similarity

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

### *Protocol assistance*

The MAH did not seek Protocol Assistance at the CHMP.

## *1.2. Steps taken for the assessment of the product*

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

Rapporteur: N/A Co-Rapporteur: Agnes Gyurasics

| Timetable | Actual Date |
|---|---|
| Start of procedure | 24 Apr 2021 |
| CHMP Co-Rapporteur Assessment Report | n/a |
| CHMP Rapporteur Assessment Report | 23 Jul 2021 |
| PRAC Rapporteur Assessment Report | 25 Jun 2021 |
| PRAC members comments | n/a |
| Updated PRAC Rapporteur Assessment Report | n/a |
| PRAC endorsed relevant sections of the assessment report[3] | 08 Jul 2021 |
| CHMP members comments | 12 Jul 2021 |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 15 Jul 2021 |
| RSI | 22 Jul 2021 |
| Submission | 13 Aug 2021 |
| CHMP Co-Rapporteur and PRAC Rapporteur Joint Assessment Report | 17 Sep 2021 |
| PRAC Rapporteur Assessment Report | n/a |
| PRAC members comments | n/a |
| Updated PRAC Rapporteur Assessment Report | n/a |
| PRAC endorsed relevant sections of the assessment report[3] | 30 Sep 2021 |
| CHMP members comments | n/a |
| Updated CHMP Rapporteur(s) (Joint) Assessment Report | 13 Oct 2021 |
| 2nd RSI | 14 Oct 2021 |
| Submission | 19 Oct 2021 |
| CHMP Co-Rapporteur | 27 Oct 2021 |
| PRAC/CHMP members comments | 03 Nov 2021 |

| | |
|---|---|
| Updated PRAC/CHMP Rapporteur Assessment Report | 05 Nov 2021 |
| Opinion | 11 Nov 2021 |
| The CHMP adopted a report on similarity (Appendix) | 11 Nov 2021 |

# 2. Scientific discussion

## *2.1. Introduction*

Kalydeco is currently approved in the EU in a combination regimen with Kaftrio (elexacaftor/tezacaftor/ivacaftor; ELX/TEZ/IVA) to treat cystic fibrosis (CF) in patients aged 12 years and older who have at least one F508del mutation in the CFTR gene, regardless of the second CFTR allele (F/any).

This type II variation application seeks to expand the indication of Kalydeco in combination with Kaftrio to patients with CF aged 6 years and older who are homozygous for the F508del mutation in the CFTR gene or heterozygous for F508del and have a minimal function (MF) mutation in the CFTR gene.

### 2.1.1. Problem statement

#### *Disease or condition*

Cystic Fibrosis (CF) is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality, and at present, there is no cure. Cystic fibrosis is caused by mutations in the CFTR gene that result in absent or deficient function of the CFTR protein at the cell surface. The CFTR protein is an epithelial chloride channel contributing to the regulation of salt and water absorption and secretion. The failure to regulate chloride transport in these organs results in the multisystem pathology associated with CF.

In people with CF, loss of chloride transport due to defects in the CFTR protein result in the accumulation of thick, sticky mucus in the bronchi of the lungs, loss of exocrine pancreatic function, impaired intestinal absorption, reproductive dysfunction, and elevated sweat chloride concentration. Lung disease is the primary cause of morbidity and mortality in people with CF.

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

*F508del* is the most common mutation in the CFTR gene, and the vast majority of CF patients (~85.8% in the US and ~82.4% in Europe) have this mutation on at least on 1 allele.

The initially claimed therapeutic indication was as follows: Kalydeco tablets are indicated in a combination regimen with ivacaftor/tezacaftor/elexacaftor tablets for the treatment of adults, adolescents, and children aged 6 years and older with cystic fibrosis (CF) who are homozygous for the F508del mutation in the CFTR gene or heterozygous for F508del and have a minimal function (MF) mutation in the CFTR gene.

## *Epidemiology and screening tools*

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

## *Aetiology and pathogenesis*

CF is an autosomal recessive disease in which disease-causing mutations are present on both *CFTR* alleles that make up a patient's genotype. Severity of CF is determined by the extent of the loss of CFTR-mediated chloride transport caused by the 2 *CFTR* mutant alleles. Historically, these *CFTR* mutations have been categorized in different ways including a class system based on their effect on CFTR protein synthesis or function (Classes I through V) and grouping based on phenotypic expression (e.g., residual CFTR function). To study the impact of CFTR modulators, the MAH has categorized mutations as follows: gating (G), residual function (RF), and minimal function (MF).

Patients with CF who have 2 alleles that result in complete or near complete loss of CFTR-mediated chloride transport (e.g., *F508del*, Class I mutations which make no CFTR protein, gating mutations such as *G551D*) demonstrate severe CF characterized by early onset and relatively rapid disease progression, with sweat chloride concentrations (an in vivo marker of CFTR function) typically greater than 90 mmol/L.

For patients with residual function mutations or those who are partially treated by existing CFTR modulator therapy, further increases in CFTR-mediated chloride transport are expected to be associated with further normalization of physiology and disease consequences.

## *Clinical presentation, diagnosis and stage/prognosis*

CFTR is an ion channel that regulates the flow of chloride and other ions across epithelia in various tissues, including the lungs, pancreas and other gastrointestinal organs, and sweat glands. Decreased CFTR quantity or function results in the failure to regulate chloride transport in these tissues leading to the multisystem pathology associated with CF. Progressive loss of lung function is the leading cause of mortality. The clinical manifestations are those of progressive airway obstruction and bronchiectasis, with periods of worsening pulmonary symptoms associated with a decline in pulmonary function and increased bacterial density in airway secretions (pulmonary exacerbations). Obstruction of airways with thick mucus, establishment of a chronic bacterial infection in the airways, and damaging inflammatory responses are all thought to play a role in causing irreversible structural changes in the lungs, leading to respiratory failure. In addition, poor growth and nutritional status have historically been common in patients with CF owing to a number of factors, including pancreatic insufficiency-related fat malabsorption, increased energy expenditure attributable to progressive lung disease, appetite suppression attributable to chronic infection, and CF-related diabetes.

[1] Cystic Fibrosis Foundation. Patient Registry: 2018 Annual Data Report. Bethesda, MD: Cystic Fibrosis Foundation; 2019.
[2] European Cystic Fibrosis Society. 2017 ECFS Patient Registry Annual Data Report. Karup, Denmark: European Cystic Fibrosis Society; 2019.

### *Management*

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

## 2.1.2. About the product

In the EU, Kalydeco tablets are indicated:

- As monotherapy for the treatment of adults, adolescents, and children aged 6 years and older and weighing 25 kg or more with cystic fibrosis (CF) who have an *R117H CFTR* mutation or one of the following gating (class III) mutations in the cystic fibrosis transmembrane conductance regulator *(CFTR)* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R* (see SmPC sections 4.4 and 5.1).
- In a combination regimen with tezacaftor/ivacaftor tablets for the treatment of adults, adolescents, and children aged 6 years and older with cystic fibrosis (CF) who are homozygous for the F508del mutation or who are heterozygous for the *F508del* mutation and have one of the following mutations in the CFTR gene: *P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T.*
- In a combination regimen with ivacaftor /tezacaftor /elexacaftor tablets for the treatment of adults and adolescents aged 12 years and older with cystic fibrosis (CF) who have at least one *F508del* mutation in the *CFTR* gene (see SmPC section 5.1).

The scope of the present application is to extend the indication of Kalydeco (tablets) in combination with Kaftrio for the treatment of adults and children aged 6 years and older with cystic fibrosis (CF) who have at least one F508del mutation in the CFTR gene.

## 2.1.3. The development programme/compliance with CHMP guidance/scientific advice

This application consisted of results from clinical study 106. No specific advice was requested/provided in relation to this application.

## *2.2. Non-clinical aspects*

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

An The updated Environmental Risk Assessment (ERA) submitted by the MAH for Kalydeco was considered acceptable by the CHMP.

## 2.2.1. Ecotoxicity/environmental risk assessment

An environmental risk assessment of VX-770 (ivacaftor) in Kalydeco (Monotherapy) was submitted in the initial Marketing Authorisation Application dossier for Kalydeco. This assessment was based on a single product at a maximum daily dose of 300 mg. As part of this application, the

MAH provided an ERA for Kalydeco as prescribed alone or in combination with other drugs. The main studies results are summarised in the table below.

**Table 1. Relevant endpoints of the environmental risk assessment of ivacaftor**

| **Substance (INN/Invented Name): VX-770**<br>**CAS-number:** 873054-44-5 | | | | | |
|---|---|---|---|---|---|
| ***PBT screening*** | | **Result** | | | **Conclusion** |
| Bioaccumulation potential –log Kow | | ➢ 4.75 at pH 7 | | | Potential PBT YES |
| ***PBT-assessment*** | | | | | |
| **Parameter** | **Result relevant for conclusion** | | | | **Conclusion** |
| Persistence | $DT_{50}$ | $DT_{50, system}$ = 1233/261 d (sandy silt loam sediment / sand sediment).<br>$DT_{50}$ soil = 166 to 316 days | | | Soil $DT_{50}$ values corrected to 12°C<br>Conclusion: vP |
| Bioaccumulation | BCF | <2000 | | | Not B |
| Toxicity | NOEC (aquatic) | | | | |
| **PBT-statement** | | | | | |
| ***Phase I*** | | | | | |
| ***Calculation*** | **Value** | **Unit** | | | **Remarks** |
| $PEC_{surfacewater}$ Refined | 0.026 | 0.081 µg/L | | | >0.01 threshold Yes |
| Other concerns (e.g. chemical class) | | | | | None |
| ***Phase II Physical-chemical properties and fate*** | | | | | |
| **Study type** | **Test protocol** | **Results** | | | **Remarks** |
| Adsorption-Desorption | OECD 106 | $K_{oc}$ =11800 (sewage sludge)<br>$K_{oc}$ = 10800 (sewage sludge)<br>$K_{oc}$ = 3710 (sandy loam)<br>$K_{oc}$ = 1970 (sandy clay loam)<br>$K_{oc}$ = 5900 (clay loam) | | | Terrestrial studies triggered |
| Ready Biodegradability Test | OECD 301 | Not conducted | | | Considered not ready biodegradable |
| Aerobic Transformation in Aquatic Sediment systems | OECD 308 | $DT_{50}$ water = 4.4 and 1.7 days<br>$DT_{50}$ sediment = 581 and 123 days<br>% shifting to sediment (99 days) =78 % and 50.3% (VX-770); 96.3 % and 96.5% (total radioactivity) | | | No decline rate in the sediment phase could be calculated. |
| ***Phase IIa Effect studies*** | | | | | |
| **Study type** | **Test protocol** | **Endpoint** | **Value** | **Unit** | **Remarks** |
| Algae, Growth Inhibition *(Pseudokirchnerilla subcapita)* | OECD 201 | NOEC | 54.7 | µg/L | Growth rate |
| *Daphnia* sp. Reproduction Test | OECD 211 | NOEC | 3.1 | µg/L | |
| Fish, Early Life Stage Toxicity *(Pimephales promelas)* | OECD 210 | NOEC | 29 | µg/L | |
| Activated Sludge, Respiration Test | OECD 209 | NOEC | 1 x $10^6$ | µg/L | |

## 2.2.2. Discussion on non-clinical aspects

The MAH did not submit new non-clinical data which is considered to be acceptable by the CHMP.

Based on available non-clinical data, the risk of ivacaftor to the environment, as previously assessed, remains low.

### 2.2.3. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of ivacaftor.

- Considering the above data, ivacaftor is not expected to pose a risk to the environment.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

### GCP

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

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

- Tabular overview of clinical studies

**Table 2. Overview of clinical studies submitted**

| Study number | design | patients | duration | Primary objectives | Phase |
|---|---|---|---|---|---|
| VX18-445-106 Part A | Open-label | 16 CF patients 6 through eleven years of age | 15 days | Evaluation of the pharmacokinetics, | completed |
| VX18-445-106 Part B | Open-label | 66 CF patients 6 through eleven years of age | 24 weeks | Evaluation of the safety and tolerability | completed |
| VX19-445-107 | Open-label | CF patients from parent study VX18-445-106 Part B 6 years of age and older | 96 weeks | Evaluation of the long-term safety and tolerability | ongoing |

### 2.3.2. Pharmacokinetics

In support of the current application, the phase 3 study 106 in paediatric CF patients was conducted to evaluate the PK of ELX, TEZ, and IVA administered in triple combination in combination with kalydeco in subjects 6 through 11 years of age, and to assess if target exposures observed in subjects ≥ 18 years of age were achieved in the younger population with the proposed dosing scheme.

For patients 6 through 11 years of age, ELX/TEZ/IVA in combination with Kalydeco is proposed to be administered with fat-containing food as follows:

- Patients weighing <30 kg: ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h (two 50/25/37.5 mg FDC film-coated tablets in the morning and one Kalydeco 75 mg film-coated tablet in the evening)
- Patients weighing ≥30 kg: ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h (two 100/50/75 mg FDC film-coated tablets in the morning and one Kalydeco 150 mg film-coated tablet in the evening)

Based on the provided study 106, in subjects 6 through 11 years of age, it was shown that applying a 30 kg cut-off for the applied normal adult for 50% of the adult dose would result in ELX, TEZ, and IVA exposures most similar to exposures in subjects ≥18 years of age while maintaining M23-ELX and M1-TEZ exposures generally within ranges seen in previous studies of ELX/TEZ/IVA and TEZ/IVA in combination with Kalydeco (see table 3 below).

Further simulation showed that, when applying a 30 kg cut-off, the majority of ELX, TEZ, and IVA exposures for the <30 kg and ≥30 kg weight group were within the exposure range for subjects ≥18 years of age. Exposures for subjects 6 through 11 years of age who weighed ≥30 kg were on the higher end of the exposure range for subjects ≥18 years of age, whereas exposures for subjects who weighed <30 kg were on the lower end of the exposure range (see figure 1 below).

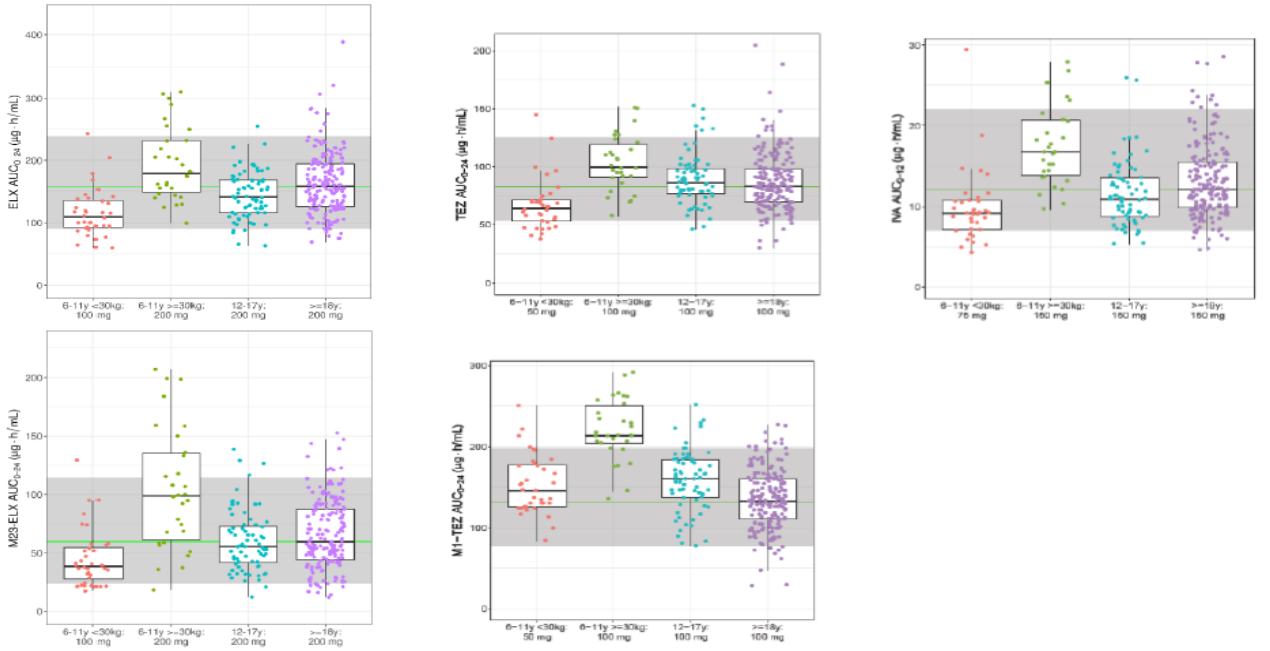
The cut-off weight in paediatric patients (30 kg) for Kaftrio is identical to that for Symkevi (tezacaftor/ivacaftor).

**Table 3. Summary of ELX, M23-ELX, TEZ, M1-TEZ, and IVA observed steady-state AUC by age group, 30-kg weight cut-off (popPK Studies Q075 and Q076)**

| Age Group, Weight | Dose Regimen (ELX/TEZ/IVA) | ELX $AUC_{0-24h}$ (µg·h/mL) | | | M23-ELX $AUC_{0-24h}$ (µg·h/mL) | | | TEZ $AUC_{0-24h}$ (µg·h/mL) | | | M1-TEZ $AUC_{0-24h}$ (µg·h/mL) | | | IVA $AUC_{0-12h}$ (µg·h/mL) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean (SD) | Min, Max | N | Mean (SD) | Min, Max | N | Mean (SD) | Min, Max | N | Mean (SD) | Min, Max | N | Mean (SD) | Min, Max |
| 6 through 11 years | *(Both doses combined)* | 66 | 152 (63.2) | 60, 310 | 66 | 71.9 (49.1) | 17.4, 207 | 66 | 83.4 (29.1) | 37.4, 151 | 66 | 183 (50.0) | 83.8, 291 | 66 | 13.3 (6.09) | 4.23, 29.4 |
| <30 kg | 100 mg qd/ 50 mg qd/ 75 mg q12h | 36 | 116 (39.4) | 60, 243 | 36 | 45.4 (25.2) | 17.4, 129 | 36 | 67.0 (22.3) | 37.4, 145 | 36 | 153 (36.5) | 83.8, 250 | 36 | 9.78 (4.50) | 4.23, 29.4 |
| ≥30 kg | 200 mg qd/ 100 mg qd/ 150 mg q12h | 30 | 195 (59.4) | 99.4, 310 | 30 | 104 (52) | 18.3, 207 | 30 | 103 (23.7) | 57.7, 151 | 30 | 220 (37.5) | 135, 291 | 30 | 17.5 (4.97) | 9.62, 27.9 |
| 12 through 17 years | 200 mg qd/ 100 mg qd/ 150 mg q12h | 72 | 144 (37.5) | 63.3, 255 | 72 | 60.1 (26.3) | 12.2, 139 | 69 | 88.9 (22.4) | 46.1, 152 | 69 | 157 (37.3) | 77.2, 252 | 69 | 11.6 (4.05) | 5.28, 26.0 |
| ≥18 years | 200 mg qd/ 100 mg qd/ 150 mg q12h | 179 | 163 (50.6) | 68.9, 389 | 179 | 65.7 (29.6) | 12, 153 | 186 | 86.4 (24.8) | 30.1, 204 | 186 | 134 (36.8) | 27.8, 227 | 186 | 13.1 (4.58) | 4.57, 28.6 |

Sources: Report Q075/Tables 7 and 8, Report Q076/Tables 7, 19, and 31
ELX: elexacaftor; IVA: ivacaftor; N: total sample size; q12h: every 12 hours; qd: once daily; TEZ: tezacaftor

*Figure 1. Summary of steady-state AUC by age group for ELX, TEZ, IVA, and metabolites (popPK Studies Q075 and Q076)*



Source: Module 5.3.3.5/Report Q075/Figure 7-12, Module 5.3.3.5/Report Q076/Figure 43, Figure 98, and Figure 153
EBE: empirical Bayes estimate; ELX: elexacaftor; IQR: interquartile range; IVA: ivacaftor; TEZ: tezacaftor; y: years of age
Notes: Green horizontal line represents the median of the adult values, and the gray shaded area indicates the 5th and 95th percentiles of the adult values. Boxplots: median is represented by a horizontal line, and the IQR is represented by a box. The whiskers mark the largest and smallest values within 1.5 × IQR. Dots represent individual EBE values.

In this paediatric application, a lower dose Kaftrio tablet is proposed (i.e., ELX 50/TEZ 25/IVA 37.5 mg FDC tablet as compared to the 'adult' ELX 100/TEZ 50/IVA 75 mg FDC tablet). In comparative bioavailability study 011, exposures of ELX, TEZ, and IVA were unchanged in terms of AUC0-inf or Cmax when the study drug was administered as 2 low-dose ELX 50/TEZ 25/IVA 37.5 mg FDC tablets or 1 ELX 100/TEZ 50/IVA 75 mg reference tablet.

## 2.3.3. Pharmacodynamics

There are no new pharmacodynamic studies submitted. However, the pharmacological parameter sweat chloride (SwCl) was studied in the main pivotal study; the results are presented and discussed in below sections of this report (see clinical section).

***Mechanism of action***

Ivacaftor is a *CFTR* potentiator that enhances the channel gating activity of the *CFTR*.

***Primary and secondary pharmacology***

No dedicated primary and secondary pharmacology studies in children 6-12 years were submitted.

## 2.3.4. Discussion on clinical pharmacology

In support of the current application, Phase 3 Study 106 in paediatric CF patients was conducted in order to evaluate the PK of ELX, TEZ, and IVA administered in triple combination in combination with Kalydeco in subjects 6 through 11 years of age, and to assess if target exposures observed in subjects ≥18 years of age were achieved in the younger population with the proposed dosing scheme.

For patients 6 through 11 years of age, ELX/TEZ/IVA in combination with Kalydeco is proposed to be administered with fat-containing food as follows:

- Patients weighing <30 kg: ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h
- Patients weighing ≥30 kg: ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h

The results of Study 106 demonstrated that for subjects 6 through 11 years of age the distributions of individual ELX, TEZ, and IVA in combination with Kalydeco exposures as indicated above were within the range of those observed in subjects ≥18 years of age.

### 2.3.5. Conclusions on clinical pharmacology

The provided integrated assessment of pediatric exposure data, popPK modeling and simulations, of clinical data from subjects 6 through 11 years of age, adolescents, and adults confirmed that from a clinical pharmacology perspective, the proposed dosages with a 30 kg weight cut-off are appropriate for the extrapolation of efficacy to CF subjects 6 through 11 years of age.

## *2.4. Clinical efficacy*

ELX/TEZ/IVA in combination with Kalydeco (ivacaftor, IVA) is currently indicated for the treatment of CF patients aged 12 years and older with at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

The application for an indication extension of ELX/TEZ/IVA in combination with Kalydeco to include CF patients 6 through 11 years of age with at least one F508del mutation was supported by one clinical trial, VX19-445-106. While the protocol of Study VX19-445-107 was submitted, no data provided yet.

- VX18-445-106: Study 106, a Phase 3, multicenter study conducted in 2 parts (Parts A and B) to evaluate the pharmacokinetics (PK), safety, and tolerability of ELX/TEZ/IVA in CF subjects 6 through 11 years of age who are heterozygous for *F508del* and a minimal function (MF) mutation (F/MF genotypes) or homozygous for *F508del* (F/F genotype).
- VX19-445-107: Study 107, a Phase 3, open-label study evaluating the long-term safety and efficacy of VX-445/TEZ/IVA combination therapy in subjects with Cystic Fibrosis who are 6 years of age and older.

Given the underlying pathophysiology of CF, the applicant considered that efficacy in the 6 through 11 years of age group might be extrapolated from data from the controlled Phase 3 studies in CF subjects ≥12 years of age.

### 2.4.1. Dose response studies

No dose-response studies in children 6-12 years were submitted.

## 2.4.2. Main study

**Title of Study:** A Phase 3 Study Evaluating the Pharmacokinetics, Safety, and Tolerability of VX-445/TEZ/IVA Triple Combination Therapy in Cystic Fibrosis Subjects 6 Through 11 Years of Age (study VX18-445-106)

Study VX18-445-106 (referred as Study 106 by the Applicant and hereinafter in this AR) was a Phase 3, open-label, 2-part (Parts A and B), multicenter study in subjects 6 through 11 years of age, with F/MF and F/F genotypes. Part A evaluated the PK, safety, and tolerability of ELX/TEZ/IVA administered for 15 days to confirm a dose for Part B. Part B evaluated the safety, tolerability, and PK of ELX/TEZ/IVA administered for 24 weeks; efficacy assessments were also included as secondary endpoints.

### *Methods*

Figure 2 shows the study design of part A. Subjects (F/F or F/MF genotypes) were planned for enrolment. A review of safety, tolerability, and available PK data was completed by an internal MAH team after Part A to confirm the doses for Part B.

**Figure 2. Part A Study Design**

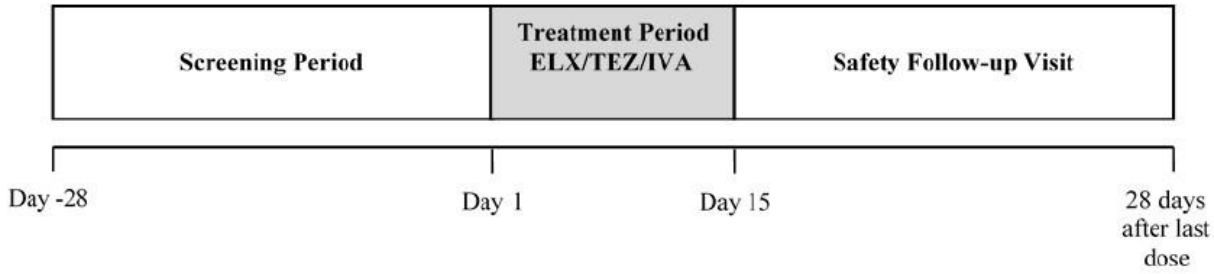
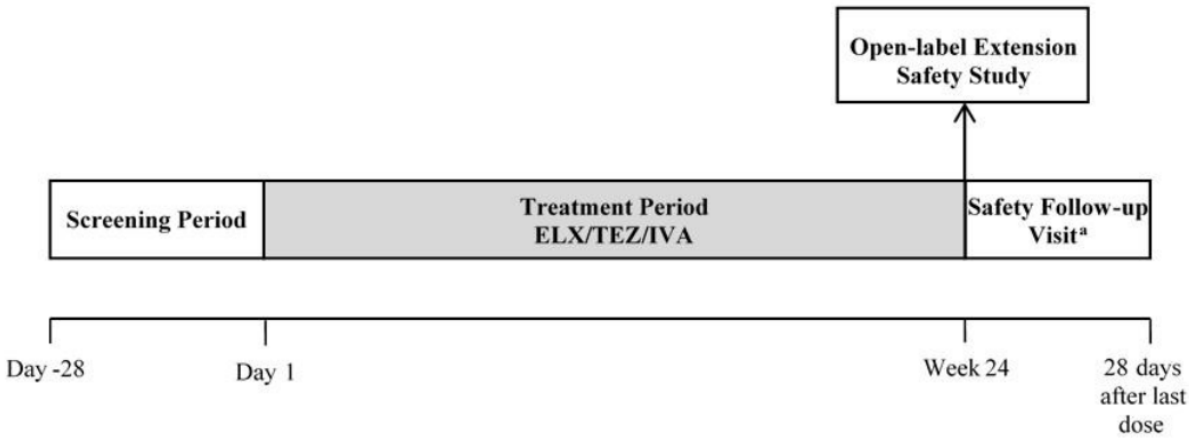



Figure 3. shows the study design of part B.

Subjects who completed the Part B Treatment Period and did not permanently discontinue the study drug could enrol in an optional open-label extension safety study (enrolment was based on the eligibility criteria specified within the Open-label Extension Safety Study protocol).

**Figure 3. Part B Study Design**



[a] The Safety Follow-up Visit was scheduled to occur 4 weeks (± 7 days) after the last dose. This visit was not required for subjects who enrolled in an optional open-label extension safety study within 28 days of the last dose.

## Study participants

The in- and exclusion criteria were identical for parts A and part B

*Inclusion criteria*

1. Subject (or his or her legally appointed and authorized representative) signed and dated an ICF, and an assent form.
2. Subjects (males and/or females), 6 through 11 years of age, inclusive, on the date of informed consent.
3. Subjects who weighed ≥ 15 kg without shoes at the Screening Visit.
4. Confirmed diagnosis of CF as determined by the investigator.
5. Subjects who are homozygous for F508del (F/F genotype) or heterozygous for F508del and an MF mutation that is not responsive to IVA and TEZ/IVA (F/MF genotypes)
    - Genotype was confirmed at the Screening Visit. This assessment did not need to be repeated for confirmed subjects in Part A who wished to participate in Part B.
    - If the screening CFTR genotype result was not received before the first dose of study drug, a previous CFTR genotype laboratory report could be used to establish eligibility.
    - Subjects who were enrolled and whose screening genotype did not confirm study eligibility were discontinued from the study
6. Subjects with FEV1 ≥40% of predicted normal for age, sex, and height using equations of the Global Lung Function Initiative (GLI) at the Screening Visit. Spirometry measurements must have met American Thoracic Society/European Respiratory Society criteria for acceptability and repeatability.
7. Subjects with stable CF disease at the start of the Treatment Period as deemed by the investigator.
8. Subjects who were willing to remain on a stable CF medication regimen (other than CFTR modulators) through Day 15 (Part A) or through Week 24 (Part B) or, if applicable, through the Safety Follow-up Visit.
9. Subjects who were able to swallow tablets.
10. Female subjects had a negative serum pregnancy test at the Screening Visit.
11. Subjects of childbearing potential and who were sexually active met the contraception requirements
12. As deemed by the investigator, the subject's legally appointed and authorized representative (e.g., parent or legal guardian) AND the subject were able to understand protocol requirements, restrictions, and instructions. The subject's legally appointed and authorized representative was able to ensure that the subject would comply with and be likely to complete the study as planned.

*Exclusion criteria*

1. History of any illness or any clinical condition that, in the opinion of the investigator, could confound the results of the study or pose an additional risk in administering study drug(s) to the subject. This included, but was not limited to, the following:
    - Clinically significant cirrhosis with or without portal hypertension.
    - Solid organ or haematological transplantation.
    - Alcohol or drug abuse in the past year, including, but not limited to, cannabis, cocaine, and opiates, as deemed by the investigator.
    - Cancer, except for squamous cell skin cancer, basal cell skin cancer, and Stage 0 cervical carcinoma in situ (all 3 with no recurrence for the last 5 years).
2. Any clinically significant laboratory abnormalities at the Screening Visit that would interfere with the study assessments or pose an undue risk for the subject (as deemed by the investigator).
3. Any of the following abnormal laboratory values at screening:
    - Hemoglobin <10 g/dL
    - Total bilirubin ≥2 × upper limit of normal (ULN)
    - Aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), or alkaline phosphatase (ALP) ≥3 × ULN
    - Abnormal renal function defined as glomerular filtration rate ≤45 mL/min/1.73 m2 (calculated by the Counahan-Barratt equation)
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. Lung infection with organisms associated with a more rapid decline in pulmonary status (including, but not limited to, *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*). For subjects who have had a history of a positive culture, the investigator will apply the following criteria to establish whether the subject is free of infection with such organisms:
    - The subject has not had a respiratory tract culture positive for these organisms within the 12 months before the date of informed consent and assent.
    - The subject has had at least 2 respiratory tract cultures negative for such organisms within the 12 months before the date of informed consent, with the first and last of these separated by at least 3 months, and the most recent one within the 6 months before the date of informed consent and assent.
6. An acute illness not related to CF (e.g., gastroenteritis) within 14 days before the first dose of study drug (Day 1).
7. Ongoing or prior participation in an investigational drug study (including studies investigating VX-445 with or without coadministration with other study drugs) within 28 days of the Screening Visit.
    - A washout period of 5 terminal half-lives of the previous investigational study drug, or **28** days, whichever is longer, must elapse before the Screening Visit.
    - The duration of the elapsed time may be longer if required by local regulations.

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

8. Use of restricted medication, including moderate or strong CYP3A inducers, moderate or strong CYP3A inhibitors, and CFTR modulators (except for study drug).
9. The subject or a close relative of the subject is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study.

## Treatments

Doses administered in the Part A and Part B of Study 106 are presented in Table 4.

Part A

The ELX dose of 100 mg qd selected for evaluation in Part A was determined based on population-PK modeling utilizing data from adults and simulating exposures over a range of body weights typical for a population of 6- to <12-year-olds, ranging from 15 to 50 kg. Based on the simulations, an ELX dose of 100 mg qd was predicted to provide exposures that would not exceed the exposures observed in adults dosed with 200 mg qd. Hence, the ELX 100-mg qd dose was predicted to be safe and was evaluated in Part A for all subject weight groups.

Part B

- ELX Dosage

Subjects in the higher weight range were administered ELX 200 mg qd. The appropriate weight cut-off for the switch from 100 mg qd to 200 mg qd was determined based on population-PK modelling that was updated with preliminary PK data from Part A and data from studies conducted in adult and adolescent CF subjects.

- TEZ and IVA Dosages

TEZ was administered as 50 mg qd and IVA was administered as 75 mg every 12 hours (q12h) in all subjects in Part A and in subjects weighing <30 kg in Part B. In part B, doses of TEZ 100 mg qd and IVA 150 mg q12h were administered in subjects weighing ≥30 kg. The dosages and weight cut-off were selected based on an evaluation of PK and safety of TEZ/IVA in CF subjects 6 to 11 years of age in Part A of Study 661-113.

**Table 4. Parts A and B Doses**

| Subject Weight at Day 1 | ELX Dose | TEZ Dose | IVA Dose |
|---|---|---|---|
| **Part A** | | | |
| All subjects | 100 mg qd | 50 mg qd | 75 mg q12h |
| **Part B** | | | |
| <30 kg | 100 mg qd | 50 mg qd | 75 mg q12h |
| ≥30 kg | 200 mg qd | 100 mg qd | 150 mg q12h |

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

*Treatment modification, interruption and discontinuation*

Modifications of the study drug dose were prohibited. Should any unacceptable toxicity arise, individual subjects were withdrawn from the study and dosing ceased.

- Liver Function Tests

In subjects who interrupted study drug for >72 hours for any reason, the investigator resumed the study drug only after a thorough investigation of the cause for the interruption. The medical monitor was to be notified.

Subjects with new treatment-emergent ALT or AST elevations of >3 × ULN, with or without total bilirubin >2 × ULN, were followed closely, including confirmatory testing performed by the central laboratory within 48 to 72 hours of the initial finding and subsequent close monitoring of ALT, AST, and bilirubin levels, as clinically indicated. If a subject could not return to the site for confirmatory testing, the use of a local laboratory was permitted.

Study drug administration was interrupted immediately (prior to confirmatory testing) if any of the following criteria were met:

• ALT or AST >8 × ULN

• ALT or AST >5 × ULN for more than 2 weeks

• ALT or AST >3 × ULN, in association with total bilirubin >2 × ULN and/or clinical jaundice.

A thorough investigation of potential causes was conducted, and the subject was followed closely for clinical progression.

Study drug administration was discontinued if the following criteria were met:

• Subsequent ALT or AST values confirmed the initial elevation that satisfied the interruption rule (above), and no convincing alternative etiology was identified, regardless of whether transaminase levels had improved.

All subjects in whom treatment was discontinued for elevated transaminases (and bilirubin, as applicable) had these levels monitored closely until levels normalized or returned to baseline.

If an alternative, reversible cause of transaminase elevation with or without increased bilirubin or clinical jaundice was identified, study drug administration was permitted to resume once transaminases returned to baseline or were ≤2 ×ULN, whichever was higher. Regardless of the duration of the interruption, the medical monitor was notified prior to resumption of the study drug.

Upon resumption of the study drug, transaminases and bilirubin were assessed weekly for 4 weeks.

If a protocol-defined transaminase elevation interruption threshold recurred within 4 weeks of rechallenge with the study drug (with confirmation of the initial elevation by repeat testing within 48 to 72 hours), then the study drug was permanently discontinued, regardless of the presumed etiology.

- Rash

Individuals who developed a generalized rash were monitored closely. Study drug dosing was interrupted if a subject developed a generalized rash of Grade 3 or higher, or a rash that was considered a serious adverse event (SAE). The investigator notified the medical monitor of any rash that resulted in interruption of study drug, is Grade 3 or higher or was an SAE. Investigators were to consider additional evaluation including laboratory testing (e.g., complete blood count with differential, liver function tests [LFTs]), photographs of the rash, and dermatology consultation. The investigator could consider resumption of study drug if considered clinically appropriate.

*Duration of Dosing*

For Part A, the 15-day duration of dosing was chosen to provide an adequate assessment of PK, safety, and tolerability of ELX/TEZ/IVA before exposing subjects to a longer duration of treatment.

For part B, the 24-week duration of dosing was chosen to provide an adequate assessment of long-term safety.

*Prohibited Medications*

Prohibited medication was identical for parts A and part B. Table 5. lists prohibited medications

**Table 5. Prohibited Medications**

| Medication | Timing of Restriction: Start of Restriction | Timing of Restriction: End of Restriction | Rationale |
|---|---|---|---|
| Moderate and strong CYP3A inducers | None allowed within 14 days before the first dose of the study drug on Day 1 | None allowed through completion of study participation | ELX, TEZ, and IVA are metabolized extensively via CYP3A4. Therefore, use of moderate and strong inducers and inhibitors of CYP3A, which have the potential to alter the exposure of ELX, TEZ, or IVA, was prohibited. |
| Moderate and strong CYP3A inhibitors (except ciprofloxacin)[a] | None allowed within 14 days before the first dose of the study drug on Day 1 | None allowed through completion of study participation | |
| CFTR modulators (investigational or approved), except for study drugs | None allowed within 28 days before the first dose of the study drug on Day 1 | None allowed until after the last dose of study drug | These agents could confound the results of this study. |

ELX: elexacaftor; IVA: ivacaftor; TEZ: tezacaftor

[a] Ciprofloxacin is not a moderate CYP3A inhibitor on the basis of results of a drug-drug interaction study conducted with IVA, a sensitive CYP3A substrate (Kalydeco [ivacaftor] US Package Insert).

*Prior and Concomitant Medications*

Prior and concomitant medication rules were identical for parts A and part B.

Information regarding prior and concomitant medications, including CF medications, other medications, and herbal and naturopathic remedies, was collected from each subject's source documentation for medications taken within 56 days before the Screening Visit through completion of study participation. Guidelines for concomitant medication use were as follows:

- Subjects were to remain on a stable treatment regimen for their CF from 28 days before the Day 1 Visit through completion of study participation.
- Subjects could receive doses of prednisone or prednisolone of up to 10 mg/day chronically, or up to 60 mg daily for up to 5 days.
- Substrates of organic anion transporting polypeptide (OATP)1B1 and OATP1B3, such as statins, glyburide, nateglinide, and repaglinide, were used with caution because ELX may inhibit OATP1B1 and OATP1B3.
- Digoxin or other substrates of P-glycoprotein (P-gp) with a narrow therapeutic index, such as cyclosporine, everolimus, sirolimus, and tacrolimus, were used with caution and appropriate monitoring because IVA is a weak inhibitor of P-gp.
- IVA may inhibit CYP2C9; therefore, during coadministration with warfarin, additional monitoring of the international normalized ratio was recommended. Other medicinal products that are CYP2C9 substrates for which exposure may be increased include glimepiride and glipizide; these were used with caution.

- Information about bronchodilator use during the study was collected and documented. Subjects who were using a bronchodilator had their spirometry assessments performed according to the guidelines.

## Objectives

**Primary Objectives**

Part A: to evaluate the pharmacokinetics (PK) of ELX, TEZ, and IVA when dosed in triple combination

Part B: to evaluate the safety and tolerability of ELX/TEZ/IVA through Week 24

**Secondary Objectives**

Part A

To evaluate the PK of ELX, TEZ, and IVA metabolites

To evaluate the safety and tolerability of ELX/TEZ/IVA

Part B

To evaluate the efficacy of ELX/TEZ/IVA through Week 24

To evaluate the PK of ELX, TEZ, and IVA

To evaluate the PK of ELX, TEZ, and IVA metabolites

## Outcomes/endpoints

**Criteria for evaluation**

Part A

- Primary: PK of ELX, TEZ, and IVA when dosed in TC
- Secondary:
  - PK of ELX, TEZ, and IVA metabolites
  - safety and tolerability of ELX/TEZ/IVA

Part B

- Primary: safety and tolerability of ELX/TEZ/IVA through Week 24:

  Adverse events (AEs), clinical laboratory assessments (serum chemistry, hematology, coagulation, and urinalysis), standard 12-lead ECGs, vital signs, pulse oximetry, ophthalmologic examinations, and physical examinations (PEs)
- Secondary:
  - PK of ELX, TEZ, and IVA metabolites
  - Efficacy and PD:

    Spirometry and sweat chloride (SwCl)

Weight, height, body mass index (BMI), Cystic Fibrosis Questionnaire-Revised (CFQ-R), multiple-breath washout, and other events related to outcome (e.g., pulmonary exacerbations [PEx])

Exploratory: Fecal elastase-1 (FE-1) and immunoreactive trypsinogen (IRT) to assess exocrine pancreatic function

*Spirometry*

The following measured spirometric values were converted to percent predicted values using the standard equations of GLI: FEV1 (L), forced vital capacity (FVC) (L), FEV1/FVC (ratio), and forced expiratory flow, midexpiratory phase (L/s).

*Multiple-breath Washout* (N2-MBW)

The final LCI value at each visit was the value provided by the LCI vendor based on the replicates.

During the Screening Period, the MBW test could be performed pre- or post-bronchodilator. At all other visits, all MBW tests were performed "pre-bronchodilator"

*Drug Acceptability Assessment*

The acceptability of study drug was assessed by the investigator and authorized designee through the Modified Facial Hedonic Scale.

Subjects were observed for their facial expressions, and the reaction was scored using a visual analog scale; any spontaneous comments in regard to likes or dislikes were also noted.

## Sample size, Randomisation and Blinding (masking)

Part A

Approximately 12 subjects (F/F or F/MF genotypes) were planned for enrolment.

Part B

Approximately 56 subjects (F/F or F/MF genotypes) were planned for enrolment to ensure approximately 45 subjects completed Part B. Target enrolment was approximately 25 subjects with F/MF genotypes and 20 subjects with F/F genotypes.

With 45 subjects expected to complete Part B, there is a 90% chance of observing an AE in at least 1 subject if the true incidence rate is 5%, and a >95% chance of observing an AE in at least 1 subject if the true incidence rate is 10%.

As all subjects were treated identically, no randomization was planned.

This was an open-label study; however, subjects and their legally appointed and authorized representative (e.g., parent or legal guardian) were not informed of their study-related spirometry and LCI, sweat chloride (SwCl), fecal elastase-1 (FE-1), and immunoreactive trypsinogen (IRT) results during the Treatment Period, regardless of whether the subject permanently discontinued treatment.

As study 106 is an open-label single arm trial, no formal sample size calculation, randomisation or blinding was performed by the MAH.

## Statistical methods

- PK Analyses

Individual concentration values of each analyte (ELX, TEZ, IVA, and relevant metabolites) were listed, and summary statistics for concentrations of each analyte were presented.

- Efficacy and PD Analyses

*Part A*
Efficacy was not an objective of Part A. Descriptive statistics based on the Full Analysis Set (FAS) were summarized for spirometry; SwCl; and weight, height, BMI, and their respective z-scores.

*Part B*
As efficacy is a secondary objective of the study, there was no multiplicity adjustment; all P values are considered nominal.

Table 6. describes the main efficacy analyses based on the FAS. Each continuous efficacy and PD endpoint was analysed using a mixed-effects model for repeated measures that included visit as the fixed effect, with the baseline value of the efficacy variable and genotype group (F/F or F/MF) as covariates. The model included all measurements of the efficacy variable up to Week 24 (inclusive), whether assessed on treatment or after treatment discontinuation.

**Table 6. Efficacy and PD Endpoints and Methods**

| Endpoint | Method of Analysis |
|---|---|
| **Primary Efficacy Endpoint** | |
| Not applicable | Not applicable |
| **Secondary Efficacy and PD Endpoints** | |
| Absolute change in $ppFEV_1$ from baseline through Week 24 | • MMRM with clinic-assessed spirometry data only<br>• LS mean (95% CI) and *P* value through Week 24<br>• Line plot<br>• Sensitivity analysis (multiple imputation analysis)<br>• Ad hoc subgroup analysis by genotype group (F/F or F/MF) |
| Absolute change in SwCl from baseline through Week 24 | • MMRM<br>• LS mean (95% CI) and *P* value through Week 24<br>• Line plot<br>• Ad hoc subgroup analysis by genotype group (F/F or F/MF) |
| Absolute change in CFQ-R RD score (Child's Version) from baseline through Week 24 | • MMRM with clinic-assessed data only<br>• LS mean (95% CI) and *P* value through Week 24<br>• Line plot<br>• Ad hoc subgroup analysis by genotype group (F/F or F/MF) |
| Absolute change in BMI and BMI-for-age z-score from baseline at Week 24 | • MMRM<br>• LS mean (95% CI) and *P* value at Week 24<br>• Line plot |
| Absolute change in weight and weight-for-age z-score from baseline at Week 24 | • MMRM<br>• LS mean (95% CI) and *P* value at Week 24<br>• Line plot |
| Absolute change in height and height-for-age z-score from baseline at Week 24 | • MMRM<br>• LS mean (95% CI) and *P* value at Week 24<br>• Line plot |
| Drug acceptability assessment using Modified Facial Hedonic Scale | • Descriptive statistics (by category) with clinic-assessed data only |
| Number of PEx and CF-related hospitalizations through Week 24 | • Descriptive statistics (annualized event rate) |
| Absolute change in $LCI_{2.5}$ from baseline through Week 24 | • MMRM<br>• LS mean (95% CI) and *P* value through Week 24<br>• Line plot<br>• Ad hoc subgroup analysis by genotype group (F/F or F/MF) |
| **Other/Exploratory Efficacy Endpoints** | |
| Absolute change in FE-1 levels from baseline at Week 24 | • Descriptive statistics<br>• Shift from baseline analysis |
| Absolute change in serum levels of IRT from baseline at Week 24 | • Descriptive statistics<br>• Shift from baseline analysis |

BMI: body mass index; CF: cystic fibrosis; CFQ-R RD: Cystic Fibrosis Questionnaire-Revised respiratory domain; COVID-19: coronavirus disease; FE-1: fecal elastase-1; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a *CFTR* minimal function mutation; IRT: immunoreactive trypsinogen; $LCI_{2.5}$: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value; LS: least squares; MMRM: mixed-effects model for repeated measures; PD: pharmacodynamic; PEx: pulmonary exacerbation; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride

Note: Due to the COVID-19 pandemic, spirometry ($ppFEV_1$), CFQ-R RD score, and the drug acceptability assessment were permitted to be assessed independently by the subjects (and the subject's parent/caregiver, as applicable) at home; these home-assessed data were not included in the clinic-assessed only analyses.

- Safety Analyses

All safety analyses were conducted for Parts A and B separately, based on data from the corresponding Treatment-emergent (TE) Period in the Safety Set (Table 7.). The overall safety profile of study drug was assessed in terms of the following safety and tolerability endpoints: treatment-emergent adverse events (TEAEs), clinical laboratory values, standard 12-lead ECGs, vital signs, pulse oximetry, and ophthalmologic examinations. All AEs were coded according to MedDRA and were classified as pre-treatment, treatment-emergent, or post-treatment. Only descriptive analysis of safety was performed;

no statistical testing was performed. For the purpose of the results, discussion, and conclusions in this clinical study report, TEAEs are referred to as AEs.

**Table 7. Safety Data Summaries**

| Assessment | Incidence | Raw Value and Change From Baseline | Subject Listing | Threshold Analysis | Shift From Baseline | Plot of Max Values |
|---|---|---|---|---|---|---|
| TEAEs | X | | X | | | |
| Non-LFT chemistry | | X | X | Selected parameters; Part B only | | |
| LFT chemistry | | X | X | X | X | Part B only |
| Hematology and coagulation | | X | X | Selected parameters; Part B only | | |
| Urinalysis | | | X | | | |
| Urine or serum pregnancy test | | | X | | | |
| 12-lead ECGs | | X | X | Selected parameters | | |
| Vital signs | | X | X | Selected parameters | | |
| Pulse oximetry | | X | X | | X | |
| PEs | | | X | | | |
| OEs | | | X | | | |

LFT: liver function test; OE: ophthalmologic examination; PE: physical examination; TEAE: treatment-emergent adverse event
Note: Analyses apply to both Parts A and B unless otherwise specified.

- **Analyses Sets**

Safety Set

The Safety Set will include all subjects who received at least 1 dose of study drug. The Safety Set will be used for all safety analyses.

Full Analysis Set (FAS)

The FAS will include all subjects who are enrolled and carry the intended CFTR allele mutation and received at least 1 dose of study drug. The FAS will be used to summarize subject demographics and baseline characteristics, and for analyses of all efficacy and PD endpoints, unless otherwise specified.

All Subjects Set

The All Subjects Set will include all subjects who are enrolled or received at least 1 dose of study drug. This analysis set will be used for all individual subject data listings and disposition summary tables, unless otherwise specified.

## *Results*

## Participant flow

In Part A, 16 subjects received at least 1 dose of study drug, all of whom completed study drug treatment and the study.

In Part B, 66 subjects received at least 1 dose of study drug, 64 (97.0%) of whom completed study drug treatment and the study; 1 subject discontinued due to an AE, and 1 subject withdrew consent (not due to AE).

**Table 8. Subject Disposition (All Subjects Set, Part B)**

| Disposition | ELX/TEZ/IVA n (%) |
|---|---|
| All Subjects Set | 66 |
| FAS | 66 |
| Safety Set | 66 |
| Completed treatment | 64 (97.0) |
| Prematurely discontinued treatment | 2 (3.0) |
| Reason for discontinuation of treatment | |
| AE | 1 (1.5) |
| Other[a] | 1 (1.5) |
| Completed study | 64 (97.0) |
| Prematurely discontinued the study | 2 (3.0) |
| Reason for discontinuation from study | |
| AE | 1 (1.5) |
| Withdrawal of consent (not due to AE) | 1 (1.5) |
| Rollover to the extension study | 64 (97.0) |

AE: adverse event; COVID-19: coronavirus disease; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; TEZ: tezacaftor

Note: The All Subjects Set included all subjects who were enrolled or received at least 1 dose of study drug (in Part B). The FAS included all enrolled subjects who carry the intended *CFTR* allele mutation and received at least 1 dose of study drug. The Safety Set included all subjects who received at least 1 dose of study drug.

[a] The subject did not want to leave home due to the COVID-19 pandemic and therefore switched to commercially available drug

## Recruitment

Part A

Subjects were enrolled at 6 sites in the US.

Study initiation: 02 October 2018 (date first eligible subject signed the informed consent form)

Study completion: 16 January 2019 (date last subject completed the last visit)

Part B

In Part B, subjects were enrolled at 21 sites in North America, Europe, and Australia.

Study initiation: 05 August 2019 (date first eligible subject signed the informed consent form)

Study completion: 07 August 2020 (date last subject completed the last visit)

## Conduct of the study

Changes in study protocol

The study protocol was amended twice. Table 9. lists the protocol versions, amendment dates, and key changes in study conduct specified in each amendment.

**Table 9. Summary of Study VX18-445-106 Protocol Changes**

| Protocol Version | Date | Key Changes |
|---|---|---|
| 1.0 | 18 May 2018 | Original version |
| 2.0 | 07 June 2019 | Due to the timing, changes were applicable to Part B only.<br>• Updated endpoints to add PEx and CF-related hospitalizations as secondary endpoints, remove $LCI_{5.0}$ exploratory endpoint, and remove Week 12 endpoints for $ppFEV_1$, SwCl, and CFQ-R.<br>• Adjusted the dose justification and weight cutoff based on Part A data. Specified that weight-based dosing would be based on Day 1 weight.<br>• Updated pregnancy testing to apply to all female subjects and updated contraception requirements accordingly.<br>• Removed G6PD deficiency and history of hemolysis as exclusion criteria; updated associated study drug interruption rules.<br>• Updated assessments to change number and timing of DNA sample; add urinalysis assessment to additional visits and further efficacy/PD assessments to the ETT visit; remove duplicative OE and provide flexibility in timing of required OE; remove a blood biomarker sample (subjects <17 kg), drug and alcohol testing, and Day 15 CFQ-R assessment; and allow FE-1 baseline sample collection at screening.<br>• Added requirement for stable CF disease in inclusion criterion 7. Also deleted exclusion criterion 12 as redundant and disallowed screening data from a previous Vertex study to be used for confirming eligibility.<br>• Specified planned target enrollments of F/MF and F/F subjects.<br>• Allowed use of herbal and dietary supplements; allowed use of OATP1B1 substrates with caution per updated data. Provided additional guidance on cycling antibiotics, P-gp and CYP2C9 substrates, prednisone, and bronchodilator use.<br>• Updated guidance on missed doses, and on study drug interruption and stopping rules.<br>• Provided additional details on efficacy/PD analysis and baseline definition, and updated FE-1 and IRT endpoints to "at" rather than "through" analysis. |
| 3.0 | 18 December 2019 | • Removed 120-minute predose assessment window due to clinical site feedback on feasibility, and given experience in other studies showing that timing of predose clinical assessments was not critical for data quality.<br>• Removed restriction against performing blood collection at the same time as sweat chloride collection in Part B; no effect on data quality was expected.<br>• In light of negative thorough QTc results, removed requirement for subjects with QTcF above threshold value to discontinue study drug treatment. |

CF: cystic fibrosis; CFQ-R: Cystic Fibrosis Questionnaire-Revised; ETT: Early Termination of Treatment; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a *CFTR* minimal function mutation; FE-1: fecal elastase-1; IRT: immunoreactive trypsinogen; $LCI_{5.0}$: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/20th of its starting value; OATP1B1: organic anion transporting polypeptide 1B1; OE: ophthalmologic examination; P-gp: P-glycoprotein; PD: pharmacodynamic; PEx: pulmonary exacerbation; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SwCl: sweat chloride

Changes in the SAP

There were no changes to the SAP. The current SAP Version 3.0 is dated 11 August 2020.

Changes in Study Conduct Due to COVID-19

Vertex implemented safety measures to provide subjects with the opportunity to continue participation in Study 106 Part B while ensuring their safety by minimizing the risk to COVID-19 exposure through travel; the conduct of Part A was not impacted by the COVID-19 pandemic. These operational adjustments were implemented to align with Health Authority guidance ensuring the protection of subjects, investigators, and site personnel while maintaining compliance with GCP and minimizing impact to study integrity.

Implemented measures were enabled based on the country and local regulations and site-level considerations (e.g., whether sites had subjects actively participating in Study 106, or site closures due to COVID-19).

In particular, subjects who missed the Week 24 visit were requested to return and complete an unscheduled visit to capture safety laboratory testing missed due to the COVID-19 pandemic, as well as any AEs related to laboratory testing. If feasible, efficacy data (spirometry, SwCl, and LCI) were also collected at the same unscheduled visit, but this was not mandatory.

In addition to their usual review of central laboratory data, investigators were responsible for reviewing local laboratory data to identify potential AEs. These data were entered into this database if all supporting documentation (e.g., laboratory certification) were received; available local laboratory data were provided in individual subject listings.

## Baseline data

Demographics and Other Baseline Characteristics

The mean population age was 9.3 years, and over half (59.1%) of the subjects were female. The majority of subjects (87.9%) were White, and none were Hispanic or Latino. A total of 29 (43.9%) subjects had an F/F genotype, and 37 (56.1%) subjects had F/MF genotypes, with 15 distinct F/MF genotypes represented. At baseline, the mean ppFEV$_1$ was 88.8% and mean SwCl was 102.2 mmol/L. The most common concomitant medications were typically used for the management of CF.

**Table 10 Subject Demographics (FAS, Part B)**

| Demographic | ELX/TEZ/IVA N = 66 |
|---|---|
| Sex, n (%) | |
| Male | 27 (40.9) |
| Female | 39 (59.1) |
| Childbearing potential[a], n (%) | |
| Yes | 39 (100.0) |
| No | 0 |
| Age at baseline (years) | |
| n | 66 |
| Mean (SD) | 9.3 (1.9) |
| Median | 9.6 |
| Min, max | 6.1, 12.1[b] |
| Ethnicity, n (%) | |
| Hispanic or Latino | 0 |
| Not Hispanic or Latino | 58 (87.9) |
| Not collected per local regulations | 8 (12.1) |
| Race, n (%) | |
| White | 58 (87.9) |
| Asian | 1 (1.5) |
| Not collected per local regulations | 8 (12.1) |
| Geographic region, n (%) | |
| North America | 47 (71.2) |
| Europe and Australia | 19 (28.8) |

ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; N: total sample size; n: size of subsample; TEZ: tezacaftor

Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. If a subject was reported to have multiple races, then the subject was counted for each race reported.

[a] Percentages of childbearing females were based on the number of females in the FAS. In Part A, which was conducted under Version 1.0 of the protocol, childbearing potential was defined as female subjects ≥10 years of age. In Part B, conducted under Version 2.0 or later, no age limit was placed on childbearing potential.

[b] One subject provided written informed consent/assent several days before her 12th birthday but enrolled after reaching 12 years of age.

**Table 11. Baseline Characteristics (FAS, Part B)**

| Characteristic | ELX/TEZ/IVA N = 66 |
|---|---|
| *CFTR* genotype group, n (%) | |
| F/F | 29 (43.9) |
| F/MF | 37 (56.1) |
| Weight group, n (%) | |
| <30 kg | 36 (54.5) |
| ≥30 kg | 30 (45.5) |
| Weight (kg) | |
| n | 66 |
| Mean (SD) | 30.0 (7.7) |
| Median | 29.0 |
| Min, max | 18.1, 53.6 |
| Weight z-score[a] | |
| n | 66 |
| Mean (SD) | -0.22 (0.76) |
| Median | -0.23 |
| Min, max | -2.45, 1.34 |
| Height z-score[a] | |
| n | 66 |
| Mean (SD) | -0.11 (0.98) |
| Median | -0.05 |
| Min, max | -2.42, 2.09 |
| BMI ($kg/m^2$)[b] | |
| n | 66 |
| Mean (SD) | 16.39 (1.69) |
| Median | 16.25 |
| Min, max | 13.36, 20.94 |
| BMI z-score[a] | |
| n | 66 |
| Mean (SD) | -0.16 (0.74) |
| Median | -0.20 |
| Min, max | -2.16, 1.13 |

| | |
|---|---|
| $ppFEV_1$ category at baseline, n (%) | |
| <70 | 10 (15.2) |
| ≥70 to ≤90 | 22 (33.3) |
| >90 | 30 (45.5) |
| Missing | 4 (6.1) |
| $ppFEV_1$ (%) at baseline | |
| n | 62 |
| Mean (SD) | 88.8 (17.7) |
| Median | 89.3 |
| Min, max | 39.0, 127.1 |
| Sweat chloride (mmol/L) at baseline | |
| n | 62 |
| Mean (SD) | 102.2 (9.1) |
| Median | 101.5 |
| Min, max | 75.5, 122.0 |
| CFQ-R respiratory domain score (child's version) at baseline | |
| n | 65 |
| Mean (SD) | 80.3 (15.2) |
| Median | 83.3 |
| Min, max | 33.3, 100.0 |
| $LCI_{2.5}$ at baseline | |
| n | 53 |
| Mean (SD) | 9.77 (2.68) |
| Median | 9.21 |
| Min, max | 6.86, 20.14 |
| Prior use of CFTR modulator, n (%)[c] | |
| Yes | 14 (21.2) |
| No | 52 (78.8) |
| Prior use of dornase alfa, n (%)[c] | |
| Yes | 54 (81.8) |
| No | 12 (18.2) |
| Prior use of azithromycin, n (%)[c] | |
| Yes | 19 (28.8) |
| No | 47 (71.2) |
| Prior use of inhaled antibiotic, n (%)[c] | |
| Yes | 8 (12.1) |
| No | 58 (87.9) |
| Prior use of any bronchodilator, n (%)[c] | |
| Yes | 61 (92.4) |
| No | 5 (7.6) |
| Prior use of any inhaled bronchodilator, n (%)[c] | |
| Yes | 61 (92.4) |
| No | 5 (7.6) |
| Prior use of any inhaled hypertonic saline, n (%)[c] | |
| Yes | 52 (78.8) |
| No | 14 (21.2) |
| Infection with *Pseudomonas aeruginosa* within 2 years prior to screening, n (%) | |
| Positive | 26 (39.4) |
| Negative | 40 (60.6) |

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

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

[a] Z-scores were calculated using National Center for Health Statistics growth charts.

[b] BMI = weight / (height × height) ($kg/m^2$).

[c] Includes medications administered during the 56 days before the first dose of study drug in Part B.

Table 12 summarizes concomitant medications received by at least 20% of subjects overall by PN. The most common concomitant medications were typically used for the management of CF.

**Table12. Concomitant Medications Received by At Least 20% of Subjects by PN (FAS, Part B)**

| Preferred Name | ELX/TEZ/IVA N = 66 n (%) |
|---|---|
| Subjects with any concomitant medication | 66 (100.0) |
| Sodium chloride | 57 (86.4) |
| Dornase alfa | 55 (83.3) |
| Salbutamol | 53 (80.3) |
| Pancreatin | 46 (69.7) |
| Fluticasone propionate | 23 (34.8) |
| Ascorbic acid/ betacarotene/ biotin/ calcium pantothenate/ colecalciferol/ cyanocobalamin/ folic acid/ nicotinamide/ phytomenadione/ pyridoxine hydrochloride/ retinol palmitate/ riboflavin/ thiamine mononitrate/ tocopherol/ zinc ascorbate | 20 (30.3) |
| Azithromycin | 20 (30.3) |
| Ibuprofen | 20 (30.3) |
| Pancrelipase | 19 (28.8) |
| Macrogol 3350 | 18 (27.3) |
| Paracetamol | 17 (25.8) |
| Omeprazole | 16 (24.2) |
| Salbutamol sulfate | 14 (21.2) |
| Vitamins NOS | 14 (21.2) |

ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; N: total sample size; NOS: not otherwise specified; PN: Preferred Name; TE: treatment-emergent; TEZ: tezacaftor; WHODrug: World Health Organization Drug Dictionary

Notes: Medications were coded using WHODrug Global, version March 2020, format B3. PNs were sorted in descending order of frequency. A subject with multiple medications with the same PN was counted only once for that PN. Concomitant medication was defined as medication that was continued or newly received during the TE Period of Part B.

## Numbers analysed

A total of 66 subjects were enrolled and received at least 1 dose of the study drug, and 64 (97.0%) subjects completed treatment and the study (Table 13). One subject discontinued due to an AE, and 1 subject withdrew consent (not due to AE).

**Table13. Subject Disposition (All Subjects Set, Part B)**

| Disposition | ELX/TEZ/IVA n (%) |
|---|---|
| All Subjects Set | 66 |
| FAS | 66 |
| Safety Set | 66 |
| Completed treatment | 64 (97.0) |
| Prematurely discontinued treatment | 2 (3.0) |
| Reason for discontinuation of treatment | |
| AE | 1 (1.5) |
| Other[a] | 1 (1.5) |
| Completed study | 64 (97.0) |
| Prematurely discontinued the study | 2 (3.0) |
| Reason for discontinuation from study | |
| AE | 1 (1.5) |
| Withdrawal of consent (not due to AE) | 1 (1.5) |
| Rollover to the extension study | 64 (97.0) |

AE: adverse event; COVID-19: coronavirus disease; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; n: size of subsample; TEZ: tezacaftor

Note: The All Subjects Set included all subjects who were enrolled or received at least 1 dose of study drug (in Part B). The FAS included all enrolled subjects who carry the intended *CFTR* allele mutation and received at least 1 dose of study drug. The Safety Set included all subjects who received at least 1 dose of study drug.

[a] The subject did not want to leave home due to the COVID-19 pandemic and therefore switched to commercially available drug (Listing 16.2.1b).

## Outcomes and estimation

- **Absolute Change in ppFEV1**

Part A

Summary statistics for post-baseline raw values and changes from baseline are provided for ppFEV1 and other lung function parameters; both absolute and relative changes are summarized. On Day 15, the within-group mean (SD) absolute change from baseline in ppFEV1 was 11.8 (8.9) percentage points.

Part B

The main analysis of absolute change in ppFEV1 from baseline through Week 24 (clinic assessed) is presented in Table 14 and Figure 4.

Treatment with ELX/TEZ/IVA resulted in within-group improvements through Week 24. The LS mean absolute change in ppFEV1 from baseline through Week 24 was 10.2 percentage points (95% CI: 7.9, 12.6; P<0.0001).

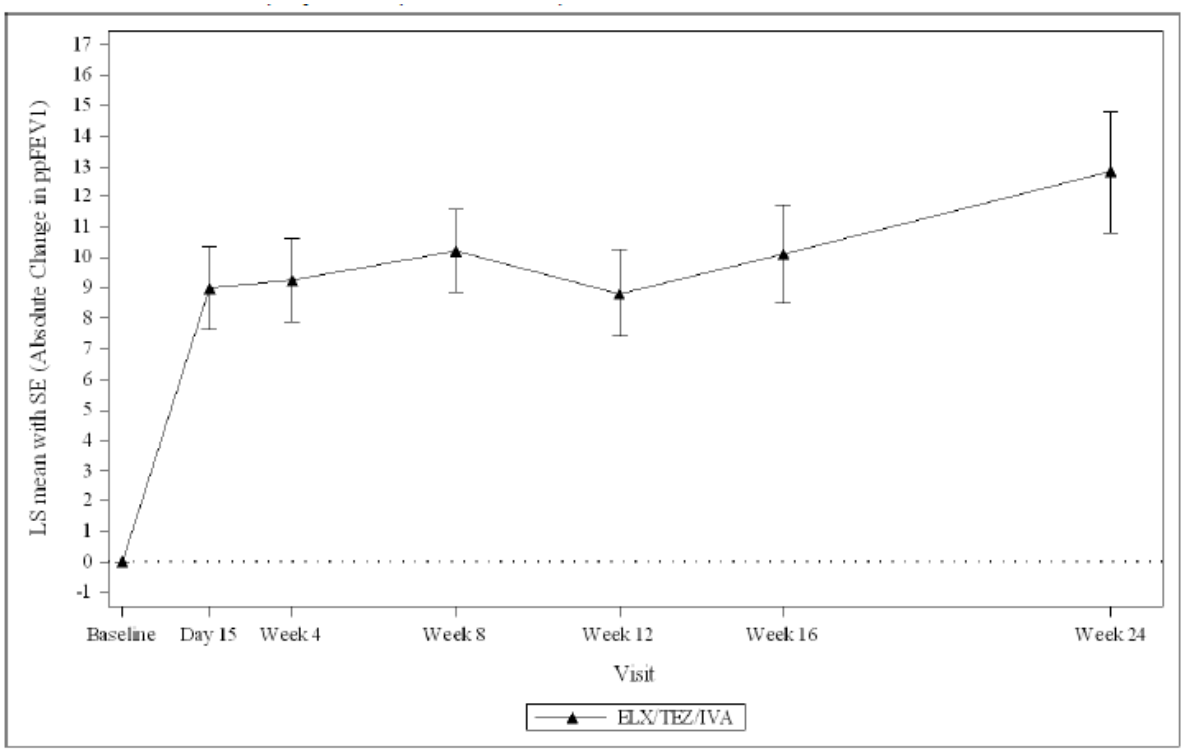
**Table 14. MMRM Analysis of Absolute Change From Baseline in ppFEV1 Through Week 24 (FAS, Part B)**

| | ELX/TEZ/IVA N = 66 |
|---|---|
| **Baseline** | |
| n | 62 |
| Mean (SD) | 88.8 (17.7) |
| **Absolute change through Week 24** | |
| n | 59 |
| LS mean (SE) | 10.2 (1.2) |
| 95% CI of LS mean | (7.9, 12.6) |
| *P* value | <0.0001 |

ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a *CFTR* minimal function mutation; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

Note: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. MMRM included clinic-assessed data up to Week 24, with visit as fixed effect and baseline $ppFEV_1$ and genotype group (F/F or F/MF) as covariates. However, the Day 15 Visit was not included in the estimation of the average treatment effect through Week 24. A Kenward-Roger approximation was used for denominator degrees of freedom. A compound symmetry covariance structure was used to model the within-subject errors.

**Figure 4. MMRM Analysis of Absolute Change From Baseline in ppFEV1 (Percentage Points) by Visit (FAS, Part B)**




ELX: elexacaftor; FAS: Full Analysis Set; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a *CFTR* minimal function mutation; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

Note: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. MMRM included clinic-assessed data up to Week 24, with visit as fixed effect and baseline $ppFEV_1$ and genotype group (F/F or F/MF) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. A compound symmetry covariance structure was used to model the within-subject errors.

Table 15 presents subjects with ppFEV1 data by visit for the main analysis (clinic-based assessments) and the additional analysis including clinic-assessed data collected from unscheduled visits conducted after Week 24 (due to the COVID-19 pandemic).

**Table 15. Number of Subjects With Data by Visit in the Main MMRM Analysis and an Additional MMRM Analysis for ppFEV1 (FAS, Part B)**

| | Number of Subjects With Data at Time Point, n | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Absolute Change at | | | | | | |
| | Baseline | D15 | WK4 | WK8 | WK12 | WK16 | WK24 | WK24-U[a] |
| ELX/TEZ/IVA (N=66) | 62 | 51 | 52 | 51 | 43 | 29 | 15 | 24 |

COVID-19: coronavirus disease; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor; U: unscheduled

[a] WK24-U includes subjects who had $ppFEV_1$ data collected at unscheduled visits conducted after Week 24 (the primary purpose of these visits was to capture safety laboratory testing missed due to the COVID-19 pandemic).

*Sensitivity and Additional Analyses*

A sensitivity analysis was performed using the multiple imputation method to assess for impact of missing data; MMRM results for the through Week 24 endpoint were consistent with the main analysis (Absolute change through Week 24 LS mean (SE) is 9.9 (1.0))

An additional prespecified analysis was performed that included home-assessed spirometry (i.e., spirometry assessed independently by the subjects at home) that was permitted due to the COVID-19 pandemic. The MMRM results for the through Week 24 endpoint were consistent with the main analysis: Absolute change through Week 24 LS mean (SE) is 10.7 (1.2).

Another prespecified analysis included all clinic-assessed spirometry data collected through completion of study participation using the extended analysis visit windows (i.e., including data from unscheduled visits that were conducted after Week 24 to capture safety laboratory testing missed due to the COVID-19 pandemic). The MMRM results for the through Week 24 endpoint were consistent with the main analysis: Absolute change through Week 24 LS mean (SE) is 10.2 (1.3)).

- **Absolute Change in SwCl From Baseline Through Week 24**

*Part A*

On Day 15, the within-group mean (SD) change from baseline in SwCl was -50.9 (13.1) mmol/L.

*Part B*

Treatment with ELX/TEZ/IVA resulted in within-group improvements (reductions) through Week 24. The LS mean absolute change in SwCl from baseline through Week 24 was -60.9 mmol/L (95% CI: -63.7, -58.2; P<0.0001) (Table 16, Figure 5).

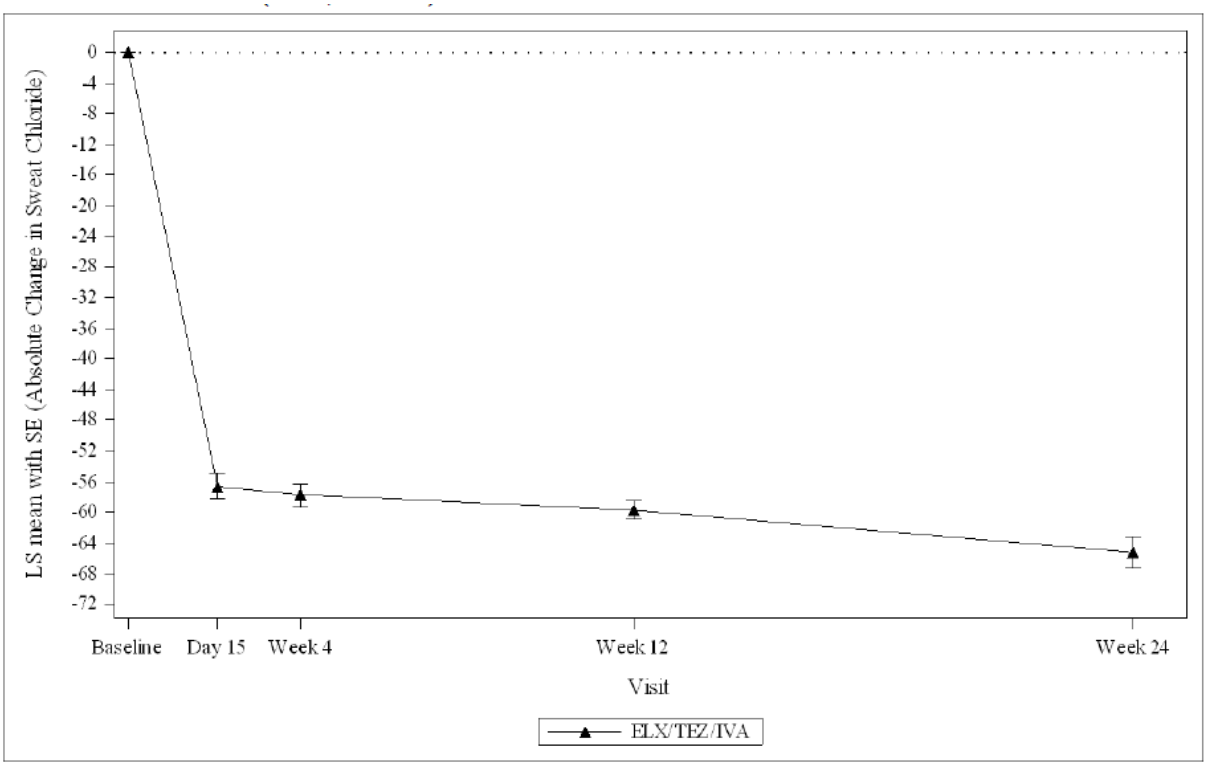
**Table 16. MMRM Analysis of Absolute Change From Baseline in SwCl Through Week 24 (FAS, Part B)**

| | ELX/TEZ/IVA N = 66 |
|---|---|
| **Baseline** | |
| n | 62 |
| Mean (SD) | 102.2 (9.1) |
| **Absolute change through Week 24** | |
| n | 60 |
| LS mean (SE) | -60.9 (1.4) |
| 95% CI of LS mean | (-63.7, -58.2) |
| *P* value | <0.0001 |

ELX: elexacaftor; FAS: Full Analysis Set; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a *CFTR* minimal function mutation; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; SwCl: sweat chloride; TEZ: tezacaftor

Note: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. MMRM included data up to Week 24, with visit as fixed effect and baseline SwCl and genotype group (F/F or F/MF) as covariates. However, the Day 15 Visit was not included in the estimation of the average treatment effect through Week 24. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors.

**Figure 5 MMRM Analysis of Absolute Change From Baseline in SwCl (mmol/L) by Visit (FAS, Part B)**




ELX: elexacaftor; FAS: Full Analysis Set; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a *CFTR* minimal function mutation; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; SwCl: sweat chloride; TEZ: tezacaftor

Note: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. MMRM included data up to Week 24, with visit as fixed effect and baseline SwCl and genotype group (F/F or F/MF) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors.

Table 17 presents subjects with SwCl data by visit for the main analysis and the additional analysis including data collected from unscheduled visits conducted after Week 24 (due to the COVID-19 pandemic).

**Table 17. Number of Subjects With Data by Visit in the Main and Additional MMRM Analyses for SwCl (FAS, Part B)**

| | Number of Subjects With Data at Time Point, n | | | | | |
|---|---|---|---|---|---|---|
| | | Absolute Change at | | | | |
| | Baseline | D15 | WK4 | WK12 | WK24 | WK24-U[a] |
| ELX/TEZ/IVA (N=66) | 62 | 56 | 56 | 50 | 28 | 40 |

COVID-19: coronavirus disease; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; SwCl: sweat chloride; TEZ: tezacaftor; U: unscheduled

[a] WK24-U includes subjects who had SwCl data collected at unscheduled visits conducted after Week 24 (the primary purpose of these visits was to capture safety laboratory testing missed due to the COVID-19 pandemic).

*Additional Analysis*

A prespecified analysis was performed that included all SwCl data collected through completion of study participation, including at unscheduled visits after Week 24. The MMRM results for the through Week 24 endpoint were consistent with the main analysis: Absolute change through Week 24 LS mean (SE) is -61.4 (1.3).

- **Absolute Change in CFQ-R Respiratory Domain Score (Child's Version) From Baseline Through Week 24**

Treatment with ELX/TEZ/IVA resulted in within-group improvements through Week 24. The LS mean absolute change in CFQ-R RD score from baseline through Week 24 was 7.0 points (95% CI: 4.7, 9.2; P<0.0001).

*Additional Analysis*

An additional prespecified analysis was performed based on pooled CFQ-R RD scores assessed at the clinic and at home. The MMRM results for the through Week 24 endpoint were consistent with the main analysis: Absolute change through Week 24 LS mean (SE) is 7.0 (1.1).

- **Absolute Change in BMI, Weight, Height, and Associated Z-Scores From Baseline at Week 24**

Analyses of absolute change in growth parameters (BMI, weight, height, and associated z-scores) from baseline at Week 24 are presented in Table 18

**Table 18. MMRM Analysis of Absolute Change From Baseline in BMI, Weight, Height, and Associated Z-Scores At Week 24 (FAS, Part B)**

| | ELX/TEZ/IVA N = 66 |
|---|---|
| **BMI ($kg/m^2$)** | |
| **Baseline** | |
| n | 66 |
| Mean (SD) | 16.39 (1.69) |
| **Absolute change at Week 24** | |
| n | 33 |
| LS mean (SE) | 1.02 (0.13) |
| 95% CI of LS mean | (0.76, 1.28) |
| *P* value | <0.0001 |
| **BMI z-score** | |
| **Baseline** | |
| n | 66 |
| Mean (SD) | -0.16 (0.74) |
| **Absolute change at Week 24** | |
| n | 33 |
| LS mean (SE) | 0.37 (0.05) |
| 95% CI of LS mean | (0.26, 0.48) |
| *P* value | <0.0001 |
| **Weight (kg)** | |
| **Baseline** | |
| n | 66 |
| Mean (SD) | 30.0 (7.7) |
| **Absolute change at Week 24** | |
| n | 33 |
| LS mean (SE) | 3.0 (0.2) |
| 95% CI of LS mean | (2.5, 3.5) |
| *P* value | <0.0001 |
| **Weight z-score** | |
| **Baseline** | |
| n | 66 |
| Mean (SD) | -0.22 (0.76) |
| **Absolute change at Week 24** | |
| n | 33 |
| LS mean (SE) | 0.25 (0.04) |
| 95% CI of LS mean | (0.16, 0.33) |
| *P* value | <0.0001 |

| Height (cm) | |
|---|---|
| **Baseline** | |
| n | 66 |
| Mean (SD) | 134.1 (12.3) |
| **Absolute change at Week 24** | |
| n | 33 |
| LS mean (SE) | 2.3 (0.2) |
| 95% CI of LS mean | (1.9, 2.7) |
| *P* value | <0.0001 |

| Height z-score | |
|---|---|
| **Baseline** | |
| n | 66 |
| Mean (SD) | -0.11 (0.98) |
| **Absolute change at Week 24** | |
| n | 33 |
| LS mean (SE) | -0.05 (0.03) |
| 95% CI of LS mean | (-0.12, 0.01) |
| *P* value | 0.1057 |

BMI: body mass index; ELX: elexacaftor; FAS: Full Analysis Set; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a *CFTR* minimal function mutation; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; TEZ: tezacaftor

Note: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. MMRM included data from all available visits up to Week 24, with visit as fixed effect and baseline value of the relevant growth parameter (BMI, weight, height, or associated z-score) and genotype group (F/F or F/MF) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors.

- **Number of PEx and CF-related Hospitalizations Through Week 24**

The annual event rate for PEx overall was 0.12 events/year. Event rates for PEx requiring hospitalization and/or IV antibiotic therapy were each 0.03 events/year (Table 19).

The annual event rates for planned and unplanned CF-related hospitalizations were each 0 events/year.

**Table 19. Summary of PEx During the PEx Analysis Period (FAS, Part B)**

| | ELX/TEZ/IVA N = 66 |
|---|---|
| Total number of days (years) of the PEx analysis period | 11060 (32.9) |
| **PEx overall** | |
| Number of subjects with events, n (%) | 4 (6.1) |
| Number of events | 4 |
| Observed event rate per year | 0.12 |
| **PEx requiring hospitalization** | |
| Number of subjects with events, n (%) | 1 (1.5) |
| Number of events | 1 |
| Observed event rate per year | 0.03 |
| **PEx requiring IV antibiotic therapy** | |
| Number of subjects with events, n (%) | 1 (1.5) |
| Number of events | 1 |
| Observed event rate per year | 0.03 |
| **PEx requiring hospitalization or IV antibiotic therapy** | |
| Number of subjects with events, n (%) | 1 (1.5) |
| Number of events | 1 |
| Observed event rate per year | 0.03 |

ELX: elexacaftor; FAS: Full Analysis Set; IV: intravenous; IVA: ivacaftor; n: size of subsample; N: total sample size; PEx: pulmonary exacerbation; TEZ: tezacaftor

Notes: PEx was defined as any new or change in antibiotic therapy (IV, inhaled, or oral) for ≥4 sinopulmonary signs/symptoms (Section 9.5.7.6.1). Total number of days = sum of the individual duration (actual number of days) of the PEx analysis period across all subjects. Total number of years = total number of days / 336. Observed event rate per year = total number of events * 336 / total number of days of the PEx analysis period. The event rate was calculated based on 336 days (48 weeks) in a year.

- **Absolute Change in LCI2.5 From Baseline Through Week 24**

Treatment with ELX/TEZ/IVA resulted in within-group improvements (reductions) through Week 24. The LS mean absolute change in LCI2.5 from baseline through Week 24 was -1.71 (95% CI: -2.11, -1.30; P<0.0001).

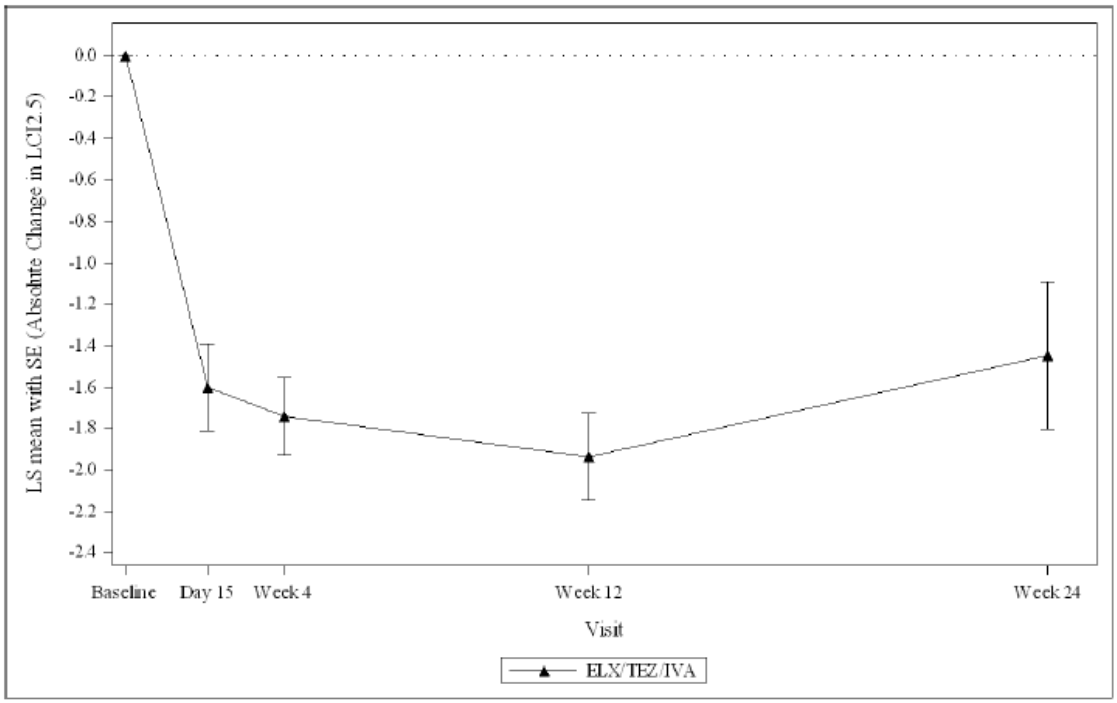
**Table 20. MMRM Analysis of Absolute Change From Baseline in LCI2.5 Through Week 24 (FAS, Part B)**

| | ELX/TEZ/IVA N = 66 |
|---|---|
| **Baseline** | |
| n | 53 |
| Mean (SD) | 9.77 (2.68) |
| **Absolute change through Week 24** | |
| n | 50 |
| LS mean (SE) | -1.71 (0.20) |
| 95% CI of LS mean | (-2.11, -1.30) |
| *P* value | <0.0001 |

ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; $LCI_{2.5}$: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; TEZ: tezacaftor

Note: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. MMRM included data up to Week 24, with visit as fixed effect and baseline $LCI_{2.5}$ and genotype group (F/F or F/MF) as covariates. However, the Day 15 Visit was not included in the estimation of the average treatment effect through Week 24. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors.

**Figure 6 MMRM Analysis of Absolute Change From Baseline in LCI2.5 by Visit (FAS, Part B)**




ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; $LCI_{2.5}$: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value; LS: least squares; MMRM: mixed-effects model for repeated measures; TEZ: tezacaftor

Note: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. MMRM included data up to Week 24, with visit as fixed effect and baseline $LCI_{2.5}$ and genotype group (F/F or F/MF) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors.

Table 21. presents subjects with LCI2.5 data by visit for the main analysis and for the additional analysis including data collected from unscheduled visits conducted after Week 24 (due to the COVID-19 pandemic).

**Table 21. Number of Subjects With LCI2.5 Data by Visit**

| | Number of Subjects With Data at Time Point, n | | | | | |
|---|---|---|---|---|---|---|
| | | Absolute Change at | | | | |
| | Baseline | D15 | WK4 | WK12 | WK24 | WK24-U[a] |
| ELX/TEZ/IVA (N=66) | 53 | 43 | 37 | 41 | 22 | 30 |

COVID-19: coronavirus disease; ELX: elexacaftor; FAS: Full Analysis Set; IVA: ivacaftor; $LCI_{2.5}$: number of lung turnovers required to reduce the end tidal inert gas concentration to 1/40th of its starting value; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; TEZ: tezacaftor; U: unscheduled

[a] WK24-U includes subjects who had $LCI_{2.5}$ data collected at unscheduled visits conducted after Week 24 (the primary purpose of these visits was to capture safety laboratory testing missed due to the COVID-19 pandemic).

*Additional Analysis*

A prespecified additional analysis was performed that included all LCI2.5 data collected through completion of study participation, including at unscheduled visits after Week 24. The MMRM results for the through Week 24 endpoint were consistent with the main analysis.

- **Drug Acceptability Assessment Using Modified Facial Hedonic Scale**

Clinic-assessed results of the drug acceptability assessment (subject reaction) using the modified facial hedonic scale at Week 24 showed that the majority of subjects either "liked it very much" or "liked it a little" at Week 24; results were similar at other evaluation time points.

## Ancillary analyses

Upon request from the CHMP, the MAH provided additional analyses of the within-group change through week 12, with all week 16 and week 24 data excluded from the analysis.

**Table 22. Modified MMRM Analysis of Absolute Change From Baseline in $ppFEV_1$ Through Week 12 (FAS, Study 106 Part B)**

| | ELX/TEZ/IVA N = 66 |
|---|---|
| **Baseline** | |
| n | 62 |
| Mean (SD) | 88.8 (17.7) |
| **Absolute change through Week 12** | |
| n | 59 |
| LS mean (SE) | 9.6 (1.1) |
| 95% CI of LS mean | (7.3, 11.9) |
| *P* value | <0.0001 |

ELX: elexacaftor; FAS: Full Analysis Set; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a *CFTR* minimal function mutation; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; *P*: probability; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; TEZ: tezacaftor

Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. MMRM included visit as fixed effect. Baseline $ppFEV_1$, visit*(baseline $ppFEV_1$) interaction, and genotype group (F/F versus F/MF) were covariates. Measurements at Weeks 4, 8, and 12 (clinic-assessed data only) were included in the estimation of the average treatment effect through Week 12.

**Table 23. Modified MMRM Analysis of Absolute Change From Baseline in SwCl Through Week 12 (FAS, Study 106 Part B)**

| | ELX/TEZ/IVA N = 66 |
|---|---|
| **Baseline** | |
| n | 62 |
| Mean (SD) | 102.2 (9.1) |
| **Absolute change through Week 12** | |
| n | 59 |
| LS mean (SE) | -58.6 (1.3) |
| 95% CI of LS mean | (-61.1, -56.1) |
| *P* value | <0.0001 |

ELX: elexacaftor; FAS: Full Analysis Set; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a *CFTR* minimal function mutation; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; *P*: probability; SwCl: sweat chloride; TEZ: tezacaftor

Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. MMRM included visit as fixed effect. Baseline SwCl, visit*(baseline SwCl) interaction, and genotype group (F/F versus F/MF) were covariates. Measurements at Weeks 4 and 12 were included in the estimation of the average treatment effect through Week 12.

**Table 24. Modified MMRM Analysis of Absolute Change From Baseline in CFQ-RRD Score (Child's Version) Through Week 12 (FAS, Study 106 Part B)**

| | ELX/TEZ/IVA N = 66 |
|---|---|
| **Baseline** | |
| n | 65 |
| Mean (SD) | 80.3 (15.2) |
| **Absolute change through Week 12** | |
| n | 65 |
| LS mean (SE) | 5.6 (1.3) |
| 95% CI of LS mean | (2.9, 8.2) |
| *P* value | <0.0001 |

CFQ-R: Cystic Fibrosis Questionnaire-Revised; ELX: elexacaftor; FAS: Full Analysis Set; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a *CFTR* minimal function mutation; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; *P*: probability; RD: respiratory domain; TEZ: tezacaftor

Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. MMRM included visit as fixed effect. Baseline CFQ-R RD score, visit*(baseline CFQ-R RD score) interaction, and genotype group (F/F versus F/MF) were covariates. Measurements at Weeks 4, 8, and 12 (clinic-assessed data only) were included in the estimation of the average treatment effect through Week 12.

**Table 25. Modified MMRM Analysis of Absolute Change From Baseline in LCI2.5 Through Week 12 (FAS, Study 106 Part B)**

| | ELX/TEZ/IVA N = 66 |
|---|---|
| **Baseline** | |
| n | 53 |
| Mean (SD) | 9.77 (2.68) |
| **Absolute change through Week 12** | |
| n | 48 |
| LS mean (SE) | -1.83 (0.17) |
| 95% CI of LS mean | (-2.18, -1.49) |
| *P* value | <0.0001 |

ELX: elexacaftor; FAS: Full Analysis Set; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a *CFTR* minimal function mutation; IVA: ivacaftor; $LCI_{2.5}$: number of lung turnovers required to reduce the end tidal inert gas concentration to $1/40^{th}$ of its starting value; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; *P*: probability; TEZ: tezacaftor

Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. MMRM included visit as fixed effect. Baseline $LCI_{2.5}$, visit*(baseline $LCI_{2.5}$) interaction, and genotype group (F/F versus F/MF) were covariates. Measurements at Weeks 4 and 12 were included in the estimation of the average treatment effect through Week 12.

**Table 26. MMRM Analysis of Absolute Change From Baseline in BMI, Weight, Height, and Associated Z-scores At Weeks 12 and 24 (FAS, Study 106 Part B)**

| | ELX/TEZ/IVA N = 66 |
|---|---|
| **BMI ($kg/m^2$)** | |
| **Baseline** | |
| n | 66 |
| Mean (SD) | 16.39 (1.69) |
| **Absolute change at Week 12** | |
| n | 58 |
| LS mean (SE) | 0.49 (0.09) |
| 95% CI of LS mean | (0.32, 0.67) |
| **Absolute change at Week 24** | |
| n | 33 |
| LS mean (SE) | 1.02 (0.13) |
| 95% CI of LS mean | (0.76, 1.28) |
| *P* value | <0.0001 |
| **BMI z-score** | |
| **Baseline** | |
| n | 66 |
| Mean (SD) | -0.16 (0.74) |
| **Absolute change at Week 12** | |
| n | 58 |
| LS mean (SE) | 0.22 (0.04) |
| 95% CI of LS mean | (0.13, 0.30) |
| **Absolute change at Week 24** | |
| n | 33 |
| LS mean (SE) | 0.37 (0.05) |
| 95% CI of LS mean | (0.26, 0.48) |
| *P* value | <0.0001 |

| | |
|---|---|
| **Weight (kg)** | |
| **Baseline** | |
| n | 66 |
| Mean (SD) | 30.0 (7.7) |
| **Absolute change at Week 12** | |
| n | 58 |
| LS mean (SE) | 1.4 (0.2) |
| 95% CI of LS mean | (1.1, 1.7) |
| **Absolute change at Week 24** | |
| n | 33 |
| LS mean (SE) | 3.0 (0.2) |
| 95% CI of LS mean | (2.5, 3.5) |
| *P* value | <0.0001 |
| **Weight z-score** | |
| **Baseline** | |
| n | 66 |
| Mean (SD) | -0.22 (0.76) |
| **Absolute change at Week 12** | |
| n | 58 |
| LS mean (SE) | 0.13 (0.03) |
| 95% CI of LS mean | (0.07, 0.18) |
| **Absolute change at Week 24** | |
| n | 33 |
| LS mean (SE) | 0.25 (0.04) |
| 95% CI of LS mean | (0.16, 0.33) |
| *P* value | <0.0001 |
| **Height (cm)** | |
| **Baseline** | |
| n | 66 |
| Mean (SD) | 134.1 (12.3) |
| **Absolute change at Week 12** | |
| n | 58 |
| LS mean (SE) | 1.1 (0.1) |
| 95% CI of LS mean | (1.0, 1.3) |
| **Absolute change at Week 24** | |
| n | 33 |
| LS mean (SE) | 2.3 (0.2) |
| 95% CI of LS mean | (1.9, 2.7) |
| *P* value | <0.0001 |
| **Height z-score** | |
| **Baseline** | |
| n | 66 |
| Mean (SD) | -0.11 (0.98) |
| **Absolute change at Week 12** | |
| n | 58 |
| LS mean (SE) | -0.03 (0.02) |
| 95% CI of LS mean | (-0.06, 0.00) |
| **Absolute change at Week 24** | |
| n | 33 |
| LS mean (SE) | -0.05 (0.03) |
| 95% CI of LS mean | (-0.12, 0.01) |
| *P* value | 0.1057 |

BMI: body mass index; ELX: elexacaftor; FAS: Full Analysis Set; F/F: homozygous for *F508del*; F/MF: heterozygous for *F508del* and a *CFTR* minimal function mutation; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; n: size of subsample; N: total sample size; *P*: probability; TEZ: tezacaftor

Notes: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. MMRM included data from all available visits up to Week 24, with visit as fixed effect and baseline value of the relevant growth parameter (BMI, weight, height, or associated z-score) and genotype group (F/F or F/MF) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within-subject errors.

## *Summary of main study*

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

**Table 27. Summary of Efficacy for trial VX18-445-106 part B**

| **Title: A Phase 3 Study Evaluating the Pharmacokinetics, Safety, and Tolerability of VX-445/TEZ/IVA Triple Combination Therapy in Cystic Fibrosis Subjects 6 Through 11 Years of Age** | | | |
|---|---|---|---|
| Study identifier | VX18-445-106 | | |
| Design | 2-part (Parts A and B), multicenter study<br><br>Part B: single arm, open-label study in CF subjects 6 through 11 years of age who are heterozygous for *F508del* and a minimal function (MF) mutation (F/MF genotypes) or homozygous for *F508del* (F/F genotype). | | |
| | Duration of main phase: Duration of Run-in phase: Duration of Extension phase: | | 24 weeks<br>not applicable<br>As extension part, patients rolled in a separate study |
| Hypothesis | Exploratory: efficacy is a secondary objective, no formal hypothesis | | |
| Treatments groups | Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) | | <u>Treatment</u><br>< 30 kg: 100 mg ELX qd/50 mg TEZ qd/75 mg IVA q12h<br>≥30 kg: 200 mg ELX qd/100 mg TEZ qd/150 mg IVA q12h<br><br><u>Duration</u><br>24 weeks<br><br><u>Number</u><br>66 in total |
| Endpoints and definitions | Secondary endpoint | percent predicted forced expiratory volume in 1 second (ppFEV1) (%) | Absolute change in ppFEV1 from baseline through week 24 |
| | Secondary endpoint | Sweat chloride (SwCl) (mmol/l) | Absolute change in SwCl from baseline through week 24 |

| | | | |
|---|---|---|---|
| | Secondary endpoint | Cystic Fibrosis Questionnaire-Revised respiratory domain (CFQ-R RD) (points) | Absolute change in CFQ-R from baseline through week 24 |
| | Secondary endpoint | lung clearance index (LCI2.5) | Absolute change in LCI2.5 from baseline through week 24 |
| Database lock | 24 August 2020 | | |

**Results and Analysis**

**The primary analysis is the analysis of the changes from baseline.**

| **Analysis description** | **Primary Analysis** | |
|---|---|---|
| Analysis population and time point description | Full Analysis Set (FAS): all subjects who are enrolled and carry the intended CFTR allele mutation and received at least 1 dose of study drug | |
| Descriptive statistics and estimate variability | Treatment group | ELX/TEZ/IVA |
| | Number of subject | 66 |
| | LS mean ppFEV$_1$ | 10.2 |
| | 95% CI of LS mean | 7.9, 12.6 |
| | p-value | <0.0001 |
| | LS mean SwCl | -60.9 |
| | 95% CI of LS mean | -63.7, -58.2 |
| | p-value | <0.0001 |
| | LS mean CFQ-R RD | 7.0 |
| | 95% CI of LS mean | 4.7,9.2 |
| | p-value | <0.0001 |
| | LS mean LFC2.5 | -1.71 |
| | 95% CI of LS mean | (-2.11,-1.30) |
| | p-value | <0.0001 |
| Notes | Not all of the 66 participants included in the FAS had data available at all timepoints, while most data are missing after week 12 because of COVID pandemic restrictions. | |

## 2.4.3. Discussion on clinical efficacy

To support an indication extension of ELX/TEZ/IVA in combination with IVA (Kalydeco) to include CF patients 6 through 11 years of age, the results of Study VX18-445-106 (Study 106) are submitted.

Study 106 is a phase 3, multicentre study conducted in 2 parts to evaluate the pharmacokinetics (PK), safety, and tolerability of ELX/TEZ/IVA in CF subjects 6 through 11 years of age who are heterozygous

for *F508del* and a minimal function (MF) mutation (F/MF genotypes) or homozygous for *F508del* (F/F genotype).

## Design and conduct of clinical studies

In Part A of study 106, patients were treated with ELX/TEZ/IVA 100 mg/50 mg/75 mg FDC tablet and IVA 75 mg tablet for 15 days.

In part B, patients were treated with ELX/TEZ/IVA for 24 weeks according to the following schedule:

- Patients weighing <30 kg: ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h (two Kaftrio 50/25/37.5 mg FDC film-coated tablets in the morning and one Kalydeco 75 mg film-coated tablet in the evening)
- Patients weighing ≥30 kg: ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h (two Kaftrio 100/50/75 mg FDC film-coated tablets in the morning and one Kalydeco 150 mg film-coated tablet in the evening)

Subjects who completed the Part B Treatment Period and did not permanently discontinue the study drug could enrol in an optional open-label extension safety study (if they met the eligibility criteria for that study).

Similar modification, interruption and discontinuation rules as well as prohibited medication rules are applied as for the adults in the initial marketing application studies and are considered acceptable by the CHMP.

The primary objectives of the study were to evaluate the pharmacokinetics (part A) and to evaluate the safety and tolerability of ELX/TEZ/IVA in combination with IVA through Week 24. Efficacy was a secondary objective.

Endpoints

As safety is the primary objective in Study 106 Part B, the proposed secondary efficacy endpoints are acceptable. Sweat chloride as a pharmacodynamic parameter is an important parameter for measuring the effect of a modulator. In CF, sweat chloride is increased and a decrease can be considered as an effect on the underlying pathology. Pulmonary function tests, spirometry and multiple breath wash-out (MBW) for calculating LCI2.5, are considered important to measure an effect on the lungs, one of the most important affected organs in CF. The LCI2.5 can measure changes in the small airways, while the ppFEV1 is more associated with large airways. In CF, the small airways are earlier affected than the large airways. Therefore, the use of the LCI2.5 as a measurement of efficacy is sensitive, given the more preserved lung function in children than in adults.

CFQ-R measures the quality of life, and changes in BMI z-score and height z-score inform over the nutritional status. Thus, all parameters inform about a different aspect of CF and are considered valuable.

Statistics

As study 106 is an open-label single-arm trial without a comparator arm, no randomisation or blinding was done. Considering, that acceptance of an extension of the indication could be based on similar exposure and safety and efficacy as in adolescents and adults, a within-group change from baseline is considered acceptable to provide evidence of comparable efficacy with adolescents and adults.

Each continuous efficacy and PD endpoint was analysed using a mixed-effects model for repeated measures that included visit as the fixed effect, with a baseline value of the efficacy variable and

genotype group (F/F or F/MF) as covariates. The model included all measurements of the efficacy variable up to Week 24 (inclusive), whether assessed on treatment or after treatment discontinuation.

For part B, safety measures were implemented to provide subjects with the opportunity to continue participation while ensuring their safety against COVID-19 exposure in alignment with Health Authority guidance. However, the adjustments made to comply with Health Authority guidance due to COVID-19 potentially impact the results of the study results. Overall, the impact on safety results is expected to be minor provided that all the safety parameters were collected, but at a different time. For the efficacy data (i.e. spirometry, SwCl, and LCI) the impact is greater because it was not mandatory to collect these data at the same unscheduled visit. Giving patients the option to provide efficacy data through an unscheduled visit during the COVID-19 pandemic may have introduced additional biases because the ability and willingness to provide efficacy data during an unscheduled visit is likely to be associated with the health of the patient at the time.

## Efficacy data and additional analyses

A total of 66 subjects were enrolled and received at least 1 dose of the study drug, and 64 (97.0%) subjects completed treatment and the study. One subject discontinued due to an AE, and 1 subject withdrew consent (not due to AE).

The mean population age was 9.3 years, and over half (59.1%) of the subjects were female. The majority of subjects (87.9%) were White, and none were Hispanic or Latino. A total of 29 (43.9%) subjects had an F/F genotype, and 37 (56.1%) subjects had F/MF genotypes, with 15 distinct F/MF genotypes represented. About 50% of the patients has already an impaired lung function, as can be expected with these F/MF and F/F mutations, that affect the organs already in early life.

Of the study population, 78.8% of the patients did not use a modulator before. For the patients with F/MF mutations no modulator therapy is currently authorised in patients aged 12 yo. However, for patients with F/F mutation, TEZ/IVA and LUM/IVA are available as modulator therapy, although TEZ/IVA became only quite recently available. As a consequence, the group of patients with F/F mutation consist of modulator experienced F/F subjects and modulator naïve F/F subjects.

Outcomes and estimation

As this was an open-label, single-arm study, the outcomes of the efficacy parameters were results compared to baseline.

For the main secondary parameter ppFEV1, the LS mean absolute change in ppFEV1 from baseline through Week 24 was 10.2% (95% CI: 7.9, 12.6; P<0.0001). This is generally similar to the results for the adolescent and adult patients in previous studies performed by the MAH. In these studies, LS mean difference from baseline was 14.3 (95%CI 12.7, 15.8) in patients with F/MF mutations and 7.8%, (95% CI 4.8,10.8) for CFTR modulator experienced F/F patients and 13.2%, (95% CI (8.5,17.9) for CFTR modulator naïve F/F patients. The benefit was thus different between the specific subgroups in the adult population, but still clinically relevant. Generally, lung function is better preserved in children compared to adults. Therefore, a slightly lower benefit would be acceptable. However, as normally a decrease in ppFEV1 will occur, an increase of 10.2% is undoubtfully clinically relevant.

Treatment with ELX/TEZ/IVA in combination with IVA resulted in the LS mean absolute change in SwCl from baseline through Week 24 of -60.9 mmol/L (95% CI: -63.7, -58.2; P<0.0001). This result is in line with results for the adolescent and adult patients in previous studies performed by the MAH: LS mean difference from baseline - 42.2 mmol/L (95% CI: -44.0, -40.4) in patients with F/MF mutations and LS mean difference from baseline was -43.4 mmol/L (95% CI: -46.9, -40.0) for patients with F/F mutations. A reduction of -10 mmol/L in SwCl has been accepted by the CHMP as clinically relevant.

The within LS mean absolute change in CFQ-R Respiratory Domain Score of 7.0 points (95% CI: 4.7, 9.2; P<0.0001) was clinically relevant, but less impressive compared with results for the adolescent and adult patients in the original marketing authorisation studies (patients with F/MF mutations 20.2 points (95% CI 17.5,23.0) and patients with F/F mutations 17.4 points 95% CI 11.8,23.0)). However, in children, the quality of life was somewhat less impaired at the start (80 points) compared with the adults and adolescents (68.3 points and 70.6 in study 102 and study 103 respectively). Moreover, the child version of the CFQ-R is not completely identical to the adult version. Furthermore, COVID-19 could also have influenced the outcome of the CFQ-R. Nevertheless, an increase of 7.0 points is above MCID of 4 points. Therefore, the results are considered clinically relevant.

An improvement in ventilation inhomogeneity measured by LCI2.5 is shown by a numerical decrease from baseline. The LS mean absolute change in LCI2.5 from baseline through Week 24 was -1.71 (95% CI: -2.11, -1.30; P<0.0001). The use of absolute change from baseline is preferred, because this endpoint will not mask deteriorations over time, if occurred. The additional analysis performed at the request of the CHMP of the LS mean absolute change in $LCI_{2.5}$ at week 12 showed that the change was -1.93 (95% CI -2.31, -1.56). A minimal clinically important difference (MCID) for the LCI2.5 is not established. Therefore, an effect larger than the natural variability might be regarded as clinically relevant. The natural variability for the LCI2.5 is 1 unit[3] or 15 % of baseline[4]. Therefore, the results are considered relevant by the CHMP.

Not all of the 66 participants included in the FAS had data available at all time points because baseline results did not meet the criteria of acceptability. A requested multiple imputation-based method to account for these data if these four patients had any post-baseline data available were consistent with the primary analyses that excluded subjects with missing baseline.

Regarding the post-baseline data, it is acknowledged that all reasonable efforts to collect data given the COVID-19 pandemic were made. However, despite the effort, the collection of data on the endpoints at week 16 and week 24 was hampered by the pandemic. At week 16, e.g. ppFEV1 data were available for 29 patients and at week 24 data were only available for 15 patients under the usual follow-up schedule and for 24 patients when patients who participated in an unscheduled visit were included. The inclusion of patient data from unscheduled visits is likely to introduce bias into the estimate of the outcome as these data may be from healthier, lower-risk patients. It is also noted that some of these data were collected much later than 24 weeks based on the timing of the unscheduled visits.

Based on the accumulating evidence from previous studies, it is accepted that the effect of a modulator can already be observed around 4 to 8 weeks following treatment. At the request of the CHMP, rather than using additional analyses to try to reach a reasonable estimate of the within-group change through week 24, additional analyses excluding all Week 16 and 24 data were performed, that were consistent with the main analyses of the secondary efficacy endpoints of ppFEV1, SwCl, CFQ-R RD score, and LCI2.5, and that demonstrated a robust and clinically meaningful improvements. Because of the many missing data and the potential bias for the 24 weeks results, CHMP considered that both the results for 12 weeks and 24 weeks should be included in the SmPC.

Some patients also had missing data up to week 12. Given the very high reported rate of study and treatment completion, the reasons why these data were missing were unclear. For the sensitivity analysis, given the way the missing categories were defined, only 2 participants would have been allocated to the missing category 1, for which it was assumed that the mean response at a particular

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

timepoint was the lower quartile of the observed data. The other participants had missing data imputed based on the mean of the observed data. Therefore, this sensitivity analysis is essentially making the same (MAR) assumptions as the MMRM model. Because the efficacy endpoints are secondary to the PK results and the lack of a control group limits the options for further sensitivity analysis, additional sensitivity analyses were not requested. Instead, at the request of the CHMP, to support the new analyses at week 12, the MAH provided the missing data patterns for the FAS population up to and including week 12, and where available, provided reasons for these missing data. Given the strength of the effect in both the week 12 and week 24 results, and the low number of "Category 1" discontinuations, no further analyses were deemed necessary by CHMP.

Upon request from CHMP, subanalyses for the F/F and F/MF patient groups were presented by the MAH. The populations F/F and F/MF were comparably represented in the overall population. The results of both populations are generally in line with the overall group. The improvements were in both groups clinically meaningful.

Indication

The population of patients with F/MF or F/F genotypes investigated in Study 106 is tighter than the population for which Kalydeco, in combination with Kaftrio, has recently been authorised by the CHMP (EMEA/H/C/002494/II/0089). In this procedure, the indication was broadened to include CF patients from the age of 12 years with F/RF and F/G mutations to the already registered CF patients with F/F and F/MF mutations, resulting in the current indication of CF in patients 12 years and older who have at least one F508del mutation in CFTR gene.

Therefore, the CHMP requested the MAH to discuss whether the available clinical data for patients aged 6 through 11 years with the F/F and F/MF mutations could be extrapolated to patients with F/Any mutations. This is discussed below.

Principle of Extrapolation

The extension of the indication to children 6 through 11 years old is based on the principle of partial extrapolation from adult and adolescents to paediatric patients in line with the indication extension of Symkevi (TEZ/IVA) (EMEA/H/C/004682/X/0015).

Consistent with the principles described in ICH E11, extrapolation of efficacy from adults to a younger population based on comparable PK exposures and safety is acceptable, because the disease process in CF patients of all age groups stems from a common aetiology of dysfunctional CFTR protein that is targeted by ELX/TEZ/IVA in combination with IVA. The defect of the defective chloride channels is already present at birth. Because ELX/TEZ/IVA in combination with IVA targets the dysfunctional CFTR, the outcome of therapy is expected to be comparable in younger age groups compared to adults.

Extrapolation of efficacy is also supported by previously demonstrated efficacy in controlled studies of CF subjects 6 through 11 years of age treated with other CFTR modulators (LUM/IVA and TEZ/IVA) in combination with Kalydeco (IVA), which was comparable to the effect observed in adults.

This is also outlined in the EMA Reflection paper on the use of extrapolation in the development of medicines for paediatrics (EMA/189724/2018) that describes the requirements of the application of the (partial) extrapolation, i.e., confirmation of the dose by PK study in children and bridging of safety and efficacy data in children.

In conclusion, the further extrapolation to CF subjects 6 through 11 years of age with F/G and F/RF mutation is acceptable based on the same arguments as for the CF patients with F/F and F/MF mutations and taking into account the additional evidence of the statistically significant benefits of

ELX/TEZ/IVA over previously available CFTR modulators (IVA or TEZ/IVA) in CF subjects ≥ 12 years of age with F/RF and F/G genotypes.

### 2.4.4. Conclusions on the clinical efficacy

The results in the efficacy endpoints generally support a benefit in the investigated population. However, the results are impacted by missing data because of the COVID-19 pandemic and related restrictions during the later stage of the study. As known from previous trials, by week 12, steady and reliable results can already be observed. The analyses excluding all Week 16 and 24 data, were consistent with the main analyses of the secondary efficacy endpoints of ppFEV1, SwCl, CFQ-R RD score, and LCI2.5, and demonstrated a robust and clinically meaningful improvements.

The extension of the indication to children 6 through 11 years old who are heterozygous for *F508del* and a minimal function (MF) mutation (F/MF genotypes) or homozygous for *F508del* (F/F genotype) is based on the principle of partial extrapolation from adult and adolescents to paediatric patients. The principle of partial extrapolation can be considered justified in CF for the CFTR therapies, because of the similar underlying genetic, and molecular aetiology of CF of children and patients ≥ 12 years. Children and adults share the same disease characteristics although they are more severe in adults because of the progression of the symptoms. Efficacy is a secondary objective in this application. The extrapolation is based on comparable exposure and safety.

Further, extrapolation of efficacy data in CF patients with F/F and F/MF mutations to CF subjects 6 through 11 years of age with F/G and F/RF mutation is acceptable considering also the additional evidence of the statistically significant benefits of ELX/TEZ/IVA over previously available CFTR modulators (IVA or TEZ/IVA) in CF subjects ≥ 12 years of age with F/RF and F/G genotypes.

Thus, the following extended indication for Kalydeco is considered acceptable by the CHMP:

*Kalydeco is indicated in a combination regimen with ivacaftor/tezacaftor/elexacaftor tablets for the treatment of adults, adolescents, and children aged 6 years and older with cystic fibrosis (CF) who have at least one F508del mutation in the CFTR gene (see section 5.1).*

## *2.5. Clinical safety*

### *Introduction*

The clinical safety of Kalydeco in combination with Kaftrio was previously assessed in the clinical study in patients aged ≥ 12 years.

The main clinical safety database to support the application in children aged 6 through 11 years includes the safety data from Study 106, a Phase 3, single arm, multi-centre study conducted in 2 parts (Parts A and B) to evaluate the pharmacokinetic (PK), safety, and tolerability of ELX/TEZ/IVA in CF subjects 6 through 11 years of age who are homozygous for F508del (F/F genotype) or heterozygous for F508del and a minimal function (MF) mutation (F/MF genotypes).

Only data from this paediatric study was provided. No integrated safety report has provided including the comparison with adult and adolescent patients. The treatment duration in part A of the study was relatively short, thus the core safety analyses are provided from part B, where patients were treated for 24 weeks. The safety assessments included adverse events (AEs), clinical laboratory assessments, standard 12-lead ECGs, vital signs, pulse oximetry, physical examinations, and ophthalmologic examinations (OEs).

Patients who completed study 106, were offered the opportunity to enrol in Study 107, a 96-week open-label extension study, in which they continue receiving treatment with ELX/TEZ/IVA. The study is currently ongoing and data will be submitted in the post-approval setting (by Q1 2023).

The study VX18-445-106 took place during the COVID-19 pandemic. Subjects who missed the Week 24 visit were requested to return and complete an unscheduled visit to capture safety laboratory testing missed due to the COVID-19 pandemic, as well as any AEs related to laboratory testing.

## *Patient exposure*

Study VX18-445-106 consists of two parts. In Part A, all patients received the same dose of ELX/TEZ/IVA and IVA. In part B, the patients received a weight-based posology based on the provided PK data of Part A.

**Part A**

A total of 16 subjects received at least 1 dose of study drug in the Part A treatment period. The mean (SD) exposure was 14.9 (0.68) days (Table 28).

**Part B**

A total of 66 subjects received at least 1 dose of study drug in the Part B treatment Period, with a mean (SD) exposure of 23.8 (3.0) weeks (Table 29).

**Table 28. Summary of exposure (Safety Set, Part A)**

| | **ELX/TEZ/IVA N = 16** |
|---|---|
| Total exposure (patient weeks) | 34.1 |
| Exposure duration (days) | |
| n | 16 |
| Mean (SD) | 14.9 (0.68) |
| Median | 15.0 |
| Min, max | 14, 16 |
| | |
| Exposure duration by interval, n (%) | |
| ≤2 days | 0 |
| >2 to ≤4 days | 0 |
| >4 to ≤8 days | 0 |
| >8 to ≤15 days | 13 (81.3) |
| >15 days | 3 (18.8) |

ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; TEZ: tezacaftor
Notes: Total exposure was defined as the sum total of the study drug exposure across all subjects. Duration of study drug exposure (days) = (last dose date – first dose date + 1), regardless of study drug interruption. Duration of study drug exposure (weeks) = duration of study drug exposure (days)/7; 1 week = 7 days.

**Table 29. Summary of exposure (Safety Set, Part B)**

| | **ELX/TEZ/IVA N = 66** |
|---|---|
| Total exposure (patient weeks) | 1570.4 |
| Total exposure (patient years) | 32.7 |
| Exposure duration (weeks) | |
| n | 66 |
| Mean (SD) | 23.8 (3.0) |
| Median | 24.1 |
| Min, max | 0.1, 24.9 |
| Exposure duration by interval, n (%) | |
| ≤15 days | 1 (1.5) |
| >15 days to ≤20 weeks | 0 |
| >20 to ≤24 weeks | 27 (40.9) |
| >24 weeks | 38 (57.6) |

ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; TEZ: tezacaftor
Notes: Total exposure was defined as the sum total of the study drug exposure across all subjects. Duration of study drug exposure (weeks) = (last dose date – first dose date + 1)/7, regardless of study drug interruption. Duration of study drug exposure (years) = (last dose date - first dose date + 1)/336, regardless of study drug interruption; 336 days = 48 weeks.

## *Adverse events*

### Adverse events part A and part B

The AEs generated in study VX18-445-106 are briefly summarized in Table below. During the study, there were no deaths reported. Most adverse events were well tolerated.
A total of one patient experience serious AEs (pneumonia, metapneumovirus infection, and rhinovirus infection), and one patient experienced an AE (rash erythematous) discontinuation. Two patients experienced AEs (one patient rash maculo-papular; one patient diarrhea, pyrexia, and vomiting), that led to interruption of treatment (Table 30).

**Table 30. Overview of the AE's (safety set, part A and Part B**

| Category | Part A N=16 n (%) | Part B N = 66 n (%) |
|---|---|---|
| **Number of AEs (total)** | 44 | 341 |
| **Subjects with any AEs** | 12 (75.0) | 65 (98.5) |
| **Subjects with AEs by strongest relationship** | | |
| Not related | 1 (6.3) | 16 (24.2) |
| Unlikely related | 2 (12.5) | 16 (24.2) |
| Possibly related | 9 (56.3) | 29 (43.9) |
| Related | 0 | 4 (6.1) |
| **Subjects with AEs by maximum severity** | | |
| Mild | 10 (62.5) | 36 (54.5) |
| Moderate | 1 (6.3) | 28 (42.4) |
| Severe | 1 (6.3) | 1 (1.5) |
| Life-threatening | 0 | 0 |
| Missing | 0 | 0 |
| **Subjects with AEs leading to study drug discontinuation** | 0 | 1 (1.5) |
| **Subjects with AEs leading to study drug interruption** | 1 (6.3) | 1 (1.5) |
| **Subjects with Grade 3/4 AEs** | 1 (6.3) | 1 (1.5) |
| **Subjects with SAEs** | 0 | 1 (1.5) |
| **Subjects with AEs leading to death** | 0 | 0 |
| **Subjects with related AEs[a]** | 9 (56.3) | 33 (50.0) |
| **Subjects with related SAE[a]** | 0 | 0 |

AE: adverse event; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; SAE: serious adverse event; TEZ: tezacaftor Notes: When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percentage of subjects, a subject with multiple events within a category was counted only once in that category.
[a] When summarizing number of subjects with related AEs and SAEs, AEs with relationship of related, possibly related, and missing were counted.

### Adverse events Part A

In part A, a total of 12 (75%) subjects had at least one AE. One (6.3%) subject had a severe AE.

No subjects discontinued study drug due to AEs, and 1 (6.3%) subject interrupted study drug due to rash maculo-papular, unlikely related to medication (Table 30)

Adverse events that occurred in ≥ 2 patients (Table 31) were cough (n=5, 31.3%), rash (n=3, 18.8%), sputum increased (n=3, 18.8%), nasal congestion (n=2, 12.5%) and productive cough (n=2, 12.5%).

Treatment related adverse events occurred in 9 patients. The most frequently reported treatment related adverse events were sputum increased (n=3, 18.8%), cough (n=2, 12.5%) and productive cough (n=2, 12.5 %) (Table 32).

**Table 31. Adverse events occurring in ≥ 2 subjects by System Organ Class and Preferred Term (Study 106, Part A, safety set**

| System Organ Class<br>Preferred Term | ELX/TEZ/IVA<br>N = 16<br>n (%) |
|---|---|
| Subjects with any AEs | 12 (75.0) |
| **Respiratory, thoracic and mediastinal disorders** | **10 (62.5)** |
| Cough | 5 (31.3) |
| Sputum increased | 3 (18.8) |
| Nasal congestion | 2 (12.5) |
| Productive cough | 2 (12.5) |
| **Skin and subcutaneous tissue disorders** | **5 (31.3)** |
| Rash | 3 (18.8) |

AE: adverse event; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; TEZ: tezacaftor
Note: A subject with multiple events within a category was counted only once in that category.

**Table 32 Treatment related AEs by System Organ Class and Preferred Term - Part A Safety Set**

| System Organ Class<br>Preferred Term | VX-445/TEZ/IVA<br>N = 16<br>n (%) |
|---|---|
| **Subjects with any treatment related AEs** | **9 (56.3)** |
| **Respiratory, thoracic and mediastinal disorders** | **6 (37.5)** |
| Sputum increased | 3 (18.8) |
| Cough | 2 (12.5) |
| Productive cough | 2 (12.5) |
| Respiration abnormal | 1 (6.3) |
| **Investigations** | **2 (12.5)** |
| Blood alkaline phosphatase increased | 1 (6.3) |
| Transaminases increased | 1 (6.3) |
| **Skin and subcutaneous tissue disorders** | **2 (12.5)** |
| Rash | 2 (12.5) |
| **Gastrointestinal disorders** | **1 (6.3)** |
| Abdominal pain upper | 1 (6.3) |
| **General disorders and administration site conditions** | 1 (6.3) |
| Chest pain | 1 (6.3) |

AE: adverse event; ALT: alanine transaminase; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; PT: Preferred Term; TEZ: tezacaftor
Notes: AEs were coded using MedDRA version 21.1. A subject with multiple events within a category was counted only once in that category. The table was sorted in descending order of frequency by System Organ Class, and by PT within each System Organ Class.

**Adverse events Part B**

In part B, a total of sixty-five (98.5%) subjects had at least 1 AE. Most subjects had AEs that were mild or moderate in severity; 1 (1.5%) subject had severe AEs. One (1.5%) subject each had SAEs, discontinued study drug due to an AE, and interrupted study drug due to AEs (Table 30).

The most frequently reported adverse events were cough (n=28, 42.4%), headache (n=16, 24.2%) and pyrexia (n=14, 21.2%).
Additional AEs reported with a frequency > 10% were oropharyngeal pain (n=12, 18.2%), upper respiratory tract infection (n=11, 6.7%), nasal congestion (n=10, 15.2%), abdominal pain (n=8, 12.1%), rash (n=8, 12.1%), rhinorrhea (n=8, 12.1%), viral upper respiratory tract infection (n=8, 12.1%), ALT increased (n=7, 10.6%), diarrhea (n=7, 10.6%), influenza (n=7, 10.6%), and vomiting (n=7, 10.6%) (Table 33).

Treatment related adverse events were reported in a total of 33 patients (50%).The most frequently reported treatment related adverse event by PT was abdominal pain (n=6, 9.1%), followed by alanine aminotransferase increase (n=5, 7.6%), rash (n=4, 6.1%) and headache (n= 4,6.1%) (Table 34).

**Table 33 Adverse events Occurring in ≥ 2 Subjects by SOC and PT -safety set part B**

| **System Organ Class**<br>**Preferred term** | **ELX/TEZ/IVA**<br>**n=66**<br>**n (%)** |
|---|---|
| **Respiratory, thoracic and mediastinal disorders** | **48 (72.7)** |
| Cough | 28 (42.4) |
| Oropharyngeal pain | 12 (18.2) |
| Nasal congestion | 10 (15.2) |
| Rhinorrhoea | 8 (12.1) |
| Productive cough | 5 (7.6) |
| Sputum increased | 3 (4.5) |
| Wheezing | 3 (4.5) |
| Bronchospasm | 2 (3.0) |
| Epistaxis | 2 (3.0) |
| **Infections and infestations** | **34 (51.5)** |
| Upper respiratory tract infection | 11 (16.7) |
| Viral upper respiratory tract infection | 8 (12.1) |
| Influenza | 7 (10.6) |
| Ear infection | 4 (6.1) |
| Conjunctivitis | 3 (4.5) |
| Infective pulmonary exacerbation of cystic fibrosis | 3 (4.5) |
| Pharyngitis | 2 (3.0) |
| **Gastrointestinal disorders** | **27 (40.9)** |
| Abdominal pain | 8 (12.1) |
| Diarrhoea | 7 (10.6) |
| Vomiting | 7 (10.6) |
| Abdominal pain upper | 5 (7.6) |
| Constipation | 4 (6.1) |
| Flatulence | 2 (3.0) |
| Nausea | 2 (3.0) |
| **General disorders and administration site conditions** | **19 (28.8)** |
| Pyrexia | 14 (21.2) |
| Fatigue | 5 (7.6) |
| **Skin and subcutaneous tissue disorders** | **19 (28.8)** |
| Rash | 8 (12.1) |

| System Organ Class<br>Preferred term | ELX/TEZ/IVA<br>n=66<br>n (%) |
|---|---|
| Rash erythematous | 3 (4.5) |
| Dermatitis contact | 2 (3.0) |
| Rash maculo-papular | 2 (3.0) |
| Rash papular | 2 (3.0) |
| **Investigations** | **16 (24.2)** |
| Alanine aminotransferase increased | 7 (10.6) |
| Activated partial thromboplastin time prolonged | 2 (3.0) |
| Aspartate aminotransferase increased | 2 (3.0) |
| Blood creatine phosphokinase increased | 2 (3.0) |
| Influenza B virus test positive | 2 (3.0) |
| International normalised ratio increased | 2 (3.0) |
| Prothrombin time prolonged | 2 (3.0) |
| **Nervous system disorders** | **16 (24.2)** |
| Headache | 16 (24.2) |
| **Injury, poisoning and procedural complications** | **7 (10.6)** |
| Skin laceration | 2 (3.0) |
| **Psychiatric disorders** | **7 (10.6)** |
| Anxiety | 2 (3.0) |
| Depressed mood | 2 (3.0) |
| **Ear and labyrinth disorders** | **5 (7.6)** |
| Ear pain | 2 (3.0) |
| **Musculoskeletal and connective tissue disorders** | **3 (4.5)** |
| **Metabolism and nutrition disorders** | **2 (3.0)** |
| Decreased appetite | 2 (3.0) |

AE: adverse event; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size;TEZ: tezacaftor

Note: A subject with multiple events within a category was counted only once in that category.

**Table 34. Treatment related adverse events by SoC and PT-safety set part B**

| System Organ Class<br>Preferred Term | ELX/TEZ/IVA<br>N = 66<br>n (%) |
|---|---|
| **Subjects with any related TEAEs** | **33 (50.0)** |
| **Gastrointestinal disorders** | **12 (18.2)** |
| Abdominal pain | 6 (9.1) |
| Abdominal pain upper | 2 (3.0) |
| Nausea | 2 (3.0) |
| Diarrhoea | 1 (1.5) |
| Post-tussive vomiting | 1 (1.5) |
| Vomiting | 1 (1.5) |
| **Respiratory, thoracic and mediastinal disorders** | **11 (16.7)** |
| Cough | 3 (4.5) |
| Sputum increased | 3 (4.5) |
| Productive cough | 2 (3.0) |
| Bronchospasm | 1 (1.5) |
| Haemoptysis | 1 (1.5) |
| Nasal congestion | 1 (1.5) |
| Pleuritic pain | 1 (1.5) |

| | |
|---|---|
| Rhinorrhoea | 1 (1.5) |
| Sputum discoloured | 1 (1.5) |
| Wheezing | 1 (1.5) |
| **Skin and subcutaneous tissue disorders** | **8 (12.1)** |
| Rash | 4 (6.1) |
| Rash erythematous | 2 (3.0) |
| Rash maculo-papular | 2 (3.0) |
| Rash papular | 1 (1.5) |
| **Investigations** | **7 (10.6**) |
| Alanine aminotransferase increased | 5 (7.6) |
| Aspartate aminotransferase increased | 1 (1.5) |
| Blood bilirubin increased | 1 (1.5) |
| Blood creatine phosphokinase increased | 1 (1.5) |
| **Nervous system disorders** | **4 (6.1)** |
| Headache | 4 (6.1) |
| **Psychiatric disorders** | **3 (4.5)** |
| Aggression | 1 (1.5) |
| Anxiety | 1 (1.5) |
| Depressed mood | 1 (1.5) |
| **General disorders and administration site conditions** | **1 (1.5)** |
| Fatigue | 1 (1.5) |
| **Injury, poisoning and procedural complications** | **1 (1.5)** |
| Accidental overdose | 1 (1.5) |

MedDRA version 23.0.
- A subject with multiple events within a category is counted only once in that category.
- Table is sorted in descending order of frequency of the ELX/TEZ/IVA column by System Organ Class, and by Preferred Term within each System Organ Class. When summarizing number of subjects with related TEAEs, TEAEs with relationship of related, possibly related, and missing are counted.

### *Adverse events of special interest*

Adverse events of special interests were AEs of elevated transaminases, rash and ophthalmic examinations. AESIs of elevated transaminases and rash occurred in both parts of the study, however, no subjects had AEs of cataract or lens opacity (see below).

- Elevated Transaminase Events

In part A, one subject (1/16, 6.3%) with a history of liver function test increased had a nonserious AE of transaminases increased 1 day after the last dose of study drug treatment; the AE was considered by the investigator to be mild in severity and possibly related to study drug

In part B, most patients had ALT and AST levels that remained in the normal range. Seven (10.6%) subjects had elevated transaminase events. All events were mild or moderate in severity. None of the events were serious or led to treatment discontinuation or interruption. The elevated transaminase events had a mean (SD) duration of 15.3 (9.0) days, and the mean (SD) time-to-onset of first event was 52.1 (62.2) days.

- Rash Events

In part A, five subjects (5/16, 31.3%) had a total of 6 rash events. All events were mild in severity, were nonserious, and had an outcome of recovered/resolved. One subject had an AE of rash maculo-papular that led to study drug interruption.

In Part B, sixteen (24.2%) subjects had at least 1 rash event. Of these 16 subjects, most subjects had rash events that were assessed as either not related or unlikely related to study drug and/or had alternative etiologies (e.g., due to viral infection or heat exposure). All rash events were mild or moderate in severity.

One subject had a rash event of moderate severity that led to treatment discontinuation.
All other rashes resolved without treatment discontinuation or interruption. The rash events had a mean (SD) duration of 6.0 (5.5) days, and the mean (SD) time-to-onset of first event was 22.7 (31.3) days.

By sex, 11 (28.2%) female subjects and 5 (18.5%) male subjects had rash events

- Ophthalmologic examinations (Part B).

Ophthalmologic examination occurred at screening and at the end of treatment. No subjects had AEs of cataract or lens opacity.

Not all patients of part B underwent a post-treatment ophthalmologic examination because of the COVID pandemic. The number of patients that underwent ophthalmologic examination before and after treatment is not reported.

## *Serious adverse event/deaths/other significant events*

During the study VX18-445-106, one SAE occurred in Part B of the study in one subject. The event was assessed as moderate in severity and unlikely related to study drug, did not lead to study treatment discontinuation or interruption, and resolved. This event is considered unlikely to be related to treatment.

No deaths occurred during the study.

## *Laboratory findings*

**Chemistry**

**Part A**

In part A, there were no trends observed in the Liver Function Test and non-Liver Function Test chemistry parameters. No subjects had ALT or AST >3 × ULN in the TE Period, nor total bilirubin >2 × ULN.

**Part B**

In part B, most subjects had ALT and AST values that remained within the normal range. Mean concentrations of LFT parameters were variable, without consistent trends over time in ALT, AST, ALP, or GGT values.

Seven (10.6%) subjects had ALT or AST >3 × ULN, and 1 (1.5%) subject had ALT or AST >5 × ULN; no subjects had ALT or AST >8 × ULN. No subject had ALT or AST >3 × ULN with concurrent total bilirubin elevation >2 × ULN (Table 35).

Most subjects had bilirubin values that remained within the normal range (Table 35); One (1.5%) subject had 2 AEs of blood bilirubin increased, neither of which were serious or led to treatment discontinuation or interruption. In one patient the AE was considered related to treatment.

No subjects had AEs of GGT increased or ALP increased, although the lab assessment showed elevations of GGT and ALP above the threshold values.

**Table 35. Threshold analyses of LFT chemistry parameters during the TE period**

| Post baseline threshold analysis criteria | ELX/TEZ/IVA N=66 |
|---|---|
| **AST (U/L)** | |
| >ULN to ≤3 × ULN | 23 (34.8) |
| >3 × ULN | 0 |
| **ALT (U/L) or AST (U/L)** | |
| (ALT>ULN to ≤3 × ULN) or (AST>ULN to ≤3 × ULN) | 44 (66.7) |
| (ALT>3 × ULN) or (AST>3 × ULN) | 7 (10.6) |
| (ALT>5 × ULN) or (AST>5 × ULN) | 1 (1.5) |
| **Total bilirubin (µmol/L)** | |
| >ULN to ≤1.5 × ULN | 7 (10.6) |
| >1.5 × to ≤2 × ULN | 4 (6.1) |
| **Direct bilirubin (µmol/L)** | |
| >ULN to ≤1.5 × ULN | 10 (15.2) |
| **Indirect bilirubin (µmol/L**) | |
| >ULN to ≤1.5 × ULN | 8 (12.3) |
| >1.5 × to ≤2 × ULN | 1 (1.5) |
| >2 × to ≤3 × ULN | 3 (4.6) |
| (**ALT or AST) and TBILI** | |
| (ALT>3 × ULN or AST>3 × ULN) and TBILI>2 × ULN | 0 |
| **Lipase ALP (U/L)** | |
| >ULN to ≤1.5 × ULN | 17 (25.8) |
| >1.5 × to ≤2.5 × ULN | 2 (3.0) |
| **GGT (U/L)** | |
| >ULN to ≤2.5 × ULN | 7 (10.6) |
| >2.5 × to ≤5 × ULN | 1 (1.5) |

ALP: alkaline phosphatase; ALT: alanine transaminase; AST: aspartate transaminase; ELX: elexacaftor; GGT: gamma-glutamyl transferase; IVA: ivacaftor; LFT: liver function test; n: number of subjects in the post-baseline category; N: total sample size; N1: number of subjects with at least 1 non-missing measurement during the TE Period in Part B; TBILI: total bilirubin; TE: treatment-emergent; TEZ: tezacaftor; ULN: upper limit of normal
Note: Within each parameter, a subject was counted in all applicable post-baseline categories based on the worst assessment during the TE Period in Part B. Percentages were evaluated as n/N1. Threshold criteria involving 2 LFT parameters could be determined by assessments at different visits during the TE Period

**Creatine Kinase**

The mean CK concentration was variable over time; overall, increases from baseline were observed. The mean (SD) increase in CK ranged from 30.2 (32.7) U/L at Week 12 to 53.4 (68.8) U/L at Week 24

Most subjects had CK levels that remained within the normal range; a total of 21 (31.8%) subjects had CK levels > ULN to ≤ 2.5 ULN, 4 (6.1%) subjects had CK levels >2.5 × ULN, and no subjects had CK levels >5 × ULN.

AEs of CK elevation occurred in 2 (3.0%) subjects; in one patient it was considered to be related to medication (Table 34). Neither AE was serious or led to study drug discontinuation or interruption, and both AEs resolved without treatment.

**Haemaotology**

Minor decreases from baseline in mean platelets, leukocytes, and neutrophils were observed: mean values of these parameters were not below the respective normal range at any assessed time point.

Two subjects had mild AEs related to haematology findings (1 subject with leukopenia, 1 subject with white blood cell count increased); none of the AEs were serious or led to treatment discontinuation or interruption.

**Coagulopathy**

There were no trends observed in coagulation parameters. Three subjects had AEs related to coagulation findings considered not to be related to treatment; none of the AEs were serious or led to treatment discontinuation or interruption.

**Vital signs**

All patients (100%) in part A and a total of n= 33 (50% of the safety set) patients in part B completed the safety measurements (blood pressure, ECG) at the end of the treatment period.

Decreases from baseline in pulse rate were observed. The mean (SD) decrease in pulse rate ranged from -1.8 (10.9) bpm at Week 16 to -4.8 (13.6) bpm at Week 4. There were no other trends observed in other vital signs parameters, including BP. No subjects had AEs related to Blood pressure of pulse rate findings.

One subject had an AE of defect conduction intraventricular, which was nonserious, not related to study drug, and did not lead to treatment discontinuation or interruption; no other subjects had AEs related to ECG findings or relevant cardiac disorders.

## *Discontinuation due to adverse events*

All patients in part A completed the study.

One patient (1.5%) in part B discontinued prematurely due to adverse events. This subject had a treatment related AE of rash erythematous of moderate severity. The study drug was withdrawn, and a single dose of cetirizine was administered: the event resolved the next day.

**Treatment interruptions due to AEs**

The treatment was temporarily interrupted in two patients: one in part A and one in part B.

In part A, one (6.3%) subject had an AE of rash maculo-papular of mild intensity. The AE resolved; the subject resumed ELX/TEZ/IVA and completed dosing. The AE was considered unrelated to treatment.

In part B, the treatment was temporarily interrupted in one patient because of AEs unlikely to be related to medication. The dose of ivacaftor was interrupted for one day and the event resolved.

**Comparisons of the safety profile in patients aged ≥ 12 and patients aged 6 through 11 years old**

Upon request from CHMP, the MAH provided a comparison of the adverse events observed in the paediatric population (children aged 6 through 11 years) and the patients aged ≥ 12 years.

The safety data for the paediatric population is obtained in study 106 part B. The safety for the patients aged ≥ 12 years is obtained in study 102. As both studies were of the same duration, the comparison of the AE incidence data is provided.

**Comparisons overall safety profile**

The overall adverse event profile by number of AE's, treatment related AE, discontinuations etc. show a comparable number of events are comparable between the paediatric population and the patients aged ≥ 12 years (Table 36).

**Table 36. Overview of Adverse Events (Study 102 Safety Set, Study 106 Part B Safety Set), Through 24 Weeks of Treatment**

| | Study 102 | | Study 106 Part B |
|---|---|---|---|
| | **Placebo** N = 201 n (%) | **ELX/TEZ/IV AN = 202** n (%) | **ELX/TEZ/IV AN = 66** n (%) |
| Number of AEs (total) | 1287 | 1098 | 341 |
| Subjects with any AEs | 193 (96.0) | 188 (93.1) | 65 (98.5) |
| Subjects with AEs by strongest relationship | | | |
| Not related | 83 (41.3) | 53 (26.2) | 16 (24.2) |
| Unlikely related | 58 (28.9) | 39 (19.3) | 16 (24.2) |
| Possibly related | 46 (22.9) | 86 (42.6) | 29 (43.9) |
| Related | 6 (3.0) | 10 (5.0) | 4 (6.1) |
| Subjects with AEs by maximum severity | | | |
| Mild | 53 (26.4) | 67 (33.2) | 36 (54.5) |
| Moderate | 125 (62.2) | 102 (50.5) | 28 (42.4) |
| Severe | 14 (7.0) | 19 (9.4) | 1 (1.5) |
| Life-threatening | 1 (0.5) | 0 (0) | 0 (0) |
| Missing | 0 (0) | 0 (0) | 0(0) |
| Subjects with AEs leading to study drug discontinuation | 0 (0) | 2 (1.0) | 1 (1.5) |
| Subjects with AEs leading to study drug interruption | 10 (5.0) | 19 (9.4) | 1 (1.5) |
| Subjects with Grade 3/4 AEs | 15 (7.5) | 19 (9.4) | 1 (1.5) |
| Subjects with related AEs[a] | 52 (25.9) | 96 (47.5) | 33 (50.0) |
| Subjects with SAEs | 42 (20.9) | 28 (13.9) | 1 (1.5) |
| Subjects with related SAEs[a] | 2 (1.0) | 6 (3.0) | 0 (0) |
| Subjects with AEs leading to death | 0 (0) | 0 (0) | 0 (0) |

AE: adverse event; ELX: elexacaftor; IVA: ivacaftor; n: size of subsample; N: total sample size; SAE: serious adverse event; TEZ: tezacaftor

Notes: When summarizing number of events, a subject with multiple events within a category was counted multiple times in that category. When summarizing number and percentage of subjects, a subject with multiple events within a category was counted only once in that category.

[a] When summarizing number of subjects with related AEs and SAEs, AEs with relationship of related, possibly related, and missing were counted.

*Adverse event irrespective of causal relationship*

In addition, to the overall adverse event profile, also a comparison of the AE by SoC and PT were presented, irrespective of the causal relationship

In the paediatric population, the following SoC showed a higher frequency (≥ 5%) compared to the ≥ 12 year old population i.e.:

- SOC Respiratory, thoracic and mediastinal i.e. 73% vs 50%
- SOC General disorders and administration site conditions 29% vs 16%

In the **SOC Respiratory, thoracic and mediastinal adverse events**, the largest difference in the AE (PT) is shown by the PT cough 42% vs 17%, nasal congestion (15% vs 9%), oropharyngeal pain (~ 18% vs 10%) and rhinorhoea (~12 vs 8%).

In the **SOC General disorders and administration site conditions**, the differences between the paediatric and adult population (29% vs 17%) is driven by the higher reported frequency of pyrexia (21% vs, 8%). In the paediatric population, none of the adverse events were considered being related to study medication.

The **SOC Investigations** showed a higher reported frequency of the PT blood creatine phosphokinase increase in the population aged ≥ 12 years (9.4% vs 3%) compared the paediatric population

**Table 37. Adverse Events by System Organ Class and Preferred Term in Study 102(Safety Set), and Study 106 Part B (Safety Set);**
**PT with a difference > 5% between study 102 and 106, of referring to an AE of specific interest**

| System Organ Class<br>PreferredTerm | Placebo<br>N = 201<br>n (%) | Study 102<br>ELX/TEZ/IVA<br>N = 202<br>n (%) | Study 106 Part B<br>ELX/TEZ/IVA<br>N = 66<br>n (%) |
|---|---|---|---|
| **Subjects with any AEs** | **193(96.0)** | **188 (93.1)** | **65 (98.5)** |
| **Infections and infestations** | **145(72.1)** | **121 (59.9)** | **34 (51.5)** |
| **Respiratory, thoracic and mediastinal** | **129(64.2)** | **100 (49.5)** | **48 (72.7)** |
| Cough | 77 (38.3) | 34 (16.8) | 28 (42.4) |
| Oropharyngeal pain | 25(12.4) | 20 (9.9) | 12 (18.2) |
| Nasal congestion | 15 (7.5) | 19 (9.4) | 10 (15.2) |
| Rhinorrhoea | 6 (3.0) | 17 (8.4) | 8 (12.1) |
| **Gastrointestinal disorders** | **58(28.9)** | **78 (38.6)** | **27 (40.9)** |
| Abdominal pain | 12 (6.0) | 20 (9.9) | 8 (12.1) |
| Vomiting | 10 (5.0) | 12 (5.9) | 7 (10.6) |
| Abdominal pain upper | 6 (3.0) | 9 (4.5) | 5 (7.6) |
| **Investigations** | **71(35.3)** | **66 (32.7)** | **16 (24.2)** |
| Alanine aminotransferase increased | 7 (3.5) | 20 (9.9) | 7 (10.6) |
| Aspartate aminotransferase increased | 4 (2.0) | 19 (9.4) | 2 (3.0) |
| Blood creatine phosphokinase increased | 9 (4.5) | 19 (9.4) | 2 (3.0) |
| Blood bilirubin increased | 2 (1.0) | 10 (5.0) | 1 (1.5) |
| **Nervous system disorders** | **40(19.9)** | **50 (24.8)** | **16 (24.2)** |
| **Skin and subcutaneous tissue disorders** | **29(14.4)** | **46 (22.8)** | **19 (28.8)** |

| | | | |
|---|---|---|---|
| Rash | 9 (4.5) | 18 (8.9) | 8 (12.1) |
| **General disorders and administration site conditions** | **55 (27.4)** | **33 (16.3)** | **19 (28.8)** |
| Pyrexia | 19 (9.5) | 17 (8.4) | 14 (21.2) |
| **Musculoskeletal and connective tissue** | **30(14.9)** | **27 (13.4)** | **3 (4.5)** |
| **Injury, poisoning and procedural complications** | **8 (4.0)** | **20 (9.9)** | **7 (10.6)** |
| **Psychiatric disorders** | **11 (5.5)** | **13 (6.4)** | **7 (10.6)** |
| **Eye disorders** | **10 (5.0)** | **8 (4.0)** | **1 (1.5)** |
| Lenticular opacities | 0 (0) | 1 (0.5) | 0 |
| **Ear and labyrinth disorders** | **4 (2.0)** | **7 (3.5)** | **5 (7.6)** |
| **Hepatobiliary disorders** | **2 (1.0)** | **7 (3.5)** | **0** |
| **Blood and lymphatic system disorders** | **5 (2.5)** | **6 (3.0)** | **1 (1.5)** |
| **Cardiac disorders** | **2 (1.0)** | **6 (3.0)** | **1 (1.5)** |
| **Renal and urinary disorders** | **10(5.0)** | **5 (2.5)** | **0** |
| **Immune system disorders** | **4 (2.0)** | **4 (2.0)** | **1 (1.5)** |
| **Vascular disorders** | **3 (1.5)** | **3 (1.5)** | **0** |
| **Congenital, familial and genetic disorders** | **3 (1.5)** | **0** | **0** |
| **Endocrine disorders** | **1 (0.5)** | **0** | **0** |
| **Product issues** | **2 (1.0)** | **0** | **0** |

*Table made by assessor in Kaftrio X/08/G procedure, The patients in study 102 are aged ≥ 12 years, in study 106 aged 6 through 11 years. Selection of the SoC and PT is based on the drug reported AE in study 106B and the incidence of n≥ 1 in study 102.*

*Differences in frequency of drug related adverse events*

Upon request, on overview of the drug related adverse event was provided (Table 38).

In the paediatric population, most drug related AE's were reported in the SOC Gastrointestinal disorders (18.2%), followed by the SOC Respiratory, Thoracic and Mediastinal disorders (16.7%), SOC Skin and subcutaneous tissue disorders (12.1%) and SOC investigations (10.6%).
For the ≥ 12 year old population, this frequency was SOC Respiratory, Thoracic and Mediastinal disorders (14.4%), SOC investigations (12%), the SOC Gastrointestinal disorders (10%), and Skin disorders (8.1%).

Regarding the **SOC investigations**, the paediatric population reported a higher frequency of treatment related ALAT increased compared with the adult population (7.6% vs 5.9 %), while the PT (ASAT increased 1.5% vs 5.4%) and blood bilurubin increase (1.5% vs 3.0%) were lower than reported in the ≥ 12 year old population.

**Table 38 Drug Related Adverse Events with by System Organ Class and Preferred Term in Study 102(Safety Set), and Study 106 Part B (Safety Set),**

| | Study 102 | | Study 106 Part B |
|---|---|---|---|
| **System Organ Class Preferred Term** | **Placebo N = 201 n (%)** | **ELX/TEZ/IVA N = 202 n (%)** | **ELX/TEZ/IVA N = 66 n (%)** |
| **Subjects with any related AEs** | **52 (25.9%** | **96 (47.5)** | **33 (50.0)** |
| **Infections and infestations** | **5 (2.5)** | **2 (1.0)** | **0 (0)** |
| **Respiratory, thoracic and mediastinal disorders** | **25 (12.4)** | **29 (14.4)** | **11 (16.7)** |
| Sputum increased | 10 (5.0) | 14 (6.9) | 3 (4.5) |
| Cough | 13 (6.5) | 7 (3.5) | 3 (4.5) |
| Productive cough | 5 (2.5) | 7 (3.5) | 2 (3.0) |
| Haemoptysis | 0 (0) | 4 (2.0) | 1 (1.5) |
| Respiration abnormal | 1 (0.5) | 4 (2.0) | 0 (0) |
| Rhinorrhoea | 3 (1.5) | 4 (2.0) | 1 (1.5) |
| Wheezing | 0 (0) | 1 (0.5) | 1 (1.5) |
| Nasal congestion | 4 (2.0) | 0 (0) | 1 (1.5) |
| Sputum discoloured | 1 (0.5) | 0 (0) | 1 (1.5) |
| Bronchospasm | 0 (0) | 0 (0) | 1 (1.5) |
| Pleuritic pain | 0 (0) | 0 (0) | 1 (1.5) |
| **Gastrointestinal disorders** | **12 (6.0)** | **22 (10.9)** | **12 (18.2)** |
| Abdominal pain | 1 (0.5) | 2 (1.0) | 6 (9.1) |
| Abdominal pain upper | 3 (1.5) | 5 (2.5) | 2 (3.0) |
| Nausea | 3 (1.5) | 4 (2.0) | 2 (3.0) |
| Diarrhea | 4 (2.0) | 4 (2.0) | 1 (1.5) |
| Vomiting | 0 (0) | 2 (1.0) | 1 (1.5) |
| Post-tussive vomiting | 0 (0) | 0 (0) | 1 (1.5) |
| **Investigations** | **9 (4.5)** | **26 (12.9)** | **7 (10.6)** |
| Alanine aminotransferase increased | 1 (0.5) | 12 (5.9) | 5 (7.6) |
| Aspartate aminotransferase increased | 0 (0) | 11 (5.4) | 1 (1.5) |
| Blood creatine phosphokinase increased | 2 (1.0) | 10 (5.0) | 1 (1.5) |
| Blood bilirubin increased | 0 (0) | 6 (3.0) | 1 (1.5) |
| **Nervous system disorders** | **10 (5.0)** | **11 (5.4)** | **4 (6.1)** |
| Headache | 8 (4.0) | 9 (4.5) | 4 (6.1) |
| **Metabolism and nutrition** | **3 (1.5)** | **6 (3.0)** | **0 (0)** |

| | | | |
|---|---|---|---|
| **disorders** | | | |
| **Skin and subcutaneous tissue disorders** | **7 (3.5)** | **18 (8.9)** | **8 (12.1)** |
| Rash | 3 (1.5) | 11 (5.4) | 4 (6.1) |
| Rash erythematous | 1 (0.5) | 0 (0) | 2 (3.0) |
| Rash maculo-papular | 0 (0) | 0 (0) | 2 (3.0) |
| Rash papular | 0 (0) | 0 (0) | 1 (1.5) |
| Pruritis | 0 (0) | 4 (2.0) | 0 (0) |
| Rash generalized | 0 (0) | 2 (1.0) | 0 (0) |
| **General disorders and administration site conditions** | **7 (3.5)** | **4 (2.0)** | **1 (1.5)** |
| Fatigue | 3 (1.5) | 3 (1.5) | 1 (1.5) |
| **Musculoskeletal and connective tissue** | **2 (1.0)** | **6 (3.0)** | **0 (0)** |
| **Injury, poisoning and procedural complications** | **0** (0) | **0 (0)** | **1 (1.5)** |
| **Accidental overdose** | 0 (0) | 0 (0) | 1 (1.5) |
| **Psychiatric disorders** | **2 (1.0)** | **3 (1.5)** | **3 (4.5)** |
| Anxiety | 0 (0) | 0 (0) | 1 (1.5) |
| Depressed mood | 0 (0) | 0 (0) | 1 (1.5) |
| Aggression | 0 (0) | 0 (0) | 1 (1.5) |

*Table made by assessor in Kaftrio X/08/G procedure, The patients in study 102 are aged ≥ 12 years, in study 106 aged 6 through 11 years. Selection of the SoC and PT is based on the drug reported AE in study 106B and the incidence of n≥ 2 in study 102.*

**Adverse event of Specific Interest**

Adverse events of special interests were AEs of elevated transaminases and AEs, rash and ocular lens opacity. As none of the paediatric patient had an AEsi of coular opacity, this will not be discussed furtherhere.

*AESI transaminase elevation*

A cross study comparison of the AESi of transaminase elevation is provided in table 39. The data show, that the occurrence of the AEsi (ALAT or ASAT ≥ 3 × ULN) were slightly higher in the paediatic population (10.6%) compared with the patients ≥ 12 years (7.9%). None of the paediatric patients reported ALT>3 × ULN or AST>3 × ULN) and TBILI>2 × ULN.

**Table 39. Analysis of Transaminase Elevations During the Treatment-emergent Period:**

| | Study 102 Placebo N=201 | Study 102 ELX/TEZ/IVA N=202 | Study 106 Part B ELX/TEZ/IVA N=66 |
|---|---|---|---|
| **ALT (U/L) or AST (U/L) cumulative** | | | |
| (ALT>3 × ULN) or (AST>3 × ULN) | 11 (5.5) | 16 (7.9) | 7 (10.6) |
| (ALT>5 × ULN) or (AST>5 × ULN) | 3 (1.5) | 5 (2.5) | 1 (1.5) |
| (**ALT or AST) and TBILI** | | | |
| (ALT>3 × ULN or AST>3 × ULN) and TBILI>2 × ULN | 0 | 2 (1.0) | 0 |

Source: table 49 EPAR Kaftrio, table overview.
ALT: alanine aminotransferase; AST: aspartate aminotransferase; IVA: ivacaftor; LFT: liver function test; n: size of subsample; N: total sample size; TEZ: tezacaftor; ULN: upper limit of normal
Table made by assessor The patients in study 102 are aged ≥ 12 years, in study 106 aged 6 through 11 years

**AESI Rash**

The generalised AEsi Rash included the PT Rash, PT Rash generalised, Rash macular, Rash pruritic, Rash erythematous, Rash maculo-papular and Rash papular.

The paediatric population showed an approximately 2 times higher reported frequency reported than in the ≥ 12 year old population for both AEsi-Rash-irrespective-of-causality (24.2 vs 10.9%), and the AEsi-Rash-treatment-related (12.1% vs 6.9%).

### *Post marketing experience*

As of 20 October 2020, it is estimated that 23,556 patients (representing 13,467.1 person-years) have been exposed to ELX/TEZ/IVA in combination with IVA through worldwide commercial access.

## 2.5.1. Discussion on clinical safety

The main safety data set to support the application in in children aged 6 through 11 consist of the safety data of part B of the single arm, open label study VX18-445-106, where 66 patients were treated for 24 weeks.

The provided safety data set to support the application is considered limited to support a medicinal product intended for chronic use. Also, because of COVID pandemic, not all patients underwent a full safety measurement after completion of the study.

In addition to its limited data set size and treatment duration, the safety data is collected in an uncontrolled, open-label study, in which the contribution from the longer disease duration is hard to distinguish from the longer drug exposure. Upon CHMP request, a cross study comparison of the safety profile obtained in the paediatric population and the patients aged ≥ 12 years was provided to support the safety profile obtained in the paediatric population.

Overall, the provided paediatric safety set shows that the treatment appears well tolerated up to 24 weeks in the paediatric population, as shown by the reported low number of serious adverse events (1.5%), treatment interruptions (1.5%) and treatment discontinuations due to AE (1.5%). Similarly to the patients aged ≥ 12 years, the treatment appears well tolerated and the safety profile is overall consistent with the known safety profile of these products.

There is an open-label extension roll over study 107 currently ongoing which should provide an opportunity to collect the missing safety data. This study will provide more prolonged safety data (up

to 96 weeks), although the included paediatric patients number will still be limited (n=64). The data will need to be submitted once the study is completed (by Q1 2023).

*Adverse events, serious adverse events and deaths*

Nearly all paediatric patients (98.5%) experienced an adverse event. The reported adverse events were most likely related to common manifestation of CF disease or common illnesses.

About 50% of patients experienced an adverse event that was considered to be related to treatment by the investigator.

A different ranking in the number or treatment related adverse events was observed between the paediatric and ≥ 12-year-old population. In the paediatric population, most drug related AE's were reported In the SOC Gastrointestinal disorders (18.2%), followed by the SOC Respiratory, Thoracic and Mediastinal disorders (16.7%), SOC Skin disorders (12.1%) and SOC investigations (10.6%).
For the population aged ≥ 12 years, most drug related AEs were observed in the SOC Respiratory, Thoracic and Mediastinal disorders (14.4%), followed by the SOC investigations (12.9%), the SOC Gastrointestinal disorders (10.9%), and Skin and subcutaneous tissue disorders (8.9%).

This ranking of the SoC is on the one hand not unexpected, as the population aged ≥ 12 years suffers more from advanced pulmonary disease, while in the paediatric population gastro-intestinal might be more prominent. However, the data may also indicate that paediatric population might be more vulnerable to skin related adverse events (see also AE of Specific interest).

Some new treatment-related adverse events were noted in the paediatric population. These adverse events were most like of mild intensity and could also be considered as signs and symptoms of CF or other as symptoms of common disease manifestations (e.g., vomiting, cough, sputum increased, bronchospasm, haemoptysis, pleuritic pain, bilirubin increased, aggression, anxiety, depressed mood, and fatigue). Most of these events were reported as related or possible related to a single subject, mild to moderate in intensity and resolved upon ongoing use of ELX/TEZ/IVA in combination with IVA. Therefore, they should not be mentioned in the ADR table of section 4.8 of the SmPC.

Cough (n=28) was reported in more subjects in the paediatric population. However, these CF related adverse events were not reported with a higher frequency in the ≥ 12 year old population compared with placebo. Therefore, the CHMP considered that they do not need to be included in SmPC section 4.8.

*Adverse events of special interest*

In the adult and adolescent trials, identified adverse events of specific interest were transaminase elevation and rash . These adverse events of interest are also applicable to the paediatric population.

<u>Transaminase elevations</u>
Transaminase elevations occur frequently in paediatric patients with CF and the inclusion of patients with transaminase elevation was limited to patients with ALT or AST < 3 × ULN. During the trial, the patients were regularly monitored. The reported incidence of transaminase elevation was (10.6%), in none of the patients did it lead to treatment discontinuation or treatment interruption.

The cross-study comparison with the safety data obtained in the patients aged ≥ 12 years showed a slightly higher incidence of transaminase elevation with the paediatric population (10.6%) compared with the patients aged ≥ 12 years (7.9%). Unlike the patients aged ≥ 12 years, none of the paediatric population showed ALT>3 × ULN or AST>3 × ULN) and TBILI>2 × ULN.

The cross-study comparison with the safety data obtained in the Symkevi trials (9.2%) and Orkambi trials (9.8%) revealed a comparable incidence of transaminase elevation (10.6%).

However, these cross-study comparisons are hampered because the exclusion criteria in the Kaftrio trials were more stringent and the longer observation period for Symkevi. In the VX-445/TEZ/IVA trials, patients were excluded when 1 out of the defined impairments were present instead of 2 (Symkevi) or 3 (Orkambi) trial, while the observation period for Symkevi was extended to 48 weeks.
Therefore, these indirect cross study comparisons indicate that the risk of AEsi-transaminase-elevated might be somewhat higher with Kaftrio compared to other CTFR modulators. Hepatoxicity is an important identified risk. Following a recent variation, the SmPC includes a warning for frequent ASAT/ALAT and bilirubin monitoring. Considering that these paediatric patients are treated in specialized clinics and will be frequently monitored, this risk appears to be sufficiently covered.

Rash
Similarly to the adult and adolescent studies, treatment related rash occurred frequently (n=8, 12.1% in part B). It resulted in discontinuation of treatment in one patient in part B of the study.

The cross-study comparison with the adult and adolescent data revealed that frequency of rash in the paediatric population was twice the frequency reported in the patients aged ≥ 12 years for both the AESI Rash-irrespective-of-causal-relationship (24.2% vs 10.9%), as well as the treatment-related Rash (12.1% vs 6.9%).

The current SmPC reports the AE-rash already as a very common adverse drug reaction (≥ 10%) in section 4.8. Therefore, no adjustment to the SmPC is considered necessary.

Ocular lens opacity
None of the patients reported AE's related to ocular lens opacity. However, ocular lens opacities occur gradually and as such might be underreported. Therefore, patients have to be examined before and after treatment. However, the study was conducted in the COVID-19 pandemic and not all patients underwent a post treatment ophthalmic examination. Most patients (n=64) rolled over to the open label extension study 107, which also includes ophthalmic examinations. The results of this study should be submitted once available (by Q1 2023).

*Incomplete safety measurements at end study due to COVID-19 pandemic*

The study took place during the COVID pandemic, which might provide an explanation that no compete safety assessment including vital signs, ECG and ophthalmic examination was conducted in the complete safety population.

Data from 33 patients (50% of safety data set) were provided for the vital signs and ECG, while for an unknown number of patients' results are provided for the additional ophthalmologic examination. The currently provided data do not raise concerns but are too limited to be conclusive. Nevertheless, the generated paediatric safety data base can be supported with the generated safety profile obtained in patients aged ≥ 12 years, while additional long-term safety data will be provided (> 24 weeks) from the long-term roll over study 107.

## 2.5.2. Conclusions on clinical safety

ELX/TEZ/IVA in combination with Kalydeco is intended for chronic use. The provided paediatric safety data set is limited, both in patient numbers (n=66) and duration of treatment i.e. 24 weeks. In addition, the safety data is obtained in an uncontrolled, open label, arm study in which the contribution from the longer disease duration versus the longer drug exposure is hard to distinguish.

The current safety data show that the treatment appears also to be well tolerated in patients from 6 years of age, however it is noted that the AESI Rash occurs twice more often in younger children compared to the older population.

The transaminase elevation occurred in the paediatric population with comparable incidence as for older patients aged ≥ 12 years. It is an important identified risk and the SmPC contains sufficient recommendations for frequent monitoring.

In conclusion, the currently provided data set shows that the product is generally well tolerated, but the safety set is of limited duration (24 weeks) for a medicinal product intended for chronic use. Therefore, the additional long-term safety data from study 107 should be provided once the data becomes available (by Q1 2023).

### 2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## *2.6. Risk management plan*

The MAH submitted an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 13.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 13.0 with the following content:

### *Safety concerns*

| | |
|---|---|
| **Important identified risks** | None |
| **Important potential risks** | • Hepatotoxicity<br>• Cataract |
| **Missing information** | • Use in pregnant and lactating women<br>• Indicated use in children aged less than 6 years |

### *Pharmacovigilance plan*

| Study/Status | Summary of Objectives | Safety Concerns Addressed | Milestones | Due Dates |
|---|---|---|---|---|
| **Category 1 – Imposed mandatory additional PV activities which are Conditions of the MA (key to benefit risk)** | | | | |
| None | | | | |
| **Category 2 – Imposed mandatory additional PV activities which are Specific Obligations in the context of a conditional MA under exceptional circumstances (key to benefit risk)** | | | | |
| None | | | | |
| **Category 3 – Required additional PV activities (by the competent authority)** | | | | |
| Study 126<br><br>Ongoing | IVA Arm<br>In subjects with CF who are <24 months of age at treatment initiation and | • Hepatotoxicity<br>• Cataract<br>• Indicated use in children aged | Final Report | December 2023 |

| Study/Status | Summary of Objectives | Safety Concerns Addressed | Milestones | Due Dates |
|---|---|---|---|---|
| | have an approved IVA-responsive mutation:<br>• To evaluate the safety of long-term IVA treatment<br>• To evaluate the PD of long-term IVA treatment<br>• To evaluate the efficacy of long-term IVA treatment<br><u>Observational Arm</u><br>To evaluate long-term safety after discontinuation of IVA treatment in subjects with CF who were <24 months of age at treatment initiation and have an approved IVA-responsive mutation | <24 months old at initiation | | |

CF: cystic fibrosis; IVA: ivacaftor; MA: market authorisation; PD: pharmacodynamics; PV: pharmacovigilance

Note: Study 126 addresses a subpopulation of the Missing Information of "Indicated use in children aged less than 6 years."

## *Risk minimisation measures*

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

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| **Use in pregnant and lactating women** | **Routine risk minimisation measure:**<br>SmPC Section 4.6 where advice is given on to use Kalydeco during pregnancy only if clearly needed and during breastfeeding if the potential benefit outweighs the potential risks.<br>PL Section 2<br>Prescription only<br>**Additional risk minimisation measures:**<br>None | **Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection**<br>Pregnancy follow-up form<br><br>**Additional PV activities:**<br>None |
| **Indicated use in children aged less than 6 years** | **Routine risk minimisation measure:**<br>SmPC Section 4.2 where the posology is described<br>SmPC Sections 4.8 and 5.2<br>PL Section 2<br>Prescription only<br>**Additional risk minimisation measures:**<br>No risk minimisation measures | **Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection**<br>None<br><br>**Additional PV activities:**<br>Study 126 |

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

## *2.7. Update of the Product information*

As a consequence of this new indication, sections 4.1, 4.2, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

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

### 2.7.1. User consultation

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

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

### 3.1.1. Disease or condition

Cystic Fibrosis (CF) is an autosomal recessive disease with serious, chronically debilitating morbidities and high premature mortality for which and at present, there is no cure. Cystic fibrosis is caused by mutations in the *CFTR* gene that result in the absence or deficient function of the *CFTR* protein at the cell surface. The *CFTR* protein is an epithelial chloride channel responsible for aiding in the regulation

of salt and water absorption and secretion. The failure to regulate chloride transport in these organs results in the multisystem pathology associated with CF. Lung disease is the primary cause of morbidity and mortality in people with CF. *F508del*, is the most common disease-causing mutation (84.7% of the individuals in the US and 81.1% of the individuals in Europe)[5,6].

In this current variation, the following indication was initially claimed:

Kalydeco, is indicated in a combination regimen with elexacftor/tezacaftor/ivacaftor tablets for the treatment of cystic fibrosis (CF) in patients aged **6** years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or heterozygous for F508del in the CFTR gene with a minimal function (MF) mutation (see section 5.1).

## 3.1.2. Available therapies and unmet medical need

In the treatment of CF, two main types of therapies can be distinguished, i.e CF therapies that target the symptoms of the disease (such as nutritional supplements, antibiotics, and mucolytics), and *CFTR* modulators (i.e. correctors and potentiators) that maintain and improve lung function, reduce the risk of infections and exacerbations; and improve quality of life.

Correctors (such as tezacaftor and elexacaftor) facilitate the cellular processing and trafficking of mutant *CFTR* to increase the quantity of functional *CFTR* at the cell surface, resulting in enhanced chloride transport. *CFTR* potentiators (like ivacaftor) enhance the channel gating activity of the *CFTR* which is delivered to the cell surface (by correctors).

Kaftrio (elexacaftor/tezacaftor/ivacaftor, ELX/TEZ/IVA) is indicated in a combination regimen with ivacaftor (Kalydeco) 150 mg tablets for the treatment of cystic fibrosis (CF) in patients aged 12 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Kalydeco (ivacaftor, IVA), Orkambi (lumacaftor/ivacaftor, LUM/IVA) and Symkevi (tezacaftor/ivacaftor, TEZ/IVA) are *CFTR* modulators approved for CF patients with specific mutations.

The registered indication in patients aged 12 years and older covers F/F genotypes, F/MF 'minimal function' genotypes, F/G 'gating' genotypes, and F/RF 'residual function' genotypes.

In children 6 through 11 years of age, approved modulator therapies are available for *F508del* homozygous patients (F/F), patient heterozygous for *F508del* and a specific residual function mutation (F/RF) or a specific gating mutation (F/G). Nevertheless, these treatments do not cure the disease and more efficacious treatments could fulfil this gap in these patients. For the populations heterozygous for *F508del* and a minimal function mutation (F/MF) no treatment is available, which is an unmet need in this subpopulation.

## 3.1.3. Main clinical studies

To support an indication extension of ELX/TEZ/IVA to include CF patients 6 through 11 years of age with F/F or F/MF mutation, the efficacy and safety data of one clinical trial, study VX18-445-106 are submitted. The pharmacokinetics of ELX/TEZ/IVA is also investigated in study 106 that confirmed the dosing.

[5] Cystic Fibrosis Foundation. Patient Registry: 2018 Annual Data Report. Bethesda, MD: Cystic Fibrosis Foundation; 2019.
[6] European Cystic Fibrosis Society. 2017 ECFS Patient Registry Annual Data Report. Karup, Denmark: European Cystic Fibrosis Society; 2019

Study 106 is conducted in 2 parts (Parts A and B) to evaluate the pharmacokinetics, safety, and tolerability of ELX/TEZ/IVA in CF subjects 6 through 11 years of age who are heterozygous for *F508del* and a minimal function mutation (F/MF genotypes) or homozygous for *F508del* (F/F genotype). Study 106 Part A evaluated ELX 100 mg once daily (qd)/TEZ 50 mg qd/IVA 75 mg every 12 hours (q12h), which is half the dose that is approved for use in CF patients ≥12 years of age. Simulations were conducted to select a dosing regimen and the updated popPK models, which included PK data from adults, adolescents, and all Study 106 to confirm the proposed dosing regimen for Study 106 Part B.

Study 106 part B evaluated the safety and efficacy of ELX/TEZ/IVA in 24 weeks. The recommended total daily dose of ELX/TEZ/IVA for patients 6 through 11 years of age was evaluated, i.e.

- Patients weighing <30 kg: ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h (two Kaftrio 50/25/37.5 mg FDC film-coated tablets in the morning and one Kalydeco 75 mg film-coated tablet in the evening)
- Patients weighing ≥30 kg: ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h (in form of two Kaftrio 100/50/75 mg FDC film-coated tablets in the morning and one Kalydeco 150 mg film-coated tablet in the evening)

The primary objective was safety; efficacy was secondary objective.

The secondary endpoints included spirometry and sweat chloride (SwCl), weight, height, body mass index (BMI) and associated z-scores, Cystic Fibrosis Questionnaire-Revised (CFQ-R), multiple-breath washout.

The extension of the indication to children 6 through 11 years old is based on the principle of partial extrapolation from adult and adolescents to paediatric patients. Consistent with the principles described in ICH E11 and EMA Reflection paper on the use of extrapolation in the development of medicines for paediatrics (EMA/189724/2018), extrapolation of efficacy from older to younger paediatric patients may be possible when a medicinal product is to be used in younger paediatric patients for the same indication as those studied in older paediatric patients, the disease process is similar, and the outcome of therapy is likely to be comparable. In CF, the disease process in all age groups stems from a common aetiology of dysfunctional CFTR protein that is targeted by ELX/TEZ/IVA and because ELX/TEZ/IVA targets the dysfunctional CFTR, the outcome of therapy is expected to be comparable in younger age groups compared to adults. Pharmacokinetic studies in the relevant age groups of paediatric patients likely to receive the medicinal product, together with safety studies, may be sufficient to provide adequate information for paediatric use.

## *3.2. Favourable effects*

*Dosing*

The results of Study 106 and popPK based simulations demonstrated that for subjects 6 through 11 years of age the distributions of individual ELX, TEZ, and IVA exposures, applying a dose of ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h dose in patients <30 kg and a dose of ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h in patients weighing ≥30 kg, were within the range of those observed in subjects ≥18 years of age.

The provided integrated assessment of paediatric exposure data, popPK modelling and simulations, of clinical data from subjects 6 through 11 years of age, adolescents, and adults confirmed that from a

clinical pharmacology perspective, the proposed dosages with a 30 kg weight cut-off for the applied dose are appropriate for the extrapolation of efficacy to CF subjects 6 through 11 years of age.

*Efficacy*

For the main secondary parameter ppFEV1, the LS mean absolute change in ppFEV1 from baseline through Week 24 was 10.2 percentage points (95% CI: 7.9, 12.6; p<0.0001). This is generally similar to the results in the adolescent and adult patients in the original marketing authorisation studies, when LS mean difference from baseline was 14.3 (95%CI 12.7, 15.8) in patients with F/MF mutations and 7.8%, (95% CI 4.8,10.8) for CFTR modulator experienced F/F patients and 13.2%, (95% CI (8.5,17.9) for CFTR modulator naïve F/F patients.

Treatment with ELX/TEZ/IVA in combination with IVA (Kalydeco) resulted in the LS mean absolute change in SwCl from baseline through Week 24 of -60.9 mmol/L (95% CI: -63.7, -58.2; p<0.0001). These results is in line with results for the adolescent and adult patients in the original marketing authorisation studies (LS mean difference from baseline - 42.2 mmol/L (95% CI: -44.0, -40.4) in patients with F/MF mutations and LS mean difference from baseline was -43.4 mmol/L (95% CI: -46.9, -40.0) and for patients with F/F mutations.

The within LS mean absolute change in CFQ-R Respiratory Domain Score of 7.0 points (95% CI: 4.7, 9.2; P<0.0001) was relevant, but less compared with results for the adolescent and adult patients in the original marketing authorisation studies (patients with F/MF mutations 20.2 points (95% CI 17.5,23.0) and patients with F/F mutations 17.4 points 95% CI 11.8,23.0).

An improvement in ventilation inhomogeneity measured by LCI2.5 is shown by a numerical decrease from baseline. The LS mean absolute change in LCI2.5 from baseline through Week 24 was -1.71 (95% CI: -2.11, -1.30; P<0.0001). The natural variability for the LCI2.5 is 1 unit[7] or 15 % of baseline[8]. Therefore, the results are considered relevant.

Upon request from the CHMP, results at week 12 were also provided. The LS mean absolute change in ppFEV1 from baseline through week 12 was 9.6 percentage points (95% CI: 7.3, 11.9). Treatment with Kalydeco in combination with Kaftrio resulted in the LS mean absolute change in SwCl from baseline through Week 12 of -58.6 mmol/L (95% CI: -61.1, -56.1). The within LS mean absolute change in CFQ-R Respiratory Domain Score was 5.6 points (95% CI: 2.9, 8.2). The LS mean absolute change in LCI2.5 from baseline through Week 12 was -1.83 (95% CI: -2.18, -1.49).

## *3.3. Uncertainties and limitations about favourable effects*

Because of the COVID-19 pandemic, many patients were unable to provide data on the efficacy endpoints toward the end of the study. Further, baseline data also appear to be missing for a small number of patients.
Despite the effort to collect as much efficacy data as possible, collection of data on the endpoints at week 16 and week 24 was hampered by the pandemic, and the option to provide efficacy data at an unscheduled visit that was intended to supplement week 24 data may have introduced bias into the estimate of the outcome as these data may be from healthier, lower-risk patients. Nevertheless, given the effect of a modulator on some parameters can already be observed around 4 to 8 weeks following treatment, additional analyses on the difference in the change through week 12 with all week 16 and week 24 data excluded from the analysis for all secondary endpoints were presented by the MAH upon request from the CHMP.

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

These analyses were consistent with the main analyses of the secondary efficacy endpoints of ppFEV1, SwCl, CFQ-R RD score, and LCI2.5, and demonstrate a robust and clinically meaningful improvements. Based on the information provided on treatment discontinuation, the sensitivity analysis is essentially making the same (MAR) assumptions as the MMRM model. The lack of a control group limits the options for further sensitivity analysis.

## *3.4. Unfavourable effects*

The safety profile is mainly determined by part B of the study, where 66 patients were treated for 24 weeks. The most frequently reported AEs (by PT are) were cough (n=28, 42.4%), headache (n=16, 24.2%) and pyrexia (n=14, 21.2%).

Most frequently treatment related AEs were was abdominal pain (n=6, 9.1%), followed by alanine aminotransferase increase (n=5, 7.6%), rash (n=4, 6.1%) and headache (n= 4, 6.1%).

One patient prematurely discontinued treatment because of an adverse event i.e. rash erythematous.

In two patients, treatment was temporality interrupted because of adverse events, i.e. rash maculo-papular, diarrhea, pyrexia, and vomiting.

Adverse events of specific interest were transaminase elevation and rash. A total of 7 (10.6%) paediatric patients experienced elevations of transaminases, and 16 (24.2%) experienced a rash.

## *3.5. Uncertainties and limitations about unfavourable effects*

The main safety data set to support the application is of limited size in patient numbers (n=66) as well as in the duration of treatment i.e. 24 weeks. In addition, the safety data is obtained in an uncontrolled, open-label, single-arm study, in which the contribution from the longer disease duration is hard to distinguish from longer drug exposure.

The cross-study comparison shows the same frequency of transaminase elevation as with the other CFTR modulators Lumacaftor and Symkevi, although the exclusion criteria for patients with pre-existing liver function impairments were more stringent in ELX/TEZ/IVA studies compared to the Orkambi trials and Symkevi, and a prolonged observation period with the Symkevi trial. —

The study was conducted during the COVID-19 pandemic, which resulted in an incomplete end of trial safety measurement. At the end of the trial, ECG and vital signs were conducted in 33 (50% of safety data set) subjects.

After completion of study 106, patients were invited to participate in the long-term safety study 107 of 96 weeks duration. A total of 64 patients rolled over. Additional long-term safety data will be provided once available (by Q1 2023).

## *3.6. Effects Table*

**Table 40. Effects Table for morning ELX/TEZ/IVA in combination with evening Kalydeco in the treatment of cystic fibrosis (CF) in patients aged 6 through 11 years of age who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or heterozygous for F508del in the CFTR gene with a minimal function (MF) mutation.**

| Effect | Short Description | Unit | Treatment | Treatment in adults and adolescents (cross-reference)<br><br>EMEA/H/C/005269/0000 | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable effects** | | | | | | |
| ppFEV1 | Change 0-24 wks LS mean (95% CI) from baseline | % | 10.2 (7.9, 12.6) | F/MF: 13.9 (12.8, 15.0)<br>F/F: 10.4 (8.6, 12.2) | **SoE:** clinically relevant.magnitude in line with studies in adults and adolescents. adolescents. Results based on analyses using data through week 12 supported conclusions of a clinically meaningful effect.<br>**Unc:** open-label, single-arm study and many missing data at week 16 and week 24, indirect comparison | Study 106 / EMEA/H/C/005269/0000 |
| SwCl | Change 0-24 wks LS mean (95% CI) from baseline | Mmol/l | -60.9 (-63.7, -58.2) | F/MF:-42.2 (-44.0, -40.4)<br>F/F: -43.4 (-46.9, -40.0) | **SoE:** clinically relevant. magnitude in line with studies in adults and adolescents. Results based on analyses using data through week 12 supported conclusions of a clinically meaningful effect.<br>**Unc:** open-label, single-arm study and many missing data at week 16 and week 24, indirect comparison | |
| CFQ-R RD | Change 0-24 wks LS mean (95% CI) from baseline | points | 7.0 (4.7, 9.2) | F/MF: 17.5 (15.6, 19.5)<br>F/F: 16.0 (12.1, 19.9) | **SoE:** clinically relevant. magnitude in line with studies in adults and adolescents. Results based on analyses using data through week 12 supported conclusions of a clinically meaningful effect.<br>**Unc:** open-label, single-arm study and many missing data at week 16 and week 24, indirect comparison | |

| Effect | Short Description | Unit | Treatment | Treatment in adults and adolescents (cross-reference)<br><br>EMEA/H/C/005269/0000 | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| BMI-z score | Change 0-24 wks LS mean (95% CI) from baseline | $Kg/m^2$ | 0.37 (0.26, 0. 48) | F/MF: 0.37 (0.25, 0.44) | **SoE:** magnitude in line with studies in adults and adolescents<br>**Unc:** open-label, single-arm study and many missing data at week 16 and week 24, indirect comparison | |
| **Unfavourable effects** | | | | | | |
| PEx | Event rate/year | | 0.12 | F/MF :0.37<br>F/F: 0.30 | **Unc:** only a few events, open label, single arm study, indirect comparison | Study 106 / EMEA/H/C/005269/0000 |
| Abdominal pain | | N, % | 8 (12.1%) | 9.9% | **Unc:** Limited data set (n=66), limited duration (24 weeks)<br>**Unc** data obtained in an open label study. | |
| ALT increased | Alanine aminotransferase increased | N, % | 7 (10.6%) | 9.9% | | |
| Rash (PT) | | N, % | 8 (12.1%) | 8.9% | | |
| Headache | | N, % | 16 (24.2%) | 17.3% | | |
| Bilirubin | | N, % | 1 (1.5%) | 5.0% | | |

Abbreviations: CFQ-R = Cystic Fibrosis Questionnaire-Revised, Pex = pulmonary exacerbation(s), ppFEV1= percent predicted forced expiratory volume in 1 second, SwCl = sweat chloride.

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

Importance of the favourable effects

The provided integrated assessment of paediatric exposure data, popPK modelling and simulations, of clinical data from subjects 6 through 11 years of age, adolescents, and adults confirmed that from a clinical pharmacology perspective, the proposed dosages with a 30 kg weight cut-off for the applied dose are appropriate for the extrapolation of efficacy to CF subjects 6 through 11 years of age.

The LS mean absolute change in ppFEV1 from baseline through Week 24 of 10.2% (95% CI: 7.9, 12.6;) is well above the accepted MCID in this population of approximately 2%. The results are considered clinically relevant.

The LS mean absolute change in SwCl from baseline through Week 24 of -60.9 mmol/l (95% CI: -63.7, -58.2) is also well above the accepted MCID of approximately 10 mmol/l. The results are considered clinically relevant.

Strength of the evidence

Pulmonary exacerbations and decline of lung function have an impact on survival in cystic fibrosis and reduce health-related quality of life. Preservation of lung function alongside reductions of the rate of pulmonary exacerbations are the main goals of the treatment of cystic fibrosis. ppFEV1 as a surrogate endpoint is a well-established endpoint and a reduction in the decline of FEV1 is related to improved survival. Observed improvements in ppFEV1 and SwCl were consistent with previous results in adults and adolescent populations. The results of ppFEV1 and SwCl are supported by all secondary parameters. CFQ-R respiratory domain, BMI z-score showed improvements well above the MCID.

Results based on analyses using data through week 12 supported conclusions of a clinically meaningful effect.

Impact of the uncertainties

Not all known MF mutations can be tested in a clinical trial as in adult studies. The clinical benefit seen in the investigated F/MF patients has such a large effect size, that it was accepted that results of in the tested MF mutations can be extrapolated to all MF mutations. Moreover, additional studies in adults in F/G and F/RF mutations have established that ELX/TEZ/IVA in combination with IVA (Kalydeco) is effective in all classes of mutations in the presence of at least one F508del mutation. Although not tested, in children a similar efficacy can be expected and extrapolation of efficacy is acceptable from paediatric patients with MF mutations to patients with at least one F508Del mutation.

*Safety*

In the adult clinical programs, ELX/TEZ/IVA in combination with IVA (Kalydeco) appeared to be well-tolerated, both in the short term and in the long-term safety studies. The reported treatment-related adverse events in the paediatric population generally aligned with the reported events in patients aged ≥ 12 years.

Similarly to patients ≥ 12 years, the AESI rash occurred very frequently. In the paediatric population the AEsi Rash occurred twice as often compared with the patients aged ≥ 12 year. No adjustment of the SmPC is needed, because rash is already reported as a very common adverse drug reaction.

The most frequently reported related adverse event was abdominal pain, followed by alanine aminotransferase elevation. In children, hepatic impairment and transaminase elevations appear to occur slightly more frequently (10.6%) than in adults and adolescents (7.9%), but this is acceptable. The cross-study comparisons suggest a somewhat higher risk with Kaftrio for transaminase elevations than with other CFTR modulators, but head-to-head comparative data is missing. Like in adults and adolescents, the transaminases and bilirubin should be closely monitored, as already mentioned in the SmPC section 4.4.

## 3.7.2. Balance of benefits and risks

This extension of indication to children 6 through 11 years old is based on the principle of partial extrapolation from adult and adolescents to paediatric patients. This application also needs to be supported by comparable PK exposures, acceptable safety and a similar PD effect.

**Indication**

The population of patients with F/MF or F/F genotypes investigated in Study 106 is tighter than the population for which Kaftrio, in combination with Kalydeco, has recently been authorised for the older age group, i.e. CF patients 12 years and older with at least one F508del mutation in CFTR gene.

Following approval of the above indication in parallel of this application and upon agreement from the CHMP, the therapeutic indication was amended to "combination regimen with kaftrio for the treatment of cystic fibrosis (CF) patients aged 6 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene".

The further extrapolation to CF subjects 6 through 11 years of age with F/G and F/RF mutation is justified based on the same arguments presented and accepted as for the CF patients with F/F and F/MF mutations. Additional evidence of the statistically significant benefits of ELX/TEZ/IVA over previously available CFTR modulators (IVA or TEZ/IVA) in CF subjects ≥ 12 years of age with F/RF and F/G genotypes was also provided.

**Dosing**

The provided integrated assessment of paediatric exposure data, popPK modelling and simulations, of clinical data from subjects 6 through 11 years of age, adolescents, and adults confirmed that from a clinical pharmacology perspective, the proposed dosages with a 30 kg weight cut-off for the applied dose are appropriate for the extrapolation of efficacy to CF subjects 6 through 11 years of age.

**Efficacy**

In this study in CF patients 6 through 11 years of age who are heterozygous for *F508del* and a minimal function mutation or homozygous for *F508del* mutation, efficacy was a secondary objective. The extrapolation is based on comparable exposure and safety.

Clinically relevant improvements were found in the changes from baseline for the ppFEV1 and SwCl. These improvements were consistent with previous results in adults and adolescent populations, confirming the justification of partial extrapolation.

Although many data were missing for the main statistical analysis, additional analyses on the change through week 12 with all week 16 and week 24 data excluded from the analysis were consistent with the main analyses of the secondary efficacy endpoints of ppFEV1, SwCl, CFQ-R RD score, and LCI2.5, and demonstrated a robust and clinically meaningful improvements.

**Safety**

The provided data show that the treatment appears to be well tolerated in the paediatric population. The reported safety profile generally appears to align with the reported data obtained in the population aged ≥ 12 years, but the data set was rather small (n=66), of limited duration ( 24 weeks) and is further hampered by missing data at the end of treatment safety follow-up due to the COVID-19 pandemic. The ongoing, extension study 107 will provide additional long-term safety and results will be provided upon completion (by Q1 2023).

Nevertheless, the safety profile of adult patients is well described, and the currently provided data did not identify new important risks. As expected, the paediatric population reported the highest frequency of adverse events in the SoC Gastro-intestinal tract, while in the patients aged ≥ 12 years Respiratory events were more frequently reported.

Similarly to patients ≥ 12 years, the AESI rash occurred very frequently. The elevation of transaminases occurred slightly more frequently in the paediatric population compared to patients aged ≥ 12 years (10.6% vs 7.9%). Hepatotoxicity is already identified as an important potential risk. The earlier introduction of the modulator therapy might be beneficial, as this modulator therapy has the potential to prevent the long-standing detrimental effects of CF. Considering that these paediatric patients are treated in specialized clinics and frequently monitored, more uncertainties regarding the safety profile are considered acceptable and manageable in clinical practice. In addition, the safety will be further substantiated in the follow-up extension study 107. Overall the safety profile is considered acceptable.

### 3.7.3. Additional considerations on the benefit-risk balance

None.

## *3.8. Conclusions*

The overall B/R of Kalydeco in combination with Kaftrio is positive.

# 4. Recommendations

## *Outcome*

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

| **Variation accepted** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I and IIIB |

Extension of indication for Kalydeco tablets in combination regiment with Kaftrio to include the treatment of adults, adolescents and children aged 6 years and older with cystic fibrosis who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. This application is based on the results of study VX18-445-106, a phase 3, open-label, multicentre study in subjects 6 through 11 years of age, with F/MF and F/F genotypes. As a consequence, sections 4.1, 4.2, 5.1, and 5.2 of the SmPC are updated. The Packaged Leaflet is updated in accordance.

Changes were also made to the PI to bring it in line with the current Agency/QRD template. RMP version 13.0 is acceptable.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

### *Amendments to the marketing authorisation*

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

### *Paediatric data*

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0163/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

### *Similarity with authorised orphan medicinal products*

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

## 5. EPAR changes

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

### *Scope*

Please refer to the Recommendations section above.

### *Summary*

Please refer to Scientific Discussion 'Kalydeco – EMEA-H-C-002494-II-0096'