swissmedic

*Date:* 2 October 2024
Swissmedic, Swiss Agency for Therapeutic Products

# *Swiss Public Assessment Report*

## *Extension of therapeutic indication*

# Trikafta

| | |
|---|---|
| **International non-proprietary name:** | elexacaftor, ivacaftor, tezacaftor (morning dose),<br>ivacaftor (evening dose) |
| **Pharmaceutical form:** | granules |
| **Dosage strength(s):** | 80 mg, 40 mg, 60 mg (morning dose), 59.5 mg (evening dose)<br>100 mg, 50 mg, 75 mg (morning dose), 75 mg (evening dose) |
| **Route(s) of administration:** | oral |
| **Marketing authorisation holder:** | Vertex Pharmaceuticals (CH) GmbH |
| **Marketing authorisation no.:** | 69212 |
| **Decision and decision date:** | approved on 13 June 2024 |

**Note:**

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

**Table of contents**

# 1 Terms, Definitions, Abbreviations

| | |
|---|---|
| ADA | Anti-drug antibody |
| ADME | Absorption, distribution, metabolism, elimination |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| API | Active pharmaceutical ingredient |
| AST | Aspartate aminotransferase |
| ATC | Anatomical Therapeutic Chemical Classification System |
| AUC | Area under the plasma concentration-time curve |
| $AUC_{0\text{-}24h}$ | Area under the plasma concentration-time curve for the 24-hour dosing interval |
| CI | Confidence interval |
| $C_{max}$ | Maximum observed plasma/serum concentration of drug |
| CYP | Cytochrome P450 |
| DDI | Drug-drug interaction |
| EMA | European Medicines Agency |
| ERA | Environmental risk assessment |
| FDA | Food and Drug Administration (USA) |
| GI | Gastrointestinal |
| GLP | Good Laboratory Practice |
| HPLC | High-performance liquid chromatography |
| $IC/EC_{50}$ | Half-maximal inhibitory/effective concentration |
| ICH | International Council for Harmonisation |
| Ig | Immunoglobulin |
| INN | International non-proprietary name |
| ITT | Intention-to-treat |
| LoQ | List of Questions |
| MAH | Marketing authorisation holder |
| Max | Maximum |
| Min | Minimum |
| MRHD | Maximum recommended human dose |
| N/A | Not applicable |
| NO(A)EL | No observed (adverse) effect level |
| PBPK | Physiology-based pharmacokinetics |
| PD | Pharmacodynamics |
| PIP | Paediatric investigation plan (EMA) |
| PK | Pharmacokinetics |
| PopPK | Population pharmacokinetics |
| PSP | Pediatric study plan (US FDA) |
| RMP | Risk management plan |
| SAE | Serious adverse event |
| SwissPAR | Swiss Public Assessment Report |
| TEAE | Treatment-emergent adverse event |
| TPA | Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21) |
| TPO | Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21) |

# 2 Background information on the procedure

## 2.1 Applicant's request(s)

**Extension(s) of the therapeutic indication(s)**
The applicant requested the addition of a new pharmaceutical form and an extension of the therapeutic indication in accordance with Article 24 TPO.

**Orphan drug status**
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a$^{decies}$ no. 1 of the TPA.
Orphan drug status was granted on 9 April 2020.

## 2.2 Indication and dosage

### 2.2.1 Requested indication

Trikafta is indicated for the treatment of cystic fibrosis (CF) in patients aged 2 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene ("Clinical efficacy").

### 2.2.2 Approved indication

Trikafta is indicated for the treatment of cystic fibrosis (CF) in patients aged 2 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator *(CFTR)* gene ("Clinical efficacy").

### 2.2.3 Requested dosage

**Table 1: Dosing recommendation for patients aged 2 to <6 years**

| Age | Weight | Morning dose | Evening dose |
|---|---|---|---|
| 2 to <6 years | <14 kg | One sachet of elexacaftor 80 mg/tezacaftor 40 mg/ivacaftor 60 mg granules | One sachet of ivacaftor 59.5 mg granules |
| 2 to <6 years | ≥14 kg | One sachet of elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg granules | One sachet of ivacaftor 75 mg granules |

### 2.2.4 Approved dosage

(see appendix)

## 2.3 Regulatory history (milestones)

| | |
|---|---|
| Application | 28 February 2023 |
| Formal control completed | 27 March 2023 |
| List of Questions (LoQ) | 25 July 2023 |
| Response to LoQ | 23 October 2023 |
| Preliminary decision | 18 January 2024 |
| Response to preliminary decision | 17 March 2024 |
| Final decision | 13 June 2024 |
| Decision | approval |

# 3 Medical context

Cystic fibrosis (CF) is a multisystem disorder caused by pathogenic mutations of the CFTR gene (CF transmembrane conductance regulator). Deranged transport of chloride and/or other CFTR-affected ions, such as sodium and bicarbonate, leads to thick, viscous secretions in the lungs, pancreas, liver, intestine, and reproductive tract and to increased salt content in sweat gland secretions. Typical symptoms and signs include persistent pulmonary infection, pancreatic insufficiency, and elevated sweat chloride (SwCl) levels. More than 2,000 mutations of this gene have been identified, although only about 10% of those are definitely disease-causing. This leads to different degrees of severity of disease – from virtually no clinical manifestations to severely hampered lung function and multi-organ manifestation.
Today, the diagnosis of CF is based on typical clinical symptoms and laboratory confirmation of the underlying dysfunction of the CFTR protein. Due to the achievements of modern diagnostics and therapy, almost all patients reach adulthood in industrialised countries today.
The most common defect is the lack of coding for phenylalanine (F508del), which leads to a processing disorder and therefore to an obstacle in the transport of CFTR to the cell surface. Approximately 45% of patients with cystic fibrosis have a homozygous defect in this allele, which leads to an extensive CFTR malfunction and therefore to severe forms of disease. In addition, there are a number of other mutations that impair CFTR function in various ways and to varying extents.

All approved CFTR-modulators lead to a significant improvement of SwCl as a sign of improved transport of chloride and/or other CFTR-affected ions. However, improvement of SwCl is not strictly correlated to the improvement of lung function and survival of CF patients, depending on the type of mutation.
The caftor (combinations) lead to an improvement in lung function (to different extents, depending on the product and the stage of the disease) for as long as these products are taken. However, the principal dysfunction of the CFTR protein/mutation is not healed. Therefore, pre-existing lung damage cannot be reversed by caftor (combinations).

There are four caftor (combinations) approved in Switzerland for the treatment of CF. However, at the time of this assessment, only two were approved in children from two to six years of age (ivacaftor and lumacaftor/ivacaftor).

Ivacaftor is only approved for a few CF mutations, which represent only approx. 1% of mutations in CF patients in Switzerland. Lumacaftor/ivacaftor is approved for children from two to six years in CF with a homozygous F508del mutation. However, about 40% of CF patients are heterozygote for the F508del mutation and cannot benefit from lumacaftor/ivacaftor .
Therefore, a medical need in this subgroup of patients from two to six years with a heterozygote F508del mutation can be attested, as there is no causative treatment for them as yet.

# 4 Quality aspects

## 4.1 Drug product

### Drug product Trikafta granules

Description and composition:
Trikafta granules in sachets is a fixed-dose combination (FDC) of the immediate-release granules containing the known active substances elexacaftor, tezacaftor and ivacaftor (80 mg/40 mg/60 mg and 100 mg/50 mg/75 mg granules in sachet). White to off-white granules with a nominal diameter of 2 mm are filled by count into sachets. The granules consist of the pharmaceutical excipients hypromellose, hypromellose acetate succinate, sodium lauryl sulphate, lactose monohydrate, mannitol, croscarmellose sodium, sucralose, magnesium stearate, colloidal silicon dioxide.

Pharmaceutical development:
Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process, including a QbD (Quality by Design) approach.

Manufacture:
The granules are manufactured including blending, direct compression and filling into sachets by count. Adequate in-process controls are established in order to ensure a consistent manufacturing process.

Specification:
The drug product specifications cover relevant physico-chemical characteristics as well as identification, assay, and purity tests. The analytical procedures are validated according to the recommendations of international guidelines.

Container closure system:
The container closure system for Trikafta granules is a foil-laminated sachet.

Stability:
Appropriate stability data have been generated in the packaging material intended for commercial use and following the relevant international guidelines. The stability study included three primary stability batches per each dose. The data show good stability of the finished product and allow for a distinct assignment of the shelf life.

### Drug product ivacaftor granules

Description and composition:
Ivacaftor drug product is an immediate-release dose form with granules in sachets containing the known active substance ivacaftor (59.5 mg). White to off-white granules with a nominal diameter of 2 mm are filled by count into sachets. The granules consist of the pharmaceutical excipients hypromellose acetate succinate, sodium lauryl sulphate, lactose monohydrate, mannitol, sucralose, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate.

Pharmaceutical development:
Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process, including a QbD (Quality by Design) approach.

Manufacture:
The granules are manufactured including blending, direct compression and filling into sachets by count. Adequate in-process controls are established in order to ensure a consistent manufacturing process.

Specification:
The drug product specifications cover relevant physico-chemical characteristics as well as identification, assay, and purity tests. The analytical procedures are validated according to the recommendations of international guidelines.

Container closure system:
The container closure system for ivacaftor granules is a foil-laminated sachet.

Stability:
Appropriate stability data have been generated in the packaging material intended for commercial use and following the relevant international guidelines. The stability study included three primary stability batches. The data show good stability of the finished product and allow for a distinct assignment of the shelf life.

## 4.2 Quality conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

# 5 Nonclinical aspects

The nonclinical documentation submitted with the initial marketing authorisation application supports the approval of Trikafta® (Elexacaftorum/Tezacaftorum/Ivacaftorum) for the new pharmaceutical form and the indication extension applied for.

# 6 Clinical aspects

## 6.1 Clinical pharmacology

### ADME

*Absorption and biopharmaceutical development*

A granule FDC dosing form containing ELX/TEZ/IVA was developed for the treatment of children between 2 to 5 years of age. The proposed commercial formulation contains the granules in a sachet.

The proposed dose strengths are

- 80/40/60 mg ELX/TEZ/IVA (morning dose) and 59.5 mg IVA (evening dose)
- 100/50/75 mg ELX/TEZ/IVA (morning dose) and 75 mg IVA (evening dose)

The ELX/TEZ/IVA exposures after fed administration of the 100/50/75 mg dose strength of the commercial FDC tablet and the granules to healthy adult subjects were similar.

**Special populations**

The pharmacokinetics of ELX, M23-ELX, TEZ, M1-TEZ and IVA in paediatric CF patients between 2 and 5 years of age were investigated in several population PK analyses. The existing pop PK models developed in patients ≥6 years of age were updated with/applied to the data of Part A and B of Study 111. This was done in three steps:

- Inclusion of the Study 111 Part A data. Part A of Study 111 included patients between 2 to 5 years of age ≥14 kg only. This step included simulations to support the selection of doses and weight cut-offs for Part B of Study 111, which included patients between 10 kg and 14 kg.

- Interim analysis of Part B data.

- Final pop PK analyses with final simulations to support the dosing recommendations in patients between 2 and 5 years of age.

The goal was to achieve exposures of the different analytes similar to those shown to be safe and efficacious in adults from Phase 3 studies.

Description of the prior pop PK models
*ELX & M23-ELX*

The ELX pop PK model was a linear, two-compartment model with four-transit compartments and a first-order absorption. The absolute bioavailability was fixed at 0.8 based on earlier study results. The effect of weight on clearance was incorporated using a body weight cut-point model where the allometric exponent was fixed to 0.75 but the clearance saturated above a threshold weight (i.e., clearance is constant when weight is above this threshold). The effect of weight on volume of distribution was incorporated using allometric scaling with an estimated allometric exponent. Additional covariates were the effect of formulation (monotherapy pills versus fixed dose combination pills) on the absorption rate and an age effect on the transit rate in the ELX pop PK model.

The M23-ELX pop PK model was developed sequentially using the empirical Bayes estimates from the ELX model assuming that 57.4% of parent is metabolised to M23-ELX. The model was a linear, two-compartment pop PK model. The effect of weight on clearance was incorporated in the M23-ELX model using a body weight cut-point model where the allometric exponent was fixed to 0.75 but the clearance saturated above a threshold weight (i.e., clearance is constant when weight is above this threshold). The effect of weight on volume of distribution was incorporated using allometric scaling with an estimated allometric exponent. Gender effects on clearance were incorporated as females, 6 to 11-year-old males, and all other subjects.

*TEZ & M1-TEZ*

The TEZ and M1-TEZ pop PK models were two-compartment models with first-order absorption and elimination. Both models included allometric body weight scaling of volume and clearance terms. In the TEZ model, separate exponents were estimated for the clearance and volume terms. In the M1-TEZ model, the allometric exponent was estimated for the clearance terms and fixed to 1.0 for the volume terms.

*IVA*

The IVA pop PK model was a one-compartment model with first-order absorption. Covariate-parameter relationships in the final IVA population PK model included: weight on CL/F and apparent volume of distribution after oral dosing (V/F), first dose adjustment on CL/F, and an adjustment on relative bioavailability for subjects 6-11 years old at steady-state. The weight effect on CL/F was described using a weight cut-point model whereby CL/F saturated above the weight cut-point, and scaled with a fixed exponent of 0.75 below the weight cut-point. The weight effect on V/F was described using an allometric model with an estimated exponent.

Inclusion of Study 111 Part A data

The main changes to the prior pop PK models for ELX, M23-ELX, IVA, TEZ and M1-TEZ after addition of the data from Part A of Study 111 were the addition CF genotype as covariate of CL and of formulation (granules, confounded with age) as covariate of F.

The proposed dose in children between 2 and 5 years of age and with a body weight ≥14 kg is the same as the approved dose for children between 6 and <12 years with a body weight of <30 kg (ELX 100 mg QD, TEZ 50 mg QD, IVA 75 mg BID).

Simulations with the final models showed that the ELX, M23-ELX, IVA and TEZ exposures in children between 2 and 5 years of age and with a body weight of ≥14 kg were higher than in children between 6 and <12 years with a body weight of <30 kg, but well within the 5$^{th}$ and 95$^{th}$ percentiles of the therapeutic exposures in adults. The exposures of M1-TEZ were higher than the 95$^{th}$ percentile of the adult exposures, but they were comparable to the exposures in children between 6 and 11 years of age with a body weight of ≥30 kg after the approved dose.

Additional simulations in a virtual patient population confirmed the appropriateness of the selected weight cut-off of 14 kg and the proposed doses for patients between 2 and 5 years of age.

Inclusion of Study 111 Part B interim data

The inclusion of the Part B data of Study 111 (children between 2 and 5 years of age with a body weight <14 kg) required minor or no changes of the prior (=> after inclusion of the Part A data) pop PK models of ELX, M23-ELX, M1-TEZ and IVA, while the TEZ model required quite a few adjustments.

Final pop PK analyses and simulations

The final datasets included additional samples, but no new subjects compared to the interim analysis of the Part B data.

*ELX*

The final ELX pop PK model from the interim analysis of the Part B data remained unchanged and described the final data quite well in all subgroups.

Covariate relationships in the final model:

- weight on clearance, inter-compartmental clearance, and volumes
- formulation on the absorption rate and bioavailability
- age on the absorption transit rate
- genotype on clearance.

*M23-ELX*

The final M23-ELX pop PK model from the interim analysis of the Part B data remained unchanged and described the final data quite well in all subgroups.

Covariate relationships in the final model:

- weight on CLM, QM, V2M, and V3M
- adult female gender on CLM
- genotype on clearance

The final simulations showed that the median ELX and M23-ELX exposures in children ≤5 years after the proposed doses were lower than in adults, but the overall exposures were within the 5$^{th}$ and 95$^{th}$ percentile of the adult data.

The proposed dosing regimen resulted in comparable ELX and M23-ELX exposures in children of 2 to 5 years of age < and ≥14 kg, confirming the appropriateness of the weight cut-off. The 14 kg weight cut-off was additionally supported by additional simulations across different weight bins.

*TEZ*

The final TEZ pop PK model from the interim analysis of the Part B data remained unchanged and described the final data quite well in all subgroups.

Covariate relationships in the final model:

- weight on CL/F, Vc/F, Vp/F, and Q/F
- a combined genotype effect of F/G + F/RF on CL/F
- a 2-5y/granule effect on ka and ALAG

The final simulations showed that the median TEZ AUCss and Cmax,ss in children ≤5 years after the proposed doses were comparable to adults and the overall exposures were within the 5$^{th}$ and 95$^{th}$ percentile of the adult data. The median TEZ Cmin in children ≤5 years was lower than in adults, but the overall data were mostly within the 5$^{th}$ and 95$^{th}$ adult percentiles.

The proposed dosing regimen resulted in comparable TEZ exposures in children of 2 to 5 years of age < and ≥14 kg, confirming the appropriateness of the weight cut-off. The 14 kg weight cut-off was additionally supported by additional simulations across different weight bins.

*M1-TEZ*

The final M1-TEZ pop PK model from the interim analysis of the Part B data remained unchanged and described the final data quite well in all subgroups.

Covariate relationships in the final model:

- weight on CL/F, Vc/F, Vp/F, and Q/F
- a combined effect of F/G and F/RF genotypes on CL/F.

The final simulations showed that the median M1-TEZ exposures in children ≤5 years after the proposed doses were higher than in adults and the overall exposures were partially outside the 5$^{th}$ and 95$^{th}$ percentile of the adult data. However, this was also the case for children between 6 to 11 years ≥30 kg after the approved dose.

The proposed dosing regimen resulted in comparable M1-TEZ exposures in children of 2 to 5 years of age < and ≥14 kg, confirming the appropriateness of the weight cut-off. The 14 kg weight cut-off was additionally supported by additional simulations across different weight bins.

*IVA*

Apart from the removal of the age/formulation effect on ka, the final IVA pop PK model from the interim analysis of the Part B data remained unchanged and described the final data quite well in all subgroups.

Covariate relationships in the final model:

- weight on CL/F and V/F
- 2-5y/granule formulation on ALAG
- an adjustment on CL=F for the first IVA dose
- an adjustment on relative bioavailability (Frel) for children 6-11y at steady state
- a combined genotype effect of F/G + F/RF on CL/F.

The final simulations showed that the median IVA AUCss and Cmax,ss in children ≤5 years after the proposed doses were comparable to adults and the overall exposures were within the 5$^{th}$ and 95$^{th}$ percentile of the adult data. The median IVA Cmin in children ≤5 years was lower than in adults, but the overall data were mostly within the 5$^{th}$ and 95$^{th}$ adult percentiles.

The proposed dosing regimen resulted in comparable IVA exposures in children of 2 to 5 years of age < and ≥14 kg, confirming the appropriateness of the weight cut-off. The 14 kg weight cut-off was additionally supported by additional simulations across different weight bins.

The final pop PK models described the data of the different analytes in all subgroups quite well and were therefore qualified for the simulations conducted. The exposures of M1-TEZ were consistently higher in children between 2 to 5 years compared to adults after the proposed doses. This was also the case for children between 6 to 11 years ≥30 kg after the approved dose. The exposures of all other analytes in children between 2 to 5 years < or ≥14 kg were with the 5$^{th}$ and 95$^{th}$ percentiles of the adult data after therapeutic dosing. Therefore, the proposed dosing regimen for children between 2 to 5 years < or ≥14 kg is acceptable from a pharmacokinetic point of view.

## 6.2 Dose finding and dose recommendation

No specific dose finding studies were conducted for this application. The proposed dosing regimen has been derived from the pop PK models as for other age groups (see Clinical Pharmacology above).

## 6.3 Efficacy

The pivotal study VX20-445-111 was a Phase 3, two-part (Parts A and B), open-label, uncontrolled, multi-centre study in CF patients from two to five years of age.
Based on similar exposures, the efficacy observed in studies in adults and older children can be extrapolated to younger age groups. The open-label, uncontrolled study design can be accepted to provide further supportive evidence of efficacy.

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, PK, PD, and efficacy of ELX/TEZ/IVA administered for 24 weeks. Part A only had safety and PK endpoints, while Part B had safety as primary endpoint and change of lung clearance index (LCI)2.5 and SwCl through to Week 24 as secondary efficacy endpoints. Subjects received the following doses for 24 weeks:

**Table 9-1 Parts A and B Doses**

| Subject Weight at Day 1 | ELX Dose | TEZ Dose | IVA Dose |
|---|---|---|---|
| **Part A** | | | |
| ≥14 kg only | 100 mg qd | 50 mg qd | 75 mg q12h |
| **Part B** | | | |
| ≥14 kg | 100 mg qd | 50 mg qd | 75 mg q12h |
| ≥10 kg to <14 kg | 80 mg qd | 40 mg qd | 60 mg qAM |

All efficacy endpoints in this study were secondary endpoints and not controlled for multiple testing. The chosen endpoints of LCI2.5 and SwCl are in line with endpoints in prior accepted studies in CF patients and are acceptable for this age group. It is recognised that FEV1 measurements, although these are used as the preferred methodology for measuring lung function and have demonstrated correlation with overall survival in CF patients, are challenging in children from two to five years of age and LCI2.5 offers an acceptable alternative. Nevertheless, the EMA guideline recommends FEV1 as the primary endpoint, which was not chosen in this study. In addition, the endpoint of LCI2.5 was only measured in children aged 3 years and older. Therefore, in this pivotal study, no measurements of lung function are available in children from 2 to 3 years of age.
The endpoint of SwCl reduction is widely used and was already accepted in prior CFTR-modulators as a pharmacodynamic endpoint.

Overall, the included study population was small, with only 75 patients in Part B. However, it is acknowledged that in the intended population larger studies would be difficult.

The results of study VX20-445-111 demonstrated a substantial reduction in sweat chloride of -57.9 mmol/L and a reduction of the LCI2.5 of -0.83 compared to baseline.
The results are somewhat difficult to interpret due to the study design without a control group. Therefore, a comparison with the study results of ELX/TEZ/IVA studies in other age groups and studies conducted with other CFTR-modulators in patients from two to five years of age was made, although comparisons between different studies always have to be interpreted with caution.

The observed reduction in LCI2.5 was less pronounced in study VX20-445-111 compared to the results for LCI2.5 in children from 6 to 12 years of age in the pivotal study with ELX/TEZ/IVA. The observed reduction in SwCI was similar in both studies.
However, compared to the IVA or LUM/IVA studies in the same age group from 2 to 5 years of age, the results for both main secondary endpoints (SwCI and LCI2.5) were better for ELX/TEZ/IVA. Therefore, ELX/TEZ/IVA seems to provide better results in this age group than the two already approved CFTR-modulators. However, the results were less convincing than in the age group 6 to 12 years.

## 6.4 Safety

A high percentage of patients had AEs (98.7%). However, there were no severe or life-threatening AEs and no deaths. No SAEs were reported in Part A. Two SAEs were reported in Part B.
The most common AEs were cough, pyrexia, rhinorrhoea, vomiting, COVID-19, nasal congestion, rash, upper respiratory tract infection, decreased appetite, ALT increased, and infective pulmonary exacerbations (PEx) of CF. This was comparable to the most common AEs in adults and older children. Furthermore, as already known from ELX/TEZ/IVA in older children, there was a high percentage of patients with elevated liver enzymes. In Part B, ALT or AST >3, >5, and >8 × ULN occurred in 6 (8.0%), 2 (2.7%), and 1 (1.3%) subjects, respectively. No subject had ALT or AST >3 × ULN with concurrent total bilirubin elevation >2 × ULN, but there was one case with AST > 20x ULN.

There were fewer pulmonary exacerbations in the study in children aged 6-12 with 4 PEx (6.1%) compared to this study with 12 PEx (16%). However, this may be due to the different definitions for pulmonary exacerbations that were used for children below or over the age of 6.

Overall, the study design with the small population and without a control group limits the interpretability of the safety data. However, no new concerns or risks were observed. Similarly to older age groups, the risk of an elevation of transaminases has to be kept in mind during treatment with Trikafta and the monitoring of liver enzymes is included in the Information for health care professionals.

## 6.5 Final clinical benefit risk assessment

CF is a multisystem disorder caused by pathogenic mutations of the *CFTR* gene. Deranged transport of chloride and/or other CFTR-affected ions, such as sodium and bicarbonate, leads to thick, viscous secretions in the lungs, pancreas, liver, intestine, and reproductive tract and to increased salt content in sweat gland secretions. Typical symptoms and signs include persistent pulmonary infection, pancreatic insufficiency, and elevated sweat chloride levels.
There are four caftor (combinations) approved in Switzerland for the treatment of CF. However, only two are approved in children from two to six years of age (ivacaftor and lumacaftor/ivacaftor).
Ivacaftor is only approved for a few CF mutations, which represent only approx. 1% of mutations in CF patients in Switzerland. Lumacaftor/ivacaftor is approved for children from two to six years of age in CF with a homozygous F508del mutation. However, about 40% of CF patients are heterozygote for the F508del mutation and cannot benefit from lumacaftor/ivacaftor.
Therefore, a medical need in this subgroup of patients from two to six years of age with a heterozygote F508del mutation can be attested, as there is no causative treatment for them as yet. However, the

principal dysfunction of the CFTR protein/mutation is not healed and pre-existing lung damage cannot be reversed by caftor (combinations).

The granule and tablet FDCs can be regarded as bioequivalent.
The final pop PK models described the plasma concentrations of ELX, M23-ELX, TEZ, M1-TEZ and IVA in all subgroups (age, body weight and others) quite well and were therefore suitable for simulations.
The proposed dosing regimen for children <6 years achieved similar exposures of ELX, M23-ELX TEZ and IVA as in adults after therapeutic dosing. The M1-TEZ exposures were higher in 2- to 5-year-olds, but this was also the case in children between 6 to 11 years ≥30 kg after the approved dose.

The pivotal study VX20-445-111 was a Phase 3, open-label, uncontrolled, multi-centre study in CF patients from two to five years of age. All efficacy endpoints in this study were secondary endpoints and not controlled for multiple testing.
The results of study VX20-445-111 demonstrated a substantial improvement in sweat chloride and a reduction of the LCI2.5 compared to baseline.

A high percentage of patients had AEs but no severe or life-threatening AEs and no deaths occurred. The most common AEs were similar as seen in adults and older children. Furthermore, as already known from Trikafta in older children, there was a high percentage of patients with elevated liver enzymes.
Overall, the study design with the small population and without a control group limits the interpretability of the safety data. However, no new concerns or risks were observed.

The proposed dosing recommendations for children <6 years are acceptable from a pharmacokinetic point of view. As the same exposure to other age groups was demonstrated, extrapolation of efficacy from adults and older children down to younger age groups can be accepted. This together with the possibility of an improved long-term lung preservation in this younger age subgroup and the supportive clinical open-label results lead to a positive benefit-risk assessment for the requested indication for children ≥10 kg and from 2 years of age.

# 7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

# 8 Appendix

## Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Trikafta was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

**Note:**
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the «Undesirable effects» section for advice on the reporting of adverse reactions.

## Trikafta

### Composition

*Active substances*

*Morning dose:*

Elexacaftor, tezacaftor, ivacaftor

*Evening dose:*

Ivacaftor

*Excipients*

*Film-coated Tablets*

*Morning dose:*

Tablet core:
Hypromellose, hypromellose acetate succinate, sodium lauryl sulfate, croscarmellose sodium, microcrystalline cellulose, magnesium stearate
Tablet film coat:
Hypromellose, hydroxypropyl cellulose, titanium dioxide, talc, iron oxide yellow, iron oxide red
Each 50 mg/25 mg/37.5 mg tablet contains 1.34 mg of sodium.
Each 100 mg/50 mg/75 mg tablet contains 2.68 mg of sodium.

*Evening dose*

Tablet core:
Colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate
Tablet film coat:
Carnauba wax, FD&C Blue #2, PEG 3350, polyvinyl alcohol, talc, titanium dioxide
Printing ink:
Ammonium hydroxide, iron oxide black, propylene glycol, shellac
Each 75 mg tablet contains 0.90 mg of sodium and 83.6 mg of lactose monohydrate.
Each 150 mg tablet contains 1.82 mg of sodium and 167.2 mg of lactose monohydrate.

*Granules in Sachet*

*Morning dose:*

Colloidal silicon dioxide, croscarmellose sodium, hypromellose, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, mannitol, sodium lauryl sulfate, sucralose
Each 80 mg/40 mg/60 mg sachet contains maximum 2.75 mg of sodium and 188.6 mg of lactose monohydrate.
Each 100 mg/50 mg/75 mg sachet contains maximum 3.44 mg of sodium and 235.7 mg of lactose monohydrate.

*Evening dose:*

Colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, mannitol, sodium lauryl sulfate, sucralose
Each 59.5 mg sachet contains maximum 1.18 mg of sodium and 87.3 mg of lactose monohydrate.
Each 75 mg sachet contains maximum 1.49 mg of sodium and 109.8 mg of lactose monohydrate.

**Pharmaceutical form and active substance quantity per unit**

*Film-coated Tablets*

*Elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg tablet and ivacaftor 75 mg tablet*

*Morning dose:*

Each 50 mg/25 mg/37.5 mg film-coated tablet contains 50 mg of elexacaftor, 25 mg of tezacaftor and 37.5 mg of ivacaftor as a fixed-dose combination tablet.
Light orange, capsule-shaped tablet debossed with «T50» on one side and plain on the other (6.4 mm x 12.2 mm).

*Evening dose:*

Each 75 mg film-coated tablet contains 75 mg of ivacaftor.

Light blue, capsule-shaped tablet printed with «V 75» in black ink on one side and plain on the other (12.7 mm x 6.8 mm).

*Elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg tablet and ivacaftor 150 mg tablet*

*Morning dose:*

Each 100 mg/50 mg/75 mg film-coated tablet contains 100 mg of elexacaftor, 50 mg of tezacaftor and 75 mg of ivacaftor as a fixed-dose combination tablet.
Orange, capsule-shaped tablet debossed with «T100» on one side and plain on the other (7.85 mm x 15.47 mm).

*Evening dose:*

Each 150 mg film-coated tablet contains 150 mg of ivacaftor.
Light blue, capsule-shaped tablet printed with «V 150» in black ink on one side and plain on the other (16.5 mm x 8.4 mm).

*Granules in Sachet*

All granules are white to off-white, sweetened, unflavored and approximately 2 mm in diameter.

*Elexacaftor 80 mg/tezacaftor 40 mg/ivacaftor 60 mg and ivacaftor 59.5 mg granules in sachet.*

*Morning Dose:*

Each sachet contains 80 mg of elexacaftor, 40 mg of tezacaftor and 60 mg of ivacaftor.

*Evening Dose:*

Each sachet contains 59.5 mg of ivacaftor

*Elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg and ivacaftor 75 mg granules in sachet Morning Dose:*

Each sachet contains 100 mg elexacaftor, 50 mg of tezacaftor and 75 mg of ivacaftor.

*Evening Dose:*

Each sachet contains 75 mg of ivacaftor.

**Indications/Uses**

Trikafta is indicated for the treatment of cystic fibrosis (CF) in patients aged 2 years and older who have at least one *F508del* mutation in the cystic fibrosis transmembrane conductance regulator *(CFTR)* gene («Clinical efficacy»).

**Dosage/Administration**

Trikafta should only be prescribed by physicians with experience in the treatment of CF. If the patient's genotype is unknown, confirm the presence of at least one *F508del* mutation using a genotyping assay.

*Usual dosage*

*Adults, adolescents and children aged 2 years and older*

**Table 1: Dosing recommendation for patients aged 2 years and older**

| Age | Weight | Morning Dose | Evening Dose |
|---|---|---|---|
| 2 to < 6 years | 10 - < 14 kg | One sachet of elexacaftor 80 mg/tezacaftor | One sachet of ivacaftor 59.5 mg granules |

| | | | |
|---|---|---|---|
| | | 40 mg/ivacaftor 60 mg granules | |
| 2 to < 6 years | ≥ 14 kg**Fehler! Textmarke nicht definiert.** | One sachet of elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg granules | One sachet of ivacaftor 75 mg granules |
| 6 to <12 years | < 30 kg | Two tablets, each containing elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg | One tablet containing ivacaftor 75 mg |
| 6 to <12 years | ≥ 30 kg | Two tablets, each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg | One tablet containing ivacaftor 150 mg |
| 12 years and older | - | Two tablets, each containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg | One tablet containing ivacaftor 150 mg |

The morning and evening dose should be taken with fat-containing food, approximately 12 hours apart (see «Mode of administration»).

*Delayed Administration*

If 6 hours or less have passed since the missed morning or evening dose, the patient should take the missed dose as soon as possible and continue on the original schedule.
If more than 6 hours have passed since:

- the missed **morning** dose, the patient should take the missed dose as soon as possible and should **not** take the evening dose. The next scheduled morning dose should be taken at the usual time.
- the missed **evening** dose, the patient should **not** take the missed dose. The next scheduled morning dose should be taken at the usual time.

Morning and evening doses should not be taken at the same time.

*Mode of administration*

For oral use.
Trikafta should be taken with fat-containing food. Examples of meals or snacks that contain fat are those prepared with butter or oils or those containing eggs, peanut butter cheeses, nuts, whole milk, or meats (see «Pharmacokinetic»).
Food or drink containing grapefruit should be avoided during treatment with Trikafta (see «Interactions»).

*Film-coated tablets*

Patients should be instructed to swallow the tablets whole. The tablets should not be chewed, broken, or dissolved before swallowing.

*Granules in sachet*

Each sachet is for single use only.
The entire contents of each sachet should be mixed with 5 mL of age-appropriate soft food or liquid and the mixture immediately consumed. Food or liquid should be at room temperature of below. Once mixed, the product has been shown to be stable for one hour, and therefore should be ingested during this period. Some examples of soft food or liquid include pureed fruits and vegetables, yogurt, applesauce, water, milk, or juice. A fat-containing meal or snack should be consumed just before or after dosing.

*Special dosage instructions*

*Patients with impaired hepatic function*

Treatment of patients with moderate hepatic impairment (Child-Pugh Class B) is not recommended. Treatment of patients with moderate hepatic impairment should only be considered when there is a clear medical need and the benefits are expected to outweigh the risks.
Studies have not been conducted in patients with severe hepatic impairment (Child-Pugh Class C). Patients with severe hepatic impairment should not be treated with Trikafta.
No dose adjustment is recommended for patients with mild hepatic impairment (Child Pugh Class A) (see «Warnings and precautions», «Undesirable effects» and «Pharmacokinetics»).

**Table 2: Recommendation for use in Patients with Hepatic Impairment**

| Age | Mild (Child-Pugh Class A) | Moderate (Child-Pugh Class B) | Severe (Child-Pugh Class C) |
|---|---|---|---|
| **2 to < 6 years** | No dose adjustment | Use not recommended. Treatment of patients with moderate hepatic impairment should only be considered when there is a clear medical need and the benefits are expected to outweigh the risks.<br>If used, Trikafta should be used with caution at a reduced dose, as follows:<br>• Day 1-3: one sachet of elexacaftor/tezacaftor/ivacaftor granules each day<br>• Day 4: no dose | Should not be used |

| | | | |
|---|---|---|---|
| | | • Day 5-6: one sachet of elexacaftor/tezacaftor/ivacaftor granules each day<br>• Day 7: no dose<br>Repeat above dosing schedule each week.<br><br>The evening dose of ivacaftor granules should not be taken. | |
| **6 years and older** | No dose adjustment | Use not recommended. Treatment of patients with moderate hepatic impairment should only be considered when there is a clear medical need and the benefits are expected to outweigh the risks.<br><br>If used, Trikafta should be used with caution at a reduced dose, as follows:<br>• Day 1: two elexacaftor/tezacaftor/ivacaftor tablets in the morning<br>• Day 2: one elexacaftor/tezacaftor/ivacaftor tablet in the morning<br>Continue alternating Day 1 and Day 2 dosing thereafter.<br><br>The evening dose of ivacaftor tablets should not be taken. | Should not be used |

*Patients with impaired renal function*

No dose adjustment is recommended for patients with mild and moderate renal impairment. Caution is recommended for patients with severe renal impairment or end-stage renal disease (see «Pharmacokinetic»).

*Concomitant use of CYP3A inhibitors*

When co-administered with moderate CYP3A inhibitors (e.g., fluconazole, erythromycin) or strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin), the dose should be reduced as in Table 3 (see «Warnings and precautions» and «Interactions»).

**Table 3: Dosing Schedule for Concomitant Use of Trikafta with Moderate and Strong CYP3A Inhibitors**

| Age | Moderate CYP3A Inhibitors | Strong CYP3A Inhibitors |
|---|---|---|
| **2 to < 6 years** | Alternate each day:<br>• One sachet of elexacaftor/tezacaftor/ivacaftor granules on the first day<br>• One sachet of ivacaftor granules on the next day<br><br>No evening sachet of ivacaftor granules. | One sachet of elexacaftor/tezacaftor/ivacaftor granules twice a week, approximately 3 to 4 days apart.<br><br>No evening sachet of ivacaftor granules. |
| **6 years and older** | Alternate each day:<br>• Two elexacaftor/tezacaftor/ivacaftor tablets on the first day<br>• One ivacaftor tablet on the next day<br><br>No evening ivacaftor tablet dose. | Two elexacaftor/tezacaftor/ivacaftor tablets twice a week, approximately 3 to 4 days apart.<br><br>No evening ivacaftor tablet dose. |

*Children*

The safety and efficacy of Trikafta in children aged less than 2 years have not been established (see «Undesirable effects» and «Properties/Effects»).

*Elderly patients*

Clinical studies of Trikafta did not include a sufficient number of patients aged 65 years and older to determine whether they respond differently from younger patients.

**Contraindications**

Hypersensitivity to the active substances or to any of the excipients (see «Composition»).

**Warnings and precautions**

*Effect on liver function tests*

Elevated transaminases are common in patients with CF and have been observed in some patients treated with Trikafta, with or without pre-existing liver disease. In some cases, these sometimes severe increases were associated with concomitant elevations in total bilirubin. In Phase 3 studies transaminase elevations occurred more frequently in the Trikafta group compared to the placebo group. Assessments of transaminases (ALT and AST) and total bilirubin are therefore recommended for all patients prior to initiating Trikafta, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of liver disease or transaminase elevations, more

frequent monitoring should be considered. In the event of ALT or AST >5 x the upper limit of normal (ULN), or ALT or AST >3 x ULN with bilirubin >2 x ULN, dosing should be interrupted and laboratory tests closely followed until the abnormalities resolve. Following the resolution of transaminase elevations, the benefits and risks of resuming treatment should be weighed up (see «Dosage/Administration», «Undesirable effects» and «Pharmacokinetics»).

*Severe elevation of transaminases and liver damage*

Liver failure leading to transplantation has been reported in a patient with cirrhosis and portal hypertension while receiving Trikafta, and therefore Trikafta should be used with caution and close monitoring in patients with pre-existing advanced liver disease (e.g., cirrhosis, portal hypertension), if after considering the benefits and risks, a patient is treated with Trikafta. Severe liver value elevations (transaminases and bilirubin) have also been reported in CF patients without prior liver disease during treatment with Trikafta. Treatment of patients with moderate hepatic impairment (Child-Pugh class B) is not recommended (see «Dosage/Administration», «Undesirable effects» and «Pharmacokinetics»).

*Hepatic impairment*

Treatment of patients with moderate hepatic impairment is not recommended. For patients with moderate hepatic impairment, the use of Trikafta should only be considered when there is a clear medical need and the benefits are expected to outweigh the risks. If used, it should be used with caution at a reduced dose (see Table 2). Patients with severe hepatic impairment should not be treated with Trikafta (see «Dosage/Administration», «Undesirable effects» and «Pharmacokinetics»).

*Depression*

Depression (including suicidal ideation and suicidal attempt) has been reported in patients treated with Trikafta, usually occurring within three months of treatment initiation and in patients with a history of psychiatric disorders. In some cases, symptom improvement was reported after dose reduction or treatment discontinuation. Patients (and caregivers) should be alerted about the need to monitor for depressed mood, suicidal thoughts, or unusual changes in behaviour and to seek medical advice immediately if these symptoms present.

*Interactions with medicinal products*

*CYP3A inducers*

Exposure to ivacaftor is significantly decreased and exposures to elexacaftor and tezacaftor are expected to decrease by the concomitant use of CYP3A inducers, potentially resulting in the reduction of Trikafta efficacy; therefore, co-administration with strong CYP3A inducers is not recommended (see «Interactions»).

*CYP3A inhibitors*

Exposure to elexacaftor, tezacaftor and ivacaftor are increased when co-administered with strong or moderate CYP3A inhibitors. Therefore, the dose of Trikafta should be reduced when used concomitantly with moderate or strong CYP3A inhibitors (see «Interactions» and Table 3 in «Dosage/Administration»).

*Cataracts*

Cases of non-congenital lens opacities without impact on vision have been reported in pediatric patients treated with ivacaftor-containing regimens. Although other risk factors were present in some cases (such as corticosteroid use, exposure to radiation) a possible risk attributable to treatment with ivacaftor cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with Trikafta (see «Preclinical data»).

*Patients after organ transplantation*

Elexacaftor/tezacaftor/ivacaftor has not been studied in CF patients after organ transplantation. Therefore, its use is not recommended in patients with organ transplants. See «Interactions» for information on interactions with cyclosporine or tacrolimus.

*Lactose*

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

*Sodium*

This medicinal product contains less than 1 mmol sodium (23 mg) per daily dose, that is to say essentially ‘sodium-free’.

**Interactions**

*Pharmacokinetic interactions*

*Medicinal products affecting the pharmacokinetics of Trikafta*

*CYP3A inducers*

Elexacaftor, tezacaftor and ivacaftor are substrates of CYP3A (ivacaftor is a sensitive substrate of CYP3A). Concomitant use of CYP3A inducers may result in reduced exposures and thus reduced Trikafta efficacy. Co-administration of ivacaftor with rifampin, a strong CYP3A inducer, significantly decreased ivacaftor area under the curve (AUC) by 89%. Elexacaftor and tezacaftor exposures are expected to decrease during co-administration with strong CYP3A inducers; therefore, co-administration of Trikafta with strong CYP3A inducers is not recommended (see «Warnings and precautions»).
Examples of strong CYP3A inducers include:

- rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort (*Hypericum perforatum*)

*CYP3A inhibitors*

Co-administration with itraconazole, a strong CYP3A inhibitor, increased elexacaftor AUC by 2.8 fold and tezacaftor AUC by 4.0- to 4.5-fold. When co-administered with itraconazole and ketoconazole, ivacaftor AUC increased by 15.6-fold and 8.5-fold, respectively. The dose of Trikafta should be reduced when co-administered with strong CYP3A inhibitors (see «Warnings and precautions» and Table 3 in «Dosage/Administration»).

Examples of strong CYP3A inhibitors include:

- ketoconazole, itraconazole, posaconazole, and voriconazole
- telithromycin and clarithromycin

Simulations indicated that co-administration with moderate CYP3A inhibitors may increase elexacaftor and tezacaftor AUC by approximately 1.9 to 2.3-fold. Co-administration of fluconazole increased ivacaftor AUC by 2.9-fold. The dose of Trikafta should be reduced when co-administered with moderate CYP3A inhibitors (see «Warnings and precautions» and Table 3 in «Dosage/Administration»).

Examples of moderate CYP3A inhibitors include:

- fluconazole
- erythromycin

Co-administration of Trikafta with grapefruit juice, which contains one or more components that moderately inhibit CYP3A, may increase exposure of elexacaftor, tezacaftor and ivacaftor. Food or drink containing grapefruit should be avoided during treatment with Trikafta (see «Dosage/Administration»).

The effects of co-administered drugs on the exposure of elexacaftor, tezacaftor and/or ivacaftor are shown in Table 4.

| Table 4: Impact of Other Drugs on Elexacaftor, Tezacaftor and/or Ivacaftor | | | | |
|---|---|---|---|---|
| **Dose and Schedule** | | **Effect on ELX, TEZ and/or IVA PK** | **Geometric Mean Ratio (90% CI) of Elexacaftor, Tezacaftor and Ivacaftor No Effect = 1.0** | |
| | | | **AUC** | **$C_{max}$** |
| Itraconazole 200 mg q12h on Day 1, followed by 200 mg qd | TEZ 25 mg qd + IVA 50 mg qd | ↑ Tezacaftor | 4.02 (3.71, 4.63) | 2.83 (2.62, 3.07) |
| | | ↑ Ivacaftor | 15.6 (13.4, 18.1) | 8.60 (7.41, 9.98) |
| Itraconazole 200 mg qd | ELX 20 mg + TEZ 50 mg single dose | ↑ Elexacaftor | 2.83 (2.59, 3.10) | 1.05 (0.977, 1.13) |
| | | ↑ Tezacaftor | 4.51 (3.85, 5.29) | 1.48 (1.33, 1.65) |
| Ketoconazole 400 mg qd | IVA 150 mg single dose | ↑ Ivacaftor | 8.45 (7.14, 10.0) | 2.65 (2.21, 3.18) |
| Ciprofloxacin 750 mg q12h | TEZ 50 mg q12h + IVA 150 mg q12h | ↔ Tezacaftor | 1.08 (1.03, 1.13) | 1.05 (0.99, 1.11) |
| | | ↑ Ivacaftor* | 1.17 (1.06, 1.30) | 1.18 (1.06, 1.31) |
| Rifampin 600 mg qd | IVA 150 mg single dose | ↓ Ivacaftor | 0.114 (0.097, 0.136) | 0.200 (0.168, 0.239) |
| Fluconazole 400 mg single dose on Day 1, followed by 200 mg qd | IVA 150 mg q12h | ↑ Ivacaftor | 2.95 (2.27, 3.82) | 2.47 (1.93, 3.17) |
| ↑ = increase, ↓ = decrease, ↔ = no change. CI = Confidence interval; ELX= elexacaftor; TEZ = tezacaftor; IVA = ivacaftor; PK = Pharmacokinetics<br>* Effect is not clinically significant | | | | |

*Medicinal products affected by Trikafta*

*CYP2C9 substrates*

Ivacaftor may inhibit CYP2C9; therefore, monitoring of the international normalized ratio (INR) during co-administration of Trikafta with warfarin is recommended. Other medicinal products for which exposure may be increased by Trikafta include glimepiride and glipizide; these medicinal products should be used with caution.

*Potential for interaction with transporters*

Co-administration of ivacaftor or tezacaftor/ivacaftor with digoxin, a sensitive P-glycoprotein (P-gp) substrate, increased digoxin AUC by 1.3-fold, consistent with weak inhibition of P-gp by ivacaftor. Administration of Trikafta may increase systemic exposure of medicinal products that are sensitive substrates of P-gp, which may increase or prolong their therapeutic effect and adverse reactions. When used concomitantly with digoxin or other substrates of P-gp with a narrow therapeutic index such as cyclosporine, everolimus, sirolimus, and tacrolimus, caution and appropriate monitoring should be used.

Elexacaftor and M23-ELX inhibit uptake by OATP1B1 and OATP1B3 *in vitro*. Tezacaftor/ivacaftor increased the AUC of pitavastatin, an OATP1B1 substrate, by 1.2-fold. Co-administration of Trikafta may increase exposures of medicinal products that are substrates of these transporters, such as statins, glyburide, nateglinide and repaglinide. When used concomitantly with substrates of OATP1B1 or OATP1B3, caution and appropriate monitoring should be used. Bilirubin is an OATP1B1 and OATP1B3 substrate. In Study 445-102, mild increases in mean total bilirubin were observed (up to 4.0 µmol/L change from baseline). This finding is consistent with the *in vitro* inhibition of bilirubin transporters OATP1B1 and OATP1B3 by elexacaftor and M23-ELX.

*Hormonal contraceptives*

Trikafta has been studied with ethinyl estradiol/levonorgestrel and was found to have no clinically relevant effect on the exposures of the oral contraceptive. Trikafta is not expected to have an impact on the efficacy of oral contraceptives.

The effects of elexacaftor, tezacaftor and/or ivacaftor on the exposure of co-administered drugs are shown in Table 5.

**Table 5: Impact of Elexacaftor, Tezacaftor and/or Ivacaftor on Other Drugs**

| Dose and Schedule | | Effect on Other Drug PK | Geometric Mean Ratio (90% CI) of Other Drug No Effect=1.0 | |
|---|---|---|---|---|
| | | | AUC | $C_{max}$ |
| Midazolam<br>2 mg single oral dose | TEZ 100 mg qd/IVA 150 mg q12h | ↔ Midazolam | 1.12<br>(1.01, 1.25) | 1.13<br>(1.01, 1.25) |
| Digoxin<br>0.5 mg single dose | TEZ 100 mg qd/IVA 150 mg q12h | ↑ Digoxin | 1.30<br>(1.17, 1.45) | 1.32<br>(1.07, 1.64) |
| Oral Contraceptive<br>Ethinyl estradiol 30 µg/Levonorgestrel 150 µg qd | ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h | ↑ Ethinyl estradiol*<br>↑ Levonorgestrel* | 1.33<br>(1.20, 1.49)<br>1.23<br>(1.10, 1.37) | 1.26<br>(1.14, 1.39)<br>1.10<br>(0.985, 1.23) |
| Rosiglitazone<br>4 mg single oral dose | IVA 150 mg q12h | ↔ Rosiglitazone | 0.975<br>(0.897, 1.06) | 0.928<br>(0.858, 1.00) |
| Desipramine<br>50 mg single dose | IVA 150 mg q12h | ↔ Desipramine | 1.04<br>(0.985, 1.10) | 1.00<br>(0.939; 1.07) |

↑ = increase, ↓ = decrease, ↔ = no change. CI = Confidence interval; ELX= elexacaftor;

TEZ = tezacaftor; IVA = ivacaftor; PK = Pharmacokinetics

* Effect not clinically significant.

**Pregnancy, lactation**

*Pregnancy*

No adequate and well-controlled studies of Trikafta in pregnant women have been conducted. Animal studies with the individual active substances did not show any direct toxicity in terms of pregnancy, embryofetal development or postnatal development (see «Preclinical Data»). As a precautionary measure, use of the therapy should be avoided during pregnancy.

*Lactation*

Limited data show that elexacaftor, tezacaftor and ivacaftor are excreted in human milk. A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy with Trikafta taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

*Fertility*

There are no data available on the effect of elexacaftor, tezacaftor, and ivacaftor on fertility in humans. In animal studies, elexacaftor and ivacaftor had an effect on the fertility of rats. In animal studies, tezacaftor showed no effect on mating behaviour and fertility parameters (see «Preclinical data»).

**Effects on ability to drive and use machines**

The influence of Trikafta on the ability to drive and use machines has not been specifically investigated.

**Undesirable effects**

*Summary of the safety profile*

The safety profile of Trikafta is based on data from 510 patients in two double-blind, controlled, phase 3 studies of 24 weeks and 4 weeks treatment duration (Studies 445-102 and 445-103). In the two controlled phase 3 studies, a total of 257 patients aged 12 years and older received at least one dose of Trikafta.
In Study 445-102, the proportion of patients who discontinued study drug prematurely due to adverse events was 1% for Trikafta-treated patients and 0% for placebo-treated patients.
Serious adverse drug reactions that occurred more frequently in Trikafta-treated patients compared to placebo were rash events in 3 (1.5%) Trikafta-treated patients vs.1 (0.5%) placebo. The most common (⩾10%) adverse drug reactions in patients treated with Trikafta were headache (17.3%), diarrhea (12.9%) and upper respiratory tract infection (11.9%).
The safety profile of Trikafta was generally similar across all subgroups of patients, including analysis by age, sex, baseline percent predicted $FEV_1$ ($ppFEV_1$), and geographic regions.

*Tabulated list of adverse reactions*

Table 6 reflects adverse reactions observed with elexacaftor/tezacaftor/ivacaftor in combination with ivacaftor, tezacaftor/ivacaftor in combination with ivacaftor and ivacaftor. Adverse drug reactions for Trikafta are ranked under the MedDRA frequency classification: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

| Table 6: Adverse reactions during use of elexacaftor/tezacaftor/ivacaftor, tezacaftor/ivacaftor and ivacaftor alone in adolescents >12 years and adults | | |
|---|---|---|
| **MedDRA System Organ Class** | **Adverse Reactions** | **Frequency** |
| **Infections and infestations** | Upper respiratory tract infection*, Nasopharyngitis | very common |
| | Rhinitis*, Influenza* | common |
| **Metabolism and nutrition disorders** | Hypoglycaemia* | common |
| **Psychiatric disorders** | Depression | not known |
| **Nervous system disorders** | Headache*, Dizziness* | very common |
| **Ear and labyrinth disorders** | Ear pain, Ear discomfort, Tinnitus, Tympanic membrane hyperaemia, Vestibular disorder | common |
| | Ear congestion | uncommon |
| **Respiratory, thoracic and mediastinal disorders** | Oropharyngeal pain, Nasal congestion* | very common |
| | Rhinorrhoea*, Sinus congestion, Pharyngeal erythema, Abnormal breathing* | common |
| | Wheezing* | uncommon |
| **Gastrointestinal disorders** | Diarrhoea*, Abdominal pain* | very common |
| | Nausea, Abdominal pain upper*, Flatulence* | common |
| **Hepatobiliary disorders** | Transaminase elevations | very common |
| | Alanine aminotransferase increased*, Aspartate aminotransferase increased* | common |
| **Skin and subcutaneous tissue disorders** | Rash* | very common |
| | Acne*, Pruritus* | common |
| **Reproductive system and breast disorders** | Breast mass | common |
| | Breast inflammation, Gynaecomastia, Nipple disorder, Nipple pain | uncommon |
| **Investigations** | Bacteria in sputum | very common |
| | Blood creatine phosphokinase increased* | common |
| | Blood pressure increased* | uncommon |
| *Adverse reactions observed during clinical studies with elexacaftor/tezacaftor/ivacaftor in combination with ivacaftor. | | |

Safety data from the following studies were consistent with the safety data observed in Study 445-102.

- A 4-week, randomized, double-blind, active-controlled study in 107 patients (Study 445-103).
- An ongoing 192-week, open-label safety and efficacy study (Study 445-105) for patients rolled over from Studies 445-102 and 445-103, with interim analysis performed on 506 patients at Week 96.
- An 8-week, randomized, double-blind, active-controlled study in 258 patients (Study 445-104).
- A 24-week, open-label study (Study 445-111) in 75 patients aged 2 to less than 6 years.

A 24-week, open-label study examined 66 patients aged 6 to less than 12 years (Study 445-106 part B). See below for details on liver and skin adverse events.

*Description of selected undesirable effects*

*Elevated Transaminases and hepatic injury*

In Study 445-102, the incidence of maximum transaminase (ALT or AST) >8, >5, or >3 x the ULN was 1.5%, 2.5%, and 7.9% in Trikafta-treated patients and 1.0%, 1.5%, and 5.5% in placebo-treated patients. The incidence of adverse reactions of transaminase elevations was 10.9% in Trikafta-treated patients and 4.0% in placebo-treated patients. No Trikafta-treated patients discontinued treatment for elevated transaminases.
During Study 445-106 part B in 66 patients aged 6 to less than 12 years, the incidence of maximum transaminase (ALT or AST) >8, >5, and >3 x ULN was 0.0%, 1.5%, and 10.6%, respectively. No Trikafta-treated patients had transaminase elevation >3 x ULN associated with elevated total bilirubin >2 x ULN or discontinued treatment due to transaminase elevations. For the adverse events of elevated transaminases the mean (SD) time to first event was 52.1 (62.2) days and the mean (SD) duration was 15.3 (9.0) days (see «Warnings and precautions»).
During Study 445-111 in patients aged 2 to less than 6 years, the incidence of maximum transaminase (ALT or AST) > 8, > 5, and >3 x ULN were 1.3%, 2.7%, and 8.0%, respectively. No Trikafta-treated patients had transaminase elevation > 3 x ULN associated with elevated total bilirubin > 2 x ULN or discontinued treatment due to transaminase elevations (see «Warnings and precautions»).

The following adverse reactions have been identified during post-approval use of Trikafta.

- Liver failure leading to transplantation in a patient with pre-existing cirrhosis and portal hypertension (see «Dosage/Administration», «Warnings and precautions» and «Pharmacokinetics»)
- Liver injury characterized by concomitant transaminase (ALT and AST) and total bilirubin elevations in CF patients with or without pre-existing liver disease (see «Dosage/Administration», «Warnings and precautions» and «Pharmacokinetics»)

*Rash Events*

In Study 445-102, the incidence of rash events (e.g., rash, rash pruritic) was 10.9% in Trikafta- and 6.5% in placebo-treated patients. The rash events were generally mild to moderate in severity. The incidence of rash events by patient sex was 5.8% in males and 16.3% in females in Trikafta-treated patients and 4.8% in males and 8.3% in females in placebo-treated patients.
A role for hormonal contraceptives in the occurrence of rash cannot be excluded. For patients taking hormonal contraceptives who develop rash, consider interrupting Trikafta and hormonal

contraceptives. Following the resolution of rash, consider resuming Trikafta without the hormonal contraceptives. If rash does not recur, resumption of hormonal contraceptives can be considered.
In the Study 445-106 part B in 66 Trikafta-treated patients aged 6 to less than 12 years, the incidence of rash (e.g., rash, pruritic rash) was 24.2% (n=16). The specific adverse events included skin rash n=8 (12.1%), erythematous rash n=3 (4.5%), maculo-papular rash n=2 (3.0%), papular rash n=2 (3.0%), skin exfoliation n=1 (1.5%), urticaria n=1 (1.5%). One patient (1.5%) had a rash that led to discontinuation of Trikafta. The remaining patients had rash events that resolved with continued Trikafta treatment.

*Increased Creatine Phosphokinase*

In Study 445-102, the incidence of maximum creatine phosphokinase >5 x the ULN was 10.4% in Trikafta- and 5.0% in placebo-treated patients. No Trikafta-treated patients discontinued treatment for increased creatine phosphokinase.

*Increased Blood Pressure*

In Study 445-102, the maximum increase from baseline in mean systolic and diastolic blood pressure was 3.5 mmHg and 1.9 mmHg, respectively for Trikafta-treated patients (baseline: 113 mmHg systolic and 69 mmHg diastolic) and 0.9 mmHg and 0.5 mmHg, respectively for placebo-treated patients (baseline: 114 mmHg systolic and 70 mmHg diastolic).
The proportion of patients who had systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg on at least two occasions was 5.0% and 3.0% in Trikafta-treated patients respectively, compared with 3.5% and 3.5% in placebo-treated patients, respectively.

*VX17-445-105 extension study over 192 weeks, interim analysis after 96 weeks*

In the open-label, uncontrolled, long-term VX17-445-105 study, 399 (78.9%) patients with an *F508del* mutation/MF mutation and 107 (21.1%) patients with a homozygous *F508del* mutation were followed up for 96 weeks. By week 96, 464 (91.7%) patients remained in the study, 42 (8.3%) patients discontinued early for various reasons. Of these, 11 (2.2%) patients discontinued due to adverse events, including 4 (0.8%) patients because of ALT, AST, and/or γ-GT elevation, and 1 (0.2%) patient because of hepatic encephalopathy.
ALT or AST elevation >3, >5, and >8 x ULN was noted in 50 (9.9%), 25 (4.9%), and 9 (1.8%) patients, respectively, of whom 2 (0.4%) were patients with ALT or AST elevation >3 x ULN with concomitant new-onset elevation of total bilirubin >2 x ULN, with one patient having medical history of Gilbert's syndrome.
Elevations of CK ≥2.5-≤5, >5-≤10 and >10 x ULN were noted in 57 (11.3%), 34 (6.7%) and 30 (5.9%) patients. CK elevation was noted as an adverse reaction in 55 (10.9%) patients. 2 (0.4%) patients experienced rhabdomyolysis without renal involvement or myoglobinuria.
Skin rashes occurred in 74 (14.6%) patients. One (0.2%) patient discontinued the treatment due to skin rash.

Mean systolic blood pressure increased between 2.7-4.9 mmHg, and mean diastolic blood pressure increased between 1.5-3.5 mmHg. The adverse reaction elevated blood pressure was noted in 12 (2.4%) cases.
There was one nonserious cataract that did not lead to a change in dosing.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

**Overdose**

*Treatment*

No specific antidote is available for overdose with Trikafta. Treatment of overdose consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient.

**Properties/Effects**

*ATC code*

R07AX32

*Mechanism of action*

Elexacaftor and tezacaftor are CFTR correctors that bind to different sites on the CFTR protein and have an additive effect in facilitating the cellular processing and trafficking of F508del-CFTR to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone. Ivacaftor potentiates the channel open probability (or gating) of the CFTR protein at the cell surface. The combined effect of elexacaftor, tezacaftor and ivacaftor is increased quantity and function of F508del-CFTR at the cell surface, resulting in increased CFTR activity as measured by CFTR mediated chloride transport. Clinical outcomes were consistent with *in vitro* results and indicate that a single *F508del* mutation is sufficient to result in a significant clinical response (see «Clinical efficacy»).

*Pharmacodynamics*

*Pharmacodynamic effects*

*Effects on sweat chloride*

In Study 445-102 (patients with an *F508del* mutation on one allele and a mutation on the second allele that results in either no CFTR protein or a CFTR protein that is not responsive to ivacaftor and tezacaftor/ivacaftor [minimal function mutation]), a reduction in sweat chloride was observed from baseline at Week 4 and sustained through the 24-week treatment period. The treatment difference of

Trikafta compared to placebo for mean absolute change in sweat chloride from baseline through Week 24 was -41.8 mmol/L (95% CI: -44.4, -39.3; *P*<0.0001).
In Study 445-103 (patients homozygous for the *F508del* mutation), the treatment difference of Trikafta compared to the tezacaftor/ivacaftor and ivacaftor regimen (tezacaftor/ivacaftor) for mean absolute change in sweat chloride from baseline at Week 4 was -45.1 mmol/L (95% CI: -50.1, -40.1, *P*<0.0001).
In Study 445-104 (patients heterozygous for the *F508del* mutation and a gating or residual function mutation on the second allele), following a 4-week ivacaftor or tezacaftor/ivacaftor run-in period, the mean absolute change in sweat chloride from baseline through Week 8 for the Trikafta group was -22.3 mmol/L (95% CI: -24.5, -20.2; *P*<0.0001). The treatment difference of Trikafta compared to the control group (ivacaftor or tezacaftor/ivacaftor) was -23.1 mmol/L (95% CI: -26.1, -20.1; *P*<0.0001).
In Study 445-106 (patients aged 6 to less than 12 years who are homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and a minimal function mutation), the mean absolute change in sweat chloride from baseline through Week 24 was -60.9 mmol/L (95% CI: -63.7, -58.2). The measured values for the sweat chloride concentration were collected on the planned measurement days in the following number of patients: baseline n=62, day 15 n=56, week 4 n=56, week 12 n=50, week 24 n=28.
In Study 445-111 (patients aged 2 to less than 6 years who are homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and a minimal function mutation), the mean absolute change in sweat chloride from baseline through Week 24 was -57.9 mmol/L (95% CI: -61.3, -54.6).

*Cardiovascular Effects*

*Effect on QT interval*

At doses up to 2 times the maximum recommended dose of elexacaftor and 3 times the maximum recommended dose of tezacaftor and ivacaftor, the QT/QTc interval in healthy subjects was not prolonged to any clinically relevant extent.

*Heart Rate*

In Study 445-102, mean decreases in heart rate of 3.7 to 5.8 beats per minute (bpm) from baseline (76 bpm) were observed in Trikafta-treated patients.

*Clinical efficacy*

The efficacy of Trikafta in patients with CF was statistically demonstrated in three Phase 3 double blind, controlled studies (Studies 445-102, 445-103 and 445-104). These studies each enrolled CF patients who had at least one *F508del* mutation. Three open-label, uncontrolled phase 3 studies (Study 445-105, Study 445-106 part B, and Study 445-111) provide additional support for efficacy. Trikafta was developed as a combination therapy containing elexacaftor, tezacaftor, and ivacaftor.

The benefit of elexacaftor alone and tezacaftor alone in comparison with the combination therapy has not been investigated in clinical studies, and these active substances are not individually available as medicinal products.

Study 445-102 was a 24-week, randomized, double-blind, placebo-controlled study in patients who had an *F508del* mutation on one allele and a minimal function (MF) mutation on the second allele that results in either no CFTR protein or a CFTR protein that is not responsive to ivacaftor and tezacaftor/ivacaftor. A total of 403 patients aged 12 years and older (mean age 26.2 years) were randomized and dosed to receive Trikafta or placebo. Patients had a $ppFEV_1$ at screening between 40-90%. The mean $ppFEV_1$ at baseline was 61.4% (range: 32.3%, 97.1%).

Study 445-103 was a 4-week, randomized, double-blind, active-controlled study in patients who are homozygous for the *F508del* mutation. A total of 107 patients aged 12 years and older (mean age 28.4 years) received tezacaftor/ivacaftor and ivacaftor regimen (tezacaftor/ivacaftor) during a 4-week open-label run-in period and were then randomized and dosed to receive Trikafta or tezacaftor/ivacaftor during a 4-week double-blind treatment period. Patients had a $ppFEV_1$ at screening between 40-90%. The mean $ppFEV_1$ at baseline, following the tezacaftor/ivacaftor run-in period was 60.9% (range: 35.0%, 89.0%).

Study 445-104 was an 8-week, randomized, double-blind, active-controlled study in patients who were heterozygous for the *F508del* (F) mutation and a gating (G) or residual function (RF) mutation on the second allele. Patients aged 12 years and older with $ppFEV_1$ between 40-90% at screening received either ivacaftor (for F/G mutation patients) or tezacaftor/ivacaftor (for F/RF mutation patients) during a 4-week open-label run-in period. Patients with F/*R117H* genotype received ivacaftor during the run-in period. Patients were then randomized to the Trikafta group or remained on the CFTR modulator therapy received during the run-in period. The mean age at baseline, following the run-in period, was 37.7 years, and the mean $ppFEV_1$ at baseline was 67.6% (range: 29.7%, 113.5%).

Study 445-106 was a two-part 24-week open-label uncontrolled study in 66 patients aged 6 to less than 12 years (mean age at baseline 9.3 years) who were homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and a minimal function mutation. Part A evaluated pharmacokinetics and preliminary safety, Part B evaluated safety, tolerability, efficacy and pharmacokinetics. Patients weighing <30 kg at baseline (36 patients, 54.5%) were administered two elexacaftor/tezacaftor/ivacaftor 50 mg/25 mg/37.5 mg tablets in the morning and one ivacaftor 75 mg tablet in the evening. Patients weighing ≥30 kg at baseline (30 patients, 45.5%) were administered two elexacaftor/tezacaftor/ivacaftor 100 mg/50 mg/75 mg tablets in the morning and one ivacaftor 150 mg tablet in the evening. Patients had a screening $ppFEV_1$ ≥40% [mean $ppFEV_1$ at baseline of 88.8% (range: 39.0%, 127.1%)] and weighed ≥15 kg (required inclusion criterion).

Study 445-111 was a 24-week, open-label study in patients aged 2 to less than 6 years (mean age at baseline 4.1 years). Patients who had at least one *F508del* mutation or a mutation known to be responsive to elexacaftor/tezacaftor/ivacaftor were eligible for the study. A total of 75 patients who

were homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation and a minimal function mutation were enrolled and dosed according to weight. Patients weighing 10 kg to < 14 kg at baseline were administered elexacaftor 80 mg once daily (qd)/tezacaftor 40 mg qd/ivacaftor 60 mg once every morning and ivacaftor 59.5 mg once every evening. Patients weighing ≥ 14 kg at baseline were administered elexacaftor 100 mg qd/tezacaftor 50 mg qd/ivacaftor 75 mg q12h.
Patients in Studies 445-102, 445-103, 445-104, 445-106 and 445-111 continued on their CF therapies (e.g., bronchodilators, inhaled antibiotics, dornase alfa, and hypertonic saline), but discontinued any previous CFTR modulator therapies, except for study drugs. Patients had a confirmed diagnosis of CF and at least one *F508del* mutation.
In studies 445-102, 445-103, 445-104, 445-106, and 445-111, patients who had lung infection with organisms associated with a more rapid decline in pulmonary status, including but not limited to *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus*, or who had an abnormal liver function test at screening (ALT, AST, ALP, or GGT ≥3 x ULN, or total bilirubin ≥2 x ULN), were excluded. In study 445-111, patients who had ALT or AST ≥2 x ULN were also excluded.
Patients in studies 445-102 and 445-103 were eligible to roll over into a 192-week, open-label extension study (Study 445-105). Patients in studies 445-104, 445-106, and 445-111 were eligible to roll over into open-label extension studies.

*Study 445-102*

In Study 445-102 the primary endpoint was mean absolute change in $ppFEV_1$ from baseline through Week 24. Treatment with Trikafta compared to placebo resulted in statistically significant improvement in $ppFEV_1$ of 14.3 percentage points (95% CI: 12.7, 15.8; *P*<0.0001) (Table 7). Mean improvement in $ppFEV_1$ was rapid in onset (Day 15) and sustained through the 24-week treatment period (Figure 1). Improvements in $ppFEV_1$ were observed regardless of age, baseline $ppFEV_1$, sex, and geographic region. A total of 18 patients receiving Trikafta had $ppFEV_1$ <40 at baseline. The safety and efficacy in this subgroup were comparable to those observed in the overall population. See Table 7 for a summary of primary and key secondary outcomes.

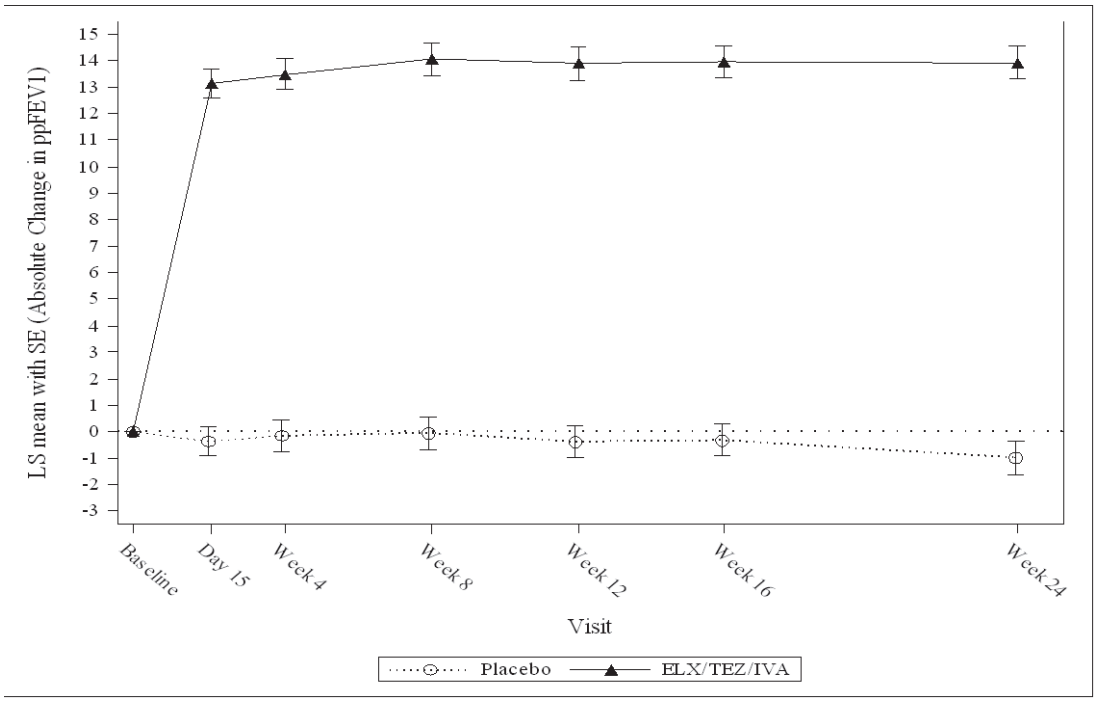
| Table 7: Primary and Key Secondary Efficacy Analyses, Full Analysis Set (Study 445-102) | | | |
|---|---|---|---|
| **Analysis** | **Statistic** | **Placebo N=203** | **Trikafta N=200** |
| **Primary efficacy analysis** | | | |
| Absolute change in $ppFEV_1$ from baseline through Week 24 (percentage points) | Treatment difference (95% CI)<br>*P* value<br>Within-group change (SE) | NA<br>NA<br>-0.4 (0.5) | 14.3 (12.7, 15.8)<br>*P*<0.0001<br>13.9 (0.6) |
| **Key secondary efficacy analyses** | | | |
| Absolute change in $ppFEV_1$ from baseline at Week 4 (percentage points) | Treatment difference (95% CI)<br>*P* value<br>Within-group change (SE) | NA<br>NA<br>-0.2 (0.6) | 13.7 (12.0, 15.3)<br>*P*<0.0001<br>13.5 (0.6) |
| Number of pulmonary exacerbations from baseline through Week 24‡ | Number of events (event rate per year††)<br>Rate ratio (95% CI)<br>*P* value | 113 (0.98)<br>NA<br>NA | 41 (0.37)<br>0.37 (0.25, 0.55)<br>*P*<0.0001 |
| Absolute change in sweat chloride from baseline through Week 24 (mmol/L) | Treatment difference (95% CI)<br>*P* value<br>Within-group change (SE) | NA<br>NA<br>-0.4 (0.9) | -41.8<br>(-44.4, -39.3)<br>*P*<0.0001<br>-42.2 (0.9) |
| Absolute change in CFQ-R respiratory domain score from baseline through Week 24 (points) | Treatment difference (95% CI)<br>*P* value<br>Within-group change (SE) | NA<br>NA<br>-2.7 (1.0) | 20.2 (17.5, 23.0)<br>*P*<0.0001<br>17.5 (1.0) |
| Absolute change in BMI from baseline at Week 24 ($kg/m^2$) | Treatment difference (95% CI)<br>*P* value<br>Within-group change (SE) | NA<br>NA<br>0.09 (0.07) | 1.04 (0.85, 1.23)<br>*P*<0.0001<br>1.13 (0.07) |
| Absolute change in sweat chloride from baseline at Week 4 (mmol/L) | Treatment difference (95% CI)<br>*P* value<br>Within-group change (SE) | NA<br>NA<br>0.1 (1.0) | -41.2<br>(-44.0, -38.5)<br>*P*<0.0001<br>-41.2 (1.0) |
| Absolute change in CFQ-R respiratory domain score from baseline at Week 4 (points) | Treatment difference (95% CI)<br>*P* value<br>Within-group change (SE) | NA<br>NA<br>-1.9 (1.1) | 20.1 (16.9, 23.2)<br>*P*<0.0001<br>18.1 (1.1) |

$ppFEV_1$: percent predicted forced expiratory volume in 1 second; CI: confidence interval; SE: Standard Error; NA: not applicable; CFQ-R: Cystic Fibrosis Questionnaire-Revised; BMI: body mass index.

‡ A pulmonary exacerbation was defined as a change in antibiotic therapy (IV, inhaled, or oral) as a result of 4 or more of 12 pre-specified sino-pulmonary signs/symptoms.

†† Estimated event rate per year was calculated based on 48 weeks per year.

**Figure 1: Absolute Change from Baseline in Percent Predicted $FEV_1$ at Each Visit in Study 445-102**



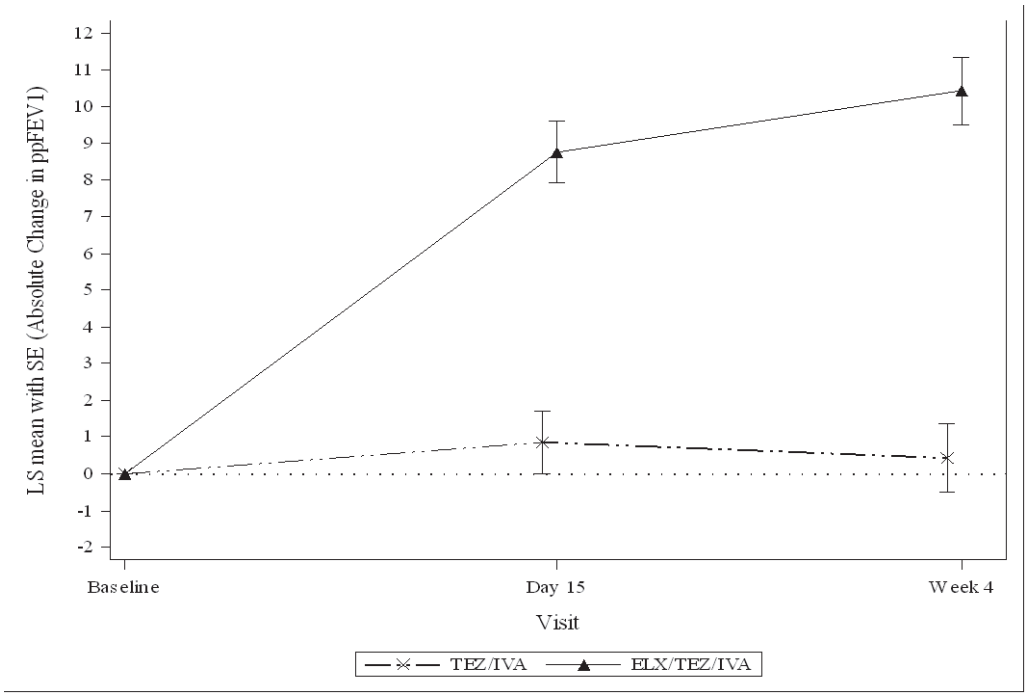

SE: Standard Error; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor

*Study 445-103*

In Study 445-103 the primary endpoint was mean absolute change in $ppFEV_1$ from baseline at Week 4 of the double-blind treatment period. Treatment with Trikafta compared to the regimen of tezacaftor/ivacaftor and ivacaftor (tezacaftor/ivacaftor) resulted in a statistically significant improvement in $ppFEV_1$ of 10.0 percentage points (95% CI: 7.4, 12.6; $P$<0.0001) (Table 8). Improvements in $ppFEV_1$ were observed regardless of age, sex, baseline $ppFEV_1$, and geographic region. See Table 8 for a summary of primary and key secondary outcomes.

| Table 8: Primary and Key Secondary Efficacy Analyses, Full Analysis Set (Study 445-103) | | | |
|---|---|---|---|
| **Analysis*** | **Statistic** | **Tezacaftor/ Ivacaftor# N=52** | **Trikafta N=55** |
| **Primary efficacy analysis** | | | |
| Absolute change in $ppFEV_1$ from baseline at Week 4 (percentage points) | Treatment difference (95% CI)<br>*P* value<br>Within-group change (SE) | NA<br><br>NA<br>0.4 (0.9) | 10.0 (7.4, 12.6)<br><br>*P*<0.0001<br>10.4 (0.9) |
| **Key secondary efficacy analyses** | | | |
| Absolute change in sweat chloride from baseline at Week 4 (mmol/L) | Treatment difference (95% CI)<br>*P* value<br>Within-group change (SE) | NA<br><br>NA<br>1.7 (1.8) | -45.1 (-50.1, -40.1)<br><br>*P*<0.0001<br>-43.4 (1.7) |
| Absolute change in CFQ-R respiratory domain score from baseline at Week 4 (points) | Treatment difference (95% CI)<br>*P* value<br>Within-group change (SE) | NA<br><br>NA<br>-1.4 (2.0) | 17.4 (11.8, 23.0)<br><br>*P*<0.0001<br>16.0 (2.0) |
| $ppFEV_1$: percent predicted forced expiratory volume in 1 second; CI: confidence interval; SE: Standard Error; NA: not applicable; CFQ-R: Cystic Fibrosis Questionnaire-Revised.<br>* Baseline for primary and key secondary endpoints is defined as the end of the 4-week tezacaftor/ivacaftor and ivacaftor run-in period.<br># Regimen of tezacaftor/ivacaftor and ivacaftor | | | |

**Figure 2: Absolute Change from Baseline in Percent Predicted $FEV_1$ at Each Visit in Study 445-103**

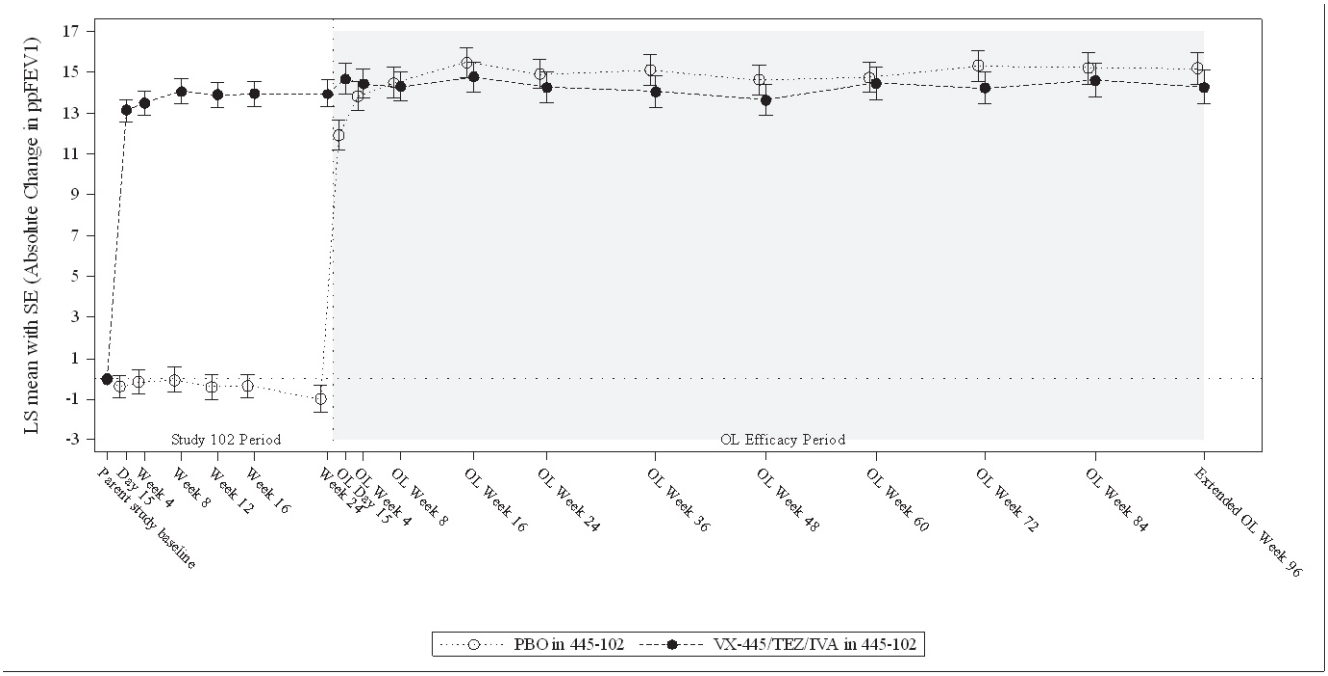



SE: Standard Error; TEZ/IVA: tezacaftor/ivacaftor; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor

*Study 445-105*

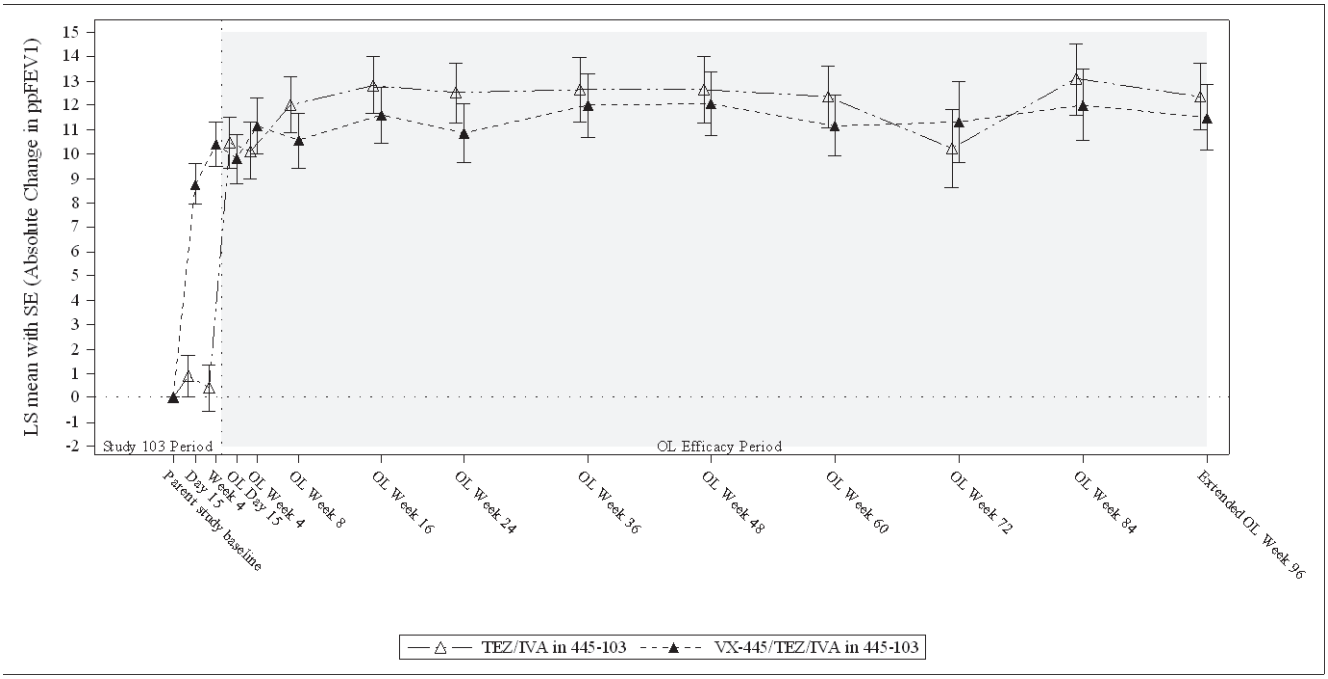
An ongoing, 192-week open-label extension study to evaluate the safety and efficacy of long-term treatment with Trikafta is being conducted in patients who rolled over from Studies 445-102 (N=399) and 445-103 (N=107). In this open-label extension study, all patients have received Trikafta for the duration of the study. An interim efficacy analysis was conducted after they completed 96 weeks in Study 445-105. In study 445-105, patients from the control arms in the parent studies showed improvements in efficacy endpoints consistent with those observed in subjects who received Trikafta in the parent studies. Patients from the control arm as well as patients who received Trikafta in the parent studies, showed sustained improvement in $ppFEV_1$ (see Figure 3 and Figure 4) and other efficacy endpoints (see Table 9), throughout the first 96 weeks of the open-label extension. BMI and BMI-z score after 96 weeks of cumulative treatment (week 96 in Study 445-105) were similar to those in patients with the genotypes studied in Study 445-102.

**Figure 3: Absolute Change in Percent Predicted $FEV_1$ From Baseline at Each Visit in Study 445-102 and in Study 445-105 for Patients that Rolled Over From Study 445-102***




$ppFEV_1$ = percent predicted Forced Expiratory Volume in 1 second; LS = Least Squares; SE = Standard Error; OL = Open Label
* Extended Week 96 window included data from the Week 96 visit, plus data from scheduled or unscheduled visits that occurred after Week 96 for subjects with missing data at Week 96.

**Figure 4: Absolute Change in Percent Predicted $FEV_1$ From Baseline at Each Visit in Study 445-103 and in Study 445-105 for Patients that Rolled Over From Study 445-103***




$ppFEV_1$ = percent predicted Forced Expiratory Volume in 1 second; LS = Least Squares; SE = Standard Error; OL = Open Label

* Extended Week 96 window included data from the Week 96 visit, plus data from scheduled or unscheduled visits that occurred after Week 96 for subjects with missing data at Week 96.

**Table 9: Study 445-105 Secondary Open-label Efficacy Analysis at Extended Week 96 (F/MF and F/F Subjects)**

| | | Study 445-105 Extended* Week 96 | | | |
|---|---|---|---|---|---|
| **Analysis** | **Statistic** | **PBO in 445-102 N = 203** | **ELX/TEZ/IVA in 445-102 N = 196** | **TEZ/IVA in 445-103 N = 52** | **ELX/TEZ/IVA in 445-103 N = 55** |
| Absolute change from baseline† in $ppFEV_1$ (percentage points) | n | 161 | 169 | 45 | 45 |
| | **LS mean** | **15.2** | **14.3** | **12.4** | **11.5** |
| | 95% CI | (13.6, 16.7) | (12.7, 15.8) | (9.6, 15.1) | (8.8, 14.2) |
| Absolute change from baseline† in SwCl (mmol/L) | n | 157 | 166 | 42 | 45 |
| | **LS mean** | **-48.6** | **-45.8** | **-48.3** | **-49.7** |
| | 95% CI | (-51.3, -45.8) | (-48.5, -43.0) | (-53.7, -42.8) | (-55.0, -44.4) |
| Number of PEx during the Cumulative TC Efficacy Period‡ | Number of events | 253 | | 53 | |
| | Estimated event rate per year (95% CI) | 0.21 (0.17, 0.26) | | 0.21 (0.14, 0.30) | |

ppFEV$_1$ = percent predicted Forced Expiratory Volume in 1 second; SwCl = Sweat Chloride; PEx = Pulmonary Exacerbation; LS = Least Squares; CI = Confidence Interval; PBO = Placebo
* Extended Week 96 window included data from the Week 96 visit, plus data from scheduled or unscheduled visits that occurred after Week 96 for subjects with missing data at Week 96.
† Baseline = parent study baseline
‡ For subjects who were randomized to the ELX/TEZ/IVA group, the Cumulative TC Efficacy Period includes data from the parent studies through 96 weeks of treatments in study 445-105. For subject who were randomized to the Placebo or TEZ/IVA group, the Cumulative TC Efficacy Period includes data from 96 weeks of treatments in study 445-105 only.

*Study 445-104*

Following a 4-week ivacaftor or tezacaftor/ivacaftor run-in period, the primary endpoint of within-group mean absolute change in ppFEV$_1$ from baseline through Week 8 for the Trikafta group resulted in the course in a statistically significant improvement of 3.7 percentage points (95% CI: 2.8, 4.6; *P*<0.0001) (see Table 10). Mean improvement in ppFEV$_1$ was observed at the first assessment on Day 15. Overall improvements in ppFEV$_1$ were observed regardless of age, sex, baseline ppFEV$_1$, geographic region, and genotype groups (F/G or F/RF).

See Table 10 for a summary of primary and secondary outcomes in the overall trial population.

| Table 10: Primary and secondary efficacy analyses, full analysis set (Study 445-104) | | | |
|---|---|---|---|
| **Analysis*** | **Statistics** | **Control group[#] N=126** | **Trikafta N=132** |
| **Primary analysis** | | | |
| Absolute change in $ppFEV_1$ from baseline through Week 8 (percentage points) | Within-group change (95% CI)<br>*p* value | 0.2 (-0.7, 1.1)<br>NA | 3.7 (2.8, 4.6)<br>*p*<0.0001 |
| **Key and other secondary analyses** | | | |
| Absolute change in sweat chloride from baseline through Week 8 (mmol/L) | Within-group change (95% CI)<br>*p* value | 0.7 (-1.4, 2.8)<br>NA | -22.3 (-24.5, -20.2)<br>*p*<0.0001 |
| Absolute change in $ppFEV_1$ from baseline through Week 8 compared to the control group (percentage points) | Treatment difference (95% CI)<br>*p* value | NA<br>NA | 3.5 (2.2, 4.7)<br>*p*<0.0001 |
| Absolute change in sweat chloride from baseline through Week 8 compared to the control group (mmol/L) | Treatment difference (95% CI)<br>*p* value | NA<br>NA | -23.1 (-26.1, -20.1)<br>*p*<0.0001 |
| Absolute change in CFQ-R respiratory domain score from baseline through Week 8 (points)[≠] | Within-group change (95% CI) | 1.6 (-0.8, 4.1) | 10.3 (8.0, 12.7) |
| Absolute change in CFQ-R respiratory domain score from baseline through Week 8 compared to the control group (points)[≠] | Treatment difference (95% CI) | NA | 8.7 (5.3, 12.1) |

$ppFEV_1$: percent predicted forced expiratory volume in 1 second; CI: confidence interval; NA: not applicable; CFQ-R: Cystic Fibrosis Questionnaire-Revised.

* Baseline for primary and secondary endpoints is defined as the end of the 4-week run-in period of ivacaftor or tezacaftor/ivacaftor.

[#] Ivacaftor group or tezacaftor/ivacaftor group.

[≠] CFQ-R outcomes were not controlled for multiplicity based on the hierarchical testing procedure

*Study 445-106 part B*

In Study 445-106 part B the primary endpoint of safety and tolerability was evaluated through 24 weeks. Secondary endpoints were evaluation of efficacy and pharmacokinetics including the

absolute change in $ppFEV_1$ (1st secondary endpoint) and the sweat chloride concentration (2nd secondary endpoint, see «pharmacodynamics» section) from baseline at Week 24; and number of pulmonary exacerbations from baseline through Week 24. Due to the conduct of the study 445-106 part B during the COVID19 pandemic, not all measurements could be performed as originally planned. The secondary endpoint measurements were affected to varying degrees by measurements not being performed. Table 11 shows the most important secondary efficacy outcomes in the overall 24-week analysis.

Measurements of $ppFEV_1$ levels were obtained on the scheduled measurement days in the following number of patients: baseline n=62, day 15 n=51, week 4 n=52, week 8 n=51, week 12 n=43, week 16 n=29, week 24 n=15.

The measured values for the sweat chloride concentration were collected on the planned measurement days in the following number of patients: baseline n=62, day 15 n=56, week 4 n=56, week 12 n=50, week 24 n=28.

**Table 11: Secondary efficacy analyses, full analysis set through 24 weeks (Study 445-106 part B)**

| Analysis | Within-group change (95% CI) for Trikafta N=66 |
|---|---|
| Absolute change in $ppFEV_1$ from baseline through Week 24 (percentage points) | 10.2 (7.9, 12.6) |
| Absolute change in sweat chloride from baseline through Week 24 (mmol/L) | -60.9 (-63.7, -58.2) |
| Number of pulmonary exacerbations through Week 24‡ | 4 (0.12) †† |

CI: Confidence Interval; $ppFEV_1$: percent predicted forced expiratory volume in 1 second.
‡ A pulmonary exacerbation was defined as a change in antibiotic therapy (IV, inhaled, or oral) as a result of 4 or more of 12 pre-specified sino-pulmonary signs/symptoms.
†† Number of events and estimated event rate per year based on 48 weeks per year.

*Study 445-111*

The pharmacokinetic profile, safety, and efficacy of Trikafta in patients with CF aged 2 to less than 6 years are supported by evidence from studies of Trikafta in patients aged 12 years and older (Studies 445-102, 445-103 and 445-104), with additional data from a 24-week, open-label, phase 3 study in 75 patients aged 2 to less than 6 years (Study 445-111).

In Study 445-111 the primary endpoint of safety and tolerability was evaluated through 24 weeks. Secondary endpoints were an evaluation of pharmacokinetics, and efficacy endpoints of absolute

change in sweat chloride (see «pharmacodynamics» section) and $LCI_{2.5}$ from baseline through Week 24. See Table 12 for a summary of secondary efficacy outcomes.

**Table 12: Secondary Efficacy Analyses, Full Analysis Set (Study 445-111)**

| Analysis | Statistic | Within-group change (95% CI) for Trikafta |
|---|---|---|
| Absolute change in sweat chloride from baseline through Week 24 (mmol/L) | N*<br>LS Mean (95% CI) | 75<br>-57.9 (-61.3, -54.6) |
| Absolute change in $LCI_{2.5}$ from baseline through Week 24 | N<br>LS Mean (95% CI) | 63‡<br>-0.83 (-1.01, -0.66) |
| Number of pulmonary exacerbations through week 24** | N<br>Number of events (estimated event rate per year) | 75<br>12 (0.32) †† |

CI: Confidence Interval; LCI: Lung Clearance Index.

* N is the number of subjects in the corresponding full analysis set
‡LCI assessed only on patients aged 3 years and older at screening.
** Age-specific definitions of PEx are used for subjects 2 through 5 years of age, and 6 years of age and older.
†† Number of events and estimated event rate per year based on 48 weeks per year.

**Pharmacokinetics**

The pharmacokinetics of elexacaftor, tezacaftor and ivacaftor are similar between healthy adult subjects and patients with CF. The pharmacokinetic parameters for elexacaftor, tezacaftor and ivacaftor in patients with CF aged 12 years and older are shown in Table 13.

**Table 13: Pharmacokinetic Parameters of Trikafta Components**

| | Elexacaftor | Tezacaftor | Ivacaftor |
|---|---|---|---|
| **General Information** | | | |
| AUC (SD), µg·h/mL[a] | 162 (47.5)[b] | 89.3 (23.2)[b] | 11.7 (4.01)[c] |
| $C_{max}$, (SD), µg/mL[a] | 9.2 (2.1) | 7.7 (1.7) | 1.2 (0.3) |
| Time to Steady State, days | Within 7 days | Within 8 days | Within 3-5 days |
| Accumulation Ratio | 2.2 | 2.07 | 2.4 |
| **Absorption** | | | |
| Absolute Bioavailability | 80% | Not determined | Not determined |
| Median $T_{max}$ (range), hours | 6 (4 to 12) | 3 (2 to 4) | 4 (3 to 6) |
| Effect of Food | AUC increases 1.9- to 2.5-fold (moderate-fat meal) | No clinically significant effect | Exposure increases 2.5- to 4-fold |
| **Distribution** | | | |

| Table 13: Pharmacokinetic Parameters of Trikafta Components | | | |
|---|---|---|---|
| | **Elexacaftor** | **Tezacaftor** | **Ivacaftor** |
| Mean (SD) Apparent Volume of Distribution, L[d] | 53.7 (17.7) | 82.0 (22.3) | 293 (89.8) |
| Protein Binding[e] | > 99% | approximately 99% | approximately 99% |
| **Elimination** | | | |
| Mean (SD) Effective Half-Life, hours[f] | 27.4 (9.31) | 25.1 (4.93) | 15.0 (3.92) |
| Mean (SD) Apparent Clearance, L/hours | 1.18 (0.29) | 0.79 (0.10) | 10.2 (3.13) |
| *Metabolism* | | | |
| Primary Pathway | CYP3A4/5 | CYP3A4/5 | CYP3A4/5 |
| Active Metabolites | M23-ELX | M1-TEZ | M1-IVA |
| Metabolite Potency Relative to Parent | Similar | Similar | approximately 1/6$^{th}$ of parent |
| *Excretion*[g] | | | |
| Primary Pathway | • Feces: 87.3% (primarily as metabolites)<br>• Urine: 0.23% | • Feces: 72% (unchanged or as M2-TEZ)<br>• Urine: 14% (0.79% unchanged) | • Feces: 87.8%<br>• Urine: 6.6% |

[a] Based on elexacaftor 200 mg and tezacaftor 100 mg once daily/ivacaftor 150 mg every 12 hours at steady state in patients with CF aged 12 year and older.
[b] $AUC_{0\text{-}24h}$.
[c] $AUC_{0\text{-}12h}$.
[d] Elexacaftor, tezacaftor and ivacaftor do not partition preferentially into human red blood cells.
[e] Elexacaftor and tezacaftor bind primarily to albumin. Ivacaftor primarily bind to albumin, alpha 1-acid glycoprotein and human gamma-globulin.
[f] Mean (SD) terminal half-lives of elexacaftor, tezacaftor and ivacaftor are approximately 24.7 (4.87) hours, 60.3 (15.7) hours and 13.1 (2.98) hours, respectively.
[g] Following radiolabeled doses.

*Absorption*

See Table 13, Pharmacokinetic Parameters of Trikafta Components

*Distribution*

See Table 13, Pharmacokinetic Parameters of Trikafta Components

*Metabolism*

See Table 13, Pharmacokinetic Parameters of Trikafta Components

*Elimination*

See Table 13, Pharmacokinetic Parameters of Trikafta Components

*Kinetics in specific patient groups*

*Hepatic impairment*

Elexacaftor alone or in combination with tezacaftor and ivacaftor has not been studied in subjects with severe hepatic impairment (Child-Pugh Class C, score 10-15). Following multiple doses of elexacaftor, tezacaftor and ivacaftor for 10 days, subjects with moderately impaired hepatic function (Child-Pugh Class B, score 7 to 9) had 25% higher AUC and 12% higher $C_{max}$ for elexacaftor, 73% higher AUC and 70% higher $C_{max}$ for M23-elexacaftor, 36% higher AUC and 24% higher $C_{max}$ for combined elexacaftor and M23-elexacaftor, 20% higher AUC but similar $C_{max}$ for tezacaftor, and a 50% higher AUC and 10% higher $C_{max}$ for ivacaftor compared with healthy subjects matched for demographics (see «Dosage/Administration»», «Warnings and precautions» and «Undesirable effects»).

*Tezacaftor and ivacaftor*

Following multiple doses of tezacaftor and ivacaftor for 10 days, subjects with moderately impaired hepatic function had an approximately 36% higher AUC and a 10% higher $C_{max}$ for tezacaftor, and a 1.5-fold higher AUC but similar $C_{max}$ for ivacaftor compared with healthy subjects matched for demographics.

*Ivacaftor*

In a study with ivacaftor alone, subjects with moderately impaired hepatic function had similar ivacaftor $C_{max}$, but an approximately 2.0-fold higher ivacaftor $AUC_{0-\infty}$ compared with healthy subjects matched for demographics.

*Renal impairment*

Elexacaftor alone or in combination with tezacaftor and ivacaftor has not been studied in patients with severe renal impairment (eGFR less than 30 mL/min/1.73 $m^2$) or in patients with end stage renal disease.
In human pharmacokinetic studies of elexacaftor, tezacaftor, and ivacaftor, there was minimal elimination of elexacaftor, tezacaftor, and ivacaftor in urine (only 0.23%, 13.7% [0.79% as unchanged drug], and 6.6% of total radioactivity, respectively).
Based on population pharmacokinetic (PK) analysis, exposure of elexacaftor was similar in patients with mild renal impairment (N=75; eGFR 60 to less than 90 mL/min/1.73 $m^2$) relative to patients with normal renal function (N=341; eGFR 90 mL/min/1.73 $m^2$ or greater).
In population PK analysis conducted in 817 patients administered tezacaftor alone or in combination with ivacaftor in phase 2 or phase 3 studies indicated that mild renal impairment (N=172; eGFR 60 to less than 90 mL/min/1.73 $m^2$) and moderate renal impairment (N=8; eGFR 30 to less than 60 mL/min/1.73 $m^2$) did not affect the clearance of tezacaftor significantly (see «Dosage/Administration»).

*Gender*

Based on population PK analysis, the exposures of elexacaftor, tezacaftor and ivacaftor are similar in males and females.

*Pediatric patients 2 to less than 18 years of age*

Elexacaftor, tezacaftor and ivacaftor exposures, and the exposures of the M1-tezacaftor and M23-elexacaftor metabolites, observed in phase 3 studies as determined using population PK analysis are presented by age group and dose administered in Table 14. Exposures of elexacaftor, tezacaftor and ivacaftor in patients aged 6 to less than 18 years of age are within the range observed in patients aged 18 years and older.

**Table 14. Mean (SD) Elexacaftor, Tezacaftor and Ivacaftor $AUC_{0\text{-}24h,ss}$ by Age Group**

| Age/Weight group | Dose | Elexacaftor $AUC_{0\text{-}24h,ss}$ (µg·h/mL) | M23-Elexacaftor $AUC_{0\text{-}24h,ss}$ (µg·h/mL) | Tezacaftor $AUC_{0\text{-}24h,ss}$ (µg·h/mL) | M1-Tezacaftor $AUC_{0\text{-}24h,ss}$ (µg·h/mL) | Ivacaftor $AUC_{0\text{-}12h,ss}$ (µg·h/mL) |
|---|---|---|---|---|---|---|
| Patients aged 2 to <6 years, <14 kg (N=16) | Elexacaftor 80 mg qd/ tezacaftor 40 mg qd/ivacaftor 60 mg qAM and ivacaftor 59.5 mg qPM | 128 (24.8) | 56.5 (29.4) | 87.3 (17.3) | 194 (24.8) | 11.9 (3.86) |
| Patients aged 2 to < 6 years, ≥14 kg (N=59) | elexacaftor 100 mg qd/ tezacaftor 50 mg qd/ivacaftor 75 mg q12h | 138 (47.0) | 59.0 (32.7) | 90.2 (27.9) | 197 (43.2) | 13.0 (6.11) |
| Patients aged 6 to <12 years; <30 kg (N=36) | elexacaftor 100 mg qd/tezacaftor 50 mg qd/ivacaftor 75 mg q12h | 116 (39.4) | 45.4 (25.2) | 67.0 (22.3) | 153 (36.5) | 9.78 (4.50) |
| Patients aged 6 to <12 years; ≥30 kg (N=30) | elexacaftor 200 mg qd/tezacaftor 100 mg qd/ivacaftor 150 mg q12h | 195 (59.4) | 104 (52) | 103 (23.7) | 220 (37.5) | 17.5 (4.97) |
| Adolescent patients aged 12 to <18 years (N=72) | elexacaftor 200 mg qd/tezacaftor 100 mg qd/ivacaftor 150 mg q12h | 147 (36.8) | 58.5 (25.6) | 88.8 (21.8) | 148 (333) | 10.6 (3.35) |
| Adult patients aged≥18 years (N=179) | elexacaftor 200 mg qd/tezacaftor 100 mg qd/ivacaftor 150 mg q12h | 168 (49.9) | 64.6 (28.9) | 89.5 (23.7) | 128 (33.7) | 12.1 (4.17) |

SD: Standard Deviation; $AUC_{ss}$: area under the concentration versus time curve at steady state.

**Preclinical data**

Elexacaftor/tezacaftor/ivacaftor

Repeated dose toxicity studies in rats and dogs in which elexacaftor, tezacaftor and ivacaftor were administered in combination to assess the potential for additive and/or synergistic toxicity did not result in unexpected toxicities or interactions. No safety pharmacology, genotoxicity, carcinogenicity or reproductive toxicity studies were performed with Trikafta. However, studies with the individual substances are available.

Elexacaftor

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, and carcinogenic potential.

*Repeat dose toxicity*

In the 6-month rat toxicity study, the primary target organs were the glandular stomach (erosion), testes and epididymis (degeneration/atropy of the seminiferous tubules, oligospermia/aspermia), and bone marrow (decreased hematopoietic cellularity). These effects were primarily observed at non-tolerated doses of ≥40 mg/kg/day in male animals and 30 mg/kg/day in female animals. Plasma exposure (AUC) in animals at NOAEL (15 mg/kg/day) was approximately 3-fold (males) and 11-fold (females) the maximum recommended dose for humans [MRHD]. In the 9-month dog toxicity study, minimal or mild non-adverse bilateral degeneration/atrophy of the seminiferous tubules of the testes was present in males administered elexacaftor at 14 mg/kg/day dose (15 times the MRHD based on summed AUCs of elexacaftor and its metabolite) that did not resolve during the limited recovery period, however without further sequelae. The human relevance of these findings is unknown.

*Reproduction toxicity*

Elexacaftor was associated with lower male and female fertility, male copulation, and female conception indices in males at 75 mg/kg/day (6 times the MRHD based on summed AUCs of elexacaftor and its metabolite) and in females at 35 mg/kg/day (7 times the MRHD based on summed AUCs of elexacaftor and its metabolite).
Elexacaftor was not teratogenic in rats at 40 mg/kg/day and at 125 mg/kg/day in rabbits (approximately 9 and 4 times, respectively, the MRHD based on summed AUCs of elexacaftor and its metabolite [for rat] and AUC of elexacaftor [for rabbit]). In rat fetuses a lower mean body weight was observed after treatment of the mother animals with ≥ 25 mg/kg/day (approximately 4 times the MRHD based on AUC). No adverse effects were noted in the rat pre- and post-natal development

study with doses of up to 10 mg/kg/day (around 1-fold the MRHD based on the summed AUCs of elexacaftor and its metabolite). Placental transfer of elexacaftor was observed in pregnant rats.

*Juvenile toxicity*

No adverse effects were noted in juvenile rats dosed from postnatal Day 7 through Day 70 with doses that led to plasma exposure of approx. 3-fold (males) and 5-fold (females) the AUC in paediatric patients (aged 12 years and older).

Tezacaftor

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential and repeated dose toxicity.

*Juvenile toxicity*

Studies in rats exposed during postnatal day 7 to 35 (PND 7-35) showed mortality and moribundity even at low doses. Findings were dose related and generally more severe when dosing with tezacaftor was initiated earlier in the postnatal period. Exposure in rats from PND 21-49 did not show toxicity at the highest dose which was approximately two times the intended human exposure. Tezacaftor and its metabolite, M1-TEZ, are substrates for P-glycoprotein. Lower brain levels of P-glycoprotein activity in younger rats resulted in higher brain levels of tezacaftor and M1-TEZ. These findings are likely not relevant for the indicated pediatric population 2 years of age and older, for whom levels of P-glycoprotein activity are equivalent to levels observed in adults.

*Reproductive toxicity*

Tezacaftor did not cause reproductive system toxicity in male and female rats at 100 mg/kg/day, the highest dose evaluated (approximately 3 times the MRHD based on summed AUCs of tezacaftor and M1 TEZ).
Tezacaftor had no effect on the fertility and reproductive performance indices of male and female rats at doses up to 100 mg/kg/day (approximately 3 times the MRHD based on the summed AUCs of tezacaftor and M1 TEZ).
Tezacaftor was not teratogenic in pregnant rats and rabbits at doses approximately 3 times and 0.2 times, respectively, the tezacaftor exposure in humans at the therapeutic dose.
In a pre-and post-natal development study, tezacaftor did not cause developmental defects in the offspring of pregnant rats dosed orally at 25 mg/kg/day (approximately 1 time the MRHD based on summed AUCs for tezacaftor and M1 TEZ). At maternally toxic doses (≥50 mg/kg/day), tezacaftor produced lower foetal body weights, a lower fertility index, and effects on estrous cyclicity (increased cycle length and decrease in number of cycles). At the highest dose (100 mg/kg/day), tezacaftor related effects in offspring included poor pup survival to weaning, preweaning developmental effects, and sexual maturation delays. Placental transfer of tezacaftor was observed in pregnant rats.

Ivacaftor

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential, and repeated dose toxicity.

*Reproductive toxicity*

Ivacaftor affected the fertility and reproductive performance indices of male and female rats at doses of 200 mg/kg/day (approximately 7 and 5 times the MRHD, respectively, based on the summed AUCs of ivacaftor and its metabolites. Among the female animals ivacaftor was associated with a reduction in overall fertility index, number of pregnancies, number of corpora lutea and implantation sites, as well as changes in the estrous cycle. Ivacaftor also increased the number of females in which all embryos were not viable and reduced the number of viable embryos. Slight decreases of the seminal vesicle weights were observed in males. These impairments of fertility and reproductive performance were attributed to severe toxicity in rats under a dose of 200 mg/kg/day. No effects on male or female fertility and reproductive performance indices were observed after doses of ≤ 100 mg/kg/day (approximately 5-fold and 3-fold, respectively, the MRHD based on the summed AUCs of ivacaftor and its metabolites).Ivacaftor was not teratogenic in rats after 200 mg/kg/day and in rabbits after 100 mg/kg/day (approximately 6 and 16 times the MRHD, respectively, based on the sum of AUCs of ivacaftor and its metabolites). Effects on fetal body weight and slight increases in common variations in skeletal development were found in rats at doses that were associated with significant toxicity in the dam.
In pre- and post-natal development study in pregnant rats at doses above 100 mg/kg/day, ivacaftor resulted in survival and lactation indices that were 92% and 98% of control values, respectively, as well as reductions in pup body weights. Placental transfer of ivacaftor was observed in pregnant rats and rabbits.

*Juvenile toxicity*

Findings of cataracts were observed in juvenile rats dosed from postnatal Day 7 through 35 with ivacaftor dose levels of 10 mg/kg/day and higher (0.2 times the MRHD based on systemic exposure of ivacaftor and its metabolites). This finding has not been observed in fetuses derived from rat dams treated with ivacaftor on gestation Days 7 to 17, in rat pups exposed to ivacaftor to a certain extent through milk ingestion up to postnatal Day 20, in 7-week-old rats, or in 3.5- to 5-month-old dogs treated with ivacaftor. The potential relevance of these findings in humans is unknown (see «Warnings and Precautions»).

**Other information**

*Shelf life*

Do not use this medicine after the expiry date («EXP») stated on the container.

*Special precautions for storage*

Do not store above 30°C.
Keep out of the sight and reach of children.

**Authorisation number**

67773, 69212 (Swissmedic)

**Packs**

Trikafta film-coated tablets

- Elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg tablet and ivacaftor 75 mg tablet
  - Pack size of 84 tablets (4 weekly wallets, each with 14 elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg film-coated tablets and with 7 ivacaftor 75 mg film-coated tablets). [A]
- Elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg tablet and ivacaftor 150 mg tablet
  - Pack size of 84 tablets (4 weekly wallets, each with 14 elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg film-coated tablets and with 7 ivacaftor 150 mg film-coated tablets). [A]

Granules in Sachet

- Elexacaftor 80 mg/tezacaftor 40 mg/ivacaftor 60 mg granules in sachet and ivacaftor 59.5 mg granules in sachet
  - Pack size of 56 sachets (4 weekly wallets, each with 7 sachets of elexacaftor 80 mg/tezacaftor 40 mg/ivacaftor 60 mg granules and 7 sachets of ivacaftor 59.5 mg granules) [A]
- Elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg granules in sachet and ivacaftor 75 mg granules in sachet
  - Pack size of 56 sachets (4 weekly wallets, each with 7 sachets of elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg granules and 7 sachets of ivacaftor 75 mg granules) [A]

**Marketing authorisation holder**

Vertex Pharmaceuticals (CH) GmbH
6300 Zug

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