swissmedic

Date: 18 December 2025
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Extension of therapeutic indication

Trikafta

International non-proprietary name:	elexacaftor, tezacaftor, ivacaftor (morning dose) ivacaftor (evening dose)
Pharmaceutical form:	film-coated tablets, granules
Dosage strength(s):	Tablets: 50 mg / 25 mg / 37.5 mg (morning dose), 75 mg (evening dose) 100 mg / 50 mg / 75 mg (morning dose), 150 mg (evening dose) Granules: 80 mg / 40 mg / 60 mg (morning dose), 59.5 mg (evening dose) 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.:	67773
Decision and decision date:	extension of therapeutic indication approved on 5 November 2025

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
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
C_{trough}	Trough concentration (concentration reached before the next dose is administered)
CYP	Cytochrome P450
DDI	Drug-drug interaction
ELX	Elexacaftor
ELX/TEZ/IVA	Elexacaftor / Tezacaftor / Ivacaftor
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
FRT	Fischer rat thyroid
GI	Gastrointestinal
GLP	Good Laboratory Practice
HBE	Human bronchial epithelial
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
IVA	Ivacaftor
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
SwCl	Sweat chloride
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TEZ	Tezacaftor

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) and information regarding procedure

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 1 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 **or a mutation in the *CFTR* gene that is responsive based on clinical and/or *in vitro* data** (see «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 **or a mutation in the *CFTR* gene that is responsive based on clinical and/or *in vitro* data** (see «Properties/effects», Table 7).

2.2.3 Requested dosage

Summary of the requested standard dosage:

No change to the dosage recommendation was requested with the application for extension of indication.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	20 November 2024
Formal control completed	5 December 2024
List of Questions (LoQ)	24 March 2025
Response to LoQ	25 May 2025
Preliminary decision	21 July 2025
Response to preliminary decision	19 September 2025
Final decision	5 November 2025
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 infections, 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.

Diagnosis of CF is based upon clinical symptoms consistent with CF in at least one organ system, or a positive newborn screen or having a sibling with CF and evidence of CFTR dysfunction. Nowadays, CF testing is part of the newborn screening programme in Switzerland.
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. CFTR modulators (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.

At the time of the assessment, four CFTR modulators (or combinations) were approved in Switzerland for the treatment of CF for specific genotypes and age groups. The approved indications for those CFTR modulators already cover a wide CF population; however, there is still a considerable number of rare CF mutations for which no CFTR modulator treatment is approved. Therefore, there is an unmet medical need for patients with rare mutations.

4 Quality aspects

Not applicable.

5 Nonclinical aspects

To support the requested extension of the indication, the applicant investigated the responsiveness of a series of additional *CFTR* mutations to ELX/TEZ/IVA in a suitable *in vitro* assay. No additional nonclinical safety studies were conducted, which is considered acceptable. The new indication is unlikely to result in any significant risk to the environment. From the nonclinical point of view, there are no objections to the approval of the extension of the indication applied for.

6 Clinical aspects

6.1 Clinical pharmacology

Pharmacokinetic samples in children ≥ 6 years, adolescents and adults with rare mutations were collected in study VX21-445-124 only ("study 124", Week 4 and Week 24). No updated pop PK analyses including these data were provided, but just graphical comparisons of C_{trough} of ELX, M23-ELX, TEZ, M1-TEZ, IVA and M1-IVA by age group and genotype. The approved doses of Trikafta were administered in study VX21-445-124. The majority of the patients in study VX21-445-124 was ≥ 18 years old. PK data were available in 19 patients ≥ 12 to < 18 years, 9 patients ≥ 6 to < 12 years, ≥ 30 kg and 14 patients ≥ 6 to < 12 years, < 30 kg.

In study VX21-445-124 (rare mutations only), C_{trough} levels of ELX, M23-ELX, TEZ and IVA were comparable in patients ≥ 18 years, ≥ 12 to < 18 years and ≥ 6 to < 12 years ≥ 30 kg. C_{trough} tended to be lower, but mostly still in the adult target range, in children ≥ 6 to < 12 years < 30 kg. C_{trough} levels of M1-TEZ and M1-IVA were higher, but mostly still in the adult target range, in children ≥ 6 to < 12 years ≥ 30 kg. This pattern is known from previous analyses.

A comparison of C_{trough} levels across genotypes included in the pivotal ELX/TEZ/IVA studies by age group did not indicate major differences between patients with rare and non-rare genotypes within each age (weight) group.

In summary, there were no relevant pharmacokinetic differences between patients with rare and non-rare mutations. This is in agreement with the results of prior pop PK analyses, where genotype never reached statistical significance as a covariate.

6.2 Dose finding and dose recommendation

No dose-finding studies were included in this submission as no changes to the already approved dosing for ELX/TEZ/IVA were proposed.

6.3 Efficacy

This submission provided data for ELX/TEZ/IVA for patients with CF and at least one ELX/TEZ/IVA-responsive, non-*F508del* CFTR mutation, including 177 FRT-responsive (in vitro data from the Fischer rat thyroid) mutations, 5 non-canonical splice mutations, and the *N1303K* mutation.

Three studies (Studies 124, 125, and CFD-016) provided clinical efficacy data for ELX/TEZ/IVA treatment in patients with at least 1 of (a) 177 FRT-responsive CFTR mutations or (b) 5 non-canonical CFTR splice mutations in patients with symptomatic CF aged 6 years and older.

Study 124 was a Phase 3, randomised, placebo-controlled, double-blind, parallel group study in CF subjects with a qualifying non-*F508del*, ELX/TEZ/IVA-responsive CFTR mutation. A total of 307 CF patients 6 years of age or older with stable CF disease, $ppFEV_1$ value ≥40% and ≤100%, and representing 18 of the most common ELX/TEZ/IVA-responsive, non-*F508del* CFTR mutations (including FRT-responsive and non-canonical splice mutations) were randomised to ELX/TEZ/IVA or placebo. In line with the EMA CF guideline and previous studies with ELX/TEZ/IVA, the primary endpoint was the absolute change from baseline in ppFEV1 through Week 24.
Treatment with ELX/TEZ/IVA resulted in a statistically and clinically significant improvement in absolute change from baseline in ppFEV1 through Week 24, with a least squares (LS) mean treatment difference from placebo of 9.2 percentage points (95% CI: 7.2, 11.3; P<0.0001). In addition,

improvement in SwCl (secondary endpoint) was observed following ELX/TEZ/IVA treatment compared to placebo.

Study 125 is an ongoing Phase 3, multicentre, open-label study for subjects who completed the last Treatment Period visit of parent Study 124 with a 96-week period of ELX/TEZ/IVA treatment. Patients on placebo in the parent Study 124 were switched to ELX/TEZ/IVA. Only efficacy data analyses based on a data cut that occurred after all subjects completed the Week 4 visit were submitted. The ELX/TEZ/IVA group from Study 124 could maintain the ppFEV1 and SwCl benefits, and the patients from the former placebo group in Study 124 showed already similar improvements in ppFEV1 and SwCl.

In addition, the observational study CFD-016 provided RWE data, demonstrating an improvement of ppFEV1 with ELX/TEZ/IVA in a population of CF patients aged 6 years and older with ELX/TEZ/IVA-responsive, non-*F508del* CFTR mutations (including FRT-responsive and non-canonical splice mutations).
Improvements in ppFEV1 were generally consistent for individuals with non-canonical splice mutations and FRT-responsive mutations.
Overall, the improvement in ppFEV1 observed in Study CFD-016 was lower compared to Study 124. However, direct comparisons between the two studies are challenging due to differences in study design, patient populations, and prior use of CFTR modulators. Despite these variations, all mutations demonstrated some level of improvement in FEV1.

In addition to the FRT-responsive mutations with clinical data (78 mutations), there are 99 additional FRT-responsive mutations for which clinical data are currently unavailable. For those additional mutations, the now demonstrated clinical response to ELX/TEZ/IVA observed in FRT-responsive mutations provides evidence that the additional FRT-responsive mutations will also be clinically responsive. Due to the ultra-rare prevalence of some ELX/TEZ/IVA-responsive, non-F508del CFTR mutations, it is acknowledged that the generation of clinical study data for every mutation is hardly possible.

In addition to the four non-canonical splice mutations for which clinical data are available, there is one mutation for which clinical data are currently unavailable. The mechanism of action of CFTR modulators, i.e. enhancing the activity of the small amount of full-length CFTR produced by non-canonical splice mutations, is the same for all non-canonical splice mutations. Therefore, based on the response observed for non-canonical splice mutations in studies 124 and 125, it can be assumed that the additional non-canonical splice mutation will also be clinically responsive.

For people with CF who have at least one N1303K mutation (but do not have an F508del mutation or another ELX/TEZ/IVA-responsive mutation), clinical evidence from three published studies were submitted.
Overall, these publications provide some supportive data that CF patients with a N1303K mutation benefit from ELX/TEZ/IVA. However, no full protocols/CSRs were available for these studies; therefore, no firm conclusions can be drawn. With its answer to the LoQ, the Applicant provided additional data from an ongoing PASS study and in vitro HBE cells. Taking this evidence together (two published investigator-initiated clinical studies, the in vitro HBE cell data and the results from the PASS subgroup), a positive benefit/risk for CF patients with the N1303K mutation can be concluded. This is also supported by the fact that these patients do not have any approved treatment options right now.

One uncertainty is the lack of data for these rare mutations in CF patients below 6 years of age. The Applicant justifies the inclusion of this age group with extrapolation of efficacy from older patients, given the common underlying disease process of dysfunctional CFTR protein targeted by ELX/TEZ/IVA. In addition, safety can be extrapolated from ELX/TEZ/IVA studies in children below 6

years of age with F508del mutations. It is indeed not expected that children with these rare mutations respond differently to ELX/TEZ/IVA compared to older patients.

6.4 Safety

Clinical safety data were only derived from Study 124. Overall, no new safety findings to the already known ELX/TEZ/IVA safety profile were identified in this Study with rare-mutation CF patients. The already known safety issue from ELX/TEZ/IVA with elevation of transaminases was also seen in this study and requires regular laboratory checks. The percentage of patients with elevation of transaminases and rash was higher in Study 124 compared to the pivotal ELX/TEZ/IVA studies. As requested, the Applicant added a section about both ADRs in the Information for healthcare professionals.

6.5 Final clinical benefit risk assessment

The clinical data from Studies 124, 125, and CFD-016, along with in vitro and real-world evidence, demonstrate that ELX/TEZ/IVA provides significant clinical benefits for CF patients aged 6 years and older with ELX/TEZ/IVA-responsive, non-F508del CFTR mutations, including FRT-responsive and non-canonical splice mutations. While some mutations show smaller improvements in ppFEV1, all studied mutations exhibit some level of benefit. For ultra-rare mutations for which no clinical data are available, the shared mechanism of action supports the likelihood of clinical responsiveness. Additionally, the N1303K mutation shows a positive benefit-risk profile, despite limited data. The lack of data for patients under 6 years of age remains a limitation, but extrapolation from older populations supports the potential efficacy and safety in this group.
In addition, the unmet medical need in CF patients with rare mutations who do not have a disease-modifying therapy available right now supports the positive benefit/risk for this submission.

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.

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 × 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 × 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 × 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 × 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 or a mutation in the *CFTR* gene that is responsive based on clinical and/or *in vitro* data (see «Properties/effects», table 7).

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 or a mutation that is responsive based on clinical and/or *in vitro* data 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 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
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 «Pharmacokinetics»).
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. If used, Trikafta should be used with caution at a reduced dose, as follows: • Day 1-3: one sachet of elexacaftor/tezacaftor/ivacaftor granules each day • Day 4: no dose • Day 5-6: one sachet of elexacaftor/tezacaftor/ivacaftor granules each day • Day 7: no dose Repeat above dosing schedule each week.	Should not be used

		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. If used, Trikafta should be used with caution at a reduced dose, as follows: • Day 1: two elexacaftor/tezacaftor/ivacaftor tablets in the morning • Day 2: one elexacaftor/tezacaftor/ivacaftor tablet in the morning Continue alternating Day 1 and Day 2 dosing thereafter. 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 «Pharmacokinetics»).

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»).
Concomitant use of ciprofloxacin is not expected to have a clinically relevant effect on the exposure of Trikafta; therefore, no dose adjustment is recommended with concomitant use of ciprofloxacin (see section «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: • One sachet of elexacaftor/tezacaftor/ivacaftor granules on the first day • One sachet of ivacaftor granules on the next day No evening sachet of ivacaftor granules.	One sachet of elexacaftor/tezacaftor/ivacaftor granules twice a week, approximately 3 to 4 days apart. No evening sachet of ivacaftor granules.
6 years and older	Alternate each day: • Two elexacaftor/tezacaftor/ivacaftor tablets on the first day • One ivacaftor tablet on the next day No evening ivacaftor tablet dose.	Two elexacaftor/tezacaftor/ivacaftor tablets twice a week, approximately 3 to 4 days apart. 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

Liver damage

Cases of liver failure leading to transplantation have been reported within the first 6 months of treatment in patients with and without pre-existing advanced liver disease. In patients with pre-existing advanced liver disease (e.g., cirrhosis, portal hypertension), Trikafta should be used with caution and close monitoring and only if the benefits are expected to outweigh the risks (see «Dosage/Administration», «Undesirable effects» and «Pharmacokinetics»).

Elevation of liver enzymes

Elevated transaminases are common in patients with CF and have also been observed in patients treated with Trikafta, with or without pre-existing liver disease. In some cases, these sometimes

severe elevations have been 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 month during the first 6 months of treatment, every 3 months during the next 6 months, and annually thereafter. For patients with a history of liver disease or transaminase elevations, more frequent monitoring should be considered. Interrupt Trikafta and promptly measure serum transaminases and total bilirubin if a patient develops clinical signs or symptoms suggestive of liver injury (e.g., jaundice and/or dark urine, unexplained nausea or vomiting, right upper quadrant pain, or anorexia). Interrupt dosing in the event of ALT or AST >5 × the upper limit of normal (ULN), or ALT or AST >3 × ULN with total bilirubin >2 × ULN. Follow laboratory tests closely until the abnormalities resolve. Following resolution, consider the benefits and risks of resuming treatment (see «Dosage/Administration», «Undesirable effects» and «Pharmacokinetics»). Patients who resume treatment after interruption should be monitored closely.

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»).

Ciprofloxacin

Trikafta was not evaluated for concomitant use with ciprofloxacin. However, ciprofloxacin had no clinically relevant effect on the exposure of tezacaftor or ivacaftor and is not expected to have a clinically relevant effect on the exposure of elexacaftor. Therefore, no dose adjustment is necessary during concomitant administration of Trikafta with ciprofloxacin.

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. * 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 2 mg single oral dose	TEZ 100 mg qd/IVA 150 mg q12h	↔ Midazolam	1.12 (1.01, 1.25)	1.13 (1.01, 1.25)
Digoxin 0.5 mg single dose	TEZ 100 mg qd/IVA 150 mg q12h	↑ Digoxin	1.30 (1.17, 1.45)	1.32 (1.07, 1.64)
Oral Contraceptive Ethinyl estradiol 30 µg/Levonorgestrel 150 µg qd	ELX 200 mg qd/TEZ 100 mg qd/IVA 150 mg q12h	↑ Ethinyl estradiol* ↑ Levonorgestrel*	1.33 (1.20, 1.49) 1.23 (1.10, 1.37)	1.26 (1.14, 1.39) 1.10 (0.985, 1.23)
Rosiglitazone 4 mg single oral dose	IVA 150 mg q12h	↔ Rosiglitazone	0.975 (0.897, 1.06)	0.928 (0.858, 1.00)
Desipramine 50 mg single dose	IVA 150 mg q12h	↔ Desipramine	1.04 (0.985, 1.10)	1.00 (0.939; 1.07)

↑ = increase, ↓ = decrease, ↔ = no change. CI = Confidence Interval; ELX= elexacaftor;
TEZ = tezacaftor; IVA = ivacaftor; PK = Pharmacokinetics.
* Effect is 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); and 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).
- A 192-week, open-label safety and efficacy study (study 445-105) for patients rolled over from studies 445-102 and 445-103.
- 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.

- A 192-week, two-part (part A and part B), open-label safety and efficacy study (study 445-107) examined patients aged 6 years and older who rolled over from study 445-106; an interim analysis of part A was performed on 64 patients at Week 96 (60 completers, 93.8%). Subsequently, 48 (75.0%) subjects were transferred to part B of the study until Week 192. 39 (60.9%) subjects completed part B. The safety profile was similar to that observed in study 445-106, however, cataracts/lens opacity were observed more frequently in the long term (in 6 subjects, 9.4%).
- A 24-week, randomized, double-blind, placebo-controlled study (study 445-124) in 307 patients aged 6 years and older.

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 × 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 × ULN was 0.0%, 1.5%, and 10.6%, respectively. No Trikafta-treated patients had transaminase elevation >3 × ULN associated with elevated total bilirubin >2 × 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 × ULN were 1.3%, 2.7%, and 8.0%, respectively. No Trikafta-treated patients had transaminase elevation >3 × ULN associated with elevated total bilirubin >2 × ULN or discontinued treatment due to transaminase elevations (see «Warnings and precautions»).
During study 445-124 in patients aged 6 years and older, the incidence of maximum transaminase (ALT or AST) >8, >5, and >3 × ULN were 2.0%, 2.0%, and 6.3% in Trikafta treated patients and 0.0% in placebo-treated patients, respectively. No Trikafta-treated patients had transaminase elevation >3 × ULN associated with elevated total bilirubin >2 × ULN. One patient discontinued treatment due to an undesired effect of 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 patients with and without pre-existing advanced liver disease (e.g., cirrhosis, 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.
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.
In study 445-124, rash events occurred in 55 (26.8%) patients in the Trikafta group and 3 (2.9%) patients in the placebo group. The majority of rash events were mild or moderate in severity.
One (0.5%) patient in the Trikafta group had a serious rash event that led to treatment discontinuation. No patients in the placebo group had rash events that led to treatment discontinuation.
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.

Increased Creatine Phosphokinase

In study 445-102, the incidence of maximum creatine phosphokinase >5 × 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

In the open-label, uncontrolled, long-term VX17-445-105 study, 400 (78.9 %) patients with an *F508del* mutation/MF mutation and 107 (21.1 %) patients with a homozygous *F508del* mutation were followed for up to 192 weeks. By Week 192, one subject never dosed, 356 (70.4 %) patients completed treatment, and 150 (29.6 %) patients discontinued early for various reasons. Of these, 13 (2.6 %) patients discontinued due to adverse events, including 8 (1.6 %) patients because of liver-related events, and 1 (0.2%) patient because of hepatic encephalopathy.
ALT or AST elevation >3, >5, and >8 × ULN was noted in 63 (12.5 %), 36 (7.1 %), and 11 (2.2 %) patients, respectively, of whom 2 (0.4 %) were patients with ALT or AST elevation >3 × ULN with concomitant new-onset elevation of total bilirubin >2 × ULN, with one patient having medical history of Gilbert's syndrome.
Elevations of CK ≥2.5-≤5, >5-≤10 and >10 × ULN were noted in 69 (13.6 %), 38 (7.5 %) and 47 (9.3 %) patients. CK elevation was noted as an adverse reaction in 72 (14.2 %) patients. Three (0.6 %) patients experienced rhabdomyolysis without renal involvement or myoglobinuria.
Skin rashes occurred in 89 (17.6 %) patients. One (0.2 %) patient discontinued the treatment due to skin rash.
Mean systolic blood pressure increased between 2.7-5.6 mmHg, and mean diastolic blood pressure increased between 1.5-3.6 mmHg. Adverse events related to blood pressure increase were noted in 20 (4.0 %) patients.
There were 5 (1.0 %) subjects with adverse events related to cataracts that did not lead to a change in dosing.

VX19-445-107 extension study over 192 weeks

An ongoing 192-week, two part (part A and part B), open label VX19-445-107 study, examined patients aged 6 years and older who rolled over from study 445-106, with interim analysis performed on 64 patients at Week 96. A total of 28 (43.8%) patients were homozygous for the *F508del* mutation and 36 (56.3%) patients had the *F508del*/MF genotype. In Part A, 61 (95.3%) of 64 patients received at least 1 dose of the study drug and completed treatment.
Elevation of ALT or AST >3, >5, and >8 × ULN occurred in 4 (6.3%), 1 (1.6%), and 0 patient(s), respectively. No patients had elevations of ALT or AST >3 × ULN concurrent with newly occurred elevation of total bilirubin >2 × ULN.
The majority of patients had CK levels that remained within the normal range. Four (6.3%) had CK levels >2.5 × ULN; no patients had CK levels >5 × ULN. No patients experienced rhabdomyolysis.
Rash occurred in 3 (4.7%) patients. None of the rash events led to interruption or discontinuation of study drug.
There were no clinically relevant increases in blood pressure.

There were 6 (9.4%) patients with events related to cataract that did not lead to change in dosing. These cataract/lens opacities were non-visually significant and were no longer observed at the end of the study in 3 of these patients."
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 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 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»).

CFTR Chloride Transport Assay in Fischer Rat Thyroid (FRT) cells expressing mutant CFTR

The chloride transport response of mutant CFTR protein to elexacaftor/tezacaftor/ivacaftor was determined in Ussing chamber electrophysiology studies using a panel of FRT cell lines transfected with individual *CFTR* mutations. Elexacaftor/tezacaftor/ivacaftor increased chloride transport in FRT cells expressing select *CFTR* mutations.

The *in vitro* CFTR chloride transport response threshold was designated as a net increase of at least 10% of normal over baseline because it is predictive or reasonably expected to predict clinical benefit. For individual mutations, the magnitude of the net change over baseline in CFTR-mediated chloride transport *in vitro* is not correlated with the magnitude of clinical response.

Table 7 lists responsive *CFTR* mutations based on clinical response and/or *in vitro* data or extrapolation in FRT cells indicating that elexacaftor/tezacaftor/ivacaftor increases chloride transport to at least 10% of normal over baseline. The presence of the *CFTR* mutations listed in Table 7 should not be used in place of a diagnosis of cystic fibrosis or as the sole factor for prescribing purposes.

Table 7: List of *CFTR* Gene Mutations that are responsive to elexacaftor/tezacaftor/ivacaftor					
Mutations responsive to Trikafta based on clinical data					
2789+5 G→A	*D1152H*	*L997F*	*P5L*	*R1066H*	
3272-26A→G	*F508del*	*L1077P*	*R117C*	*S945L*	
3849+10 kbC→T	*G85E*	*M1101K*	*R347H*	*T338I*	
A455E	*L206W*	*N1303K*	*R347P*	*V232D*	
Mutations responsive to Trikafta based on in vitro data					
3141del 9	*E588V*	*G970D*	*L165S*	*R117G*	*S589N*
546insC TA	*E822K*	*G1061R*	*L320V*	*R117H*	*S737F*
A46D	*F191V*	*G1069R*	*L346P*	*R117L*	*S912L*
A120T	*F311del*	*G1244E*	*L453S*	*R117P*	*S977F*
A234D	*F311L*	*G1249R*	*L967S*	*R170H*	*S1159F*
A349V	*F508C*	*G1349D*	*L1324P*	*R258G*	*S1159P*
A554E	*F508C;S1251N*†	*H139R*	*L1335P*	*R334L*	*S1251N*
A1006E	*F575Y*	*H199Y*	*L1480P*	*R334Q*	*S1255P*
A1067T	*F1016S*	*H939R*	*M152V*	*R347L*	*T1036N*
D110E	*F1052V*	*H1054D*	*M265R*	*R352Q*	*T1053I*
D110H	*F1074L*	*H1085P*	*M952I*	*R352W*	*V201M*
D192G	*F1099L*	*H1085R*	*M952T*	*R553Q*	*V456A*
D443Y	*G27R*	*H1375P*	*P67L*	*R668C*	*V456F*
D443Y;G576A; R668C†	*G126D*	*I148T*	*P205S*	*R751L*	*V562I*
D579G	*G178E*	*I175V*	*P574H*	*R792G*	*V754M*
D614G	*G178R*	*I336K*	*Q98R*	*R933G*	*V1153E*

D836Y	*G194R*	*I502T*	*Q237E*	*R1070Q*	*V1240G*
D924N	*G194V*	*I601F*	*Q237H*	*R1070W*	*V1293G*
D979V	*G314E*	*I618T*	*Q359R*	*R1162L*	*W361R*
D1270N	*G463V*	*I807M*	*Q1291R*	*R1283M*	*W1098C*
E56K	*G480C*	*I980K*	*R31L*	*R1283S*	*W1282R*
E60K	*G551D*	*I1027T*	*R74Q*	*S13F*	*Y109N*
E92K	*G551S*	*I1139V*	*R74W*	*S341P*	*Y161D*
E116K	*G576A*	*I1269N*	*R74W; D1270N*†	*S364P*	*Y161S*
E193K	*G576A;R668C*†	*I1366N*	*R74W;V201M*†	*S492F*	*Y563N*
E403D	*G622D*	*K1060T*	*R74W;V201M; D1270N*†	*S549N*	*Y1014C*
E474K	*G628R*	*L15P*	*R75Q*	*S549R*	*Y1032C*
Mutations responsive to Trikafta based on extrapolation from Trial 445-124					
711+3A→G	*E831X*				
† Complex/compound mutations where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.					

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).
In study 445-124 (patients aged 6 years and older with a qualifying non-*F508del*, elexacaftor/tezacaftor/ivacaftor-responsive mutation [see Table 8]), the mean absolute change in sweat chloride from baseline through Week 24 compared to placebo was -28.3 mmol/L (95% CI:-32.1, -24.5 mmol/L; *P*<0.0001).

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 four phase 3, double-blind, controlled studies (studies 445-102, 445-103, 445-104, and 445-124). These studies each enrolled CF patients who had at least one *F508del* mutation or a mutation responsive to Trikafta listed in Table 8. Four open-label, uncontrolled Phase 3 studies (study 445-105, study 445-106 part B, study 445-111, and study 445-107) 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.

Study 445-124 was a 24-week, randomized, placebo-controlled, double-blind, parallel group study in patients aged 6 years and older. Patients who had at least one qualifying non-*F508del*, elexacaftor/tezacaftor/ivacaftor-responsive mutation (see Table 8) and did not have an exclusionary (other elexacaftor/tezacaftor/ivacaftor-responsive) mutation were eligible for the study. A total of 307 patients were enrolled and dosed according to age and weight. Patients ≥6 to <12 years weighing <30 kg at baseline were administered elexacaftor 100 mg qd/tezacaftor 50 mg qd/ivacaftor 75 mg q12h. Patients ≥6 to <12years weighing ≥30 kg at baseline were administered elexacaftor 200 mg qd/tezacaftor 100 mg qd/ivacaftor 150 mg q12h. Patients ≥12 years at baseline were administered elexacaftor 200 mg qd/tezacaftor 100 mg qd/ivacaftor 150 mg q12h. Patients had a $ppFEV_1$ ≥40% and ≤100% and aged 6 years or older at screening. The mean $ppFEV_1$ at baseline was 67.7% (range: 34.0%, 108.7%).

Table 8: Eligible elexacaftor/tezacaftor/ivacaftor-responsive *CFTR* Mutations				
2789+5G>A	*D1152H*	*L997F*	*R117C*	*T338I*
3272-26A>G	*G85E*	*M1101K*	*R347H*	*V232D*
3849+10kbC>T	*L1077P*	*P5L*	*R347P*	
A455E	*L206W*	*R1066H*	*S945L*	

Patients in studies 445-102, 445-103, 445-104, 445-106, 445-111 and 445-124 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 met study eligibility criteria.

In studies 445-102, 445-103, 445-104, 445-106, 445-111 and 445-124 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 × ULN, or total bilirubin ≥2 × ULN), were excluded. In study 445-111, patients who had ALT or AST ≥2 × ULN were also excluded. Patients in studies 445-102 and 445-103 were eligible to roll over into the 192-week open-label extension study (study 445-105). Patients in studies 445-104, 445-106 part B, 445-111, and 445-124 were eligible to roll over into separate 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) (see Table 9). Mean improvement in $ppFEV_1$ was rapid in onset (Day 15) and sustained through the 24-week treatment period (see 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 9 for a summary of primary and key secondary outcomes.

Table 9: Primary and Key Secondary Efficacy Analyses, Full Analysis Set (Study 445-102)

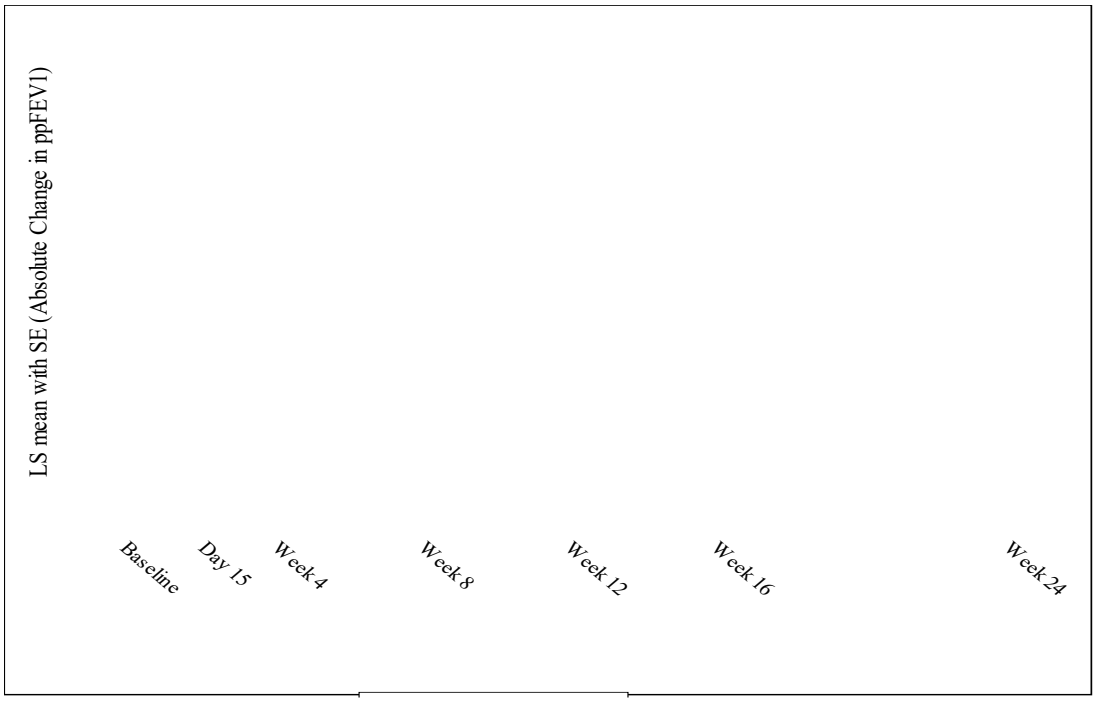
Analysis	Statistic	Placebo N=203	Trikafta N=200
Primary efficacy analysis			
Absolute change in $ppFEV_1$ from baseline through Week 24 (percentage points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -0.4 (0.5)	14.3 (12.7, 15.8) *P*<0.0001 13.9 (0.6)
Key secondary efficacy analyses			
Absolute change in $ppFEV_1$ from baseline at Week 4 (percentage points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -0.2 (0.6)	13.7 (12.0, 15.3) *P*<0.0001 13.5 (0.6)
Number of pulmonary exacerbations from baseline through Week 24‡	Number of events (event rate per year††) Rate ratio (95% CI) *P* value	113 (0.98) NA NA	41 (0.37) 0.37 (0.25, 0.55) *P*<0.0001
Absolute change in sweat chloride from baseline through Week 24 (mmol/L)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -0.4 (0.9)	-41.8 (-44.4, -39.3) *P*<0.0001 -42.2 (0.9)
Absolute change in CFQ-R respiratory domain score from baseline through Week 24 (points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -2.7 (1.0)	20.2 (17.5, 23.0) *P*<0.0001 17.5 (1.0)
Absolute change in BMI from baseline at Week 24 (kg/m^2)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 0.09 (0.07)	1.04 (0.85, 1.23) *P*<0.0001 1.13 (0.07)
Absolute change in sweat chloride from baseline at Week 4 (mmol/L)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 0.1 (1.0)	-41.2 (-44.0, -38.5) *P*<0.0001 -41.2 (1.0)
Absolute change in CFQ-R respiratory domain score from baseline at Week 4 (points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -1.9 (1.1)	20.1 (16.9, 23.2) *P*<0.0001 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) (see Table 10). Improvements in $ppFEV_1$ were observed regardless of age, sex, baseline $ppFEV_1$, and geographic region. See Table 10 for a summary of primary and key secondary outcomes.

Table 10: 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) *P* value Within-group change (SE)	NA NA 0.4 (0.9)	10.0 (7.4, 12.6) *P*<0.0001 10.4 (0.9)
Key secondary efficacy analyses			
Absolute change in sweat chloride from baseline at Week 4 (mmol/L)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 1.7 (1.8)	-45.1 (-50.1, -40.1) *P*<0.0001 -43.4 (1.7)
Absolute change in CFQ-R respiratory domain score from baseline at Week 4 (points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -1.4 (2.0)	17.4 (11.8, 23.0) *P*<0.0001 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. * Baseline for primary and key secondary endpoints is defined as the end of the 4-week tezacaftor/ivacaftor and ivacaftor run-in period. # Regimen of tezacaftor/ivacaftor and ivacaftor.			

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

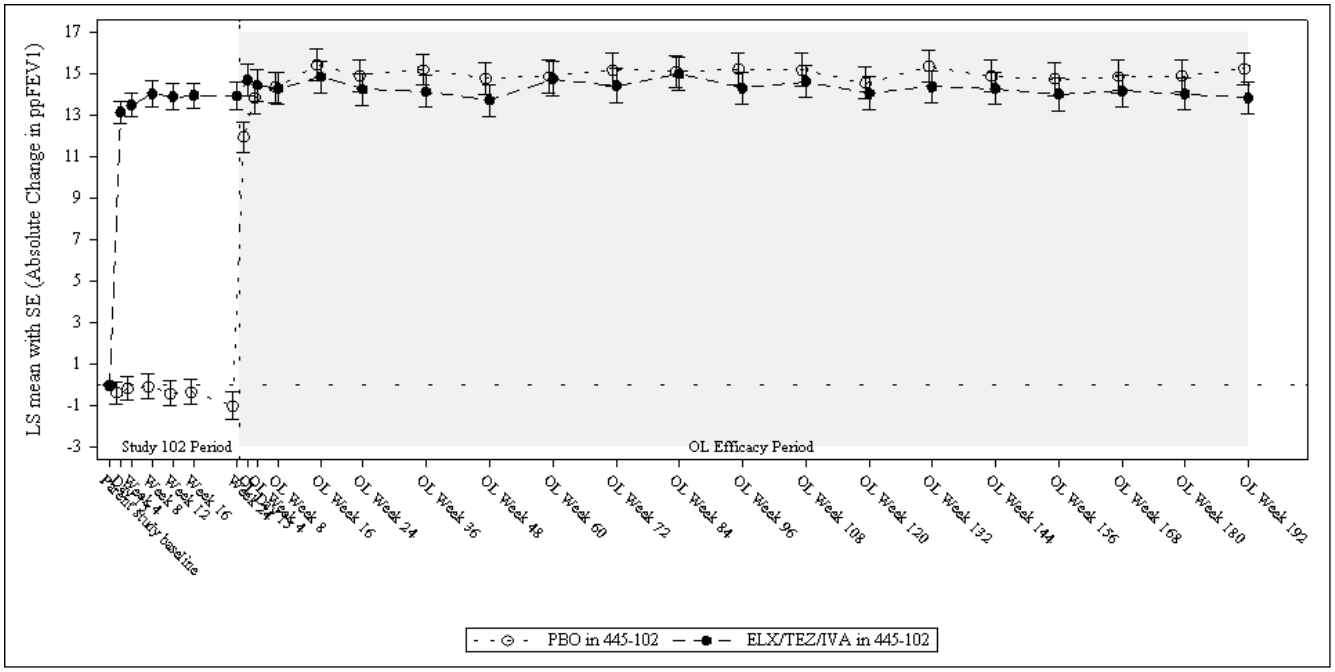
SE: Standard Error; TEZ/IVA: tezacaftor/ivacaftor; ELX/TEZ/IVA: elexacaftor/tezacaftor/ivacaftor

Study 445-105

Study 445-105 was a 192-week open-label extension study to evaluate the safety and efficacy of long-term treatment with Trikafta 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.

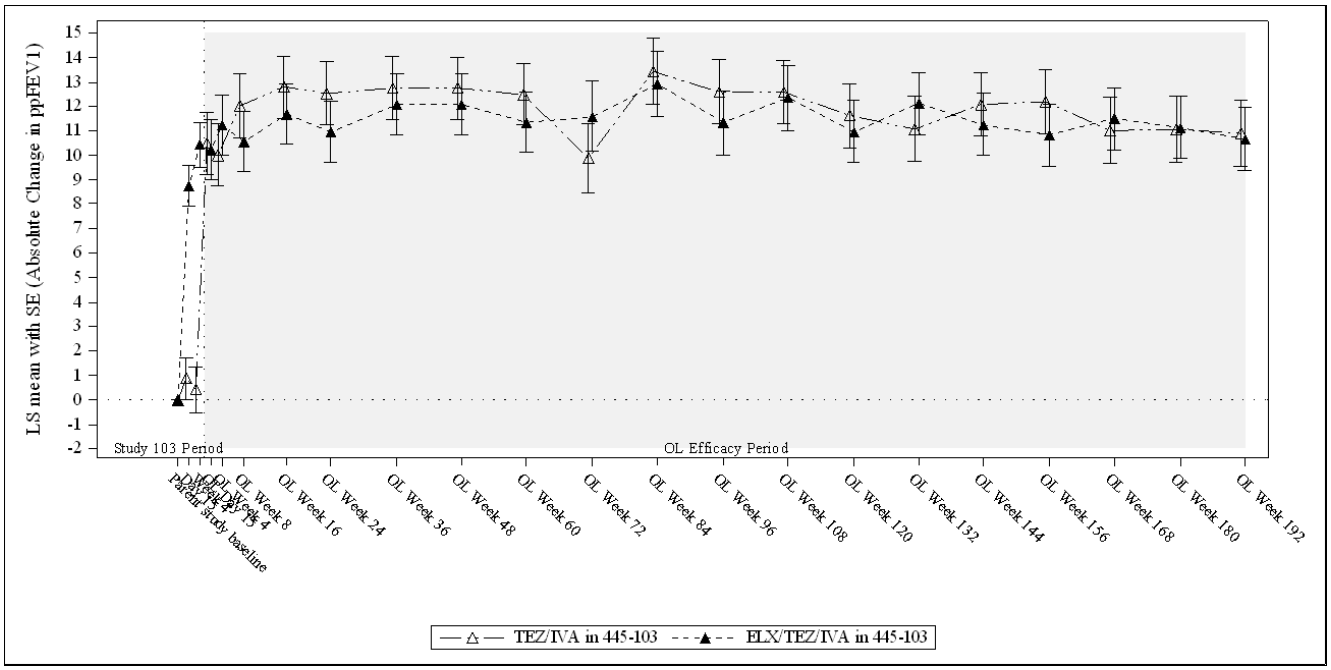
In Study 445-105, patients from the control arms in the parent studies showed improvements in efficacy endpoints consistent with those observed in subjects who received Trikafta in the parent studies. Patients from the control arm as well as patients who received Trikafta in the parent studies, showed sustained improvement in $ppFEV_1$ (see Figure 3 and Figure 4) and other efficacy endpoints (see Table 11). 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

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

Table 11: Study 445-105 Secondary Open-label Efficacy Analysis, Full Analysis Set (F/MF and F/F Subjects)

Analysis	Statistic	Study 445-105 Week 192			
		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 **LS mean** 95% CI	136 **15.3** (13.7, 16.8)	133 **13.8** (12.3, 15.4)	32 **10.9** (8.2, 13.6)	36 **10.7** (8.1, 13.3)
Absolute change from baseline* in SwCl (mmol/L)	n **LS mean** 95% CI	133 **-47.0** (-50.1, -43.9)	128 **-45.3** (-48.5, -42.2)	31 **-48.2** (-55.8, -40.7)	38 **-48.2** (-55.1, -41.3)
Number of PEx during the Cumulative TC Efficacy Period†	Number of events Estimated event rate per year (95% CI)	385 0.21 (0.17, 0.25)		71 0.18 (0.12, 0.25)	

ppFEV$_1$ = percent predicted Forced Expiratory Volume in 1 second; SwCl = Sweat Chloride; PEx = Pulmonary Exacerbation; LS = Least Squares; CI = Confidence Interval; PBO = Placebo; TC = Triple Combination.
* 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 192 weeks of treatments in Study 445-105 (N=255, including 4 patients that did not rollover into study 445-105). For subjects who were randomized to the Placebo or TEZ/IVA group, the Cumulative TC Efficacy Period includes data from 192 weeks of treatments in Study 445-105 only (N=255).

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 12). 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 12 for a summary of primary and secondary outcomes in the overall trial population.

Table 12: 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) *P* value	0.2 (-0.7, 1.1) NA	3.7 (2.8, 4.6) *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) *P* value	0.7 (-1.4, 2.8) NA	-22.3 (-24.5, -20.2) *p*<0.0001
Absolute change in $ppFEV_1$ from baseline through Week 8 compared to the control group (percentage points)	Treatment difference (95% CI) *P* value	NA NA	3.5 (2.2, 4.7) *p*<0.0001
Absolute change in sweat chloride from baseline through Week 8 compared to the control group (mmol/L)	Treatment difference (95% CI) *P* value	NA NA	-23.1 (-26.1, -20.1) *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 13 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 13: 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 445-107

A 192-week, two-part (part A and part B), open-label extension study to evaluate the safety and efficacy of long-term treatment with Trikafta was conducted in patients who completed study 445-106. The analysis of part A (96 weeks) was conducted in 64 pediatric patients aged 6 years and older and showed sustained improvements in ppFEV1 and SwCl consistent with the results observed in the study 445-106. Subsequently, 48 (75.0%) subjects were transferred to part B of the study until

Week 192. 39 (60.9%) subjects completed part B and confirmed the continued efficacy. Secondary efficacy endpoints of the interim and the final analysis are summarized in Table 14.

Table 14: Secondary Efficacy Analysis, Full Analysis Set (N = 64) (Study 445-107)

Analysis	Statistic	Absolute Change from Baseline* at Week 96	Absolute Change from Baseline* at Week 192
$ppFEV_1$ (percentage points)	n LS mean 95% CI	45 11.2 (8.3, 14.2)	27 9.6 (5.4, 13.7)
SwCl (mmol/L)	n LS mean 95% CI	56 -62.3 (-65.9, -58.8)	35 -57.9 (-63.3, -52.5)
PEx during the Cumulative Triple Combination (TC) Efficacy Period†	Number of events Observed event rate per year	7 0.04	11 0.045

$ppFEV_1$ = percent predicted Forced Expiratory Volume in 1 second; SwCl = Sweat Chloride; PEx = Pulmonary Exacerbation; LS = Least Squares; CI = Confidence Interval; TC = Triple Combination.

* Baseline = parent study baseline

† The Cumulative TC Efficacy Period includes data from the 66 patients who were enrolled and received at least of one dose of treatment in the parent study (study 445-106 Part B) and/or received at least one dose during study 445-107.

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 15 for a summary of secondary efficacy outcomes.

Table 15: 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[*] LS Mean (95% CI)	75 -57.9 (-61.3, -54.6)
Absolute change in $LCI_{2.5}$ from baseline through Week 24	N LS Mean (95% CI)	63[‡] -0.83 (-1.01, -0.66)
Number of pulmonary exacerbations through Week 24[**]	N Number of events (estimated event rate per year)	75 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.		

Study 445-124

The safety and efficacy of Trikafta in patients with CF aged 6 years and older without an *F508del* mutation were evaluated (study 445-124).

In study 445-124, the primary endpoint of efficacy was $ppFEV_1$. Secondary endpoints were absolute change in sweat chloride, CFQ-R respiratory domain score, growth parameters (BMI, weight), and number of PEx. See Table 16 for a summary of primary and secondary efficacy outcomes.

Table 16: Primary and Secondary Efficacy Analyses, Full Analysis Set (study 445-124)			
Analysis	**Statistic**	**Placebo N = 102**	**ELX/TEZ/IVA N = 205**
Primary			
Absolute change in $ppFEV_1$ from baseline through Week 24 (percentage points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -0.4 (0.8)	9.2 (7.2, 11.3) *P*<0.0001 8.9 (0.6)
Secondary			
Absolute change in sweat chloride from baseline through Week 24 (mmol/L)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 0.5 (1.6)	-28.3 (-32.1, -24.5) *P*<0.0001 -27.8 (1.1)
Absolute change in CFQ-R respiratory domain score from baseline through Week 24 (points)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA -2.0 (1.6)	19.5 (15.5, 23.5) *P*<0.0001 17.5 (1.2)
Absolute change from baseline in BMI at Week 24 (kg/m^2)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 0.35 (0.09)	0.47 (0.24, 0.69) *P*<0.0001 0.81 (0.07)
Absolute change from baseline in weight at Week 24 (kg)	Treatment difference (95% CI) *P* value Within-group change (SE)	NA NA 1.2 (0.3)	1.3 (0.6, 1.9) *P*<0.0001 2.4 (0.2)
Number of PEx through Week 24	Rate ratio (95% CI) *P* value Number of events Estimated event rate per year	NA NA 40 0.63	0.28 (0.15, 0.51) *P*<0.0001 21 0.17
BMI: body mass index; CFQ-R RD: Cystic Fibrosis Questionnaire-Revised Respiratory Domain; ELX: elexacaftor; IVA: ivacaftor; N: total sample size; *P*: probability; PEx: pulmonary exacerbation; $ppFEV_1$: percent predicted forced expiratory volume in 1 second; SE: standard error; TEZ: tezacaftor.			

Study CFD-016

The efficacy of Trikafta in patients with CF aged 6 years and older was also evaluated in a retrospective study evaluating real-world clinical outcomes in patients with CF that do not have an *F508del* mutation using data from the US Cystic Fibrosis Foundation Patient Registry. In study CFD-016, the primary endpoint of efficacy was $ppFEV_1$. The mean change from baseline in $ppFEV_1$ was 4.53 percentage points (n=422; 95% CI: 3.50, 5.56).

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 17.

Table 17: 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			
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 1/6th of parent
Excretion[g]			
Primary Pathway	• Feces: 87.3% (primarily as metabolites) • Urine: 0.23%	• Feces: 72% (unchanged or as M2-TEZ) • Urine: 14% (0.79% unchanged)	• Feces: 87.8% • 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 years 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 17, Pharmacokinetic Parameters of Trikafta Components

Distribution

See Table 17, Pharmacokinetic Parameters of Trikafta Components

Metabolism

See Table 17, Pharmacokinetic Parameters of Trikafta Components

Elimination

See Table 17, 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 18. 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 18: 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	147 (36.8)	58.5 (25.6)	88.8 (21.8)	148 (333)	10.6 (3.35)

	qd/ivacaftor 150 mg q12h					
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/atrophy 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 pediatric 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 fetal 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

Date of revision of the text

July 2025