Simulations indicated that co-administration with moderate CYP3A inhibitors may increase elexacaftor and tezacaftor AUC by approximately 1.9- to 2.3-fold and 2.1-fold, respectively. Co-administration of fluconazole increased ivacaftor AUC by 2.9-fold. The dosage of TRIKAFTA should be reduced when co-administered with moderate CYP3A inhibitors *[see Dosage and Administration (2.3), Warnings and Precautions (5.3) and Clinical Pharmacology (12.3)]*.

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; therefore, food or drink containing grapefruit should be avoided during treatment with TRIKAFTA *[see Dosage and Administration (2.3)]*.

7.3 Ciprofloxacin

Ciprofloxacin had no clinically relevant effect on the exposure of tezacaftor or ivacaftor and is not expected to affect the exposure of elexacaftor. Therefore, no dose adjustment is necessary during concomitant administration of TRIKAFTA with ciprofloxacin *[see Clinical Pharmacology (12.3)]*.

Potential for elexacaftor/tezacaftor/ivacaftor to affect other drugs

7.4 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 *[see Clinical Pharmacology (12.3)]*.

7.5 Transporters

Co-administration of ivacaftor or tezacaftor/ivacaftor with digoxin, a sensitive 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 *[see Clinical Pharmacology (12.3)]*.

Elexacaftor and M23-ELX inhibit uptake by OATP1B1 and OATP1B3 *in vitro*. 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 *[see Clinical Pharmacology (12.3)]*. Bilirubin is an OATP1B1 and OATP1B3 substrate.

7.6 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are limited and incomplete human data from clinical trials on the use of TRIKAFTA or its individual components, elexacaftor, tezacaftor and ivacaftor, in pregnant women to inform a drug-associated risk. Although there are no animal reproduction studies with the concomitant administration of elexacaftor, tezacaftor and ivacaftor, separate reproductive and developmental studies were conducted with each active component of TRIKAFTA in pregnant rats and rabbits.

In animal embryo fetal development (EFD) studies oral administration of elexacaftor to pregnant rats and rabbits during organogenesis demonstrated no teratogenicity or adverse developmental effects at doses that produced maternal exposures up to approximately 2 times the exposure at the maximum recommended human dose (MRHD) in rats and 4 times the MRHD in rabbits [based on summed AUCs of elexacaftor and its metabolite (for rat) and AUC of elexacaftor (for rabbit)]. Oral administration of tezacaftor to pregnant rats and rabbits during organogenesis demonstrated no teratogenicity or adverse developmental effects at doses that produced maternal exposures up to approximately 3 times the exposure at the MRHD in rats and 0.2 times the MRHD in rabbits (based on summed AUCs of tezacaftor and M1-TEZ). Oral administration of ivacaftor to pregnant rats and rabbits during organogenesis demonstrated no teratogenicity or adverse developmental effects at doses that produced maternal exposures up to approximately 5 and 14 times the exposure at the MRHD, respectively [based on summed AUCs of ivacaftor and its metabolites (for rat) and AUC of ivacaftor (for rabbit)]. No adverse developmental effects were observed after oral administration of elexacaftor, tezacaftor or ivacaftor to pregnant rats from the period of organogenesis through lactation at doses that produced maternal exposures approximately 1 time, approximately 1 time and 3 times the exposures at the MRHD, respectively [based on summed AUCs of parent and metabolite(s)] (*see Data*).

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Elexacaftor

In an EFD study in pregnant rats dosed during the period of organogenesis from gestation Days 6-17, elexacaftor was not teratogenic and did not affect fetal survival at exposures up to 9 times the MRHD (based on summed AUC for elexacaftor and its metabolite at maternal doses up to 40 mg/kg/day). Lower mean fetal body weights were observed at doses ≥25 mg/kg/day that produced maternal exposures ≥4 times the MRHD. In an EFD study in pregnant rabbits dosed during the period of organogenesis from gestation Days 7-20, elexacaftor was not teratogenic at exposures up to 4 times the MRHD (based on AUC of elexacaftor at maternal doses up to 125 mg/kg/day). In a pre- and postnatal development (PPND) study in pregnant rats dosed from gestation Day 6 through lactation Day 18, elexacaftor did not cause developmental defects in pups at maternal doses up to 10 mg/kg/day (approximately 1 time the MRHD based on summed AUCs of elexacaftor and its metabolite). Placental transfer of elexacaftor was observed in pregnant rats.

Tezacaftor

In an EFD study in pregnant rats dosed during the period of organogenesis from gestation Days 6-17 and in pregnant rabbits dosed during the period of organogenesis from gestation Days 7-20, tezacaftor was not teratogenic and did not affect fetal development or survival at exposures up to 3 and 0.2 times,

respectively the MRHD (based on summed AUCs of tezacaftor and M1-TEZ). Lower fetal body weights were observed in rabbits at a maternally toxic dose that produced exposures approximately 1 time the MRHD (based on summed AUCs of tezacaftor and M1-TEZ at a maternal dose of 50 mg/kg/day). In a PPND study in pregnant rats dosed from gestation Day 6 through lactation Day 18, tezacaftor had no adverse developmental effects on pups at an exposure of approximately 1 time the MRHD (based on summed AUCs for tezacaftor and M1-TEZ at a maternal dose of 25 mg/kg/day). Decreased fetal body weights and early developmental delays in pinna detachment, eye opening and righting reflex occurred at a maternally toxic dose (based on maternal weight loss) that produced exposures approximately 1 time the exposure at the MRHD (based on summed AUCs for tezacaftor and M1-TEZ at a maternal oral dose of 50 mg/kg/day). Placental transfer of tezacaftor was observed in pregnant rats.

Ivacaftor
In an EFD study in pregnant rats dosed during the period of organogenesis from gestation Days 7-17 and in pregnant rabbits dosed during the period of organogenesis from gestation Days 7-19, ivacaftor was not teratogenic and did not affect fetal survival at exposures up to 5 and 14 times, respectively, the MRHD [based on summed AUCs of ivacaftor and its metabolites (for rat) and AUC of ivacaftor (for rabbit)]. In a PPND study in pregnant rats dosed from gestation Day 7 through lactation Day 20, ivacaftor had no effects on delivery or growth and development of offspring at exposures up to 3 times the MRHD (based on summed AUCs for ivacaftor and its metabolites at maternal oral doses up to 100 mg/kg/day). Decreased fetal body weights were observed at a maternally toxic dose that produced exposures 5 times the MRHD (based on summed AUCs of ivacaftor and its metabolites). Placental transfer of ivacaftor was observed in pregnant rats and rabbits.

8.2 Lactation

Risk Summary

There is no information regarding the presence of elexacaftor, tezacaftor, or ivacaftor in human milk, the effects on the breastfed infant, or the effects on milk production. Elexacaftor, tezacaftor, and ivacaftor are excreted into the milk of lactating rats *(see Data)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRIKAFTA and any potential adverse effects on the breastfed child from TRIKAFTA or from the underlying maternal condition.

Data

Elexacaftor
Lacteal excretion of elexacaftor in rats was demonstrated following a single oral dose (10 mg/kg) of ^{14}C-elexacaftor administered 6 to 10 days postpartum to lactating dams. Exposure of ^{14}C-elexacaftor in milk was approximately 0.4 times the value observed in plasma (based on $AUC_{0\text{-}72h}$).

Tezacaftor
Lacteal excretion of tezacaftor in rats was demonstrated following a single oral dose (30 mg/kg) of ^{14}C-tezacaftor administered 6 to 10 days postpartum to lactating dams. Exposure of ^{14}C-tezacaftor in milk was approximately 3 times higher than in plasma (based on $AUC_{0\text{-}72h}$).

Ivacaftor
Lacteal excretion of ivacaftor in rats was demonstrated following a single oral dose (100 mg/kg) of ^{14}C-ivacaftor administered 9 to 10 days postpartum to lactating dams. Exposure of ^{14}C-ivacaftor in milk was approximately 1.5 times higher than in plasma (based on $AUC_{0\text{-}24h}$).

8.4 Pediatric Use

The safety and effectiveness of TRIKAFTA for the treatment of CF have been established in pediatric patients aged 2 to less than 18 years who have at least one *F508del* mutation in the *CFTR* gene or a mutation in the *CFTR* gene that is responsive based on *in vitro* data. Use of TRIKAFTA for this indication for pediatric patients 12 years of age and older was supported by evidence from two adequate and well-controlled studies (Trials 1 and 2) in CF patients aged 12 years and older *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

Use of TRIFAFTA for this indication in pediatric patients 2 to less than 12 years of age is based on the following:

- Trial 1, 56 pediatric patients aged 12 to less than 18 years who had 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 *[see Adverse Reactions (6) and Clinical Studies (14)]*.
- Trial 2, 16 pediatric patients aged 12 to less than 18 years who were homozygous for the *F508del* mutation *[see Adverse Reactions (6) and Clinical Studies (14)]*.
- Trial 3, 66 pediatric patients aged 6 to less than 12 years who were homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation with 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 *[see Adverse Reactions (6) and Clinical Pharmacology (12.3)]*.
- Trial 4, 75 pediatric patients aged 2 to less than 6 years who had at least one *F508del* mutation or a mutation known to be responsive to TRIKAFTA *[see Adverse Reactions (6) and Clinical Pharmacology (12.3)]*.

The effectiveness of TRIKAFTA in patients aged 2 to less than 12 years was extrapolated from patients aged 12 years and older with support from population pharmacokinetic analyses showing elexacaftor, tezacaftor, and ivacaftor exposure levels in patients aged 2 to less than 12 years within the range of exposures observed in patients aged 12 years and older *[see Clinical Pharmacology (12.3)]*. Safety of TRIKAFTA in patients aged 6 to less than 12 years was derived from a 24-week, open-label, clinical trial in 66 patients aged 6 to less than 12 years (mean age at baseline 9.3 years) administered either a total dose of elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg in the morning and ivacaftor 75 mg in the evening (for patients weighing less than 30 kg) or a total dose of elexacaftor 200 mg/tezacaftor 100 mg/ivacaftor 150 mg in the morning and ivacaftor 150 mg in the evening (for patients weighing 30 kg or more) (Trial 3). Safety of TRIKAFTA in patients aged 2 to less than 6 years was derived from a 24-week, open-label, clinical trial in 75 patients aged 2 to less than 6 years (mean age at baseline 4.1 years) administered either a total dose of elexacaftor 80 mg/tezacaftor 40 mg/ivacaftor 60 mg in the morning and ivacaftor 59.5 mg in the evening (for patients weighing 10 kg to less than 14 kg) or a total dose of elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg in the morning and ivacaftor 75 mg in the evening (for patients weighing 14 kg or more) (Trial 4). The safety profile of patients in these trials was similar to that observed in Trial 1 *[see Adverse Reactions (6)]*.

The safety and effectiveness of TRIKAFTA in patients with CF younger than 2 years of age have not been established.

Juvenile Animal Toxicity Data

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 (0.21 times the MRHD based on systemic exposure of ivacaftor and its metabolites). This finding has not been observed in older animals *[see Warnings and Precautions (5.4)]*.

Studies were conducted with tezacaftor in juvenile rats starting at postnatal day (PND) 21 and ranging up to PNDs 35 to 49. Findings of convulsions and death were observed in juvenile rats that received a tezacaftor dose level of 100 mg/kg/day (approximately equivalent to 1.9 times the MRHD based on summed AUCs of tezacaftor and its metabolite, M1-TEZ). A no effect dose level was identified at 30 mg/kg/day (approximately equivalent to 0.8 times the MRHD based on summed AUCs of tezacaftor and its metabolite, M1-TEZ). Findings were dose related and generally more severe when dosing with tezacaftor was initiated earlier in the postnatal period (PND 7, which would be approximately equivalent to a human neonate). 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 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.

8.5 Geriatric Use
Clinical studies of TRIKAFTA did not include any patients aged 65 years and older.

8.6 Renal Impairment
TRIKAFTA has not been studied in patients with severe renal impairment or end-stage renal disease. No dosage adjustment is recommended in patients with mild (eGFR 60 to <90 mL/min/1.73 m^2) or moderate (eGFR 30 to <60 mL/min/1.73 m^2) renal impairment. Use with caution in patients with severe (eGFR <30 mL/min/1.73 m^2) renal impairment or end-stage renal disease *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment
- Mild Hepatic Impairment (Child-Pugh Class A): No dose modification is recommended. Liver function tests should be closely monitored.

- Moderate Hepatic Impairment (Child-Pugh Class B): Treatment is not recommended. Use of TRIKAFTA in patients with moderate hepatic impairment should only be considered when there is a clear medical need, and the benefit exceeds the risk. If used in patients with moderate hepatic impairment, TRIKAFTA should be used at a reduced dose *[see Dosage and Administration (2.2)]*. Liver function tests should be closely monitored.

  In a clinical study of 11 subjects with moderate hepatic impairment, one subject developed total and direct bilirubin elevations >2 x ULN, and a second subject developed direct bilirubin elevation >4.5 x ULN *[see Clinical Pharmacology (12.3)]*.

- Severe Hepatic Impairment (Child-Pugh Class C): Should not be used. TRIKAFTA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C), but the exposure is expected to be higher than in patients with moderate hepatic impairment *[see Dosage and Administration (2.2), Warnings and Precautions (5.1), Adverse Reactions (6) and Clinical Pharmacology (12.3)]*.

8.8 Patients with Severe Lung Dysfunction
Trial 1 included a total of 18 patients receiving TRIKAFTA with $ppFEV_1$ <40 at baseline. The safety and efficacy in this subgroup were comparable to those observed in the overall population.

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

11 DESCRIPTION
TRIKAFTA is a co-package of elexacaftor, tezacaftor and ivacaftor fixed-dose combination tablets or granules and ivacaftor tablets or granules. Both tablets and granules are for oral administration.

The elexacaftor, tezacaftor and ivacaftor fixed-dose combination tablets are available as: orange, capsule-shaped, film-coated tablet containing 100 mg of elexacaftor, 50 mg of tezacaftor, 75 mg of ivacaftor, or light-orange, capsule-shaped, film-coated tablet containing 50 mg of elexacaftor, 25 mg of tezacaftor, 37.5 mg of ivacaftor. The fixed-dose combination tablet contains the following inactive ingredients: croscarmellose sodium, hypromellose, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The tablet film coat contains hydroxypropyl cellulose, hypromellose, iron oxide red, iron oxide yellow, talc, and titanium dioxide.

The ivacaftor tablet is available as a light blue, capsule-shaped, film-coated tablet containing 150 mg or 75 mg of ivacaftor and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose and sodium lauryl sulfate. The tablet film coat contains carnauba wax, FD&C Blue #2, PEG 3350, polyvinyl alcohol, talc, and titanium dioxide. The printing ink contains ammonium hydroxide, iron oxide black, propylene glycol, and shellac.

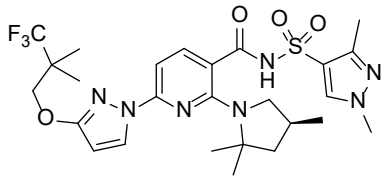
The elexacaftor, tezacaftor and ivacaftor fixed-dose combination oral granules are white to off-white, sweetened, unflavored granules approximately 2 mm in diameter enclosed in unit-dose packets. Each unit-dose packet contains 100 mg of elexacaftor, 50 mg of tezacaftor, 75 mg of ivacaftor or 80 mg of elexacaftor, 40 mg of tezacaftor, 60 mg of ivacaftor and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, mannitol, sodium lauryl sulfate, and sucralose.

The ivacaftor oral granules are white to off-white, sweetened, unflavored granules approximately 2 mm in diameter enclosed in unit-dose packets. Each unit-dose packet contains 75 mg or 59.5 mg of ivacaftor and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, mannitol, sodium lauryl sulfate, and sucralose.

The active ingredients of TRIKAFTA are described below.

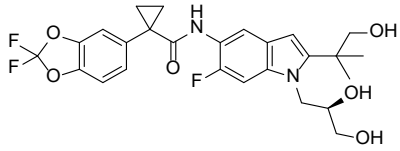
Elexacaftor

Elexacaftor is a white solid that is practically insoluble in water (<1 mg/mL). Its chemical name is N-(1,3-dimethyl-1H-pyrazole-4-sulfonyl)-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1H-pyrazol-1-yl]-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide. Its molecular formula is $C_{26}H_{34}N_7O_4SF_3$ and its molecular weight is 597.66. Elexacaftor has the following structural formula:



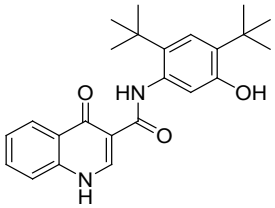
Tezacaftor

Tezacaftor is a white to off-white solid that is practically insoluble in water (<5 microgram/mL). Its chemical name is 1-(2,2-difluoro-2H-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl}cyclopropane-1-carboxamide. Its molecular formula is $C_{26}H_{27}N_2F_3O_6$ and its molecular weight is 520.50. Tezacaftor has the following structural formula:



Ivacaftor

Ivacaftor is a white to off-white crystalline solid that is practically insoluble in water (<0.05 microgram/mL). Pharmacologically it is a CFTR potentiator. Its chemical name is *N*-(2,4-di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide. Its molecular formula is $C_{24}H_{28}N_2O_3$ and its molecular weight is 392.49. Ivacaftor has the following structural formula:



12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Elexacaftor and tezacaftor bind to different sites on the CFTR protein and have an additive effect in facilitating the cellular processing and trafficking of select mutant forms of CFTR (including F508del-CFTR) to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone. Ivacaftor potentiates the channel open probability (or gating) of the CFTR protein at the cell surface.

The combined effect of elexacaftor, tezacaftor and ivacaftor is increased quantity and function of CFTR at the cell surface, resulting in increased CFTR activity as measured by CFTR mediated chloride transport.

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 *CFTR* mutations that result in CFTR protein being delivered to the cell surface.

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 5 lists responsive *CFTR* mutations based on *in vitro* data in FRT cells indicating that elexacaftor/tezacaftor/ivacaftor increases chloride transport to at least 10% of normal over baseline.

Table 5: List of *CFTR* Gene Mutations that are Responsive to TRIKAFTA					
3141del9	*E822K*	*G1069R*	*L967S*	*R117L*	*S912L*
546insCTA	*F191V*	*G1244E*	*L997F*	*R117P*	*S945L*
A46D	*F311del*	*G1249R*	*L1077P*	*R170H*	*S977F*
A120T	*F311L*	*G1349D*	*L1324P*	*R258G*	*S1159F*
A234D	*F508C*	*H139R*	*L1335P*	*R334L*	*S1159P*
A349V	*F508C;S1251N*†	*H199Y*	*L1480P*	*R334Q*	*S1251N*
A455E	*F508del**	*H939R*	*M152V*	*R347H*	*S1255P*
A554E	*F575Y*	*H1054D*	*M265R*	*R347L*	*T338I*
A1006E	*F1016S*	*H1085P*	*M952I*	*R347P*	*T1036N*
A1067T	*F1052V*	*H1085R*	*M952T*	*R352Q*	*T1053I*
D110E	*F1074L*	*H1375P*	*M1101K*	*R352W*	*V201M*
D110H	*F1099L*	*I148T*	*P5L*	*R553Q*	*V232D*
D192G	*G27R*	*I175V*	*P67L*	*R668C*	*V456A*
D443Y	*G85E*	*I336K*	*P205S*	*R751L*	*V456F*
D443Y;G576A;R668C†	*G126D*	*I502T*	*P574H*	*R792G*	*V562I*
D579G	*G178E*	*I601F*	*Q98R*	*R933G*	*V754M*
D614G	*G178R*	*I618T*	*Q237E*	*R1066H*	*V1153E*
D836Y	*G194R*	*I807M*	*Q237H*	*R1070Q*	*V1240G*
D924N	*G194V*	*I980K*	*Q359R*	*R1070W*	*V1293G*
D979V	*G314E*	*I1027T*	*Q1291R*	*R1162L*	*W361R*
D1152H	*G463V*	*I1139V*	*R31L*	*R1283M*	*W1098C*
D1270N	*G480C*	*I1269N*	*R74Q*	*R1283S*	*W1282R*
E56K	*G551D*	*I1366N*	*R74W*	*S13F*	*Y109N*
E60K	*G551S*	*K1060T*	*R74W;D1270N*†	*S341P*	*Y161D*
E92K	*G576A*	*L15P*	*R74W;V201M*†	*S364P*	*Y161S*
E116K	*G576A;R668C*†	*L165S*	*R74W;V201M;D1270N*†	*S492F*	*Y563N*
E193K	*G622D*	*L206W*	*R75Q*	*S549N*	*Y1014C*
E403D	*G628R*	*L320V*	*R117C*	*S549R*	*Y1032C*
E474K	*G970D*	*L346P*	*R117G*	*S589N*	
E588V	*G1061R*	*L453S*	*R117H*	*S737F*	

* *F508del* is a responsive *CFTR* mutation based on both clinical and *in vitro* data *[see Clinical Studies (14)]*.
† 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.

12.2 Pharmacodynamics

Sweat Chloride Evaluation

In Trial 1 (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 ivacaftor and tezacaftor/ivacaftor), a reduction in sweat chloride was observed from baseline at Week 4 and sustained through the 24-week treatment period *[see Clinical Studies (14.1)]*. In Trial 2 (patients homozygous for the *F508del* mutation), a reduction in sweat chloride was observed from baseline at Week 4 *[see Clinical Studies (14.2)]*. In Trial 3 (patients aged 6 to less than 12 years who are homozygous for the *F508del* mutation or heterozygous for the *F508del* mutation 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), the mean absolute change in sweat chloride from baseline through Week 24 was -60.9 mmol/L (95% CI: -63.7, -58.2). In Trial 4 (patients aged 2 to less than 6 years who had at least one *F508del* mutation or a mutation known to be responsive to TRIKAFTA, the mean absolute change in sweat chloride from baseline through Week 24 was -57.9 mmol/L (95% CI: -61.3, -54.6).

Cardiac Electrophysiology

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.

12.3 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 6.

Table 6: Pharmacokinetic Parameters of TRIKAFTA Components			
	Elexacaftor	**Tezacaftor**	**Ivacaftor**
General Information			
AUC_{ss} (SD), mcg·h/mL[a]	162 (47.5)[b]	89.3 (23.2)[b]	11.7 (4.01)[c]
C_{max} (SD), mcg/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			

Table 6: Pharmacokinetic Parameters of TRIKAFTA Components			
	Elexacaftor	**Tezacaftor**	**Ivacaftor**
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.
AUC_{ss}: area under the concentration versus time curve at steady state; SD: Standard Deviation; C_{max}: maximum observed concentration; T_{max}: time of maximum concentration; AUC: area under the concentration versus time curve.

Specific Populations

Pediatric Patients 2 to Less Than 12 Years of Age

Elexacaftor, tezacaftor and ivacaftor exposures observed in patients aged 2 to less than 12 years as determined using population PK analysis are presented by age group and dose administered in Table 7. Elexacaftor, tezacaftor and ivacaftor exposures in this patient population are within the range observed in patients aged 12 years and older.

Table 7: Mean (SD) Elexacaftor, Tezacaftor and Ivacaftor Exposures Observed at Steady State by Age Group and Dose Administered				
Age Group	**Dose**	**Elexacaftor $AUC_{0\text{-}24h,ss}$ (µg·h/mL)**	**Tezacaftor $AUC_{0\text{-}24h,ss}$ (µg·h/mL)**	**Ivacaftor $AUC_{0\text{-}12h,ss}$ (µg·h/mL)**
Patients aged 2 to less than 6 years weighing less than 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)	87.3 (17.3)	11.9 (3.86)
Patients aged 2 to less than 6 years weighing 14 kg or more (N = 59)	elexacaftor 100 mg qd/tezacaftor 50 mg qd/ivacaftor 75 mg q12h	138 (47.0)	90.2 (27.9)	13.0 (6.11)
Patients aged 6 to less than 12 years weighing less than 30 kg (N = 36)	elexacaftor 100 mg qd/tezacaftor 50 mg qd/ivacaftor 75 mg q12h	116 (39.4)	67.0 (22.3)	9.78 (4.50)
Patients aged 6 to less than 12 years weighing 30 kg or more (N = 30)	elexacaftor 200 mg qd/ tezacaftor 100 mg qd/ ivacaftor 150 mg q12h	195 (59.4)	103 (23.7)	17.5 (4.97)

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

Pediatric Patients 12 to Less Than 18 Years of Age

The following conclusions about exposures between adults and the pediatric population are based on population pharmacokinetic (PK) analyses.
Following oral administration of TRIKAFTA to patients 12 to less than 18 years of age (elexacaftor 200 mg qd/tezacaftor 100 mg qd/ivacaftor 150 mg q12h), the mean (±SD) AUC_{ss} was 147 (36.8) mcg·h/mL, 88.8 (21.8) mcg·h/mL and 10.6 (3.35) mcg·h/mL, respectively for elexacaftor, tezacaftor and ivacaftor, similar to the AUC_{ss} in adult patients.

Patients with Renal Impairment

Renal excretion of elexacaftor, tezacaftor and ivacaftor is minimal. Elexacaftor alone or in combination with tezacaftor and ivacaftor has not been studied in subjects with severe (eGFR <30 mL/min/1.73 m^2) renal impairment or end-stage renal disease. Based on population PK analyses, the clearance of elexacaftor and tezacaftor was similar in subjects with mild (eGFR 60 to <90 mL/min/1.73 m^2) or moderate (eGFR 30 to <60 mL/min/1.73 m^2) renal impairment relative to patients with normal renal function *[see Use in Specific Populations (8.6)]*.

Patients with 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). In a clinical study, following multiple doses of elexacaftor, tezacaftor and ivacaftor for 10 days, subjects with moderately impaired hepatic function (Child-Pugh Class B, score 7-9) had 25% higher AUC and 12% higher C_{max} for elexacaftor, 73% higher AUC and 70% higher C_{max} for M23-ELX, 36% higher AUC and 24% higher C_{max} for combined elexacaftor and M23-ELX, 20% higher AUC but similar C_{max} for tezacaftor and 1.5-fold higher AUC and 10% higher C_{max} for ivacaftor compared with healthy subjects matched for demographics *[see Dosage and Administration (2.2), Warnings and Precautions (5.1), Adverse Reactions (6) and Use in Specific Populations (8.7)]*.

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 in 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.

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

Drug Interaction Studies
Drug interaction studies were performed with elexacaftor, tezacaftor and/or ivacaftor and other drugs likely to be co-administered or drugs commonly used as probes for pharmacokinetic interaction studies *[see Drug Interactions (7)]*.

Potential for Elexacaftor, Tezacaftor and/or Ivacaftor to Affect Other Drugs
Based on *in vitro* results, elexacaftor and tezacaftor have a low potential to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, whereas ivacaftor has the potential to inhibit CYP2C8, CYP2C9 and CYP3A. However, clinical studies showed that the combination regimen of tezacaftor/ivacaftor is not an inhibitor of CYP3A and ivacaftor is not an inhibitor of CYP2C8 or CYP2D6.

Based on *in vitro* results, elexacaftor, tezacaftor and ivacaftor are not likely to induce CYP3A, CYP1A2 and CYP2B6.

Based on *in vitro* results, elexacaftor and tezacaftor have a low potential to inhibit the transporter P-gp, while ivacaftor has the potential to inhibit P-gp. Co-administration of tezacaftor/ivacaftor with digoxin, a sensitive P-gp substrate, increased digoxin exposure by 1.3-fold in a clinical study. Based on *in vitro* results, elexacaftor and M23-ELX may inhibit OATP1B1 and OATP1B3 uptake. Tezacaftor has a low potential to inhibit BCRP, OCT2, OAT1, or OAT3. Ivacaftor is not an inhibitor of the transporters OCT1, OCT2, OAT1, or OAT3.

The effects of elexacaftor, tezacaftor and/or ivacaftor on the exposure of co-administered drugs are shown in Table 8 *[see Drug Interactions (7)]*.

Table 8: 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 not clinically significant *[*see *Drug Interactions (7.6)]*.

Potential for Other Drugs to Affect Elexacaftor, Tezacaftor and/or Ivacaftor
In vitro studies showed that elexacaftor, tezacaftor and ivacaftor are all metabolized by CYP3A. Exposure to elexacaftor, tezacaftor and ivacaftor may be reduced by concomitant CYP3A inducers and increased by concomitant CYP3A inhibitors.

In vitro studies showed that elexacaftor and tezacaftor are substrates for the efflux transporter P-gp, but ivacaftor is not. Elexacaftor and ivacaftor are not substrates for OATP1B1 or OATP1B3; tezacaftor is a substrate for OATP1B1, but not OATP1B3. Tezacaftor is a substrate for BCRP.

The effects of co-administered drugs on the exposure of elexacaftor, tezacaftor and/or ivacaftor are shown in Table 9 *[see Dosage and Administration (2.3) and Drug Interactions (7)]*.

Table 9: 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)

Table 9: 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}**
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 [see *Drug Interactions (7.3)*].				

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies of carcinogenicity, mutagenicity, or impairment of fertility were conducted with the combination of elexacaftor, tezacaftor and ivacaftor; however, separate studies of elexacaftor, tezacaftor and ivacaftor are described below.

Elexacaftor

A 6-month study in Tg.rasH2 transgenic mice showed no evidence of tumorigenicity at 50 mg/kg/day dose, the highest dose tested.

A two-year study was conducted in rats to assess the carcinogenic potential of elexacaftor. No evidence of tumorigenicity was observed in rats at elexacaftor oral doses up to 10 mg/kg/day (approximately 2 and 5 times the MRHD based on summed AUCs of elexacaftor and its metabolite in male and female rats, respectively).

Elexacaftor was negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, *in vitro* mammalian cell micronucleus assay in TK6 cells, and *in vivo* mouse micronucleus test.

Elexacaftor did not cause reproductive system toxicity in male rats at 55 mg/kg/day and female rats at 25 mg/kg/day, equivalent to approximately 6 times and 4 times the MRHD, respectively (based on summed AUCs of elexacaftor and its metabolite). Elexacaftor did not cause embryonic toxicity at 35 mg/kg/day which was the highest dose tested, equivalent to approximately 7 times the MRHD (based on summed AUCs of elexacaftor and its metabolite). Lower male and female fertility, male copulation and female conception indices were observed in males at 75 mg/kg/day and females at 35 mg/kg/day, equivalent to approximately 6 times and 7 times, respectively, the MRHD (based on summed AUCs of elexacaftor and its metabolite).

Tezacaftor

A two-year study in Sprague-Dawley rats and a 6-month study in Tg.rasH2 transgenic mice were conducted to assess the carcinogenic potential of tezacaftor. No evidence of tumorigenicity from tezacaftor was observed in male and female rats at oral doses up to 50 and 75 mg/kg/day (approximately 1 and 2 times the MRHD based on summed AUCs of tezacaftor and its metabolites in males and females, respectively). No evidence of tumorigenicity was observed in male and female Tg.rasH2 transgenic mice at tezacaftor doses up to 500 mg/kg/day.

Tezacaftor was negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, *in vitro* chromosomal aberration assay in Chinese hamster ovary cells and *in vivo* mouse micronucleus test.

There were no effects on male or female fertility and early embryonic development in rats at oral tezacaftor doses up to 100 mg/kg/day (approximately 3 times the MRHD based on summed AUC of tezacaftor and M1-TEZ).

Ivacaftor

Two-year studies were conducted in CD-1 mice and Sprague-Dawley rats to assess the carcinogenic potential of ivacaftor. No evidence of tumorigenicity from ivacaftor was observed in mice or rats at oral doses up to 200 mg/kg/day and 50 mg/kg/day, respectively (approximately equivalent to 2 and 7 times the MRHD, respectively, based on summed AUCs of ivacaftor and its metabolites).

Ivacaftor was negative for genotoxicity in the following assays: Ames test for bacterial gene mutation, *in vitro* chromosomal aberration assay in Chinese hamster ovary cells and *in vivo* mouse micronucleus test.

Ivacaftor impaired fertility and reproductive performance indices in male and female rats at 200 mg/kg/day (approximately 7 and 5 times, respectively, the MRHD based on summed AUCs of ivacaftor and its metabolites). Increases in prolonged diestrus were observed in females at 200 mg/kg/day. Ivacaftor also increased the number of females with all nonviable embryos and decreased corpora lutea, implantations and viable embryos in rats at 200 mg/kg/day (approximately 5 times the MRHD based on summed AUCs of ivacaftor and its metabolites) when dams were dosed prior to and during early pregnancy. These impairments of fertility and reproductive performance in male and female rats at 200 mg/kg/day were attributed to severe toxicity.

14 CLINICAL STUDIES

Efficacy:

The efficacy of TRIKAFTA in patients with CF aged 12 years and older was evaluated in two double-blind, controlled trials (Trials 1 and 2).

Trial 1 was a 24-week, randomized, double-blind, placebo-controlled study in patients who had 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. An interim analysis was planned when at least 140 patients completed Week 4 and at least 100 patients completed Week 12.

Trial 2 was a 4-week, randomized, double-blind, active-controlled study in patients who are homozygous for the *F508del* mutation. Patients received tezacaftor 100 mg qd/ivacaftor 150 mg q12h during a 4-week, open-label run-in period and were then randomized and dosed to receive TRIKAFTA or tezacaftor 100 mg qd/ivacaftor 150 mg q12h during a 4-week, double-blind treatment period.

Patients in Trials 1 and 2 had a confirmed diagnosis of CF and at least one *F508del* mutation. Patients discontinued any previous CFTR modulator therapies, but continued on their other standard-of-care CF therapies (e.g., bronchodilators, inhaled antibiotics, dornase alfa and hypertonic saline). Patients had a $ppFEV_1$ at screening between 40-90%. Patients with a history of colonization with organisms associated with a more rapid decline in pulmonary status, including but not limited to *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus*, or who had an abnormal liver function test at screening (ALT, AST, ALP, or GGT ≥3 x ULN, or total bilirubin ≥2 x ULN), were excluded from the trials. Patients in Trials 1 and 2 were eligible to roll over into a 96-week, open-label extension study.

14.1 Trial 1

Trial 1 evaluated 403 patients (200 TRIKAFTA, 203 placebo) with CF aged 12 years and older (mean age 26.2 years). The mean $ppFEV_1$ at baseline was 61.4% (range: 32.3%, 97.1%). The primary endpoint assessed at the time of interim analysis was mean absolute change in $ppFEV_1$ from baseline at Week 4. The final analysis tested all key secondary endpoints in the 403 patients who completed the 24-week study participation, including absolute change in $ppFEV_1$ from baseline through Week 24; absolute change in sweat chloride from baseline at Week 4 and through Week 24; number of pulmonary exacerbations through Week 24; absolute change in BMI from baseline at Week 24, and absolute change in CFQ-R Respiratory Domain Score (a measure of respiratory symptoms relevant to patients with CF, such as cough, sputum production and difficulty breathing) from baseline at Week 4 and through Week 24.

Of the 403 patients included in the interim analysis, the treatment difference between TRIKAFTA and placebo for the mean absolute change from baseline in $ppFEV_1$ at Week 4 was 13.8 percentage points (95% CI: 12.1, 15.4; $P<0.0001$).

The treatment difference between TRIKAFTA and placebo for mean absolute change in $ppFEV_1$ from baseline through Week 24 was 14.3 percentage points (95% CI: 12.7, 15.8; $P<0.0001$). Mean improvement in $ppFEV_1$ was observed at the first assessment on 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. See Table 10 for a summary of primary and key secondary outcomes in Trial 1.

Table 10: Primary and Key Secondary Efficacy Analyses (Trial 1)

Analysis	Statistic	Treatment Difference[*] for TRIKAFTA (N=200) vs Placebo (N=203)
Primary (Interim Full Analysis Set)[**]		
Absolute change in $ppFEV_1$ from baseline at Week 4 (percentage points)	Treatment difference (95% CI) *P* value	13.8 (12.1, 15.4) *P*<0.0001
Key Secondary (Full Analysis Set)[#]		
Absolute change in $ppFEV_1$ from baseline through Week 24 (percentage points)	Treatment difference (95% CI) *P* value	14.3 (12.7, 15.8) *P*<0.0001
Number of pulmonary exacerbations from baseline through Week 24[‡$]	Rate ratio (95% CI) *P* value	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	-41.8 (-44.4, -39.3) *P*<0.0001
Absolute change in CFQ-R respiratory domain score from baseline through Week 24 (points)	Treatment difference (95% CI) *P* value	20.2 (17.5, 23.0) *P*<0.0001
Absolute change in BMI from baseline at Week 24 (kg/m^2)	Treatment difference (95% CI) *P* value	1.04 (0.85, 1.23) *P*<0.0001
Absolute change in sweat chloride from baseline at Week 4 (mmol/L)	Treatment difference (95% CI) *P* value	-41.2 (-44.0, -38.5) *P*<0.0001
Absolute change in CFQ-R respiratory domain score from baseline at Week 4 (points)	Treatment difference (95% CI) *P* value	20.1 (16.9, 23.2) *P*<0.0001

$ppFEV_1$: percent predicted Forced Expiratory Volume in 1 second; CI: Confidence Interval; CFQ-R: Cystic Fibrosis Questionnaire-Revised; BMI: Body Mass Index.

[*] Treatment difference provided as the outcome measure for changes in $ppFEV_1$, sweat chloride, CFQ-R and BMI; Rate ratio provided as the outcome measure for the number of pulmonary exacerbations.

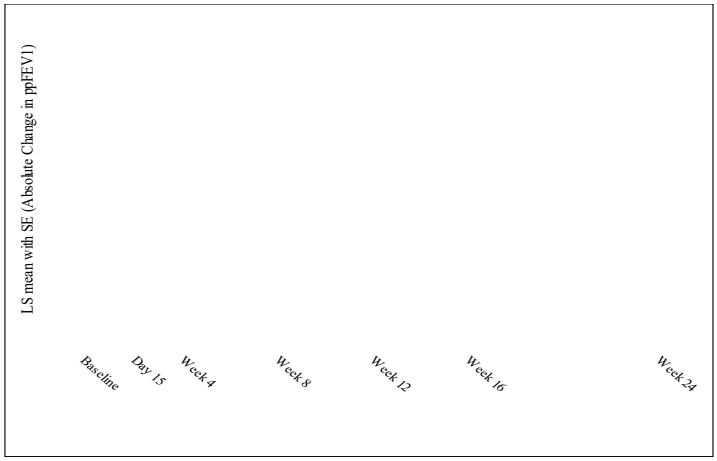
[**] Primary endpoint was based on interim analysis in 403 patients.

[#] Key secondary endpoints were tested at the final analysis in 403 patients.

[‡] 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 pulmonary exacerbation events (event rate per year calculated based on 48 weeks per year) in the TRIKAFTA group were 41 (0.37) and 113 (0.98) in the placebo group.

Figure 1: Absolute Change from Baseline in Percent Predicted FEV_1 at Each Visit in Trial 1



14.2 Trial 2

Trial 2 evaluated 107 patients with CF aged 12 years and older (mean age 28.4 years). The mean $ppFEV_1$ at baseline, following the 4-week, open-label run-in period with tezacaftor/ivacaftor was 60.9% (range: 35.0%, 89.0%). The primary endpoint was mean absolute change in $ppFEV_1$ from baseline at Week 4 of the double-blind treatment period. The key secondary efficacy endpoints were absolute change in sweat chloride and CFQ-R Respiratory Domain Score from baseline at Week 4. Treatment with TRIKAFTA compared to tezacaftor/ivacaftor resulted in a statistically significant improvement in $ppFEV_1$ of 10.0 percentage points (95% CI: 7.4, 12.6; $P<0.0001$). Mean improvement in $ppFEV_1$ was observed at the first assessment on Day 15. Improvements in $ppFEV_1$ were observed regardless of age, sex, baseline $ppFEV_1$ and geographic region. See Table 11 for a summary of primary and key secondary outcomes.

Table 11: Primary and Key Secondary Efficacy Analyses, Full Analysis Set (Trial 2)

Analysis*	Statistic	Treatment Difference for TRIKAFTA (N=55) vs Tezacaftor/Ivacaftor# (N=52)
Primary		
Absolute change in $ppFEV_1$ from baseline at Week 4 (percentage points)	Treatment difference (95% CI) *P* value	10.0 (7.4, 12.6) *P*<0.0001
Key Secondary		
Absolute change in sweat chloride from baseline at Week 4 (mmol/L)	Treatment difference (95% CI) *P* value	-45.1 (-50.1, -40.1) *P*<0.0001
Absolute change in CFQ-R respiratory domain score from baseline at Week 4 (points)	Treatment difference (95% CI) *P* value	17.4 (11.8, 23.0) *P*<0.0001

$ppFEV_1$: percent predicted Forced Expiratory Volume in 1 second; CI: Confidence Interval; CFQ-R: Cystic Fibrosis Questionnaire-Revised.
* Baseline for primary and key secondary endpoints is defined as the end of the 4-week tezacaftor/ivacaftor run-in period.
# Regimen of tezacaftor 100 mg qd/ivacaftor 150 mg q12h.

16 HOW SUPPLIED/STORAGE AND HANDLING

TRIKAFTA tablets are supplied in a co-packaged blister pack sealed into a printed wallet, containing elexacaftor, tezacaftor and ivacaftor fixed-dose combination tablets and ivacaftor tablets. Four such wallets are placed in a printed outer carton.

- The elexacaftor 50 mg, tezacaftor 25 mg, and ivacaftor 37.5 mg tablets are supplied as light orange, capsule-shaped tablets; each containing 50 mg of elexacaftor, 25 mg of tezacaftor and 37.5 mg of ivacaftor. Each tablet is debossed with "T50" on one side and plain on the other. Ivacaftor 75 mg tablets are supplied as light blue, film-coated, capsule-shaped tablets; each containing 75 mg of ivacaftor. Each tablet is printed with the characters "V 75" in black ink on one side and plain on the other. TRIKAFTA is supplied as:

  84-count tablet carton **NDC** 51167-106-02
  (4 wallets, each wallet containing 14 tablets of elexacaftor, tezacaftor and ivacaftor and 7 tablets of ivacaftor)

- The elexacaftor 100 mg, tezacaftor 50 mg, and ivacaftor 75 mg tablets are supplied as orange, capsule-shaped tablets; each containing 100 mg of elexacaftor, 50 mg of tezacaftor and 75 mg of ivacaftor. Each tablet is debossed with "T100" on one side and plain on the other. Ivacaftor 150 mg tablets are supplied as light blue, film-coated, capsule-shaped tablets; each containing 150 mg of ivacaftor. Each tablet is printed with the characters "V 150" in black ink on one side and plain on the other. TRIKAFTA is supplied as:

  84-count tablet carton **NDC** 51167-331-01
  (4 wallets, each wallet containing 14 tablets of elexacaftor, tezacaftor and ivacaftor and 7 tablets of ivacaftor)

TRIKAFTA oral granules are supplied in morning and evening unit-dose packets. The morning dose packets contain a fixed-dose combination of elexacaftor, tezacaftor, and ivacaftor oral granules. The evening dose packets contain ivacaftor oral granules. The packets are placed into a printed wallet. Four such wallets are placed in a printed outer carton.

- The elexacaftor 80 mg, tezacaftor 40 mg and ivacaftor 60 mg oral granules are supplied as white to off-white, sweetened, unflavored granules approximately 2 mm in diameter enclosed in unit-dose packets each containing 80 mg of elexacaftor, 40 mg of tezacaftor and 60 mg of ivacaftor. The packets are white and blue. The ivacaftor 59.5 mg oral granules are supplied as white to off-white, sweetened, unflavored granules approximately 2 mm in diameter enclosed in unit-dose packets each containing 59.5 mg of ivacaftor. The packets are white and green. TRIKAFTA is supplied as:

  56-count packet carton **NDC** 51167-445-01
  (4 wallets, each containing 7 packets of elexacaftor, tezacaftor, and ivacaftor and 7 packets of ivacaftor)

- The elexacaftor 100 mg, tezacaftor 50 mg and ivacaftor 75 mg oral granules are supplied as white to off-white, sweetened, unflavored granules approximately 2 mm in diameter enclosed in unit-dose packets each containing 100 mg of elexacaftor, 50 mg of tezacaftor and 75 mg of ivacaftor. The packets are white and orange. The ivacaftor 75 mg oral granules are supplied as white to off-white, sweetened, unflavored granules approximately 2 mm in diameter enclosed in unit-dose packets each containing 75 mg of ivacaftor. The packets are white and pink. TRIKAFTA is supplied as:

  56-count packet carton **NDC** 51167-446-01
  (4 wallets, each containing 7 packets of elexacaftor, tezacaftor, and ivacaftor and 7 packets of ivacaftor)

Store at 20ºC - 25ºC (68ºF - 77ºF); excursions permitted to 15ºC - 30ºC (59ºF - 86ºF) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Elevated Transaminases and Hepatic Injury

Inform the patients that liver failure leading to transplantation has been reported in a patient with cirrhosis with portal hypertension while receiving TRIKAFTA. Avoid use of TRIKAFTA in patients with pre-existing advanced liver disease (e.g., cirrhosis, portal hypertension, ascites, hepatic encephalopathy) unless the benefits are expected to outweigh the risks. If used in these patients, they should be closely monitored after the initiation of treatment *[see Dosage and Administration (2.2), Warnings and Precautions (5.1), Adverse Reactions (6), Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

Inform patients that isolated elevation of transaminases or bilirubin have occurred in patients treated with TRIKAFTA. In some instances, transaminase elevations have been associated with concomitant elevations in total bilirubin and/or INR and have resulted in patients being hospitalized for intervention, including in patients without a history of pre-existing liver disease. Liver function tests (ALT, AST and bilirubin) should be assessed prior to initiating TRIKAFTA, every 3 months during the first year of treatment, and annually thereafter. More frequent monitoring should be considered in patients with a history of hepatobiliary disease or liver function test elevations *[see Dosage and Administration (2.2), Warnings and Precautions (5.1), Adverse Reactions (6), Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

Drug Interactions with CYP3A Inducers and Inhibitors

Ask patients to tell you all the medications they are taking including any herbal supplements or vitamins. Co-administration of TRIKAFTA with strong CYP3A inducers (e.g., rifampin, St. John's wort) is not recommended, as they may reduce the efficacy of TRIKAFTA. Dose reduction to two elexacaftor/tezacaftor/ivacaftor tablets or one elexacaftor/tezacaftor/ivacaftor oral granules packet twice a week, taken approximately 3 to 4 days apart is recommended when co-administered with strong CYP3A inhibitors, such as ketoconazole. Advise the patient not to take the evening dose of ivacaftor. Dose reduction to two elexacaftor/tezacaftor/ivacaftor tablets or one elexacaftor/tezacaftor/ivacaftor oral granules packet and one ivacaftor tablet or ivacaftor oral granules packet, taken on alternate days, is recommended when co-administered with moderate CYP3A inhibitors, such as fluconazole. Advise the patient not to take the evening dose of ivacaftor. Food or drink containing grapefruit should be avoided *[see Dosage and Administration (2.3), Warnings and Precautions (5), Drug Interactions (7) and Clinical Pharmacology (12.3)]*.

Use in Patients with Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh Class A, score 5-6). See Table 2. Liver function tests should be closely monitored.

Treatment is not recommended for patients with moderate hepatic impairment (Child-Pugh Class B, score 7-9). Use of TRIKAFTA in patients with moderate hepatic impairment should only be considered when there is a clear medical need, and the benefit exceeds the risk. If used in patients with moderate hepatic impairment, TRIKAFTA should be used with caution at a reduced dose (see Table 2). Liver function tests should be closely monitored.

TRIKAFTA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C, score 10-15), but the exposure is expected to be higher than in patients with moderate hepatic impairment. TRIKAFTA should not be used in patients with severe hepatic impairment. Inquire and/or assess whether patients have liver impairment *[see Dosage and Administration (2.2), Warnings and Precautions (5.1), Adverse Reactions (6), Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

Cataracts

Inform patients that abnormality of the eye lens (cataract) has been noted in some children and adolescents receiving ivacaftor-containing regimens. Baseline and follow-up ophthalmological examinations should be performed in pediatric patients initiating treatment with TRIKAFTA *[see Warnings and Precautions (5.4) and Use in Specific Populations (8.4)]*.

Administration

Inform patients that TRIKAFTA is best absorbed by the body when taken with food that contains fat. A typical CF diet will satisfy this requirement. Examples include eggs, butter, peanut butter, whole-milk dairy products (such as whole milk, cheese and yogurt), etc. *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3)]*.

Patients should be informed about what to do in the event they miss a dose *[see Dosage and Administration (2.4)]* of TRIKAFTA:

- If 6 hours or less have passed since the missed morning or evening dose is usually taken, patients should be instructed to take the prescribed dose with fat-containing food as soon as possible.
- If more than 6 hours have passed since:

  - the time the morning dose is usually taken, patients should be instructed to take the morning dose as soon as possible, and not take the evening dose. Patients should take the next scheduled morning dose at the usual time.
  - the time the evening dose is usually taken, patients should be instructed to not take the missed evening dose. Patients should take the next scheduled morning dose at the usual time.
- Patients should be instructed to not take the morning and evening doses at the same time.
- Patients should be advised to contact their health care provider if they have questions.

Manufactured for
Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA 02210

Approved April 2023

Patient Information

TRIKAFTA® (tri-KAF-tuh)

(elexacaftor, tezacaftor, and ivacaftor tablets; ivacaftor tablets), co-packaged for oral use
(elexacaftor, tezacaftor, and ivacaftor oral granules; ivacaftor oral granules), co-packaged

What is TRIKAFTA?

- TRIKAFTA is a prescription medicine used for the treatment of cystic fibrosis (CF) in people aged 2 years and older who have at least one copy of the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene or another mutation that is responsive to treatment with TRIKAFTA.
- Talk to your doctor to learn if you have an indicated CF gene mutation.

It is not known if TRIKAFTA is safe and effective in children under 2 years of age.

Before taking TRIKAFTA, tell your doctor about all of your medical conditions, including if you:

- have kidney problems.
- have or have had liver problems.
- are pregnant or plan to become pregnant. It is not known if TRIKAFTA will harm your unborn baby. You and your doctor should decide if you will take TRIKAFTA while you are pregnant.
- are breastfeeding or planning to breastfeed. It is not known if TRIKAFTA passes into your breast milk. You and your doctor should decide if you will take TRIKAFTA while you are breastfeeding.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

TRIKAFTA may affect the way other medicines work and other medicines may affect how TRIKAFTA works. The dose of TRIKAFTA may need to be adjusted when taken with certain medicines. Ask your doctor or pharmacist for a list of these medicines if you are not sure.

Especially tell your doctor if you take:

- antibiotics such as rifampin (RIFAMATE®, RIFATER®) or rifabutin (MYCOBUTIN®)
- seizure medicines such as phenobarbital, carbamazepine (TEGRETOL®, CARBATROL®, EQUETRO®), or phenytoin (DILANTIN®, PHENYTEK®)
- St. John's wort
- antifungal medicines including ketoconazole, itraconazole (such as SPORANOX®), posaconazole (such as NOXAFIL®), voriconazole (such as VFEND®), or fluconazole (such as DIFLUCAN®).
- antibiotics including telithromycin, clarithromycin (such as BIAXIN®), or erythromycin (such as ERY-TAB®).

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take TRIKAFTA?

- Take TRIKAFTA exactly as your doctor tells you to take it.
- Take TRIKAFTA by mouth only.
- TRIKAFTA consists of 2 different doses (a morning dose and an evening dose). Each dose has different ingredients.
- **Always take TRIKAFTA oral granules or tablets with food that contains fat**. Examples of fat-containing foods include butter, oil, eggs, peanut butter, nuts, meat, and whole-milk dairy products such as whole milk, cheese, and yogurt.
- TRIKAFTA oral granules (age 2 to less than 6 years weighing less than 14 kg):
  - The white and blue packets each contain the medicines elexacaftor, tezacaftor, and ivacaftor. Take one morning dose packet in the morning.
  - The white and green color packets each contain the medicine ivacaftor. Take one evening dose packet in the evening.
- TRIKAFTA oral granules (age 2 to less than 6 years weighing 14 kg or more):
  - The white and orange packets each contain the medicines elexacaftor, tezacaftor, and ivacaftor. Take one morning dose packet in the morning.
  - The white and pink color packets each contain the medicine ivacaftor. Take one evening dose packet in the evening.
- To prepare TRIKAFTA oral granules:
  - Hold the packet with the cut line on top.
  - Shake the packet gently to settle the TRIKAFTA oral granules.

- Tear or cut the packet open along the cut line.
- Carefully pour all the TRIKAFTA oral granules in the packet into 1 teaspoon (5 mL) of soft food or liquid in a small container (like an empty bowl). The food or liquid should be at or below room temperature. Some examples of soft foods or liquids include pureed fruits or vegetables, yogurt, applesauce, water, milk, or juice.
- Mix the TRIKAFTA granules with food or liquid.
- After mixing, give TRIKAFTA within 1 hour. Make sure all the medicine is taken.

- TRIKAFTA tablets (age 6 to less than 12 years weighing less than 30 kg):
  - The light orange tablet is marked with 'T50' and each tablet contains the medicines elexacaftor, tezacaftor and ivacaftor. Take 2 light orange tablets in the morning.
  - The light blue tablet is marked with 'V 75' and contains the medicine ivacaftor. Take 1 light blue tablet in the evening.
- TRIKAFTA tablets (age 6 to less than 12 years weighing 30 kg or more, and age 12 years and older):
  - The orange tablet is marked with 'T100' and each tablet contains the medicines elexacaftor, tezacaftor and ivacaftor. Take 2 orange tablets in the morning.
  - The light blue tablet is marked with 'V 150' and contains the medicine ivacaftor. Take 1 light blue tablet in the evening.
- Take TRIKAFTA tablets whole.
- Take the morning and the evening doses about **12** hours apart.
- If you miss a dose of TRIKAFTA and:
  - it is **6 hours or less** from the time you usually take the morning dose or the evening dose, **take the missed dose** with food that contains fat as soon as you can. Then take your next dose at your usual time.
  - it is **more than 6 hours** from the time you usually take the morning dose, **take the missed dose** with food that contains fat as soon as you can. **Do not take the evening dose**.
  - it is **more than 6 hours** from the time you usually take the evening dose, **do not take the missed dose**. Take your next morning dose at the usual time with food that contains fat.
  - **Do not** take more than your usual dose of TRIKAFTA to make up for a missed dose.
  - **Do not** take the morning and evening doses at the same time.
  - If you are not sure about your dosing, call your doctor.

What should I avoid while taking TRIKAFTA?

- Avoid food or drink that contains grapefruit while you are taking TRIKAFTA.

What are the possible side effects of TRIKAFTA?

TRIKAFTA can cause serious side effects, including:

- **Liver damage and worsening liver function** in people with severe liver disease that can be serious and may require transplantation. Liver damage has also happened in people without liver disease.
  High liver enzymes in the blood is a common side effect in people treated with TRIKAFTA. These can be serious and may be a sign of liver injury. Your doctor will do blood tests to check your liver:
  - before you start TRIKAFTA
  - every 3 months during your first year of taking TRIKAFTA
  - then every year while you are taking TRIKAFTA

  Your doctor may do blood tests to check the liver more often if you have had high liver enzymes in your blood in the past.

  Call your doctor right away if you have any of the following symptoms of liver problems:
  - pain or discomfort in the upper right stomach (abdominal) area
  - yellowing of your skin or the white part of your eyes
  - loss of appetite
  - nausea or vomiting
  - dark, amber-colored urine

- **Abnormality of the eye lens (cataract)** has happened in some children and adolescents treated with TRIKAFTA. If you are a child or adolescent, your doctor should perform eye examinations before and during treatment with TRIKAFTA to look for cataracts.

The most common side effects of TRIKAFTA include:

- headache
- upper respiratory tract infection (common cold) including stuffy and runny nose
- stomach (abdominal) pain
- diarrhea
- increase in liver enzymes
- increase in a certain blood enzyme called creatine phosphokinase
- flu (influenza)
- inflamed sinuses

- rash
- increase in blood bilirubin

Tell your doctor if you have any side effect that bothers you or that does not go away.
These are not all the possible side effects of TRIKAFTA. For more information, ask your doctor or pharmacist.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TRIKAFTA?

- Store TRIKAFTA at room temperature between 68ºF to 77ºF (20ºC to 25ºC).

Keep TRIKAFTA and all medicines out of the reach of children.

General information about the safe and effective use of TRIKAFTA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use TRIKAFTA for a condition for which it was not prescribed. Do not give TRIKAFTA to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or doctor for information about TRIKAFTA that is written for health professionals.

What are the ingredients in TRIKAFTA?

Elexacaftor/tezacaftor/ivacaftor tablets:
Active ingredients: elexacaftor, tezacaftor and ivacaftor.
Inactive ingredients: croscarmellose sodium, hypromellose, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate. The tablet film coat contains hydroxypropyl cellulose, hypromellose, iron oxide red, iron oxide yellow, talc, and titanium dioxide.

Ivacaftor tablets:
Active ingredients: ivacaftor.
Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate.
The tablet film coat contains carnauba wax, FD&C Blue #2, PEG 3350, polyvinyl alcohol, talc, and titanium oxide.
The printing ink contains ammonium hydroxide, iron oxide black, propylene glycol, and shellac.

Elexacaftor/tezacaftor/ivacaftor oral granules:
Active ingredients: elexacaftor, tezacaftor, and ivacaftor.
Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, mannitol, sodium lauryl sulfate, and sucralose.

Ivacaftor oral granules:
Active ingredients: ivacaftor.
Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, mannitol, sodium lauryl sulfate, and sucralose.

VERTEX

Manufactured for: Vertex Pharmaceuticals Incorporated; 50 Northern Avenue, Boston, MA 02210

For more information, go to www.trikafta.com or call 1-877-752-5933.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 04/2023