TRIKAFTA®–

APPROVED TO TREAT **EVEN MORE PATIENTS** WITHOUT AN *F508del* MUTATION[1]

Jason has taken TRIKAFTA and was compensated for his participation.

A breakthrough treatment available for patients with cystic fibrosis (CF) aged 2 years and older[1,2]

INDICATIONS AND USAGE

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.

If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one indicated mutation.

trikafta®

(elexacaftor/tezacaftor/ivacaftor and ivacaftor)

100 mg/50 mg/75 mg and 150 mg tablets
50 mg/25 mg/37.5 mg and 75 mg tablets
100 mg/50 mg/75 mg and 75 mg oral granules
80 mg/40 mg/60 mg and 59.5 mg oral granules

IMPORTANT SAFETY INFORMATION

WARNING: DRUG-INDUCED LIVER INJURY AND LIVER FAILURE

TRIKAFTA can cause serious and potentially fatal drug-induced liver injury. Cases of liver failure leading to transplantation and death have been reported in patients with and without a history of liver disease taking TRIKAFTA, in both clinical trials and the postmarketing setting. Liver injury has been reported within the first month of therapy and up to 15 months following initiation of TRIKAFTA.

Assess liver function tests (ALT, AST, alkaline phosphatase, and bilirubin) in all patients prior to initiating TRIKAFTA, then every month during the first 6 months of treatment, every 3 months for the next 12 months, and at least annually thereafter. Consider more frequent monitoring for patients with a history of liver disease or liver function test (LFT) elevations at baseline.

Interrupt TRIKAFTA for significant elevations in LFTs or in the event of signs or symptoms of liver injury. Consider referral to a hepatologist. Follow patients closely with clinical and laboratory monitoring until abnormalities resolve. If resolved, resume treatment only if benefit is expected to outweigh risk. Closer monitoring is advised after resuming TRIKAFTA.

TRIKAFTA should not be used in patients with severe hepatic impairment (Child-Pugh Class C). TRIKAFTA is not recommended in patients with moderate hepatic impairment (Child-Pugh Class B). If used, use with caution at a reduced dosage and monitor patients closely.

CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator.

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WARNINGS AND PRECAUTIONS

Drug-Induced Liver Injury and Liver Failure

- TRIKAFTA can cause serious and potentially fatal drug-induced liver injury. Liver failure leading to transplantation and death has been reported in patients with and without a history of liver disease taking TRIKAFTA. Liver injury has been reported within the first month of therapy and up to 15 months following initiation of TRIKAFTA
- Assess LFTs (ALT, AST, alkaline phosphatase, and bilirubin) in all patients prior to initiating TRIKAFTA, then every month during the first 6 months of treatment, every 3 months for the next 12 months, and at least annually thereafter. Consider more frequent monitoring for patients with a history of liver disease or LFT elevations at baseline
- Interrupt TRIKAFTA in the event of signs or symptoms of liver injury, which may include:
  - Significant elevations in LFTs (e.g., ALT or AST >5× the upper limit of normal (ULN) or ALT or AST >3× ULN with bilirubin >2× ULN)
  - Clinical symptoms suggestive of liver injury (e.g., jaundice, right upper quadrant pain, nausea, vomiting, altered mental status, ascites)

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IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

Drug-Induced Liver Injury and Liver Failure (cont'd)

- Consider referral to a hepatologist and follow patients closely with clinical and laboratory monitoring until abnormalities resolve. If resolved, and if benefit is expected to outweigh risk, resume TRIKAFTA with close monitoring
- TRIKAFTA should not be used in patients with severe hepatic impairment. TRIKAFTA is not recommended in patients with moderate hepatic impairment and should only be considered when there is a clear medical need and benefit outweighs risk. If used, use with caution at a reduced dosage and monitor patients closely

Hypersensitivity Reactions, Including Anaphylaxis

- Hypersensitivity reactions, including cases of angioedema and anaphylaxis, have been reported in the postmarketing setting. If signs or symptoms of serious hypersensitivity reactions develop during treatment, discontinue TRIKAFTA and institute appropriate therapy. Consider benefits and risks for the individual patient to determine whether to resume treatment with TRIKAFTA

Concomitant Use With CYP3A Inducers

- Exposure to ivacaftor is significantly decreased and exposure to elexacaftor and tezacaftor are expected to decrease by concomitant use of strong CYP3A inducers, which may reduce the therapeutic effectiveness of TRIKAFTA. Concomitant use with strong CYP3A inducers is not recommended

Concomitant Use With CYP3A Inhibitors

- Exposure to elexacaftor, tezacaftor, and ivacaftor are increased when used concomitantly with strong or moderate CYP3A inhibitors. The dose of TRIKAFTA should be reduced when used concomitantly with moderate or strong CYP3A inhibitors

Cataracts

- Non-congenital lens opacities have been reported in pediatric patients treated with ivacaftor-containing regimens. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with TRIKAFTA

ADVERSE REACTIONS

Serious Adverse Reactions

- Serious adverse reactions that occurred more frequently in patients treated with TRIKAFTA compared to placebo were rash (1% vs <1%) and influenza (1% vs 0%)

Most Common Adverse Reactions

- The most common adverse reactions occurring in ≥5% of patients treated with TRIKAFTA and higher than placebo by ≥1% were headache, upper respiratory tract infection, abdominal pain, diarrhea, rash, alanine aminotransferase increased, nasal congestion, blood creatine phosphokinase increased, aspartate aminotransferase increased, rhinorrhea, rhinitis, influenza, sinusitis, blood bilirubin increased and constipation

USE IN SPECIFIC POPULATIONS

Pediatric Use

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

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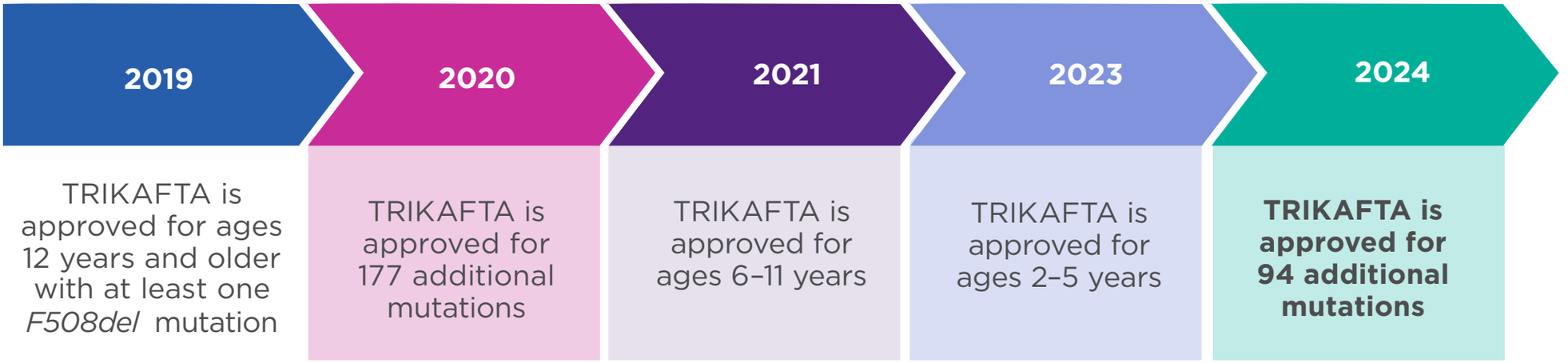
More patients continue to become eligible for TRIKAFTA[1,3]

272 mutations are approved for TRIKAFTA



Since 2020, patients have not needed an *F508del* mutation to be eligible for TRIKAFTA

We continue to conduct research and development with the goal of bringing treatment to all patients with CF

CLICK HERE TO CHECK PATIENT ELIGIBILITY BASED ON AGE AND MUTATIONS
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INDICATIONS AND USAGE

TRIKAFTA is a combination of ivacaftor, a CFTR potentiator, tezacaftor, and elexacaftor indicated for the treatment of cystic fibrosis (CF) in patients aged 2 years and older who have at least one F508del mutation in the CFTR gene or a mutation in the CFTR gene that is responsive based on clinical and/or in vitro data.

If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one indicated mutation.

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Non-*F508del* mutations approved for TRIKAFTA are supported by clinical response and/or *in vitro* data or based on extrapolation of efficacy[1]

Trial 5 is the first randomized controlled clinical trial demonstrating efficacy and safety of TRIKAFTA in patients without a *F508del* mutation[1]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Drug-Induced Liver Injury and Liver Failure

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- Assess LFTs (ALT, AST, alkaline phosphatase, and bilirubin) in all patients prior to initiating TRIKAFTA, then every month during the first 6 months of treatment, every 3 months for the next 12 months, and at least annually thereafter. Consider more frequent monitoring for patients with a history of liver disease or LFT elevations at baseline
- Interrupt TRIKAFTA in the event of signs or symptoms of liver injury, which may include:
  - Significant elevations in LFTs (e.g., ALT or AST >5× the upper limit of normal (ULN) or ALT or AST >3× ULN with bilirubin >2× ULN)
  - Clinical symptoms suggestive of liver injury (e.g., jaundice, right upper quadrant pain, nausea, vomiting, altered mental status, ascites)
- Consider referral to a hepatologist and follow patients closely with clinical and laboratory monitoring until abnormalities resolve. If resolved, and if benefit is expected to outweigh risk, resume TRIKAFTA with close monitoring
- TRIKAFTA should not be used in patients with severe hepatic impairment. TRIKAFTA is not recommended in patients with moderate hepatic impairment and should only be considered when there is a clear medical need and benefit outweighs risk. If used, use with caution at a reduced dosage and monitor patients closely

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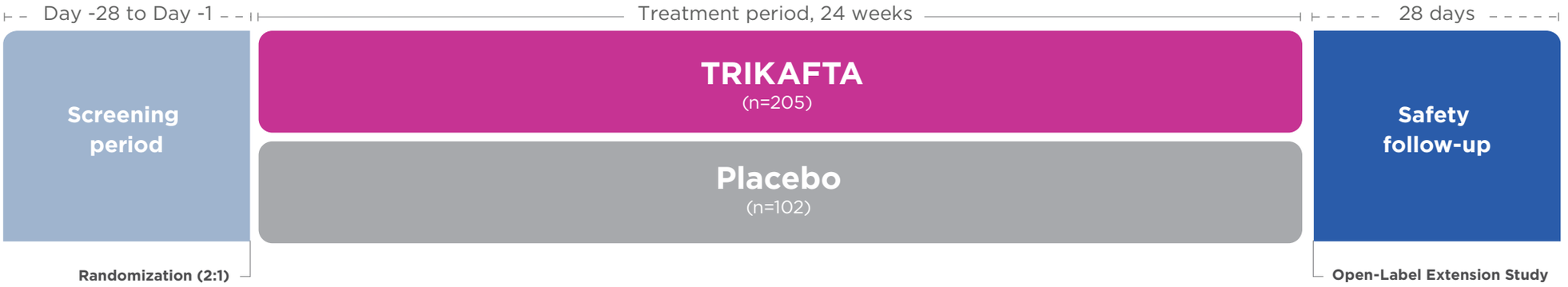
A phase 3 randomized, placebo-controlled trial in patients with CF aged 6+ years with at least 1 of 18 qualifying non-*F508del* mutations responsive to TRIKAFTA[1,4]



Phase 3, randomized, double-blind, placebo-controlled study

KEY INCLUSION CRITERIA

- Aged 6+ years with at least 1 of 18 qualifying non-*F508del* mutations responsive to TRIKAFTA.[a,b] Eligible mutations included 15 previously approved mutations responsive to TRIKAFTA, as well as 3 noncanonical splice mutations

PRIMARY ENDPOINT

- Absolute change from baseline in ppFEV$_1$ through Week 24

SELECT SECONDARY ENDPOINTS

- Absolute change from baseline through Week 24 in sweat chloride
- Absolute change from baseline through Week 24 in CFQ-R Respiratory Domain score
- Absolute change from baseline at Week 24 in BMI
- Number of pulmonary exacerbations through Week 24
- Safety and tolerability as determined by adverse events, clinical laboratory assessments, ECGs, vital signs, and pulse oximetry

[a]FRT-responsive mutations included: *P5L, R117C, L206W, V232D, T338I, R347H, A455E, S945L, L997F, R1066H, D1152H, G85E, R347P, L1077P,* and *M1101K.* Noncanonical splice mutations included: *2789+5G>A, 3272-26A>G,* and *3849+10kbC>T.*

[b]Excluded mutations were *F508del, R117H, G178R, S549N, S549R, G551D, G551S, G1244E, S1251N, S1255P, G1349D.*

BMI, body mass index; CFQ-R, Cystic Fibrosis Questionnaire Revised; ECG, electrocardiogram; ppFEV$_1$, percent predicted forced expiratory volume in 1 second.

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Select baseline characteristics for patients enrolled in Trial 5[4]

	TRIKAFTA (n=205)	Placebo (n=102)
Sex, n (%)		
Male	92 (44.9)	50 (49.0)
Female	113 (55.1)	52 (51.0)
Baseline age group, n (%)		
≥6 to <12 years	23 (11.2)	8 (7.8)
≥12 to <18 years	21 (10.2)	12 (11.8)
≥18 years	161 (78.5)	82 (80.4)
Baseline age (years), mean (SD)	33.3 (15.9)	33.9 (16.4)
Baseline ppFEV$_1$, mean (SD)	67.5 (17.6)	68.1 (18.1)
Baseline sweat chloride (mmol/L), mean (SD)[a]	79.5 (26.9)	75.2 (28.7)
Baseline CFQ-R RD, mean (SD)[b]	64.1 (20.7)	65.8 (21.3)
Baseline BMI (kg/m^2), mean (SD)	22.45 (4.60)	22.48 (4.16)
Weight (kg), mean (SD)	61.9 (18.5)	63.2 (16.7)

[a]TRIKAFTA, n=202 and placebo, n=100
[b]TRIKAFTA, n=202 and placebo, n=102

CFQ-R RD, Cystic Fibrosis Questionnaire-Revised Respiratory Domain

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TRIKAFTA demonstrated benefits versus placebo in patients with CF aged 6 years and older with at least 1 of 18 qualifying non-*F508del* responsive mutations[1]

Primary endpoints	
Improvements of lung function[1]	9.2 % points — Mean absolute change from baseline in ppFEV$_1$ through Week 24 (95% CI: 7.2, 11.3; *P*<0.0001)
Select secondary endpoints	
Reductions in sweat chloride concentration[1]	28.3 mmol/L — Mean absolute change from baseline in sweat chloride concentration through Week 24 (95% CI: -32.1, -24.5; *P*<0.0001)
Improvements in CFQ-R Respiratory Domain score[1]	19.5 points — Mean absolute change from baseline in CFQ-R Respiratory Domain score through Week 24 (95% CI: 15.5, 23.5; *P*<0.0001)
Improvements in BMI[1]	0.47 kg/m^2 — Mean absolute change from baseline in BMI at Week 24 (95% CI: 0.24, 0.69; *P*<0.0001)
Reductions in pulmonary exacerbations[1,4]	72% reduction — Estimated pulmonary exacerbation event rate per year[a] of 0.63 for placebo vs 0.17 for TRIKAFTA (95% CI: 0.15, 0.51; *P*<0.0001) (Rate ratio of 0.28)[b]
Safety and tolerability profile[1,4]	Treatment was generally consistent with the established profile of TRIKAFTA

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

Concomitant Use With CYP3A Inducers

- Exposure to ivacaftor is significantly decreased and exposure to elexacaftor and tezacaftor are expected to decrease by concomitant use of strong CYP3A inducers, which may reduce therapeutic effectiveness of TRIKAFTA. Concomitant use with strong CYP3A inducers is not recommended

[a]For analysis purposes, 1 year was defined as 48 weeks or 336 days.[1]
[b]Pulmonary exacerbation data is based on number of pulmonary exacerbations through Week 24.[1]

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Safety profile in patients with non-*F508del* mutations was generally similar to prior experience with TRIKAFTA[1,4]

Discontinuations and serious adverse events (SAEs)[4]:

- 5 patients (2.4%) experienced adverse events leading to discontinuation vs 0 with placebo
- 18 patients (8.8%) experienced SAEs vs 15 (14.7%) with placebo; 2/205 (1%) in the TRIKAFTA arm were deemed related to study drug vs 0 with placebo[a]
- 1 patient (0.5%) experienced an adverse event leading to death, which was determined to be unrelated to the study drug, vs 0 with placebo

Most frequent treatment-emergent adverse events (≥5% either arm)[5]

	TRIKAFTA n (%) (n=205)	**Placebo** n (%) (n=102)
Rash	45 (22.0)	1 (1.0)
Nasopharyngitis	42 (20.5)	20 (19.6)
Headache	37 (18.0)	13 (12.7)
Cough	36 (17.6)	26 (25.5)
Infective pulmonary exacerbation of CF	31 (15.1)	37 (36.3)
Pyrexia	27 (13.2)	14 (13.7)
Diarrhea	26 (12.7)	10 (9.8)
Rhinitis	20 (9.8)	6 (5.9)
Sputum increased	20 (9.8)	13 (12.7)
COVID-19	19 (9.3)	10 (9.8)
Influenza	18 (8.8)	2 (2.0)
Abdominal pain	17 (8.3)	13 (12.7)
Oropharyngeal pain	17 (8.3)	10 (9.8)
Upper respiratory tract infection	17 (8.3)	10 (9.8)
Constipation	15 (7.3)	4 (3.9)
Vomiting	15 (7.3)	7 (6.9)
Hemoptysis	12 (5.9)	6 (5.9)
Abdominal pain upper	10 (4.9)	7 (6.9)
Nasal congestion	6 (2.9)	8 (7.8)
Productive cough	6 (2.9)	6 (5.9)

[a]One patient experienced maculopapular rash, while 1 patient experienced subileus.[5]

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The adverse event profile was generally similar to previous clinical trials with TRIKAFTA[1,4]

Incidence of maximum transaminase elevations[5]		TRIKAFTA n (%) (n=205)	Placebo n (%) (n=102)
Elevated ALT or AST, n (%)	>3x ULN	13 (6.3)	0
	>5x ULN	4 (2.0)	0
	>8x ULN	4 (2.0)	0
Elevated ALT and/or AST leading to treatment discontinuation		1 (0.5)	0
Elevated ALT and/or AST leading to treatment interruption		3 (1.5)	0

Rash events[1,5]

- The majority of rash events were mild to moderate in severity. The incidence of rash was higher in female patients (27%) than in male patients treated with TRIKAFTA (20%). A role of hormonal contraceptives in the occurrence of rash cannot be excluded
- 15 patients on TRIKAFTA (7.3%) interrupted and 1 patient (0.5%) in the TRIKAFTA arm discontinued due to a serious adverse event of rash considered related to study drug
- Median time-to-onset of first rash was 11 days (mean: 25 days) in the TRIKAFTA arm and 57 days (mean: 78 days) in the placebo arm. Median duration was 9.5 days (mean: 15.3 days) in the TRIKAFTA arm and 37 days (mean: 33 days) in the placebo arm

Creatine phosphokinase[1,5]

- The incidence of maximum CPK >5× ULN was 5.4% (11/205) in patients on TRIKAFTA vs. 1.0% (1/102) on placebo
- The incidence of maximum CPK >10x ULN was 2.4% (5/205) in patients on TRIKAFTA vs 1.0% (1/102) on placebo
- Among the patients treated with TRIKAFTA with creatine phosphokinase elevation >10x ULN, two patients, who had exercised within the preceding 72 hours, developed rhabdomyolysis without evidence of renal involvement, resulting in treatment interruption in 1 patient

Blood pressure[5]

- 5 patients (2.4%) on TRIKAFTA had hypertension-related adverse events vs 1 patient (1%) on placebo; no events were serious or required change to study drug dosing
- Mean systolic and diastolic blood pressure increases from baseline at Week 24 were 1.2 and 1.3 mm Hg in patients on TRIKAFTA vs 2.1 and 0.1 mm Hg on placebo, respectively

There were no other notable findings from vital sign assessments[5]

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; ECG, electrocardiogram; ULN, upper limit of normal.

Summary of safety and efficacy results for Trial 5

Safety findings through Week 24[4]

- Treatment with TRIKAFTA was generally consistent with the established safety profile
- Please click here for the safety profile for patients aged 6 years and older in Trial 5

Benefits compared with baseline across all endpoints studied[4]

- $ppFEV_1$
- Sweat chloride
- CFQ-R Respiratory Domain score
- BMI
- Number of pulmonary exacerbations

BENEFITS WERE OBSERVED OVER 24 WEEKS ACROSS MULTIPLE ENDPOINTS IN A CLINICAL SETTING FOR PATIENTS WITH NON-*F508del* MUTATIONS

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

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References: 1. TRIKAFTA [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; December 2024. **2.** Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. REF-4142 (v1.0); 2019. **3.** Drugs@FDA database. Available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm. Accessed February 1, 2025. **4.** Castellani C, Mondejar-Lopez P, Quon BS, et al. Efficacy and safety of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) in people with cystic fibrosis and ELX/TEZ/IVA-responsive, non-*F508del* genotypes: A phase 3, randomised, placebo-controlled trial. Presented at: 47th European Cystic Fibrosis Conference; June 5-8, 2024; Glasgow, UK. **5.** Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. REF-25740 (v3.0); 2024.

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