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

A **BREAKTHROUGH** TREATMENT THAT PROVIDES SUSTAINED BENEFITS FOR **PEDIATRIC PATIENTS AS YOUNG AS 2 YEARS**[1,2]

Modify the course of disease for patients as young as 2 years of age who are eligible for TRIKAFTA[1,3]

Clayton, 5
F508del/G542X

People with CF pictured may or may not be taking TRIKAFTA.

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 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 F508del mutation or a mutation that is responsive based on in vitro data.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Elevated Transaminases and Hepatic Injury

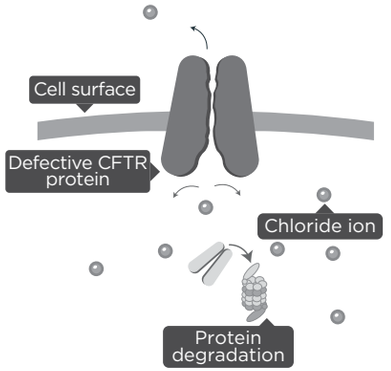
- Liver failure leading to transplantation has been reported in a patient with cirrhosis and portal hypertension while receiving TRIKAFTA. Avoid use of TRIKAFTA in patients with pre-existing advanced liver disease (e.g., as evidenced by cirrhosis, portal hypertension, ascites, hepatic encephalopathy) unless the benefits are expected to outweigh the risks. If used in these patients, they should be closely monitored after the initiation of treatment

CF, cystic fibrosis.

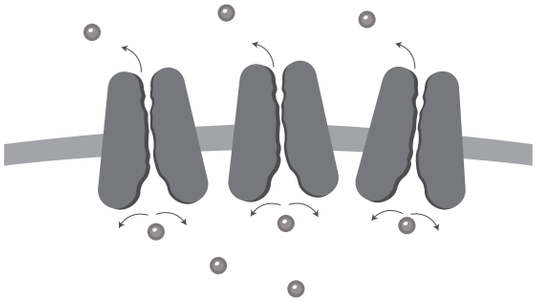
Please click for Important Safety Information and full Prescribing Information for TRIKAFTA.

CF is a systemic, multiorgan disease that is caused by mutations in both CFTR alleles[4]

Overall CFTR function may be decreased by[5]:



and/or



- Impaired cellular processing and trafficking
- Reduced channel-open probability

- This results in abnormal mucociliary clearance and airway inflammation, which leads to progressive lung damage, including mucus plugging, air trapping, airwall thickening, and bronchiectasis[4]

Diagnosing CF [6,7]

- Sweat chloride concentration is the standard for diagnosing CF, and also an important marker of CFTR function
  - Patients whose sweat chloride levels are below 30 mmol/L are unlikely to be diagnosed with CF
  - Those with sweat chloride concentrations equal to or above 60 mmol/L can be diagnosed with the disease

One retrospective analysis of the US CFF Patient Registry showed that sweat chloride concentration at time of CF diagnosis may be associated with clinical outcomes[8]

CFF, Cystic Fibrosis Foundation; CFTR, cystic fibrosis transmembrane conductance regulator.

Evidence of underlying structural and functional lung disease has been detected in children with CF as young as 2 years old, often before signs and symptoms of CF[9]

- Prospective, cross-sectional study aimed to evaluate the potential of MRI to detect abnormal lung structure and perfusion in young children with CF, and to monitor the response to antibiotic therapy for pulmonary exacerbation[9]
- MRI studies were performed in 50 children with CF, 40 of whom were in stable clinical condition[9]
- The MRI scans show wall thickening and/or bronchiectasis (white arrows) and mucus plugging (white arrowheads). Perfusion abnormalities are indicated by black arrowheads[9]
- This study found that approximately 90% (19/21) of the patients aged 2 through 5 years had wall thickening/ bronchiectasis changes found in MRI[9]
- Approximately 95% (20/21) of the patients aged 2 through 5 years also had lung perfusion abnormalities[9]

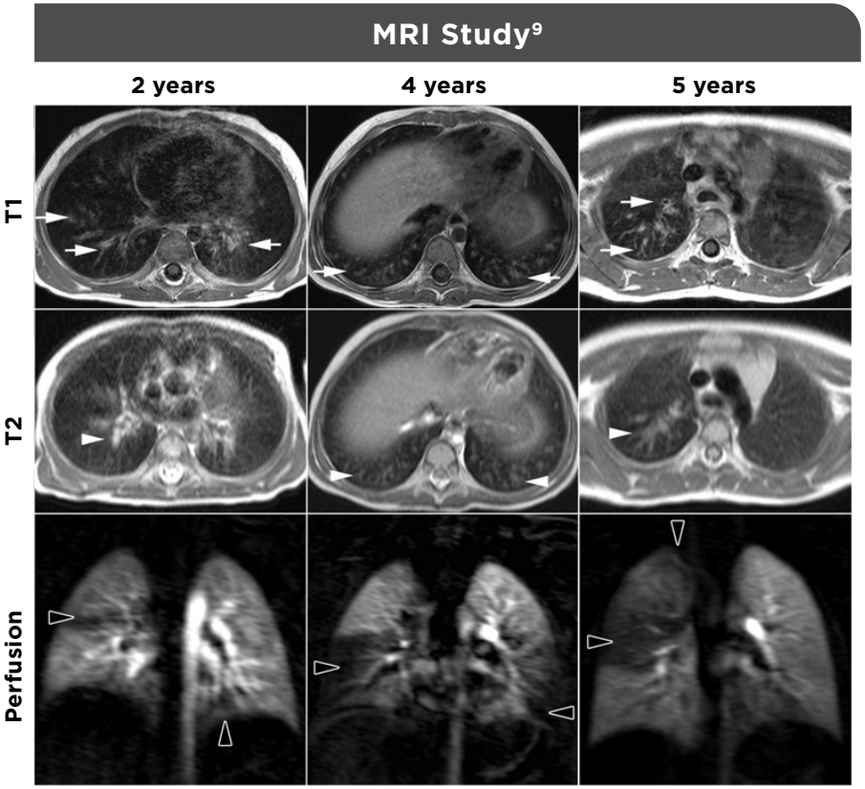


Figure 1 adapted from: Wielpütz MO, et al. Example of structural changes and abnormal perfusion in early CF lung disease detected by MRI. *Am J Respir Crit Care Med*. 2014;189(8):956-965; reprinted with permission.

MRI, magnetic resonance imaging.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Elevated Transaminases and Hepatic Injury

- Liver failure leading to transplantation has been reported in a patient with cirrhosis and portal hypertension while receiving TRIKAFTA. Avoid use of TRIKAFTA in patients with pre-existing advanced liver disease (e.g., as evidenced by 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
- Isolated elevations of transaminases or bilirubin have been observed in patients with CF treated with TRIKAFTA. In some instances, transaminase elevations have been associated with concomitant elevations in total bilirubin and/or international normalized ratio (INR) and have resulted in patients being hospitalized for intervention, including in patients without a history of pre-existing liver disease
- Assessments of liver function tests (ALT, AST, and bilirubin) are recommended prior to initiating TRIKAFTA, every 3 months during the first year of treatment, and annually thereafter
- In the event of significant elevations in liver function tests, e.g. ALT or AST >5x the upper limit of normal (ULN) or ALT or AST >3x ULN with bilirubin >2x ULN, dosing should be interrupted and laboratory tests closely followed until the abnormalities resolve. Following the resolution of liver function test elevations, consider the benefits and risks of resuming treatment
- For patients with a history of hepatobiliary disease or liver function test elevations, more frequent monitoring should be considered

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 the 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 the concomitant use of strong CYP3A inducers, which may reduce the therapeutic effectiveness of TRIKAFTA. Co-administration with strong CYP3A inducers is not recommended

Concomitant Use With CYP3A Inhibitors

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

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

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IMPORTANT SAFETY INFORMATION (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Cataracts

- Cases of 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 (N=202) and higher than placebo (N=201) by ≥1% in the 24-week placebo-controlled, parallel-group Phase 3 trial (Trial 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, and blood bilirubin increased
- The safety profile for the patients with CF receiving TRIKAFTA (N=55) enrolled in the 4-week, randomized, double-blind, active-controlled Phase 3 trial (Trial 2) was similar to that observed in Trial 1
- The safety profile in patients age 6 through 11 years from an open-label trial (Trial 3; N=66) was similar to that observed in Trial 1. The safety profile in patients age 2 through 5 years from an open-label trial (Trial 4; N=75) was similar to that observed in Trial 1

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

People with CF pictured may or may not be taking TRIKAFTA.

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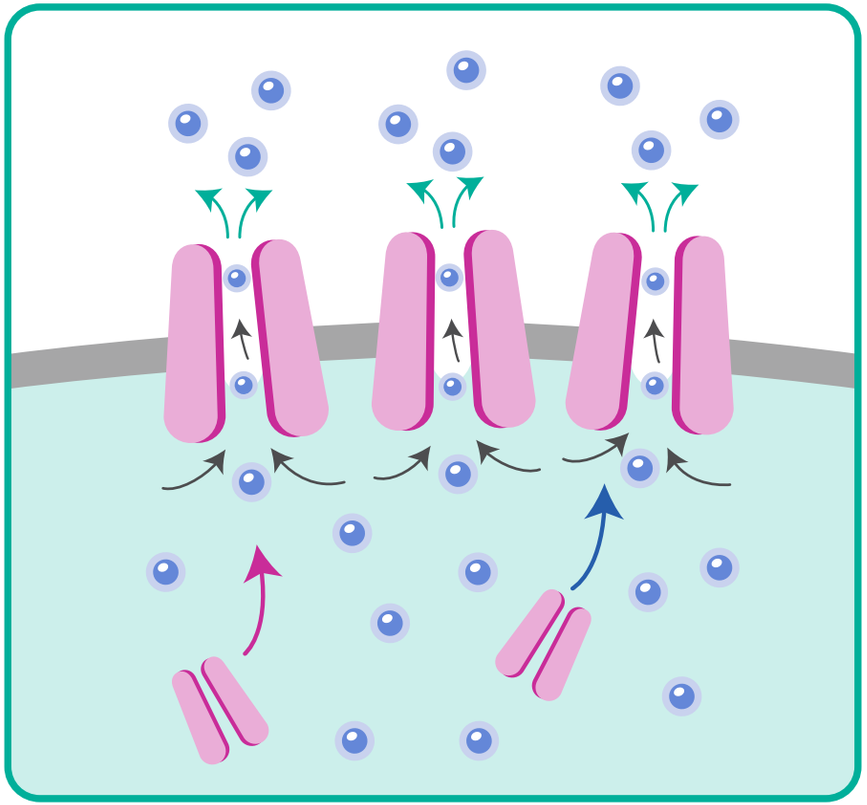
TRIKAFTA works to improve function of CFTR proteins[10]

- **Elexacaftor** and **tezacaftor** work to improve cellular processing and trafficking, allowing for more CFTR proteins to come to the cell surface[1]
- **Ivacaftor** potentiates the channel open probability (or gating) of the CFTR protein at the cell surface[1]
- The combined effect of **elexacaftor**, **tezacaftor**, and **ivacaftor** is increased quantity and function of CFTR at the cell surface, resulting in increased CFTR activity[1]



TRIKAFTA IS APPROVED FOR PATIENTS WITH CF 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 *IN VITRO* DATA[1]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

Elevated Transaminases and Hepatic Injury (cont'd)

- Isolated elevations of transaminases or bilirubin have been observed in patients with CF treated with TRIKAFTA. In some instances, transaminase elevations have been associated with concomitant elevations in total bilirubin and/or international normalized ratio (INR) and have resulted in patients being hospitalized for intervention, including in patients without a history of pre-existing liver disease

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Overview of clinical trial experience in more than 600 patients

PATIENTS AGED 2 THROUGH 5 YEARS[1,3,11]

Trial 4

Heterozygous for *F508del* and another specific mutation,[a] or homozygous for *F508del* mutation

Phase 3, 24-week, open-label study (N=75)

→ **Extension Study**

Phase 3, 192-week, open-label Extension Study (N=70)
***Study ongoing**, current IA at Extension Week 48*

PATIENTS AGED 6 THROUGH 11 YEARS[12,13]

Trial 3

Heterozygous for *F508del* and another specific mutation, or homozygous for *F508del* mutation

Phase 3, 24-week open-label study (N=66)

→ **Extension Study**

Phase 3, 192-week, open-label Extension Study (N=64)
***Study ongoing**, current IA at Extension Week 144*

PATIENTS AGED 12 YEARS AND OLDER[1,5,14,15]

Trial 1

Heterozygous for *F508del* and another specific mutation[a]

Phase 3, 24-week, placebo-controlled study (N=403)

Trial 2

Homozygous for *F508del* mutation

Phase 3, 4-week, active-controlled study with 4-week run-in period (N=107)

→ **Extension Study**

Phase 3, 192-week, open-label Extension Study (N=506)
Final analysis presented at Extension Week 192

TRIKAFTA IS INDICATED FOR PATIENTS WITH CF AGED 2 YEARS AND OLDER WITH AT LEAST ONE OF 178 MUTATIONS BASED ON CLINICAL DATA OR *IN VITRO* DATA. VISIT WWW.TRIKAFTAHCP.COM OR REFER TO THE FULL PRESCRIBING INFORMATION TO SEE WHICH MUTATIONS ARE ELIGIBLE[1]

[a]Patients heterozygous for the *F508del* mutation must also have one of approximately 200 other mutations in the *CFTR* gene that results in either: no CFTR protein or a CFTR protein that lacks baseline activity and is not responsive to ivacaftor and tezacaftor/ivacaftor.[1]
IA, interim analysis.

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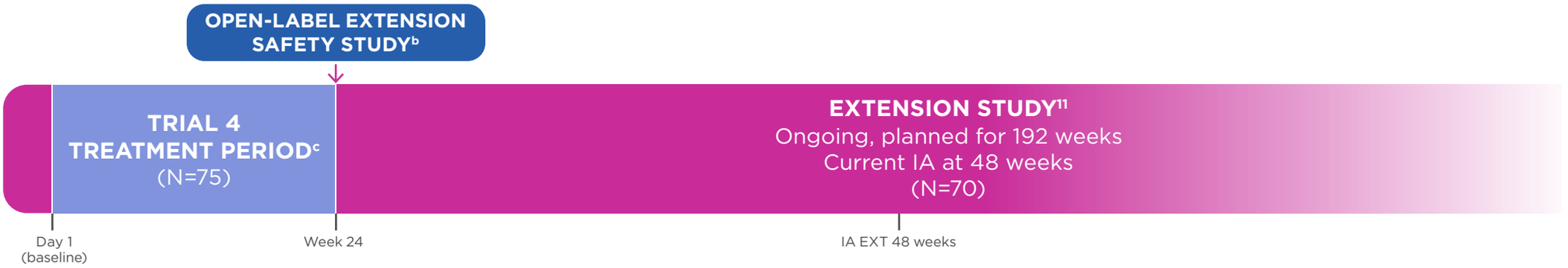
TRIKAFTA was studied in patients aged 2 through 5 years[1,3]

TRIAL DESIGN[a]



<14 kg (n=16): 80 mg/40 mg/60 mg of elexacaftor/tezacaftor/ivacaftor qam and 59.5 mg of ivacaftor qpm
≥14 kg (n=59): 100 mg/50 mg/75 mg of elexacaftor/tezacaftor/ivacaftor qam and 75 mg of ivacaftor qpm[1,3,16]

TRIAL 4: Phase 3, 24-week, open-label study[1,3,16]

SELECT INCLUSION CRITERIA*
- Confirmed CF diagnosis
- Patients who had at least one *F508del* mutation or a mutation known to be responsive to TRIKAFTA were eligible for the study
- Stable CF as deemed by the investigator at screening
- Aged 2 through 5 years on the date of informed consent
- Body weight ≥10 kg at screening

PRIMARY ENDPOINT
- Safety and tolerability as determined by adverse events and clinical and laboratory assessments

SELECT SECONDARY ENDPOINTS
- Absolute change from baseline through Week 24 in sweat chloride concentration
- Absolute change from baseline through Week 24 in lung clearance index$_{2.5}$[d]

SELECT ADDITIONAL ENDPOINTS
- Absolute change from baseline at Week 24 in BMI
- Absolute change from baseline at Week 24 in BMI-for-age z-score

EXTENSION STUDY: Phase 3, 192-week, ongoing, open-label Extension Study of Trial 4[11]

SELECT INCLUSION CRITERIA*
- Completed 24 weeks of TRIKAFTA treatment in Trial 4

PRIMARY ENDPOINT
- Long-term safety and tolerability

SELECT SECONDARY ENDPOINTS
- Absolute change from baseline through Week 48 in sweat chloride concentration
- Absolute change from baseline through Week 48 in lung clearance index$_{2.5}$[d]

SELECT ADDITIONAL ENDPOINTS
- Absolute change from baseline at Week 48 in BMI
- Absolute change from baseline at Week 48 in BMI-for-age z-score

***Key exclusion criteria included clinically significant cirrhosis with or without portal hypertension, lung infection with organisms associated with a more rapid decline in pulmonary status (including, but not limited to, *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*), and solid organ or hematologic transplantation.[16]**

[a]Patients on CFTR modulators were asked to washout for 4 weeks prior to Day 1.[16]

[b]All patients who completed the last treatment period visit and did not permanently discontinue the study drug were enrolled in the open-label Extension Study.[3,16,17]

[c]Trial 4 was a 2-part study: Part A was a pharmacokinetic and safety study while Part B evaluated safety, pharmacokinetics, pharmacodynamics, and efficacy.[3]

[d]Lung clearance index (LCI), derived from multiple breath washout tests, is an established research outcome for individuals with CF. It involves following an inert gas washed out from the lungs during relaxed tidal breathing. Key advantages of LCI over ppFEV$_1$ include an increased sensitivity to early changes in airway obstruction and ability to be performed repeatedly even in very young children with growing lungs.[18]

BMI, body mass index; ppFEV$_1$, percent predicted forced expiratory volume in 1 second; qam, every morning; qpm, every evening.

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Selected baseline characteristics for Trial 4 and the Extension Study

	TRIAL 4 (N=75)[3]	EXTENSION STUDY (N=70)[11,19a]
Sex, female, n (%)	41 (54.7)	39 (55.7)
Mean age, years (SD)	4.1 (1.1)	4.1 (1.0)
Mean sweat chloride, mmol/L (SD)	100.7 (11.2)	100.7 (11.5)
Mean BMI, kg/m^2 (SD)	15.79 (1.06)	15.79 (1.05)
Mean BMI-for-age z-score (SD)	0.09 (0.85)	0.09 (0.85)
Mean lung clearance index$_{2.5}$, units (SD)	8.41 (1.48)	8.26 (1.32)

Trial 4 and its Extension Study limitations and disclosures[1,3,16,20,21]

- Trial 4 and its Extension Study were open-label with no placebo control; therefore, causality cannot be attributed to drug effect
- All patients and investigators in the study knew patients were on an active drug, which may have introduced bias related to awareness of treatment
- Enrollment in the Extension Study was limited to only those patients who met the inclusion criteria for Trial 4, completed Trial 4, and elected to enroll in the Extension Study
- Although the Extension Study was a longer-term study, clinical trials cannot always detect rare adverse events
- Some results from Trial 4 and the Extension Study are not included in the approved full Prescribing Information, and the FDA did not consider either study in the initial approval of TRIKAFTA
- This Extension Study may not meet the FDA definition of an adequate and well-controlled study due to its design
- Trial 4 required patients to remain on their usual prescribed CF regimens. In the Extension Study, patients may have had changes in their stable medication regimens, but the data set was not large enough to assess the effect that changes in concomitant drugs could have had on the efficacy and safety results

Results from Trial 4 and the Extension Study are based on uncontrolled, open-label studies with the Extension Study ongoing. Click here for more trial design information.

[a]Baseline characteristics were based on the baseline of the parent study treatment period.[11]
SD, standard deviation.

Trial 4 and Extension Study safety results

TRIAL 4

Discontinuations and serious adverse events[3]

- 2 patients (2.7%) experienced serious adverse events
  - One patient experienced abnormal behavior that led to study drug discontinuation. The patient had a history of behavioral and developmental issues, and developed hyperactivity, aggression, increased urinary urgency, and enuresis, which resolved after treatment discontinuation. The investigator assessed the events as possibly related to treatment
  - One patient had a pulmonary exacerbation, which was considered not related to treatment and resolved without change in treatment
- There were no deaths in Trial 4[22]

EXTENSION STUDY WEEK 48 IA

Discontinuations and serious adverse events[11]

- 13 patients (18.6%) experienced a serious adverse event; 1 (1.4%) was considered related to treatment
  - Seven patients (10%) had infective pulmonary exacerbations of CF
- 3 patients (4.3%) had an adverse event that led to treatment interruption, and 2 patients (2.9%) discontinued treatment due to non-serious adverse events of increased alanine/aspartate aminotransferase (n=1) and behavioral changes (n=1) that were considered possibly related to study drug

Most frequent treatment-emergent adverse events (≥15%) in Trial 4 and its Extension Study[11a]

	TRIAL 4 n (%) (N=75)	EXTENSION STUDY n (%) (N=70)
Subjects with any treatment-emergent adverse events (TEAEs)	**74 (98.7)**	**69 (98.6)**
Cough	46 (61.3)	55 (78.6)
Pyrexia	26 (34.7)	37 (52.9)
Rhinorrhea	25 (33.3)	28 (40.0)
Vomiting	21 (28.0)	25 (35.7)
Nasal congestion	13 (17.3)	22 (31.4)
Upper respiratory tract infection	11 (14.7)	17 (24.3)
Productive cough	3 (4.0)	16 (22.9)
Infective PEx of cystic fibrosis	8 (10.7)	14 (20.0)
COVID-19	14 (18.7)	9 (12.9)
Rash	12 (16.0)	5 (7.1)

[a]When summarizing number and percentage of participants, a participant with multiple events within a category was counted only once in that category.
AE, adverse event; PEx, pulmonary exacerbation.[11]

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Trial 4 and Extension Study safety results (cont'd)

Incidence of maximum transaminase and maximum total bilirubin elevations[16,19]

		TRIAL 4 n (%) (N=75)	EXTENSION STUDY n (%) (N=70)
Elevated ALT or AST, n (%)	>3x ULN	6 (8.0)	4 (5.7)
	>5x ULN	2 (2.7)	1 (1.4)
	>8x ULN	1 (1.3)	0
ALT or AST >3x ULN and total bilirubin >2x ULN		0	0
Adverse events of elevated ALT and/or AST		8 (10.7)	7 (10.0)

- One patient required treatment interruption during Trial 4 and later discontinued TRIKAFTA during the open-label Extension Study due to transaminase elevations[3,11]

People with CF pictured may or may not be taking TRIKAFTA.

TRIAL 4

Rash events[3,16]

- 15 patients (20.0%) experienced rash events[a]
  - 12 patients had rash events that were assessed as unlikely/not related to study drug or were confounded by concurrent viral symptoms
  - 2 patients had interruptions and resumed study drug without recurrence of rash. No patients discontinued due to rash events
- Rash events were more frequent among males (32.4%) than females (9.8%)

EXTENSION STUDY WEEK 48 IA

Rash events[23]

- 8 patients (11.4%) experienced rash events[a]
  - No patients experienced a serious adverse event or discontinued treatment due to a rash event
  - One patient (1.4%) interrupted treatment due to a rash event that was assessed as unlikely related to study drug
- Rash events were more frequent among males (12.9%) than females (10.3%)

[a]Rash events were determined to be mild or moderate in severity. Includes rash, rash erythematous, rash maculopapular, rash papular, and urticaria.[3,16]

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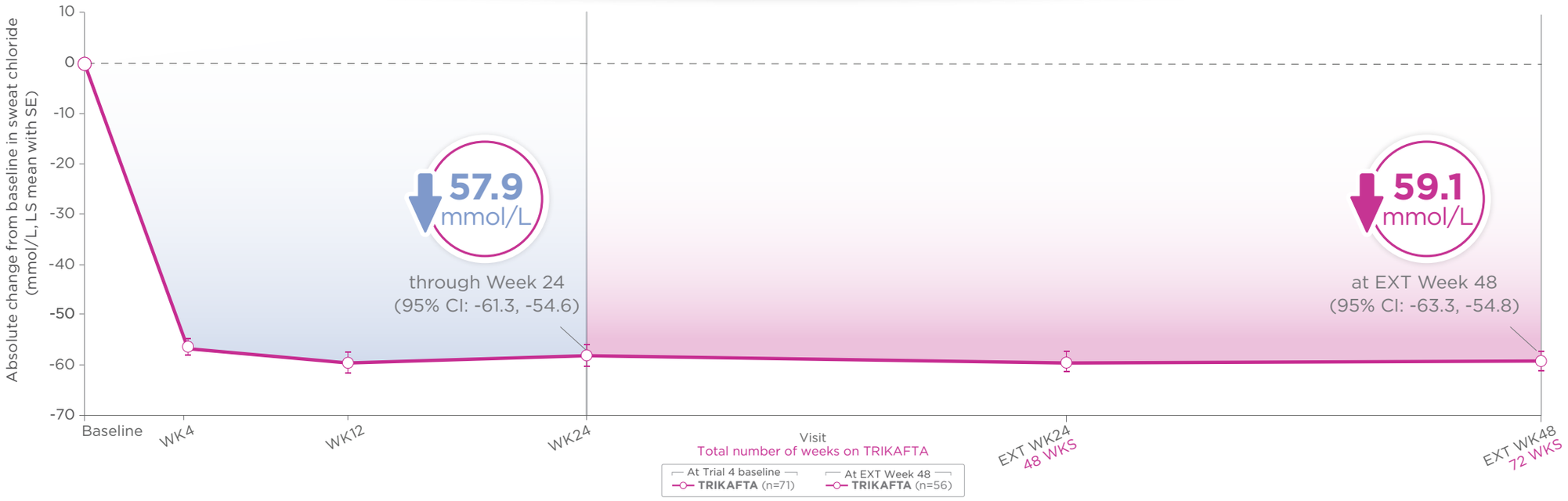
Reduction in sweat chloride concentration was observed as early as Week 4 with TRIKAFTA[3,11]

SECONDARY ENDPOINT: ABSOLUTE CHANGE FROM BASELINE IN SWEAT CHLORIDE CONCENTRATION[a]



Results from Trial 4 and the Extension Study are based on uncontrolled, open-label studies with the Extension Study ongoing. Please see additional information for trial design and limitations and disclosures for Trial 4 and the Extension Study.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

Elevated Transaminases and Hepatic Injury (cont'd)

- Assessments of liver function tests (ALT, AST, and bilirubin) are recommended prior to initiating TRIKAFTA, every 3 months during the first year of treatment, and annually thereafter

[a]In Trial 4, mean baseline sweat chloride (SD) was 100.7 mmol/L (11.2) for all patients receiving TRIKAFTA in this study.[3]
F/F, homozygous for the *F508del* mutation; F/MF, heterozygous for the *F508del* and a minimal function mutation; SE, standard error; WK, week.

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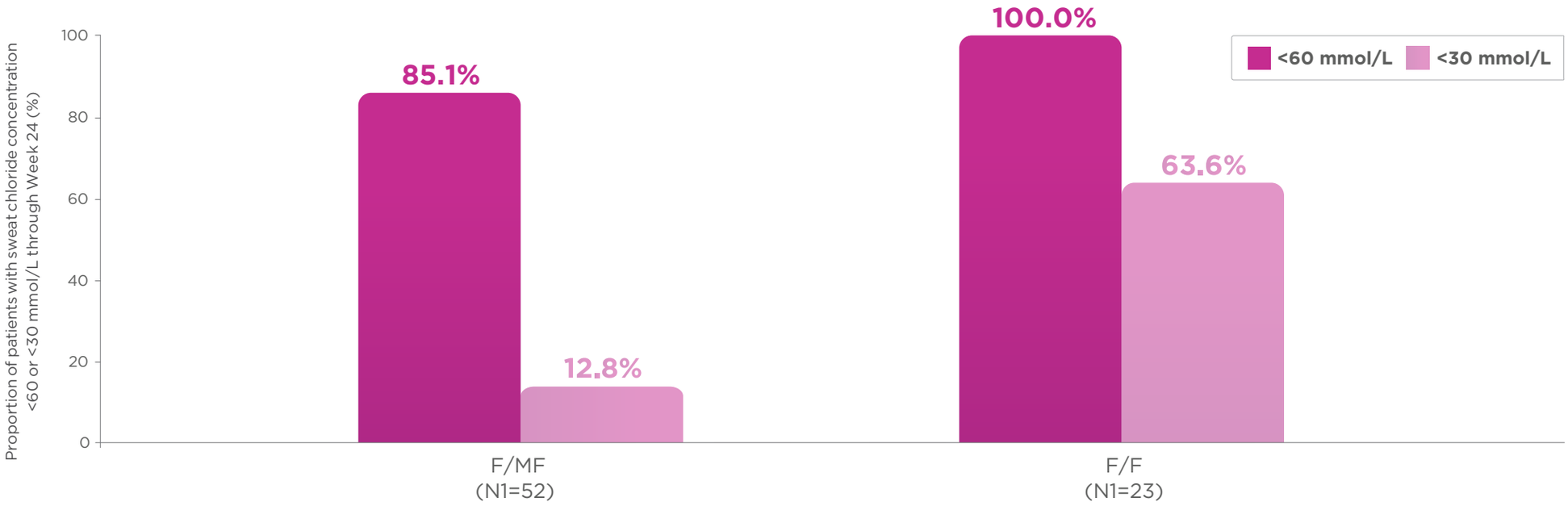
In Trial 4: 85% of patients heterozygous for *F508del* and another specific mutation and 100% of patients homozygous for *F508del* mutation had sweat chloride concentrations <60 mmol/L through Week 24[3,16a]

PROPORTION OF PATIENTS WITH SWEAT CHLORIDE CONCENTRATION <60 OR <30 mmol/L THROUGH WEEK 24 (%)[b]



- 1 patient in the study, of F/MF genotype, had a sweat chloride concentration <60 mmol/L at baseline[16]

Results from Trial 4 are based on an uncontrolled, open-label study.
Please see additional information for trial design and limitations and disclosures for Trial 4.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

Elevated Transaminases and Hepatic Injury (cont'd)

- In the event of significant elevations in liver function tests, e.g. ALT or AST >5x the upper limit of normal (ULN) or ALT or AST >3x ULN with bilirubin >2x ULN, dosing should be interrupted and laboratory tests closely followed until the abnormalities resolve. Following the resolution of liver function test elevations, consider the benefits and risks of resuming treatment

[a]Sweat chloride threshold data was not available for patients beyond Week 24.[3]
[b]Percentages were calculated by dividing n (the number of patients with sweat chloride concentration below the indicated threshold at Week 24) by N1, where N1 is the number of patients with evaluable data. Patients with missing data were considered missing at random and were not counted in the denominator.[3,16]

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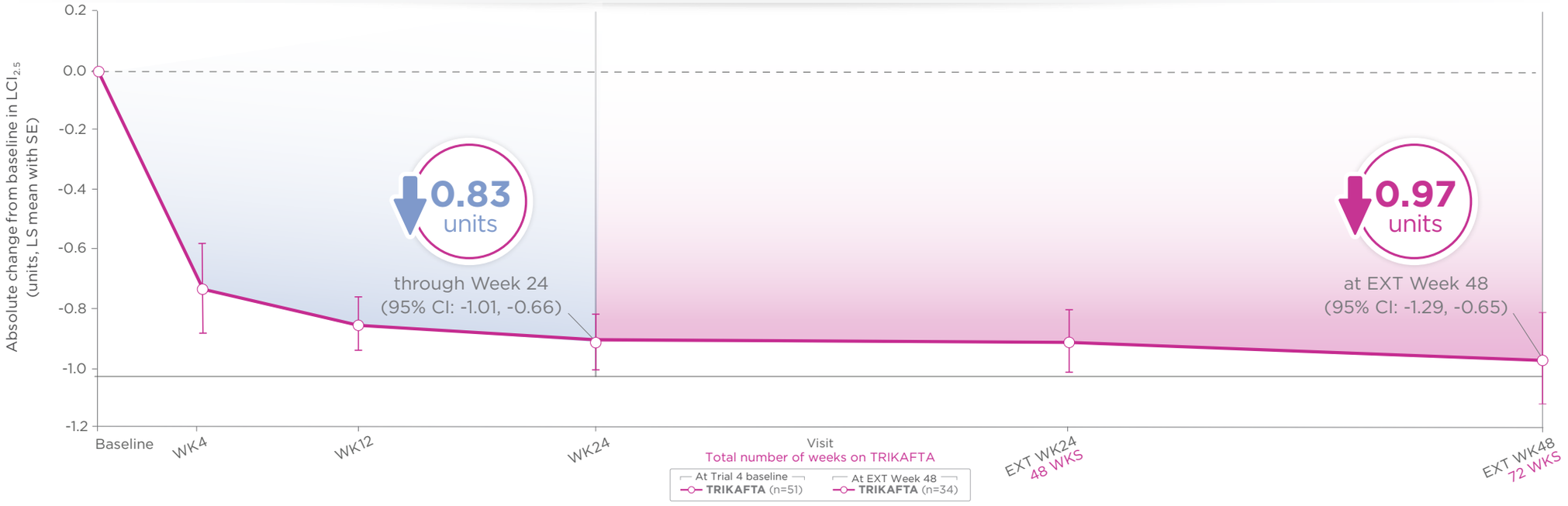
Decrease in mean lung clearance index$_{2.5}$ was observed at Extension Study Week 48 with TRIKAFTA[3,11]

SECONDARY ENDPOINT: ABSOLUTE CHANGE FROM BASELINE IN LUNG CLEARANCE INDEX$_{2.5}$[a-c]



Results from Trial 4 and the Extension Study are based on uncontrolled, open-label studies with the Extension Study ongoing. Please see additional information for trial design and limitations and disclosures for Trial 4 and the Extension Study.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

Elevated Transaminases and Hepatic Injury (cont'd)

- For patients with a history of hepatobiliary disease or liver function test elevations, more frequent monitoring should be considered

Lung clearance index (LCI), derived from multiple breath washout tests, is an established research outcome for individuals with CF. It involves following an inert gas washed out from the lungs during relaxed tidal breathing. Key advantages of LCI over ppFEV$_1$ include an increased sensitivity to early changes in airway obstruction and ability to be performed repeatedly even in very young children with growing lungs.[18]

[a]In Trial 4, mean baseline lung clearance index$_{2.5}$ was 8.41 units (SD, 1.48) for patients receiving TRIKAFTA.[3]

[b]Lung clearance index represents a measure of the number of times the volume of a gas in the lung at the start of a washout must be turned over to wash out tracer gas to the predefined endpoint.[18]

[c]LCI$_{2.5}$ was collected for subjects ≥3 years of age at screening in the parent study.[3]

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The safety results of TRIKAFTA in patients aged 2 through 5 years were similar to the results established in Trial 1[3]

Primary endpoint	TRIAL 4	EXTENSION STUDY
Safety profile	**The safety results of TRIKAFTA in patients aged 2 through 5 years were similar to the safety results established in Trial 1[3]**	**The safety results observed at Extension Study Week 48 were similar to those observed in Trial 4[11]**

Select secondary endpoints	TRIAL 4	EXTENSION STUDY
Change in sweat chloride concentration	57.9 mmol/L — LS-mean absolute change from baseline in sweat chloride concentration through Week 24 (95% CI: -61.3, -54.6). Mean (SD) at baseline: 100.7 mmol/L (11.2)[3]	Changes in sweat chloride concentration were generally maintained at Extension Study Week 48[11]
Change in lung clearance index$_{2.5}$[a]	0.83 units — LS-mean absolute change from baseline in lung clearance index$_{2.5}$ through Week 24 (95% CI: -1.01, -0.66). Mean (SD) at baseline: 8.41 units (1.48)[3]	Changes in lung clearance index$_{2.5}$ were generally maintained at Extension Study Week 48[11]

Select additional endpoints	TRIAL 4	EXTENSION STUDY
Growth measurements	0.03 kg/m^2 — LS-mean absolute change from baseline in BMI at Week 24 (95% CI: -0.10, 0.17). Mean (SD) at baseline: 15.79 kg/m^2 (1.06)[3] 0.10 — LS-mean absolute change from baseline in BMI-for-age z-score at Week 24 (95% CI: 0.0, 0.20). Mean (SD) at baseline: 0.09 (0.85)[3]	-0.01 kg/m^2 — LS-mean absolute change from baseline in BMI at Extension Study Week 48 (95% CI: -2.08, 1.71)[19] 0.09 — LS-mean absolute change from baseline in BMI-for-age z-score at Extension Study Week 48 (95% CI: -0.02, 0.20)[11]

Results from Trial 4 and the Extension Study are based on uncontrolled, open-label studies with the Extension Study ongoing. Final results may vary.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

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 the benefits and risks for the individual patient to determine whether to resume treatment with TRIKAFTA

Lung clearance index (LCI), derived from multiple breath washout tests, is an established research outcome for individuals with CF. It involves following an inert gas washed out from the lungs during relaxed tidal breathing. Key advantages of LCI over ppFEV$_1$ include an increased sensitivity to early changes in airway obstruction and ability to be performed repeatedly even in very young children with growing lungs.[18]

[a]At screening, lung clearance index$_{2.5}$ was assessed in patients aged 3 to 5 years only.[3]

CI, confidence interval; LS, least squares.

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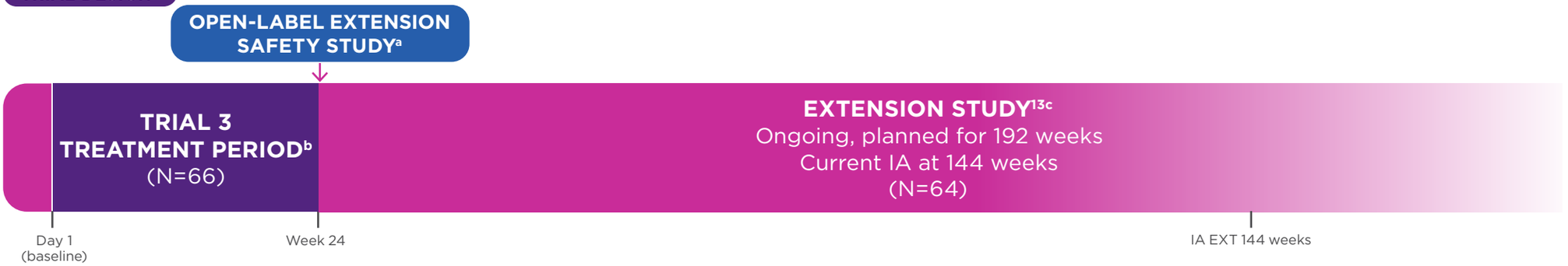
TRIKAFTA was studied in patients aged 6 through 11 years[12,24]

TRIAL DESIGN



<30 kg (n=36): 100 mg/50 mg/75 mg of elexacaftor/tezacaftor/ivacaftor qam and 75 mg of ivacaftor qpm
≥30 kg (n=30): 200 mg/100 mg/150 mg of elexacaftor/tezacaftor/ivacaftor qam and 150 mg of ivacaftor qpm[12]

TRIAL 3: Phase 3, 24-week, open-label study[12,24]

KEY INCLUSION CRITERIA*
- Confirmed CF diagnosis, clinically stable, and aged 6 through 11 years
- Homozygous or heterozygous for the *F508del* mutation[d]
- Weight ≥15 kg without shoes at screening visit
- $ppFEV_1$ ≥40 at screening

PRIMARY ENDPOINT
- Safety and tolerability as determined by adverse events and clinical and laboratory assessments[e]

SELECT SECONDARY ENDPOINTS
- Absolute change from baseline through Week 24 in $ppFEV_1$, sweat chloride concentration, CFQ-R Respiratory Domain score, and lung clearance $index_{2.5}$
- Absolute change from baseline at Week 24 in BMI and BMI-for-age z-score

EXTENSION STUDY: Phase 3, 192-week, ongoing, open-label Extension Study of Trial 3[13]

KEY INCLUSION CRITERIA
- Completed 24 weeks of TRIKAFTA treatment in Trial 3

PRIMARY ENDPOINT
- Long-term safety and tolerability

SELECT SECONDARY ENDPOINTS
- Absolute change from baseline in parent study at Extension Study Week 144 in $ppFEV_1$, sweat chloride concentration, CFQ-R Respiratory Domain score, BMI, BMI-for-age z-score, and lung clearance $index_{2.5}$

Lung clearance index (LCI), derived from multiple breath washout tests, is an established research outcome for individuals with CF. It involves following an inert gas washed out from the lungs during relaxed tidal breathing. Key advantages of LCI over $ppFEV_1$ include an increased sensitivity to early changes in airway obstruction and ability to be performed repeatedly even in very young children with growing lungs.[18]

***Key exclusion criteria included clinically significant cirrhosis with or without portal hypertension, lung infection with organisms associated with a more rapid decline in pulmonary status (including, but not limited to, *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*), and solid organ or hematologic transplantation.[24]**

[a] All patients who completed the last treatment period visit and did not permanently discontinue the study drug were enrolled in the open-label Extension Study.[24]

[b] Trial 3 was a 2-part study: Part A was a pharmacokinetic, safety, and tolerability study, and Part B evaluated safety, tolerability, efficacy, and pharmacokinetics. Patients who completed Part A were enrolled in Part B.[12,24]

[c] The Extension Study is an ongoing, open-label study planned for up to 192 weeks; all patients who completed Trial 3 were eligible to enroll in the Extension Study. Results presented here are from an interim analysis of the Extension Study. The data cutoff occurred when the last ongoing participant in the Extension Study reached their Week 144 visit.[13]

[d] If a patient is heterozygous for the *F508del* mutation, they must also have one of approximately 200 other mutations in the *CFTR* gene that results in either: no CFTR protein or a CFTR protein that lacks baseline function and is not responsive to ivacaftor and tezacaftor/ivacaftor.[24]

[e] Safety and tolerability assessments were based on adverse events, clinical laboratory values, electrocardiograms, vital signs, pulse oximetry, and ophthalmologic examinations.[24]

CFQ-R, Cystic Fibrosis Questionnaire-Revised.

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Open-label study in patients with CF aged 6 through 11 years[12,24]

- The Trial 3 24-week safety study overlapped with the COVID-19 pandemic, therefore some patients were unable to complete in-person evaluations at all time points. For patients who were unable to complete in-person visits, data were collected remotely and those patients remained in the study. Additional analyses were performed to evaluate data collected from unscheduled visits and to evaluate home-based data. The results of those analyses were consistent with the main analysis.

Safety analysis (primary endpoint)

- All patients (N=66) in the study were included in the safety analysis. If a patient was unable to complete an in-clinic visit, safety information was collected remotely with site personnel
- If a patient was unable to complete laboratory tests at the scheduled Week 24 time point, unscheduled visits were conducted after Week 24

Efficacy analysis (secondary endpoints)

- N values declined over time for each efficacy endpoint, as some patients were unable to complete in-clinic visits due to the pandemic
- The N values differ across endpoints due to varying restrictions placed on data collection during the pandemic

Trial 3 and its Extension Study limitations and disclosures[1,12,13,20,21,24]

- Trial 3 and its Extension Study were open-label with no placebo control; therefore, causality cannot be attributed to drug effect
- All patients and investigators in the study knew patients were on an active drug, which may have introduced bias related to awareness of treatment
- Enrollment in the Extension Study was limited to only those patients who met strict inclusion criteria for Trial 3, completed Trial 3, and elected to enroll in the Extension Study
- Although the Extension Study was a longer-term study, clinical trials cannot always detect rare adverse events
- Some results from Trial 3 and the Extension Study are not included in the approved full Prescribing Information, and the FDA did not consider either study in the initial approval of TRIKAFTA
- This Extension Study may not meet the FDA definition of an adequate and well-controlled study due to its design
- Trials required patients to remain on their usual prescribed CF regimens. In the Extension Study, patients may have had changes in their stable medication regimens, but the data set was not large enough to assess the effect that changes in concomitant drugs could have had on the efficacy and safety results

Results from Trial 3 and the Extension Study are based on uncontrolled, open-label studies with the Extension Study ongoing. Click here for more trial design information.

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Selected baseline characteristics for Trial 3 and the Extension Study[a]

	TRIAL 3 (N=66)[12]	EXTENSION STUDY (N=64)[13,25]
Sex, female, %	59.1	60.9
Mean age, years (SD)	9.3 (1.9)	9.3 (1.8)
Mean $ppFEV_1$ (SD)	88.8 (17.7)	88.3 (17.6)
Mean sweat chloride, mmol/L (SD)	102.2 (9.1)	102.2 (9.2)
Mean CFQ-R Respiratory Domain score, points (SD)	80.3 (15.2)	79.8 (15.2)
Mean BMI, kg/m^2 (SD)	16.39 (1.69)	16.32 (1.66)
Mean BMI-for-age z-score (SD)	-0.16 (0.74)	-0.19 (0.73)
Mean lung clearance $index_{2.5}$, units (SD)	9.77 (2.68)	9.87 (2.68)

Results from Trial 3 and the Extension Study are based on uncontrolled, open-label studies with the Extension Study ongoing. Click here for more trial design information.

Lung clearance index (LCI), derived from multiple breath washout tests, is an established research outcome for individuals with CF. It involves following an inert gas washed out from the lungs during relaxed tidal breathing. Key advantages of LCI over $ppFEV_1$ include an increased sensitivity to early changes in airway obstruction and ability to be performed repeatedly even in very young children with growing lungs.[18]

[a]Baseline characteristics were based on the baseline of the parent study treatment period.[13]

Trial 3 and Extension Study safety results[12,13,24,25,26]

TRIAL 3

Serious adverse events and discontinuations[12]

- 1 patient (1.5%) experienced concurrent serious adverse events (rhinovirus infection, metapneumovirus infection, and pneumonia)
- 1 patient (1.5%) discontinued treatment due to an adverse event (erythematous rash)

EXTENSION STUDY WEEK 144 IA

Serious adverse events and discontinuations[13,26]

- 5 patients (7.8%) experienced at least 1 serious adverse event, 1 of which was considered related to study treatment
- 1 patient (1.6%) had an adverse event of aggression that was considered by the study investigator to be moderate in severity and unlikely related to study drug; it resolved after study drug discontinuation. Another patient (1.6%) discontinued due to a non-serious AE of increased alanine aminotransferase level, which was considered possibly related to study drug by the study investigator

- There were no deaths in either Trial 3 or through Week 144 interim analysis of the Extension Study[12,25]

Incidences of maximum transaminase and maximum total bilirubin elevations with TRIKAFTA[24,25]

		TRIAL 3 n (%) (N=66)	EXTENSION STUDY WEEK 144 IA n (%) (N=64)
Elevated ALT or AST, n (%)	>3x ULN	7 (10.6)	3 (4.7)
	>5x ULN	1 (1.5)	2 (3.1)
	>8x ULN	0	0
ALT or AST >3x ULN and total bilirubin >2x ULN		0	0
Adverse events of elevated ALT or AST		7 (10.6)	6 (9.4)

- There were no serious adverse events of elevated ALT or AST in Trial 3[12]
- There were no adverse events in Trial 3 and 1 adverse event in the Extension Study due to elevated transaminases leading to discontinuation of treatment[12,13]

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Trial 3 and Extension Study safety results[12,13,24,25,27] (cont'd)

TRIAL 3

Rash events[12,24,27]

- 15 patients (22.7%) experienced rash events[a]
- 1 patient (1.5%) discontinued due to rash erythematous
- All other rash events resolved without treatment interruption

EXTENSION STUDY WEEK 144 IA

Rash events[25]

- 4 patients (6.3%) experienced rash events[a]
- No patients discontinued or had a treatment interruption due to a rash

- In Trial 3, the most common adverse events to occur in ≥10% of patients treated with TRIKAFTA were cough, headache, pyrexia, oropharyngeal pain, upper respiratory tract infection, nasal congestion, rash, abdominal pain, rhinorrhea, viral upper respiratory tract infection, alanine aminotransferase increased, diarrhea, influenza, and vomiting[12]
- In the Extension Study, the majority of adverse events were considered mild to moderate in severity
  - Mild (35.9%), moderate (60.9%), severe (3.1%), and life-threatening (0%)[13]
- 64 patients (100.0%) experienced TEAEs at Extension Study Week 144 IA[13]

Most common TEAEs occurring in ≥20% of patients at Extension Study Week 144 IA, n (%) (N=64)[13]	
Cough	34 (53.1)
Pyrexia	23 (35.9)
Headache	22 (34.4)
Nasal congestion	21 (32.8)
Oropharyngeal pain	19 (29.7)
Rhinorrhea	18 (28.1)
Upper respiratory tract infection	17 (26.6)
Vomiting	16 (25.0)
COVID-19	16 (25.0)
Abdominal pain	13 (20.3)

Click here for more information about the impact of COVID-19 on the study.

[a]Rash events were determined to be mild or moderate in severity. Includes rash, rash erythematous, rash maculopapular, rash papular, skin exfoliation, and urticaria.[12]

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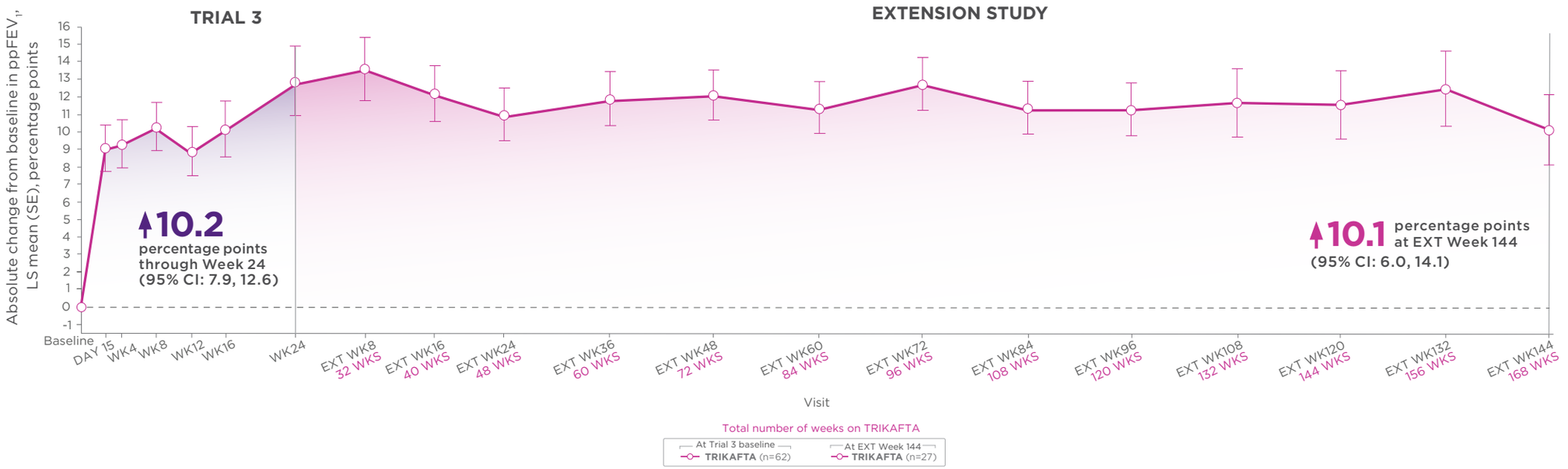
Lung function results with TRIKAFTA[12,13,25]

SECONDARY ENDPOINT: MEAN ABSOLUTE CHANGE FROM BASELINE IN $ppFEV_1$[a]



Results from Trial 3 and the Extension Study are based on uncontrolled, open-label studies with the Extension Study ongoing. Please see additional information for trial design and limitations and disclosures for Trial 3 and the Extension Study.

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 the concomitant use of strong CYP3A inducers, which may reduce the therapeutic effectiveness of TRIKAFTA. Co-administration with strong CYP3A inducers is not recommended

Concomitant Use With CYP3A Inhibitors

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

[a]In Trial 3, mean (SD) baseline $ppFEV_1$ was 88.8 percentage points (17.7) for patients receiving TRIKAFTA.[12]
The text in magenta below the graphs here and on the following pages reflects the number of consecutive weeks patients have been on TRIKAFTA, beginning from the end of Trial 3 up to the latest available interim analysis data.
LS, least squares.

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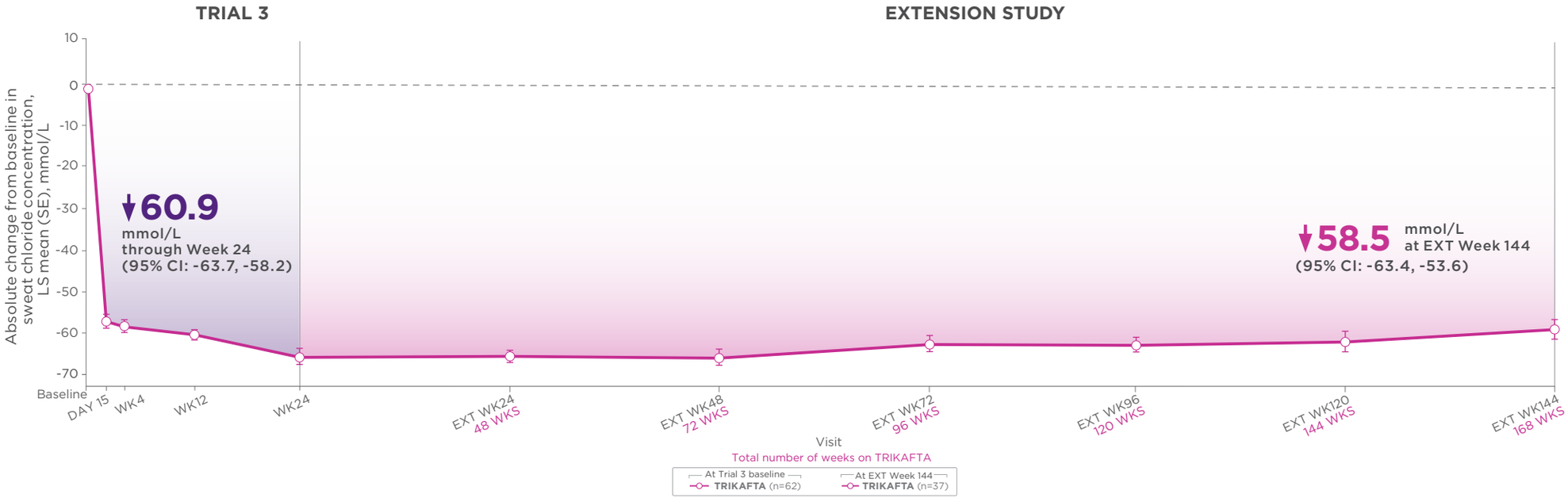
Results for sweat chloride with TRIKAFTA[12,13,25]

SECONDARY ENDPOINT: ABSOLUTE CHANGE FROM BASELINE IN SWEAT CHLORIDE[a]



Results from Trial 3 and the Extension Study are based on uncontrolled, open-label studies with the Extension Study ongoing. Please see additional information for trial design and limitations and disclosures for Trial 3 and the Extension Study.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

Cataracts

- Cases of 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)

[a]In Trial 3, mean (SD) baseline sweat chloride was 102.2 mmol/L (9.1) for patients receiving TRIKAFTA.[12]

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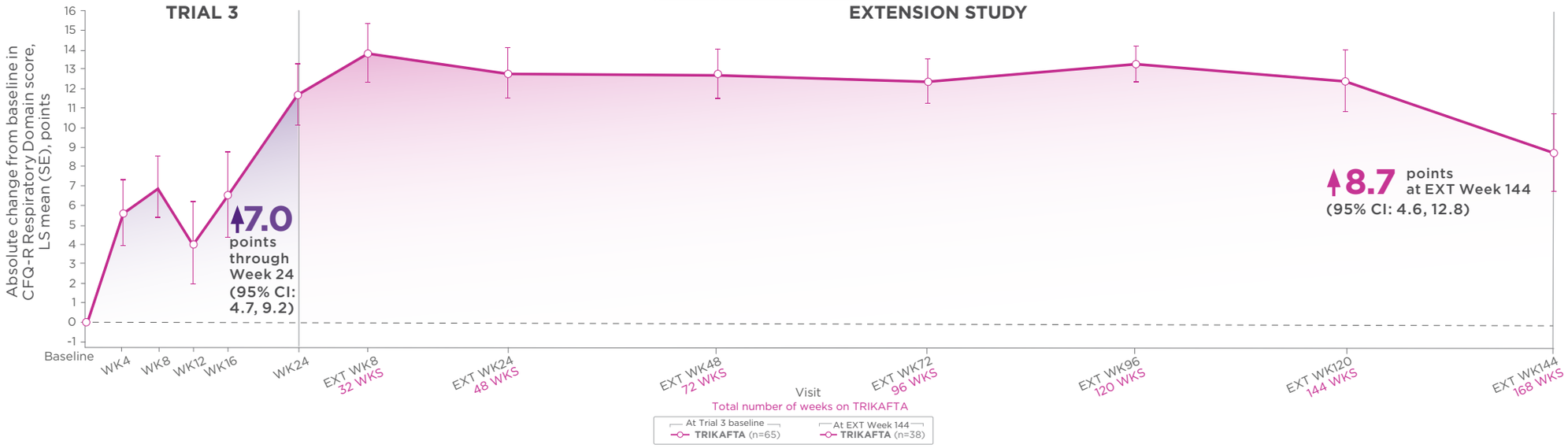
Please click for Important Safety Information and full Prescribing Information for TRIKAFTA.

Results for CFQ-R Respiratory Domain score with TRIKAFTA[12,13,25]

SECONDARY ENDPOINT: ABSOLUTE CHANGE FROM BASELINE IN CFQ-R RESPIRATORY DOMAIN SCORE[a]



Results from Trial 3 and the Extension Study are based on uncontrolled, open-label studies with the Extension Study ongoing. Please see additional information for trial design and limitations and disclosures for Trial 3 and the Extension Study.

CFQ-R Respiratory Domain score measures composite patient-reported **outcomes** in the following **respiratory symptoms**: waking up from coughing, coughing, difficulty breathing, wheezing, congestion, and mucus production.[28]

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS (cont'd)

Most Common Adverse Reactions

- The most common adverse reactions occurring in ≥5% of patients treated with TRIKAFTA (N=202) and higher than placebo (N=201) by ≥1% in the 24-week placebo-controlled, parallel-group Phase 3 trial (Trial 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, and blood bilirubin increased

[a]In Trial 3, mean (SD) baseline CFQ-R Respiratory Domain Score was 80.3 points (15.2) for patients receiving TRIKAFTA.[12]
MCID, minimal clinically important difference. The MCID threshold for CFQ-R Respiratory Domain score is 4 points in patients with CF with stable respiratory symptoms and represents the minimal change a patient can detect.[29]

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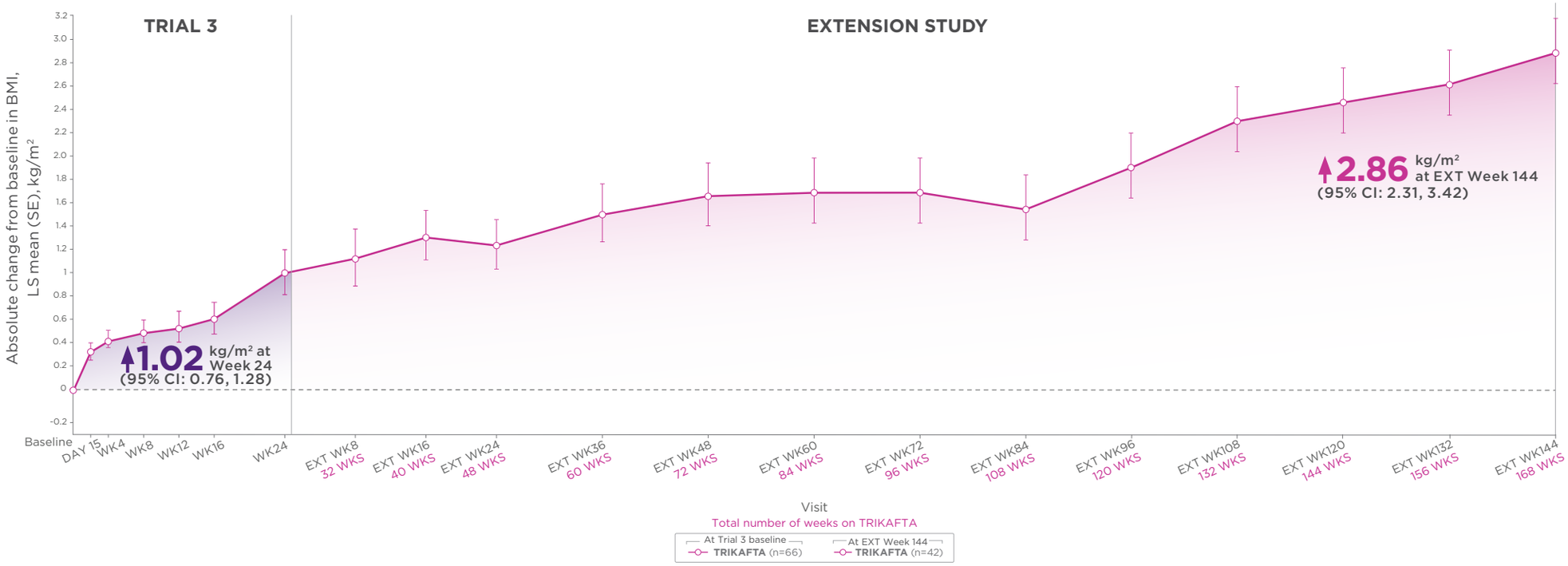
BMI results with TRIKAFTA[12,13,24,25]

SECONDARY ENDPOINT: ABSOLUTE CHANGE FROM BASELINE IN BMI[a]



Results from Trial 3 and the Extension Study are based on uncontrolled, open-label studies with the Extension Study ongoing. Please see additional information for trial design and limitations and disclosures for Trial 3 and the Extension Study.

IMPORTANT SAFETY INFORMATION

ADVERSE REACTIONS (cont'd)

Most Common Adverse Reactions (cont'd)

- The safety profile for the patients with CF receiving TRIKAFTA (N=55) enrolled in the 4-week, randomized, double-blind, active-controlled Phase 3 trial (Trial 2) was similar to that observed in Trial 1
- The safety profile in patients age 6 through 11 years from an open-label trial (Trial 3; N=66) was similar to that observed in Trial 1. The safety profile in patients age 2 through 5 years from an open-label trial (Trial 4; N=75) was similar to that observed in Trial 1

[a]In Trial 3, mean (SD) baseline BMI was 16.39 kg/m² (1.69) for patients receiving TRIKAFTA.[24]

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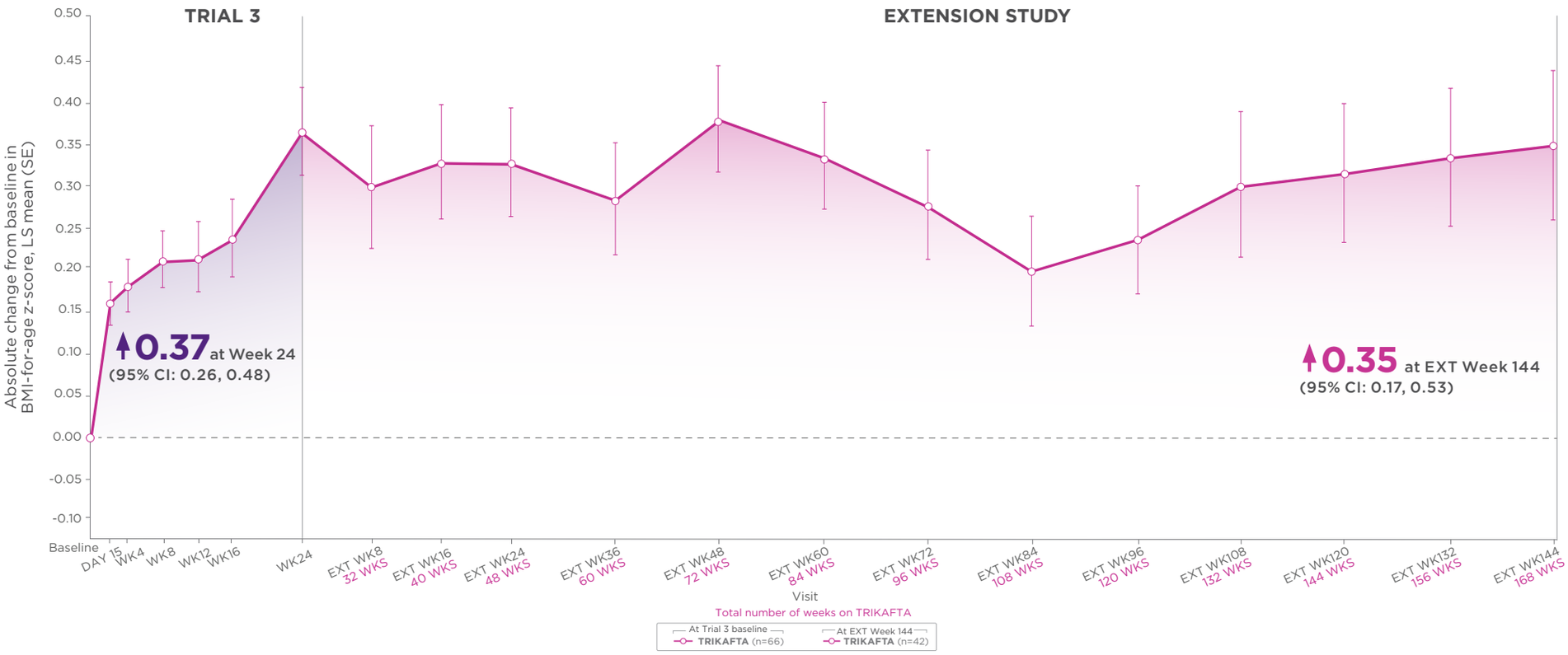
BMI-for-age z-score results with TRIKAFTA[12,13,24,25]

SECONDARY ENDPOINT: ABSOLUTE CHANGE FROM BASELINE IN BMI-FOR-AGE Z-SCORE[a]



Body mass index z-scores, also called BMI SD scores, are measures of relative weight adjusted for a child's age and sex.[30]

Results from Trial 3 and the Extension Study are based on uncontrolled, open-label studies with the Extension Study ongoing. Please see additional information for trial design and limitations and disclosures for Trial 3 and the Extension Study.

IMPORTANT SAFETY INFORMATION

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

[a]In Trial 3, mean (SD) baseline BMI-for-age z-score was -0.16 (0.74) for patients receiving TRIKAFTA.[24]

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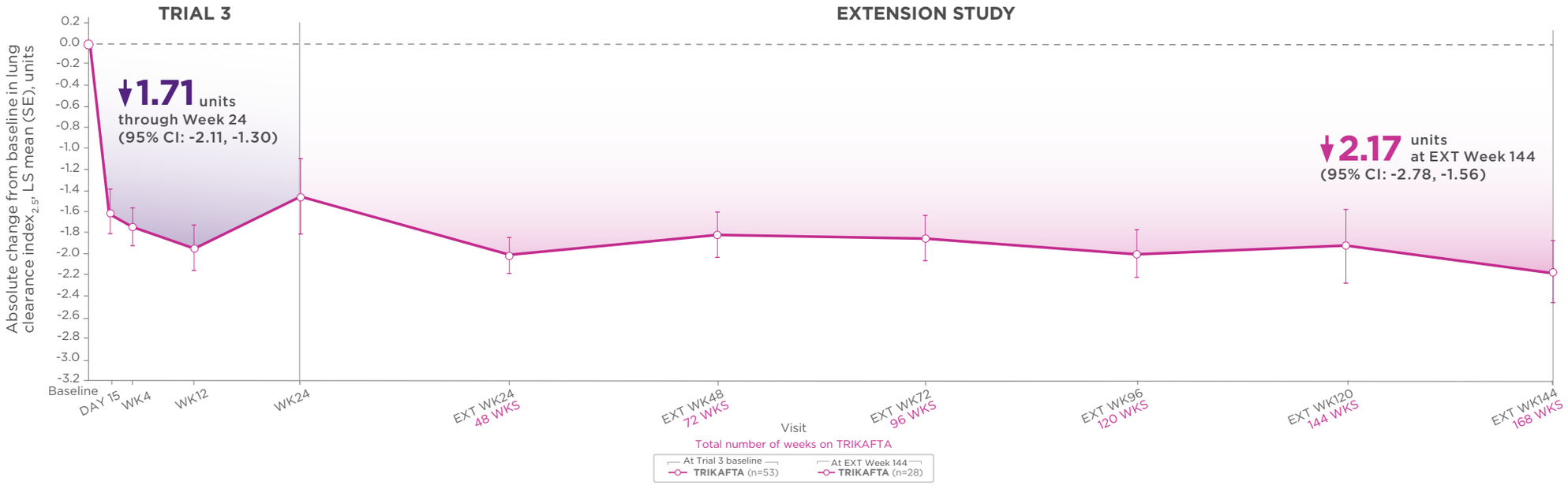
Lung clearance index$_{2.5}$ results with TRIKAFTA[12,13,25]

SECONDARY ENDPOINT: ABSOLUTE CHANGE FROM BASELINE IN LCI$_{2.5}$[a]



Lung clearance index is a measure of lung physiology derived from multiple-breath washout tests. Lung clearance index represents a measure of the number of times the volume of gas in the lung at the start of the washout must be turned over in order to wash out the tracer gas to the predefined endpoint. With increasing disease severity, lung clearance index increases.[18]

Results from Trial 3 and the Extension Study are based on uncontrolled, open-label studies with the Extension Study ongoing. Please see additional information for trial design and limitations and disclosures for Trial 3 and the Extension Study.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Elevated Transaminases and Hepatic Injury

- Liver failure leading to transplantation has been reported in a patient with cirrhosis and portal hypertension while receiving TRIKAFTA. Avoid use of TRIKAFTA in patients with pre-existing advanced liver disease (e.g., as evidenced by 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

[a]In Trial 3, mean (SD) baseline lung clearance index$_{2.5}$ was 9.77 units (2.68) for patients receiving TRIKAFTA.[12]

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The safety results of TRIKAFTA in patients aged 6 through 11 years were similar to the established safety results of Trial 1[1]

TRIKAFTA endpoints summary

	TRIAL 3[1,12]	EXTENSION STUDY[13]
Safety and tolerability profile	**The safety results of TRIKAFTA in patients aged 6 through 11 years were similar to the established safety results in Trial 1**	**The safety results observed at Extension Study Week 144 were similar to those observed in Trial 3**
Change in lung function[a]	**10.2** percentage points — LS-mean absolute change from baseline in ppFEV$_1$ through Week 24 (95% CI: 7.9, 12.6)	Changes in lung function were generally maintained at Extension Study Week 144
Change in sweat chloride concentration[b]	**60.9** mmol/L — LS-mean absolute change from baseline in sweat chloride concentration through Week 24 (95% CI: -63.7, -58.2)	Changes in sweat chloride concentration were generally maintained at Extension Study Week 144

Results from Trial 3 and the Extension Study are based on uncontrolled, open-label studies with the Extension Study ongoing. Final results may vary.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

Elevated Transaminases and Hepatic Injury (cont'd)

- Isolated elevations of transaminases or bilirubin have been observed in patients with CF treated with TRIKAFTA. In some instances, transaminase elevations have been associated with concomitant elevations in total bilirubin and/or international normalized ratio (INR) and have resulted in patients being hospitalized for intervention, including in patients without a history of pre-existing liver disease
- Assessments of liver function tests (ALT, AST, and bilirubin) are recommended prior to initiating TRIKAFTA, every 3 months during the first year of treatment, and annually thereafter

[a] In Trial 3, mean (SD) baseline ppFEV$_1$ was 88.8 percentage points (17.7) for patients receiving TRIKAFTA.[12]
[b] In Trial 3, mean (SD) baseline sweat chloride was 102.2 mmol/L (9.1) for patients receiving TRIKAFTA.[12]

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The safety results of TRIKAFTA in patients aged 6 through 11 years were similar to the established safety results of Trial 1 (cont'd)[1]

TRIKAFTA endpoints summary

	TRIAL 3[1,12,24]	EXTENSION STUDY[13]
Change in CFQ-R Respiratory Domain score	**7.0 points** LS-mean absolute change from baseline in CFQ-R Respiratory Domain score through Week 24 (95% CI: 4.7, 9.2)	Changes in CFQ-R Respiratory Domain score were generally maintained at Extension Study Week 144
Change in BMI and BMI-for-age z-score	**1.02 kg/m²** LS-mean absolute change from baseline in BMI at Week 24 (95% CI: 0.76, 1.28)	Mean BMI increased over the 144-week treatment period
	0.37 LS-mean absolute change from baseline in BMI-for-age z-score at Week 24 (95% CI: 0.26, 0.48)	Changes in mean BMI-for-age-z-score were generally maintained at Extension Study Week 144
Change in lung clearance index$_{2.5}$	**1.71 units** LS-mean absolute change from baseline in lung clearance index$_{2.5}$ through Week 24 (95% CI: -2.11, -1.30)	Changes in lung clearance index$_{2.5}$ were generally maintained at Extension Study Week 144

Results from Trial 3 and the Extension Study are based on uncontrolled, open-label studies with the Extension Study ongoing. Final results may vary.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

Elevated Transaminases and Hepatic Injury (cont'd)

- In the event of significant elevations in liver function tests, e.g. ALT or AST >5x the upper limit of normal (ULN) or ALT or AST >3x ULN with bilirubin >2x ULN, dosing should be interrupted and laboratory tests closely followed until the abnormalities resolve. Following the resolution of liver function test elevations, consider the benefits and risks of resuming treatment

Lung clearance index (LCI), derived from multiple breath washout tests, is an established research outcome for individuals with CF. It involves following an inert gas washed out from the lungs during relaxed tidal breathing. Key advantages of LCI over ppFEV$_1$ include an increased sensitivity to early changes in airway obstruction and ability to be performed repeatedly even in very young children with growing lungs.[18]

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AGED 12+ YEARS — TRIAL 1/EXTENSION STUDY: HETEROZYGOUS FOR *F508DEL* AND ANOTHER SPECIFIC MUTATION

AGED 12+ YEARS — TRIAL 2/EXTENSION STUDY: HOMOZYGOUS FOR *F508DEL* MUTATION

Design for Trials 1 and 2 and the open-label Extension Study[1,15]

TRIAL 1: Phase 3, double-blind, 24-week, placebo-controlled study[1,5,31]

KEY INCLUSION CRITERIA*
- Confirmed CF diagnosis, clinically stable, and at least 12 years of age
- Heterozygous for the *F508del* mutation and another specific mutation[a]
- ppFEV$_1$ ≥40 and ≤90 at screening

PRIMARY ENDPOINT
- Absolute change from baseline at Week 4 in ppFEV$_1$

SELECT SECONDARY ENDPOINTS[b]
- Absolute change from baseline through Week 24 in ppFEV$_1$, sweat chloride, number of pulmonary exacerbations, and CFQ-R Respiratory Domain score[cd]
- Absolute change from baseline at Week 24 in BMI
- Safety and tolerability of TRIKAFTA

TRIAL 2: Phase 3, double-blind, 4-week, active-controlled study[1,14]

KEY INCLUSION CRITERIA*
- Confirmed CF diagnosis, clinically stable, and at least 12 years of age
- Homozygous for the *F508del* mutation
- ppFEV$_1$ ≥40 and ≤90 at screening

PRIMARY ENDPOINT
- Absolute change from baseline at Week 4 in ppFEV$_1$

SELECT SECONDARY ENDPOINTS[b]
- Absolute change from baseline at Week 4 in sweat chloride concentration and CFQ-R Respiratory Domain score
- Safety and tolerability of TRIKAFTA

EXTENSION STUDY: Open-label Extension Study of Trials 1 and 2[15]

KEY INCLUSION CRITERIA
- Completed either Trial 1 or Trial 2

PRIMARY ENDPOINT
- Long-term safety and tolerability of TRIKAFTA

SELECT SECONDARY ENDPOINTS
- Absolute change from parent study baseline at Extension Study Week 192 in ppFEV$_1$, sweat chloride, number of pulmonary exacerbations, CFQ-R Respiratory Domain score, and BMI

***Key exclusion criteria included clinically significant cirrhosis with or without portal hypertension, a history of colonization with organisms associated with a more rapid decline in pulmonary status (including, but not limited to, *Burkholderia cenocepacia*, *Burkholderia dolosa*, and *Mycobacterium abscessus*), and solid organ or hematologic transplantation.[31,32]**

[a] Patients heterozygous for the *F508del* mutation must also have one of approximately 200 other mutations in the *CFTR* gene that results in either: no CFTR protein or a CFTR protein that lacks baseline function and is not responsive to ivacaftor and tezacaftor/ivacaftor.[31]

[b] A hierarchical testing procedure was performed for key secondary endpoints. For an endpoint to be significant, both it and all previous tests in the hierarchy had to achieve $P<0.05$.[31]

[c] CFQ-R Respiratory Domain score was also assessed from Baseline at Week 4 as a secondary endpoint.[1]

[d] In Trial 1, a pulmonary exacerbation was defined as a change in antibiotic therapy (IV, inhaled, or oral) as a result of 4 or more of 12 prespecified sinopulmonary signs/symptoms.[1]

IV, intravenous.

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Baseline characteristics for Trials 1 and 2[5,14]

	Trial 1 (N=403)		**Trial 2** (N=107)	
	TRIKAFTA (n=200)	**Placebo** (n=203)	**TRIKAFTA** (n=55)	**Comparator** (n=52)
Sex, female %	48.0	48.3	56	54
Mean age, years (SD)	25.6 (9.7)	26.8 (11.3)	28.8 (11.5)	27.9 (10.8)
Mean ppFEV$_1$ (SD)	61.6 (15.0)	61.3 (15.5)	61.6 (15.4)	60.2 (14.4)
Mean sweat chloride, mmol/L (SD)	102.3 (11.9)	102.9 (9.8)	91.4 (11.0)	90.0 (12.3)
Mean CFQ-R Respiratory Domain score, points (SD)	68.3 (16.9)	70.0 (17.8)	70.6 (16.2)	72.6 (17.9)
Mean BMI, kg/m^2 (SD)	21.49 (3.07)	21.31 (3.14)	21.75 (3.19)	21.88 (4.12)

Extension Study limitations and disclosures[1,15,20,21,33]

- The study was not placebo-controlled; therefore, causality cannot be attributed, and hypothesis testing cannot determine whether within-arm changes were due to drug effect
- The Extension Study may not meet the FDA definition of an adequate and well-controlled study due to its design
- All patients and investigators knew that subjects were on active drug, which may have introduced bias related to awareness of treatment
- Enrollment was limited to patients who completed Trial 1 or Trial 2 and elected to enroll in the Extension Study
- The safety data were pooled across all cohorts
- Trials 1 and 2 required patients to remain on their usual prescribed CF regimens. In the Extension Study, patients may have had changes in their stable medication regimen, but the data set was not large enough to assess the effect that changes in concomitant drugs could have had on the efficacy and safety profile
- Although the Extension Study was a longer-term study, clinical trials cannot always detect rare adverse events
- Data from the Extension Study are not included in the full Prescribing Information for TRIKAFTA and the FDA did not consider these data in approving the product
- This open-label Extension Study overlapped with the COVID-19 pandemic and may have had an effect on pulmonary exacerbations

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TRIKAFTA demonstrated benefits vs control arms in patients aged 12 years and older[a]

	TRIAL 1[1,14]	TRIAL 2[1,13]	EXTENSION STUDY[15]
Change in lung function[bc]	13.8 percentage points: LS-mean absolute change from baseline in ppFEV$_1$ at Week 4 vs placebo (95% CI: 12.1, 15.4; *P*<0.0001) 14.3 percentage points: LS-mean absolute change from baseline in ppFEV$_1$ through Week 24 vs placebo (95% CI: 12.7, 15.8; *P*<0.0001)	10.0 percentage points: LS-mean absolute change from baseline in ppFEV$_1$ at Week 4 vs active comparator (95% CI: 7.4, 12.6; *P*<0.0001)	For patients who stayed on or transitioned to TRIKAFTA, improvements in lung function were generally maintained at Extension Study Week 192
Safety and tolerability profile	Please click here for safety results for Trial 1	The safety results for the patients treated with TRIKAFTA in Trial 2 was similar to that observed in Trial 1	TRIKAFTA safety findings at Extension Study Week 192 were consistent with the established safety profile in Trial 1
Change in rates of pulmonary exacerbation	63% reduction: In Trial 1, the number of pulmonary exacerbation events (event rate per year calculated based on 48 weeks per year) was 113 (0.98) in the placebo group and 41 (0.37) in the TRIKAFTA group. The difference in rates was 0.37 (95% CI: 0.25, 0.55; *P*<0.0001)	Pulmonary exacerbations were not an efficacy outcome in Trial 2, but there was a reduction in reported adverse events of infective pulmonary exacerbation of CF in the group on treatment vs the comparator group	The rate of pulmonary exacerbation was 0.21 (95% CI: 0.17, 0.25) per 48 weeks across Trial 1 and Extension Study[d]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

Elevated Transaminases and Hepatic Injury (cont'd)

- For patients with a history of hepatobiliary disease or liver function test elevations, more frequent monitoring should be considered

[a]Extension Study results are from the final analysis at Week 192.[15]
[b]Trial 1, mean baseline ppFEV$_1$ was 61.6 percentage points (range: 33.8, 97.1) for patients receiving TRIKAFTA and 61.3 percentage points (range: 32.3, 93.7) for patients receiving placebo.[34]
[c]Trial 2, mean baseline ppFEV$_1$ was 61.6 percentage points (range: 35.0, 87.4) for patients receiving TRIKAFTA and 60.2 percentage points (range: 35.0, 89.0) for patients receiving the active comparator.[35]
[d]Pulmonary exacerbation rates were calculated based on the cumulative efficacy analysis period, which was defined as the time from the first dose of TRIKAFTA in the parent studies until the last efficacy assessment in the Extension Study. Restrictions on social interactions due to the COVID-19 pandemic may have contributed to the low incidence of pulmonary exacerbations.[33]

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TRIKAFTA demonstrated benefits vs control arms in patients aged 12 years and older[a] (cont'd)

	TRIAL 1[1,5,31]	TRIAL 2[1,14]	EXTENSION STUDY[15]
Change in sweat chloride[bc]	**41.8** mmol/L LS-mean absolute change from baseline in sweat chloride through Week 24 vs placebo (95% CI: -44.4, -39.3; *P*<0.0001)	**45.1** mmol/L LS-mean absolute change from baseline in sweat chloride at Week 4 vs active comparator (95% CI: -50.1, -40.1; *P*<0.0001)	For patients who stayed on and transitioned onto TRIKAFTA, reductions in sweat chloride were generally maintained at Extension Study Week 192
Change in CFQ-R Respiratory Domain score	**20.2** points LS-mean absolute change from baseline in CFQ-R Respiratory Domain score through Week 24 vs placebo (95% CI: 17.5, 23.0; *P*<0.0001)	**17.4** points LS-mean absolute change from baseline in CFQ-R Respiratory Domain score at Week 4 vs active comparator (95% CI: 11.8, 23.0; *P*<0.0001)	For patients who stayed on and transitioned onto TRIKAFTA, changes in CFQ-R Respiratory Domain score were generally maintained at Extension Study Week 192
Change in BMI	**1.04** kg/m^2 LS-mean absolute change from baseline in BMI at Week 24 vs placebo (95% CI: 0.85, 1.23; *P*<0.0001)	**0.60** kg/m^2 LS-mean absolute change from baseline in BMI at Week 4 vs active comparator (95% CI: 0.41, 0.79)*	For patients who stayed on and transitioned onto TRIKAFTA, changes in BMI were generally maintained at Extension Study Week 192

*BMI was not a predefined endpoint for Trial 2; it was measured as part of the physical assessment. Analysis was not corrected for multiplicity.[14]

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (cont'd)

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 the benefits and risks for the individual patient to determine whether to resume treatment with TRIKAFTA

[a]Extension Study results are from the final analysis at Week 192.[15]
[b]Trial 1, mean baseline sweat chloride was 102.3 mmol/L (range: 22.5, 156.0) for patients receiving TRIKAFTA and 102.9 mmol/L (range: 68.5, 137.0) for those receiving placebo.[34]
[c]In Trial 2, mean baseline sweat chloride was 91.4 mmol/L (range: 67.0, 114.0) for patients receiving TRIKAFTA and 90.0 mmol/L (range: 60.5, 112.0) for patients receiving the active comparator.[35]

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Safety results demonstrated in Trials 1 and 2, and the Extension Study

- A total of 257 patients in Trials 1 and 2 received a dose of TRIKAFTA, and a total of 506 patients received a dose in the Extension Study[1,15]
- The safety results of the Extension Study are consistent with safety findings found in Trial 1[15]
- The safety results for the patients with CF enrolled in Trial 2 was similar to that observed in Trial 1[1]

TRIAL 1[1,5]

Discontinuations and serious adverse events

- 2 patients (1%) on treatment discontinued due to adverse events vs 0 patients (0%) on placebo
- Serious adverse events that occurred more frequently in patients on treatment vs placebo were rash (1% vs <1%) and influenza (1% vs 0%)
- There were no deaths in Trial 1

Liver-related adverse events

- The incidence of elevated ALT/AST >8x, >5x, or >3x ULN was reported in 3 (1%), 5 (2%), and 16 (8%) patients on treatment vs 2 (1%), 3 (1%), and 11 (5%) patients on placebo
- The incidence of adverse events of transaminase elevations (AST and/or ALT) was 11% in patients on treatment vs 4% on placebo
- No patients treated with TRIKAFTA discontinued treatment due to transaminase elevations

EXTENSION STUDY[5,33,36]

Discontinuations and serious adverse events

- 18 patients (3.6%) had adverse events leading to treatment discontinuation
- Serious adverse events occurring in ≥1% of patients on treatment were infective pulmonary exacerbation of CF (16.4%), hemoptysis (2.2%), DIOS (1.8%), influenza (1.4%), constipation (1.2%), and pneumonia (1.2%)
- 1 death occurred during the study due to an adverse event of oxycodone toxicity that was considered unrelated to study drug

Liver-related adverse events

- ALT/AST levels >3x, >5x, >8x, and >20x ULN were reported in 63 (12.5%), 36 (7.1%), 11 (2.2%), and 2 (0.4%) patients, respectively
- Adverse events of elevated transaminases (AST and/or ALT) occurred in 88 (17.4%) patients; of these, 7 patients (1.4%) discontinued treatment due to elevated transaminase events

DIOS, distal intestinal obstruction syndrome.

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Incidence of rash events, increased creatine phosphokinase, and elevated blood pressure in patients treated with TRIKAFTA

TRIAL 1[1]

Rash events

- The overall incidence of rash events was 10% in patients on treatment vs 5% on placebo

Increased creatine phosphokinase

- The incidence of maximum CPK >5x ULN was 10% in patients on treatment vs 5% on placebo
- 14% (3/21) of TRIKAFTA-treated patients with CPK >5x ULN required treatment interruptions and 0 discontinued treatment

Increased blood pressure

- 4% of patients on treatment had an increase in systolic blood pressure >140 mm Hg and 10 mm Hg on at least 2 occasions from baseline vs 1% on placebo
- 1% of patients on treatment had an increase in diastolic blood pressure >90 mm Hg and 5 mm Hg on at least 2 occasions from baseline vs 2% on placebo

EXTENSION STUDY[36]

Rash events

- 89 patients (17.6%) experienced at least 1 rash event at the time of the final analysis
- 2 patients (0.4%) experienced serious rash events. Treatment with TRIKAFTA was discontinued for 1 of these 2 patients

Increased creatine phosphokinase

- 38 patients (7.5%) had CPK >5x ULN to ≤10x ULN, and 47 patients (9.3%) had CPK >10x ULN
- 7 patients (1.4%) required treatment interruption, and 1 patient (0.2%) discontinued treatment

Increased blood pressure

- Blood pressure data from the Extension Study were consistent with those from Trials 1 and 2

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CPK, creatine phosphokinase.

Most common adverse events experienced on TRIKAFTA

- In Trial 1, the most common adverse events to occur in both trial arms (≥5% of patients treated with TRIKAFTA and higher than placebo by ≥1%) were headache, upper respiratory tract infection,[a] abdominal pain,[b] diarrhea, rash,[c] ALT increased, nasal congestion, blood CPK increased, AST increased, rhinorrhea, rhinitis, influenza, sinusitis, blood bilirubin increased[1]
- In Trial 2, the most common adverse events (occurring in ≥4 participants in either trial group) were cough, nasopharyngitis, oropharyngeal pain, upper respiratory tract infection, headache, hemoptysis, and pulmonary exacerbation[14]
- In the Extension Study, the majority of adverse events were considered mild to moderate in severity
  - Mild (12.8%), moderate (60.7%), severe (24.7%), and life-threatening (1.4%)[15]
- 504 patients (99.6%) experienced TEAEs at Extension Study Week 192[15]

Most common TEAEs occurring in ≥20% of patients at Extension Study Week 192, n (%) (N=506)[15]	
Infective PEx of cystic fibrosis	245 (48.4)
Cough	231 (45.7)
Headache	178 (35.2)
COVID-19	171 (33.8)
Oropharyngeal pain	166 (32.8)
Nasopharyngitis	154 (30.4)
Pyrexia	148 (29.2)
Sputum increased	128 (25.3)
Upper respiratory tract infection	120 (23.7)
Fatigue	118 (23.3)
Nasal congestion	113 (22.3)

[a]Includes upper respiratory tract infection and viral upper respiratory tract infection.[1]
[b]Includes abdominal pain, abdominal pain upper, and abdominal pain lower.[1]
[c]Includes rash, rash generalized, rash erythematous, rash macular, and rash pruritic.[1]

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Oral granules dosing of TRIKAFTA

Recommended dosage

For patients aged 2 through 5 years weighing <14 kg (<31 lb)[1,37]

~12 hours apart

MORNING

NDC: 51167-445-01

elexacaftor **80 mg**
tezacaftor **40 mg**
ivacaftor **60 mg**

1 white and blue packet

EVENING

ivacaftor **59.5 mg**

1 white and green packet

For patients aged 2 through 5 years weighing ≥14 kg (≥31 lb)[1,37]

~12 hours apart

MORNING

NDC: 51167-446-01

elexacaftor **100 mg**
tezacaftor **50 mg**
ivacaftor **75 mg**

1 white and orange packet

EVENING

ivacaftor **75 mg**

1 white and pink packet

- It is important that patients consume the entire granules mixture with each dose[1]

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How to administer oral granule doses of TRIKAFTA[1]

1 Preparation

- Caregiver should hold the packet with the perforation on top, shake the packet gently to settle the granules, and tear or cut the packet open along the perforation
- Caregiver should mix all granules into 1 teaspoon (5 mL) of age-appropriate soft food or liquid
- Food or liquid should be at or below room temperature

Note: Use thickened food/purée in younger patients who are adjusting to solid foods.

Note: Examples of soft or liquids include:


Puréed fruits or vegetables


Yogurt or applesauce


Milk, juice, or water

2 Administration

- After mixing granules, caregiver should give the dose within 1 hour
- Caregiver should make sure the child finishes the dose completely

3 Give fat-containing food

- Food that contains fat must be taken just before or after the oral granules dose

Examples of fat-containing foods include:
- Eggs • Avocado • Nuts • Butter • Peanut butter • Cheese pizza
- Whole-milk dairy products (eg, whole milk, cheese, and yogurt)

Note: The list above includes only examples. Parents/caretakers can try other fat-containing foods that work best for the patient. **Food or drink containing grapefruit should be avoided during treatment with TRIKAFTA.**

IT IS IMPORTANT FOR PATIENTS TO CONSUME THE ENTIRE DOSE OF ORAL GRANULES WITHIN 1 HOUR AFTER MIXING

Refer your patients' caregivers to TRIKAFTA.com for more information on administering TRIKAFTA granules.

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Tablets dosing of TRIKAFTA

Dosing information[1]

- For oral use. Patients should be instructed to swallow the tablets whole
- TRIKAFTA should be taken with fat-containing meals or snacks. Examples include food prepared with butter or oils or those containing peanut butter, eggs, cheeses, nuts, whole milk, or meats
- **Food or drink containing grapefruit should be avoided during treatment with TRIKAFTA**

Recommended dosage

For patients aged 6 through 11 years weighing <30 kg (<66 lb)[1,37]

MORNING ← **~12 hours apart** → **EVENING**

elexacaftor **50 mg**/
tezacaftor **25 mg**/
ivacaftor **37.5 mg**

2 light orange tablets

ivacaftor **75 mg**

1 light blue tablet

Tablets are not actual size.

Product packaging[1]

- TRIKAFTA is supplied in cartons containing 4 weekly wallets, each with 21 tablets
- TRIKAFTA is a fixed-dose combination containing elexacaftor 50 mg, tezacaftor 25 mg, and ivacaftor 37.5 mg co-packaged with ivacaftor 75 mg tablets
- The elexacaftor, tezacaftor, and ivacaftor tablets are light orange, capsule-shaped, and debossed with “T50” on one side and plain on the other
- The ivacaftor tablets are light blue, capsule-shaped, and printed with “V 75” in black ink on one side and plain on the other

For patients aged 6 through 11 years weighing <30 kg (<66 lb)

NDC: 51167-106-02
Tablets are not actual size.

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Tablets dosing of TRIKAFTA (cont'd)

Recommended dosage

For patients aged 6 through 11 years weighing ≥30 kg (≥66 lb) and 12 years and older[1,37]

MORNING ←— **~12 hours apart** —→ **EVENING**

elexacaftor **100 mg**/
tezacaftor **50 mg**/
ivacaftor **75 mg**

2 orange tablets

ivacaftor **150 mg**

1 light blue tablet

Tablets are not actual size.

Product packaging[1]

- TRIKAFTA is supplied in cartons containing 4 weekly wallets, each with 21 tablets
- TRIKAFTA is a fixed-dose combination containing elexacaftor 100 mg, tezacaftor 50 mg, and ivacaftor 75 mg co-packaged with ivacaftor 150 mg tablets
- The elexacaftor, tezacaftor, and ivacaftor tablets are orange, capsule-shaped, and debossed with “T100” on one side and plain on the other
- The ivacaftor tablets are light blue, capsule-shaped, and printed with “V 150” in black ink on one side and plain on the other

For patients aged 6 through 11 years weighing ≥30 kg (≥66 lb) and 12 years and older

NDC: 51167-331-01
Tablets are not actual size.

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Dosing adjustments for TRIKAFTA

MISSED DOSE[1]

MISSED MORNING DOSE

- If ≤6 hours have passed, take as soon as possible and take the evening dose as scheduled
- If >6 hours have passed, take the missed morning dose as soon as possible, but do **not** take evening dose and continue as scheduled the following day

MISSED EVENING DOSE

- If ≤6 hours have passed, take as soon as possible and take next morning dose as scheduled
- If >6 hours have passed, do **not** take missed dose and take next morning dose as scheduled the following day

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

Recommended dosage for use of TRIKAFTA in patients with hepatic impairment[1]

Age	Mild[a] (Child Pugh Class A)	Moderate[a] (Child Pugh Class B)	Severe[b] (Child Pugh Class C)
2 through 5 years	No dose adjustment	**Use of TRIKAFTA is not recommended and 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: • Days 1-3: one packet of elexacaftor/tezacaftor/ivacaftor granules each day • Day 4: no dose • Day 5-6: one packet of elexacaftor/tezacaftor/ivacaftor granules each day • Day 7: no dose Repeat above dosing schedule each week. The evening dose of the ivacaftor granules should not be taken.	**Should not be used**
6 years and older	No dose adjustment	**Use of TRIKAFTA is not recommended and should only be considered when there is a clear medical need, and the benefit exceeds the risk.** If used, TRIKAFTA should be used with caution at a reduced dose, as follows: • Day 1: take two elexacaftor/tezacaftor/ivacaftor tablets in the morning • Day 2: take one elexacaftor/tezacaftor/ivacaftor tablet in the morning Continue alternating Day 1 and Day 2 dosing thereafter. No evening dose of ivacaftor tablet should be taken.	**Should not be used**

- No dosage adjustment is recommended in patients with mild (eGFR 60 to <90 mL/min/1.73 m²) or moderate (eGFR 30 to <60 mL/min/1.73 m²) renal impairment. TRIKAFTA has not been studied in patients with severe (eGFR <30 mL/min/1.73 m²) renal impairment or end-stage renal disease and should be used with caution in these patients[1]

[a]Liver function tests should be closely monitored.[1]
[b]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.[1]

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Please click for Important Safety Information and full Prescribing Information for TRIKAFTA.

Drug interactions[1]

Drug interaction profiles and related dosing considerations[1]

Clinical considerations for TRIKAFTA are based on drug interaction studies, modeling, other clinical factors, and/or predicted interactions due to elimination pathways. **Dosage adjustments are required for concomitant use with strong and moderate CYP3A inhibitors.**

For patients aged 2 through 5 years weighing <14 kg (<31 lb)[1,37]

	Dose recommendation	TRIKAFTA interaction
Strong CYP3A inducers including: rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, St. John's wort *(Hypericum perforatum)*	CONCOMITANT USE NOT RECOMMENDED	↓ **Reduced exposure of TRIKAFTA expected with strong CYP3A inducers** • The concomitant use of CYP3A inducers may reduce TRIKAFTA therapeutic effectiveness
Strong CYP3A inhibitors including: ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, clarithromycin	IN THE MORNING (TWICE A WEEK) DAY 1: elexacaftor 80 mg/tezacaftor 40 mg/ivacaftor 60 mg — 1 white and blue packet DAY 4[a]: elexacaftor 80 mg/tezacaftor 40 mg/ivacaftor 60 mg — 1 white and blue packet NO PACKET IN THE EVENING	↑ **Increased exposure of TRIKAFTA expected with strong or moderate CYP3A inhibitors** • Coadministration 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
Moderate CYP3A inhibitors including: fluconazole, erythromycin	ALTERNATE PACKETS EVERY MORNING DAY 1: elexacaftor 80 mg/tezacaftor 40 mg/ivacaftor 60 mg — 1 white and blue packet DAY 2[b]: ivacaftor 59.5 mg — 1 white and green packet NO PACKET IN THE EVENING	
CYP2C9 substrates including: warfarin, glimepiride, glipizide **P-glycoprotein (P-gp) substrates including:** digoxin, cyclosporine, everolimus, sirolimus, tacrolimus **OATP1B1 and OATP1B3 substrates including:** statins, glyburide, nateglinide, repaglinide	Caution and appropriate monitoring should be used with CYP2C9, P-gp, and OATP1B1 and OATP1B3 substrates	↑ **Increased exposure of substrates may occur with TRIKAFTA** • Ivacaftor may inhibit CYP2C9 • Ivacaftor or tezacaftor/ivacaftor increases digoxin exposure and may increase exposure of other sensitive P-gp substrates • Elexacaftor and M23-ELX (active metabolite) inhibit OATP1B1 and OATP1B3 *in vitro*

[a]Continue dosing with 1 elexacaftor/tezacaftor/ivacaftor packet twice a week, approximately 3 to 4 days apart.[1]
[b]Continue dosing with 1 elexacaftor/tezacaftor/ivacaftor packet and 1 ivacaftor packet on alternate days.[1]
CYP, cytochrome P450; M23-ELX, active metabolite of elexacaftor; OATP, organic anion transporting polypeptide; P-gp, P-glycoprotein.

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Drug interactions[1] (cont'd)

Drug interaction profiles and related dosing considerations[1]

For patients aged 2 through 5 years weighing ≥14 kg (≥31 lb)[1,37]

	Dose recommendation	TRIKAFTA interaction
Strong CYP3A inducers including: rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, St. John's wort *(Hypericum perforatum)*	CONCOMITANT USE NOT RECOMMENDED	**↓ Reduced exposure of TRIKAFTA expected with strong CYP3A inducers** • The concomitant use of CYP3A inducers may reduce TRIKAFTA therapeutic effectiveness
Strong CYP3A inhibitors including: ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, clarithromycin	IN THE MORNING (TWICE A WEEK) **DAY 1**: elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg — 1 white and orange packet **DAY 4[a]**: elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg — 1 white and orange packet NO PACKET IN THE EVENING	**↑ Increased exposure of TRIKAFTA expected with strong or moderate CYP3A inhibitors** • Coadministration 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
Moderate CYP3A inhibitors including: fluconazole, erythromycin	ALTERNATE PACKET EVERY MORNING **DAY 1**: elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg — 1 white and orange packet **DAY 2[b]**: ivacaftor 75 mg — 1 white and pink packet NO PACKET IN THE EVENING	
CYP2C9 substrates including: warfarin, glimepiride, glipizide	Caution and appropriate monitoring should be used with CYP2C9, P-gp, and OATP1B1 and OATP1B3 substrates	**↑ Increased exposure of substrates may occur with TRIKAFTA** • Ivacaftor may inhibit CYP2C9 • Ivacaftor or tezacaftor/ivacaftor increases digoxin exposure and may increase exposure of other sensitive P-gp substrates • Elexacaftor and M23-ELX (active metabolite) inhibit OATP1B1 and OATP1B3 *in vitro*
P-glycoprotein (P-gp) substrates including: digoxin, cyclosporine, everolimus, sirolimus, tacrolimus		
OATP1B1 and OATP1B3 substrates including: statins, glyburide, nateglinide, repaglinide		

[a]Continue dosing with 1 elexacaftor/tezacaftor/ivacaftor packet twice a week, approximately 3 to 4 days apart.[1]
[b]Continue dosing with 1 elexacaftor/tezacaftor/ivacaftor packet and 1 ivacaftor packet on alternate days.[1]

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Drug interactions[1] (cont'd)

Drug interaction profiles and related dosing considerations[1]

Clinical considerations for TRIKAFTA are based on drug interaction studies, modeling, other clinical factors, and/or predicted interactions due to elimination pathways. **Dosage adjustments are required for concomitant use with strong and moderate CYP3A inhibitors.**

For patients aged 6 through 11 years weighing <30 kg (<66 lb)[1,37]

	Dose recommendation	TRIKAFTA interaction
Strong CYP3A inducers including: rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, St. John's wort *(Hypericum perforatum)*	CONCOMITANT USE NOT RECOMMENDED	↓ **Reduced exposure of TRIKAFTA expected with strong CYP3A inducers** • The concomitant use of CYP3A inducers may reduce TRIKAFTA therapeutic effectiveness
Strong CYP3A inhibitors including: ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, clarithromycin	IN THE MORNING (TWICE A WEEK) **DAY 1**: elexacaftor **50 mg**/tezacaftor **25 mg**/ivacaftor **37.5 mg**, 2 light orange tablets **DAY 4**[a]: elexacaftor **50 mg**/tezacaftor **25 mg**/ivacaftor **37.5 mg**, 2 light orange tablets NO TABLET IN THE EVENING	↑ **Increased exposure of TRIKAFTA expected with strong or moderate CYP3A inhibitors** • Coadministration 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
Moderate CYP3A inhibitors including: fluconazole, erythromycin	ALTERNATE TABLETS EVERY MORNING **DAY 1**: elexacaftor **50 mg**/tezacaftor **25 mg**/ivacaftor **37.5 mg**, 2 light orange tablets **DAY 2**[b]: ivacaftor **75 mg**, 1 light blue tablet NO TABLET IN THE EVENING	
CYP2C9 substrates including: warfarin, glimepiride, glipizide **P-glycoprotein (P-gp) substrates including:** digoxin, cyclosporine, everolimus, sirolimus, tacrolimus **OATP1B1 and OATP1B3 substrates including:** statins, glyburide, nateglinide, repaglinide	Caution and appropriate monitoring should be used with CYP2C9, P-gp, and OATP1B1 and OATP1B3 substrates	↑ **Increased exposure of substrates may occur with TRIKAFTA** • Ivacaftor may inhibit CYP2C9 • Ivacaftor or tezacaftor/ivacaftor increases digoxin exposure and may increase exposure of other sensitive P-gp substrates • Elexacaftor and M23-ELX (active metabolite) inhibit OATP1B1 and OATP1B3 *in vitro*

[a]Continue dosing with 2 elexacaftor/tezacaftor/ivacaftor tablets twice a week, approximately 3 to 4 days apart.[1]
[b]Continue dosing with 2 elexacaftor/tezacaftor/ivacaftor tablets and 1 ivacaftor tablet on alternate days.[1]

trikafta®
(elexacaftor/tezacaftor/ivacaftor and ivacaftor)

Drug interactions[1] (cont'd)

Drug interaction profiles and related dosing considerations[1]

For patients aged 6 through 11 years weighing ≥30 kg (≥66 lb) and 12 years and older[1,37]

	Dose recommendation	TRIKAFTA interaction
Strong CYP3A inducers including: rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, St. John's wort *(Hypericum perforatum)*	CONCOMITANT USE NOT RECOMMENDED	**↓ Reduced exposure of TRIKAFTA expected with strong CYP3A inducers** • The concomitant use of CYP3A inducers may reduce TRIKAFTA therapeutic effectiveness
Strong CYP3A inhibitors including: ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, clarithromycin	IN THE MORNING (TWICE A WEEK) **DAY 1**: elexacaftor **100 mg**/tezacaftor **50 mg**/ivacaftor **75 mg** — 2 orange tablets **DAY 4[a]**: elexacaftor **100 mg**/tezacaftor **50 mg**/ivacaftor **75 mg** — 2 orange tablets NO TABLET IN THE EVENING	**↑ Increased exposure of TRIKAFTA expected with strong or moderate CYP3A inhibitors** • Coadministration 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
Moderate CYP3A inhibitors including: fluconazole, erythromycin	ALTERNATE TABLETS EVERY MORNING **DAY 1**: elexacaftor **100 mg**/tezacaftor **50 mg**/ivacaftor **75 mg** — 2 orange tablets **DAY 2[b]**: ivacaftor **150 mg** — 1 light blue tablet NO TABLET IN THE EVENING	
CYP2C9 substrates including: warfarin, glimepiride, glipizide	Caution and appropriate monitoring should be used with CYP2C9, P-gp, and OATP1B1 and OATP1B3 substrates	**↑ Increased exposure of substrates may occur with TRIKAFTA** • Ivacaftor may inhibit CYP2C9 • Ivacaftor or tezacaftor/ivacaftor increases digoxin exposure and may increase exposure of other sensitive P-gp substrates • Elexacaftor and M23-ELX (active metabolite) inhibit OATP1B1 and OATP1B3 *in vitro*
P-glycoprotein (P-gp) substrates including: digoxin, cyclosporine, everolimus, sirolimus, tacrolimus		
OATP1B1 and OATP1B3 substrates including: statins, glyburide, nateglinide, repaglinide		

[a]Continue dosing with 2 elexacaftor/tezacaftor/ivacaftor tablets twice a week, approximately 3 to 4 days apart.[1]
[b]Continue dosing with 2 elexacaftor/tezacaftor/ivacaftor tablets and 1 ivacaftor tablet on alternate days.[1]

trikafta®
(elexacaftor/tezacaftor/ivacaftor and ivacaftor)

trikafta®

(elexacaftor/tezacaftor/ivacaftor
and ivacaftor)

Considerations for Initiating Patients Onto TRIKAFTA Who Were Previously Treated With Another CFTR Modulator

Considerations for transitioning patients are intended only for patients eligible for TRIKAFTA. These are patients with CF aged 2 years and older with at least one *F508del* mutation or a mutation that is responsive based on *in vitro* data.[1]

ORKAMBI®
(lumacaftor/ivacaftor)
100/125 mg • 200/125 mg tablets
75/94 mg • 100/125 mg • 150/188 mg oral granules

Clinical considerations when transitioning patients[38]

Clinical considerations when transitioning patients from ORKAMBI to TRIKAFTA® (elexacaftor/tezacaftor/ivacaftor and ivacaftor) are based on drug interaction studies, modeling, other clinical factors, and/or predicted interactions due to elimination pathways.

ORKAMBI	TRIKAFTA

- Patients will still continue to receive ivacaftor, but in combination with elexacaftor and tezacaftor instead of lumacaftor
- **The initial dose of TRIKAFTA should be taken in the morning, approximately 12 hours after the final dose of ORKAMBI**
- During approximately the first 2 weeks after transition:

Blood levels of elexacaftor will be increasing

Blood levels of tezacaftor will be increasing

Blood levels of lumacaftor will be decreasing

Blood levels of ivacaftor may decrease slightly before returning to steady state

Elexacaftor, tezacaftor, and ivacaftor are expected to reach steady state within 1 to 2 weeks

- **When patients have no identified drug-drug interactions at the time of transition to TRIKAFTA, consider waiting 2 weeks before initiating any new concomitant medications that interact with ORKAMBI as lumacaftor-mediated interactions may persist during this period**

ORKAMBI®
(lumacaftor/ivacaftor)
100/125 mg • 200/125 mg tablets
75/94 mg • 100/125 mg • 150/188 mg oral granules

Select drug-drug interactions

Only those drugs listed below are expected to have interactions with TRIKAFTA® (elexacaftor/tezacaftor/ivacaftor and ivacaftor). Drugs within a class may have different metabolic profiles, and therefore clinical recommendations apply only to the drugs listed here and not the class.

Select drug-drug interactions to consider in patients transitioning from ORKAMBI to TRIKAFTA[38]

	Recommendation	Interaction
Antibiotics clarithromycin, erythromycin, telithromycin	**Consider waiting 2 weeks before starting these antibiotics** • Dose adjustment of TRIKAFTA is recommended; see the dosing and administration table on page 42	• Co-administration of strong and moderate CYP3A inhibitors, such as those listed, increased exposures to TRIKAFTA • Residual CYP induction by lumacaftor during transition may potentially reduce exposure to these antibiotic agents
Antidepressants citalopram, escitalopram, mirtazapine, paroxetine, sertraline, trazodone	**No dose adjustments of these drugs are recommended during treatment with TRIKAFTA** **If dose was increased during treatment with ORKAMBI, consider dose reduction during the transition period**	• Lumacaftor-mediated CYP3A induction will decrease as ORKAMBI exposure decreases. For patients whose doses of these medications were increased during co-administration with ORKAMBI, the exposure of these concomitant medications may increase if dose is held constant during transition to TRIKAFTA
Antifungals fluconazole	**Consider waiting 2 weeks before starting with this antifungal** • Dose adjustment is recommended. The dose of TRIKAFTA should be reduced when co-administered with fluconazole and other moderate CYP3A inhibitors; see the dosing and administration table on page 42	• Fluconazole, a moderate CYP3A inhibitor, may increase TRIKAFTA exposures
Itraconazole, ketoconazole, posaconazole, voriconazole	**Consider waiting 2 weeks before starting these antifungals** • Dose adjustment of TRIKAFTA is recommended; see the dosing and administration table on page 42	• Co-administration of strong CYP3A inhibitors, such as those listed, may increase exposure to TRIKAFTA • Residual CYP3A induction by lumacaftor during transition may potentially reduce exposure to these antifungal agents

Continued on next page.

ORKAMBI®
(lumacaftor/ivacaftor)
100/125 mg • 200/125 mg tablets
75/94 mg • 100/125 mg • 150/188 mg oral granules

Select drug-drug interactions (cont'd)

Clinical considerations when transitioning patients from ORKAMBI to TRIKAFTA® (elexacaftor/tezacaftor/ivacaftor and ivacaftor) are based on drug interaction studies, modeling, other clinical factors, and/or predicted interactions due to elimination pathways.

Select drug-drug interactions to consider in patients transitioning from ORKAMBI to TRIKAFTA[38]

	Recommendation	Interaction
Anti-inflammatories	**No dose adjustments of these drugs are recommended during treatment with TRIKAFTA** **If dose was increased during treatment with ORKAMBI, consider dose reduction during the transition period**	• Lumacaftor-mediated CYP3A induction will decrease as ORKAMBI exposure decreases. For patients whose doses of these medications were increased during co-administration with ORKAMBI, the exposure of these concomitant medications may increase if dose is held constant during transition to TRIKAFTA
Benzodiazepines midazolam, triazolam	**Consider waiting 2 weeks before starting certain benzodiazepines**	• Residual CYP3A induction by lumacaftor during transition may potentially reduce drug exposures
Alprazolam, diazepam	**No dose adjustments of these drugs are recommended during treatment with TRIKAFTA** **If dose was increased during treatment with ORKAMBI, consider dose reduction during the transition period**	• Lumacaftor-mediated CYP induction will decrease as ORKAMBI exposure decreases. For patients whose doses of these medications were increased during co-administration with ORKAMBI, the exposure of these concomitant medications may increase if dose is held constant during transition to TRIKAFTA
Food or drink grapefruit	**Food or drink containing grapefruit should be avoided during treatment with TRIKAFTA**	• Co-administration of TRIKAFTA with food or drink containing grapefruit, which contains one or more components that moderately inhibit CYP3A, may increase exposure of TRIKAFTA

Continued on next page.

ORKAMBI®
(lumacaftor/ivacaftor)
100/125 mg • 200/125 mg tablets
75/94 mg • 100/125 mg • 150/188 mg oral granules

Select drug-drug interactions (cont'd)

When patients have no identified drug-drug interactions at the time of transition to TRIKAFTA® (elexacaftor/tezacaftor/ivacaftor and ivacaftor), consider waiting 2 weeks before initiating any new concomitant medications that interact with ORKAMBI as lumacaftor-mediated interactions may persist during this period.[1]

Select drug-drug interactions to consider in patients transitioning from ORKAMBI to TRIKAFTA[1,38]

	Recommendation	Interaction
Hormonal contraceptives	**Hormonal contraceptives should not be considered effective for at least 2 weeks after transition**	• TRIKAFTA is not expected to have an impact on the efficacy of oral contraceptives[2] • 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[2]
Immunosuppressants cyclosporine, everolimus, sirolimus, tacrolimus	**Consider waiting 2 weeks before starting certain immunosuppressants** • If used after 2 weeks, caution and appropriate monitoring should be used with certain immunosuppressants	• Concomitant use of TRIKAFTA may increase levels of cyclosporine, everolimus, sirolimus, and tacrolimus due to P-gp inhibition by ivacaftor. Increased immunosuppression may occur • Residual CYP3A induction by lumacaftor during transition may potentially reduce drug exposures
Oral hypoglycemics nateglinide, repaglinide	**Co-administration of TRIKAFTA may increase exposure of nateglinide and repaglinide due to OATP1B1/B3 inhibition by ELX and M23-ELX. Caution and appropriate monitoring is recommended[2]** **If dose was increased during treatment with ORKAMBI, consider dose reduction during the transition period**	• Lumacaftor-mediated CYP induction will decrease as ORKAMBI exposure decreases. For patients whose doses of these medications were increased during co-administration with ORKAMBI, the exposure of these concomitant medications may increase if dose is held constant during transition to TRIKAFTA
Proton pump inhibitors (PPIs) and H2 blockers esomeprazole, lansoprazole, omeprazole, ranitidine	**No dose adjustments of these drugs are recommended during treatment with TRIKAFTA** **If dose was increased during treatment with ORKAMBI, consider dose reduction during the transition period**	
Systemic corticosteroids methylprednisolone, prednisone, prednisolone		

Other drug interactions are predicted with ORKAMBI and/or TRIKAFTA, including:

• Antiarrhythmics (digoxin) • Anticoagulants (warfarin) • Anticonvulsants (carbamazepine, phenobarbital, phenytoin) • Herbals (St. John's wort)

Please click here to see dose adjustments for TRIKAFTA.

ORKAMBI®
(lumacaftor/ivacaftor)
100/125 mg • 200/125 mg tablets
75/94 mg • 100/125 mg • 150/188 mg oral granules

INDICATION AND IMPORTANT SAFETY INFORMATION FOR ORKAMBI

INDICATION AND USAGE

ORKAMBI is a combination of lumacaftor and ivacaftor indicated for the treatment of cystic fibrosis (CF) in patients aged 1 year and older who are homozygous for the F508del mutation in the CFTR gene. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the F508del mutation on both alleles of the CFTR gene.

Limitations of Use

The efficacy and safety of ORKAMBI have not been established in patients with CF other than those homozygous for the F508del mutation.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Use in Patients With Advanced Liver Disease

- Worsening of liver function, including hepatic encephalopathy, in patients with advanced liver disease has been reported. Liver function decompensation, including liver failure leading to death, has been reported in CF patients with pre-existing cirrhosis with portal hypertension while receiving ORKAMBI. Use ORKAMBI with caution in patients with advanced liver disease and only if the benefits are expected to outweigh the risks. If ORKAMBI is used in these patients, they should be closely monitored after the initiation of treatment and the dose should be reduced

Liver-related Events

- Serious adverse reactions related to elevated transaminases have been reported in patients with CF receiving ORKAMBI. In some instances, these elevations have been associated with concomitant elevations in total serum bilirubin
- It is recommended that ALT, AST, and bilirubin be assessed prior to initiating ORKAMBI, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of ALT, AST, or bilirubin elevations, more frequent monitoring should be considered. Patients who develop increased ALT, AST, or bilirubin should be closely monitored until the abnormalities resolve
- Dosing should be interrupted in patients with ALT or AST >5x upper limit of normal (ULN) when not associated with elevated bilirubin. Dosing should also be interrupted in patients with ALT or AST elevations >3x ULN when associated with bilirubin elevations >2x ULN. Following resolution of transaminase elevations, consider the benefits and risks of resuming dosing

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 ORKAMBI and institute appropriate therapy. Consider the benefits and risks for the individual patient to determine whether to resume treatment with ORKAMBI

Respiratory Events

- Respiratory events (e.g., chest discomfort, dyspnea, and respiration abnormal) were observed more commonly in patients during initiation of ORKAMBI compared to those who received placebo. These events have led to drug discontinuation and can be serious, particularly in patients with advanced lung disease (percent predicted FEV_1 ($ppFEV_1$) <40). Clinical experience in patients with $ppFEV_1$ <40 is limited, and additional monitoring of these patients is recommended during initiation of therapy

Please click for full Prescribing Information for ORKAMBI.

ORKAMBI®
(lumacaftor/ivacaftor)
100/125 mg • 200/125 mg tablets
75/94 mg • 100/125 mg • 150/188 mg oral granules

INDICATION AND IMPORTANT SAFETY INFORMATION FOR ORKAMBI (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Effect on Blood Pressure

- Increased blood pressure has been observed in some patients treated with ORKAMBI. Blood pressure should be monitored periodically in all patients being treated with ORKAMBI

Drug Interactions

- Substrates of CYP3A

  Lumacaftor is a strong inducer of CYP3A. Administration of ORKAMBI may decrease systemic exposure of medicinal products that are substrates of CYP3A, which may decrease therapeutic effect. Co-administration with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index is not recommended. ORKAMBI may substantially decrease hormonal contraceptive exposure, reducing their effectiveness and increasing the incidence of menstruation-associated adverse reactions, e.g., amenorrhea, dysmenorrhea, menorrhagia, menstrual irregular. Hormonal contraceptives, including oral, injectable, transdermal, and implantable, should not be relied upon as an effective method of contraception when co-administered with ORKAMBI

- Strong CYP3A Inducers

  Ivacaftor is a substrate of CYP3A4 and CYP3A5 isoenzymes. Use of ORKAMBI with strong CYP3A inducers, such as rifampin, significantly reduces ivacaftor exposure, which may reduce the therapeutic effectiveness of ORKAMBI. Therefore, co-administration with strong CYP3A inducers is not recommended

Cataracts

- Cases of non-congenital lens opacities have been reported in pediatric patients treated with ORKAMBI and ivacaftor, a component of ORKAMBI. Although other risk factors were present in some cases (such as corticosteroid use and exposure to radiation), a possible risk attributable to ivacaftor cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with ORKAMBI

ADVERSE REACTIONS

Serious Adverse Reactions

- Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in patients treated with ORKAMBI included pneumonia, hemoptysis, cough, increased blood creatine phosphokinase, and transaminase elevations. These occurred in 1% or less of patients

Most Common Adverse Reactions

- The most common adverse reactions in patients age 12 years and older in Phase 3 trials (Trials 1 and 2) occurring in ≥5% of patients treated with ORKAMBI (N=369) vs placebo (N=370) and at a rate higher than placebo were dyspnea, nasopharyngitis, nausea, diarrhea, upper respiratory tract infection, fatigue, respiration abnormal, blood creatine phosphokinase increased, rash, flatulence, rhinorrhea, and influenza
- The safety profile in patients age 6 through 11 years from an open-label trial (Trial 3; N=58) and a placebo-controlled trial (Trial 4; patients treated with ORKAMBI, N=103 vs placebo, N=101) was similar to that observed in Trials 1 and 2. Additional common adverse reactions were reported in Trial 4, but were not reported in Trials 1 and 2. The adverse reactions in Trial 4 that occurred in ≥5% of patients treated with ORKAMBI with an incidence of ≥3% higher than placebo included: productive cough, nasal congestion, headache, abdominal pain upper, and sputum increased
- The safety profile in patients age 2 through 5 years from an open-label trial (Trial 6; N=60) was similar to that in patients aged 6 years and older. The safety profile in patients age 1 through 2 years from an open-label trial (Trial 7; N=46) was similar to that in patients aged 2 years and older

USE IN SPECIFIC POPULATIONS

Pediatric Use

- The safety and effectiveness of ORKAMBI in patients with CF younger than 1 year of age have not been established

Please click for full Prescribing Information for ORKAMBI.

kalydeco (ivacaftor) tablets 150 mg oral granules 5.8•13.4•25•50•75 mg

Select drug-drug interactions and clinical considerations when transitioning patients[38]

Clinical considerations when transitioning patients from KALYDECO to TRIKAFTA® (elexacaftor/tezacaftor/ivacaftor and ivacaftor) are based on drug interaction studies, modeling, other clinical factors, and/or predicted interactions due to elimination pathways. Additional drug-drug interactions for KALYDECO that are similar to those for TRIKAFTA are not listed here.

KALYDECO	TRIKAFTA

- Patients will still continue to receive the same amount of ivacaftor, but elexacaftor and tezacaftor will be added with the transition to TRIKAFTA
- **The initial dose of TRIKAFTA should be taken in the morning, approximately 12 hours after the final dose of KALYDECO**
- During approximately the first week after transition:

Blood levels of ivacaftor will be maintained

Blood levels of elexacaftor will be increasing

Blood levels of tezacaftor will be increasing

Elexacaftor and tezacaftor are expected to reach steady state within 1 week

Select drug-drug interactions to consider in patients transitioning from KALYDECO to TRIKAFTA[1]

	Recommendation
Midazolam	• No dose adjustments are considered necessary with TRIKAFTA

INDICATION AND IMPORTANT SAFETY INFORMATION FOR KALYDECO

INDICATIONS AND USAGE

KALYDECO is indicated for the treatment of cystic fibrosis (CF) in patients age 1 month and older who have at least one mutation in the CFTR gene that is responsive to ivacaftor potentiation based on clinical and/or in vitro assay data.

If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Transaminase (ALT or AST) Elevations

- Elevated transaminases have been reported in patients with CF receiving KALYDECO. Transaminase elevations were more common in patients with a history of transaminase elevations or in patients who had abnormal transaminases at baseline. ALT and AST should be assessed prior to initiating KALYDECO, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations, consider more frequent monitoring of liver function tests
- Patients who develop increased transaminase levels should be closely monitored until the abnormalities resolve. Dosing should be interrupted in patients with ALT or AST of greater than 5 times the upper limit of normal (ULN). Following resolution of transaminase elevations, consider the benefits and risks of resuming KALYDECO

Hypersensitivity Reactions, Including Anaphylaxis

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

Concomitant Use With CYP3A Inducers

- Use of KALYDECO with strong CYP3A inducers, such as rifampin, substantially decreases the exposure of ivacaftor, which may reduce the therapeutic effectiveness of KALYDECO. Co-administration of KALYDECO with strong CYP3A inducers, such as rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort, is not recommended

Cataracts

- Cases of non-congenital lens opacities/cataracts have been reported in pediatric patients treated with KALYDECO. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with KALYDECO

ADVERSE REACTIONS

Serious Adverse Reactions

- Serious adverse reactions, whether considered drug-related or not by the investigators, which occurred more frequently in patients treated with KALYDECO included abdominal pain, increased hepatic enzymes, and hypoglycemia

Please click for full Prescribing Information for KALYDECO.

INDICATION AND IMPORTANT SAFETY INFORMATION FOR KALYDECO (cont'd)

ADVERSE REACTIONS (cont'd)

Most Common Adverse Reactions

- The most common adverse reactions in the 221 patients treated with KALYDECO were headache (17%), upper respiratory tract infection (16%), nasal congestion (16%), nausea (10%), rash (10%), rhinitis (6%), dizziness (5%), arthralgia (5%), and bacteria in sputum (5%)
- The safety profile for the CF patients enrolled in clinical trials (Trials 3-8) was similar to that observed in the 48-week, placebo-controlled trials (Trials 1 and 2)

USE IN SPECIFIC POPULATIONS

Pediatric Use

- The safety and effectiveness of KALYDECO in patients with CF younger than 1 month of age have not been established. The use of KALYDECO in children under the age of 1 month is not recommended
- Use of KALYDECO in patients aged 1 to less than 6 months born at a gestational age less than 37 weeks has not been evaluated

Please click for full Prescribing Information for KALYDECO.

symdeko® (tezacaftor/ivacaftor and ivacaftor)
100/150 mg and 150 mg tablets
50/75 mg and 75 mg tablets

Clinical considerations when transitioning patients[38]

Clinical considerations when transitioning patients from SYMDEKO to TRIKAFTA® (elexacaftor/tezacaftor/ivacaftor and ivacaftor) are based on drug interaction studies, modeling, other clinical factors, and/or predicted interactions due to elimination pathways.

SYMDEKO	TRIKAFTA

- Patients will still continue to receive the same amount of ivacaftor and tezacaftor, but elexacaftor will be added with the transition to TRIKAFTA
- **The initial dose of TRIKAFTA should be taken in the morning, approximately 12 hours after the final dose of SYMDEKO**
- During approximately the first week after transition:

Blood levels of elexacaftor will be increasing

Blood levels of tezacaftor are expected to be maintained

Blood levels of ivacaftor are expected to be maintained

Elexacaftor is expected to reach steady state within 1 week

symdeko®
(tezacaftor/ivacaftor and ivacaftor)
100/150 mg and 150 mg tablets
50/75 mg and 75 mg tablets

Select drug-drug interactions

Only those drugs listed below are expected to have interactions with TRIKAFTA® (elexacaftor/tezacaftor/ivacaftor and ivacaftor). Drugs within a class may have different metabolic profiles, and therefore clinical considerations apply only to the drugs listed here and not the class.

Additional drug-drug interactions for SYMDEKO that are similar to those for TRIKAFTA are not listed here.

Select drug-drug interactions to consider in patients transitioning from SYMDEKO to TRIKAFTA[1]

	Recommendation	Interaction
HMG-CoA reductase inhibitors (statins)[2]	**When co-administration is required, caution and appropriate monitoring should be used**	**Concomitant use of TRIKAFTA may increase the levels of some statins** • Potential inhibition of OATP1B1 and OATP1B3 by elexacaftor and M23-ELX (active metabolite) may occur
nateglinide, repaglinide, glimepiride, glipizide, glyburide		• Exposures of glimepiride and glipizide may increase due to potential for inhibition of CYP2C9 by ivacaftor • Exposures of glyburide, nateglinide, and repaglinide may increase due to potential OATP1B1 and OATP1B3 inhibition by elexacaftor and M23-ELX (active metabolite)

symdeko®
(tezacaftor/ivacaftor and ivacaftor)
100/150 mg and 150 mg tablets
50/75 mg and 75 mg tablets

INDICATION AND IMPORTANT SAFETY INFORMATION FOR SYMDEKO

INDICATIONS AND USAGE

SYMDEKO is indicated for the treatment of cystic fibrosis (CF) in patients age 6 years and older who are homozygous for the F508del mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that is responsive to tezacaftor/ivacaftor based on in vitro data and/or clinical evidence.

If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Transaminase (ALT or AST) Elevations

- Elevated transaminases have been observed in patients with CF receiving SYMDEKO, as well as with ivacaftor monotherapy. Assessments of transaminases (ALT and AST) are recommended prior to initiating SYMDEKO, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations, more frequent monitoring should be considered
- Dosing should be interrupted in patients with significant elevations of transaminases (e.g., ALT or AST >5x upper limit of normal [ULN], or ALT or AST >3x ULN with bilirubin >2x ULN) and laboratory tests should be closely followed until abnormalities resolve. Following resolution of transaminase elevations, consider the benefits and risks of resuming treatment

Hypersensitivity Reactions, Including Anaphylaxis

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

Concomitant Use With CYP3A Inducers

- Exposure to ivacaftor is significantly decreased and exposure to tezacaftor may be reduced by concomitant use of CYP3A inducers, which may reduce the therapeutic effectiveness of SYMDEKO. Co-administration of SYMDEKO with strong CYP3A inducers, such as rifampin, rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort, is not recommended

Cataracts

- Cases of non-congenital lens opacities have been reported in pediatric patients treated with SYMDEKO, as well as with ivacaftor monotherapy. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with SYMDEKO

Please click for full Prescribing Information for SYMDEKO.

symdeko (tezacaftor/ivacaftor and ivacaftor)
100/150 mg and 150 mg tablets
50/75 mg and 75 mg tablets

INDICATION AND IMPORTANT SAFETY INFORMATION FOR SYMDEKO (cont'd)

ADVERSE REACTIONS

Serious Adverse Reactions

- Serious adverse reactions, whether considered drug-related or not by the investigators, that occurred more frequently in patients treated with SYMDEKO compared to placebo included distal intestinal obstruction syndrome, 3 (0.6%) patients treated with SYMDEKO vs. 0 placebo patients

Most Common Adverse Reactions

- The most common adverse reactions in Trials 1 and 3 occurring in ≥3% of patients treated with SYMDEKO (N=334) and at a higher rate than for placebo (N=343) were headache, nausea, sinus congestion, and dizziness
- The safety profile in patients age 6 to less than 12 years from an open-label Phase 3 trial (N=70) was similar to that observed in Trials 1 and 3

USE IN SPECIFIC POPULATIONS

Pediatric Use

- The safety and effectiveness of SYMDEKO in patients with CF younger than 6 years of age have not been studied

Please click for full Prescribing Information for SYMDEKO.

TRIKAFTA has been studied among different age groups using multiple endpoints in a clinical setting[1,11,13,15a]

PATIENTS AGED 2 THROUGH 5 YEARS[1,11] — TRIAL 4 AND EXTENSION STUDY

More than 70 patients with
~1.5 YEARS
of data

- The safety results at the time of the interim analysis remained generally consistent with the safety results observed in Trial 4
- The current interim analysis at Extension Study Week 48 shows that TRIKAFTA offers sustained benefits across all efficacy endpoints studied

PATIENTS AGED 6 THROUGH 11 YEARS[1,13] — TRIAL 3 AND EXTENSION STUDY

More than 60 patients with
>3 YEARS
of data

- The safety results at the time of the interim analysis remained generally consistent with the safety results observed in Trial 3
- The current interim analysis at Extension Study Week 144 shows that TRIKAFTA offers sustained benefits across all efficacy endpoints studied

PATIENTS AGED 12 YEARS AND OLDER[1,15] — TRIAL 1, TRIAL 2, AND EXTENSION STUDY

More than 500 patients with
>4 YEARS
of data

- The safety results at the time of the interim analysis remained generally consistent with the safety results observed in Trial 1
- The Extension Study shows that TRIKAFTA offers sustained benefits across all endpoints studied

TRIKAFTA IS A BREAKTHROUGH TREATMENT FOR PATIENTS WITH CF 2 YEARS AND OLDER WITH RESPONSIVE MUTATIONS[1,2]

Trials 1 and 2 were controlled studies and the Extension Study is completed. Trials 3 and 4 and their Extension Studies are based on controlled, open-label studies, with the Extension Studies ongoing. Final results may vary.

Please click here for full safety information for ages 2 through 5 years, click here for ages 6 through 11 years, and click here for ages 12 years and older.

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[a]There is approximately 1 year (48 weeks) of long-term extension study data for patients aged 2 through 5 years, approximately 3 years (144 weeks) for patients aged 6 through 11 years, and approximately 4 years (192 weeks) for patients aged 12 years and older.

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