Policy and Procedure	
PHARMACY PRIOR AUTHORIZATION POLICY AND CRITERIA ORPTCRES005.0625	**RESPIRATORY AGENTS** **CFTR MODULATORS** See Table 1 for medications
Effective Date: 8/1/2025	**Review/Revised Date**: 06/12, 06/13, 04/14, 02/15, 06/15, 12/15, 05/16, 10/16, 05/17, 09/17, 06/18, 07/18, 08/18, 11/18, 05/19, 09/19, 02/20, 03/20, 11/20, 03/21, 05/21, 08/21, 04/22, 12/22, 05/23, 08/23, 05/24, 04/25, 04/25 (MTW)
Original Effective Date: 08/12	**P&T Committee Meeting Date**: 06/12, 06/13, 04/14, 06/14, 02/15, 06/15, 12/15, 06/16,12/16, 06/17, 10/17, 06/18, 08/18, 09/18, 12/18, 06/19, 08/19, 10/19, 02/20, 06/20. 10/20 (off-cycle), 12/20, 04/21, 06/21, 10/21, 06/22, 12/22, 06/23, 08/23, 06/24, 04/25, 06/25
Approved by: Oregon Region Pharmacy and Therapeutics Committee	

SCOPE:
Providence Health Plan and Providence Health Assurance as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:
Commercial
Medicaid

POLICY CRITERIA:

COVERED USES:
All Food and Drug Administration (FDA) approved indications not otherwise excluded from the benefit.

REQUIRED MEDICAL INFORMATION:

For ivacaftor (Kalydeco®):

- Diagnosis of cystic fibrosis with documentation of at least one copy of a cystic fibrosis transmembrane regulator (CFTR) gene mutation that is responsive to ivacaftor (See Appendix 1 and/ or package insert)

For lumacaftor-ivacaftor (Orkambi®):

- Diagnosis of cystic fibrosis with documentation of homozygous *F508del* mutation in the CFTR gene

For tezacaftor-ivacaftor (Symdeko™):

- Diagnosis of cystic fibrosis with documentation of homozygous *F508del* mutation in the CFTR gene or a mutation in the *CFTR* gene that is responsive to tezacaftor-ivacaftor based on clinical evidence and/or in vitro data (See Appendix 2 and/ or package insert)

For elexacaftor- tezacaftor-ivacaftor (Trikafta™):

- Diagnosis of cystic fibrosis with documentation of at least one *F508del* mutation in the *CFTR* gene or a mutation in the CFTR gene that is responsive to

elexacaftor- tezacaftor-ivacaftor based on in vitro data (See Appendix 3 and/or package insert)

For vanzacaftor/Tezacaftor/Deutivacaftor (Alyftrek®):

- Diagnosis of cystic fibrosis with documentation of at least one F508del mutation in the CFTR gene or a mutation in the CFTR gene that is responsive to vanzacaftor- tezacaftor-deutivacaftor based on in vitro data (See Appendix 4 and/or package insert)

EXCLUSION CRITERIA: N/A

AGE RESTRICTIONS:

- Ivacaftor (Kalydeco®): one month or older
- Lumacaftor/Ivacaftor (Orkambi®): one year or older
- Tezacaftor/Ivacaftor (Symdeko®): six years or older
- Elexacaftor/Tezacaftor-ivacaftor (Trikafta®): two years or older
- Vanzacaftor/Tezacaftor/Deutivacaftor (Alyftrek®): six years or older

PRESCRIBER RESTRICTIONS:
Must be prescribed by or in consultation with a pulmonologist or provider at a Cystic Fibrosis Center.

COVERAGE DURATION:
Authorization will be approved until no longer eligible with the plan, subject to formulary or benefit changes

QUANTITY LIMIT:

- Ivacaftor (Kalydeco®): two tablets/granule packets per day
- Lumacaftor-ivacaftor (Orkambi®): four tablets per day; two granule packets per day
- Tezacaftor-ivacaftor (Symdeko™): two tablets per day
- Elexacaftor-tezacaftor-ivacaftor (Trikafta™): three tablets per day, two packets per day
- Vanzacaftor-tezacaftor-deutivacaftor (Alyftrek®):
    - 4-20-50 mg: three tablets per day
    - 10-50-125 mg: two tablets per day

Requests for indications that were approved by the FDA within the previous six (6) months may not have been reviewed by the health plan for safety and effectiveness and inclusion on this policy document. These requests will be reviewed using the New Drug and or Indication Awaiting P&T Review; Prior Authorization Request ORPTCOPS047.

Requests for a non-FDA approved (off-label) indication requires the proposed indication be listed in either the American Hospital Formulary System (AHFS), Drugdex, or the National Comprehensive Cancer Network (NCCN) and is considered subject to evaluation of the prescriber's medical rationale, formulary alternatives, the available published evidence-based research and whether the proposed use is determined to be experimental/investigational.

Coverage for Medicaid is limited to a condition that has been designated a covered line item number by the Oregon Health Services Commission listed on the Prioritized List of Health Care Services.

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case.

INTRODUCTION:

Cystic fibrosis (CF) is a rare, progressive, life-threatening autosomal recessive disorder that affects approximately 80,000 children and adults worldwide. It is a multisystem disorder that affects the lungs, pancreas, liver, and intestines. CF is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene which encodes the CFTR protein, an anion transporter, that is involved with bicarbonate-chloride exchange. CFTR modulators are recommended in patients with CFTR variant due to potential for altering the disease process, therefore all CF patients should undergo genotyping.[17-19]

Ivacaftor (Kalydeco®) is an oral medication used to treat cystic fibrosis (CF). It is only indicated to treat CF patients with certain mutations in the CF transmembrane conductance regulator (CFTR) protein. Ivacaftor is a potentiator of the CFTR channel at the cell surface to increase chloride transport. It is part of the standard of care in patients with gating mutations according to European CF Society 2018. Ivacaftor has also shown efficacy in mutations with residual CFTR function (residual function mutations, splice mutations, and conduction mutations).

Lumacaftor-ivacaftor (Orkambi®) is an oral medication used to treat CF in patients with homozygous *F508del* mutation. Lumacaftor is a corrector of intracellular trafficking of CFTR protein.

Tezacaftor-ivacaftor (Symdeko™) is an oral medication used to treat CF in patients with homozygous *F508del* mutation or patients with at least one copy of certain mutations that has been shown to be responsive to tezacaftor-ivacaftor based on clinical and/or in vitro assay data. Tezacaftor is a corrector, like lumacaftor, but has been associated with fewer drug interactions and less side effects, such as chest discomfort.

Elexacaftor-tezacaftor-ivacaftor (Trikafta™) is an oral medication used to treat CF in patients with at least one copy of the *F508del* mutation or patients with at least one

copy of certain mutations that has been shown to be responsive to tezacaftor-ivacaftor based on in vitro data. Elexacaftor is a second-generation CFTR corrector. Elexacaftor and tezacaftor bind to different sites on the CFTR protein and provide additive effect.

Vanzacaftor-tezacaftor-deutivacaftor (Alyftrek®) is an oral medication used for the treatment of cystic fibrosis (CF) in patients 6 years of age and older who have at least one *F508del* mutation or another responsive mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Vanzacaftor-tezacaftor-deutivacaftor is a cystic fibrosis transmembrane conductance regulator corrector/potentiator.

FDA APPROVED INDICATIONS:
Ivacaftor (Kalydeco®): Treatment of cystic fibrosis (CF) in patients age one month or 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 (See Appendix 1)
Limitations of Use: Not effective in patients with CF who are homozygous for the F508del mutation of the CFTR gene.

Lumacaftor-ivacaftor (Orkambi®): Treatment of Cystic fibrosis, in patients age one and older who are homozygous for the *F508del* mutation in the CFTR gene

Tezacaftor-ivacaftor (Symdeko™): Treatment of cystic fibrosis in patients six (6) years and older who have a homozygous *F508del* mutation or at least one copy of a 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. [see Appendix 2]

Elexacaftor- tezacaftor-ivacaftor (Trikafta™): Treatment of cystic fibrosis in patients two 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. [see Appendix 3]

For vanzacaftor/Tezacaftor/Deutivacaftor (Alyftrek®): Treatment of cystic fibrosis (CF) in patients 6 years of age and older who have at least one *F508del* mutation or another responsive mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene [see Appendix 4]

For all CFTR modulators: 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.

POSITION STATEMENT:
The cystic fibrosis conductance regulator (CFTR) is a chloride channel present at the surface of epithelial cells in multiple organs. Mutations in this gene can lead to thickened secretions in several organs, which may lead to difficulty breathing as well as increased risk for infection.

Ivacaftor (Kalydeco®):

- Ivacaftor is a potentiator of the cystic fibrosis transmembrane conductance regulator (CFTR) protein, a chloride channel present at the surface of epithelial cells in multiple organs. Ivacaftor facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the G551D-CFTR protein.
- The safety and efficacy of ivacaftor in patients 6 years and older with CF who have a G551D, G1244E, G1349D, G178R, G551S, R117H, S1251N, S1255P, S549N, or S549R mutation in the *CFTR* gene have been demonstrated in multiple randomized, double-blind, placebo-clinical trials. The primary efficacy endpoint measured was improvement in lung function as determined by the mean absolute change from baseline in percent predicted force expiratory volume in 1 second ($ppFEV_1$) through a predefined treatment period.
- The efficacy and response of ivacaftor to other gene mutations have been shown through clinical and/or in vitro assay data.
- The most common adverse drug reactions reported (≥ 8% of CF patients with G551D mutation) were headache, oropharyngeal pain, upper respiratory tract infection, nasal congestion, abdominal pain, nasopharyngitis, diarrhea, rash, nausea, and dizziness. Additional warnings include elevated transaminase (ALT or AST), drug-drug interactions with CYP3A inducers and cataracts in pediatric patients.

Lumacaftor-ivacaftor (Orkambi®)

- Orkambi® is a combination product including ivacaftor and lumacaftor, which improves the conformational stability of F508del-CFTR, resulting in increased processing and trafficking of mature protein to the cell surface.
- Lumacaftor-ivacaftor was evaluated in two phase three randomized, double-blind, placebo-controlled trials including a total of 1108 patients with homozygous F508del mutation. A pooled analysis of the two trials revealed an improvement of 2.8 percentage point difference in absolute change from baseline in ppFEV1 to Week 24, compared to placebo. Pulmonary exacerbations occurred less frequently with lumacaftor-ivacaftor, but this was not tested for statistical significance due to the prespecified hierarchical testing procedure.
- Regarding safety of lumacaftor-ivacaftor, more patients in the active treatment group discontinued therapy due to adverse effects (4.2% with lumacaftor-ivacaftor compared to 1.6% with placebo). There were seven subjects treated

with lumacaftor-ivacaftor who had serious adverse events related to abnormal liver function.

Tezacaftor-ivacaftor (Symdeko®)

- Symdeko® is a combination product comprising of ivacaftor and tezacaftor)a corrector that improves conformational stability of CFTR and facilitates intracellular trafficking of CFTR).
- The safety and efficacy of tezacaftor-ivacaftor in patients with homozygous *F508del* mutation has been demonstrated in a double-blind, placebo-controlled trial which showed a 4.0 percentage point improvement with tezacaftor-ivacaftor, compared to placebo, in the absolute change from baseline in $ppFEV_1$ at Week 24.
- The EXPAND trial compared tezacaftor-ivacaftor versus ivacaftor alone, as well as each agent compared to placebo, and found tezacaftor-ivacaftor resulted in statistically significant improvement in $ppFEV_1$ in patients with heterozygous *F508del* mutation. The mean treatment difference in absolute change from baseline in ppFEV1 at Week 24 was 6.8 percentage points between tezacaftor-ivacaftor and placebo (95% CI: 5.7, 7.8; $p < 0.0001$), and 2.1 percentage points between tezacaftor-ivacaftor and ivacaftor alone (95% CI:1.2, 2.9; $p < 0.0001$).
- Adverse reactions may include headache (15%), nausea (9%), dizziness (4%), sinus congestion (4%),distal intestinal obstruction syndrome, elevated AST/ALT, and cataracts.

Elexacaftor- tezacaftor-ivacaftor (Trikafta®):

- Elexacaftor-tezacaftor-ivacaftor (Trikafta®) is the first triple CFTR modulator therapy in patients with cystic fibrosis with at least one copy of *F508del* mutation
    - Heterozygous *F508del* mutation:
        - In Middleton et al. 2019, Trikafta demonstrated substantial improvement in lung function and quality of life when compared to placebo.
        - Patients who have a single copy of *F508del* mutation and a minimal function mutation that does not respond to previous CFTR modulator therapies were included in this study with baseline pFEV of 40 to 90% at screening.
        - Mean treatment difference of absolute change from baseline in ppFEV1 at Week four (Trikafta vs. placebo): 13.8 percentage points (95 CI: 12.1 to 15.4), $p<0.001$
        - Key secondary endpoints – Mean treatment difference of absolute change from baseline through Week 24
            - ppFEV1: 14.3 percentage points (12.7 to 15.8)
            - Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score: 20.2 (17.5 to 23.0)

        - Sweat chloride (SwCl) concentration: -41.8 mmol/L (-44.4 to -39.3)
    - Homozygous *F508del* mutation:
        - In Heijerman et al. 2019, Trikafta® was compared to tezacaftor-ivacaftor with baseline pFEV of 40 to 90% at screening. Note: 9.3% of patients pFEV1 declined to less than 40% (severe lung disease) from screening to baseline
        - Mean treatment difference in absolute change from baseline in percentage of predicted FEV1 at Week 4: 10.0 percentage points (95 CI: 7.4 to 12.6), p<0.001
        - Key secondary endpoints – Absolute change from baseline through Week four**:**
            - CFQ-R respiratory domain score: 17.4 (11.8 to 23.0)
            - SwCl: -45.1 mmol/L (-50.1 to -40.1)
        - Trials in the same patient population, Orkambi only had a mean treatment difference of 2.6 to 3.0 percentage points in absolute change from baseline in ppFEV to Week 24, when compared to placebo.
- According to CF guidelines, low FEV1 is strongly associated with increased mortality and decreased QOL. A difference of 5.0 to 10.0 percentage points has been considered as thresholds of meaningful changes in FEV1 in previous CF trials. Therefore, a percentage point difference of 10.0 to 13.8 percentage points is considered to be statistically and clinically significant, when comparing Trikafta® to placebo or tezacaftor-ivacaftor.
- CFQ-R is widely used to measure patient reported outcomes in CF, such as general quality of life, daily activities, and symptoms
    - Likert scale, items within domains are summed and standardized, scores range from 0 to 100, higher scores indicating better quality of life
    - Minimum clinically important difference for stable CF patients has been estimated 4.0 points. Therefore, a mean treatment difference of 17.4 to 20.2 points is considered to be statistically and clinically significant.
- Exclusion criteria of these clinical trials include acute respiratory infection, lung infection with organisms associated with a more rapid decline in pulmonary status (including, but not limited to, *Burkholderia cenocepacia* and *Mycobacterium abscessus*). More criteria listed in detail in article's supplementary appendix (e.g. pregnancy, cancer, elevated LFTs, GFR less than or equal to 50 ml/min/1.73m^2)
- Elexacaftor-tezacaftor-ivacaftor (Trikafta®) carries a black boxed warning for liver injury and liver failure.

For vanzacaftor/tezacaftor/deutivacaftor (Alyftrek®):

- Vanzacaftor-tezacaftor-deutivacaftor, manufactured by Vertex pharmaceuticals, contains a similar indication as to elexacaftor-tezacaftor-ivacaftor (Trikafta®) which also has the same manufacturer. However, some mutations in the CFTR gene are responsive only to vanzacaftor-tezacaftor-deutivacaftor and not elexacaftor-tezacaftor-ivacaftor.
- Vanzacaftor-tezacaftor-deutivacaftor was FDA approved based on two randomized, double-blind, phase 3 clinical trials (SKYLINE 102 and SKYLINE 103) that vanzacaftor-tezacaftor-deutivacaftor is non-inferior to elexacaftor-tezacaftor-ivacaftor. Both trials compared vanzacaftor-tezacaftor-deutivacaftor to an already approved triple combination regimen (Trikafta [elexacaftor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA)]). The primary endpoint evaluated non-inferiority in mean absolute change in the percent of predicted forced expiratory volume in one second (ppFEV1) from baseline through week 24. The key secondary endpoints for both trials were tested for superiority in the following hierarchical order: 1) absolute change from baseline to week 24 in sweat chloride concentration; 2) proportion of patients with sweat chloride concentration <60 mmol/L through week 24 (pooled from both trials); and 3) proportion of patients with sweat chloride concentration <30 mmol/L through week 24 (pooled from both trials).
- Common adverse effects include: nasopharyngitis, upper respiratory infection, headache, fatigue, influenza, rash, ALT/SGPT level raised, creatine kinase level above reference range, aspartate transaminase level above reference range, congestion of nasal sinus

Drug interactions

- There are many medications which interact with ivacaftor, a component of CFTR modulator therapies. A full drug interaction review needs to be completed when a CFTR modulator is initiated and when new medications are added. Ivacaftor is a major CYP3A4 substrate and Lumacaftor is a CYP3A4 inducer.
- When used with Orkambi®, hormonal birth control cannot be relied on, and menstruation-related adverse effects may occur.

Table 1

Brand Name	Generic Name
Alyftrek®	vanzacaftor/tezacaftor/deutivacaftor
Kalydeco®	ivacaftor
Orkambi®	lumacaftor/ivacaftor
Symdeko®	tezacaftor/ivacaftor
Trikafta®	elexacaftor/tezacaftor-ivacaftor

REFERENCE/RESOURCES:

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2. Orkambi (lumacaftor-ivacaftor) package insert. Boston, MA: Vertex Pharmaceuticals Inc; 2024 December.
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Appendix 1: List of CFTR Gene Mutations that are Responsive to Kalydeco®

711+3A→G*	F311del	I148T	R75Q	S589N
2789+5G→A *	F311L	I175V	R117C *	S737F
3272-26A→G *	F508C	I807M	R117G	S945L *
3849+10kbC→T *	F508C;S1251N †	I1027T	R117H *	S977F *
A120T	F1052V	I1139V	R117L	S1159F
A234D	F1074L	K1060T	R117P	S1159P
A349V	G178E	L206W *	R170H	S1251N *
A455E *	G178R *	L320V	R347H *	S1255P *
A1067T	G194R	L967S	R347L	T338I
D110E	G314E	L997F	R352Q *	T1053I
D110H	G551D *	L1480P	R553Q	V232D
D192G	G551S *	M152V	R668C	V562I
D579G *	G576A	M952I	R792G	V754M
D924N	G970D	M952T	R933G	V1293G
D1152H *	G1069R	P67L *	R1070Q	W1282R
D1270N	G1244E *	Q237E	R1070W *	Y1014C
E56K	G1249R	Q237H	R1162L	Y1032C
E193K	G1349D *	Q359R	R1283M	
E822K	H939R	Q1291R	S549N *	
E831X *	H1375P	R74W	S549R *	

* Clinical data exists for theses mutations
† Complex/compound mutations where a single allele of the CFTR gene has multiple mutations; these exist independent of the presence of mutation on the other allele

Appendix 2: List of CFTR Gene Mutations that are Responsive to Symdeko™

546insCTA	E92K	G576A	L346P	R117G	S589N
711+3A→G*	E116K	G576A;R668C †	L967S	R117H	S737F
2789+5G→A*	E193K	G622D	L997F	R117L	S912L
3272-26A→G*	E403D	G970D	L1324P	R117P	S945L *
3849+10kbC→T *	E588V	G1069R	L1335P	R170H	S977F*
A120T	E822K	G1244E	L1480P	R258G	S1159 F
A234D	E831X	G1249R	M152V	R334L	S1159 P
A349V	F191V	G1349D	M265R	R334Q	S1251 N
A455E *	F311del	H939R	M952I	R347H *	S1255 P

A554E	F311L	H1054D	M952T	R347L	T338I
A1006E	F508C	H1375P	P5L	R347P	T1036N
A1067T	F508C;S1251N †	I148T	P67L *	R352Q *	T1053I
D110E	F508del ‡	I175V	P205S	R352W	V201M
D110H *	F575Y	I336K	Q98R	R553Q	V232D
D192G	F1016S	I601F	Q237E	R668C	V562I
D443Y	F1052V	I618T	Q237H	R751L	V754M
D443Y;G576A;R668C †	F1074L	I807M	Q359R	R792G	V1153E
D579G *	F1099L	I980K	Q1291R	R933G	V1240G
D614G	G126D	I1027T	R31L	R1066H	V1293G
D836Y	G178E	I1139V	R74Q	R1070Q	W1282R
D924N	G178R	I1269N	R74W	R1070W *	Y109N
D979V	G194R	I1366N	R74W;D1270N †	R1162L	Y161S
D1152H *	G194V	K1060T	R74W;V201M †	R1283M	Y1014C
D1270N	G314E	L15P	R74W;V201M;D1270N †	R1283S	Y1032C
E56K	G551D	L206W *	R75Q	S549N	
E60K	G551S	L320V	R117C *	S549R	

* Clinical data exists for theses mutations
† Complex/compound mutations where a signle allele of the CFTR gene has multiple mutations; these exist independent of the presence of mutation on the other allele
‡ A patient must have two copies of the F508del mutation or at least one copy of a responsive mutation present in appendix 2 to be indicated

Appendix 3: List of CFTR Gene Mutations that are Responsive to Trikafta®

3141del9	E822K	G1069R	L967S	R117L	S912L
546insCTA	F191V	G1244E	L997F	R117P	S945L
A46D	F311del	G1249R	L1077P	R170H	S977F
A120T	F311L	G1349D	L1324P	R258G	S1159F
A234D	F508C	H139R	L1335P	R334L	S1159P
A349V	F508C; S1251N*	H199Y	L1480P	R334Q	S1251N
A455E	F508del †	H939R	M152V	R347H	S1255P
A554E	F575Y	H1054D	M265R	R347L	T338I
A1006E	F1016S	H1085P	M952I	R347P	T1036N

A1067T	F1052V	H1085R	M952T	R352Q	T1053I
D110E	F1074L	H1375P	M1101K	R352W	V201M
D110H	F1099L	I148T	P5L	R553Q	V232D
D192G	G27R	I175V	P67L	R668C	V456A
D443Y	G85E	I336K	P205S	R751L	V456F
D443Y; G576A; R668C*	G126D	I502T	P574H	R792G	V562I
D579G	G178E	I601F	Q98R	R933G	V754M
D614G	G178R	I618T	Q237E	R1066H	V1153E
D836Y	G194R	I807M	Q237H	R1070Q	V1240G
D924N	G194V	I980K	Q359R	R1070W	V1293G
D979V	G314E	I1027T	Q1291R	R1162L	W361R
D1152H	G463V	I1139V	R31L	R1283M	W1098C
D1270N	G480C	I1269N	R74Q	R1283S	W1282R
E56K	G551D	I1366N	R74W	S13F	Y109N
E60K	G551S	K1060T	R74W; D1270N*	S341P	Y161D
E92K	G576A	L15P	R74W; V201M*	S364P	Y161S
E116K	G576A; R668C*	L165S	R74W; V201M; D1270N*	S492F	Y563N
E193K	G622D	L206W	R75Q	S549N	Y1014C
E403D	G628R	L320V	R117C	S549R	Y1032C
E474K	G970D	L346P	R117G	S589N	
E588V	G1061R	L453S	R117H	S737F	
Mutations responsive to TRIKAFTA based on extrapolation from Trial 5§					
4005+2T→C	2789+2*ins*A	3849+40A→G	5T;TG13		
1341G→A	296+28A→G	3489+4A→G	621+3A→G		
1898+3A→G	3041-15T→G	3850-3T→G	711+3A→G		
2752-26A→G	3600G→A	5T;TG12	E831X		

*Complex/compound mutations where a single allele of the CFTR gene has multiple mutations; these exist independent of the presence of mutations on the other allele.
† F508del is a responsive CFTR mutation based on both clinical and in vitro data

Appendix 4: List of CFTR Gene Mutations that are Responsive to Alyftrek®

Based on Clinical Data*						
A455E	G551D	L1077P†	R352Q	S549N	V754M	
D1152H	G85E†	L206W	R75Q	S549R	W1098C†	
F508del†	H1054D	M1101K†	S1159F	S945L	W1282R	

G1244E	I336K	R1066H	S1251N	V562I	Y563N†	
Based on in vitro Data‡						
1507_1515del9	E116Q	G424S	I556V	P140S	R334L	T1053I
2183A→G	E193K	G463V	I601F	P205S	R334Q	T1086I
3141del9	E292K	G480C	I618T	P499A	R347H	T1246I
3195del6	E403D	G480S	I807M	P5L	R347L	T1299I
3199del6	E474K	G551A	I980K	P574H	R347P	T338I
546insCTA	E56K	G551S	K1060T	P67L	R352W	T351I
A1006E	E588V	G576A	K162E	P750L	R516G	T604I
A1067P	E60K	G576A;R668C§	K464E	P99L	R516S	V1153E
A1067T	E822K	G622D	L1011S	Q1100P	R553Q	V1240G
A107G	E92K	G628R	L102R	Q1291R	R555G	V1293G
A120T	F1016S	G91R	L1065P	Q1313K	R560S	V201M
A234D	F1052V	G970D	L1324P	Q237E	R560T	V232D
A309D	F1074L	G970S	L1335P	Q237H	R668C	V392G
A349V	F1099L	H1085P	L137P	Q359R	R709Q	V456A
A46D	F1107L	H1085R	L1480P	Q372H	R74Q	V456F
A554E	F191V	H1375P	L15P	Q452P	R74W	V520F
A559T	F200I	H139R	L165S	Q493R	R74W;D1270N§	V603F
A559V	F311del	H199R	L320V	Q552P	R74W;V201M§	W361R
A561E	F311L	H199Y	L333F	Q98R	R74W;V201M;D1270N§	Y1014C
A613T	F508C	H609R	L333H	R1048G	R75L	Y1032C
A62P	F508C;S1251N§	H620P	L346P	R1066C	R751L	Y109N
A72D	F575Y	H620Q	L441P	R1066L	R792G	Y161D
C491R	F587I	H939R	L453S	R1066M	R933G	Y161S
D110E	G1047R	H939R;H949L	L619S	R1070Q	S1045Y	Y301C
D110H	G1061R	I1027T	L967S	R1070W	S108F	Y569C
D1270N	G1069R	I105N	L997F	R1162L	S1118F	Y913C
D1445N	G1123R	I1139V	M1101R	R117C	S1159P	
D192G	G1247R	I1234Vdel6aa	M1137V	R117C;G576A;R668C	S1235R	
D443Y	G1249R	I125T	M150K	R117G	S1255P	
D443Y;G576A;R668C§	G126D	I1269N	M152V	R117H	S13F	
D513G	G1349D	I331N	M265R	R117L	S341P	
D565G	G149R	I1366N	M952I	R117P	S364P	
D579G	G178E	I1398S	M952T	R1283M	S492F	

D614G	G178R	I148N	N1088D	R1283S	S549I	
D836Y	G194R	I148T	N1303I	R170H	S589N	
D924N	G194V	I175V	N1303K§	R258G	S737F	
D979V	G27E	I502T	N186K	R297Q	S912L	
D993Y	G27R	I506L	N187K	R31C	S977F	
E116K	G314E	I506T	N418S	R31L	T1036N	
Based on Extrapolation¶						
1341G→A	2789+2insA	3041-15T→G	3849+10kbC→T	3850-3T→G	5T;TG13	711+3A→G
1898+3A→G	2789+5G→A	3272-26A→G	3849+4A→G	4005+2T→C	621+3A→G	E831X
2752-26A→G	296+28A→G	3600G→A	3849+40A→G	5T;TG12		

* Clinical data is obtained from Trials 1 and 2.
† This mutation is also predicted to be responsive by FRT assay with ALYFTREK.
‡ The N1303K mutation is predicted to be responsive only by HBE assay. All other mutations predicted to be responsive with in vitro data are supported by FRT assay.
§ Complex/compound mutations where a single allele of the CFTR gene has multiple mutations; these exist independent of the presence of mutations on the other allele.
¶ Efficacy is extrapolated to certain non-canonical splice mutations because clinical trials in all mutations in this subgroup are infeasible and these mutations are not amenable to interrogation by FRT system.