NEW THERAPIES IN ONCOLOGY AND CYSTIC FIBROSIS

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CFTR Modulators
A pharmacogenomic approach to treating cystic fibrosis

William Allan Prescott Jr., PharmD
Clinical Associate Professor, Pediatric Pharmacotherapy
University at Buffalo School of Pharmacy and Pharmaceutical Sciences
Department of Pharmacy Practice

Respond at PollEv.com/williampresc537
Text WILLIAMMPRESC537 to 22333 once to join
Limited to 50 participants
Learning Objectives - Pharmacists

1. Describe the pathophysiology of cystic fibrosis (CF) lung disease
2. Cite evidence for the safety and effectiveness of CFTR modulators in the treatment of CF lung disease

Learning Objectives – Pharmacy Technicians

1. Recall the basics of cystic fibrosis (CF) pathophysiology
2. List three CFTR modulators that are FDA approved for the treatment of CF lung disease
Your poll will show here

1. Install the app from pollev.com/app
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or
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Epidemiology of CF

- CF is a genetically inherited disease that results in chloride channel dysfunction.
- CF is the most common lethal genetically inherited disease affecting the Caucasian population.

~ 30,000 persons with CF in the U.S.

~ 1,000 children born w/ CF in the U.S. annually

Morbidity & Mortality of CF

Outcome dependent upon…
- Disease genotype / severity
- Patient management
- Compliance with therapies

Since the CFTR gene was discovered in 1989, more than 1600 CFTR mutations have been identified.

Prevalence of CF Mutations

- Class I
- Class II
- Class III
- Class IV
- Class V
# Cystic Fibrosis Pathophysiology: CFTR

## F508del Mutation Prevalence

<table>
<thead>
<tr>
<th>F508del Mutation</th>
<th>Percent of All People with CF</th>
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</thead>
<tbody>
<tr>
<td>Homozygous F508del</td>
<td>45.8</td>
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<tr>
<td>Heterozygous F508del</td>
<td>40.7</td>
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<tr>
<td>Neither F508del or Unknown</td>
<td>13.5</td>
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</table>

## Prevalence of the 10 most common CFTR mutations

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Cystic Fibrosis Pathophysiology: CFTR

Normal CFTR | Class III Mutation (e.g., G551D) | Class IV Mutation (e.g., R117H) | Class V Mutation (e.g., A445E)

Chloride

Golgi Apparatus | Class II mutation (e.g., delF508)

Endoplasmic Reticulum

Nucleus | Class I mutation (e.g., G542x)

CF Pulmonary Disease Pathophysiology

- Pulmonary

Diagram:
- Mutated CFTR Gene
- Loss of CFTR Function
- Dehydrated mucus
- Obstruction
- Sodium (Na+), Chloride (Cl-), Water (H2O)
CF Pulmonary Disease Pathophysiology

- Pulmonary

- Mutated CFTR Gene
  - Loss of CFTR Function
    - Impaired Bacterial Eradication
      - Infection
        - Inflammation
          - Airway Remodeling
            - Airway Obstruction
              - Bronchiectasis

- Obstruction
  - Infection
  - Inflammation

- Obstruction
CF Pulmonary Disease Pathophysiology

- Pulmonary

- Mutated CFTR Gene
  - Loss of CFTR Function
    - Impaired Bacterial Eradication
      - Infection
        - Inflammation
          - Airway Remodeling
            - Airway Obstruction
              - Bronchiectasis

- Infection

- Obstruction

- Inflammation

- Tissue Damage
CF Pulmonary Disease – Tissue Damage

CF Lung

Healthy Lung
CF Pulmonary Disease – Tissue Damage
Traditional Pharmacologic Approaches to Treat CF Lung Disease

Anti-inflammatory agents
- Azithromycin
- Ibuprofen (high-dose)

Mucolytic / hydrating agents / Bronchodilators
- Dornase alfa
- Hypertonic saline
- Albuterol (if asthma present)

Antibiotics
- Inhaled tobramycin
- Inhaled aztreonam
- Systemic antibiotics

Adapted from CFF Patient Registry, 2015.
Treatment Impact on Pulmonary Function

Median FEV₁ Percent Predicted, by Age and Birth Cohort

Median FEV₁ Percent Predicted in 18-Year-Olds, 1986–2016

Infection
Inflammation
Obstruction

Mucolytic / hydrating agents / Bronchodilators
- Dornase alfa
- Hypertonic saline
- Albuterol (if asthma present)

Anti-inflammatory agents
- Azithromycin
- Ibuprofen (high-dose)

Antibiotics
- Inhaled tobramycin
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- Systemic antibiotics

New Frontier in the Treatment of CF Lung Disease

Adapted from CFF Patient Registry, 2015.
New Frontier in the Treatment of CF Lung Disease

Timeline of CFTR Modulator FDA Approvals

- **JANUARY 31, 2012**
  - **Ivacaftor** approved for those 6 years and older with the G551D mutation

- **FEBRUARY 21, 2014**
  - **Ivacaftor** approved for those 6 years and older with the additional gating S549N, G1244E, G178R, S549R, S1251N, G551S, G1349D, and S1255P mutations

- **DECEMBER 29, 2014**
  - **Ivacaftor** approved for those 6 years and older with the R117H mutation

- **MARCH 18, 2015**
  - **Ivacaftor** approved for those 2 to 5 years with a previously approved mutation

- **JULY 2, 2015**
  - **Ivacaftor and Lumacaftor** approved for those 12 years and older with two copies of the F508del mutation

- **SEPTEMBER 28, 2016**
  - **Ivacaftor and Lumacaftor** approved for those 6 to 11 years with two copies of the F508del mutation

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FDA Clears Tezacaftor/Ivacaftor Combo for Cystic Fibrosis

Megan Brooks
February 13, 2018

The US Food and Drug Administration (FDA) has approved a third drug from Vertex Pharmaceuticals directed at an underlying cause of cystic fibrosis (CF), the company has announced.

The new treatment combines ivacaftor (*Kalydeco*), approved in 2012, with tezacaftor. It will be sold under the brand name *Symdeko*. In 2015, Vertex’s combination of lumacaftor and ivacaftor (*Orkambi*) became the first drug approved by the FDA to treat the underlying cause of CF.

*Symdeko* is indicated for the treatment of CF in people aged 12 years and older who have two copies of the F508del mutation in the CF transmembrane conductance regulator (*CFTR*) gene or who have at least one mutation that is responsive to tezacaftor/ivacaftor.

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CFTR Modulators: Ivacaftor

- Ivacaftor (Kalydeco™)
  - Facilitates opening of the chloride channel (“CFTR Potentiator”)

Ex. G551D
Ex. R117H

Cystic Fibrosis Pathophysiology: CFTR

**Prevalence of the 10 most common CFTR mutations**

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CFTR Modulators: Lumacaftor / Ivacaftor

- Lumacaftor/Ivacaftor (Orkambi™)
  - Lumacaftor component fixes the defective CFTR protein so it can move to the proper place on the airway cell surface (“CFTR corrector”)
  - Ivacaftor serves as the CFTR “potentiator”

Cystic Fibrosis Pathophysiology: CFTR

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CFTR Modulators: Tezacaftor / Ivacaftor

- Tezacaftor/Ivacaftor (Symdeko™)
  - Tezacaftor component fixes the defective CFTR protein so it can move to the proper place on the airway cell surface ("CFTR corrector")
  - Ivacaftor serves as the CFTR "potentiator"


Cystic Fibrosis Pathophysiology: CFTR

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Table 4: List of CFTR Gene Mutations that Produce CFTR Protein and are Responsive to SYMDEKO

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*A patient must have two copies of the F508del mutation or at least one copy of a responsive mutation presented in Table 4 to be indicated.
CFTR Modulators: Ivacaftor

- STRIVE trial - Phase 3, randomized, DB, PC study
  - Study population: CF with $\geq 1$ G551D-CFTR mutation; FEV$_1$ 40-90%
  - Demographics: Age $\geq 12$ y (mean age 26 y); mean FEV$_1$ = 64%
  - Ivacaftor 150mg PO q12h (n=83) vs. placebo (n=78)
  - Primary outcome: Mean change in FEV$_1$ at 24 weeks
  - Results:
    - Improved FEV$_1$ at 24 / 48 w (p<0.001)
    - Similar safety profile

CFTR Modulators: Ivacaftor

- ENVISION trial - Phase 3, randomized, DB, PC study
  - Study population: CF with ≥ 1 G551D-CFTR mutation; FEV₁ 40-105%
  - Demographics: Age 6-11 y (mean age 9 y); mean FEV₁ = 84%
  - Ivacaftor 150mg PO q12h (n=26) vs. placebo (n=26)
  - Primary outcome: Mean change in FEV₁ at 24 weeks
  - Results:
    - Improved FEV₁ at 24 / 48 w (p<0.001)
    - Similar safety profile

CFTR Modulators: Ivacaftor

- PERSIST study – Open-label, Extension study (of STRIVE / ENVISION)
  - Ivacaftor 150mg q12h (n=192) x 96 weeks (up to 144 weeks)
  - Results:
    - Similar safety profile (vs. previous studies)
    - Persisting efficacy…

CFTR Modulators: Lumacaftor / Ivacaftor

- TRAFFIC & TRANSPORT trials - Phase 3, randomized, DB, PC studies
  - Study population: CF; homozygous F508del-CFTR mutation; FEV$_1$ 40-90%
  - Demographics: Age $\geq$ 12 y (mean age 25 y); mean FEV$_1$ = 60%
  - L-600mg q24h + I-250mg q12h (n=368) / L-400mg + I-250mg q12h (n=369)
  - Primary outcome: Mean change in FEV$_1$ at 24 weeks
  - Results – Both treatment groups demonstrated:
    - Improved FEV$_1$ at 24 w (p<0.001)
    - Similar safety profile

CFTR Modulators: Lumacaftor / Ivacaftor

- PROGRESS study – DB, Extension study (of TRAFFIC / TRANSPORT)
  - L-400mg + I-250mg q12h (n=516) x 96 weeks (up to 120 weeks)
  - Results:
    - Similar safety profile (vs. previous studies)
    - Persisting efficacy…

CFTR Modulators: Lumacaftor / Ivacaftor

- Phase 3, randomized, DB, PC study
  - Study population: CF; homozygous F508del-CFTR mutation; FEV₁ ≥ 70%
  - Demographics: Age ≥ 6-11 y (mean age 9 y); mean FEV₁ = 90%
  - L-200mg + I-250 mg q12h (n=103)
  - Primary outcome: Mean change in LCI₂.₅ up to end of treatment (24 weeks)
  - Results:
    - Similar safety profile
    - Improved LCI₂.₅ (vs. BSL and vs. placebo) (p<0.001)

![Graph showing changes in LCI₂.₅ over time with error bars]

FEV₁ Normal/Mild (≥70%)
FEV₁ Moderate (40% to 69%)
FEV₁ Severe (<40%)

CFTR Modulators: Tezacaftor + Ivacaftor

- **EVOLVE trial - Phase 3, randomized, DB, PC study**
  - Study population: CF; homozygous F508del-CFTR mutation; FEV\(_1\) 40-90%
  - Demographics: Age ≥ 12 y (mean age ~26 y); mean FEV\(_1\) = 60%
  - T-100mg PO Q24h + I-150mg PO Q12H (n=251) vs. placebo (n=258)
  - Primary outcome: Absolute change in FEV\(_1\) at 24 weeks
  - Results:
    - Improved FEV\(_1\) at 24 w (p<0.001)
    - Similar safety profile

CFTR Modulators: Tezacaftor + Ivacaftor

- EXPAND trial - Phase 3, randomized, DB, PC, cross-over study
  - Study population: CF; heterozygous F508del-CFTR mutation + CFTR mutation with residual function; FEV₁ 40-90%
  - Demographics: Age ≥ 12 y (mean age 35 y); mean FEV₁ = 62%
  - T-100mg Q24H + I-150mg Q12H (n=83) vs. I-150mg Q12H (n=81) vs. placebo (n=80)
  - Primary outcome: Mean of the absolute change in FEV₁ at 4 and 8 weeks
  - Results:
    - Improved FEV₁ (p<0.001)
    - Similar safety profile

Comparison of CFTR Modulators

Treatment Effect, Absolute Δ % Predicted FEV1 (percentage points)

- Ivacaftor - G551D, age 12+ y
- Ivacaftor - G551D, age 6-11 y
- Lumacaftor/Ivacaftor - F508del homozygous, age 12+ y
- Lumacaftor/Ivacaftor - F508del homozygous, age 6-11 y
- Tezacaftor/Ivacaftor - F508del homozygous, age 12+ y
- Tezacaftor/Ivacaftor - F508del heterozygous, age 12+ y

Comparison of CFTR Modulators

Treatment Effect, Absolute $\Delta$ % Predicted FEV1

- **Ivacaftor - G551D, age 12+ y**: 10%
- **Ivacaftor - G551D, age 6-11 y**: 13%
- **Lumacaftor/Ivacaftor - F508del homozygous, age 12+ y**: 3%
- **Lumacaftor/Ivacaftor - F508del homozygous, age 6-11 y**: 2%
- **Tezacaftor/Ivacaftor - F508del homozygous, age 12+ y**: 4%
- **Tezacaftor/Ivacaftor - F508del heterozygous, age 12+ y**: 7%

**Standard CF Treatments - Treatment Effect, Absolute $\Delta$ % Predicted FEV1**

- **Dornase-alfa**: 8%
- **Azithromycin**: 6%

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Comparison of CFTR Modulators

<table>
<thead>
<tr>
<th>Study</th>
<th>CFTR Modulator</th>
<th>CFTR</th>
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<th>APE Rate</th>
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<th>BMI</th>
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<tbody>
<tr>
<td>Ramsey et al</td>
<td>Ivacaftor</td>
<td>G551D</td>
<td>≥ 12 y</td>
<td>55% ↓</td>
<td>↑</td>
<td>NR</td>
<td>↑</td>
</tr>
<tr>
<td>Davies et al</td>
<td>Ivacaftor</td>
<td>G551D</td>
<td>6-11 y</td>
<td>NR</td>
<td>↑</td>
<td>↑</td>
<td>NC</td>
</tr>
<tr>
<td>Wainwright et al</td>
<td>Lumacaftor + Ivacaftor</td>
<td>F508del homo</td>
<td>≥ 12 y</td>
<td>39% ↓</td>
<td>NR</td>
<td>↑</td>
<td>NC</td>
</tr>
<tr>
<td>Ratjen et al</td>
<td>Lumacaftor + Ivacaftor</td>
<td>F508del homo</td>
<td>6-11 y</td>
<td>NR</td>
<td>NR</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Taylor et al</td>
<td>Tezacaftor + Ivacaftor</td>
<td>F508del homo</td>
<td>≥ 12 y</td>
<td>35% ↓</td>
<td>NR</td>
<td>NC</td>
<td>↑</td>
</tr>
<tr>
<td>Rowe et al</td>
<td>Tezacaftor + Ivacaftor</td>
<td>F508del homo</td>
<td>≥ 12 y</td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td>↑</td>
</tr>
</tbody>
</table>

Comparison of CFTR Modulators

- Ivacaftor: Data derived from STRIVE, ENVISION, & PERSIST vs. CFFPR cohort
  - Reduced est. annual rate of FEV1 decline: -0.91% vs. -1.72% (p=0.03)

- Lumacaftor-Ivacaftor: Data derived from TRAFFIC & TRANSPORT vs. CFFPR cohort
  - Reduced est. annual rate of FEV1 decline: -1.33% vs. -2.29% (p<0.001)

Impact of CFTR Modulators in the “Real” World

**Outcome**
- Positive response

**Homozygous F508del CFTR mutation**

**PFTs - % Predicted**
- Lumacaftor-Ivacaftor Initiation

**Last FEV1 Date:** 03/19/2018  
**Last FEV1 Value:** 2.76

**Last FVC Date:** 03/19/2018  
**Last FVC Value:** 3.57

**Last FEF25-75 Date:** 03/19/2018  
**Last FEF25-75 Value:** 2.35

**Nutritional Trend**
- Lumacaftor-Ivacaftor Initiation

**Outcome**
- Positive response
Impact of CFTR Modulators in the “Real” World

Homozygous F508del CFTR mutation

Lumacaftor-Ivacaftor Initiation

OUTCOME
Equivocal response

Nutritional Trend

Lumacaftor-Ivacaftor Initiation

Last FEV1 Date: 12/18/2017  
Last FEV1 Value: 1.68

Last FVC Date: 12/18/2017  
Last FVC Value: 2.68

Last FEF25-75 Date: 12/18/2017  
Last FEF25-75 Value: 0.9
Comparison of CFTR Modulators

AWP / 28-day supply

- Ivacaftor
- Lumacaftor/Ivacaftor
- Tezacaftor/Ivacaftor


# CFTR Modulator Dosing

<table>
<thead>
<tr>
<th>CFTR Modulator</th>
<th>Age</th>
<th>Dosing</th>
<th>Special Directions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivacaftor</td>
<td>2-5 years (&lt;14kg)</td>
<td>50mg BID</td>
<td>Take w/ fat-containing meal.</td>
</tr>
<tr>
<td></td>
<td>2-5 years (≥14kg)</td>
<td>75mg BID</td>
<td>Dose reduction required in moderate-severe hepatic dysfunction.</td>
</tr>
<tr>
<td></td>
<td>≥ 6 years</td>
<td>150mg BID</td>
<td></td>
</tr>
<tr>
<td>Lumacaftor (L) + Ivacaftor (I)</td>
<td>6-11 years</td>
<td>L-100mg + I-125mg / tab: 2 BID</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥ 12 years</td>
<td>L-200mg + I-125mg / tab: 2 BID</td>
<td></td>
</tr>
<tr>
<td>Tezacaftor (T) + Ivacaftor (I)</td>
<td>≥ 12 years</td>
<td>T-100mg + I-150mg / tab: 1 QAM AND I-150mg / tab: 1 QPM</td>
<td></td>
</tr>
</tbody>
</table>
## CFTR Modulator DDIs

- Ivacaftor: CYP3A substrate
- Tezacaftor: CYP3A substrate, Mild CYP3A inducer
- Lumacaftor: Strong CYP3A inducer

<table>
<thead>
<tr>
<th>Mechanism of DDI</th>
<th>Medication: Examples</th>
<th>CFTR Mod.</th>
<th>AUC</th>
<th>Cmax</th>
<th>Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A inhibition (mod.)</td>
<td>Erythromycin Fluconazole</td>
<td>Ivacaftor</td>
<td>↑</td>
<td>↑</td>
<td>Once daily I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tezacaftor</td>
<td>?</td>
<td>?</td>
<td>QOD, alternating between T+I and I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lumacaftor</td>
<td>↑</td>
<td>↑</td>
<td>Twice weekly T+I</td>
</tr>
<tr>
<td>CYP3A inhibition (strong)</td>
<td>Clarithromycin Itraconazole</td>
<td>Ivacaftor</td>
<td>↑↑</td>
<td>↑↑</td>
<td>Twice weekly T+I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tezacaftor</td>
<td>↑</td>
<td>↑</td>
<td>Twice weekly T+I</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lumacaftor</td>
<td>↓↓</td>
<td>↓↓</td>
<td>Avoid concomitant use</td>
</tr>
<tr>
<td>CYP3A induction</td>
<td>Rifampin Carbamazepine Phenobarbital Phenytoin St. John’s wort</td>
<td>Ivacaftor</td>
<td>↓↓</td>
<td>↓↓</td>
<td>Avoid concomitant use</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tezacaftor</td>
<td>?</td>
<td>?</td>
<td></td>
</tr>
</tbody>
</table>
Lumacaftor / Ivacaftor dose adjustment:

- **Scenario: Co-treatment with CYP3A inhibitors:**
  - Lumacaftor / ivacaftor added to a regimen that includes a strong CYP3A inhibitor (e.g., itraconazole)… decrease lumacaftor / ivacaftor dose to 1 tablet daily during the first week of treatment
  - Strong CYP3A inhibitor (e.g., itraconazole) added to a regimen that includes lumacaftor / ivacaftor… no dose adjustment needed

---

**CFTR Modulator DDIs**

- Ivacaftor: CYP3A substrate
- Tezacaftor: CYP3A substrate, Mild CYP3A inducer
- Lumacaftor: Strong CYP3A inducer
Are we achieving our vision?

Prevalence of the 10 most common CFTR mutations

<table>
<thead>
<tr>
<th>Legacy Name</th>
<th>cDNA Name</th>
<th>Protein Name</th>
<th>Mutation Class</th>
<th>Number of Individuals</th>
<th>Percent of All People with CF</th>
</tr>
</thead>
<tbody>
<tr>
<td>F508del</td>
<td>c.1521_1523delCTT</td>
<td>p.Phe508del</td>
<td>2</td>
<td>24,901</td>
<td>86.4</td>
</tr>
<tr>
<td>G542X</td>
<td>c.1624G&gt;T</td>
<td>p.Gly542X</td>
<td>1</td>
<td>1,342</td>
<td>4.7</td>
</tr>
<tr>
<td>G551D</td>
<td>c.1652G&gt;A</td>
<td>p.Gly551Asp</td>
<td>3</td>
<td>1,280</td>
<td>4.4</td>
</tr>
<tr>
<td>R117H</td>
<td>c.350G&gt;A</td>
<td>p.Arg117His</td>
<td>4</td>
<td>865</td>
<td>3.0</td>
</tr>
<tr>
<td>N1303K</td>
<td>c.3909C&gt;G</td>
<td>p.Asn1303Lys</td>
<td>2</td>
<td>703</td>
<td>2.4</td>
</tr>
<tr>
<td>W1282X</td>
<td>c.3846G&gt;A</td>
<td>p.Trp1282X</td>
<td>1</td>
<td>658</td>
<td>2.3</td>
</tr>
<tr>
<td>R553X</td>
<td>c.1657C&gt;T</td>
<td>p.Arg553X</td>
<td>1</td>
<td>527</td>
<td>1.8</td>
</tr>
<tr>
<td>1717-1G&gt;A</td>
<td>c.1585-1G&gt;A</td>
<td></td>
<td>1</td>
<td>456</td>
<td>1.6</td>
</tr>
<tr>
<td>3849+10kbC&gt;T</td>
<td>c.3717+12191C&gt;T</td>
<td></td>
<td>5</td>
<td>435</td>
<td>1.5</td>
</tr>
<tr>
<td>621+1G&gt;T</td>
<td>c.489+1G&gt;T</td>
<td></td>
<td>1</td>
<td>431</td>
<td>1.5</td>
</tr>
</tbody>
</table>

**VX-659 + tezacaftor + ivacaftor**

**STATUS**
Phase Three

**THERAPEUTIC APPROACH**
Restore CFTR Function

This program is testing VX-659 in combination with tezacaftor and ivacaftor. VX-659 and tezacaftor (VX-661) are new CFTR correctors. Correctors are drugs designed to fix the defective CFTR protein so that it can move to the proper place on the cell surface. Once CFTR protein reaches the cell surface, ivacaftor helps facilitate the opening of the chloride channel to allow chloride and sodium (salt) to move in and out of the cell.

**Status**
A phase 3 study to test the safety and effectiveness of VX-659 in people with CF age 12 years or older is underway.

---

**VX-445 + tezacaftor + ivacaftor**

**STATUS**
Phase Three

**THERAPEUTIC APPROACH**
Restore CFTR Function

This program is testing VX-445 in combination with tezacaftor and ivacaftor. VX-445 and tezacaftor (VX-661) are new CFTR correctors. Correctors are drugs designed to fix the defective CFTR protein so that it can move to the proper place on the cell surface. Once CFTR protein reaches the cell surface, ivacaftor helps facilitate the opening of the chloride channel to allow chloride and sodium (salt) to move in and out of the cell.

**Status**
A phase 1 and 2 study to test the safety and tolerability of VX-445 is underway. A phase 3 study will begin soon.
Summary

- CF is caused by a defect in the CFTR gene, which results in defective chloride transport, culminating in a cycle of obstruction, infection, and inflammation in the CF lung.

- Chronic treatment of CF lung disease is directed toward targeting the CFTR with CFTR modulators, while continuing to treat airway obstruction, infection and inflammation.

- All approved CFTR modulators have been shown to improve pulmonary function, albeit to different degrees, and have been shown to reduce the incidence of acute pulmonary exacerbations.
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Questions