4 – 7 JUNE 2025
MILAN, ITALY

48th EUROPEAN CYSTIC FIBROSIS CONFERENCE

Vanzacaftor-tezacaftor-deutivacaftor

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Vanzacaftor/Tezacaftor/ Deutivacaftor

(VTD)

- **Approval: December 20, 2024**
  - Alyftrek™
- **Eligibility:**
  - At least 6 years old
  - ETI mutations plus one of the 31 additional mutations
    - On December 20, ETI was also approved for an additional 94 mutations.

Not actual size.

Boxed Warnings

- **What are the ETI and VTD boxed warnings?**
  - BOXED WARNING: DRUG-INDUCED LIVER INJURY AND LIVER FAILURE
- **Why?**
  - Liver enzyme elevations have been seen in people with cystic fibrosis treated with the drugs.
  - Based on the FDA's review of the safety profile, they have recommended the change in monitoring.
- **Liver function tests?**
  - Prior to start
  - Every month during the first 6 months of treatment
  - Every 3 months during the next 12 months
  - At least annually thereafter

Vanzacaftor/Tezacaftor/ Deutivacaftor

(VTD)

- **What's the difference between VTD and ETI?**
  - Clinical trial results showed improvements in lung function comparable to those seen with ETI
  - Reduction in sweat chloride levels that exceeded treatment with ETI
  - Once daily
  - Cost: about 7% more expensive

- **Are there mental health side effects with VTD?**
  - Like ETI, clinical trials for VTD did not identify mental health side effects
  - Currently studying

Not actual size.

Vanzacaftor/Tezacaftor/Deutivacaftor (VTD)

VTD clinical trial participants were required to be **stable on a full dose of ETI.**

Excluded PWCF that modified or discontinued ETI due to mental health or liver injury.

Key clinical questions for PWCF intolerant of ETI standard dosing due to mental health or liver-related reasons…

1. How likely is it that this group will tolerate VTD?
2. Are they at elevated risk for similar side effects they had on ETI?

Restarting Triple Therapy with Robust Monitoring for Adverse Events (RETRIAL)

Multi-site, prospective, observational study of what happens when PWCF ages 6+ start VTD who previously experienced mental health, neurocognitive, sleep, or liver injury on ETI that resulted in a modification or discontinuation of standard ETI dosing.

RETRIAL-MH (n=150)

Mental health surveys
pre-VTD, biweekly through 6mos, 9 & 12mos

Daily diaries
-2 weeks pre-VTD through 1mo post

Enroll subset of n=50 RETRIAL-MH with no previous liver concerns on as RETRIAL-Liver controls

RETRIAL-Liver (n=50)

Liver injury
pre-/post-VTD liver function tests, case report forms through 12mos

Liver-related survey data
pre-VTD, 1, 3, 6, 9, and 12mos

RETRIAL-Neuro (n=60)

Neurocognitive testing
pre-VTD, 1mo post

Optional for ages 7+ who had neurocognitive side effects on elexacaftor/tezacaftor/ivacaftor

RETRIAL-Bio

Biobanking
pre-VTD, 1mo post

Blood

Stool

Nasal swabs

Optional for all

RETRIAL
RESTARTING TRIPLE THERAPY WITH ROBUST MONITORING FOR ADVERSE EVENTS

Objectives: RETRIAL-MH and RETRIAL-Neuro

Primary: To examine the incidence of RETRIAL-MH participants discontinuing or changing from VTD standard dosing.

Secondary: To examine changes in mental health symptoms of participants in RETRIAL-MH who are starting VTD.

Tertiary (exploratory): To examine the neurocognitive response of participants in RETRIAL-Neuro who are starting VTD.

Objectives: RETRIAL-Liver

Primary: To determine the proportion of RETRIAL-Liver participants starting VTD who develop a diagnosis of drug-induced liver injury (DILI) defined by expert consensus.

Secondary: To examine discontinuation or change from VTD standard dosing based upon increased transaminases/bilirubin.

Tertiary: To examine rates of VTD discontinuation due to liver enzyme elevation in RETRIAL-Liver compared to RETRIAL-MH participants enrolled as a part of RETRIAL-Liver control group.

RETRIAL Progress

- Protocol completed
- BCH IRB submitted
- CFF Award #1 submitted + approved
- STRC protocol review
- DSMB charter
- Site selection
- Measure creation

- CFF Award #2 Submitted+ approved
- BCH IRB Full Board Review
- 1st DSMB Mtg + Ratification
- IRB Approval
- Site budgets finalized
- Reliance and contracting started

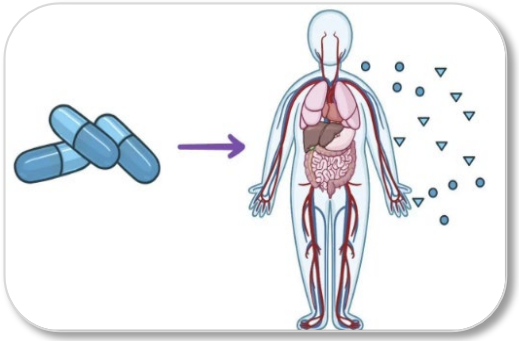
- TDN's CREC review completed
- Contracts in progress
- Reliance agreements in progress
- Site trainings initiated

- REDCap finalized
- **1st Training (3 sites)**
- Supplies purchased
- Supplies shipped
- All-Site PI Call Series started
- All-Site RC Call series started

- 2 sites activated
- May 5th – 1st recruited
- 2nd Training (late May)
- 6 sites to be activated (late May)

Individual variations in modulator metabolism

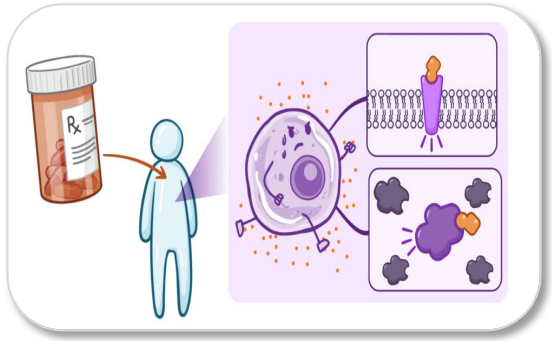
Pharmacokinetics (PK)



What the body does to the drug

- Absorption
- Distribution
- Metabolism
- Excretion

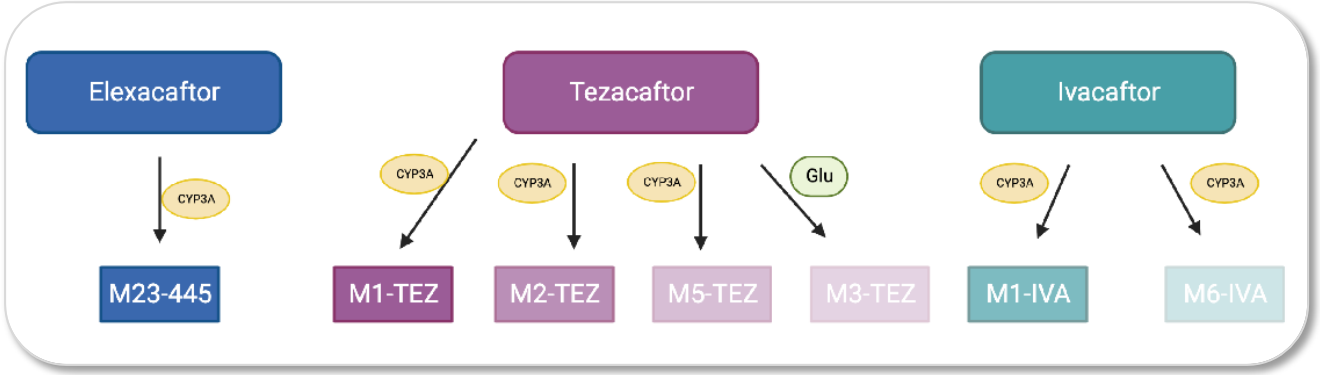
Pharmacodynamics (PD)



What the drug does to the body

- Efficacy
- Toxicity

http://www.osmosis.org



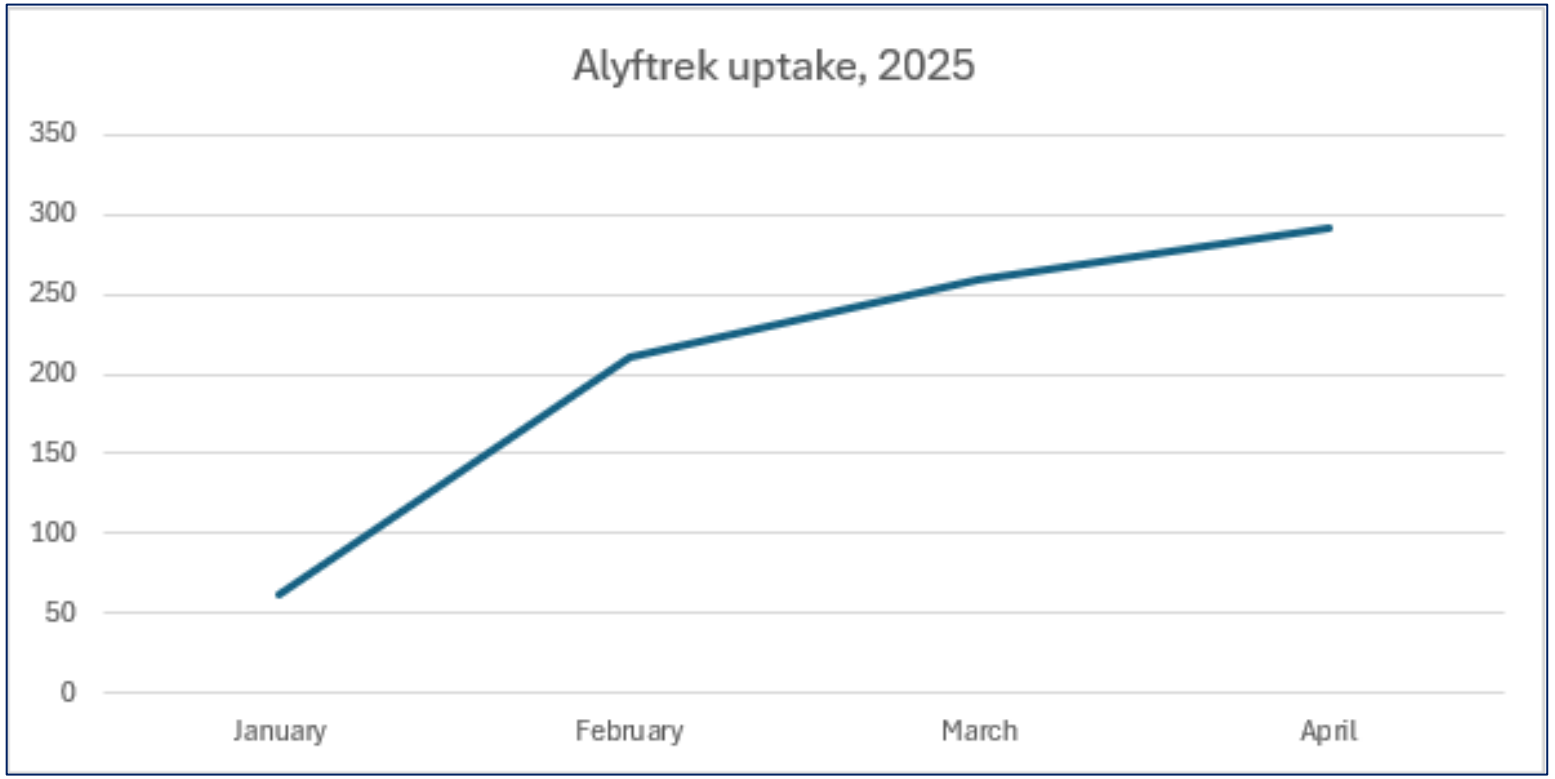
- Drug and metabolite concentrations could contribute to differences in patient response
- No data yet correlating concentrations to modulator adverse events

Figure 1. Parent CFTR modulators and Metabolites (darker metabolite = more relative potency).
**Courtesy of Emma Tillman, PharmD, PhD, created using BioRender*

VTD Usage

Current usage:

- 850 people have been prescribed VTD
- Compared to ETI, there were 5,000 prescriptions in 2 months.



VTD Usage

Barriers:

- Insurance coverage
- Reluctance
- Increased safety monitoring

Subjective feedback (Listserv)

- Auditory and visual hallucinations
- Rash
- Abdominal pain
- No mental health side effect compared to ETI

Conclusions

- VTD is at least as effective as ETI
- Increased safety labs
- Studies are being conducted to evaluate mental health and liver side effects
- The uptake in the U.S. is slower than it was for ETI

Questions?

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