GEMs of the Week

Volume 5 - Issue 20

What's in this week's issue?

Week of June 2 - June 6, 2025

SPOTLIGHT:
Ensifentrine: Unlocking New Possibilities in COPD Care

- **The Role of Survodutide in the Management of MASH**
- **Two Visits a Year, Stay in the Clear: Lenacapavir for HIV Prevention**

Ensifentrine: Unlocking New Possibilities in COPD Care

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Ensifentrine, A Novel Phosphodiesterase 3 and 4 Inhibitor for the Treatment of Chronic Obstructive Pulmonary Disease: Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase III Trials (The ENHANCE Trials)

Anzueto A, Barjaktarevic IZ, Siler TM, et al. Ensifentrine, a Novel Phosphodiesterase 3 and 4 Inhibitor for the Treatment of Chronic Obstructive Pulmonary Disease: Randomized, Double-Blind, Placebo-controlled, Multicenter Phase III Trials (the ENHANCE Trials). *Am J Respir Crit Care Med*. 2023;208(4):406-416. doi:10.1164/rccm.202306-0944OC

KEY TAKEAWAY: Ensifentrine improves lung function in patients with moderate to severe chronic obstructive pulmonary disease (COPD).

STUDY DESIGN: Multicenter, randomized, double-blind, parallel-group, placebo-controlled trials

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: The standard treatment for COPD has consisted of inhaled bronchodilators and corticosteroids for more than four decades. Ensifentrine arised as a complementary alternative, acting as a selective, dual inhibitor of phosphodiesterase three (PDE3) and PDE4, which intervenes on airway smooth muscle contraction and suppresses the inflammatory response.

PATIENTS: Adults with moderate to severe symptomatic COPD

INTERVENTION: Ensifentrine

CONTROL: Placebo

PRIMARY OUTCOME: Lung function

Secondary Outcome: Peak forced expiratory volume in one second (FEV1), COPD exacerbation rate, COPD symptoms

METHODS (BRIEF DESCRIPTION):

- Included patients were adults 40–80 years old with a diagnosis of COPD and:
  - Post-bronchodilator FEV1 30–70% predicted normal
  - FEV1/forced vital capacity (FVC) ratio <0.7
  - Modified Medical Research Council dyspnea scale score ≥2
  - Smoking history >10 pack-years
  - No asthma diagnosis
- Patients were blinded and randomized to one of the following treatments:
  - Standard treatment + ensifentrine 3 mg twice daily via a standard jet nebulizer
  - Standard treatment + placebo twice daily via a standard jet nebulizer
- The primary outcome measured the improvement in lung function measured as FEV1 area under the curve over 12 hours (AUC0–12h) post-dose, at week 12 of treatment.
- The following were measured as the secondary outcomes:
  - Peak FEV1 at week 12 of treatment was measured as the maximum value in the four hours after dosing.
  - COPD exacerbations were assessed over 24 weeks of treatment.
  - An improvement in COPD symptoms was measured with the Evaluating-Respiratory Symptoms (E-RS) score which assesses the severity of symptoms. Scores range from 0–40, with higher scores indicating more severe symptoms.

INTERVENTION (# IN THE GROUP):

- ENHANCE-1 trial: 477
- ENHANCE-2 trial: 498

COMPARISON (# IN THE GROUP):

- ENHANCE-1: 283
- ENHANCE-2: 291

FOLLOW-UP PERIOD: 24 weeks

RESULTS:

Primary Outcome –

- Ensifentrine significantly improved lung function compared to placebo:
  - ENHANCE-1 trial (least squares mean difference [LSMD] 87 mL; 95% CI, 55–119)
  - ENHANCE-2 trial (LSMD 94 mL; 95% CI, 65–124)

Secondary Outcome –

- Ensifentrine increased peak FEV1 compared to placebo:
  - ENHANCE-1 trial (LSMD 147 mL; 95% CI, 111–183)

    - ENHANCE-2 trial (LSMD 146 mL; 95% CI, 113–179)
- Ensifentrine decreased COPD exacerbations in the ENHANCE-2 trial compared to placebo (rate ratio [RR] 0.64; 95% CI, 0.38–0.87).
- Ensifentrine did not decrease COPD exacerbations in the ENHANCE-1 trial compared to placebo.
- Ensifentrine decreased COPD symptoms in the ENHANCE-1 trial compared to placebo (LSMD –0.1; 95% CI, –1.7 to –0.2).
- Ensifentrine did not improve COPD symptoms in the ENHANCE-2 trial compared to placebo.

LIMITATIONS:

- The COVID-19 pandemic may have affected results.
- Patients taking dual bronchodilator therapy and triple therapy were excluded so it is unknown how ensifentrine works in combination with these medications.

Javier Viteri Quincha, MD
Southern Illinois University - Quincy FMRP
Quincy, IL

The Role of Survodutide in the Management of MASH

A Phase 2 Randomized Trial of Survodutide in MASH and Fibrosis

Sanyal AJ, Bedossa P, Fraessdorf M, et al. A Phase 2 Randomized Trial of Survodutide in MASH and Fibrosis. *N Engl J Med.* 2024;391(4):311-319. doi:10.1056/NEJMoa2401755

KEY TAKEAWAY: Survodutide may improve metabolic dysfunction-associated steatohepatitis (MASH) and reduce MASH-associated fibrosis compared to placebo.

STUDY DESIGN: Multicenter, double-blind randomized trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to disease-oriented outcome and lack of statistical comparison)

BRIEF BACKGROUND INFORMATION: Although glucagon-like peptide-1 (GLP-1) receptor agonists have emerged as promising treatments for MASH, their effects are limited to indirect, extrahepatic benefits, such as improved glucose control and weight loss. Survodutide is a GLP-1 and glucagon receptor dual agonist that works directly on hepatocytes and has the potential to not only improve MASH but also reverse MASH-associated fibrosis.

PATIENTS: Adults with MASH and fibrosis

INTERVENTION: Survodutide

CONTROL: Placebo

PRIMARY OUTCOME: Histologic MASH improvement

Secondary Outcome: Decrease in liver fat content, fibrosis stage reduction, adverse effects

METHODS (BRIEF DESCRIPTION):

- This phase two study was conducted at 155 sites located in 25 high and middle-income countries.
- Included participants were 18–80 years old with:
  - Biopsy proven MASH, a fibrosis stage F1 to F3 (where F1 indicates mild fibrosis and F3 indicates severe fibrosis)
  - Stable body weight
  - Liver fat content of at least 8% measured via magnetic resonance imaging (MRI), and liver stiffness of >6.0 kPa measured via FibroScan
    - Normal liver stiffness: 2–6 kPa
    - Mild fibrosis: 6–8 kPa
    - Moderate fibrosis: 8–10 kPa
    - Severe fibrosis: 10–14 kPa
- All participants had liver biopsies obtained at baseline and had MASH activity scores calculated, which measure the degree of steatosis, inflammation, and cellular inflammation. Scores range from 4–8, with higher scores indicating more severe disease.
- Participants were excluded if they had alcohol associated liver disease or cirrhosis, were on hepatotoxic medications 12 weeks before screening, or had a history of other chronic liver diseases (such as cancer or viral or autoimmune liver disease).
- Participants were randomly assigned to receive Survodutide injections subcutaneously once weekly at doses of 2.4 mg, 4.8 mg, or 6.0 mg.
- The comparison group received placebo injections weekly.
- Participants in the intervention group started Survodutide 0.3 mg weekly with doses escalated by 0.3 mg every two weeks for up to 24 weeks until their target dose was reached.
  - This was then followed by a 24-week maintenance phase.
- Histologic MASH improvement was obtained through liver biopsy performed after 48 weeks of treatment.
  - MASH improvement was defined as a ≥2-point decrease in the nonalcoholic fatty liver disease (NAFLD) activity score with a ≥1 point decrease in either lobular inflammation or hepatocellular ballooning.
- For secondary outcomes, MRI was used to measure the liver fat content (looking for at least 30% decrease) while biopsy assessment was used to determine fibrosis improvement (defined as ≥1 stage decrease).

INTERVENTION (# IN THE GROUP):

- 2.4 mg: 73
- 4.8 mg: 72
- 6.0 mg: 74

COMPARISON (# IN THE GROUP): 74

FOLLOW-UP PERIOD: 48 weeks

RESULTS:

Primary Outcome –

- 2.4 mg Survodutide improved histologic MASH in participants compared to baseline (47%; 95% CI, 36–58).
- 4.8 mg Survodutide improved histologic MASH in participants compared to baseline (62%; 95% CI, 51–73).
- 6.0 mg Survodutide improved histologic MASH in participants compared to baseline (43%; 95% CI, 33–35).
- Placebo improved histologic MASH in participants compared to baseline (14%; 95% CI, 8–23).
- A quadratic dose-response curve showed that the increased dose responses were statistically significant (*P*<.001).

Secondary Outcome –

- All doses of Survodutide improved fibrosis compared to baseline.
  - 34% of participants in the 2.4 mg group
  - 36% of participants in the 4.8 mg group
  - 34% of participants in the 6 mg group
  - 22% of participants in the placebo group
- All doses of Survodutide decreased liver fat content of ≥30% compared to baseline.
  - 63% of participants in the 2.4 mg group
  - 67% of participants in the 4.8 mg group
  - 57% of participants in the 6.0 mg group
  - 14% of participants in the placebo group
- The most common adverse effects included nausea, vomiting, and diarrhea, with a higher occurrence in participants in all three Survodutide groups (82%) and a lower occurrence in the placebo group (49%).

LIMITATIONS:

- The primary study results are biopsy-based, which limits clinical applicability.
- Confidence intervals or p-values were not reported for the secondary outcomes.
- Most of the participants identified as White, which limits generalizability to a larger, more diverse population.
- Survodutide is not yet FDA approved for MASH and fibrosis treatment.
- This was a phase two study, and the authors did not conduct statistical testing to determine if the difference between the intervention and placebo groups was statistically significant.

Jordan A Fischer, MD
Camp Lejeune Naval Medical Center FMRP
Camp Lejeune, NC

The views expressed herein are those of the author and do not necessarily reflect the official policy of the Department of the Army, Defense Health Agency, Department of Defense, or the U.S. Government.

Two Visits a Year, Stay in the Clear: Lenacapavir for HIV prevention

Twice-Yearly Lenacapavir for HIV Prevention in Men and Gender-Diverse Persons

Kelley CF, Acevedo-Quiñones M, Agwu AL, et al. Twice-Yearly Lenacapavir for HIV Prevention in Men and Gender-Diverse Persons. *N Engl J Med*. 2025;392(13):1261-1276. doi:10.1056/NEJMoa2411858

KEY TAKEAWAY: Subcutaneous lenacapavir reduces human immunodeficiency virus (HIV) incidence in high risk individuals compared to a modeled background incidence among the screened population.

STUDY DESIGN: Phase 3, multicenter, double-blind, randomized, active-controlled trial

LEVEL OF EVIDENCE: STEP 3 (downgraded due to lack of generalizability)

BRIEF BACKGROUND INFORMATION: While HIV transmission has undergone a global decrease by 35% in the last 15 years, new transmissions are still disproportionately prevalent among gender-diverse persons of color. In these populations, the global rates of initiating and adhering to pre-exposure prophylaxis (PrEP) are low- only at 17% of the goal set by Joint United Nations Program on HIV and acquired immunodeficiency syndrome (AIDS). This study investigated the efficacy of lenacapavir, a highly potent HIV-1 capsid inhibitor with a long half-life, as an effective alternative to the daily oral treatment in these populations with higher HIV incidence.

PATIENTS: Biological males, transgender men, and gender diverse persons at higher risk for HIV

INTERVENTION: Subcutaneous lenacapavir

CONTROL: Oral emtricitabine-tenofovir disoproxil fumarate (F/TDF)

PRIMARY OUTCOME: HIV incidence vs background HIV incidence

Secondary Outcome: HIV incidence vs F/TDF

METHODS (BRIEF DESCRIPTION):

- A double-blind randomized active-controlled trial was conducted on patients who were screened and recruited from 92 trial sites in areas of significant HIV transmission across several nations.
- Patients were included if they met one of the following qualifications:
  - Cisgender men, transgender women, transgender men, and gender nonbinary persons who were engaging in condomless receptive anal sex with partners assigned male at birth
  - Patients ≥16 years old
  - Patients who tested negative for HIV at baseline
  - Patients who did not have HIV testing or use PrEP in the three months before screening
- During the screening process, participants were tested for HIV and if negative, they were randomized in a 2:1 ratio to receive treatment with either subcutaneous lenacapavir every 26 weeks or daily oral F/TDF treatment.
  - In the lenacapavir treatment group, participants were given initial oral loading doses of two 300 mg tablets of lenacapavir each on the first two days and then treated with subcutaneous lenacapavir every 26 weeks.
  - In the F/TDF group, participants were given two placebo tablets and then treated with daily oral F/TDF.
- Other than the personnel who prepared and administered the injections, all participants and trial personnel were purposefully left unaware of the assignments.
- All participants were then followed with testing by rapid point-of-care and 4th generation antigen-antibody HIV testing at weeks four, eight, 13, and every 13 weeks afterwards.
- The primary outcome of the study measured the incidence of new HIV infection among the participants receiving lenacapavir injections compared to the calculated background incidence of HIV in screened participants.
  - The background incidence of HIV infection in the screening was calculated using a recent infection testing algorithm which generated an estimate of the background incidence within the screened population using additional recent infection testing data from those who tested positive for HIV during the screening.
- The secondary outcome of the study measured the incidence of new HIV infection among participants

receiving lenacapavir compared to the incidence of HIV in participants receiving oral F/TDF treatment.
- Analysis of efficacy was completed using a modified intention-to-treat approach.

INTERVENTION (# IN THE GROUP): 2,183
COMPARISON (# IN THE GROUP): 1,086

FOLLOW-UP PERIOD: 52 weeks

RESULTS:
Primary Outcome –
- Subcutaneous lenacapavir decreased HIV incidence compared to the background HIV incidence (incidence rate ratio [IRR] 0.04; 95% CI, 0.01–0.18).

Secondary Outcome –
- Subcutaneous lenacapavir decreased HIV incidence compared to oral F/TDF treatment (IRR 0.11; 95% CI, 0.02–0.51).

LIMITATIONS:
- Sampling bias in that the study drew participants from specific populations with increased HIV transmission could limit the generalizability of the study findings to the general population without increased HIV transmission rates.
- The calculation of the background HIV incidence may not be representative of the true HIV incidence of general population, estimated to be conservative.
- Multiple trial centers across distinct nations and cultures could introduce uncontrolled biases or nuances in different procedures or methods of providing treatment that remained in spite of standardized protocols.
- The duration of one year may be a false representation of the measure of the true efficacy of the lenacapavir treatment.
- Testing for resistant HIV strains was done; however, comparison data was not reported and may represent an unmeasured confounding variable.

Catherine Kim, MD
Northeast Georgia Medical Center FMRP
Gainesville, GA