NEXLETOL® (bempedoic acid) Tablet, ezetimibe and atorvastatin combination lowered bad cholesterol by 60.5% vs. placebo in Phase 2 study

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- Results of bempedoic acid, ezetimibe and atorvastatin triple therapy study published in March issue of Atherosclerosis -

- Combining three orally administered once-daily LDL-C lowering medicines has not been previously studied, though combination therapy is common in other areas of cardiovascular medicine[1] -

- Results of this Phase 2 study suggest oral combination therapy could play a role in helping more patients achieve guideline-specified LDL-C goals -

ANN ARBOR, Mich., March 17, 2021 (GLOBE NEWSWIRE) -- Esperion (NASDAQ: ESPR) today announced that the results of a Phase 2 study evaluating the combination of NEXLETOL® (bempedoic acid) 180 mg Tablet, ezetimibe 10 mg and atorvastatin 20 mg in patients with hypercholesterolemia were published in *Atherosclerosis*, demonstrating reduction in low-density lipoprotein cholesterol (LDL-C) levels by 60.5% vs. placebo.[2]

The combination of multiple once-daily, orally administered medicines that impact LDL-C levels via different mechanisms has not been previously studied, and 83% of lipid-lowering treatment is statin monotherapy.[3] Even at the highest approved dose, only one-third of patients achieve guideline LDL-C levels of <70 mg/dL with atorvastatin alone.[4,5] The results of this Phase 2 study suggest oral once-daily combination therapy could play a role in helping more patients achieve guideline-specified LDL-C goals: at week 6, more than 90% of patients in the treatment arm reached LDL-C levels of <70 mg/dL, and 58% of patients reached a target of <55 mg/dL, compared with no patients in the placebo group meeting either treatment goal.[2]

“Nearly 9 million patients in the U.S. who take statins are not meeting their cholesterol-lowering goals, indicating a need for additional and combination therapy. On behalf of those patients and their physicians, we are encouraged by the results of this study, and recognize more research is needed,” said Ashley Hall, chief development officer of Esperion. “There are millions of patients globally whose needs aren’t being met by currently available LDL-C lowering treatments, and that is why we continue the urgent work to lower bad cholesterol.”

The aim of this Phase 2 study was to evaluate LDL-C lowering when NEXLETOL was initiated together with ezetimibe (10 mg) and atorvastatin (20 mg), as compared with placebo. The primary endpoint was percent change from baseline in LDL-C vs. placebo, with patients randomized 2:1 to triple therapy (n=43) or placebo (n=20) once daily following a washout of lipid-lowering drugs. After six weeks, all patients randomized to triple therapy showed a reduction in LDL-C, with 95% of patients achieving a decrease in LDL-C ≥50% from baseline. The mean age of patients in this randomized, double-blind, placebo-controlled study was 61.2, and mean baseline LDL-C was 154.8 mg/dL. The majority of study participants were female (63%), supporting Esperion’s commitment to diversity in clinical development.[2]

Most common adverse events (occurring in two or more patients) in either treatment group included headache, diarrhea, fatigue, increase in hepatic enzyme, osteoarthritis, pain in extremity, rash and muscle spasm. Adverse events were predominantly mild or moderate in severity.[2]

Although the study was adequately powered, the small number of enrolled patients and short study duration limit the ability to draw definitive conclusions on long-term treatment effect as well as safety and tolerability.

The dosing of NEXLETOL and ezetimibe used in the treatment arm of the study (180 mg and 10 mg, respectively) is the same as the dosing of the fixed combination drug product NEXLIZET® (bempedoic acid and ezetimibe) Tablet.

The 2020 approval of NEXLETOL in the U.S. was supported by a global pivotal Phase 3 LDL-C-lowering program conducted in more than 3,000 patients with atherosclerotic cardiovascular disease (ASCVD) and/or heterozygous familial hypercholesterolemia (HeFH). In these studies, NEXLETOL provided an average of 18% placebo-corrected LDL-C lowering at week 12 when used with moderate or high-intensity statins. The most common (incidence ≥2% and greater than placebo) adverse reactions were upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anemia and elevated liver enzymes. NEXLETOL is indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or established ASCVD who require additional lowering of LDL-C. The effect of bempedoic acid on cardiovascular morbidity and mortality has not been determined and is currently being investigated in 14,014 patients across 32 countries as part of the CLEAR Outcomes study.[6] Please see important safety information below.

NEXLETOL® (bempedoic acid) Tablet and NEXLIZET® (bempedoic acid and ezetimibe) Tablet

Indication and Limitation of Use

NEXLETOL and NEXLIZET are indicated as adjuncts to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL-C. The effect of NEXLETOL and NEXLIZET on cardiovascular morbidity and mortality has not been determined.

Important Safety Information
Contraindications: NEXLETOL has no contraindications. NEXLIZET is contraindicated in patients with a known hypersensitivity to ezetimibe tablets. Hypersensitivity reactions including anaphylaxis, angioedema, rash, and urticaria have been reported with ezetimibe.

Warnings and Precautions:

- Hyperuricemia: Bempedoic acid, a component of NEXLETOL and NEXLIZET, may increase blood uric acid levels. Hyperuricemia may occur early in treatment and persist throughout treatment, and may lead to the development of gout, especially in patients with a history of gout. Assess uric acid levels periodically as clinically indicated. Monitor for signs and symptoms of hyperuricemia, and initiate treatment with urate-lowering drugs as appropriate.
- Tendon Rupture: Bempedoic acid is associated with an increased risk of tendon rupture or injury. In clinical trials, tendon rupture occurred in 0.5% of patients treated with bempedoic acid versus 0% of patients treated with placebo, and involved the rotator cuff (the shoulder), biceps tendon, or Achilles tendon. Tendon rupture occurred within weeks to months of starting bempedoic acid. Tendon rupture may occur more frequently in patients over 60 years of age, patients taking corticosteroid or fluoroquinolone drugs, patients with renal failure, and patients with previous tendon disorders. Discontinue NEXLETOL or NEXLIZET at the first sign of tendon rupture. Avoid NEXLETOL and NEXLIZET in patients who have a history of tendon disorders or tendon rupture.

Adverse Reactions:

- In NEXLETOL clinical trials, the most commonly reported adverse reactions were upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anemia, and elevated liver enzymes. Reactions reported less frequently, but still more often than with placebo, included benign prostatic hyperplasia and atrial fibrillation.
- In the NEXLIZET clinical trial, the most commonly reported adverse reactions observed with NEXLIZET, but not observed in clinical trials of bempedoic acid or ezetimibe, a component of NEXLIZET, and occurring more frequently than with placebo, were urinary tract infection, nasopharyngitis, and constipation.
- Adverse reactions reported in clinical trials of ezetimibe, and occurring at an incidence greater than with placebo, included upper respiratory tract infection, diarrhea, arthralgia, sinusitis, pain in extremity, fatigue, and influenza. Other adverse reactions reported in postmarketing use of ezetimibe included hypersensitivity reactions, including anaphylaxis, angioedema, rash, and urticaria; erythema multiforme; myalgia; elevated creatine phosphokinase; myopathy/rhabdomyolysis; elevations in liver transaminases; hepatitis; abdominal pain; thrombocytopenia; pancreatitis; nausea; dizziness; paresthesia; depression; headache; cholelithiasis; cholecystitis.

Drug Interactions:

- Simvastatin and Pravastatin: Concomitant use with bempedoic acid results in increased concentrations and increased risk of simvastatin or pravastatin-related myopathy. Use of either NEXLETOL or NEXLIZET with greater than 20 mg of simvastatin or 40 mg of pravastatin should be avoided.
- Cyclosporine: Caution should be exercised when using NEXLIZET and cyclosporine concomitantly due to increased exposure to both ezetimibe and cyclosporine. Monitor cyclosporine concentrations in patients receiving NEXLIZET and cyclosporine. In patients treated with cyclosporine, the potential effects of the increased exposure to ezetimibe from concomitant use should be carefully weighed against the benefits of alterations in lipid levels provided by NEXLIZET.
- Fibrates: Coadministration of NEXLIZET with fibrates other than fenofibrate is not recommended. Fenofibrate and ezetimibe may increase cholesterol excretion into the bile, leading to cholelithiasis. If cholelithiasis is suspected in a patient receiving NEXLIZET and fenofibrate, gallbladder studies are indicated and alternative lipid-lowering therapy should be considered.
- Cholestyramine: Concomitant use of NEXLIZET and cholestyramine decreases ezetimibe concentration. This may result in a reduction of efficacy. Administer NEXLIZET either at least 2 hours before, or at least 4 hours after, bile acid sequestrants.

Lactation and Pregnancy: It is not recommended that NEXLETOL or NEXLIZET be taken during breastfeeding. Discontinue NEXLETOL or NEXLIZET when pregnancy is recognized, unless the benefits of therapy outweigh the potential risks to the fetus. Based on the mechanism of action of bempedoic acid, NEXLETOL and NEXLIZET may cause fetal harm.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit **www.fda.gov/medwatch** or call 1-800-FDA-1088 or report side effects to Esperion at 833-377-7633 (833 ESPRMED).

Please see the full Prescribing Information for NEXLETOL.
Please see the full Prescribing Information for NEXLIZET.

Esperion Therapeutics

ESPERION is The Lipid Management Company. Our goal is lipid management for everybody, that's why we work hard to make our medicines easy to get, easy to take and easy to have. We discover, develop and commercialize innovative medicines and combinations to lower cholesterol, especially for patients whose needs aren't being met by the status quo. Our entrepreneurial team of industry leaders is inclusive, passionate and resourceful. We are singularly focused on managing cholesterol so you can improve your health easily. For more information, please visit www.esperion.com and follow us on Twitter at www.twitter.com/EsperionInc.

Forward-Looking Statements

This press release contains forward-looking statements that are made pursuant to the safe harbor provisions of the federal securities laws, including statements regarding commercialization plans for bempedoic acid tablet. Any express or implied statements contained in this press release that are not statements of historical fact may be deemed to be forward-looking statements. Forward-looking statements involve risks and uncertainties that could cause Esperion's actual results to differ significantly from those projected, including, without limitation, delays or failures in Esperion's clinical development and commercialization plans, or approval of expanded indications, that existing cash resources may be used more quickly than anticipated, the impact of COVID-19 on our business, clinical activities and commercial development plans, and the risks detailed in Esperion's filings with the Securities and Exchange Commission. Any forward-looking statements contained in this press release speak only as of the date hereof, and Esperion disclaims any obligation or undertaking to update or revise any forward-looking statements contained in this press release, other than to the extent required by law.

References

[1] M. Banach, P.E. Penson, Lipid-lowering therapies: Better together, Atherosclerosis. 320 (2021) 86–88.

[2] J. Rubino, D.E. MacDougall, L.R. Sterling, et al., Combination of bempedoic acid, ezetimibe, and atorvastatin in patients with hypercholesterolemia: A randomized clinical trial, Atherosclerosis. 320 (2021) 122–128.

[3] K.K. Ray, B. Molemans, W.M. Schoonen, et al., EU-wide cross-sectional observational study of lipid-modifying therapy use in secondary and primary care: the DA VINCI study, Eur J Prev Cardiol (2020), https://doi.org/10.1093/eurjpc/zwaa047.

[4] S.M. Grundy, N.J. Stone, A.L. Bailey, et al., AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American college of cardiology/American heart association task force on clinical practice guidelines, J. Am. Coll. Cardiol. 73 (2018) e285–e350, 2019.

[5] E. Marrett, C. Zhao, N.J. Zhang, et al., Limitations of real-world treatment with atorvastatin monotherapy for lowering LDL-C in high-risk cardiovascular patients in the US, Vasc. Health Risk Manag. 10 (2014) 237–246.

[6] S.J. Nicholls et al., Rationale and design of the CLEAR-outcomes trial: Evaluating the effect of Bempedoic acid on cardiovascular events in patients with statin intolerance, American Heart Journal (2020), https://doi.org/10.1016/j.ahj.2020.10.060.

Contact:
Kaitlyn Brosco
Esperion
corporateteam@esperion.com