Novartis PARALLAX data provides further evidence of the potential benefit of Entresto® in patients with HFpEF

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- *PARALLAX met one of its co-primary endpoints, showing a significant reduction in NT-proBNP with Entresto (sacubitril/valsartan) compared to individualized medical therapy (IMT) at 12 weeks[1]; no significant difference observed in other co-primary endpoint (6-minute walk distance) or secondary endpoints compared with IMT[1]*
- *A post-hoc analysis suggested Entresto reduced the risk of heart failure events leading to hospitalization over 24 weeks; an exploratory analysis suggested a lesser decline in eGFR, a measure of renal function, over 24 weeks with use of Entresto[1]*
- *The overall benefit-risk profile of Entresto demonstrated in PARALLAX was comparable to the active-controlled PARAGON-HF trial and remains positive[1]*

East Hanover, August 30, 2020 — Novartis today announced full results from its active-controlled PARALLAX study, further investigating the potential benefit of Entresto (sacubitril/valsartan) in patients with heart failure with preserved ejection fraction (HFpEF), a life-threatening condition with no approved treatment.[2-4] These new study results were presented at the ESC Congress 2020, the annual meeting of the European Society of Cardiology.

PARALLAX was a 24-week prospective, randomized, active-controlled, double-blind multi-center clinical trial of patients with chronic HFpEF (EF>40%), examining the effects of Entresto compared to individualized medical therapy (IMT), which could consist of the ACE inhibitor enalapril, the ARB valsartan, or placebo.[1]

For the co-primary endpoint, change in N-terminal pro-B-type natriuretic peptide (NT-proBNP) at week 12, Entresto significantly reduced NT-proBNP, an important prognostic biomarker in heart failure, by a 16% (adjusted geometric mean ratio: 0.84; 95% CI: 0.80, 0.88; p<0.0001) greater extent compared to individualized medical therapy (IMT).[1,5] The study did not show a statistically significant difference compared with IMT in the functional co-primary endpoint, 6-minute walk distance at week 24 (adjusted mean difference -2.5 m, 95% CI: -8.5, 3.5 m; p=0.42) or in secondary endpoints such as change in Kansas City Cardiomyopathy Questionnaire (KCCQ-23) clinical summary score, New York Heart Association (NYHA) class or Short Form-36 (SF-36) physical component clinical summary score.[1]

Data from a post-hoc analysis suggest patients in the Entresto group had a lower risk of heart failure events leading to hospitalization over 24 weeks (HR (95% CI): 0.49 (0.30,0.81)).[1] This post-hoc analysis utilized cardiac failure events leading to hospitalization that were reported as adverse events and were not adjudicated.[1] A prespecified exploratory analysis suggested estimated glomerular filtration rate (eGFR) declined less in the Entresto group over 24 weeks (adjusted mean difference (95% CI): 1.10 mL/min/1.73 m^2 (0.02, 1.99)) compared to IMT.[1] The overall benefit-risk profile of Entresto demonstrated in PARALLAX was comparable to what was seen in the active-controlled PARAGON-HF trial, the largest trial completed in

patients with HFpEF and remains positive.[1,6,7]

“PARALLAX adds to the growing body of evidence highlighting the potential benefits of Entresto in HFpEF, a life-threatening condition that affects about 3 million people in the US and lacks approved treatments,” said David Soergel, M.D., Global Head of Cardiovascular, Renal and Metabolic Drug Development at Novartis. “The findings, which build on the PARAGON-HF and PARAMOUNT trials, confirm the effect of Entresto on lowering NT-proBNP, a diagnostic and prognostic marker of heart failure. Post-hoc analyses also suggested a lowered risk of heart failure related hospitalizations, one of the most burdensome complications of the illness. We are committed to working with FDA on the potential approval of Entresto as the first-ever medicine for HFpEF in our efforts to reimagine heart failure treatment.”

In June the FDA accepted the supplemental New Drug Application (sNDA) for use of Entresto in heart failure patients with HFpEF. Currently, Entresto is an approved treatment for patients with HFrEF,[8] also known as systolic heart failure, which is typically defined as ejection fraction less than 40%.[9] This is based on its superiority to the angiotensin-converting enzyme (ACE) inhibitor enalapril, an active comparator, in reducing cardiovascular death and heart failure hospitalizations, as demonstrated in the PARADIGM-HF trial.[10] Entresto is a first-choice therapy that helps improve the heart’s ability to pump blood to the body in patients with HFrEF.[8,5]

About Entresto for heart failure with reduced ejection fraction

Entresto (sacubitril/valsartan) is a prescription medicine used to reduce the risk of cardiovascular death and heart failure hospitalization in adults with long-lasting (chronic) heart failure (HFrEF).[8] Entresto is usually used with other heart failure therapies in place of an angiotensin-converting enzyme (ACE) inhibitor or other angiotensin II receptor blocker (ARB) therapy.[8] Entresto is a twice-a-day prescription medicine that works by enhancing the beneficial neurohormonal systems (natriuretic peptide system) while simultaneously inhibiting the harmful effects of the overactive renin-angiotensin-aldosterone system (RAAS).[8,11] Most other heart failure medicines only block the harmful effects of the overactive RAAS. Entresto contains the neprilysin inhibitor sacubitril and the ARB valsartan.[8] Entresto film-coated tablets are available in three dosage strengths: 24/26 mg, 49/51 mg and 97/103 mg (sacubitril/valsartan).[8] These doses are referred to as 50 mg, 100 mg and 200 mg in the clinical trial literature including *The New England Journal of Medicine* publication of the results of PARADIGM-HF.[8] In adult patients, the target maintenance dose of Entresto is 97/103 mg twice daily as tolerated by the patient.[8]

IMPORTANT SAFETY INFORMATION

Entresto can harm or cause death to an unborn baby. Patients should talk to their doctor about other ways to treat heart failure if they plan to become pregnant. If a patient gets pregnant while taking Entresto, she should tell her doctor right away.

Patients are not to take Entresto if they are allergic to sacubitril or valsartan or any of the ingredients in Entresto; have had an allergic reaction including swelling of the face, lips, tongue, throat or trouble breathing while taking a type of medicine called an ACE inhibitor or ARB; or take an ACE inhibitor medicine. Patients are not to take Entresto for at least 36 hours before or after they take an ACE inhibitor medicine. Patients should talk with their doctor or pharmacist before taking Entresto if they are not sure if they take an ACE inhibitor medicine. Patients are not to take Entresto if they have diabetes and take a medicine that contains aliskiren.

Before they take Entresto, patients should tell their doctor about all of their medical conditions, including if they have kidney or liver problems; or a history of hereditary angioedema; are pregnant or plan to become

pregnant; are breastfeeding or plan to breastfeed. Patients should either take Entresto or breastfeed. They should not do both.

Patients should tell their doctor about all the medicines they take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. They should especially tell their doctor if they take potassium supplements or a salt substitute; nonsteroidal anti-inflammatory drugs (NSAIDs); lithium; or other medicines for high blood pressure or heart problems such as an ACE inhibitor, ARB, or aliskiren.

Entresto may cause serious side effects including serious allergic reactions causing swelling of the face, lips, tongue, and throat (angioedema) that may cause trouble breathing and death. Patients are to get emergency medical help right away if they have symptoms of angioedema or trouble breathing. Patients are not to take Entresto again if they have had angioedema while taking Entresto. People who are black or who have had angioedema may have a higher risk of having angioedema if they take Entresto. Entresto may cause low blood pressure (hypotension). Patients are to call their doctor if they become dizzy or lightheaded, or they develop extreme fatigue. Entresto may cause kidney problems or an increased amount of potassium in the blood.

The most common side effects in adults were low blood pressure, high potassium, cough, dizziness, and kidney problems.

Please see full Prescribing Information, including Boxed WARNING available at http://www.pharma.us.novartis.com/product/pi/pdf/entresto.pdf

Patients are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 1-800-FDA-1088.

About Novartis

Located in East Hanover, NJ Novartis Pharmaceuticals Corporation – an affiliate of Novartis – is reimagining medicine to improve and extend people's lives. As a leading global medicines company, we use innovative science and digital technologies to create transformative treatments in areas of great medical need. In our quest to find new medicines, we consistently rank among the world's top companies investing in research and development. Novartis employs about 15,000 people in the United States. For more information, please visit https://www.novartis.us.

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