New Novartis study supports Entresto as foundational HFrEF therapy and in-hospital initiation in appropriate stabilized heart failure patients

Nov 11, 2018

- Entresto® (sacubitril/valsartan) outperformed commonly used heart failure medicine enalapril in landmark study; delivered significantly greater and more rapid reductions in an established biomarker for heart failure severity and prognosis(1)
- Significant 46% reduction in serious clinical outcomes endpoint, primarily by reducing death and heart failure re-hospitalization, compared to enalapril over 8 weeks in pre-specified exploratory analysis(1)
- Safety and tolerability comparable to enalapril, including rates of hypotension, hyperkalemia, renal complications and risk of angioedema(1)
- Currently, patients with heart failure with reduced ejection fraction (HFrEF) who need to be admitted to the hospital for an acute decompensation event are at high risk of short-term death and costly heart failure re-hospitalizations(2,3)

EAST HANOVER, N.J., Nov. 11, 2018 /PRNewswire/ -- Novartis announced today results of the landmark PIONEER-HF trial showing that in-hospital initiation of Entresto tablets provided superior benefit compared to enalapril—a heart failure medication commonly used—in patients with HFrEF who had been stabilized following admission for an acute decompensation heart failure (ADHF) event.[1] Results were presented as a late-breaker at the American Heart Association's Scientific Sessions 2018 and published in The New England Journal of Medicine.

Patients on Entresto in PIONEER-HF had a 29% greater reduction in time-averaged N-terminal pro–B-type natriuretic peptide (NT-proBNP) at weeks 4 and 8 (the primary endpoint) compared to enalapril patients (95% CI: 0.63, 0.81; P<0.0001).[1] Significant reductions in NT-proBNP were observed in Entresto patients as early as 1 week after treatment initiation.[1] NT-proBNP is an established biomarker used to assess the severity and determine the prognosis of heart failure.[4] Notably, the superior NT-proBNP reduction with Entresto was consistent across diverse HFrEF patient populations stabilized following admission for ADHF, including those newly diagnosed with HFrEF, those not receiving an ACEi/ARB treatment and African Americans.[1]

In a pre-specified exploratory analysis of PIONEER-HF, Entresto also showed a significant 46% reduction in the risk of a composite of death, heart failure re-hospitalization (hospital stay >24 hours), requirement for left ventricular assist device (LVAD) insertion or listing for cardiac transplantation compared to enalapril over 8 weeks.[1] This result was driven primarily by reductions in death and HF re-hospitalization among patients treated with Entresto.[1] There were no new safety signals identified.[1] Entresto is indicated to reduce the risk of CV death or HF hospitalization in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction.[5]

"The results of this landmark study should help inform our basic approach to treating hospitalized patients with acute heart failure," said Eric Velazquez, MD, Berliner Professor of Cardiology at Yale School of Medicine and PIONEER-HF principal study investigator. "With the PIONEER-HF trial results—once acute heart failure is diagnosed, patients are hemodynamically stabilized, and a low ejection fraction is confirmed—sacubitril/valsartan should be started promptly to reduce neurohormonal activation and reduce the risk of post-discharge heart failure hospitalization."

"PIONEER-HF further confirmed the safety and benefit, as reflected in the reduction of an important biomarker, of in-hospital initiation of Entresto treatment in HFrEF patients stabilized following ADHF," said Shreeram Aradhye, MD, Chief Medical Officer and Global Head, Medical Affairs, Novartis Pharmaceuticals. "Together with data from the PARADIGM-HF study, which demonstrated the superior benefit of Entresto compared to an ACEi on cardiovascular mortality and HF hospitalizations in ambulatory patients, there is now consistent evidence in the in and outpatient settings supporting the use of Entresto. Through the Entresto scientific program, we are reimagining the standard of care for HFrEF patients and the use of Entresto as foundation therapy."

Patients with heart failure who need to be admitted to the hospital due to decompensation of their disease are at high short-term risk of death or being re-admitted to the hospital.[2,3] PIONEER-HF showed that Entresto can be initiated in the hospital in these patients safely, once they have been stabilized, with a tolerability profile comparable to enalapril.[1] Rates of hypotension (low blood pressure), hyperkalemia (elevated levels of potassium) or renal (kidney) complications were similar and there was no greater risk of angioedema in patients treated with Entresto.[1] There were no new safety signals identified, and the safety profile was comparable to that seen in PARADIGM-HF.[1,6] These results add to learnings from the TRANSITION study (an open label parallel group design), which explored the initiation of Entresto shortly after patients were stabilized following an acute heart failure episode, both in the hospital and out-patient settings.[7,8] Initial TRANSITION results were presented at the European Society of Cardiology Congress in August 2018.[7] Additional bio-marker data from TRANSITION will be presented at AHA.

About the PIONEER-HF Trial
PIONEER-HF is a prospective, multicenter, double-blind, randomized, controlled trial designed to assess the safety, tolerability, and efficacy of in-hospital initiation of Entresto compared with enalapril in appropriate, stable HFrEF patients who had been admitted for acute decompensation.[1,9]

The study enrolled patients 18 years of age and older with ejection fraction (EF) ≤40% and an elevated amino terminal-pro b-type natriuretic peptide (NT-proBNP) ≥1600 pg/mL or b-type natriuretic peptide (BNP) ≥400 pg/mL, irrespective of both duration of diagnosis or treatment with angiotensin converting-enzyme inhibitors (ACEi) and/or angiotensin receptor blockers (ARB).[1,9]

A total of 881 patients, with an average age of 61 years, were randomly assigned to in-hospital initiation of Entresto or enalapril twice daily, following stabilization.[1,9] Patients were eligible for screening no earlier than 24 hours and up to 10 days from initial presentation while still hospitalized.[1,9] All patients were treated with the objective to optimize therapy to the maximum tolerated dose based on an SBP-based algorithm.[1,9] Patients were predominantly male (approximately 72%), and half of patients had a BMI>30 kg/m^2.[1,9] Notably, more than one-third of patients (36%) were African American.[1,9] Approximately 34% of patients were newly diagnosed, having no prior history of heart failure, and slightly more than 50% of patients were not receiving ACEi/ARB therapy at the time of admission.[1,9]

The primary endpoint was the time-averaged proportional change in NT-proBNP from baseline through weeks

4 and 8.[1,9] Patients treated with Entresto achieved a 47% reduction from baseline in time-averaged NT-proBNP, compared to a 25% reduction with enalapril, translating into a statistically significant 29% greater reduction with Entresto over the ACE inhibitor (95% CI: 0.63, 0.81; P<0.0001).[1] Significant reductions in NT-proBNP were observed in Entresto patients as early as one week after treatment initiation.[1] Rates of serious adverse events occurring with a frequency of ≥0.5% were similar between the Entresto and enalapril groups.[1]

Safety and tolerability analyses found:

- Similar levels of symptomatic hypotension in both arms (enalapril 12.7%, Entresto 15.0%; RR: 1.18; 95% CI: 0.85, 1.64). Low BP-related AEs were similar between the groups.[1]
- Hyperkalemia was comparable between the two groups (enalapril 9.3% vs. Entresto 11.6% RR: 1.25; 95% CI: 0.84, 1.84).[1]
- Kidney-related AEs between the groups were similar (enalapril n= 75, Entresto n=75, RR: 1.00; CI: 0.75, 1.34).[1]
- There were 6 adjudicated cases of angioedema in the enalapril arm (all in African Americans) versus 1 with Entresto (in a Caucasian patient).[1]
- Nearly 60% of patients were able to be up-titrated to the highest approved dose of Entresto within 6 weeks.[1]

In a pre-specified exploratory analysis, the composite endpoint of death, re-hospitalization for HF, LVAD implantation or listing for cardiac transplant occurred in 41 (9.3%) patients in the Entresto group and 74 (16.8%) in the enalapril group (hazard ratio [HR] 0.54, 95% CI 0.37–0.79; p=.001).[1] The benefit was driven by reductions in death and re-hospitalization among patients treated with Entresto. The number needed to treat to prevent one such clinical event during 8 weeks of follow up was 13.[1]

About NT-proBNP

NT-proBNP is a biomarker commonly used to assess the severity and determine the prognosis of heart failure.[4] Levels of NT-proBNP increase when heart muscle cells are subjected to stress (such as stretching) that occurs in people with heart failure.[4] Studies suggest that HF patients with elevated NT-proBNP are at an increased risk of CV death or HF hospitalization and that reducing levels of NT-proBNP in people with heart failure is associated with a lower risk of these negative clinical outcomes.[4] Entresto was also shown to reduce plasma NT-proBNP compared with enalapril in the PIONEER-HF and PARADIGM-HF trials.[1,6]

About Heart Failure

Heart failure (HF) is a chronic and progressive condition, which impacts 6.5 million Americans and is the leading cause of hospitalization among Americans over the age of 65.[10,11] About half of people with HF have heart failure with reduced ejection fraction (HFrEF), also known as systolic HF.[12,13] Reduced ejection fraction means the heart does not contract with enough force, so less blood is pumped out.[14] HF presents a major and growing health-economic burden that currently exceeds $30 billion in the United States, which accounts for both direct and indirect costs.[15]

Novartis has established the largest global clinical program in the HF disease area across the pharma industry to date. Known as FortiHFy, it is comprised of more than 40 active or planned clinical studies designed to generate an array of additional data on symptom reduction, efficacy, quality of life benefits and real-world evidence with Entresto, as well as to extend understanding of heart failure.

About Entresto

Entresto is a prescription medicine used to reduce the risk of death and hospitalization in people with certain

types of long-lasting (chronic) heart failure.[5] Entresto is usually used with other heart failure therapies, in place of an ACE inhibitor or other ARB therapy.[5] Entresto is a twice-a-day prescription medicine that reduces the strain on the failing heart. It does this by enhancing the beneficial neurohormonal systems (natriuretic peptide system) while simultaneously inhibiting the harmful effects of the overactive renin-angiotensin-aldosterone system (RAAS).[5,16] Most other heart failure medicines only block the harmful effects of the overactive RAAS. Entresto contains the neprilysin inhibitor sacubitril and the angiotensin receptor blocker (ARB) valsartan.[12] Entresto film-coated tablets are available in three dosage strengths: 24/26 mg, 49/51 mg, and 97/103 mg (sacubitril/valsartan).[5] 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.[5] The target maintenance dose of Entresto is 97/103 mg twice daily.[5]

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 angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (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 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.

Novartis is committed to providing patients with affordable access and resources through Entresto Central. For more information, please call 1-888-ENTRESTO or visit www.entresto.com.

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