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Novartis late-breaking data further support initiation of Entresto in hospital and as a first-choice systolic heart failure therapy in stabilized patients

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- - Outcomes from PIONEER-HF 4-week open-label extension reinforce initial 8-week findings, showing Entresto® (sacubitril/valsartan) continued to deliver reductions in NT-proBNP, an established biomarker for heart failure severity and prognosis(1)
- - In-hospital initiation of Entresto, compared to enalapril, resulted in reduction in an exploratory serious clinical outcomes endpoint from week 8 to week 12(1)
- - Safety and tolerability at 12 weeks were comparable for patients who began Entresto in the hospital and those who switched from enalapril at 8 weeks(1)
- - Findings further substantiate benefits of Entresto and suggest that initiating Entresto in patients stabilized after an acute decompensation event may avoid subsequent serious clinical composite events(1)

EAST HANOVER, N.J., March 16, 2019 /PRNewswire/ -- Novartis announced today new results from a 4-week extension of the landmark PIONEER-HF trial, presented as a late-breaker at the American College of Cardiology's 68th Annual Scientific Session. Data from the 8-week double-blind PIONEER-HF trial, first presented in November 2018 at the American Heart Association Scientific Sessions, showed the benefits of in-hospital initiation in appropriate stabilized patients of Entresto tablets on a systolic heart failure (HF) biomarker, safety and clinical outcome.[2]

All patients received open-label Entresto during the 4-week extension period, and data showed reductions in both groups in the HF biomarker N-terminal pro–B-type natriuretic peptide (NT-proBNP) with use of Entresto, which was safe and well tolerated.[1] Patients in the control group who were treated during the initial 8-week double-blind period with a HF therapy, enalapril, showed a substantial reduction in NT-proBNP when switched to Entresto for the open-label period.[1] Further, patients who started on Entresto in the hospital had a greater overall reduction in NT-proBNP after 12 weeks, compared with patients started on enalapril in the hospital and switched to Entresto at the 8-week mark.[1]

In addition, the greater improvement in a pre-specified, exploratory post-discharge outcome at 8 weeks with Entresto was maintained throughout 12 weeks, suggesting that initiating Entresto after stabilization following an acute systolic HF admission may result in a reduction in a composite of serious clinical events.[1,2]

The serious clinical composite occurred in a lower percentage of patients who initiated Entresto in the hospital compared with those who initiated enalapril in the hospital and switched to Entresto after 8 weeks post-discharge.[1] The composite, which was explored as part of a pre-specified exploratory analysis, consisted of death, re-hospitalization for HF (hospital stay >24 hours), requirement for a left ventricular assist device (LVAD) insertion, or listing for a cardiac transplantation.[1]

"The evidence generated through the Entresto clinical trial program, which includes PIONEER-HF, TRANSITION-HF and PARADIGM-HF, contributes to the reimagining of heart failure treatment," said Marcia Kayath, MD, Head, U.S. Medical Affairs, Novartis Pharmaceuticals. "Data from this 4-week extension of PIONEER-HF clearly support Entresto as a first-choice treatment upon systolic heart failure diagnosis or worsening of symptoms and underscore the importance of initiating Entresto in the hospital."

Patients with systolic HF 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.[3,4] 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.[2] The safety profile in PIONEER-HF was similar to that seen in the pivotal PARADIGM-HF trial.[2,5] Rates of symptomatic hypotension (low blood pressure), hyperkalemia (elevated levels of potassium) or worsening renal (kidney) function were similar among treatment groups and there was a numerically lower incidence of angioedema in patients treated with Entresto.[2] There were no new safety signals identified during the 4-week extension of PIONEER-HF.[1]

"This extension of the landmark PIONEER-HF study further demonstrates that starting appropriate patients on Entresto in the hospital is safe and provides important clinical benefit compared to starting patients on enalapril. We now know that initiating Entresto in the hospital, instead of waiting to switch post-discharge, can improve outcomes and can keep more of an especially vulnerable patient population out of the hospital longer," said Eugene Braunwald, MD, Founding Chairman, TIMI Study Group, Brigham & Women's Hospital; Distinguished Hershey Professor of Medicine, Harvard Medical School; and Chariman, PIONEER-HF.

Entresto is indicated to reduce the risk of cardiovascular (CV) death or HF hospitalization in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction.[6]

About the PIONEER-HF 4-Week Extension Study
Of 881 systolic heart failure patients enrolled in PIONEER-HF, 832 (94%) continued into the 4-week open-label study after the 8-week initial study period, with 415 (50%) switched from enalapril to Entresto and 417 (50%) continued on Entresto at the time of the open-label extension.[1] All patients had been admitted for acute decompensated heart failure (ADHF) and started on study drug following stabilization, while still hospitalized.[1] The objectives were to describe changes in NT-proBNP by randomized treatment arm and to collect further safety and exploratory clinical data in both groups.[1]

Change in NT-proBNP from week 8 to week 12 was -18.5%, (95% CI: -11.8, -24.7) in patients who had been on Entresto during the original 8-week study period and remained on Entresto for the 4-week extension and -35.8% (95% CI: -30.6, -40.7) in patients who had been given enalapril during the original 8-week study period and then switched to Entresto for 4 weeks.[1] In the 8-week double-blind period, as previously reported, from baseline to weeks 4 and 8, the time-averaged ratio of change was 0.71 (95% CI: 0.63, 0.81; p<0.001) in the group treated with Entresto compared to the group treated with enalapril.[2]

Safety and tolerability analyses found during weeks 8-12:

- Similar levels of symptomatic hypotension in both arms: 2.9% for patients who were on Entresto for the first 8 weeks and continued on Entresto for the last 4 weeks compared to 3.9% for patients randomized to enalapril and then switched to Entresto for the last 4 weeks (RR 0.75; 95% CI:0.36, 1.56).[1]
- Hyperkalemia was comparable between the two groups: 2.4% for patients who were on Entresto for the first 8 weeks and continued on Entresto for the last 4

weeks compared to 4.1% for patients randomized to enalapril and then switched to Entresto for the last 4 weeks (RR: 0.59; 95% CI: 0.27, 1.26)[1]

- Worsening renal function was comparable between the two groups: 8.6% for patients who were on Entresto for the first 8 weeks and continued on Entresto for the last 4 weeks compared to 9.6% for patients randomized to enalapril and then switched to Entresto for the last 4 weeks (RR: 0.89; 95% CI: 0.58, 1.37).[1]
- There were no additional angioedema events in either arm.[1]
- 56.8% of patients in the study were receiving the highest approved dose of Entresto and 75.2% were receiving at least the middle dose recommended in the package insert by 12 weeks.[1]

Over the 12-week study, in total, there was a 33% relative risk reduction (95% CI: 0.48, 0.94) in the serious clinical composite event endpoint in the patients treated and maintained with Entresto compared to those patients started on enalapril and then switched to Entresto for the 4-week open-label phase.[1] The absolute risk reduction was 5.64%.[1] During the initial 8-week period, the serious clinical composite endpoint reduction was known to have been driven by a reduction in HF hospitalization and death.[2]

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.[2,7]

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).[2,7]

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.[2,7] Patients were eligible for screening no earlier than 24 hours and up to 10 days from initial presentation while still hospitalized.[2,7] All patients were treated with the objective to optimize therapy to the maximum tolerated dose based on an SBP-based algorithm.[2,7] Patients were predominantly male (approximately 72%), and half of patients had a BMI>30 kg/m^2.[2,7] Notably, more than one-third of patients (36%) were African American.[2,7] 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.[2,7]

The primary endpoint was the time-averaged proportional change in NT-proBNP from baseline through weeks 4 and 8.[2,7] 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).[2] Reductions in NT-proBNP were observed in Entresto patients as early as 1 week after treatment initiation.[2] Rates of serious adverse events occurring with a frequency of ≥0.5% were similar between the Entresto and enalapril groups.[2]

Safety and tolerability analyses found during the double-blind period:

- 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.[2]
- Hyperkalemia was comparable between the two groups (enalapril 9.3% vs. Entresto 11.6% RR: 1.25; 95% CI: 0.84, 1.84).[2]
- Kidney-related AEs between the groups were similar (enalapril n= 75, Entresto n=75, RR: 1.00; CI: 0.75, 1.34).[2]
- There were 6 (1.4%) adjudicated cases of angioedema in the enalapril arm (all in African Americans) versus 1 (0.2%) with Entresto (in a Caucasian patient) (RR: 0.17; CI: 0.02, 1.38).[2]
- Nearly 60% of patients were able to be up-titrated to the highest approved dose of Entresto within 6 weeks.[2]

In a pre-specified exploratory analysis, the composite endpoint of death, re-hospitalization for HF, requirement for a left ventricular assist device (LVAD) insertion, 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) during the double-blind period.[2] The benefit was driven by reductions in death and re-hospitalization among patients treated with Entresto.[2]

About Heart Failure and Hospitalization

Heart failure (HF) is a chronic and progressive condition, which impacts 6.2 million Americans and is the leading cause of hospitalization among Americans over the age of 65.[8,9] Rates of heart failure in America are increasing, despite significant medical advances.[10] It is expected that by 2030 more than 8 million people will have this condition.[10] About half of people with HF have heart failure with reduced ejection fraction (HFrEF), also known as systolic HF.[11,12] Reduced ejection fraction means the heart does not contract with enough force, so less blood is pumped out.[13] 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.[10]

HF accounts for ~900,000 hospitalizations annually in the U.S., approximately 2 hospitalizations every minute.[8] Eighty-three percent of HF patients are hospitalized due to an acute HF episode at least once, and nearly half (43%) are hospitalized at least four times.[11] Outlook for patients in first 30 days following hospitalization is poor, with one in four re-admitted during this vulnerable period and up to 10% likely to die.[3,4] On average, a HF patient remains in hospital for five to 10 days.[14]

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 CV death and HF hospitalization in people with certain types of long-lasting (chronic) heart failure.[6] 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.[6] Entresto is a twice-a-day prescription medicine that reduces the strain on the failing heart.[6,15] 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).[6,15] 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.[6] Entresto film-coated tablets are available in three dosage strengths: 24/26 mg, 49/51 mg, and 97/103 mg

(sacubitril/valsartan).[6] 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.[6]

About NT-proBNP

NT-proBNP is a biomarker commonly used to assess the severity and determine the prognosis of heart failure.[16] Levels of NT-proBNP increase when heart muscle cells are subjected to stress (such as stretching) that occurs in people with heart failure.[16] 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.[16] Entresto was also shown to reduce plasma NT-proBNP compared with enalapril in the PIONEER-HF and PARADIGM-HF trials.[1,5]

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 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 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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About Novartis

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