Patient-reported outcomes tool revealed significant improvement in symptom frequency and quality of life domains with Entresto®

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- - Overall summary score was also significantly higher for Entresto patients than for patients not taking Entresto, as measured by the 12-item Kansas City Cardiomyopathy Questionnaire (KCCQ-12)1
- - These improvements were reported early by Entresto patients, with a median follow-up time of 32 days1
- - 21.4 percent of patients treated with Entresto in this interim data cut reported a large improvement (>20-point difference from baseline) in the overall summary score versus 12.5 percent of patients not taking Entresto1

EAST HANOVER, N.J., May 28, 2018 /PRNewswire/ -- Novartis announced today new real world evidence from the CHAMP-HF registry comparing Entresto® (sacubitril/valsartan) patients to patients not taking Entresto.[1] This pre-specified analysis of an interim data cut from the CHAMP-HF registry showed that chronic heart failure (HF) patients with reduced ejection fraction (HFrEF) taking Entresto reported early, statistically significant improvement in health status, as measured by the KCCQ-12 overall summary score (KCCQ-OS).[1] This finding was driven by statistically significant improvements in symptom frequency and quality of life domains of the KCCQ-12.[1] The study findings were presented today by lead investigator Yevgeniy Khariton, MD, MSc, Saint Luke's Hospital, Mid-America Heart Institute, University of Missouri-Kansas City, as a part of a late-breaking session at the European Society of Cardiology Heart Failure (ESC-HF) Congress in Vienna, Austria.

"Key goals in managing chronic heart failure are to improve patients' symptoms and quality of life," said CHAMP-HF Chair Gregg C. Fonarow, MD and Director of the Ahmanson-UCLA Cardiomyopathy Center, Co-Chief of UCLA's Division of Cardiology, and Co-director of UCLA's Preventative Cardiology Program. "These findings in a real world setting are important because they suggest that taking sacubitril/valsartan may help patients achieve these goals."

"In addition to the already reported reduction in risk of cardiovascular death and heart failure hospitalization in HFrEF patients treated with Entresto, we now show its potential to improve patient-reported health status," said Shreeram Aradhye, MD, Chief Medical Officer and Global Head, Medical Affairs, Novartis Pharmaceuticals.[1,2] "What we find most encouraging is that both our Entresto clinical program and now this real world analysis have shown health status benefits as measured by KCCQ."

About KCCQ-12

KCCQ-12 is a self-administered, health status tool for patients with heart failure.[3] There are four domains: physical limitation (showering/bathing, walking one block on level ground, hurrying or jogging), symptom frequency (shortness of breath, fatigue and swelling of the feet, ankles and legs), social limitation (hobbies/recreational activities, working/doing household chores, visiting family/friends out of the home) and quality of life (impact on lifestyle and satisfaction of spending rest of life with current HF status).[3] Each domain is scored separately, and the overall summary score is equal to the mean of the four domain scores.[3] Higher KCCQ-12 scores from baseline represent better health status.[3] An intra-individual change in a patient's score

of 3 to 5 points, or a ≥5 point mean group difference, is defined as a minimal clinically important difference for the KCCQ-12 summary score.[3]

About the CHAMP-HF Registry

CHAnge the Management of Patients with Heart Failure (CHAMP-HF) is an ongoing, prospective, observational outpatient disease registry in patients with chronic HFrEF (left ventricular ejection fraction ≤40%).[4] CHAMP-HF has enrolled approximately 5,000 patients from 150 geographically diverse US sites, following these patients, including those who have been hospitalized, for a maximum duration of 24 months.[4] Participating sites are collecting data from providers (HF history, examination findings, and results of diagnostic studies, pharmacotherapy treatment patterns, decision-making factors, and clinical outcomes) and patients (medication adherence and patient-reported outcomes such as KCCQ-12).[4] The primary endpoint of CHAMP-HF is to examine the rationale for HF treatment changes.[4] Secondary outcomes include examining patient and provider decisions and perceptions of treatments, as well as HF related health care resource utilization.[4] Quality of life measures, such as KCCQ-12 and European Quality of Life Five Dimensions (EQ-5D) Questionnaire, and depression screening (PHQ-2), are also being examined as exploratory outcomes.[4] This real world contemporary registry provides a unique opportunity to study practice patterns, patient-reported outcomes and the adoption of new HF therapies across a diverse mix of health care providers and practices in the US that care for HFrEF patients.[4]

About the Real World Evidence Analysis

Presented today was a pre-specified analysis of an interim data cut from CHAMP-HF.[1] The aim of this analysis was to assess short-term, health status benefits of Entresto in real world US clinical practice.[1] Propensity score matching was conducted using 365 Entresto patients and 730 patients not receiving Entresto (1:2 match).[1]

Patients taking Entresto had statistically significant improvement in health status as measured by the mean group difference in KCCQ overall summary score (KCCQ-OS) compared to those not taking Entresto (6.01±19 vs. 3.55±17, p=0.014).[1] This improvement in the KCCQ score was seen early with a median follow up of 32 days reported (interquartile range 26, 53).[1] Patients on Entresto scored numerically higher on all domains compared to patients not taking Entresto, but the improvement in the KCCQ-OS score was driven by statistically significant improvements in two domains: symptom frequency (5.07 vs. 1.60, p=0.007) and quality of life (7.53 vs. 4.09, p=0.021).[1] The proportion of patients with a large improvement in overall score (defined as a greater than 20-point improvement from baseline) was 21.4% (78 out of 365 patients) for those taking Entresto vs. 12.5% (91 out of 730 patients) for those not taking Entresto, suggesting a number needed to treat (NNT) of 11.[1]

The overall findings of this real world matched analysis are in line with the KCCQ findings in the PARADIGM-HF study, which showed that Entresto had a positive impact on the health status of patients with chronic heart failure.[5,6]

Methods

Study Design[1]

- This is a comparative real world effectiveness analysis in which Entresto and non-Entresto groups were propensity matched based on 6 sociodemographic characteristics, 25 clinical characteristics and most recent KCCQ
- Study sample: Patients in the CHAMP-HF registry, who were not previously taking Entresto prior to enrollment, had ≥1 KCCQ assessment before their Entresto start and no contraindications to Entresto

- Cohort definition:
  - Entresto use: New Entresto starts (any report of use after enrollment)
  - No Entresto use: Patients with no report of any use of Entresto after enrollment
- Outcome evaluated:
  - KCCQ-12 overall summary scores (primary) and 4 domain scores (secondary) at first assessment after Entresto initiation

It is important to note that the nature of this real world evidence has some limitations:

- 50% of patients in the comparison arm did not receive an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB) during matching, which may impact the findings
- Observational analyses have the potential for residual confounding and can only test for associations as opposed to causality (tested via randomized clinical trials)
- It was not possible to exclude patient bias resulting from open-label Entresto use, which could cause a placebo effect on the Entresto arm

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.[7,8] About half of people with HF have heart failure with reduced ejection fraction (HFrEF), also known as systolic HF.[9,10] Reduced ejection fraction means the heart does not contract with enough force, so less blood is pumped out.[11] 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.[12]

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.[2] Entresto is usually used with other heart failure therapies, in place of an ACE inhibitor or other ARB therapy.[2] Entresto is a twice-a-day prescription medicine that reduces the strain on the failing heart.[2] It does this by enhancing the protective neurohormonal systems (natriuretic peptide system) while simultaneously inhibiting the harmful effects of the overactive renin-angiotensin-aldosterone system (RAAS).[2,13] Other heart failure medicines only block the harmful effects of the overactive RAAS.[10] Entresto contains the neprilysin inhibitor sacubitril and the angiotensin receptor blocker (ARB) valsartan.[2] Entresto film-coated tablets are available in three dosage strengths: 24/26 mg, 49/51 mg, and 97/103 mg (sacubitril/valsartan).[2] 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. The target maintenance dose of Entresto is 97/103 mg twice daily.[2]

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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regarding such products could be affected by, among other things, the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data; regulatory actions or delays or government regulation generally; global trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures; our ability to obtain or maintain proprietary intellectual property protection; the particular prescribing preferences of physicians and patients; general political and economic conditions; safety, quality or manufacturing issues; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

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