New Novartis Entresto® real world evidence data shows beneficial impact on quality of life in people living with heart failure

- Entresto reversed trend of worsening New York Heart Association (NYHA) class – a key measure of the severity of a patient’s heart failure symptoms – improving common physical activity such as exercise and other daily activities at 90 and 180 days after treatment initiation in a retrospective database study in patients with heart failure with reduced ejection fraction (HFrEF) in Germany\(^1\)

- Entresto significantly reduced levels of NT-proBNP, a key blood marker associated with cardiovascular risk in patients with heart failure; the magnitude of the decrease was similar to that observed in the PARADIGM-HF study\(^1\)

- Results are consistent with other real world data published in 2017 which showed Entresto improves NYHA class\(^2\) as well as exercise capacity\(^2\)

- Majority of patients in this cohort started and stayed on the lowest dose of Entresto, highlighting the potential to further improve patient outcomes by increasing treatment to recommended target maintenance dose

- Data were shared today at the American Heart Association’s Scientific Sessions 2017, building on existing evidence that Entresto has beneficial effects on the quality of life in addition to reducing cardiovascular death and heart failure hospitalization

Basel, November 12, 2017 – Novartis today announced new results from a real-world database study of patients in Germany prescribed Entresto® (sacubitril/valsartan) for heart failure with reduced ejection fraction (HFrEF). The findings further substantiate the beneficial effect of Entresto on heart failure symptoms and patients’ quality of life observed in the PARADIGM-HF study and in other real-world cohorts. Results were presented today as a poster at the American Heart Association’s Scientific Sessions 2017.

“People living with heart failure experience symptoms that severely limit their physical activities and quality of life,” said Shreeram Aradhya, Chief Medical Officer and Global Head, Medical Affairs, Novartis Pharmaceuticals. “We are excited to see the growing body of evidence showing that Entresto has a beneficial effect on the quality of life in heart failure, in addition to reducing cardiovascular death and heart failure hospitalization.”

The non-interventional, retrospective database study examined changes in clinical characteristics of 1,643 patients in Germany on Entresto in the 12 months after their first dose. All patients with available data were analyzed and the results included:

- The majority of patients had a stable New York Heart Association (NYHA) class over time. Before Entresto more patients had a trend of worsening NYHA class. The trend of worsening NYHA was reversed after switching to Entresto at Day 90 (n=121) and 180 (n=81)\(^1\). NYHA classification is used to grade the severity of a patient’s heart
failure symptoms, with physicians determining class based on specific criteria (e.g., the level of discomfort associated with physical activity)

- There was an approximately 30% mean decrease (~503pg/mg; p<0.001; n=119) in NT-proBNP, a blood marker used to diagnose heart failure and to determine prognosis. Levels of NT-proBNP are typically higher in patients with worse outcomes
- The majority of patients had a documented first dose of Entresto at the lowest level (24/26mg twice daily). Of these patients, 36% from the primary care practices and 41% from the cardiology practices had their dose up-titrated during follow-up; however, <11% received the target dose (97/103mg twice daily) at the last recorded prescription

These results are consistent with other real world data published in 2017, which show that Entresto has a beneficial impact on quality of life:

- Canada (n=276): 45% of patients switched to Entresto report feeling better after four weeks, 56% after 12 weeks
- France (n=200): in patients treated with Entresto improvement in NYHA class and exercise capacity was observed

These data results were also consistent with post-hoc analyses of the landmark PARADIGM-HF clinical trial published between 2015 and 2017, which show that:

- In surviving patients, treatment with Entresto improved patients’ quality of life, including heart failure symptoms and physical limitations as compared with enalapril, as measured by KCCQ; this effect is sustained over 36 months
- Entresto improved seven out of 10 activities when compared with enalapril, with the most significant changes in household chores and intimate/sexual relationships
- Among patients who had been hospitalized for heart failure, Entresto has been shown to slow the further decline in health-related quality of life in approximately half of patients compared to enalapril, as measured by KCCQ
- Patients were less likely to have NYHA functional class deterioration on Entresto compared with enalapril

KCCQ is a self-administered health-related quality of life (HRQL) measure for HF patients, with higher scores indicating fewer symptoms and physical limitations associated with HF. The questionnaire quantifies physical function, symptoms (recent change, frequency and burden), social function, self-efficacy and knowledge, and quality of life. Scores are transformed to a range of 0-100, in which higher scores reflect better health status.

About the German Disease Analyzer Study
This non-interventional, retrospective database study, ‘Dosing patterns and evolution of clinical parameters in patients prescribed sacubitril/valsartan in Germany,’ was initiated to assess dosing patterns and the evolution of clinical parameters in patients who were prescribed Entresto® (sacubitril/valsartan) in the primary care or cardiology setting in Germany. Patients aged 18 and above were identified via electronic medical records from the German IMS® Disease Analyzer database, which contained data from 1,095 primary care practices and 43 cardiology practices at the time of the study. The study period was January 1, 2016 to December 31, 2016, with a maximum look-back period to January 1, 2015.

The study population included 1,643 patients with a subset of patients having available data for analysis (n=119 evaluated for impact on NT-proBNP and n=121 evaluated for impact on NYHA classification trend).

About the PARASAIL study
The PARASAIL study, ‘Patient reported outcomes from the Canadian real world experience use of sacubitril/valsartan in patients with heart failure and reduced ejection fraction (HFrEF),’
is an ongoing, multi-center, open-label, prospective, post-approval (Phase IV) study being conducted in 302 patients with HFrEF at 32 study sites across Canada. It aims to characterize the tolerability, safety and therapeutic effectiveness of Entresto® (sacubitril/valsartan) 97/103mg twice daily in Canadian patients with HFrEF.

In addition to primary and secondary efficacy and safety endpoints, the study included pre-specified exploratory endpoints to evaluate heart failure symptoms and quality of life (QoL): changes in Patient Global Assessment (PGA - a seven-point patient self-evaluation scale that determines how a patient feels at subsequent visits compared with baseline), Minnesota Living with Heart Failure Questionnaire (MLHFQ - a validated questionnaire representative on how heart failure is impacting key dimensions of QoL) and EuroQoL questionnaire (EQ-5D - an instrument consisting of five domains [morbidity, self-care, usual activity, pain, and anxiety and depression among patients] and a visual analogue scale to assess the current health status of patients) from baseline to weeks four, 12 and 24.

The interim analysis of this study evaluated these pre-specified exploratory endpoints in the first 276 patients who completed their initial 12 weeks of Entresto treatment. Results showed early signs of improvement in two of the three validated QoL questionnaires: nearly half of the patients reported feeling better (using PGA questionnaire) and there was a significant improvement in MLHFQ scores. No changes were detected based on the EQ-5D score.

These results were published in the September 2017 supplement of the European Journal of Heart Failure. 2017;19: p34.

**About the France Study**

The study 'Results of a single center experience on 200 consecutive patients treated with Entresto® (sacubitril/valsartan),' evaluates results from a monocentric cohort of 200 consecutive heart failure with reduced ejection fraction (HFrEF) patients treated with Entresto. Between October 2015 and September 2016, 200 patients received Entresto; 180 were evaluated one month after introduction, 157 three months after, and 99 after six months of follow up.

Entresto was initiated at half dosage or less depending on the fragility of the patient (78% at 49mg/51 mg twice daily and 22% at 24/26mg twice daily). Patients attended a first follow-up appointment after one month of treatment, and if tolerance was good, the dosage was increased. At three months, 82% of patients received the target dose of 97/103mg. After one month of treatment, functional class improved significantly with 4.5% New York Heart Association (NYHA) 1, 81% NYHA 2, and 14.5% NYHA 3 (p= <0.001), as the 6-minute walk distance (511 vs 461m, p <0.0001). These improvements occurred from the first month of treatment with the half dosage of Entresto and were still significantly present after six months of follow up.

These results were published in the September 2017 supplement of the European Journal of Heart Failure. 2017;19: p296.

**About Entresto® (sacubitril/valsartan)**

Entresto is a twice-a-day medicine that reduces the strain on the failing heart. 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). 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.

In Europe, Entresto is indicated in adult patients for the treatment of symptomatic chronic heart failure with reduced ejection fraction. In the United States, Entresto is indicated for the treatment of heart failure (New York Heart Association class II-IV) in patients with systolic dysfunction. It has been shown to reduce the rate of cardiovascular death and heart failure
hospitalization compared to enalapril, and also to reduce the rate of all-cause mortality compared to enalapril. Entresto is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other angiotensin receptor blocker (ARB). Approved indications may vary depending upon the individual country.

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