CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

207620Orig1s018

Trade Name:	ENTRESTO
Generic or Proper Name:	sacubitril and valsartan
Sponsor:	Novartis Pharmaceuticals Corp.
Approval Date:	February 16, 2021
Indication:	• To reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal. • For the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. ENTRESTO reduces NT-proBNP and is expected to improve cardiovascular outcomes.

CENTER FOR DRUG EVALUATION AND RESEARCH

213026Orig1s000

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

NDA 207620/S-018

SUPPLEMENT APPROVAL

Novartis Pharmaceuticals Corp.
Attention: Amol Parekh, PharmD
Global Program Regulatory Director
One Health Plaza
Building 315
East Hanover, NJ 07936

Dear Dr. Parekh:

Please refer to your supplemental new drug application (sNDA) dated April 20, 2020, received April 20, 2020, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Entresto (sacubitril/valsartan), Film Coated Tablets.

This Prior Approval supplemental new drug application provides for updates to the United States Prescribing Information (USPI) and the Patient Package Insert (PPI) related to the PARAGON-HF trial, including substantive revisions to Indications and Usage and Clinical Studies; additional revisions were made throughout labeling.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, and Patient Package Insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, contact Alexis Childers, Regulatory Project Manager, at 301-796-0442.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology,
Endocrinology, & Nephrology
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NORMAN L STOCKBRIDGE
02/16/2021 10:15:01 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ENTRESTO safely and effectively. See full prescribing information for ENTRESTO.

ENTRESTO® (sacubitril and valsartan) tablets, for oral use
Initial U.S. Approval: 2015

WARNING: FETAL TOXICITY
See full prescribing information for complete boxed warning.
- **When pregnancy is detected, discontinue ENTRESTO as soon as possible. (5.1)**
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. (5.1)**

----------RECENT MAJOR CHANGES----------
- Indications and Usage, Adult Heart Failure (1.1) 2/2021

----------INDICATIONS AND USAGE----------
ENTRESTO is indicated:
- to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal. (1.1).
- for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. ENTRESTO reduces NT-proBNP and is expected to improve cardiovascular outcomes. (1.2)

----------DOSAGE AND ADMINISTRATION----------

Indication	Titration Step Dose (twice daily)		
	Starting	**Second**	**Final**
Adult Heart Failure	49/51 mg	97/103 mg	
Pediatric Heart Failure Patients less than 40 kg	1.6 mg/kg	2.3 mg/kg	3.1 mg/kg
Pediatric Heart Failure Patients at least 40 kg, less than 50 kg	24/26 mg	49/51 mg	72/78 mg
Pediatric Heart Failure Patients at least 50 kg	49/51 mg	72/78 mg	97/103 mg

- Adjust adult doses every 2 to 4 weeks and pediatric doses every 2 weeks to the target maintenance dose, as tolerated by the patient. (2.2, 2.3)
- Reduce starting dose to half the usually recommended starting dosage for:
  – patients not currently taking an ACE inhibitor or ARB or previously taking a low dose of these agents (2.5)
  – patients with severe renal impairment (2.6)
  – patients with moderate hepatic impairment (2.7)

----------DOSAGE FORMS AND STRENGTHS----------
- Film-coated tablets: 24/26 mg; 49/51 mg; 97/103 mg (3)

----------CONTRAINDICATIONS----------
- Hypersensitivity to any component. (4)
- History of angioedema related to previous ACEi or ARB therapy. (4)
- Concomitant use with ACE inhibitors. (4, 7.1)
- Concomitant use with aliskiren in patients with diabetes. (4, 7.1)

----------WARNINGS AND PRECAUTIONS----------
- Observe for signs and symptoms of angioedema and hypotension. (5.2, 5.3)
- Monitor renal function and potassium in susceptible patients. (5.4, 5.5)

----------ADVERSE REACTIONS----------
Adverse reactions occurring ≥ 5% are hypotension, hyperkalemia, cough, dizziness, and renal failure. (6 1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Avoid concomitant use with aliskiren in patients with eGFR < 60. (7.1)
- Potassium-sparing diuretics: May lead to increased serum potassium. (7.2)
- NSAIDs: May lead to increased risk of renal impairment. (7 3)
- Lithium: Increased risk of lithium toxicity. (7.4)

----------USE IN SPECIFIC POPULATIONS----------
- Lactation: Breastfeeding or drug should be discontinued. (8.2)
- Severe Hepatic Impairment: Use not recommended. (2.7, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 2/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: FETAL TOXICITY

- **When pregnancy is detected, discontinue ENTRESTO as soon as possible *(5.1)***
- **Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus (*5.1)***

1 INDICATIONS AND USAGE

1.1 Adult Heart Failure

ENTRESTO is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal.

LVEF is a variable measure, so use clinical judgment in deciding whom to treat *[see Clinical Studies (14.1)]*.

1.2 Pediatric Heart Failure

ENTRESTO is indicated for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. ENTRESTO reduces NT-proBNP and is expected to improve cardiovascular outcomes.

2 DOSAGE AND ADMINISTRATION

2.1 General Considerations

ENTRESTO is contraindicated with concomitant use of an angiotensin-converting enzyme (ACE) inhibitor. If switching from an ACE inhibitor to ENTRESTO allow a washout period of 36 hours between administration of the two drugs *[see Contraindications (4) and Drug Interactions (7.1)]*.

2.2 Adult Heart Failure

The recommended starting dose of ENTRESTO is 49/51 mg orally twice-daily.

Double the dose of ENTRESTO after 2 to 4 weeks to the target maintenance dose of 97/103 mg twice daily, as tolerated by the patient.

2.3 Pediatric Heart Failure

Refer to Table 1 for the recommended dose for pediatric patients aged one year and older. Take the recommended dose orally twice daily. Adjust pediatric patient doses every 2 weeks, as tolerated by the patient.

Table 1: Recommended Dose Titration

	Titration Step Dose (twice daily)		
	Starting	**Second**	**Final**
Pediatric Patients Less than 40 kg[†]	1.6 mg/kg	2.3 mg/kg	3.1 mg/kg
Pediatric Patients At least 40 kg, less than 50 kg	24/26 mg	49/51 mg	72/78 mg[‡]
Pediatric Patients At least 50 kg	49/51 mg	72/78 mg[‡]	97/103 mg

[†]Use of the Oral Suspension recommended in these patients. Recommended mg/kg doses are of the combined amount of both sacubitril and valsartan *[see Dosage and Administration (2.4)]*.
[‡]Doses of 72/78 mg can be achieved using three 24/26 mg tablets *[see Dosage Forms and Strengths (3)]*.

2.4 Preparation of Oral Suspension

ENTRESTO oral suspension can be substituted at the recommended tablet dosage in patients unable to swallow tablets.

ENTRESTO 800 mg/200 mL oral suspension can be prepared in a concentration of 4 mg/mL (sacubitril/valsartan 1.96/2.04 mg/mL). Use ENTRESTO 49/51 mg tablets in the preparation of the suspension.

To make an 800 mg/200 mL (4 mg/mL) oral suspension, transfer eight tablets of ENTRESTO 49/51 mg film-coated tablets into a mortar. Crush the tablets into a fine powder using a pestle. Add 60 mL of Ora-Plus® into the mortar and triturate gently with pestle for 10 minutes, to form a uniform suspension. Add 140 mL of Ora-Sweet® SF into mortar and triturate with pestle for another 10 minutes, to form a uniform suspension. Transfer the entire contents from the mortar into a clean 200 mL amber colored PET or glass bottle. Place a press-in bottle adapter and close the bottle with a child resistant cap.

The oral suspension can be stored for up to 15 days. Do not store above 25°C (77°F) and do not refrigerate. Shake before each use.

*Ora-Sweet SF® and Ora-Plus® are registered trademarks of Paddock Laboratories, Inc.

2.5 Dose Adjustment for Patients Not Taking an ACE inhibitor or ARB or Previously Taking Low Doses of These Agents

In patients not currently taking an ACE inhibitor or an angiotensin II receptor blocker (ARB) and for patients previously taking low doses of these agents, start ENTRESTO at half the usually recommended starting dose. After initiation, increase the dose every 2 to 4 weeks in adults and every 2 weeks in pediatric patients to follow the recommended dose escalation thereafter *[see Dosage and Administration (2.2, 2.3)]*.

Note: Initiate pediatric patients weighing 40 to 50 kg who meet this criterion at 0.8 mg/kg twice daily using the oral suspension *[see Dosage and Administration (2.3, 2.4)]*.

2.6 Dose Adjustment for Severe Renal Impairment

In adults and pediatric patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2), start ENTRESTO at half the usually recommended starting dose. After initiation, increase the dose to follow the recommended dose escalation thereafter *[see Dosage and Administration (2.2, 2.3)]*.

Note: Initiate pediatric patients weighing 40 to 50 kg who meet this criterion at 0.8 mg/kg twice daily using the oral suspension *[see Dosage and Administration (2.3, 2.4)]*.

No starting dose adjustment is needed for mild or moderate renal impairment.

2.7 Dose Adjustment for Hepatic Impairment

In adults and pediatric patients with moderate hepatic impairment (Child-Pugh B classification), start ENTRESTO at half the usually recommended starting dose. After initiation, increase the dose to follow the recommended dose escalation thereafter *[see Dosage and Administration (2.2, 2.3)]*.

Note: Initiate pediatric patients weighing 40 to 50 kg who meet this criterion at 0.8 mg/kg twice daily using the oral suspension *[see Dosage and Administration (2.3, 2.4)]*.

No starting dose adjustment is needed for mild hepatic impairment.

Use in patients with severe hepatic impairment is not recommended.

3 DOSAGE FORMS AND STRENGTHS

ENTRESTO is supplied as unscored, ovaloid, film-coated tablets in the following strengths:

ENTRESTO 24/26 mg, (sacubitril 24 mg and valsartan 26 mg) are violet white and debossed with “NVR” on one side and “LZ” on the other side.

ENTRESTO 49/51 mg, (sacubitril 49 mg and valsartan 51 mg) are pale yellow and debossed with “NVR” on one side and “L1” on the other side.

ENTRESTO 97/103 mg, (sacubitril 97 mg and valsartan 103 mg) are light pink and debossed with “NVR” on one side and “L11” on the other side.

4 CONTRAINDICATIONS

ENTRESTO is contraindicated:

- in patients with hypersensitivity to any component
- in patients with a history of angioedema related to previous ACE inhibitor or ARB therapy *[see Warnings and Precautions (5.2)]*

- with concomitant use of ACE inhibitors. Do not administer within 36 hours of switching from or to an ACE inhibitor *[see Drug Interactions (7.1)]*
- with concomitant use of aliskiren in patients with diabetes *[see Drug Interactions (7.1)]*

5 WARNINGS AND PRECAUTIONS

5.1 Fetal Toxicity

ENTRESTO can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. When pregnancy is detected, consider alternative drug treatment and discontinue ENTRESTO. However, if there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system, and if the drug is considered lifesaving for the mother, advise a pregnant woman of the potential risk to the fetus *[see Use in Specific Populations (8.1)]*.

5.2 Angioedema

ENTRESTO may cause angioedema *[see Adverse Reactions (6.1)]*. If angioedema occurs, discontinue ENTRESTO immediately, provide appropriate therapy, and monitor for airway compromise. ENTRESTO must not be re-administered. In cases of confirmed angioedema where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, administer appropriate therapy, e.g., subcutaneous epinephrine/adrenaline solution 1:1000 (0.3 mL to 0.5 mL) and take measures necessary to ensure maintenance of a patent airway.

ENTRESTO has been associated with a higher rate of angioedema in Black than in non-Black patients.

Patients with a prior history of angioedema may be at increased risk of angioedema with ENTRESTO *[see Adverse Reactions (6.1)]*. ENTRESTO must not be used in patients with a known history of angioedema related to previous ACE inhibitor or ARB therapy *[see Contraindications (4)]*. ENTRESTO should not be used in patients with hereditary angioedema.

5.3 Hypotension

ENTRESTO lowers blood pressure and may cause symptomatic hypotension *[see Adverse Reactions (6.1)]*. Patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients (e.g., those being treated with high doses of diuretics), are at greater risk. Correct volume or salt depletion prior to administration of ENTRESTO or start at a lower dose. If hypotension occurs, consider dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension (e.g., hypovolemia). If hypotension persists despite such measures, reduce the dosage or temporarily discontinue ENTRESTO. Permanent discontinuation of therapy is usually not required.

5.4 Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system (RAAS), decreases in renal function may be anticipated in susceptible individuals treated with ENTRESTO *[see Adverse Reactions (6.1)]*. In patients whose renal function depends upon the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with ACE inhibitors and angiotensin receptor antagonists has been associated with oliguria, progressive azotemia and, rarely, acute renal failure and death. Closely monitor serum creatinine, and down-titrate or interrupt ENTRESTO in patients who develop a clinically significant decrease in renal function *[see Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

As with all drugs that affect the RAAS, ENTRESTO may increase blood urea and serum creatinine levels in patients with bilateral or unilateral renal artery stenosis. In patients with renal artery stenosis, monitor renal function.

5.5 Hyperkalemia

Through its actions on the RAAS, hyperkalemia may occur with ENTRESTO *[see Adverse Reactions (6.1)]*. Monitor serum potassium periodically and treat appropriately, especially in patients with risk factors for hyperkalemia such as severe renal impairment, diabetes, hypoaldosteronism, or a high potassium diet. Dosage reduction or interruption of ENTRESTO may be required *[see Dosage and Administration (2.6)]*.

6 ADVERSE REACTIONS

Clinically significant adverse reactions that appear in other sections of the labeling include:

- Angioedema *[see Warnings and Precautions (5.2)]*
- Hypotension *[see Warnings and Precautions (5.3)]*
- Impaired Renal Function *[see Warnings and Precautions (5.4)]*
- Hyperkalemia *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 6,622 heart failure patients were treated with ENTRESTO in the PARADIGM-HF (vs. enalapril) and PARAGON-HF (vs. valsartan) clinical trials. Of these, 5,085 were exposed for at least 1 year.

Adult Heart Failure

In PARADIGM-HF, patients were required to complete sequential enalapril and ENTRESTO run-in periods of (median) 15 and 29 days, respectively, prior to entering the randomized double-blind period comparing ENTRESTO and enalapril. During the enalapril run-in period, 1,102 patients (10.5%) were permanently discontinued from the study, 5.6% because of an adverse event, most commonly renal dysfunction (1.7%), hyperkalemia (1.7%) and hypotension (1.4%). During the ENTRESTO run-in period, an additional 10.4% of patients permanently discontinued treatment, 5.9% because of an adverse event, most commonly renal dysfunction (1.8%), hypotension (1.7%) and hyperkalemia (1.3%). Because of this run-in design, the adverse reaction rates described below are lower than expected in practice.

In the double-blind period, safety was evaluated in 4,203 patients treated with ENTRESTO and 4,229 treated with enalapril. In PARADIGM-HF, patients randomized to ENTRESTO received treatment for up to 4.3 years, with a median duration of exposure of 24 months; 3,271 patients were treated for more than one year. Discontinuation of therapy because of an adverse event during the double-blind period occurred in 450 (10.7%) of ENTRESTO treated patients and 516 (12.2%) of patients receiving enalapril.

Adverse reactions occurring at an incidence of ≥ 5% in patients who were treated with ENTRESTO in the double-blind period of PARADIGM-HF are shown in Table 2.

In PARADIGM-HF, the incidence of angioedema was 0.1% in both the enalapril and ENTRESTO run-in periods. In the double-blind period, the incidence of angioedema was higher in patients treated with ENTRESTO than enalapril (0.5% and 0.2%, respectively). The incidence of angioedema in Black patients was 2.4% with ENTRESTO and 0.5% with enalapril *[see Warnings and Precautions (5.2)]*.

Orthostasis was reported in 2.1% of patients treated with ENTRESTO compared to 1.1% of patients treated with enalapril during the double-blind period of PARADIGM-HF. Falls were reported in 1.9% of patients treated with ENTRESTO compared to 1.3% of patients treated with enalapril.

Table 2: Adverse Reactions Reported in ≥ 5% of Patients Treated with ENTRESTO in the Double-Blind Period of PARADIGM-HF

	ENTRESTO (n = 4,203) %	**Enalapril (n = 4,229) %**
Hypotension	18	12
Hyperkalemia	12	14
Cough	9	13
Dizziness	6	5
Renal failure/acute renal failure	5	5

In PARAGON-HF, no new adverse reactions were identified.

Pediatric Heart Failure

The adverse reactions observed in pediatric patients 1 to < 18 years old who received treatment with ENTRESTO were consistent with those observed in adult patients.

Laboratory Abnormalities

Hemoglobin and Hematocrit

Decreases in hemoglobin/hematocrit of > 20% were observed in approximately 5% of both ENTRESTO- and enalapril-treated patients in the double-blind period in PARADIGM-HF. Decreases in hemoglobin/hematocrit of >20% were observed in approximately 7% of ENTRESTO-treated patients and 9% of valsartan-treated patients in the double-blind period in PARAGON-HF.

Serum Creatinine

During the double-blind period in PARADIGM-HF, approximately 16% of both ENTRESTO- and enalapril-treated patients had increases in serum creatinine of > 50%. During the double-blind period in PARAGON-HF, approximately 17% of ENTRESTO-treated patients and 21% of valsartan-treated patients had increases in serum creatinine of > 50%.

Serum Potassium

During the double-blind period of PARADIGM-HF, approximately 16% of both ENTRESTO- and enalapril-treated patients had potassium concentrations > 5.5 mEq/L. During the double-blind period of PARAGON-HF, approximately 18% of ENTRESTO-treated patients and 20% of valsartan-treated patients had potassium concentrations > 5.5 mEq/L.

6.2 Postmarketing Experience

The following additional adverse reactions have been reported in postmarketing experience. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity including rash, pruritus, and anaphylactic reaction

7 DRUG INTERACTIONS

7.1 Dual Blockade of the Renin-Angiotensin-Aldosterone System

Concomitant use of ENTRESTO with an ACE inhibitor is contraindicated because of the increased risk of angioedema *[see Contraindications (4)]*.

Avoid use of ENTRESTO with an ARB, because ENTRESTO contains the angiotensin II receptor blocker valsartan.

The concomitant use of ENTRESTO with aliskiren is contraindicated in patients with diabetes *[see Contraindications (4)]*. Avoid use with aliskiren in patients with renal impairment (eGFR < 60 mL/min/1.73 m^2).

7.2 Potassium-Sparing Diuretics

As with other drugs that block angiotensin II or its effects, concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium *[see Warnings and Precautions (5.5)]*.

7.3 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) Including Selective Cyclooxygenase-2 Inhibitors (COX-2 Inhibitors)

In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, concomitant use of NSAIDs, including COX-2 inhibitors, with ENTRESTO may result in worsening of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically.

7.4 Lithium

Increases in serum lithium concentrations and lithium toxicity have been reported during concomitant administration of lithium with angiotensin II receptor antagonists. Monitor serum lithium levels during concomitant use with ENTRESTO.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

ENTRESTO can cause fetal harm when administered to a pregnant woman. Use of drugs that act on the renin-angiotensin system during the second and third trimesters of pregnancy reduces fetal renal function and increases fetal and neonatal morbidity and death. Most epidemiologic studies examining fetal abnormalities after exposure to antihypertensive use in the first trimester have not distinguished drugs affecting the renin-angiotensin system from other antihypertensive agents. In animal reproduction studies, ENTRESTO treatment during organogenesis resulted in increased embryo-fetal lethality in rats and rabbits and teratogenicity in rabbits. When pregnancy is detected, consider alternative drug treatment and discontinue ENTRESTO. However, if there is no appropriate alternative to therapy with drugs affecting the renin-angiotensin system, and if the drug is considered lifesaving for the mother, advise a pregnant woman of the potential risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Oligohydramnios in pregnant women who use drugs affecting the renin-angiotensin system in the second and third trimesters of pregnancy can result in the following: reduced fetal renal function leading to anuria and renal failure, fetal lung hypoplasia, skeletal deformations, including skull hypoplasia, hypotension, and death.

Perform serial ultrasound examinations to assess the intra-amniotic environment. Fetal testing may be appropriate, based on the week of gestation. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. If oligohydramnios is observed, consider alternative drug treatment. Closely observe neonates with histories of *in utero* exposure to ENTRESTO for hypotension, oliguria, and hyperkalemia. In neonates with a history of *in utero* exposure to ENTRESTO, if oliguria or hypotension occurs, support blood pressure and renal perfusion. Exchange transfusions or dialysis may be required as a means of reversing hypotension and replacing renal function.

Data

Animal Data

ENTRESTO treatment during organogenesis resulted in increased embryo-fetal lethality in rats at doses ≥ 49 mg sacubitril/51 mg valsartan/kg/day (≤ 0.06 [LBQ657, the active metabolite] and 0.72 [valsartan]-fold the maximum recommended human dose [MRHD] of 97/103 mg twice-daily on the basis of the area under the plasma drug concentration-time curve [AUC]) and rabbits at doses ≥ 5 mg sacubitril/5 mg valsartan/kg/day (2-fold and 0.03-fold the MRHD on the basis of valsartan and LBQ657 AUC, respectively). ENTRESTO is teratogenic based on a low incidence of fetal hydrocephaly, associated with maternally toxic doses, which was observed in rabbits at an ENTRESTO dose of ≥ 5 mg sacubitril/5 mg valsartan/kg/day. The adverse embryo-fetal effects of ENTRESTO are attributed to the angiotensin receptor antagonist activity.

Pre- and postnatal development studies in rats at sacubitril doses up to 750 mg/kg/day (2.2-fold the MRHD on the basis of LBQ657 AUC) and valsartan at doses up to 600 mg/kg/day (0.86-fold the MRHD on the basis of AUC) indicate that treatment with ENTRESTO during organogenesis, gestation and lactation may affect pup development and survival.

8.2 Lactation

Risk Summary

There is no information regarding the presence of sacubitril/valsartan in human milk, the effects on the breastfed infant, or the effects on milk production. Sacubitril/valsartan is present in rat milk. Because of the potential for serious adverse reactions in breastfed infants from exposure to sacubitril/valsartan, advise a nursing woman that breastfeeding is not recommended during treatment with ENTRESTO.

Data

Following an oral dose (15 mg sacubitril/15 mg valsartan/kg) of [^{14}C] ENTRESTO to lactating rats, transfer of LBQ657 into milk was observed. After a single oral administration of 3 mg/kg [^{14}C] valsartan to lactating rats, transfer of valsartan into milk was observed.

8.4 Pediatric Use

The safety and effectiveness of ENTRESTO in pediatric heart failure patients 1 to < 18 years old are supported by the reduction from baseline to 12 weeks in NT-proBNP in a randomized, double-blind clinical study *[see Clinical Studies (14.2)]*. The analysis of NT-proBNP included 90 patients age 6 to 18 years and 20 patients age 1 to 6 years.

Safety and effectiveness have not been established in pediatric patients less than 1 year of age.

Animal Data

Sacubitril given orally to juvenile rats from postnatal day (PND) 7 to PND 35 or PND 70 (an age approximately equivalent to neonatal through pre-pubertal development or adulthood in humans) at doses ≥ 400 mg/kg/day (approximately 2-fold the AUC exposure to the active metabolite of sacubitril, LBQ657, at an ENTRESTO pediatric clinical dose of 3.1 mg/kg twice daily) resulted in decreases in body weight, bone length, and bone mass. The decrease in body weight was transient from PND 10 to PND 20 and the effects for most bone parameters were reversible after treatment stopped. Exposure at the No-Observed-Adverse-Effect-Level (NOAEL) of 100 mg/kg/day was approximately 0.5-fold the AUC exposure to LBQ657 at the 3.1 mg/kg twice daily dose of ENTRESTO. The mechanism underlying bone effects in rats and the translatability to pediatric patients are unknown.

Valsartan given orally to juvenile rats from PND 7 to PND 70 (an age approximately equivalent to neonatal through adulthood in humans) produced persistent, irreversible kidney damage at all dose levels. Exposure at the lowest tested dose of 1 mg/kg/day was approximately 0.2-fold the exposure at 3.1 mg/kg twice daily dose of ENTRESTO based on AUC. These kidney effects in neonatal rats represent expected exaggerated pharmacological effects that are observed if rats are treated during the first 13 days of life.

8.5 Geriatric Use

No relevant pharmacokinetic differences have been observed in elderly (≥ 65 years) or very elderly (≥ 75 years) patients compared to the overall population *[see Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

No dose adjustment is required when administering ENTRESTO to patients with mild hepatic impairment (Child-Pugh A classification). The recommended starting dose in patients with moderate hepatic impairment (Child-Pugh B classification) is 24/26 mg twice daily. The use of ENTRESTO in patients with severe hepatic impairment (Child-Pugh C classification) is not recommended, as no studies have been conducted in these patients *[see Dosage and Administration (2.6), Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

No dose adjustment is required in patients with mild (eGFR 60 to 90 mL/min/1.73 m^2) to moderate (eGFR 30 to 60 mL/min/1.73 m^2) renal impairment. The recommended starting dose in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2) is 24/26 mg twice daily *[see Dosage and Administration (2.5), Warnings and Precautions (5.4), and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Limited data are available with regard to overdosage in human subjects with ENTRESTO. In healthy volunteers, a single dose of ENTRESTO 583 mg sacubitril/617 mg valsartan, and multiple doses of 437 mg sacubitril/463 mg valsartan (14 days) have been studied and were well tolerated.

Hypotension is the most likely result of overdosage due to the blood pressure lowering effects of ENTRESTO. Symptomatic treatment should be provided.

ENTRESTO is unlikely to be removed by hemodialysis because of high protein binding.

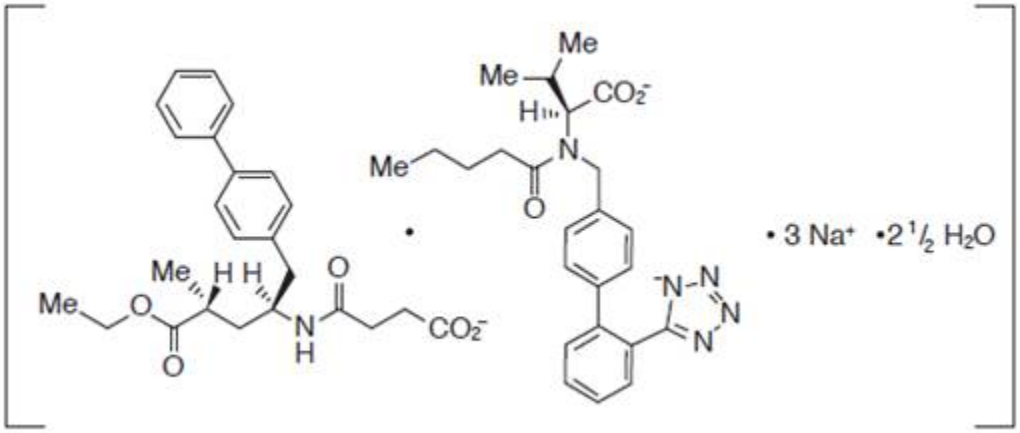
11 DESCRIPTION

ENTRESTO (sacubitril and valsartan) is a combination of a neprilysin inhibitor and an angiotensin II receptor blocker.

ENTRESTO contains a complex comprised of anionic forms of sacubitril and valsartan, sodium cations, and water molecules in the molar ratio of 1:1:3:2.5, respectively. Following oral administration, the complex dissociates into sacubitril (which is further metabolized to LBQ657) and valsartan. The complex is chemically described as Octadecasodiumhexakis(4-{[(1S,3R)-1-([1,1´-biphenyl]-4-ylmethyl)-4-ethoxy-3-methyl-4-oxobutyl]amino}-4-

oxobutanoate)hexakis(N-pentanoyl-N-{[2´-(1H-tetrazol-1-id-5-yl)[1,1´-biphenyl]-4-yl]methyl}-L-valinate)—water (1/15).

Its empirical formula (hemipentahydrate) is $C_{48}H_{55}N_6O_8Na_3$ 2.5 H_2O. Its molecular mass is 957.99 and its schematic structural formula is:



ENTRESTO is available as film-coated tablets for oral administration, containing 24 mg of sacubitril and 26 mg of valsartan; 49 mg of sacubitril and 51 mg of valsartan; and 97 mg of sacubitril and 103 mg of valsartan. The tablet inactive ingredients are microcrystalline cellulose, low-substituted hydroxypropylcellulose, crospovidone, magnesium stearate (vegetable origin), talc, and colloidal silicon dioxide. The film-coat inactive ingredients are hypromellose, titanium dioxide (E 171), Macrogol 4000, talc, and iron oxide red (E 172). The film-coat for the 24 mg of sacubitril and 26 mg of valsartan tablet and the 97 mg of sacubitril and 103 mg of valsartan tablet also contains iron oxide black (E 172). The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet contains iron oxide yellow (E 172).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ENTRESTO contains a neprilysin inhibitor, sacubitril, and an angiotensin receptor blocker, valsartan. ENTRESTO inhibits neprilysin (neutral endopeptidase; NEP) via LBQ657, the active metabolite of the prodrug sacubitril, and blocks the angiotensin II type-1 (AT_1) receptor via valsartan. The cardiovascular and renal effects of ENTRESTO in heart failure patients are attributed to the increased levels of peptides that are degraded by neprilysin, such as natriuretic peptides, by LBQ657, and the simultaneous inhibition of the effects of angiotensin II by valsartan. Valsartan inhibits the effects of angiotensin II by selectively blocking the AT_1 receptor, and also inhibits angiotensin II-dependent aldosterone release.

12.2 Pharmacodynamics

The pharmacodynamic effects of ENTRESTO were evaluated after single and multiple dose administrations in healthy subjects and in patients with heart failure, and are consistent with simultaneous neprilysin inhibition and renin-angiotensin system blockade.

In a 7-day valsartan-controlled study in patients with reduced ejection fraction (HFrEF), administration of ENTRESTO resulted in a significant non-sustained increase in natriuresis, increased urine cGMP, and decreased plasma MR-proANP and NT-proBNP compared to valsartan.

In a 21-day study in HFrEF patients, ENTRESTO significantly increased urine ANP and cGMP and plasma cGMP, and decreased plasma NT-proBNP, aldosterone and endothelin-1. ENTRESTO also blocked the AT_1-receptor as evidenced by increased plasma renin activity and plasma renin concentrations. In PARADIGM-HF, ENTRESTO decreased plasma NT-proBNP (not a neprilysin substrate) and increased plasma BNP (a neprilysin substrate) and urine cGMP compared with enalapril.

In PARAMOUNT, a randomized, double-blind, 36-week study in patients with heart failure with LVEF ≥ 45% comparing 97/103 mg of ENTRESTO (n=149) to 160 mg of valsartan (n =152) twice-daily, ENTRESTO decreased NT-proBNP by 17% while valsartan increased NT-proBNP by 8% at Week 12 (p = 0.005).

In PARAGON-HF, ENTRESTO decreased NT-proBNP by 24% (Week 16) and 19% (Week 48) compared to 6% and 3% reductions on valsartan, respectively.

QT Prolongation: In a thorough QTc clinical study in healthy male subjects, single doses of ENTRESTO 194 mg sacubitril/206 mg valsartan and 583 mg sacubitril/617 mg valsartan had no effect on cardiac repolarization.

Amyloid-β: Neprilysin is one of multiple enzymes involved in the clearance of amyloid-β (Aβ) from the brain and cerebrospinal fluid (CSF). Administration of ENTRESTO 194 mg sacubitril/206 mg valsartan once-daily for 2 weeks to healthy subjects was associated with an increase in CSF $A\beta_{1-38}$ compared to placebo; there were no changes in concentrations of CSF $A\beta_{1-40}$ or CSF $A\beta_{1-42}$. The clinical relevance of this finding is unknown *[see Nonclinical Toxicology (13)]*.

Blood Pressure: Addition of a 50 mg single dose of sildenafil to ENTRESTO at steady state (194 mg sacubitril/206 mg valsartan once daily for 5 days) in patients with hypertension was associated with additional blood pressure (BP) reduction (~ 5/4 mmHg, systolic/diastolic BP) compared to administration of ENTRESTO alone.

Co-administration of ENTRESTO did not significantly alter the BP effect of intravenous nitroglycerin.

12.3 Pharmacokinetics

Absorption

Following oral administration, ENTRESTO dissociates into sacubitril and valsartan. Sacubitril is further metabolized to LBQ657. The peak plasma concentrations of sacubitril, LBQ657, and valsartan are reached in 0.5 hours, 2 hours, and 1.5 hours, respectively. The oral absolute bioavailability of sacubitril is estimated to be ≥ 60%. The valsartan in ENTRESTO is more bioavailable than the valsartan in other marketed tablet formulations; 26 mg, 51 mg, and 103 mg of valsartan in ENTRESTO is equivalent to 40 mg, 80 mg, and 160 mg of valsartan in other marketed tablet formulations, respectively.

Following twice-daily dosing of ENTRESTO, steady state levels of sacubitril, LBQ657, and valsartan are reached in 3 days. At steady state, sacubitril and valsartan do not accumulate significantly, whereas LBQ657 accumulates by 1.6-fold. ENTRESTO administration with food has no clinically significant effect on the systemic exposures of sacubitril, LBQ657, or valsartan. Although there is a decrease in exposure to valsartan when ENTRESTO is administered with food, this decrease is not accompanied by a clinically significant reduction in the therapeutic effect. ENTRESTO can therefore be administered with or without food.

Distribution

Sacubitril, LBQ657 and valsartan are highly bound to plasma proteins (94% to 97%). Based on the comparison of plasma and CSF exposures, LBQ657 crosses the blood brain barrier to a limited extent (0.28%). The average apparent volumes of distribution of valsartan and sacubitril are 75 and 103 L, respectively.

Metabolism

Sacubitril is readily converted to LBQ657 by esterases; LBQ657 is not further metabolized to a significant extent. Valsartan is minimally metabolized; only about 20% of the dose is recovered as metabolites. A hydroxyl metabolite has been identified in plasma at low concentrations (< 10%).

Elimination

Following oral administration, 52% to 68% of sacubitril (primarily as LBQ657) and ~ 13% of valsartan and its metabolites are excreted in urine; 37% to 48% of sacubitril (primarily as LBQ657), and 86% of valsartan and its metabolites are excreted in feces. Sacubitril, LBQ657, and valsartan are eliminated from plasma with a mean elimination half-life ($T_{1/2}$) of approximately 1.4 hours, 11.5 hours, and 9.9 hours, respectively.

Linearity/Nonlinearity

The pharmacokinetics of sacubitril, LBQ657, and valsartan were linear over an ENTRESTO dose range of 24 mg sacubitril/26 mg valsartan to 194 mg sacubitril/206 mg valsartan.

Drug Interactions:

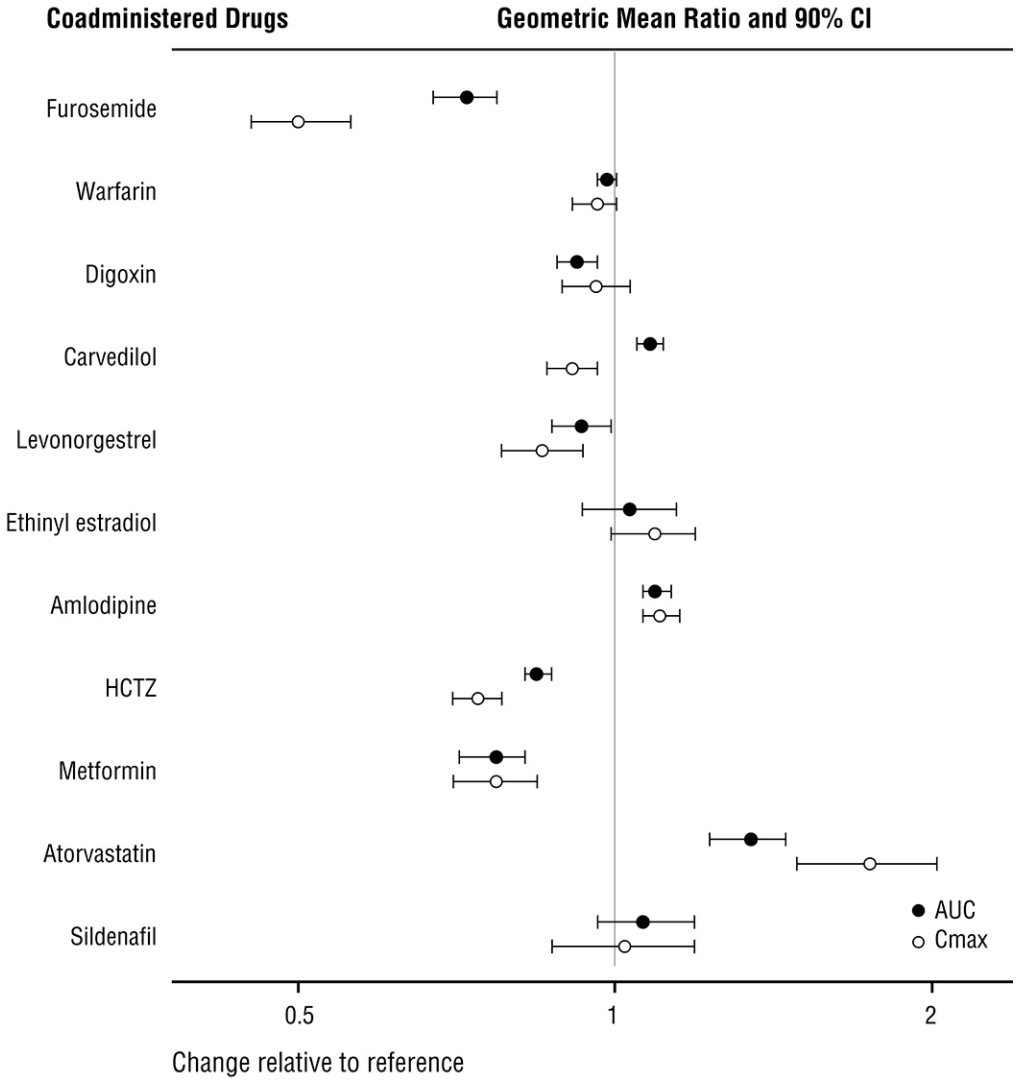
Effect of Co-administered Drugs on ENTRESTO:

Because CYP450 enzyme-mediated metabolism of sacubitril and valsartan is minimal, coadministration with drugs that impact CYP450 enzymes is not expected to affect the pharmacokinetics of ENTRESTO. Dedicated drug interaction studies demonstrated that coadministration of furosemide, warfarin, digoxin, carvedilol, a combination of levonorgestrel/ethinyl estradiol, amlodipine, omeprazole, hydrochlorothiazide (HCTZ), metformin, atorvastatin, and sildenafil, did not alter the systemic exposure to sacubitril, LBQ657 or valsartan.

Effect of ENTRESTO on Co-administered Drugs:

In vitro data indicate that sacubitril inhibits OATP1B1 and OATP1B3 transporters. The effects of ENTRESTO on the pharmacokinetics of coadministered drugs are summarized in Figure 1.

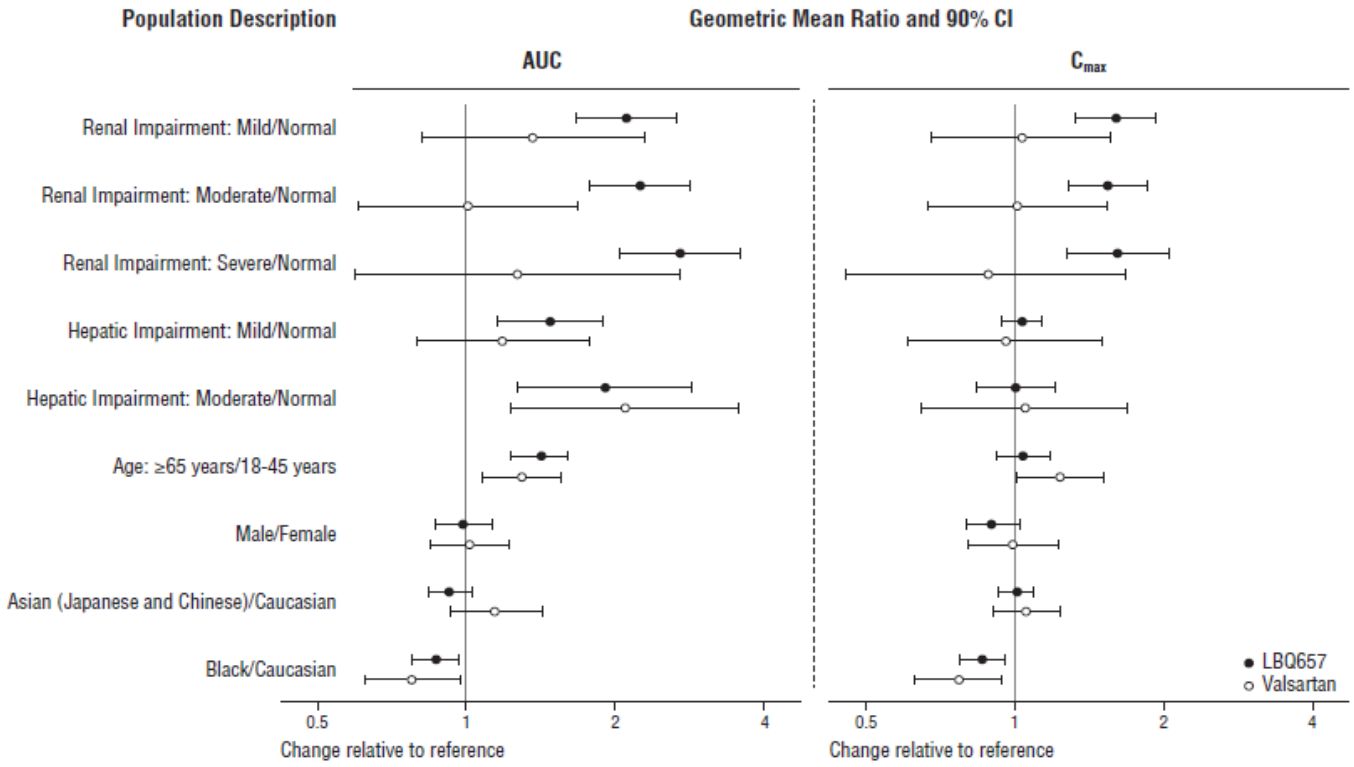
Figure 1: Effect of ENTRESTO on Pharmacokinetics of Coadministered Drugs



Specific Populations

Effect of specific populations on the pharmacokinetics of LBQ657 and valsartan are shown in Figure 2.

Figure 2: Pharmacokinetics of ENTRESTO in Specific Populations



Note: Child-Pugh Classification was used for hepatic impairment.

Pediatric Patients:

The pharmacokinetics of ENTRESTO were evaluated in pediatric heart failure patients 1 to < 18 years old administered oral doses of 0.8 mg/kg and 3.1 mg/kg of ENTRESTO. Pharmacokinetic data indicated that exposure to ENTRESTO in pediatric and adult patients is similar.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Carcinogenicity studies conducted in mice and rats with sacubitril and valsartan did not identify any carcinogenic potential for ENTRESTO. The LBQ657 C_{max} at the high dose (HD) of 1200 mg/kg/day in male and female mice was, respectively, 14 and 16 times that in humans at the MRHD. The LBQ657 C_{max} in male and female rats at the HD of 400 mg/kg/day was, respectively, 1.7 and 3.5 times that at the MRHD. The doses of valsartan studied (high dose of 160 and 200 mg/kg/day in mice and rats, respectively) were about 4 and 10 times, respectively, the MRHD on a mg/m^2 basis.

Mutagenicity and clastogenicity studies conducted with ENTRESTO, sacubitril, and valsartan did not reveal any effects at either the gene or chromosome level.

Impairment of Fertility

ENTRESTO did not show any effects on fertility in rats up to a dose of 73 mg sacubitril/77 mg valsartan/kg/day (≤ 1.0-fold and ≤ 0.18-fold the MRHD on the basis of the AUCs of valsartan and LBQ657, respectively).

13.2 Animal Toxicology and/or Pharmacology

The effects of ENTRESTO on amyloid-β concentrations in CSF and brain tissue were assessed in young (2 to 4 years old) cynomolgus monkeys treated with ENTRESTO (24 mg sacubitril/26 mg valsartan/kg/day) for 2 weeks. In this study, ENTRESTO affected CSF Aβ clearance, increasing CSF Aβ 1-40, 1-42, and 1-38 levels in CSF; there was no corresponding increase in Aβ levels in the brain. In addition, in a toxicology study in cynomolgus monkeys treated with ENTRESTO at 146 mg sacubitril/154 mg valsartan/kg/day for 39-weeks, there was no amyloid-β accumulation in the brain.

14 CLINICAL STUDIES

Dosing in clinical trials was based on the total amount of both components of ENTRESTO, i.e., 24/26 mg, 49/51 mg, and 97/103 mg were referred to as 50 mg, 100 mg, and 200 mg, respectively.

14.1 Adult Heart Failure

PARADIGM-HF

PARADIGM-HF was a multinational, randomized, double-blind trial comparing ENTRESTO and enalapril in 8,442 adult patients with symptomatic chronic heart failure (NYHA class II–IV) and systolic dysfunction (left ventricular ejection fraction ≤ 40%). Patients had to have been on an ACE inhibitor or ARB for at least four weeks and on maximally tolerated doses of beta-blockers. Patients with a systolic blood pressure of < 100 mmHg at screening were excluded.

The primary objective of PARADIGM-HF was to determine whether ENTRESTO, a combination of sacubitril and a RAS inhibitor (valsartan), was superior to a RAS inhibitor (enalapril) alone in reducing the risk of the combined endpoint of cardiovascular (CV) death or hospitalization for heart failure (HF).

After discontinuing their existing ACE inhibitor or ARB therapy, patients entered sequential single-blind run-in periods during which they received enalapril 10 mg twice-daily, followed by ENTRESTO 100 mg twice-daily, increasing to 200 mg twice-daily. Patients who successfully completed the sequential run-in periods were randomized to receive either ENTRESTO 200 mg (N = 4,209) twice-daily or enalapril 10 mg (N = 4,233) twice-daily. The primary endpoint was the first event in the composite of CV death or hospitalization for HF. The median follow-up duration was 27 months and patients were treated for up to 4.3 years.

The population was 66% Caucasian, 18% Asian, and 5% Black; the mean age was 64 years and 78% were male. At randomization, 70% of patients were NYHA Class II, 24% were NYHA Class III, and 0.7% were NYHA Class IV. The mean left ventricular ejection fraction was 29%. The underlying cause of heart failure was coronary artery disease in 60% of patients; 71% had a history of hypertension, 43% had a history of myocardial infarction, 37% had an eGFR < 60 mL/min/1.73m^2, and 35% had diabetes mellitus. Most patients were taking beta-blockers (94%), mineralocorticoid antagonists (58%), and diuretics (82%). Few patients had an implantable cardioverter-defibrillator (ICD) or cardiac resynchronization therapy-defibrillator (CRT-D) (15%).

PARADIGM-HF demonstrated that ENTRESTO, a combination of sacubitril and a RAS inhibitor (valsartan), was superior to a RAS inhibitor (enalapril), in reducing the risk of the combined endpoint of cardiovascular death or hospitalization for heart failure, based on a time-to-event analysis (hazard ratio [HR] 0.80; 95% confidence interval [CI], 0.73, 0.87, $p < 0.0001$). The treatment effect reflected a reduction in both cardiovascular death and heart failure hospitalization; see Table 3 and Figure 3. Sudden death accounted for 45% of cardiovascular deaths, followed by pump failure, which accounted for 26%.

ENTRESTO also improved overall survival (HR 0.84; 95% CI [0.76, 0.93], $p = 0.0009$) (Table 3). This finding was driven entirely by a lower incidence of cardiovascular mortality on ENTRESTO.

Table 3: Treatment Effect for the Primary Composite Endpoint, its Components, and All-cause Mortality in PARADIGM-HF

	ENTRESTO N = 4,187 n (%)	**Enalapril N = 4,212 n (%)**	**Hazard Ratio (95% CI)**	***p*-value**
Primary composite endpoint of cardiovascular death or heart failure hospitalization	914 (21.8)	1,117 (26.5)	0.80 (0.73, 0.87)	< 0.0001
Cardiovascular death as first event	377 (9.0)	459 (10.9)		
Heart failure hospitalization as first event	537 (12.8)	658 (15.6)		
Number of patients with events: [*]				
Cardiovascular death[**]	558 (13.3)	693 (16.5)	0.80 (0.71, 0.89)	
Heart failure hospitalizations	537 (12.8)	658 (15.6)	0.79 (0.71, 0.89)	
All-cause mortality	711 (17.0)	835 (19.8)	0.84 (0.76, 0.93)	0.0009

[*]Analyses of the components of the primary composite endpoint were not prospectively planned to be adjusted for multiplicity

[**]Includes patients who had heart failure hospitalization prior to death

The Kaplan-Meier curves presented below (Figure 3) show time to first occurrence of the primary composite endpoint (3A), and time to occurrence of cardiovascular death at any time (3B) and first heart failure hospitalization (3C).

Figure 3: Kaplan-Meier Curves for the Primary Composite Endpoint (A), Cardiovascular Death (B), and Heart Failure Hospitalization (C)

Figure A

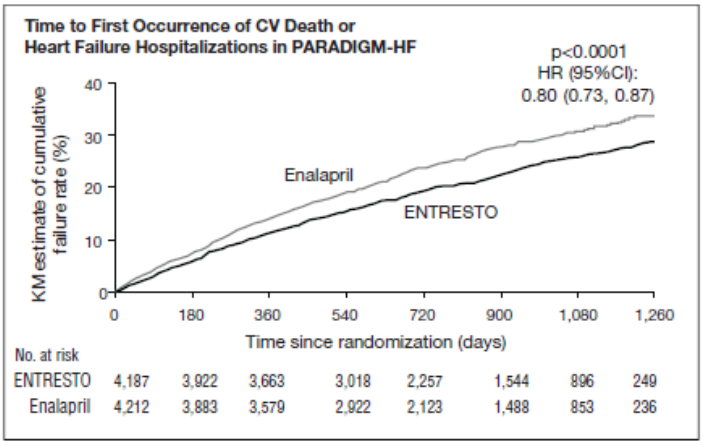


Figure B

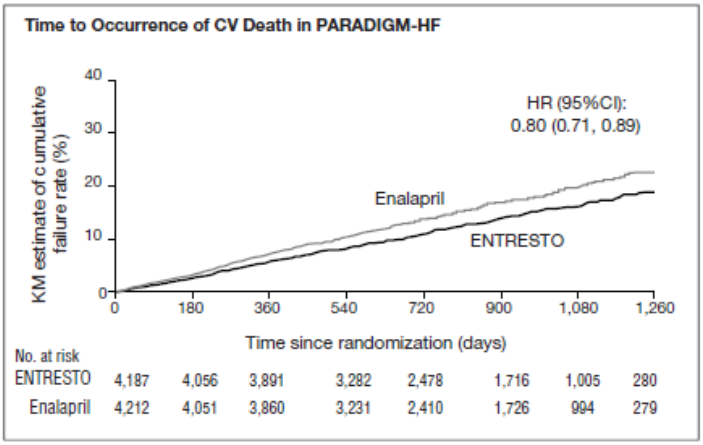
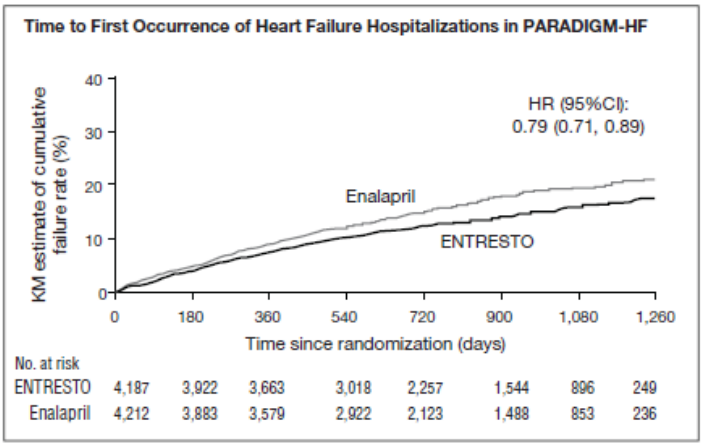


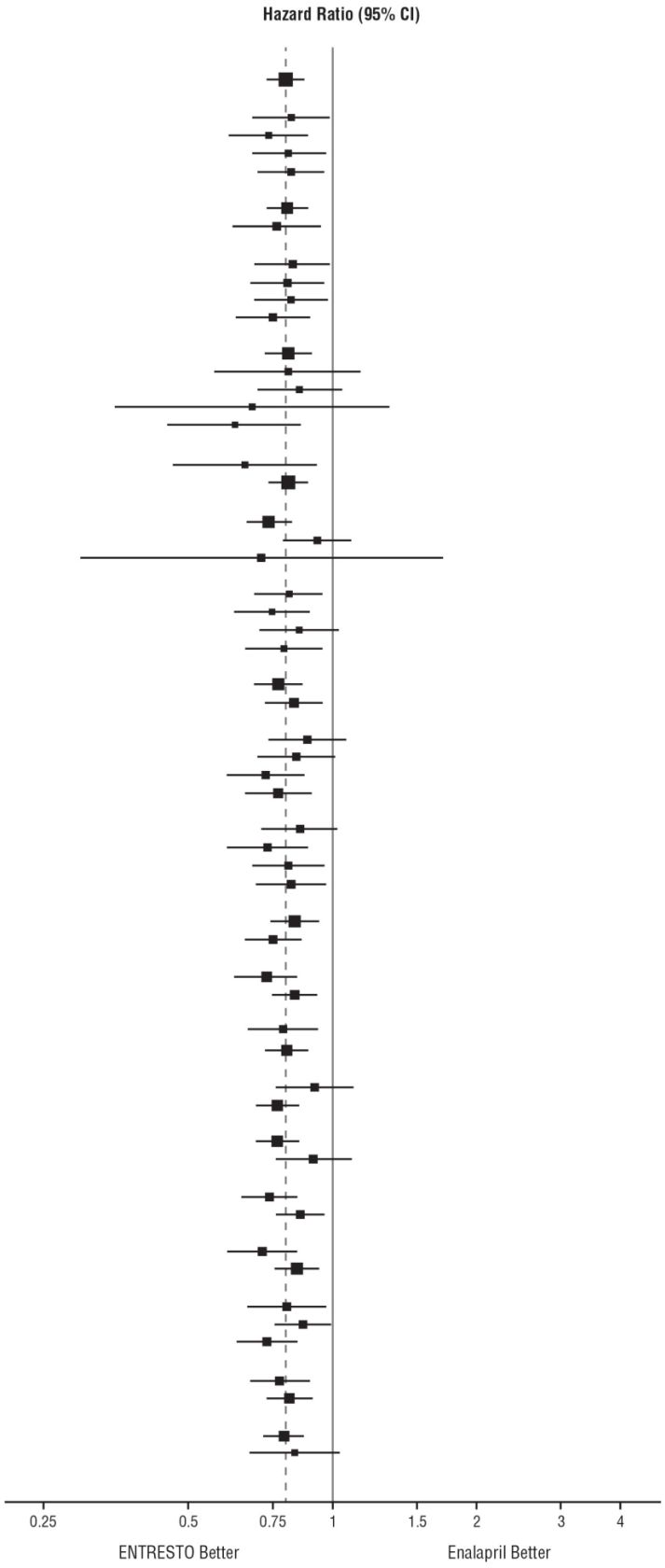
Figure C



A wide range of demographic characteristics, baseline disease characteristics, and baseline concomitant medications were examined for their influence on outcomes. The results of the primary composite endpoint were consistent across the subgroups examined (Figure 4).

Figure 4: Primary Composite Endpoint (CV Death or HF Hospitalization) - Subgroup Analysis (PARADIGM-HF)

Subgroup	Percentage of total population (%)	ENTRESTO n/N	ENTRESTO (%)	Enalapril n/N	Enalapril (%)
Overall	100	914/4,187	(21.8)	1,117/4,212	(26.5)
Age (years)					
<57	24.3	222/1,043	(21.3)	248/ 994	(24.9)
57 - <64	22.7	182/ 917	(19.8)	263/ 992	(26.5)
64 - <72	25.8	229/1,084	(21.1)	273/1,081	(25.3)
≥72	27.2	281/1,143	(24.6)	333/1,145	(29.1)
Gender					
Male	78.2	756/3,308	(22.9)	902/3,259	(27.7)
Female	21.8	158/ 879	(18.0)	215/ 953	(22.6)
Weight (kg)					
<67.5	25.0	221/1,037	(21.3)	269/1,061	(25.4)
67.5 - <79	24.8	241/1,041	(23.2)	287/1,038	(27.6)
79 - <91.7	25.2	231/1,048	(22.0)	283/1,069	(26.5)
≥91.7	25.1	221/1,060	(20.8)	278/1,044	(26.6)
Race					
Caucasian	66.0	598/2,763	(21.6)	717/2,781	(25.8)
Black	5.1	58/ 213	(27.2)	72/ 215	(33.5)
Asian	18.0	179/ 759	(23.6)	204/ 750	(27.2)
Native American	2.0	15/ 84	(17.9)	22/ 88	(25.0)
Other	8.9	64/ 368	(17.4)	102/ 378	(27.0)
Region					
US	5.2	58/ 225	(25.8)	77/ 209	(36.8)
Outside-US	94.8	856/3,962	(21.6)	1,040/4,003	(26.0)
NYHA Class					
NYHA class II	70.5	578/2,998	(19.3)	742/2,921	(25.4)
NYHA class III	24.0	292/ 969	(30.1)	329/1,049	(31.4)
NYHA class IV	0.7	10/ 33	(30.3)	11/ 27	(40.7)
Estimated GFR (mL/min/1.73m²)					
<54	24.7	280/1,021	(27.4)	344/1,054	(32.6)
54 - <66	24.0	218/1,018	(21.4)	279/1,000	(27.9)
66 - <79	24.9	205/1,037	(19.8)	238/1,054	(22.6)
≥79	26.4	211/1,111	(19.0)	256/1,104	(23.2)
Diabetes					
No	65.4	519/2,736	(19.0)	661/2,756	(24.0)
Yes	34.6	395/1,451	(27.2)	456/1,456	(31.3)
Systolic blood pressure (mmHg)					
<110	20.8	208/ 834	(24.9)	249/ 913	(27.3)
110 - <120	23.0	223/ 990	(22.5)	249/ 941	(26.5)
120 - <130	24.5	202/1,041	(19.4)	264/1,018	(25.9)
≥130	31.7	281/1,322	(21.3)	355/1,340	(26.5)
Ejection fraction (%)					
<25	19.4	215/ 784	(27.4)	271/ 849	(31.9)
25 - <30	20.8	191/ 861	(22.2)	255/ 885	(28.8)
30 - <34	28.5	243/1,229	(19.8)	281/1,162	(24.2)
≥34	31.3	265/1,313	(20.2)	310/1,315	(23.6)
Atrial fibrillation					
No	63.2	552/2,670	(20.7)	637/2,638	(24.1)
Yes	36.8	362/1,517	(23.9)	480/1,574	(30.5)
NT-proBNP					
≤Median	49.9	299/2,079	(14.4)	403/2,116	(19.0)
>Median	49.9	614/2,103	(29.2)	711/2,087	(34.1)
Hypertension					
No	29.3	245/1,218	(20.1)	303/1,241	(24.4)
Yes	70.7	669/2,969	(22.5)	814/2,971	(27.4)
Prior use of ACE inhibitor					
No	22.2	221/ 921	(24.0)	246/ 946	(26.0)
Yes	77.8	693/3,266	(21.2)	871/3,266	(26.7)
Prior use of ARB					
No	77.5	691/3,258	(21.2)	866/3,249	(26.7)
Yes	22.5	223/ 929	(24.0)	251/ 963	(26.1)
Prior use of aldosterone antagonist					
No	44.4	399/1,916	(20.8)	494/1,812	(27.3)
Yes	55.6	515/2,271	(22.7)	623/2,400	(26.0)
Prior hospitalization for heart failure					
No	37.2	262/1,580	(16.6)	348/1,545	(22.5)
Yes	62.8	652/2,607	(25.0)	769/2,667	(28.8)
Time since diagnosis of heart failure					
≤1 year	30.0	202/1,275	(15.8)	240/1,248	(19.2)
>1-5 years	38.5	392/1,621	(24.2)	447/1,611	(27.7)
>5 years	31.5	320/1,291	(24.8)	430/1,353	(31.8)
Cause of heart failure					
Non-ischemic	40.0	339/1,681	(20.2)	420/1,682	(25.0)
Ischemic	60.0	575/2,506	(22.9)	697/2,530	(27.5)
Any ICD (including CRT-D)					
No	85.2	761/3,564	(21.4)	942/3,592	(26.2)
Yes	14.8	153/ 623	(24.6)	175/ 620	(28.2)



Note: The figure above presents effects in various subgroups, all of which are baseline characteristics. The 95% confidence limits that are shown do not take into account the number of comparisons made, and may not reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

PARAGON-HF

PARAGON-HF, was a multicenter, randomized, double-blind trial comparing ENTRESTO and valsartan in 4,796 adult patients with symptomatic heart failure with left ventricular ejection fraction ≥45%, and structural heart disease [either left atrial enlargement (LAE) or left ventricular hypertrophy (LVH)]. Patients with a systolic blood pressure of < 110 mmHg and patients with any prior echocardiographic LVEF <40% at screening were excluded.

The primary objective of PARAGON-HF was to determine whether ENTRESTO reduced the rate of the composite endpoint of total (first and recurrent) heart failure (HF) hospitalizations and cardiovascular (CV) death.

After discontinuing their existing ACE inhibitor or ARB therapy, patients entered sequential single-blind run-in periods during which they received valsartan 80 mg twice-daily, followed by ENTRESTO 100 mg twice-daily. Patients on prior low doses of an ACEi or ARB began the run-in period receiving valsartan 40 mg twice-daily for 1-2 weeks. Patients who successfully completed the sequential run-in periods were randomized to receive either ENTRESTO 200 mg (N=2,419) twice-daily or valsartan 160 mg (N=2,403) twice-daily. The median follow-up duration was 35 months and patients were treated for up to 4.7 years.

The population was 81% Caucasian, 13% Asian, and 2% Black; the mean age was 73 years and 52% were female. At randomization, 77% of patients were NYHA Class II, 19% were NYHA Class III, and 0.4% were NYHA Class IV. The median left ventricular ejection fraction was 57%. The underlying cause of heart failure was of ischemic etiology in 36% of patients. Furthermore, 96% had a history of hypertension, 23% had a history of myocardial infarction, 46% had an eGFR < 60 mL/min/1.73 m^2, and 43% had diabetes mellitus. Most patients were taking beta-blockers (80%) and diuretics (95%).

PARAGON-HF demonstrated that ENTRESTO had a numerical reduction in the rate of the composite endpoint of total (first and recurrent) HF hospitalizations and CV death, based on an analysis using a proportional rates model (rate ratio [RR] 0.87; 95% CI [0.75, 1.01], $p = 0.06$); see Table 4. The treatment effect was primarily driven by the reduction in total HF hospitalizations in patients randomized to ENTRESTO (RR 0.85; 95% CI [0.72, 1.00]).

Table 4: Treatment Effect for the Primary Composite Endpoint and its Components in PARAGON-HF

	ENTRESTO N = 2,407		Valsartan N = 2,389		Effect Size (95% CI)
Efficacy Endpoints	**n**	**Event Rate[a]**	**n**	**Event Rate[a]**	
Composite of total (first and recurrent) HF hospitalizations and CV death	894	12.8	1,009	14.6	RR = 0.87 (0.75, 1.01) *p*-value 0.06
Total HF Hospitalizations	690	9.9	797	11.6	RR = 0.85 (0.72, 1.00)
CV Death[b]	204	2.9	212	3.1	HR = 0.95 (0.79, 1.16)

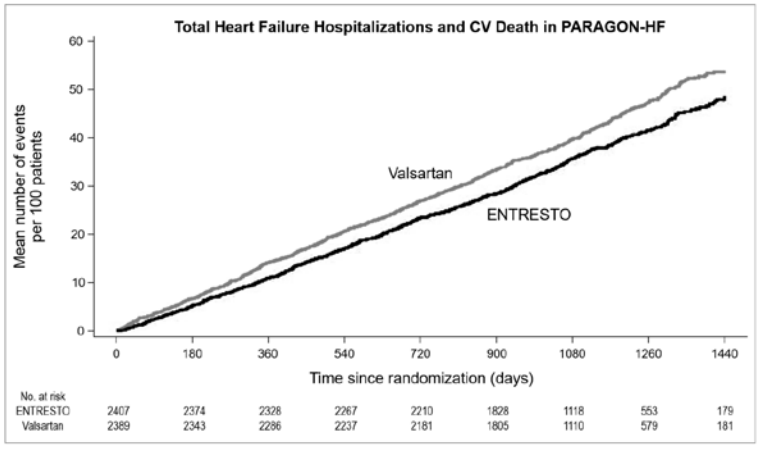
Abbreviations: RR = rate ratio, HR = hazard ratio

[a] Event rate per 100 patient-years

[b] Includes patients who had CV death following HF hospitalization event

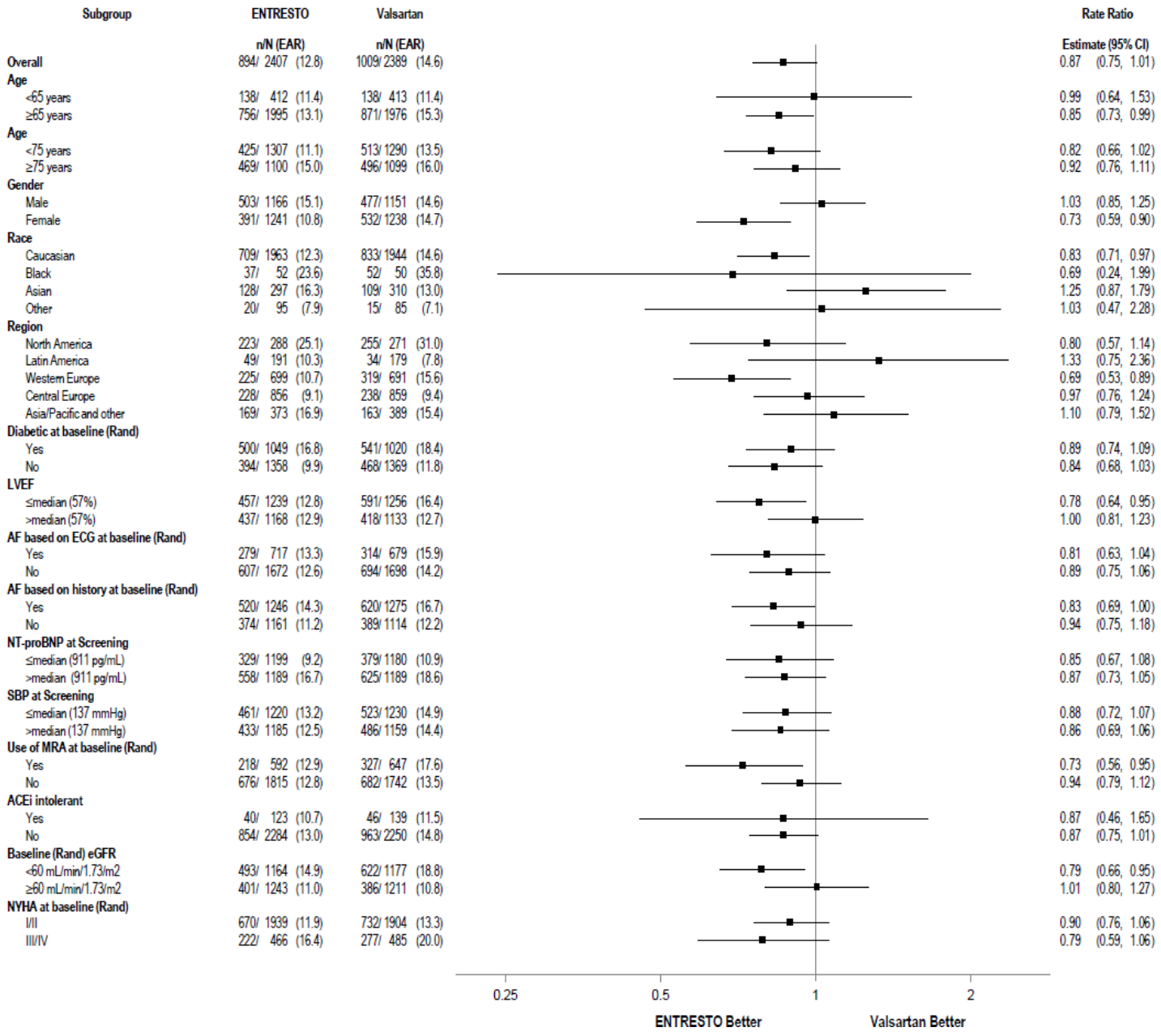
Figure 5 shows the mean number of composite endpoint events of total HF hospitalizations and CV death over time.

Figure 5: Mean Number of Events Over Time for the Primary Composite Endpoint of Total HF Hospitalizations and CV Death



A wide range of demographic characteristics, baseline disease characteristics, and baseline concomitant medications were examined for their influence on outcomes (Figure 6).

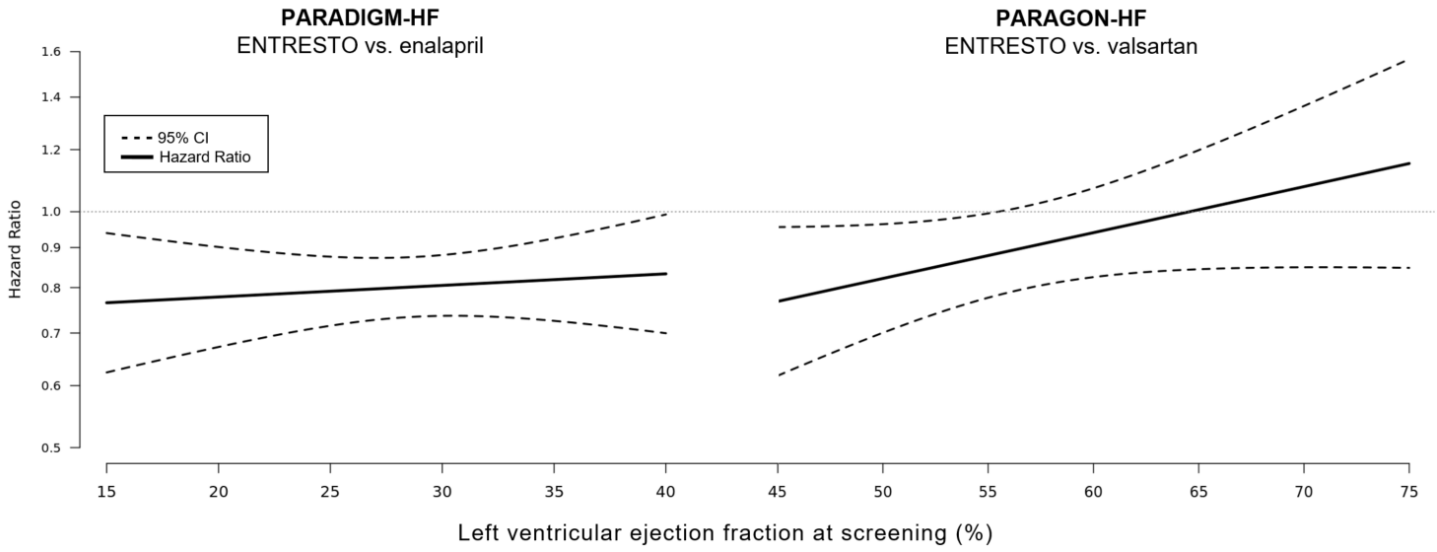
Figure 6: Primary Composite Endpoint of Total HF Hospitalizations and CV Death – Subgroup Analysis (PARAGON-HF)



Note: The figure above presents effects in various subgroups, all of which are baseline characteristics. The 95% confidence limits that are shown do not take into account the number of comparisons made, and may not reflect the effect of a particular factor after adjustment for all other factors.

In an analysis of the relationship between LVEF and outcome in PARADIGM-HF and PARAGON-HF, patients with LVEF below normal treated with ENTRESTO experienced greater risk reduction (Figure 7).

Figure 7: Treatment Effect for the Composite Endpoint of Time to First HF Hospitalization or CV Death by LVEF in PARADIGM-HF and PARAGON-HF



14.2 Pediatric Heart Failure

PANORAMA-HF

The efficacy of ENTRESTO was evaluated in a multinational, randomized, double-blind trial comparing ENTRESTO and enalapril based on an analysis in 110 pediatric patients 1 to < 18 years old with heart failure (NYHA/Ross class II-IV) due to systemic left ventricular systolic dysfunction (LVEF ≤ 40%). Patients with systemic right ventricles and single ventricles were excluded from the trial. The target maintenance dose of ENTRESTO in pediatric patients 1 to < 18 years old was 3.1 mg/kg twice daily.

The endpoint was the between-group difference in the change in plasma NT-proBNP from baseline to 12 weeks. The reduction from baseline in NT-proBNP was 44% and 33% in the ENTRESTO and enalapril groups, respectively. While the between-group difference was not statistically significant, the reductions for ENTRESTO and enalapril were similar to or larger than what was seen in adults; these reductions did not appear to be attributable to post-baseline changes in background therapy.

Because ENTRESTO improved outcomes and reduced NT-proBNP in PARADIGM-HF, the effect on NT-proBNP was considered a reasonable basis to infer improved cardiovascular outcomes in pediatric patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

ENTRESTO (sacubitril/valsartan) is available as unscored, ovaloid, biconvex, film-coated tablets, containing 24 mg of sacubitril and 26 mg of valsartan; 49 mg of sacubitril and 51 mg of valsartan; and 97 mg of sacubitril and 103 mg of valsartan. All strengths are packaged in bottles as described below.

Tablet	**Color**	**Debossment**	**NDC # 0078-XXXX-XX**	
Sacubitril/Valsartan		"NVR" and	Bottle of 60	Bottle of 180
24 mg/26 mg	Violet white	LZ	0659-20	0659-67
49 mg/51 mg	Pale yellow	L1	0777-20	0777-67
97 mg/103 mg	Light pink	L11	0696-20	0696-67

Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Patient Information).

Pregnancy: Advise female patients of childbearing age about the consequences of exposure to ENTRESTO during pregnancy. Discuss treatment options with women planning to become pregnant. Ask patients to report pregnancies to their physicians as soon as possible *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)]*.

Angioedema: Advise patients to discontinue use of their previous ACE inhibitor or ARB. Advise patients to allow a 36 hour wash-out period if switching from or to an ACE inhibitor *[see Contraindications (4)* and *Warnings* and *Precautions (5.2)]*.

Patient Information
ENTRESTO (en-TRESS-toh)
(sacubitril and valsartan) tablets

What is the most important information I should know about ENTRESTO?

ENTRESTO can harm or cause death to your unborn baby. Talk to your doctor about other ways to treat heart failure if you plan to become pregnant. If you get pregnant during treatment with ENTRESTO, tell your doctor right away.

What is ENTRESTO?

ENTRESTO is a prescription medicine used to treat:

- adults with long-lasting (chronic) heart failure to help reduce the risk of death and hospitalization. ENTRESTO works better when the heart cannot pump a normal amount of blood to the body.
- certain children 1 year of age and older who have symptomatic heart failure.

It is not known if ENTRESTO is safe and effective in children under 1 year of age.

Do not take ENTRESTO if you:

- are allergic to any of the ingredients in ENTRESTO. See the end of this Patient Information leaflet for a complete list of ingredients in ENTRESTO.
- have had an allergic reaction including swelling of your face, lips, tongue, throat, or trouble breathing while taking a type of medicine called an ACE inhibitor or ARB.
- take an ACE inhibitor medicine. **Do not take ENTRESTO for at least 36 hours before or after you take an ACE inhibitor medicine**. Talk with your doctor or pharmacist before taking ENTRESTO if you are not sure if you take an ACE inhibitor medicine.
- have diabetes and take a medicine that contains aliskiren.

Before taking ENTRESTO, tell your doctor about all of your medical conditions, including if you:

- have a history of hereditary angioedema
- have kidney or liver problems
- are pregnant or plan to become pregnant. See **"What is the most important information I should know about ENTRESTO?"**
- are breastfeeding or plan to breastfeed. It is not known if ENTRESTO passes into your breast milk. You and your doctor should decide if you will take ENTRESTO or breastfeed. You should not do both.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Using ENTRESTO with certain other medicines may affect each other. Using ENTRESTO with other medicines can cause serious side effects. Especially tell your doctor if you take:

- potassium supplements or a salt substitute
- nonsteroidal anti-inflammatory drugs (NSAIDs)
- lithium
- other medicines for high blood pressure or heart problems such as an ACE inhibitor, ARB, or aliskiren

Keep a list of your medicines to show your doctor and pharmacist when you get a new medicine.

How should I take ENTRESTO?

- Take ENTRESTO exactly as your doctor tells you to take it.
- Take ENTRESTO 2 times each day. Your doctor may change your dose of ENTRESTO during treatment.
- If your child cannot swallow tablets, or if tablets are not available in the prescribed strength, your pharmacist will prepare ENTRESTO as a liquid suspension for your child. If your child switches between taking the tablet and the suspension, your doctor will adjust the dose as needed. Shake the bottle of suspension well before measuring the dose of medicine to give to your child.
- If you miss a dose, take it as soon as you remember. If it is close to your next dose, do not take the missed dose. Take the next dose at your regular time.
- If you take too much ENTRESTO, call your doctor right away.

What are the possible side effects of ENTRESTO?

ENTRESTO may cause serious side effects including:

- See **"What is the most important information I should know about ENTRESTO?"**
- **Serious allergic reactions causing swelling of your face, lips, tongue, and throat (angioedema) that may cause trouble breathing and death.** Get emergency medical help right away if you have symptoms of angioedema or trouble breathing. Do not take ENTRESTO again if you have had angioedema during treatment with ENTRESTO.
- People who are Black and take ENTRESTO may have a higher risk of having angioedema than people who are not Black and take ENTRESTO.
- People who have had angioedema before taking ENTRESTO may have a higher risk of having angioedema than people who have not had angioedema before taking ENTRESTO. See **"Who should not take ENTRESTO?"**
- **Low blood pressure (hypotension).** Low blood pressure may be more common if you also take water pills. Call your doctor if you become dizzy or lightheaded, or you develop extreme fatigue.
- **Kidney problems.** Your doctor will check your kidney function during your treatment with ENTRESTO. If you have changes in your kidney function tests, you may need a lower dose of ENTRESTO or may need to stop taking ENTRESTO for a period of time.
- **Increased amount of potassium in your blood (hyperkalemia).** Your doctor will check your potassium blood level during your treatment with ENTRESTO.

These are not all the possible side effects of ENTRESTO. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ENTRESTO?

- Store ENTRESTO tablets at room temperature between 68°F to 77°F (20°C to 25°C).
- Protect ENTRESTO tablets from moisture.
- Store bottles of ENTRESTO oral suspension at room temperature less than 77°F (25°C) for up to 15 days. Do not refrigerate ENTRESTO oral suspension.

Keep ENTRESTO and all medicines out of the reach of children.

General information about the safe and effective use of ENTRESTO.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use ENTRESTO for a condition for which it was not prescribed. Do not give ENTRESTO to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or doctor for information about ENTRESTO that is written for health professionals.

What are the ingredients in ENTRESTO?

Active ingredients: sacubitril and valsartan

Inactive ingredients: microcrystalline cellulose, low-substituted hydroxypropylcellulose, crospovidone, magnesium stearate (vegetable origin), talc, and colloidal silicon dioxide. Film coat: hypromellose, titanium dioxide (E 171), Macrogol 4000, talc, iron oxide red (E 172). The film-coat for the 24 mg of sacubitril and 26 mg of valsartan tablet and the 97 mg of sacubitril and 103 mg of valsartan tablet also contains iron oxide black (E 172). The film-coat for the 49 mg of sacubitril and 51 mg of valsartan tablet contains iron oxide yellow (E 172).

Prepared ENTRESTO oral suspension also contains Ora-Sweet SF and Ora-Plus.

Distributed by: Novartis Pharmaceuticals Corporation East Hanover, New Jersey 07936

For more information, go to www.ENTRESTO.com or call 1-888-368-7378 (1-888-ENTRESTO).

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: February 2021

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NORMAN L STOCKBRIDGE
02/16/2021 10:15:01 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207620Orig1s018

CLINICAL REVIEW(S)

Clinical and Statistical Review

Table 1. Administrative Application Information

Category	Application Information
Application type	Efficacy Supplement
Application number(s)	207620
Priority or standard	Standard
Submit date(s)	4/21/2020
Received date(s)	4/21/2020
PDUFA goal date	2/20/2021
Division/office	Division of Cardiovascular and Renal Products (DCaRP)
Review completion date	2/12/2021
Established name	Sacubitril/valsartan
(Proposed) trade name	Entresto
Pharmacologic class	Neprilysin inhibitor/ angiotensin II receptor blocker
Code name	LCZ696
Applicant	Novartis
Dose form/formulation(s)	24/26 (50) mg; 49/51 (100) mg; 97/103 (200) mg film-coated tablets

<table>
<tr><th>Category</th><th colspan="2">Application Information</th></tr>
<tr><td>Dosing regimen</td><td>Indication</td><td>Dosing Recommendation</td></tr>
<tr><td></td><td>To reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction</td><td>Starting dose: 49/51 mg twice daily
Target dose: 97/103 mg twice daily</td></tr>
<tr><td></td><td>For the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. Entresto reduces NT-proBNP and is expected to improve cardiovascular outcomes.</td><td>
<table>
<tr><td>Indication</td><td colspan="3">Titration Step Dose (twice daily)</td></tr>
<tr><td></td><td>Starting</td><td>Second</td><td>Final</td></tr>
<tr><td>Pediatric Heart Failure Patients less than 40 kg</td><td>1.6 mg/kg</td><td>2.3 mg/kg</td><td>3.1 mg/kg</td></tr>
<tr><td>Pediatric Heart Failure Patients at least 40 kg, less than 50 kg</td><td>24/26 mg</td><td>49/51 mg</td><td>72/78 mg</td></tr>
<tr><td>Pediatric Heart Failure Patients at least 50 kg</td><td>49/51 mg</td><td>72/78 mg</td><td>97/103 mg</td></tr>
</table>
</td></tr>
<tr><td>Applicant proposed indication(s)/ population(s)</td><td colspan="2">To reduce worsening heart failure (total heart failure hospitalizations and urgent heart failure visits) in patients with chronic heart failure and preserved ejection fraction with LVEF below normal</td></tr>
<tr><td>Proposed SNOMED indication</td><td colspan="2">Heart Failure with Preserved Ejection Fraction</td></tr>
<tr><td>Regulatory action</td><td colspan="2">Approval</td></tr>
<tr><td>Approved indication(s)/population(s) (if applicable)</td><td colspan="2">ENTRESTO is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal.
LVEF is a variable measure, so use clinical judgment in deciding whom to treat</td></tr>
<tr><td>Approved SNOMED indication</td><td colspan="2">Systolic Heart Failure</td></tr>
</table>

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Glossary

AAC	angioedema adjudication committee
ACEi	angiotensin converting enzyme inhibitor
AE	adverse event
AESI	adverse event of special interest
ARB	angiotensin receptor blocker
BNP	brain natriuretic peptide
BP	blood pressure
CEC	clinical event committee
CV	cardiovascular
DBP	diastolic blood pressure
DCN	Division of Cardiology and Nephrology
DM	diabetes mellitus
EAIR	exposure adjusted incident rate
ESC	European Society of Cardiology
FMQ	FDA MedDRA query
HF	heart failure
HHF	hospitalization for heart failure
HFmrEF	heart failure with mid-range ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
ITT	Intention-to-Treat
LVEF	left ventricular ejection fraction
MedDRA	medical dictionary for regulatory activities
NCV	non-cardiovascular

NMQ	Novartis MedDRA query
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
SAE	serious adverse event
SBP	systolic blood pressure
SMQ	standard MedDRA query
sNDA	supplemental new drug application
TOPCAT	Treatment of Preserved Cardiac Function Heart Failure
US	United States

I. Executive Summary

1. Summary of Regulatory Action

Conclusion and Rationale

Entresto was approved in 2015 to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure and reduced ejection fraction, based on the PARADIGM-HF trial. The PARAGON-HF trial was conducted by the Applicant to support a claim for HFpEF but did not meet the pre-specified criteria for success. However, DCN agreed to review the data from this trial because of a marginally significant result (p 0.06), established benefit of Entresto in heart failure, and a consistent Rate Ratio demonstrated by exploratory and sensitivity analyses.

The review team concluded that PARAGON-HF did not support the first-ever claim in a fundamentally different form of heart failure, but it did support an expansion of its prior claim.

The recommendation to approve Entresto for the review team's proposed indication was based on the following: **1)** there is no citation in the Code of Federal Regulations which identifies a p-value cutoff that defines persuasive evidence of benefit; **2)** there is concordance of positive results between the Intention-to-Treat (ITT) subjects in the antecedent PARADIGM-HF trial that met the success criteria, and the subgroup of subjects with reduced LVEF in the PARAGON-HF trial; **3)** the safety profile is similar in PARADIGM-HF and PARAGON-HF regardless of LVEF; **4)** the results from the PARAGON-HF ITT population narrowly missed

statistical significance but crossed the threshold for statistical significance when analyzing: ***a)*** the pre-specified expanded primary efficacy endpoint, ***b)*** the investigator-reported primary efficacy endpoint events rather than the adjudicated primary efficacy endpoint events, and ***c)*** data that incorporated an independent blinded re-adjudication of originally negatively adjudicated events by assigning a probability that such events may be positive; **5)** there is precedence in approving drugs despite the respective pivotal trials failing to meet the pre-specified criteria for success albeit under different circumstances than this application; and **6)** there was concordance among CRDAC, DCN and MPPRC that data from PARAGON-HF supported the expansion of indicated population to include patients with mildly reduced LVEF.

Brief history of the review process leading to the recommended regulatory action

The PARAGON-HF trial compared Entresto (n=2407) to valsartan (n=2389) in adults with NYHA class II-IV heart failure, LVEF $\geq$ 45%, elevated natriuretic peptides, and structural heart disease. The primary efficacy endpoint in PARAGON-HF was the adjudicated composite of cardiovascular death and total (first and recurrent) hospitalization for heart failure. A prospectively planned exploratory analysis was conducted using an expanded composite endpoint combining the adjudicated primary efficacy endpoint with urgent heart failure visits (no overnight hospitalization was required).

The definition of HFpEF varies across clinical trials (i.e., $\geq$ 40% or $\geq$ 45% or $\geq$ 50%). The American Society of Echocardiography (ASE) defines normal mean LVEF ± SD (2-SD range) as 62 ± 5 % (52-72) in males and 64 ± 5 % (54-74) in females. Hence, as in PARAGON-HF, when HFpEF is defined as LVEF $\geq$ 45%, it includes patients with mildly reduced and normal left ventricular ejection fraction. The 2016 European Society of Cardiology Guidelines for the diagnosis and treatment of acute and chronic heart failure introduced the term “heart failure with mid-range ejection fraction” (HFmrEF) to describe heart failure patients with LVEF from 40 to 49%.

The results of the PARAGON-HF trial for the adjudicated primary efficacy endpoint did not meet the pre-specified criteria for success (Rate Ratio 0.87, 95% CI 0.75-1.01, p 0.06). This marginal result was driven primarily by reduction in total heart failure hospitalization (Rate Ratio 0.85, 95% CI 0.72-1.00). For cardiovascular death, the Rate Ratio approached neutrality: 0.95 (95% CI 0.79-1.16). The expanded composite endpoint based on the pre-specified exploratory analysis demonstrated a similar rate ratio with a smaller p-value (Rate Ratio 0.86, 95% CI 0.75-0.99, p 0.04).

In the PARAGON-HF trial, 46% of the ITT population had an LVEF < 55%. Subgroup analyses of the PARAGON-HF trial for the adjudicated primary efficacy endpoint showed that subjects with an LVEF below the median (LVEF 57%) appeared to derive benefit (rate ratio 0.78, 95% CI 0.64-0.95) more than subjects with an LVEF above the median (rate ratio 1.00, 95% CI 0.81-1.23). The apparent benefit in subjects with reduced LVEF was consistent with the evidence from the PARADIGM-HF trial. The benefit was not apparent in the population with normal LVEF as defined by the ASE. The review team considered PARAGON-HF to provide supportive evidence of efficacy in the heart failure population with reduced LVEF as already demonstrated in the PARADIGM-HF trial, but with an expanded range of LVEF below normal.

The Applicant argued that the adjudication process, in an effort to maximize specificity for the primary efficacy endpoint, resulted in the rejection of events that could have been positively adjudicated. Investigator assessment of events as endpoints were reportedly adjudicated as non-events because of missing data that were required by the adjudication charter (e.g., chest x-ray, lab, physical findings. The PARAGON-HF study governance opined that such missing data would not have reversed an investigator-based endpoint diagnosis during the adjudication if more clinical judgement flexibility was provided in the adjudication process. A sensitivity analysis referencing investigator-reported primary efficacy endpoint events showed a Rate Ratio of 0.84 (95% CI 0.74-0.97, p 0.01).

The Applicant was asked to convene a new independent adjudication committee to re-assess negatively adjudicated endpoints and assign a probability that these endpoints may have been positive.

DCN was willing to file the sNDA and convene an Advisory Committee to ascertain whether there was support for any claim and to address the utility of a graded rather than a dichotomous adjudication process. Of interest to DCN were: 1) the value of adjudication in lieu of basing a regulatory decision on investigator-determined findings; and 2) the value of dichotomization in the adjudication decision (i.e., yes or no) rather than use of an ordinal variable that utilizes a hierarchy of evidence, thus yielding a probability distribution of positively adjudicated events.

The review team's analysis of the re-adjudication yielded results intermediate between those results from investigator reported events and the originally adjudicated events (i.e., Rate Ratio 0.86, 95% CI 0.75-1.00, p 0.04).

The Advisory Committee voted 12 (yes), 1 (no), 0 (abstention) for an indication based on the totality of the evidence. Various proposals were advanced for the precise wording of the indication. Such proposals included prevention of heart failure hospitalizations in patients with an ejection fraction "less than the lower limit of normal," or a "mildly reduced ejection fraction." Several members favored using an LVEF range of 45-55%. Other members debated inclusion of LVEF $\leq$ 57% based on the belief this would capture the higher threshold in women. One member raised concerns over imprecision in echocardiography. There was also substantial deliberation on use of the term "mildly reduced" ejection fraction because of subjectivity among treating physicians. The Advisory Committee thought that the evidence from PARAGON-HF supported the idea of a "continuum" of heart failure rather than distinct classifications of HFpEF and HFrEF. There was also support for a graded adjudication process.

Although approval based on a pivotal trial that failed to meet its pre-specified success criteria is unusual, it is not unprecedented. Some examples are: 1) Enalapril was approved for use in asymptomatic left ventricular dysfunction on the basis of the SOLVD-Prevention trial; 2) Digoxin was approved for heart failure on the basis of the DIG study; 3) Carvedilol was approved for reduced ejection fraction following myocardial infarction on the basis of the CAPRICORN study; and 4) Bivalirudin was approved for use after percutaneous coronary intervention on the basis of post-hoc pooling of the BAT studies.

The safety findings in the PARAGON-HF trial were consistent with the safety profile of Entresto from the PARADIGM-HF trial. The current label was considered sufficient to manage these known risks. The marginal benefit seen in the PARAGON-HF ITT population infers a less favorable benefit-risk evaluation compared to PARADIGM-HF. However, the benefit-risk in the subgroup of subjects with a reduced LVEF in PARAGON-HF reflects comparability with that from PARADIGM-HF.

2. Benefit-Risk Assessment

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Heart failure (HF) is a chronic condition that affects over 6 million adults in the United States with an annual incidence of > 650,000. Approximately 50% of these cases are considered to have heart failure with preserved ejection fraction (HFpEF). Registry data demonstrate that the rates of mortality and re-admission during 60- to 90-day post discharge for patients with HFpEF and heart failure with reduced ejection fraction (HFrEF) are similar i.e., 9.5% vs. 9.8% and 29.2% vs. 29.9%, respectively. • HFrEF is defined as HF with left ventricular ejection fraction (LVEF) < 40%. The term "HFpEF" was coined to describe HF patients not included in HFrEF. Clinical trials have used various LVEF cut-offs to describe a HFpEF population such as HF with LVEF ≥ 40% or ≥ 45% or ≥ 50%. LVEF is the proportion of blood ejected during LV systole and is an indirect measure of global left ventricular systolic function. Transthoracic echocardiogram is the most common modality used in clinical practice to estimate LVEF. American Society of Echocardiography (ASE) defines normal mean LVEF ± SD (2-SD range) as 62 ± 5 % (52-72) in males and 64 ± 5 % (54-74) in females (measued by echocardiography). Hence, when HFpEF is defined as LVEF ≥ 40% or ≥ 45%, it includes patients with mildly reduced and normal left ventricular ejection fraction. The 2016 European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic HF introduced the term HF with mid-range ejection fraction (HFmrEF) to describe patients with HF with LVEF from 40 to 49%. • HFpEF is associated with several co-morbidities that somewhat overlap with those observed in HFrEF.	• HFpEF is a clinical syndrome of HF without a well-defined parameter to demarcate it from HFrEF. The definition of HFpEF remains controversial and continues to evolve. Nevertheless, it is a chronic condition that is associated with significant morbidity and mortality. • In this sNDA, the Applicant defines HFpEF as HF with LVEF ≥ 45% which includes patients with mildly reduced and normal LVEF i.e.; those with and without evidence of left ventricular systolic dysfunction.
Current Treatment Options	• Currently, there is no FDA approved pharmacotherapy to treat patients with HFpEF. Clinical trials of drugs approved to treat patients with HFrEF such as angiotensin receptor blockers, angiotensin converting enzyme inhibitors and beta blockers have not demonstrated efficacy in patients with HFpEF. In clinical practice, patients with HFpEF receive treatment for their co-morbidities such as hypertension, diabetes mellitus, obesity, sleep apnea, etc. and diuretics to treat fluid overload.	There is no approved treatment for patients with HFpEF.

Benefit	• Entresto is approved to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction. This approval was based on findings of PARADIGM-HF trial that compared Entresto versus enalapril in patients with HFrEF, i.e.; patients with HF with LVEF < 40%. • PARAGON-HF was the pivotal trial designed to demonstrate superiority of Entresto versus valsartan in patients with HFpEF defined by the Applicant as HF with LVEF ≥ 45%. PARAGON-HF narrowly missed the pre-defined threshold for statistical significance for the primary composite endpoint of adjudicated total hospitalization for heart failure (HHF) and cardiovascular (CV) death. The primary composite endpoint results were rate ratio (RR) of 0.87 (95% CI 0.75, 1.01; p 0.06). Additional analyses evaluating endpoints such as 1) prespecified expanded composite endpoint of total HHF, urgent HF visits and CV death, 2) prespecified investigator-reported primary composite endpoint of total HHF and CV death (sensitivity analysis), and 3) post-hoc re-adjudicated primary composite endpoint of total HHF and CV death added HF events to the primary composite endpoint and demonstrated a consistent RR of approximately 0.87, with p-values < 0.05. These findings suggested some treatment effect of Entresto in patients with HF with LVEF ≥ 45%. • Further subgroup analyses in PARAGON-HF demonstrated a heterogeneity of treatment effect by sex and LVEF. The trial population (N 4796) was 52% female (n 2479) and had a median LVEF of 57%. The RR for the primary composite endpoint was 1.03 (CI 0.85, 1.25) and 0.73 (CI 0.59, 0.90) for males versus females, respectively. The RR for the primary composite endpoint was 1 (CI 0.81, 1.23) and 0.78 (CI 0.64, 0.95) for patients with LVEF > 57% and ≤ 57%, respectively. • At the time of submission of this sNDA, the Applicant defined the intended population as "patients with chronic heart failure and preserved ejection fraction," which referred to the entire population of PRAGON-HF. During the review cycle, the Applicant revised the intended population to "patients with chronic heart failure and preserved ejection fraction with LVEF below normal," which refers to approximately half of the trial population of PARAGON-HF. Rationale for the revised definition of the intended population was as follows: 1) subgroup analysis finding of a RR of 0.78 in patients with LVEF ≤ 57% in PARAGON-HF, and 2) consideration of overlapping HF pathophysiology and hence response to Entresto between patients with mildly reduced/abnormal LVEF included in the subgroup of LVEF ≤ 57% and the adjacent patient population of HFrEF (LVEF < 40%) studied in PARADIGM-HF. Additionally, the Applicant sought an indication	• Although PARAGON-HF narrowly missed statistically significance for the primary composite endpoint, additional prespecified exploratory and post-hoc analyses support a treatment effect of Entresto versus valsartan. • The patient population enrolled in PARAGON-HF was heterogenous i.e.; it included patients with mildly reduced /abnormal and normal LVEF. Subgroup analyses demonstrated a heterogeneity of treatment effect by sex and LVEF suggesting that females and patients with LVEF ≤ 57%, derive a greater benefit with Entresto compared to males and patients with LVEF > 57%. • Analysis of treatment effect by LVEF as a continuous variable demonstrated that the following populations derive benefit with Entresto a) both males and females, albeit females benefit over a higher LVEF range, and b) patients with mildly reduced/abnormal LVEF. Similar trends in treatment effect by LVEF were observed with candesartan in CHARM program and with spironolactone in RALES+TOPCAT. These observations indicate that patients with mildly reduced LVEF or mild left ventricular systolic dysfunction resemble patients with moderate to severely reduced LVEF in terms of therapeutic response to these therapies.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	to reduce worsening heart failure (total heart failure hospitalizations and urgent heart failure visits) which was a prespecified exploratory endpoint in PARAGON-HF.	

Dimension	Evidence and Uncertainties	Conclusions and Reasons

Risk and Risk Management	• Entresto is currently approved to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction and to reduce NT-proBNP in pediatric patients aged one year and older who have symptomatic heart failure with systemic left ventricular systolic dysfunction. The approved Entresto label contains:
	  ◦ warnings and precautions for angioedema, hypotension, impaired renal function and hyperkalemia;
	  ◦ adverse reactions occurring ≥ 5% including hypotension, hyperkalemia, cough, dizziness, and renal failure;
	  ◦ additional adverse reactions in post market experience including hypersensitivity.
	• Safety assessment of Entresto in PARAGON-HF focused on predefined adverse events of special interest (AESIs) based on the potential risks in the same class.
	  ◦ The overall incidence of death, serious adverse events (SAEs), and adverse events (AEs) leading to discontinuation is similar between the Entresto and valsartan arm.
	  ◦ More subjects had hypotension-related AEs in Entresto (26.3%) than valsartan (19.4%) but the number of subjects who had hypotension-related SAEs is balanced (3.1% vs 3.2%) between the two treatment arms.
	  ◦ Similar number of subjects reported angioedema-related AEs (8.0% vs 8.4%) and SAEs (0.6% vs 0.6%) in the Entresto and valsartan arm. The number of Angioedema Adjudication Committee (AAC) confirmed angioedema-related AEs is low in both arms with a higher number in Entresto than valsartan arm (0.6% vs 0.2%).
	  ◦ Although the label carries a warning and precaution for renal dysfunction and hyperkalemia, fewer subjects had renal impairment-related AEs and SAEs in Entresto (25.0% for AE and 5.8% for SAE) than valsartan arm (28.3% for AE and 7.4% for SAE). Fewer subjects had hyperkalemia-related AEs and SAEs in Entresto (11.2% and 0.8%) than valsartan arm (15.1% and 1.8%).
	  ◦ Similar number of patients had cognitive impairment and hypersensitivity in Entresto and valsartan arm, 1.9% vs 2.2% and 15.7% vs 16.0%, respectively.
		• No new Entresto-associated risks were identified in the PARAGON-HF trial. Consistent with PARADIGM-HF, Entresto has a higher risk for angioedema and hypotension.
		• Current labeling is considered sufficient to manage these risks.
		• Fewer patients taking Entresto had renal impairment-related AEs and SAEs as well as hyperkalemia.
		• There is no notable difference in the risk of cognitive impairment or hypersensitivity between the treatment arms.

Conclusions Regarding Benefit-Risk

Entresto is a fixed drug combination of an angiotensin receptor blocker (valsartan) and neprilysin inhibitor (sacubitril) that is approved to reduce the risk of cardiovascular (CV) death and hospitalization for heart failure (HHF) in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction, and for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. On April 21, 2020, Novartis (Applicant) submitted an efficacy supplement for Entresto for the proposed indication "to reduce worsening heart failure (total heart failure hospitalizations and urgent heart failure visits) in patients with chronic heart failure and preserved ejection fraction." On September 22, 2020, the Applicant submitted a revised indication "to reduce worsening heart failure (total heart failure hospitalizations and urgent heart failure visits) in patients with chronic heart failure and preserved ejection fraction with LVEF below normal."

To support the proposed indication the Applicant submitted results of a single pivotal trial - PARAGON-HF, a phase 3, randomized, double-blind, active-controlled trial comparing with valsartan in patients with symptomatic heart failure (NYHA class II-IV) with left ventricular ejection fraction (LVEF) ≥ 45%. PARAGON-HF randomized 4,796 adult patients to either Entresto 200 mg or valsartan 160 mg twice daily in a ratio of 1:1 at 755 sites in 43 countries. The study population comprised of 52% women, 83% aged ≥ 65 years with mean age of 73 years (range, 50 to 98 years), 82% Caucasian and 36% from Central Europe (29% Western Europe, 16% Asia/Pacific, 12% North America, 8% Latin America).

The primary composite endpoint of PARAGON-HF was adjudicated total HHF (first and recurrent hospitalizations) and CV death. The primary efficacy endpoint results were rate ratio (RR) of 0.87 (95% CI 0.75, 1.01) with a p-value of 0.06, narrowly missing statistical significance. Additional analyses evaluating the endpoints - 1) prespecified expanded composite endpoint of total HHF, urgent HF visits and CV death, 2) investigator-reported primary composite endpoint of total HHF and CV death, and 3) re-adjudicated primary composite endpoint of total HHF and CV death added HF events to the primary composite endpoint and demonstrated a consistent RR of approximately 0.87, with p-values < 0.05. These findings support a treatment effect of Entresto in patients with HF with LVEF≥ 45%. The findings of efficacy of Entresto in adjacent HF population in PARADIGM-HF provide additional supportive evidence of treatment effect with Entresto.

The American Society of Echocardiography (ASE) defines normal mean LVEF ± SD (2-SD range) as 62 ± 5 % (52-72) in males and 64 ± 5 % (54-74) in females as measured by echocardiography. Based on this definition, PARAGON-HF enrolled a heterogenous patient population that included patients both with mildly reduced/abnormal and normal LVEF.

Subgroup analyses in PARAGON-HF demonstrated a heterogeneity of treatment effect in two major subgroups, by sex and LVEF. The trial population (N 4796) was 52% female (n 2479) and had a median LVEF of 57%. The RR for the primary composite endpoint

was 1.03 (CI 0.85, 1.25) and 0.73 (CI 0.59, 0.90) for males versus females, respectively. The RR for the primary composite endpoint was 1 (CI 0.81, 1.23) and 0.78 (CI 0.64, 0.95) for patients with LVEF > 57% and ≤ 57%, respectively.

Analysis of treatment effect by LVEF as a continuous variable demonstrated that the following populations derive benefit with Entresto a) both males and females, albeit females benefit over a higher LVEF range, and b) patients with mildly reduced (abnormal) LVEF / mild left ventricular systolic dysfunction. Similar trends in treatment effect by LVEF were observed with candesartan in CHARM program and with spironolactone in RALES+TOPCAT. These observations suggest that patients with mildly reduced (abnormal) LVEF / mild left ventricular systolic dysfunction resemble patients with moderate to severely reduced/ abnormal LVEF, i.e.; patients with HFrEF in terms of treatment response to some of these therapies.

The safety findings in PARAGON-HF were consistent with the well-known safety profile of Entresto. Similar to the findings in PARADIGM-HF, Entresto was associated with a higher risk for angioedema and hypotension, compared to active comparator, valsartan. Current labeling is considered sufficient to manage these risks.

The overall benefit risk assessment supports the approval of Entresto to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure, where the benefit appeared to be driven by patients with left ventricular ejection fraction below normal.

II. Interdisciplinary Assessment

3. Introduction

The Applicant has submitted a single, phase 3 trial (PARAGON-HF) in support of the supplemental new drug application (sNDA) for Entresto (sacubitril/valsartan) for the following new indication:

"ENTRESTO is indicated for the treatment of chronic heart failure: to reduce worsening heart failure (total HF hospitalizations and urgent heart failure visits) in patients with chronic heart failure and preserved ejection fraction with LVEF below normal."

Entresto is approved in US for the following indications:

- To reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction (2015)

- For the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. Entresto reduces NT-proBNP and is expected to improve cardiovascular outcomes (2019)

Entresto is a fixed drug combination of an angiotensin receptor blocker (valsartan) and neprilysin inhibitor (sacubitril). Sacubitril is a first-in-class neprilysin inhibitor and is converted to the active metabolite sacubitrilat. Sacubitrilat inhibits the enzyme neprilysin thereby increasing the level of vasoactive peptides such as natriuretic peptides, adrenomedullin, endothelin-1, angiotensin II and bradykinin. Other than angiotensin II, these vasoactive peptides have vasodilatory, natriuretic, and anti-fibrotic effects that are beneficial in heart failure (HF). Natriuretic peptides activate membrane bound guanylyl cyclase-coupled receptors, resulting in increased concentration of the second messenger cyclic guanosine monophosphate (cGMP), thereby promoting vasodilation, natriuresis and diuresis, increased glomerular filtration rate and renal blood flow, inhibition of renin and aldosterone release, reduction of sympathetic activity, and anti-hypertrophic and antifibrotic effects. Angiotensin II causes vasoconstriction, fluid retention, fibrosis, and cardiac remodeling. Valsartan in Entresto blocks these adverse effects of angiotensin II. Increase in bradykinin level is known to be associated with increased risk for angioedema.

Entresto was approved to treat patients with heart failure with reduced ejection fraction (HFrEF) based on PARADIGM-HF study that demonstrated superiority of Entresto compared to enalapril in symptomatic patients with HFrEF defined as HF with left ventricular ejection fraction (LVEF) $\leq$ 40% (N=8442) in reducing the incidence of cardiovascular (CV) death and hospitalization for heart failure (HHF).

The Applicant has submitted Study D2301 (PARAGON-HF) to support claim for CV benefit with Entresto compared to valsartan in symptomatic patients with HFpEF defined as HF with LVEF $\geq$ 45% (N=4822). The dose of Entresto in this review refers to the total dose strength of

both components i.e.; 200 mg which is equivalent to sacubitril/valsartan component strengths of 97/103 mg, respectively.

3.1. Intended Population: Chronic Heart Failure and Preserved Ejection Fraction with LVEF below Normal

Definition of Heart Failure

Heart Failure (HF) is a clinical syndrome characterized by typical symptoms (e.g., breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g., elevated jugular venous pressure, pulmonary crackles and peripheral edema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.[1]

Classification of Heart Failure based on Left Ventricular Ejection Fraction

Historically, HF has been classified based on LVEF as HFrEF or HFpEF.

LVEF is the proportion of blood ejected during LV systole. It is an indirect measure of global left ventricular systolic function. American Society of Echocardiography (ASE)[2] defines normal mean LVEF ± SD (2-SD range) as 62 ± 5 % (52-72) in males and 64 ± 5 % (54-74) in females. The normal reference range for LVEF is derived from a "normal" population that excluded subjects with any of the following criteria: systolic blood pressure > 140 mm Hg, diastolic blood pressure > 80 mm Hg, history of drug-treated hypertension, diagnosis of diabetes, impaired fasting glucose > 100 mg/dL, body mass index > 30 kg/m^2, creatinine > 1.3 mg/dL, estimated glomerular filtration rate < 60 mL/min/1.73 m^2 , total cholesterol > 240 mg/dL, low-density lipoprotein cholesterol > 130 mg/dL, and total triglycerides > 150 mg/dL. Table 3 displays normal and abnormal ranges for LVEF by sex.

[1] Piotr Ponikowski, Adriaan A Voors, Stefan D Anker, Héctor Bueno, John G F Cleland, Andrew J S Coats, Volkmar Falk, José Ramón González-Juanatey, Veli-Pekka Harjola, Ewa A Jankowska, Mariell Jessup, Cecilia Linde, Petros Nihoyannopoulos, John T Parissis, Burkert Pieske, Jillian P Riley, Giuseppe M C Rosano, Luis M Ruilope, Frank Ruschitzka, Frans H Rutten, Peter van der Meer, ESC Scientific Document Group, 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC, European Heart Journal, Volume 37, Issue 27, 14 July 2016, Pages 2129–2200

[2] Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28:1-39.e14.

Table 3. Normal and Abnormal Range of Left Ventricular Ejection Fraction (LVEF) by Sex

	Male				Female			
	Normal Range	Mildly Abnormal	Moderately Abnormal	Severely Abnormal	Normal Range	Mildly Abnormal	Moderately Abnormal	Severely Abnormal
LVEF (%)	52-72	41-51	30-40	<30	54-74	41-53	30-40	<30

Source: Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28:1-39.e14.

The foundation for HF classification based on LVEF was primarily the enrichment strategy of excluding HF patients with LVEF > 35 to 40% from HF trials with the primary endpoint of mortality. This led to an evidence void for therapies effective in patients with LVEF > 40% who were then grouped under the term HFpEF. Pfeffer et al describe that in 1997 CHARM-Preserved trial enrolled patients with LVEF > 40% to address this "*therapeutic void rather than a mechanistic distinction*."[3] The term HFpEF was intended to distinguish from the well-studied lower LVEF groups and not to imply normal structure and function.

In 2013, the ACCF/AHA guidelines[4] classified HF based on LVEF as HFrEF when LVEF ≤ 40%, HFpEF when LVEF ≥ 50%, HFpEF borderline when LVEF is 41 to 49%, and HFpEF improved when LVEF > 40% in patients who previously had HFrEF.

In 2016, the European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic heart failure[5] reclassified patients with HF with LVEF 40 - 49%, from HFpEF described in 2012 guidelines[6] to HF with mid-range ejection fraction (HFmrEF). The proposed rationale to categorize patients based on LVEF was the difference in the prevalence of underlying etiologies, demographics, co-morbidities, and response to therapies[7] such as angiotensin converting enzyme inhibitors (ACEI), ARB, mineralocorticoid receptor antagonists (MRA) and beta blockers based on LVEF. The ESC guidelines also state that, "identifying *HFmrEF as a separate group will stimulate research into the underlying characteristics, pathophysiology and treatment of this group of patients. Patients with HFmrEF most probably have primarily mild systolic dysfunction, but with features of diastolic dysfunction*."

[3] Pfeffer MA, Shah AM, Borlaug BA. Heart Failure With Preserved Ejection Fraction In Perspective. Circ Res. 2019;124(11):1598-1617. doi:10 1161/CIRCRESAHA.119.313572.

[4] 2013 ACCF/AHA Guideline for the Management of Heart Failure

[5] Piotr Ponikowski, Adriaan A Voors, Stefan D Anker, Héctor Bueno, John G F Cleland, Andrew J S Coats, Volkmar Falk, José Ramón González-Juanatey, Veli-Pekka Harjola, Ewa A Jankowska, Mariell Jessup, Cecilia Linde, Petros Nihoyannopoulos, John T Parissis, Burkert Pieske, Jillian P Riley, Giuseppe M C Rosano, Luis M Ruilope, Frank Ruschitzka, Frans H Rutten, Peter van der Meer, ESC Scientific Document Group, 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC, European Heart Journal, Volume 37, Issue 27, 14 July 2016, Pages 2129–2200

[6] McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A; ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012 Jul;33(14):1787-847. doi: 10 1093/eurheartj/ehs104. Epub 2012 May 19. Erratum in: Eur Heart J. 2013 Jan;34(2):158.

[7] Butler J, Fonarow GC, Zile MR, Lam CS, Roessig L, Schelbert EB, Shah SJ, Ahmed A, Bonow RO, Cleland JGF, Cody RJ, Chioncel O, Collins SP, Dunnmon P, Filippatos G, Lefkowitz MP, Marti CN, McMurray JJ, Misselwitz F, Nodari S, O'Connor C, Pfeffer MA, Pieske B, Pitt B, Rosano G, Sabbah HN, Senni M, Solomon SD, Stockbridge N, Teerlink JR, Georgiopoulou VV, Gheorghiade M. Developing therapies for heart failure with preserved ejection fraction: current state and future directions. JACC Heart Fail 2014;2:97–112.

In this sNDA, the Applicant defines HFpEF as HF with LVEF ≥ 45%. When HFpEF is defined as LVEF ≥ 45%, it includes a heterogenous population of HF patients, those with mildly reduced/abnormal LVEF and normal LVEF.

Pitfalls of Classification of Heart Failure based on Left Ventricular Ejection Fraction

First, the foundation of HF classification based on LVEF as described above is shaky. Second, the most common modality used to measure LVEF, two-dimensional (2-D) echocardiography, can have up to 5-10% inter and intra-observer and temporal variability in assessment of LVEF depending on the technique(s) used.[8] Hence, there can be a significant overlap between patients with LVEF < 40% and ≥ 45%. Third, LVEF can change over time depending on loading conditions. Fourth, patients with normal LVEF may still have abnormal systolic function as measured by global longitudinal strain or mid wall fractional shortening and ejection fraction.[9,10] Hence, a normal LVEF is not synonymous with normal left ventricular (LV) systolic function.

Heart Failure with Preserved Ejection Fraction

The origin of clinical entity "HFpEF" is vague[11] and continues to evolve. HF trials have defined HFpEF as HF with LVEF ≥ 40% or ≥ 45% or ≥ 50%.[12]

The pathophysiologic mechanisms described in HFpEF such as diastolic dysfunction, longitudinal left ventricular systolic dysfunction (despite a normal LVEF), pulmonary hypertension, abnormal exercise-induced vasodilation, abnormal ventricular-arterial and ventriculoatrial coupling, chronotropic incompetence, and extracardiac volume overload are also observed, to varying degrees, in HFrEF.[13] The pathologic activation of renin-angiotensin-aldosterone axis, natriuretic peptides, and the sympathetic nervous system have been described in both HFpEF and HFrEF.[14]

Despite these similarities, distinct ventricular structural and cellular perturbations have been described in HFpEF and HFrEF. For example, left ventricular chamber dilation is the main characteristic in HFrEF whereas ventricular chamber size is normal or near normal with increased wall thickness in HFpEF.[15] Tromp et al describe that the biological pathways unique to HFpEF are related more to inflammation, neutrophil degranulation, and integrin signaling,

[8] Thavendiranathan P, Grant AD, Negishi T, Plana JC, Popović ZB, Marwick TH. Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes: application to patients undergoing cancer chemotherapy. J Am Coll Cardiol. 2013 Jan 8;61(1):77-84. doi: 10.1016/j.jacc.2012.09.035. Epub 2012 Nov 28.
[9] Yu CM, Lin H, Yang H, Kong SL, Zhang Q, Lee SW. Progression of systolic abnormalities in patients with "isolated" diastolic heart failure and diastolic dysfunction. Circulation 2002;105:1195–1201.
[10] Borlaug BA, Lam CS, Roger VL, Rodeheffer RJ, Redfield MM. Contractility and ventricular systolic stiffening in hypertensive heart disease insights into the pathogenesis of heart failure with preserved ejection fraction. J Am Coll Cardiol. 2009 Jul 28;54(5):410-8.
[11] Borlaug BA, Paulus WJ. Heart failure with preserved ejection fraction: pathophysiology, diagnosis, and treatment. *Eur Heart J*. 2011;32(6):670-679.
[12] Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol. 2007 Aug 21;50(8):768-77.
[13] Oktay AA, Rich JD, Shah SJ. The emerging epidemic of heart failure with preserved ejection fraction. Curr Heart Fail Rep. 2013;10:401-410.
[14] Borlaug BA, Redfield MM. Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. Circulation. 2011 May 10;123(18):2006-13; discussion 2014.
[15] Borlaug BA, Redfield MM. Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. Circulation. 2011 May 10;123(18):2006-13; discussion 2014.

whereas in HFrEF are associated with increased metabolism and cellular hypertrophy indicative of distinct mechanism(s) for HFpEF and HFrEF.[16]

Table 4 displays the clinical characteristics of patients with HF by LVEF. HF patients with higher LVEF compared to lower LVEF are older, have a higher prevalence of females and hypertension, a lower prevalence of myocardial infraction, experience a worse functional status, have a similar or slightly lower rate of total HHF and a lower rate of CV death.

Table 4. Clinical Characteristics of Patients with Heart Failure by LVEF

Characteristic	HFrEF (n=15135)	HFmrEF (n=4078)	HFpEF (n=9911)
LVEF	<40%	40-50%	≥51%
Mean (median) age (years)	64 (64)	69 (70)	72 (72)
Female (%)	22	37	57
Medical History (%)			
Hypertension	66	79	89
Myocardial Infarction	42	41	22
Atrial Fibrillation	35	39	39
Diabetes	31	35	36
NYHA class I/II, III/IV (%)	73, 27	60, 40	55, 45
Mean LVEF (%)	29	47	61
Mean systolic BP (mmHg)	122	132	133
Median NT pro BNP (pg/ml)	1420	997	602
Rate of First Hospitalization for Heart Failure (per 100 patient years)	6.9	6.6	5.6
Rate of Total Hospitalization for Heart Failure (per 100 patient years)	10.8	11.0	9.6
Rate of Cardiovascular Death (per 100 patient years)	7.2	4.9	3.1

HFrEF: Heart failure with reduced ejection fraction, HFmrEF: heart failure with mid-range ejection fraction, HFpEF: heart failure with preserved ejection fraction, NYHA: New York Heart Association, LVEF: left ventricular ejection fraction, BP: blood pressure, NT pro BNP: N-terminal pro-brain natriuretic peptide

The rates of hospitalization for heart failure and cardiovascular death are derived by the Applicant from combining the following trials: ATMOSPHERE[17], PARADIGM-HF, CHARM-Preserved, IPreserve, PARAGON-HF, TOPCAT-Americas

Source: Applicant Material for Cardiovascular and Renal Drugs Advisory Committee

[16] Tromp J, Westenbrink BD, Ouwerkerk W, van Veldhuisen DJ, Samani NJ, Ponikowski P, Metra M, Anker SD, Cleland JG, Dickstein K, Filippatos G, van der Harst P, Lang CC, Ng LL, Zannad F, Zwinderman AH, Hillege HL, van der Meer P, Voors AA. Identifying Pathophysiological Mechanisms in Heart Failure With Reduced Versus Preserved Ejection Fraction. J Am Coll Cardiol. 2018;72:1081-1090.
[17] Kristensen SL, Mogensen UM, Tarnesby G, Gimpelewicz CR, Ali MA, Shao Q, Chiang Y, Jhund PS, Abraham WT, Dickstein K, McMurray JJV, Køber L. Aliskiren alone or in combination with enalapril vs. enalapril among patients with chronic heart failure with and without diabetes: a subgroup analysis from the ATMOSPHERE trial. Eur J Heart Fail. 2018 Jan;20(1):136-147.

HFpEF trials for therapies used to treat HFrEF such as ACEI, ARB and MRA did not succeed on the predefined primary efficacy endpoints (Table 5). However, exposure adjusted rate of total HHF was lower in the ACEI/ARB/MRA arms compared to placebo and would have been statistically significant if total HHF was the pre-specified primary endpoint. These data indicate that ACEI/ARB/MRA have some efficacy in patients with HF with LVEF >40-45% classified as HFpEF.

Table 5. Results of Outcome Trials in Heart Failure with Preserved Ejection Fraction

Trial Drug Class	N	Inclusion, Baseline LVEF	Treatment arms Follow-up Duration	Primary Efficacy Endpoint	Primary Endpoint Results, Intervention vs. Comparator	Total number of HHF/Number of patients (%), intervention vs comparator
CHARM-Preserved, 2003[18] ARB	3023	> 40%, mean: 54%	Candesartan 32 mg vs. Placebo Median: 36.6 months	Time to CV death or HHF	22% vs. 24%, covariate adjusted HR 0.86, CI 0.74-1.0, p=0.05	26.5% vs. 37.5%, p=0.014
PEP-CHF, 2006[19] ACEI	852	> 40%, median: 65%	Perindopril 4 mg vs. Placebo Mean: 26.2 months	Time to all-cause mortality or HHF	Annual incidence of 13.2% vs 12.2%, HR 0.92, CI 0.70-1.21, p=0.545	8.0% vs. 12.4% during the first year of follow-up (HR 0.63; CI 0.41–0.97; p=0.033)
I-PRESERVE, 2008[20] ARB	4563	≥ 45%, mean: 60%	Irbesartan 300 mg vs. Placebo Mean: 49.5 months	Time to all-cause mortality or CV hospitalization	100.4 and 105.4 per 1000 patient-years, HR 0.95, CI 0.86 to 1.05, p=0.35	Not reported
TOPCAT, 2014[21] MRA	3445	≥ 45%, median: 56%	Spironolactone 15 to 45 mg vs. Placebo Mean: 3.3 years	Time to CV death or aborted cardiac arrest or HHF	18.6% vs 20.4%, HR 0.89, CI 0.77-1.04, p=0.14	6.8 vs. 8.3 per 100 person-years; p=0.03

LVEF: left ventricular ejection fraction, vs.: versus, ARB: angiotensin receptor blocker, ACEI: angiotensin converting enzyme inhibitor, MRA: mineralocorticoid receptor antagonist, CV: cardiovascular, HHF: hospitalization for heart failure, HR: hazard ratio, CI: 95% confidence interval, p: p-value, SBP: systolic blood pressure, DBP: diastolic blood pressure

Source: Reviewer's compilation

[18] Yusuf S, Pfeffer MA, Swedberg K, et al for the CHARM Investigators and Committees (2003) Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved trial. Lancet; 362:777-781.
[19] Cleland GF, Tendera M, Adamus J (2006) The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J; 27:2338-45.
[20] Massie BM, Carson PE, McMurray JJ, et al for the I-PRESERVE Investigators (2008) Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med; 359:2456-67.
[21] Pitt B, Pfeffer MA, Assmann SF, et al for the TOPCAT Investigators (2014) Spironolactone for Heart Failure with Preserved Ejection Fraction. N Engl J Med; 370:1383-92.

The efficacy of β-blockers (BB) in HFpEF remains unresolved.[22] Observational data from OPTIMIZE-HF registry[23] compared outcomes in patients with HFpEF (N=21,149) and HFrEF (N=20,118) hospitalized for HF and demonstrated no significant relationship between discharge use of a BB or an ACEI/ARB and 60- to 90-day mortality and rehospitalization rates in patients with HFpEF. Whereas, in patients with HFrEF, use of a BB or an ACEI/ARB was associated with a lower risk for 60- to 90-day mortality and rehospitalization. These findings are limited by a short follow-up duration and observational data.

The failure of HFpEF trials has been attributed to distinct systemic and myocardial signaling in HFpEF and to diversity of HFpEF phenotypes. Hence, a different approach of phenotyping HFpEF patients into pathophysiologically homogenous groups has been proposed.[24,25] Patients with HFpEF are predominantly elderly females and have multiple comorbidities such as overweight/obesity (84%),[26] arterial hypertension (60%–80%),[27] type 2 diabetes mellitus (20%–45%), renal insufficiency, and sleep apnea. Rare etiologies of HFpEF such as constrictive pericarditis, valvular heart disease, high-output failure, or infiltrative cardiomyopathies are generally excluded in HFpEF clinical trials.

It is theorized that systemic inflammation and/or release of proinflammatory mediators by epicardial tissue may cause microcirculatory dysfunction and myocardial fibrosis of the adjacent tissue, thus impairing left ventricular distensibility, increasing diastolic stiffness and LV filling pressure.[28] Other myocardial structural and chemical perturbations observed in HFpEF include reduced nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) because of altered paracrine communication between inflamed microvascular endothelial cells and cardiomyocytes, and left ventricular hypertrophy. This is distinct from HFrEF where cardiac remodeling is primarily driven by cardiomyocyte injury and death due to ischemia, infection, or toxicity.[29]

The proposed HFpEF predisposition phenotypes include a) overweight/obese/metabolic syndrome/type 2 diabetes mellitus, b) arterial hypertension, c) renal dysfunction and d) coronary artery disease; and clinical presentation phenotypes include a) lung congestion, b) chronotropic incompetence, c) pulmonary hypertension, d) skeletal muscle weakness and e) atrial fibrillation.[8] Compared to non-obese HFpEF patients, obesity-related HFpEF patients display greater biventricular remodeling, volume overload, more right ventricular dysfunction, greater ventricular interaction and pericardial restraint, worse exercise capacity, more profound hemodynamic derangements, and impaired pulmonary vasodilation.[30] Usually there is some

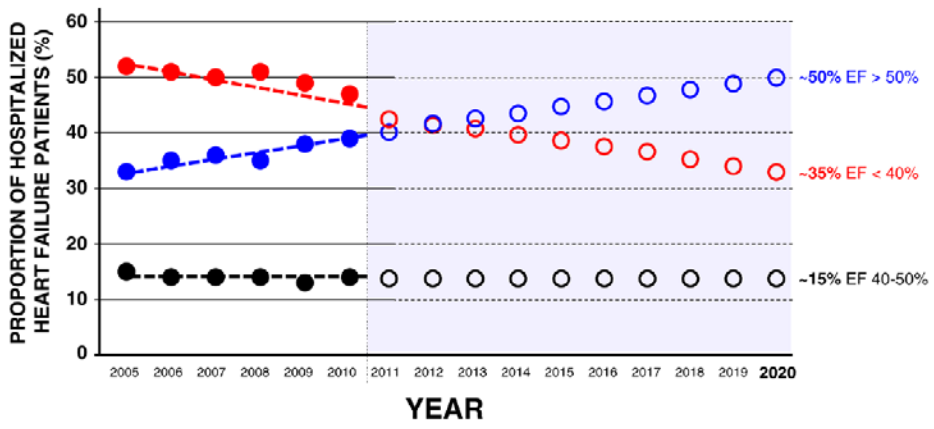
[22] Borlaug BA, Redfield MM. Diastolic and systolic heart failure are distinct phenotypes within the heart failure spectrum. Circulation. 2011 May 10;123(18):2006-13; discussion 2014.
[23] Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, O'Connor CM, Sun JL, Yancy CW, Young JB. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol. 2007; *50*:768–777.
[24] Reddy YN, Borlaug BA. Heart failure with preserved ejection fraction. Curr Probl Cardiol. 2016;41:145–188.
[25] Shah SJ, Kitzman DW, Borlaug BA, van Heerebeek L, Zile MR, Kass DA, Paulus WJ. Phenotype-specific treatment of heart failure with preserved ejection fraction: a multiorgan roadmap. Circulation. 2016;134:73–90.
[26] Haass M, Kitzman DW, Anand IS, Miller A, Zile MR, Massie BM, Carson PE. Body mass index and adverse cardiovascular outcomes in heart failure patients with preserved ejection fraction: results from the Irbesartan in Heart Failure with Preserved Ejection Fraction (I-PRESERVE) trial.Circ Heart Fail. 2011; 4:324–331.
[27] Dhingra A, Garg A, Kaur S, Chopra S, Batra JS, Pandey A, Chaanine AH, Agarwal SK. Epidemiology of heart failure with preserved ejection fraction.Curr Heart Fail Rep. 2014; 11:354–365.
[28] Mohammed SF, Hussain S, Mirzoyev SA, Edwards WD, Maleszewski JJ, Redfield MM. Coronary microvascular rarefaction and myocardial fibrosis in heart failure with preserved ejection fraction. Circulation 2015;131:550–559.
[29] González A, Ravassa S, Beaumont J, López B, Díez J. New targets to treat the structural remodeling of the myocardium. J Am Coll Cardiol. 2011;58:1833–1843.
[30] Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence Supporting the Existence of a Distinct Obese Phenotype of Heart Failure With Preserved Ejection Fraction. Circulation. 2017;136(1):6-19.

degree of overlap between the proposed predisposition and clinical phenotypes. There have been no prospective intervention trials categorizing treatment based on a phenotypic definition of HFpEF.

Burden of Heart Failure

HF is a chronic condition associated with premature mortality and significant morbidity, largely due to high rates of HHF.[31] It afflicts 1 to 3% of the population worldwide, with higher prevalence in the elderly, ≥10% in those age ≥65 years. The annual incidence of HF in the United States (US) is > 650,000 and continues to rise with the aging population. Approximately half of the total HF cases are attributed to HFpEF[32] and the incidence of HFpEF is increasing.[33,34] Figure 1 displays the proportion of hospitalized patients with HF by LVEF by time. In 2007 Fonarow et al[35] reported that the rate of mortality and re-admission during 60- to 90-day post discharge for patients with HFpEF and HFrEF were similar i.e., 9.5% vs. 9.8% and 29.2% vs. 29.9%, respectively.

Figure 1. Proportion of Hospitalized Patients with Heart Failure by LVEF Categories by Time



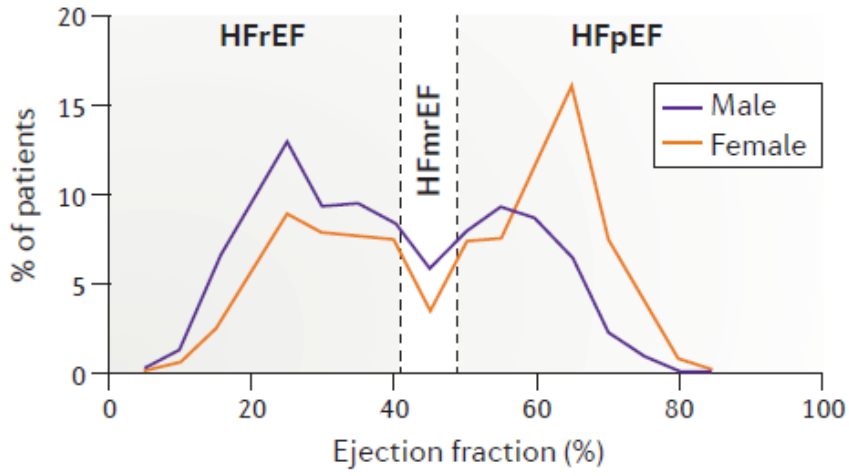
The Changing Landscape of Heart Failure: The Projected Trajectory of HFpEF in Hospitalized Heart Failure Patients. Based on results from Get With the Guidelines-Heart Failure (GWTG-HF) Study (Steinberg et al. [11••]; N=110,621), using actual data on the proportion of hospitalization patients with three types of HF (HFpEF [EF>50 %]; HFrEF [EF<40 %]; and HF borderline-EF [EF 40–50 %]) at each time point between 2005–2010. The trajectories for 2011–2020 were estimated for HFpEF and HFrEF using linear regression analyses, while HF borderline-EF was held at a constant 14 % proportion of hospitalized HF patients. The regression equation for the projected HFpEF trajectory= −0.86(Year)+1771 (*P*=0.015 for the trend of decreasing HFrEF over time); the equation for the projected HFrEF trajectory= 1.086(Year)-2144 (*P*=0.008 for the trend of increasing HFpEF over time).

Source: Oktay AA, Rich JD, Shah SJ. The emerging epidemic of heart failure with preserved ejection fraction. Curr Heart Fail Rep. 2013;10(4):401-410.

[31] Dunlay, S., Roger, V. & Redfield, M. Epidemiology of heart failure with preserved ejection fraction. *Nat Rev Cardiol* **14,** 591–602 (2017).
[32] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013 Oct 15;62(16):e147-239.
[33] Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP, et al. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. Circulation. 2012;126:65–75.
[34] Oktay AA, Rich JD, Shah SJ. The emerging epidemic of heart failure with preserved ejection fraction. Curr Heart Fail Rep. 2013;10:401-410.
[35] Fonarow GC, Stough WG, Abraham WT, Albert NM, Gheorghiade M, Greenberg BH, et al. Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalized for heart failure: a report from the OPTIMIZE-HF Registry. J Am Coll Cardiol. 2007 Aug 21;50(8):768-77.

Based on epidemiologic data, Dunlay et al (2017) state that i) after adjusting for age and other risk factors, the risk of HFpEF is fairly similar in men and women; however, the risk of HFrEF is much lower in women than men, and that ii) the majority of deaths in patients with HFpEF are CV, but the proportion of non-CV deaths is higher in HFpEF than HFrEF. Figure 2 displays the unadjusted incidence rate of HF by LVEF by sex (Dunlay et al 2017).

Figure 2. Incidence of Heart Failure By LVEF in Males and Females (Dunlay et al 2017)



Distribution of left ventricular ejection fraction (LVEF) in incident heart failure. The distribution of ejection fraction in 1,223 patients with incident heart failure (defined by Framingham criteria) from Olmsted County, Minnesota, USA, according to sex.

HFrEF, heart failure with reduced ejection fraction, HFmrEF: heart failure with mid-range ejection fraction, HFpEF: heart failure with preserved ejection fraction.

Source: Dunlay, S., Roger, V. & Redfield, M. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol 14, 591–602 (2017).

HFpEF Treatment Recommendations

Currently, there is no FDA approved pharmacotherapy to treat patients with HFpEF.

The 2017 ACC/AHA recommendations[36] to treat patients with HFpEF include the following:

- Class I recommendation to treat hypertension
- Class I recommendation to use of diuretics for symptomatic relief
- Class IIa recommendation for coronary revascularization for concomitant symptomatic (or evidence of significant myocardial ischemia) coronary artery disease; and guideline directed management of atrial fibrillation
- Class IIb recommendation to use MRA in appropriately selected patients with HFpEF with LVEF ≥45%, elevated brain natriuretic peptide (BNP) levels or HF admission within 1 year, estimated glomerular filtration rate (eGFR) >30 mL/min, creatinine <2.5 mg/dL, potassium <5.0 mEq/L, based on the findings from the Treatment of Preserved Cardiac Function Heart Failure trial (TOPCAT).[4]

[36] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017;136:e137–e161.

- Class IIb recommendation to use angiotensin receptor blockers (ARBs) to decrease hospitalizations for patients with HFpEF.

Conclusion
HFpEF is a heterogenous disease that is not well-defined. Nevertheless, it represents a serious condition with significant unmet need.

3.2. Approach to the Review

This is a joint clinical and statistical review. Charu Gandotra and Jennifer Clark focused on the data supporting efficacy, and Claire Ji focused on the data supporting safety. There were no relevant nonclinical or clinical pharmacology data for review.

Table 6 summarizes the controlled clinical studies pertinent to the proposed indication (except phase 1 and clinical pharmacology studies). This review focused on Study D2301 (PARAGON-HF) to evaluate efficacy and safety of Entresto in the intended population. Findings from phase 3 Study D2302 (PARALLAX-HF) and phase 2 Study B2214 (PARAMOUNT) were briefly reviewed as supportive data (see Appendices).

Data from studies in patients with HFrEF i.e.; phase 3 Study B2314 (PARADIGM-HF), phase 3 open-label extension Study B2317 (PARADIGM-OLE), and phase 4 Studies BUS01, B2401, B3301, BUS13, BUS14, BCA02 are referenced as needed and were not reviewed in detail.

Study B2314 (PARADIGM-HF) has been previously evaluated by FDA and led to the initial approval of Entresto for treatment of patients with HFrEF. Findings from PARADIGM-HF are also referenced as needed.

Clinical pharmacology studies B2115 and B2132, and population pharmacokinetic modeling reports are not reviewed here because these data do not add any new information and are not being used to inform labeling changes.

Table 6. Completed Clinical Trials Submitted with Supplement 18 of New Drug Application 207620 in the Intended Population of Heart Failure with Preserved Ejection Fraction

Trial Identifier	Trial Population	Trial Design	Treatment, Number Treated Duration
B2214 PARAMOUNT	Patients with HF with LVEF ≥ 45%	A 36-week, randomized, double-blind, multi-center, parallel group, active controlled study to evaluate the efficacy, safety and tolerability of LCZ696 compared to valsartan in patients with chronic heart failure and preserved left ventricular ejection fraction Control Type: Active (valsartan) Randomization: 1:1 Blinding: Double-blind Biomarkers: NT-proBNP	Drug: Entresto 200 mg BID Number treated: 149 Duration: 252.0 days
D2302 PARALLAX-HF	Patients with HF with LVEF > 40% with NYHA class II-IV	A 24-week, randomized, double-blind, multi-center, parallel group, active controlled study to evaluate the effect of LCZ696 on NT-proBNP, exercise capacity, symptoms and safety compared to individualized medical management of comorbidities in patients with heart failure and preserved ejection fraction Control Type: Active (valsartan or enalapril) or placebo Randomization: 1:1 Blinding: Double-blind Biomarkers: NT-proBNP	Drug: Entresto 200 mg BID Number treated: 1286 Duration: 23 weeks
D2301 PARAGON-HF	Patients with HF with LVEF ≥ 45% with NYHA class II-IV	A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to valsartan, on morbidity and mortality in heart failure patients (NYHA Class II-IV) with preserved ejection fraction Control Type: Active (valsartan) Randomization: 1:1 Blinding: Double-blind Biomarkers: NT-proBNP	Drug: Entresto 200 mg BID Number treated: 2419 Duration: 35 months

Abbreviations: HF: heart failure, LVEF: left ventricular ejection fraction, NYHA: New York Heart Association, NT-proBNP: N-terminal pro-brain natriuretic peptide, BID: twice daily.

Source: Reviewer's compilation

4. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

The population pharmacokinetic (PK) model was updated to include data in HFpEF patients. No labeling changes to clinical pharmacology section have been proposed with this sNDA.

5. Evidence of Benefit (Assessment of Efficacy)

5.1. Assessment of Dose and Potential Effectiveness

A single dose regimen of Entresto 200 mg BID was evaluated in the pivotal phase 3 trial D2301 and in the supporting studies D2302 and B2214. Hence, a dose-response assessment is not applicable.

5.2. Design of Clinical Trials Intended to Demonstrate Benefit to Patients

5.2.1. Trial # CLCZ696D2301 (PARAGON-HF)

Title: A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to valsartan, on morbidity and mortality in heart failure patients (NYHA Class II-IV) with preserved ejection fraction

Study: July 18, 2014 (first subject first visit) to June 7, 2019 (last subject last visit)

Phase: 3

Objectives and Endpoints:

Primary objective and endpoint: The primary objective was to compare Entresto to valsartan in reducing the rate of the composite endpoint of cardiovascular (CV) death and total (first and recurrent) HHF, in patients with HFpEF (NYHA Class II-IV) (LVEF ≥ 45%). The primary endpoint was the rate of the composite endpoint of total (first and recurrent) HHF and CV death. Instead of the more traditional time-to-first-event analysis, this primary endpoint accounted for recurrent hospitalizations considered to represent the true burden of HF.

The Applicant's rationale for the recurrent event primary endpoint was that patients with HFpEF have a higher rate of HHF and a lower rate of CV death compared to patients with HFrEF.[37,38,39] The frequency of repeated HHF increases after the first HHF and is an indicator of disease progression. Investigator-reported trial endpoints of HHF and CV death were adjudicated.

[37] Characteristics, treatments, and outcomes of patients with preserved systolic function hospitalizes for heart failure: A report from the OPTIMIZE-HF registry. J Am Coll Cardiol; 50:768-7.
[38] Differences between patients with a preserved and a depressed left ventricular function: a report from the EuroHeart Failure Survey. Eur Heart J; 25(14):1214-20.
[39] Mortality associated with heart failure with preserved vs. reduced ejection fraction in a prospective international multi-ethnic cohort study. Eur Heart J; 39(20):1770-780

Secondary objectives and endpoints were as follows:

1) To compare Entresto to valsartan on changes in the clinical summary score for HF symptoms and physical limitations, as assessed by change in Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score (CSS). The KCCQ CSS includes the total symptom score (TSS) based on HF symptoms and the physical limitation score (PLS).
2) To compare Entresto to valsartan in improving NYHA functional classification assessed by change in NYHA functional classification from baseline to Month 8.
3) To compare Entresto to valsartan in delaying the time to first occurrence of a composite renal endpoint, defined as: renal death, or reaching end stage renal disease (ESRD), or ≥ 50% decline in estimated glomerular filtration rate (eGFR) relative to baseline (whichever occurs first).
4) To compare Entresto to valsartan in delaying the time to all-cause mortality.

One of the **pre-specified exploratory endpoints** was a composite of total worsening HF events (total HHF and urgent heart failure visits) and CV death.
A **pre-specified sensitivity analysis** of the primary composite endpoint of total HHF and CV death using investigator-reported events was conducted.

In addition, FDA recommended a retrospective blinded, independent re-adjudication of investigator-reported HHF events that had been eliminated in the initial adjudication process. The rationale for the recommended re-adjudication was to recategorize negatively adjudicated events where there was some probability of a true HHF event. Possibly, some true HHF events may have been negatively adjudicated primarily due to a lack of documentation of data elements needed to meet the adjudication criteria for HHF. The re-adjudication committee members were allowed to use clinical judgment to assign probabilities of HHF to these negatively adjudicated investigator-reported HHF events. These probabilities were used to obtain an average probability for each event. A multiple imputation approach was used to integrate the re-adjudicated events in the primary endpoint analysis.

Hence, a post-hoc analysis of the primary composite endpoint of total HHF and CV death using combined adjudicated and re-adjudicated events was conducted.

Study Design: Study CLCZ696D2301 (PARAGON-HF) was a phase 3, randomized, double-blind, active-controlled trial designed to evaluate the efficacy and safety of Entresto versus valsartan in patients with symptomatic heart failure (NYHA class II-IV) with left ventricular ejection fraction (LVEF) ≥ 45%. All eligible patients were randomized via Interactive Response Technology (IRT) to either Entresto 200 mg bid (+valsartan placebo) (dose level 3) or valsartan 160 mg bid (+ Entresto placebo) (dose level 3) in a ratio of 1:1 at Visit 199/201.

Patients were instructed to take the study drug at approximately 8:00 AM and 7:00 PM, with or without food.

Dose selection rationale: Per Applicant, the 200 mg bid dose of Entresto was chosen because it was similar to the approved regimen to treat patients with HFrEF and based on biomarker and modeling data was expected to reach approximately 90% of its maximal neprilysin (NEP) inhibition. Twice daily dosing schedule was considered necessary for sustained NEP inhibition over a 24-hour and was anticipated to reduce the incidence of hypotension in HF patients,

particularly in the elderly. Valsartan was selected as an active comparator in this trial because current management of HFpEF allows use of ACEI or ARB to treat comorbidities in this patient population. Approximately 85% of the patients in TOPCAT[40] were on an ACEI or ARB at baseline. Valsartan being a component of Entresto, using valsartan as the comparator will allow demonstration of incremental benefit of Entresto versus valsartan. Note that the valsartan component of Entresto is more bioavailable than the valsartan in Diovan and other marketed tablet formulations, i.e., 26 mg, 51 mg, and 103 mg of valsartan in Entresto provides similar valsartan exposure as 40, 80 and 160 mg of valsartan in Diovan and other marketed tablet formulations, respectively.

PARAGON-HF trial had three phases—screening, treatment-run-in, and randomized.

Screening (2 weeks): During the screening patient eligibility was determined. LVEF measurements were obtained locally from echocardiograms performed within 6 months of Visit 1. If no echocardiogram was available, then echocardiogram was performed during the screening visit. A patient considered to be a screen failure could be re-screened up to two times with a minimum of 2 weeks between re-screenings. Screening NT-proBNP, potassium, eGFR, and liver function tests were assessed at the central laboratory.

Treatment Run-in (3-8 weeks): Patients who met the eligibility and safety monitoring criteria (Table 7) received single-blind treatment with valsartan 80 mg twice a day for 1 to 2 weeks followed by Entresto 100 mg twice a day for 2 to 4 weeks. If patients had been on ACEI or ARB at doses lower than the specified minimum pre-study doses, then they were started on valsartan 40 mg twice a day for 1-2 weeks, titrated up to 80 mg twice a day. The run-in was used to determine tolerance to half the target doses of the study drugs. Half the target doses were selected because only a small incremental effect on blood pressure was expected when dose is increased from 100 to 200 mg of Entresto twice daily and in PARADIGM-HF, majority of the patients who tolerated 100 mg twice daily dose of Entresto were able to tolerate 200 mg twice daily dose.

Either local or central laboratory could be used for the assessment of potassium and eGFR at the end of treatment run-in visit. Patients who were not able to tolerate study drug at the doses prescribed during the treatment run-in or developed angioedema were discontinued and were not eligible to be re-screened. The concomitant use of open-label ACEI, ARB or renin inhibitor in addition to study drug during the treatment run-in was strictly prohibited. Background medications could be adjusted if the study drug was not tolerated to ensure trial eligibility.

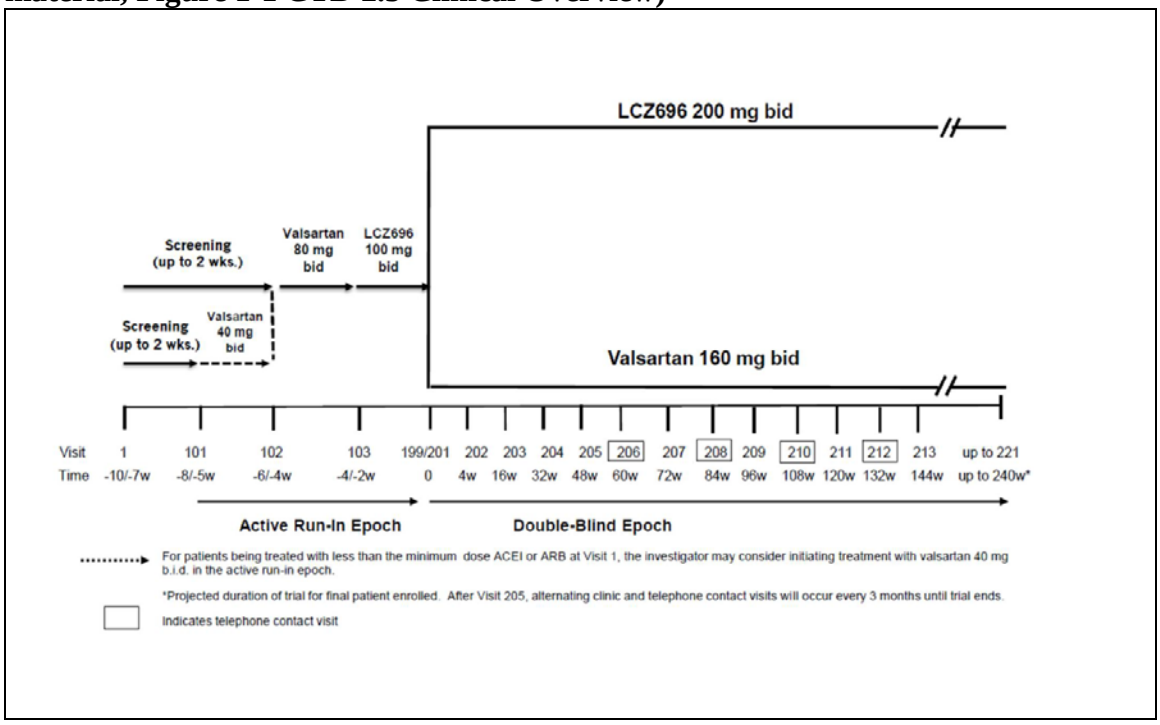
Randomized Treatment : Patients who demonstrated tolerance to the study drugs during the treatment run-in were randomized in 1:1 ratio to 200 mg twice daily dose of Entresto or 160 mg twice daily dose of valsartan. This was a double-dummy design trial. Patients who were randomized to Entresto active also received valsartan placebo and vice versa. For intolerance to study medication, the investigator could consider adjusting background medications prior to down-titrating study medication, as appropriate. Study drug dose level adjustments were to be based on overall safety and tolerability with special focus on a) hyperkalemia, b) symptomatic hypotension, and c) clinically significant decrease in eGFR/increase in serum creatinine. The three dose levels were 200, 100, or 50 mg of Entresto or 160, 80, or 40 mg of valsartan twice a

[40] Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM; TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med. 2014 Apr 10;370(15):1383-92.

day. Patients had to be followed until at least 1847 primary composite events occurred or at least 26 months after the last patient was randomized, whichever occurred last.

Figure 3 displays the study design of PARAGON-HF.

Figure 3. Study Design CLCZ696D2301 (PARAGON-HF) (Source: Sponsor material, Figure 1-1 CTD 2.5 Clinical Overview)



Source: Sponsor material CLCZ696D2301 Clinical Study Report Figure 9-1

Table 7. Safety monitoring criteria to be met at Visit 1 (screening), Visit 103 and Visit 199/201, PARAGON-HF

Parameter	Visit 1 (screening)	Visits 103 (treatment run-in) and Visit 199/201 (end of treatment run-in/randomization)
Potassium level	K ≤5.2 mmol/L (mEq/L)	K ≤5.4 mmol/L (mEq/L)
Kidney function	eGFR ≥30 mL/min/1.73m^2	eGFR ≥25 mL/min/1.73m^2 eGFR reduction <35% compared to Visit 1
Blood pressure	SBP ≥110 mmHg	No symptomatic hypotension as determined by the investigator and SBP ≥100 mmHg.
AEs or conditions	No conditions that preclude continuation according to the investigator's judgment	No postural symptoms or any AEs that preclude continuation according to the investigator's judgment

Source: Sponsor material CLCZ696D2301 Clinical Study Report Table 9-2

Study Population:

Key inclusion criteria are listed below:

- Male and female patients ≥ 50 years of age
- LVEF ≥ 45% within 6 months prior to screening
- Evidence of structural heart disease such as left atrial enlargement or left ventricular hypertrophy
- HF symptoms – NYHA functional class II-IV
- Requiring diuretic therapy for at least 30 days prior to screening
- NT-proBNP > 200 pg/mL if the patient had been hospitalized for HF within the past 9 months or > 300 pg/mL without a recent HHF. For patients with atrial fibrillation, NT-proBNP > 600 pg/mL if the patient had been hospitalized for HF within the past 9 months or > 900 pg/mL without a recent HHF.
- Patients with atrial fibrillation captured on electrocardiogram (ECG) on Visit 1 were limited to one third of the total study population

All patients were required to have a qualifying echocardiogram (echo) for study entry defined as either a locally obtained echocardiogram performed within 6 months prior to Visit 1 or based on a qualifying echocardiogram performed during the screening Period. For patients enrolled in India, all ejection fractions were required be performed using 2D volumetric methods. For a subset of approximately 1200 patients at selected centers, the qualifying echocardiograms were sent to a core laboratory for assessment.

The rationale for using LVEF cut-off of 45% was to exclude patients who had borderline heart failure with reduced ejection fraction (HFrEF). Patients had to be on an optimal medical regimen of diuretics and background medications to treat co-morbidities such as hypertension (HTN), diabetes mellitus (DM), atrial fibrillation (AF) and coronary artery disease (CAD).

Key exclusion criteria are listed below:

- Any prior LVEF measurement of < 40%
- Alternative diagnosis that could account for patient's symptoms such as severe pulmonary disease, hemoglobin < 10 g/dl or BMI > 40 kg/m^2
- Current acute decompensated heart failure
- Systolic blood pressure (SBP) < 110 or ≥ 180 mm Hg
- Symptomatic hypotension
- SBP > 150 and < 180 mm Hg unless receiving three antihypertensive medications at screening
- Acute coronary syndrome (including MI, cardiac surgery, other major CV surgery), or urgent percutaneous coronary intervention (PCI) within the 3 months prior to Visit 1 or an elective PCI within 30 days prior to Visit 1
- Any clinical event within the 6 months prior to Visit 1 that could have reduced the LVEF (e.g., MI, coronary artery bypass graft [CABG]), unless an echo measurement was performed after the event confirming the LVEF to be ≥ 45%
- Known history of angioedema
- Patients with one of the following:

  - eGFR < 30 mL/min/1.73m2 as calculated by the Modification in Diet in Renal Disease (MDRD) formula at Visit 1, or
  - eGFR < 25 mL/min/1.73m2 at Visit 103 or Visit 199/201, or
  - eGFR reduction > 35% (compared to Visit 1) at Visit 103 or Visit 199/201
- Patients with either of the following:
  - serum potassium > 5.2 mmol/L (mEq/L) at Visit 1
  - serum potassium > 5.4 mmol/L (mEq/L) at Visit 103 or Visit 199/201
- Patients with history of any dilated cardiomyopathy, including peripartum cardiomyopathy, chemotherapy induced cardiomyopathy, or viral myocarditis
- Evidence of right sided HF in the absence of left-sided structural heart disease
- Known pericardial constriction, genetic hypertrophic cardiomyopathy, or infiltrative cardiomyopathy
- Clinically significant congenital heart disease that could be the cause of the patient's symptoms and signs of HF
- Presence of hemodynamically significant valvular heart disease in the opinion of the investigator
- Stroke, transient ischemic attack, carotid surgery or carotid angioplasty within the 3 months prior to Visit 1
- Coronary or carotid artery disease or valvular heart disease likely to require surgical or percutaneous intervention during the trial
- Life-threatening or uncontrolled dysrhythmia, including symptomatic or sustained ventricular tachycardia and atrial fibrillation or flutter with a resting ventricular rate >110 beats per minute (bpm)
- Patients with a cardiac resynchronization therapy (CRT) device
- Evidence of hepatic disease as determined by any one of the following: SGOT (AST) or SGPT (ALT) values exceeding 3x the upper limit of normal (ULN), bilirubin >1.5 mg/dl at Visit 1

Study Drug Dose Adjustment, Interruption or Discontinuation

Study drug dose could be adjusted or interrupted for patients unable to tolerate protocol-specified randomized dosing scheme, despite adjustment of concomitant medications. A patient could continue to receive the lower dose or be off the study treatment for a recommended of 1 to 4 weeks prior to being re-challenged with the next higher dose. Other reasons for temporary or permanent study drug discontinuation included open-label use of AEI, ARB or renin inhibitor; or pregnancy or lactation . Open-label ACEIs, ARBs or a renin inhibitor could be used during the study only if the patient had study treatment discontinued, temporarily or permanently. Study treatment was permanently discontinued for withdrawal of informed consent, suspected angioedema, investigator decision for patient safety, severe suspected drug-related AE, protocol deviation resulting in serious risk to patient safety, or after emergency unblinding.

Concomitant Cardiovascular Medications

Caution was recommended when co-administering Entresto with atorvastatin or other statins (e.g. simvastatin, pravastatin) that are substrates of OATP1B1 and OATP1B3 because of the potential to raise plasma statin levels.

Study Completion

Trial was completed when target number of composite events had accrued.

Treatment Compliance

Patients were asked to return the unused study medication at follow-up visits. The returned tablets were counted, and percentage of study medication tablets consumed relative to the number of tablets that were expected to be consumed were entered in the patient's electronic case report form (eCRF).

NT-proBNP

NT-proBNP was analyzed for all patients that provided a sample at the pre-valsartan run-in visit (Visit 1, 101/102), (N= 2774 patients). Sampling occurred prior to study drug administration at five visits: baseline (pre-valsartan run in visit V101/V102); pre-Entresto run-in (V103), randomization (V199/V201), Week 16 (V203) and Week 48 (V205). The central lab performed all biomarker analyses in complete patient sets by laboratory personnel blinded to treatment allocation and clinical outcomes.

Data Monitoring Committee

An independent external data monitoring committee (DMC) monitored the study conduct, reviewed the results of the interim analyses for efficacy and safety on a regular basis, and determined the safety of continuing the study according to the protocol.

Adjudication

Investigator reported events, which could potentially fulfill criteria for primary, secondary, or other clinical endpoints were assessed by the Clinical Endpoint Committee (CEC) for adjudication. The CEC was accountable for review and adjudication of the following events:

- All deaths
- Total heart failure hospitalizations
- Urgent HF visits
- Myocardial infarctions and all hospitalizations for myocardial ischemia (Note: hospitalizations for myocardial ischemia were not endpoints in this study, but were adjudicated for possible myocardial infarctions)
- Stroke/Transient ischemic attack (TIA) (Note: TIA was not an endpoint in this study but was adjudicated for possible strokes)
- End stage renal disease
- New onset atrial fibrillation/atrial flutter (NOAF)

- New onset diabetes mellitus (NODM)
- Angioedema or angioedema-like event

Protocol Amendments

There were 4 amendments to the study protocol # CLCZ696D2301 dated June 10, 2014; May 6, 2015; December 4, 2015; and December 9, 2015. Key changes that may impact assessment of efficacy are listed below:

Protocol Version 03 dated December 4, 2015:

There were 1508 patients randomized into the trial at the time of this amendment.

- Sample size was increased from 4300 to 4600 to increase statistical power from 81 to 85% to detect a 25% reduction in recurrent HHF.
- The target number of primary events was increased to 1847.
- Statistical stopping rules for superiority of Entresto over valsartan were modified from one-sided p-value of <0.0001 for the primary endpoint to one sided p-value of <0.001 for both the primary endpoint and CV death at the interim efficacy analysis.

Statistical Analysis Plan

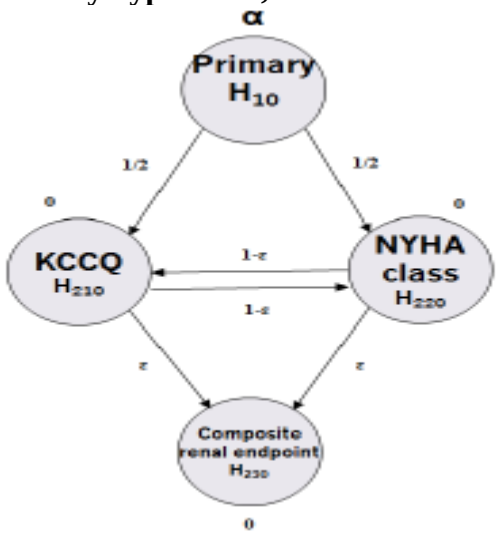
The pre-specified analysis for the primary composite endpoint of CV death or HHF was a semi-parametric proportional rates model, stratified by region and with treatment as a fixed-effect. This recurrent event analysis yields an estimated rate ratio (RR) with a corresponding 95% confidence interval and one-sided and two-sided p-values. Different analysis methods were specified for components of the composite to better accommodate for the type of endpoint event. In order to account for the competing risk of CV death, the HHF component was analyzed using a joint gamma frailty model adjusted for region. An estimated RR and 95% confidence interval from this model were used in the results section. The CV death component was analyzed using a Cox regression model stratified by region. A hazard ratio (HR) and corresponding 95% confidence interval were estimated from the model.

The same methods were used for the investigator reported primary composite endpoint events. These were also used with the expanded composite endpoint, with the same gamma frailty model used to analyze the urgent HF visits component.

A Bonferroni multiplicity adjustment with an alpha of 0.001 (one-sided) was used to adjust for the planned interim analysis.

A sequentially rejective multiple test procedure with a graphical illustration of weights for alpha relocation was specified for testing the hypotheses of the primary and secondary endpoints (Figure 4). The null hypothesis for the primary endpoint was tested at full alpha first, so a rejection of this hypothesis would stop the testing procedure. A 1-sided null hypothesis of no or worsening treatment effect was pre-specified against an alternative of a favorable treatment effect. A 1-sided alpha level of 0.024, which is adjusted for the interim analysis, was pre-specified to control for type 1 error.

Figure 4. Weights for alpha relocation in the sequentially rejective multiple test procedure for the secondary hypotheses, PARAGON-HF



Source: Figure 9-2 of the Statistical Analysis Plan dated 12-Jun-2019

This pre-specified alpha allocation plan for PARAGON-HF was considered acceptable.
A post-hoc re-adjudication analysis was run at the request of FDA that incorporated investigator reported events which were originally negatively adjudicated. These events were re-adjudicated with an assigned probability of being a HF event. The probability of being an event was used with a multiple imputation when incorporating the events into the post-hoc recurrent events analysis as described earlier for the primary composite and HHF endpoints. The multiple imputation analysis used 1,000 imputed datasets to incorporate re-adjudicated events with the assigned event probabilities.

5.3. Results of Analyses of Clinical Trials/Studies Intended to Demonstrate Benefit to Patients

5.3.1. Trial # CLCZ696D2301 (PARAGON-HF)

Patient Disposition

First patient first visit was on July 18, 2014 and last patient last visit occurred on June 7, 2019 with 4822 patients randomized at 755 sites in 43 countries. The trial recruitment and follow-up s were 2.6 and 2.2 years, respectively. A total of 1903 CEC- confirmed primary composite endpoints (target primary endpoint events: 1847) were observed. April 30, 2019 was the cut-off date for all efficacy endpoints. For safety analysis, all available data were included, regardless of date of onset of the AE.
A total of 10,359 patients were screened; 5747 patients met the eligibility criteria and were enrolled; 5746 patients entered the valsartan run-in; 5204 patients entered the Entresto run-in; and 4822 patients who completed the run-ins were randomized – 2419 to Entresto and 2403 to valsartan. During the run-in, the median duration of exposure to valsartan was 14 days

(interquartile range 12 to 21 days), while the median duration of exposure to sacubitril/valsartan was 19 days (interquartile range 14 to 23 days). Failure rate for Entresto and valsartan run-in was 7.4 and 9.4 %, respectively. Hypotension, renal impairment, and hyperkalemia were the most common reasons for treatment discontinuation and were fairly balanced between the Entresto and valsartan run-ins. The number of patients discontinued from the randomized treatment was balanced between the two treatment arms. There were 26 patients (12 Entresto, 14 valsartan) that were not included in the full analysis set (FAS) due to Good Clinical Practice (GCP) violations. 2055 (84.4%) and 2030 (85%) patients completed the randomized treatment in Entresto and valsartan arm, respectively. Table 8 summarizes patient disposition.

Table 8. Patient Screening, Randomization and Disposition, PARAGON-HF

	Entresto	Valsartan	Total
Screened	.	.	10359
Screen Failure	.	.	4606
Run-in Failure	.	.	925
Not Assigned	.	.	6
Randomized	2419	2403	4822
GCP issues	12 (0.5%)	14 (0.6%)	26
Full Analysis Set	2407	2389	4796
Completed	2055 (85.4%)	2030 (85%)	4085
Died	347 (14.4%)	355 (14.9%)	702
Discontinued	5 (0.2%)	4 (0.2%)	9
Completion is defined as completing through April 30, 2019			

Source Data: adsl, adeff

Baseline Demographic and Clinical Characteristics

Randomized Patients versus Patients with Run-in Failure: The baseline demographic and clinical characteristics of patients in the randomized set versus run-in failure were generally similar except the median eGFR was 62 and 56 mL/min/1.73 m^2 in patients in the randomized set versus run-in failure, respectively, and patients in the run-in failure group tended to have a lower mean screening SBP than in the randomized set (134 vs. 137 mmHg).

Full Analysis Set (FAS): The trial population comprised of white (81% with 13% Asian; 2% Black, 1% Native American) males (48%) and females (52%) with a mean age of 73 years (range, 50 to 98 years) and mean body mass index of 30 kg/m^2 (range: 15 to 47 kg/m^2). Majority of patients were NYHA class II (72%) with a baseline median ejection fraction of 57%, median NT-proBNP level of 911 pg/mL (IQR, 464–1613 pg/mL), median blood pressure of 130/75 mm Hg, and median eGFR of 60 mL/min/m^2. Main etiology of HF was non-ischemic (64% with 36% ischemic), 48% patients had a prior HHF, 96% had a history of hypertension, 43% had diabetes mellitus, and 53% had a history of atrial fibrillation. Baseline demographic and clinical characteristics were generally similar between the two treatment groups. Table 9 summarizes the baseline demographic and clinical characteristics of the PARAGON-HF trial population.

Table 9. Baseline Demographic and Clinical Characteristics, PARAGON-HF

Characteristic	Category	Entresto	Valsartan
		N=2407	N=2389
Age 65	Below 65	412 (17.1%)	413 (17.3%)
	At least 65	1995 (82.9%)	1976 (82.7%)
Sex	Male	1166 (48.4%)	1151 (48.2%)
	Female	1241 (51.6%)	1238 (51.8%)
Race	White	1963 (81.6%)	1944 (81.4%)
	Black	52 (2.2%)	50 (2.1%)
	Asian	297 (12.3%)	310 (13.0%)
	Am. Indian Or Alaska Native	28 (1.2%)	23 (1.0%)
	Pacific Islander	0 (0.0%)	1 (0.0%)
	Other	67 (2.8%)	61 (2.6%)
Ethnicity	Hispanic or Latino	241 (10.0%)	224 (9.4%)
	Not Hispanic or Latino	2007 (83.4%)	2004 (83.9%)
	Not Reported	98 (4.1%)	109 (4.6%)
	Unknown	61 (2.5%)	52 (2.2%)
Region	N. America	288 (12.0%)	271 (11.3%)
	W. Europe	699 (29.0%)	691 (28.9%)
	C. Europe	856 (35.6%)	859 (36.0%)
	L. America	191 (7.9%)	179 (7.5%)
	Asia or Other	373 (15.5%)	389 (16.3%)
LVEF Category	Below 60%	1351 (56.1%)	1375 (57.6%)
	At least 60%	1056 (43.9%)	1014 (42.4%)
Diabetes	No	1358 (56.4%)	1369 (57.3%)
	Yes	1049 (43.6%)	1020 (42.7%)
Hypertension	No	103 (4.3%)	109 (4.6%)
	Yes	2304 (95.7%)	2280 (95.4%)
NYHA Class	Missing	90 (3.7%)	87 (3.6%)
	1	70 (2.9%)	64 (2.7%)
	2	1792 (74.4%)	1776 (74.3%)
	3	447 (18.6%)	453 (19.0%)
	4	8 (0.3%)	9 (0.4%)
Age	N	2407	2389
	Mean (SD)	72.7 (8.3)	72.8 (8.5)
	Median (Min, Max)	74.0 (50.0, 98.0)	74.0 (50.0, 96.0)
LVEF	N	2407	2389
	Mean (SD)	57.6 (7.8)	57.5 (8.0)
	Median (Min, Max)	57.0 (30.0, 89.0)	57.0 (45.0, 89.0)
NT proBNP (pg/ml)	N	2388	2369

Characteristic	Category	Entresto	Valsartan
		N=2407	N=2389
	Mean (SD)	1288 (1350)	1316 (1700)
	Median (Min, Max)	904 (13, 19240)	915 (13, 31522)
BMI	N	2406	2388
	Mean (SD)	30.2 (4.9)	30.3 (5.1)
	Median (Min, Max)	29.8 (15.7, 45.5)	29.9 (15.0, 46.7)
SBP	N	2407	2388
	Mean (SD)	130.5 (15.6)	130.6 (15.3)
	Median (Min, Max)	130.0 (100.0, 200.0)	130.0 (92.0, 185.0)
DBP	N	2407	2388
	Mean (SD)	74.3 (10.6)	74.3 (10.4)
	Median (Min, Max)	75.0 (36.0, 113.0)	75.0 (43.0, 117.0)

LVEF: Left ventricular ejection fraction, NYHA: New York Heart Association, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure

Source Data: adsleff, adslsub, advs, adsl

Treatment Exposure

The overall mean follow-up in the trial was 35 months. During the randomized treatment 32.5 and 34.5% of patients in Entresto and valsartan group, respectively permanently discontinued treatment prematurely mostly due to AEs. During the randomized treatment 26% of patients in both treatment arms temporarily interrupted treatment mostly due to AEs. Mean compliance while patients were taking study medication was approximately 96% and was comparable in both treatment arms. A total of 53% of patients in each arm had a dose reduction or temporarily interrupted study treatment. Approximately half of the patients remained on the target dose throughout the study (200 mg bid sacubitril/valsartan or 160 mg bid valsartan). A similar percentage of patients were on the target dose (200 mg bid) of Entresto (60%) or the target dose (160 mg bid) of valsartan (61%) at the last available record. The mean duration of study treatment exposure (including temporary interruptions) was 31 months in Entresto and valsartan arms. The mean duration of study treatment exposure (excluding temporary interruptions) was 31 months in Entresto arm and 30 months in valsartan arm. During the randomized, the mean daily dose per patient of Entresto and valsartan was 363 (±74) and 296 (±51) mg, respectively.

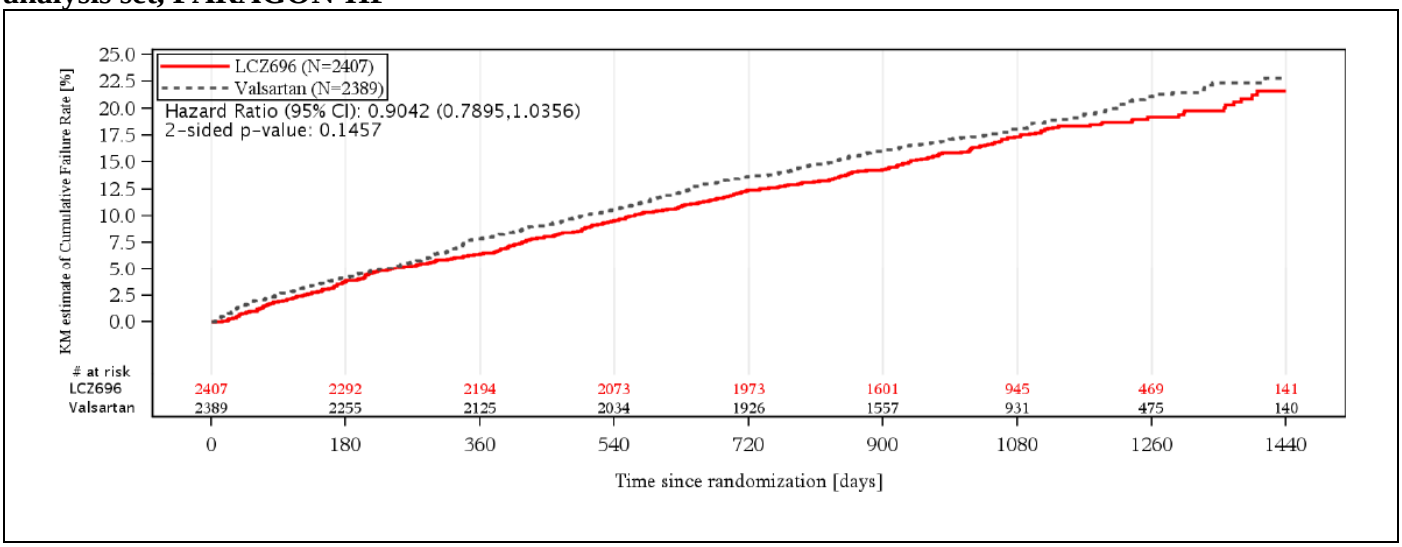
Primary Efficacy Results

PARAGON-HF trial (CLCZ696D2301) randomized 4,822 adult patients with symptomatic heart failure with LVEF ≥45% to Entresto versus valsartan. A total of 1903 primary composite endpoints, including 1487 heart failure hospitalizations (78.1%) and 416 CV deaths (21.9%) were experienced by 1083 patients in the full analysis set (FAS; N=4796). Entresto reduced the rate of composite endpoint of total (first and recurrent) HHF and CV death with a rate ratio (RR) of 0.87, 95% CI 0.75, 1.01, $p = 0.06$. There were 894 (12.8 per 100 patient-years) primary composite events (CEC-confirmed total heart failure hospitalizations and CV deaths) in the Entresto arm compared to 1009 (14.6 per 100 patient-years) in the valsartan arm, a difference of 115 events.

The effect of Entresto on the primary endpoint was driven primarily by the total HHF component. Overall, 690 (9.9 per 100 patient-years) total HHF events occurred in the Entresto arm compared to 797 (11.6 per 100 patient-years) in the valsartan arm, a difference of 107 events with a relative rate reduction of 15% (RR=0.85, 95% CI: 0.72, 1.0; 1-sided p=0.028; 2-sided p=0.06). There were 28 fewer patients in Entresto arm versus valsartan arm who experienced ≥ 1 HHF. Figure 5 displays the Kaplan-Meier plot of first CEC confirmed HHF in the full analysis set.

Note that an alpha of 0.001 (one-sided alpha) was spent for the comparison of primary endpoint at the interim analysis and the rest of alpha (one-sided 0.024) was designated to be utilized for the primary endpoint at the final analysis. There was no difference between treatment arms with regards to CV death risk (HR=0.95; 95% CI: 0.79, 1.16; 1-sided p=0.31; 2-sided p=0.62). But CV death trended in favor of Entresto.

Figure 5. Kaplan-Meier plot of first CEC confirmed hospitalization for heart failure Full analysis set, PARAGON-HF



Source: Clinical Study Report CLCZ696D2301 Sponsor Figure 14.2-1.4.3

Concomitant Medications: A total of 27% patients in the Entresto arm and 30% in the valsartan arm were taking an aldosterone antagonist. The use of all other background cardiovascular or heart failure therapies was similar across both arms.

Analysis of the Primary and Supportive Pre-Specified Efficacy Endpoints in PARAGON-HF

Clinical Event Distribution

Endpoint events for CV death, HHF, and urgent HF visits were conveyed as either investigator-reported, adjudicated, or both. Table 10 shows the distribution of the numbers of patients in each arm experiencing the composite endpoint of HHF and CV death. Most events were both adjudicated and investigator-reported, but there were more investigator-reported events. There

were a total of 2305 and 1903 investigator-reported and adjudicated events, respectively (data not shown). Results based on the investigator reported events were examined alongside the pre-specified adjudicated event endpoints to assess the consistency of results.

There are 2407 patients in the Entresto arm with an observed follow up of 6966 patient years; there are 2389 patients in the valsartan arm with an observed follow up of 6897 patient years.

Table 10. Event Endpoint distribution for Cardiovascular Death + Total Hospitalization for Heart Failure, PARAGON-HF

	Adjudicated		Investigator Reported	
N Events	Valsartan	Entresto	Valsartan	Entresto
0	1832 (76.68%)	1881 (78.15%)	1765 (73.88%)	1820 (75.61%)
1	337 (14.11%)	334 (13.88%)	336 (14.06%)	341 (14.17%)
2	126 (5.27%)	108 (4.49%)	150 (6.28%)	142 (5.90%)
3	45 (1.88%)	43 (1.79%)	69 (2.89%)	49 (2.04%)
4	16 (0.67%)	16 (0.66%)	28 (1.17%)	23 (0.96%)
5	14 (0.59%)	10 (0.42%)	15 (0.63%)	12 (0.50%)
6	9 (0.38%)	11 (0.46%)	12 (0.50%)	12 (0.50%)
7	2 (0.08%)	3 (0.12%)	5 (0.21%)	5 (0.21%)
8	3 (0.13%)	0 (0.00%)	4 (0.17%)	1 (0.04%)
9	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
10	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.04%)
11	2 (0.08%)	0 (0.00%)	2 (0.08%)	0 (0.00%)
13	0 (0.00%)	0 (0.00%)	1 (0.04%)	0 (0.00%)
14	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)
15	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.04%)
18	1 (0.04%)	0 (0.00%)	1 (0.04%)	0 (0.00%)
19	0 (0.00%)	0 (0.00%)	1 (0.04%)	0 (0.00%)

Source: Reviewer's analysis

Table 11 shows a breakdown of the events as adjudicated only, adjudicated and investigator reported, or negatively adjudicated (investigator reported only). Categories shown in the rows are based on the adjudicated events dataset. There were 30 events that were reported to a different category from which they were adjudicated, these events are classified as "Adjudicated Only" in Table 11. The four events that were adjudicated as urgent HF visits but reported as HHF were not included in some of the investigator reported endpoint analyses. Removing these four events did not make a substantive difference in the investigator reported results.

Events shown in the blue boxes are events that are included in the pre-specified primary composite endpoint. Events shown in the red boxes are included in the investigator reported primary composite endpoint. Events shown in the yellow boxes are included in the supportive expanded composite endpoint which adds in urgent HF visits. These events are also shown in Figure 6 where the different composites with their event components are broken out separately in side-by-side dot plots.

Figure 7 has similar results to Figure 6 but puts all the different endpoints on the same plot for easier comparison. The composite endpoints are shown in blue for adjudicated events, and red for investigator reported events. Event components which make up the composites are also shown in black for adjudicated events, and grey for investigator reported events. In general, the proportion of events when comparing Entresto to valsartan trends similarly for the events with rare events showing little to null trends favoring Entresto, and HHF showing the biggest difference between treatment arms.

Trends are similar between the adjudicated primary composite, the expanded composite, and the investigator reported composite endpoints. However, there are more events in the expanded composite as well as the investigator reported composite endpoint. Although the ratios of events are similar, and thereby the point estimates for a treatment effects would be similar, having more events in a statistical analysis does impact hypothesis testing results.

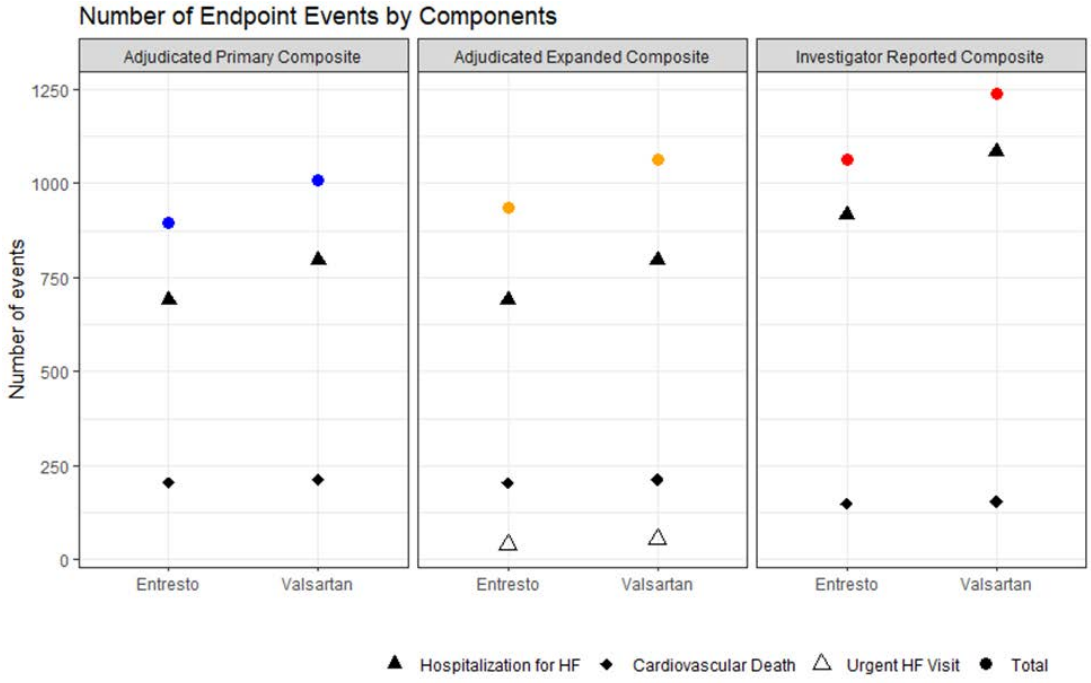
Table 11. Endpoint Event Categories by Adjudication Status, PARAGON-HF

		Adjudicated Only	Adj + Inv. Rep.*	Negative Adj.	Category Diff.
Sacubitril/valsartan	HHF	22 (2.35%)	668 (71.29%)	247 (26.36%)	8
	CVD	69 (31.80%)	135 (62.21%)	13 (5.99%)	.
	Urgent HF Visit	2 (1.53%)	38 (29.01%)	91 (69.47%)	1
Valsartan	HHF	28 (2.52%)	769 (69.15%)	315 (28.33%)	18
	CVD	73 (32.16%)	139 (61.23%)	15 (6.61%)	.
	Urgent HF Visit	7 (4.32%)	48 (29.63%)	107 (66.05%)	3

*30 Events which had different Adjudicated and Inv. Rep. categories were included as Adjudicated Only and not included in Inv. Rep. events

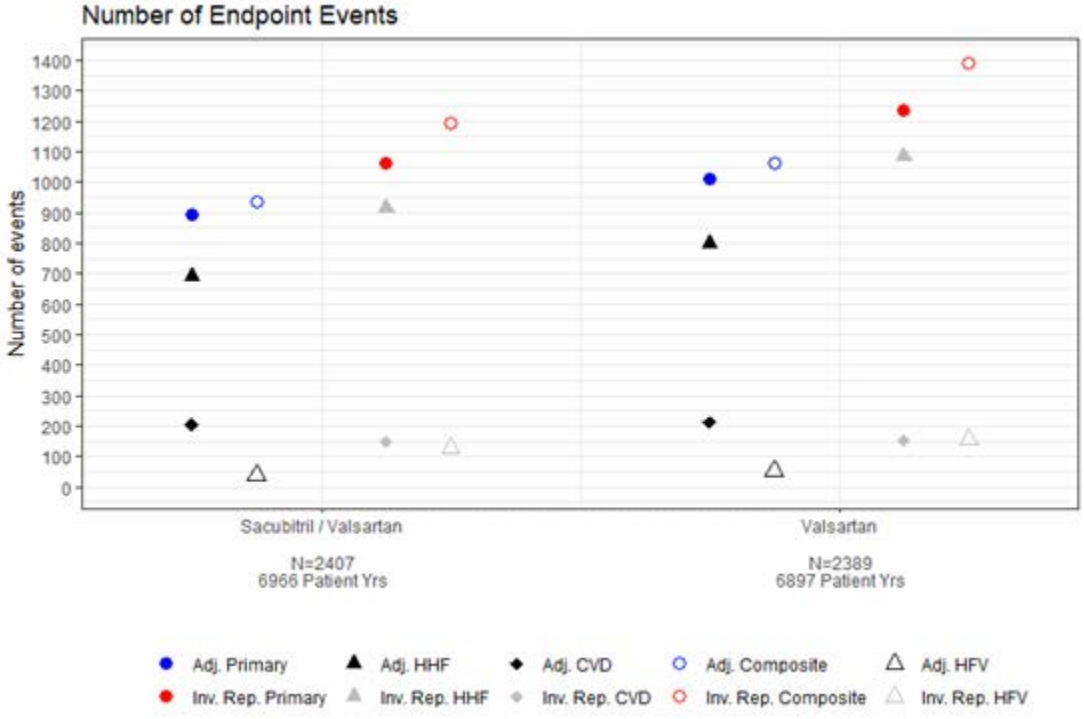
Source: Reviewer's analysis

Figure 6. Composite Endpoint Event Breakdowns, PARAGON-HF



Source: Reviewer's analysis

Figure 7. Endpoint Event Totals, PARAGON-HF



Source: Reviewer's analysis

Study Results

Table 12 shows study results for the adjudicated and investigator reported events in the primary composite, expanded composite, and individual components of the composites. It should be noted that results for different endpoints are based on different analysis methods as described in the statistical analysis plan. The time to CV death results are a hazard ratio (HR), all other endpoints use a type of recurrent events analysis with a rate ratio (RR) analysis result.

Table 12. Endpoint Results, PARAGON-HF

Endpoint	n Events		RR/HR (95% CI)	2-sided p-value
	Entresto (N=2407)	Valsartan (N=2389)		
Adjudicated Endpoints				
Primary Composite	894	1009	0.87 (0.75, 1.01)	0.059
Expanded Composite	934	1064	0.86 (0.75, 0.99)	0.040
HHF	690	797	0.85 (0.72, 1.00)	0.056
HF Events (HHF + Urgent HF Visits)	730	852	0.84 (0.71, 0.98)	0.031
CV Death	204	212	0.95 (0.79, 1.16)	0.624
Investigator Reported Endpoints				
Primary Composite	1064	1241	0.84 (0.74, 0.97)	0.014
Expanded Composite	1200	1414	0.83 (0.73, 0.95)	0.006
HHF	916	1087	0.82 (0.71, 0.96)	0.010
HF Events (HHF + Urgent HF Visits)	1053	1260	0.82 (0.72, 0.94)	0.005

Observed follow-up time, calculated in 100 patient years, was 69.66 for Entresto and 68.97 for valsartan

Source: Reviewer's analysis on adeff, cross reference Sponsor's results

Study results are in line with what we would expect based on the number of observed events for each arm. The 1-sided p-value of 0.029 for the adjudicated primary composite endpoint did not meet the pre-specified criteria of $p<0.024$. So, while the RR shows a trend in favor of Entresto, we fail to reject the null hypothesis of no or worsening treatment effect. Since the primary endpoint failed the hypothesis test, the testing hierarchy stops and no further hypotheses for secondary endpoints will be considered here.

Given the failed hypothesis test for the primary endpoint, establishing evidence of a strong consistency of a treatment effect through other means is needed. When further examining these endpoint events within the investigator reported data as well as separate components there is some consistency when looking at HF events, either as just HHF or HHF with urgent HF visits. Treatment benefit in the primary composite is due primarily to a reduction in these HF events. When looking only at the first events using a Cox proportional hazards model for the composite and HF event components, there does seem to be a trend showing some benefit favoring Entresto

(Table 13). Favorable trends for the composite for first and recurrent events are primarily due to outcomes seen in HF events. Although there are some differences seen when comparing results for the adjudicated and the investigator reported events, they are generally consistent with the investigator reported events showing slightly more beneficial trends.

Table 13. Endpoint Results for first events, PARAGON-HF

	Events/N		
	Entresto	**Valsartan**	**HR (95% CI)**
Adjudicated			
Primary Composite	526 / 2407	557 / 2389	0.92 (0.81, 1.03)
Expanded Composite	542 / 2407	585 / 2389	0.90 (0.80, 1.01)
CV Death	204 / 2407	212 / 2389	0.95 (0.79, 1.16)
HHF	405 / 2407	433 / 2389	0.90 (0.79, 1.04)
HHF or Urgent HF Visit	422 / 2407	462 / 2389	0.88 (0.77, 1.00)
Investigator Reported			
Primary Composite	587 / 2407	624 / 2389	0.91 (0.81, 1.02)
Expanded Composite	641 / 2407	692/ 2389	0.89 (0.80, 0.99)
HHF	515 / 2407	550 / 2389	0.90 (0.80, 1.02)
HHF or Visit	573 / 2407	620 / 2389	0.88 (0.79, 0.99)

Source: Reviewer's analysis on adeff and adttee, cross reference Sponsor's results

Post-hoc Re-adjudication Analysis Results

All 566 negatively adjudicated HHF events, including the four that were previously positively adjudicated as urgent HF visits, were sent for re-adjudication. The four (1 Entresto, 3 valsartan) events were not included in the FDA re-adjudication analysis. Differences in the analysis results were negligible when these events were excluded. The re-adjudication event probability distribution for the average event probability is shown in Table 14.

Table 14. Average Re-adjudicated HHF Event Probability Distribution, PARAGON-HF

Re-Adjudication Probability	Entresto	Valsartan	Total
1	11	6	17
0.92	12	17	29
0.83	17	19	36
0.75	20	13	33
0.67	9	33	42
0.58	23	23	46
0.50	22	23	45
0.42	17	17	34
0.33	18	22	40
0.25	15	32	47
0.17	21	29	50
0.08	22	26	48
0	40	55	95

Re-Adjudication Probability	Entresto	Valsartan	Total
Total	247	315	562

Source: Reviewer's analysis

One thousand imputations were used with the average re-adjudication probability associated with the 562 negatively adjudicated events. This added approximately 104 events to the Entresto arm, and 124 events to the valsartan arm. Results based on this re-adjudication analysis are shown in Table 15. Point estimates for the primary composite and HHF are the same, but because there are more events upon which to estimate the treatment effect, we see tighter confidence intervals around these estimates. Adding in these additional events does not seem to change the point estimates. The statistical implications from adding events are as we would expect, tighter confidence intervals which also directly links with a smaller p-value.

Table 15. Post-hoc Re-adjudication Analysis Results, PARAGON-HF

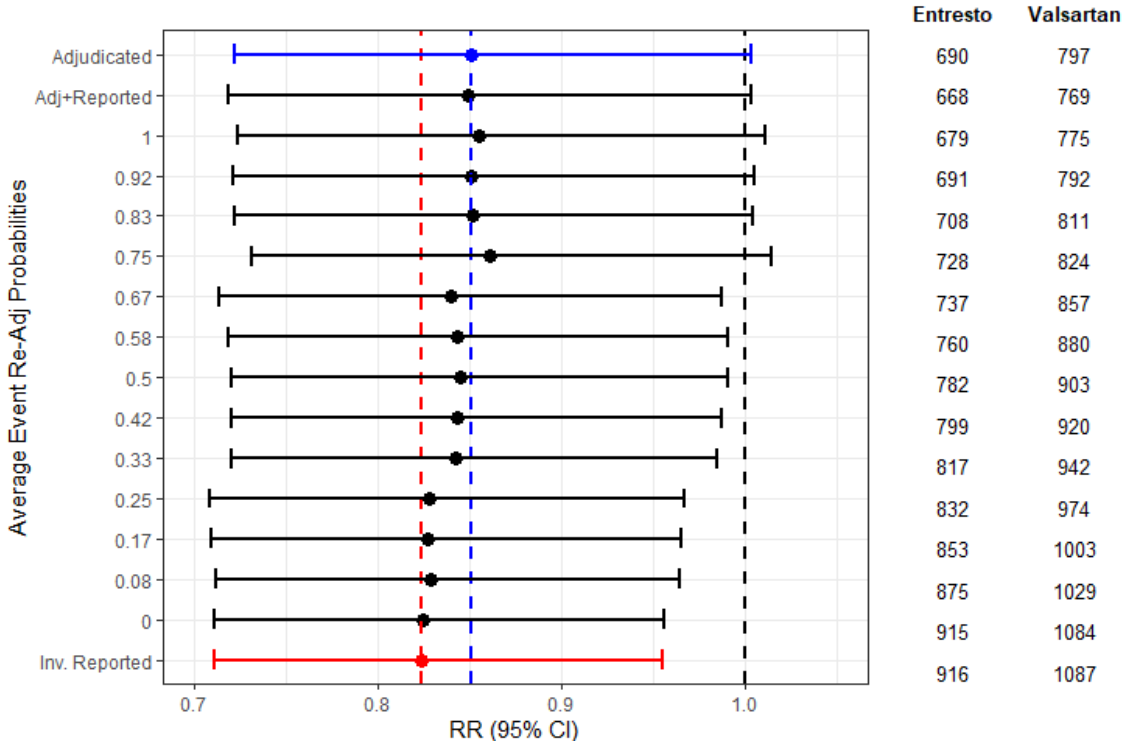
Endpoint	RR (95% CI)	2-sided p-value
Primary Composite	0.87 (0.75, 0.997)	0.0453
HHF	0.85 (0.72, 0.99)	0.0392

Source: Reviewer's analysis

The re-adjudication analysis can be viewed as a hybrid of the adjudicated events and the investigator reported events analysis results. The point estimates for the treatment effect line up with the results seen in the adjudicated events analysis showing consistency, and the additional events contribute to the tighter confidence bands around the point estimate.

The re-adjudicated event probabilities can further be used to connect the adjudicated and investigator reported events. Figure 8 shows analysis results for HHF using the adjudicated events data and adding in events based on re-adjudicated probabilities until all investigator reported events were added in. Considering the scale of the x-axis, results are largely consistent with point estimates ranging from 0.82 for the investigator reported RR, to 0.86. The lengths of the confidence intervals were relatively similar running from 0.25 to 0.29. A combination of adding in events along with ratios of additional events which favored Entresto helped to improve the RR slightly to what was seen in the investigator reported results.

Figure 8. Recurrent Events Analysis results for Adjudicated, Re-Adjudicated and Investigator reported events, PARAGON-HF



Source: Reviewer's analysis

In general, the post-hoc re-adjudication analysis results are supportive in showing consistency with the pre-specified adjudicated composite primary endpoint.

Discussion of the Statistical Results

In hypothesis testing, alpha is used to define the cut-off for the rejection region. After a study has closed and been analyzed, the only conclusions we can make regarding the hypothesis test is whether the statistical test rejects the pre-specified null hypothesis defined by the cut-off for the rejection region. The p-value is a summary measure of the evidence in the study centered around the null hypothesis. Based solely on the data from this study as summarized by the p-value, there is not enough evidence against the null to meet the pre-specified cut-off, so for the PARAGON-HF study we fail to reject the null hypothesis.

Failure to reject a null hypothesis should not be interpreted as evidence that Entresto does not have any effect. Rather, we interpret this as the study itself does not provide the level of evidence for a treatment effect that was laid out in the protocol using the pre-specified primary endpoint and analysis population. Weaker than anticipated evidence against the null hypothesis should be considered in whole with the rest of the study results.

Pre-specification of the study attributes and statistical testing criteria are essential when conducting a Phase 3 confirmatory study. We have a greater assurance of the credibility and strength of the study findings when protocols are implemented, and the completed data meet the pre-specified levels of evidence around which the study is designed to achieve. Failure to meet these levels does not completely nullify the study results, but it is impactful and should be

considered when assessing the strength of evidence that this study provides. Results based on endpoints and analyses which were not pre-specified with a necessary level of evidence for/against a hypothesis do provide some level of support, but they do not have the rigor to provide the strength of evidence that pre-specification provides.

***Reviewer's Comments**: Generally, even when the results of clinical trials are statistically significant, a comparison of the statistical significance should not be used to compare the magnitude of treatment effect because the magnitude of statistical significance is largely dependent on the number of patients studied or events observed. For example, a small trial of a highly effective therapy could have a statistically significant result that is smaller than a result from a large trial of a modestly effective treatment.[41] In PARAGON-HF the primary efficacy analysis was statistically not significant. Several post-hoc analyses that added events to both treatment arms resulted in a similar rate ratio, but the magnitude of statistical significance improved which reflects increase in number of events with similar treatment effect as the adjudicated ones and does not change the interpretation of magnitude of treatment effect observed with the primary efficacy analysis in PARAGON-HF.*

Subgroup Analyses

Prespecified subgroup analyses were conducted to explore consistency of treatment effect across 14 subgroups: age groups (<65, ≥65; <75, ≥75 years), sex, race (Caucasian, Black, Asian, Other), region, diabetes (yes/no), baseline LVEF (≤ median and > median), baseline atrial fibrillation on ECG (yes/no), baseline atrial fibrillation by history (yes/no), baseline NT-proBNP (≤ median and > median), baseline SBP (≤ median and > median), baseline aldosterone antagonist use (yes/no), ACEi intolerant (yes/no), baseline eGFR (<60 vs ≥60 mL/min/1.73 m^2), and baseline NYHA class (I/II vs III/IV).

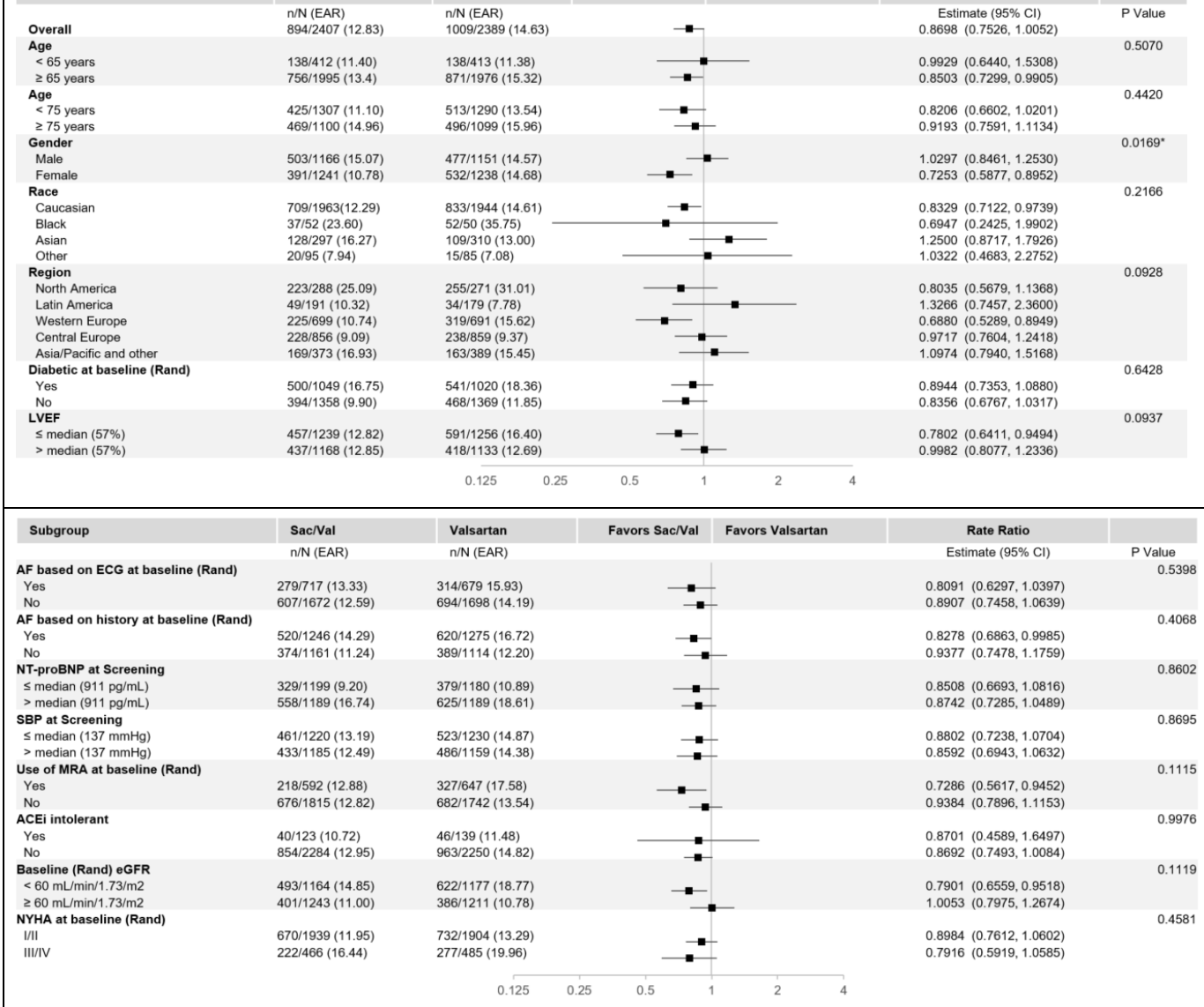
In univariate analysis, the treatment effect of Entresto was generally consistent across these subgroups except for a nominal significant interaction p value < 0.1 for LVEF, sex and region.

Table 16 shows the subgroup forest plot for the primary composite endpoint of CEC-confirmed total HHF and CV death.

[41] Faraone SV. Interpreting estimates of treatment effects: implications for managed care. *P T*. 2008;33(12):700-711.

Table 16. Subgroup forest plot of rate ratios (95% CIs) from LWYY for recurrent CEC confirmed primary composite endpoint (cardiovascular death and total hospitalizations for heart failure) (Full Analysis Set), PARAGON-HF

Subgroup	Sac/Val	Valsartan	Rate Ratio	
	n/N (EAR)	n/N (EAR)	Estimate (95% CI)	P Value
Overall	894/2407 (12.83)	1009/2389 (14.63)	0.8698 (0.7526, 1.0052)	
Age				0.5070
< 65 years	138/412 (11.40)	138/413 (11.38)	0.9929 (0.6440, 1.5308)	
≥ 65 years	756/1995 (13.4)	871/1976 (15.32)	0.8503 (0.7299, 0.9905)	
Age				0.4420
< 75 years	425/1307 (11.10)	513/1290 (13.54)	0.8206 (0.6602, 1.0201)	
≥ 75 years	469/1100 (14.96)	496/1099 (15.96)	0.9193 (0.7591, 1.1134)	
Gender				0.0169*
Male	503/1166 (15.07)	477/1151 (14.57)	1.0297 (0.8461, 1.2530)	
Female	391/1241 (10.78)	532/1238 (14.68)	0.7253 (0.5877, 0.8952)	
Race				0.2166
Caucasian	709/1963(12.29)	833/1944 (14.61)	0.8329 (0.7122, 0.9739)	
Black	37/52 (23.60)	52/50 (35.75)	0.6947 (0.2425, 1.9902)	
Asian	128/297 (16.27)	109/310 (13.00)	1.2500 (0.8717, 1.7926)	
Other	20/95 (7.94)	15/85 (7.08)	1.0322 (0.4683, 2.2752)	
Region				0.0928
North America	223/288 (25.09)	255/271 (31.01)	0.8035 (0.5679, 1.1368)	
Latin America	49/191 (10.32)	34/179 (7.78)	1.3266 (0.7457, 2.3600)	
Western Europe	225/699 (10.74)	319/691 (15.62)	0.6880 (0.5289, 0.8949)	
Central Europe	228/856 (9.09)	238/859 (9.37)	0.9717 (0.7604, 1.2418)	
Asia/Pacific and other	169/373 (16.93)	163/389 (15.45)	1.0974 (0.7940, 1.5168)	
Diabetic at baseline (Rand)				0.6428
Yes	500/1049 (16.75)	541/1020 (18.36)	0.8944 (0.7353, 1.0880)	
No	394/1358 (9.90)	468/1369 (11.85)	0.8356 (0.6767, 1.0317)	
LVEF				0.0937
≤ median (57%)	457/1239 (12.82)	591/1256 (16.40)	0.7802 (0.6411, 0.9494)	
> median (57%)	437/1168 (12.85)	418/1133 (12.69)	0.9982 (0.8077, 1.2336)	
AF based on ECG at baseline (Rand)				0.5398
Yes	279/717 (13.33)	314/679 15.93)	0.8091 (0.6297, 1.0397)	
No	607/1672 (12.59)	694/1698 (14.19)	0.8907 (0.7458, 1.0639)	
AF based on history at baseline (Rand)				0.4068
Yes	520/1246 (14.29)	620/1275 (16.72)	0.8278 (0.6863, 0.9985)	
No	374/1161 (11.24)	389/1114 (12.20)	0.9377 (0.7478, 1.1759)	
NT-proBNP at Screening				0.8602
≤ median (911 pg/mL)	329/1199 (9.20)	379/1180 (10.89)	0.8508 (0.6693, 1.0816)	
> median (911 pg/mL)	558/1189 (16.74)	625/1189 (18.61)	0.8742 (0.7285, 1.0489)	
SBP at Screening				0.8695
≤ median (137 mmHg)	461/1220 (13.19)	523/1230 (14.87)	0.8802 (0.7238, 1.0704)	
> median (137 mmHg)	433/1185 (12.49)	486/1159 (14.38)	0.8592 (0.6943, 1.0632)	
Use of MRA at baseline (Rand)				0.1115
Yes	218/592 (12.88)	327/647 (17.58)	0.7286 (0.5617, 0.9452)	
No	676/1815 (12.82)	682/1742 (13.54)	0.9384 (0.7896, 1.1153)	
ACEi intolerant				0.9976
Yes	40/123 (10.72)	46/139 (11.48)	0.8701 (0.4589, 1.6497)	
No	854/2284 (12.95)	963/2250 (14.82)	0.8692 (0.7493, 1.0084)	
Baseline (Rand) eGFR				0.1119
< 60 mL/min/1.73/m2	493/1164 (14.85)	622/1177 (18.77)	0.7901 (0.6559, 0.9518)	
≥ 60 mL/min/1.73/m2	401/1243 (11.00)	386/1211 (10.78)	1.0053 (0.7975, 1.2674)	
NYHA at baseline (Rand)				0.4581
I/II	670/1939 (11.95)	732/1904 (13.29)	0.8984 (0.7612, 1.0602)	
III/IV	222/466 (16.44)	277/485 (19.96)	0.7916 (0.5919, 1.0585)	



Within subgroup estimated treatment effect, 95% CI and subgroup-by-treatment interaction p-value are based on the proportional rate model (abbreviated as LWYY) with treatment, subgroup and subgroup-by-treatment fixed effect factors and stratified by region (the region stratification is waived for the region subgroup analysis). n: Total number of events; N: Total number of patients; T(100 patient years): total up-to-terminal-event/censoring duration summarized over patients in the respective treatment group; EAR (Exposure-adjusted rate per 100 patient years) = n/T. Events occurred in randomized treatment Period up to 30APR2019 are included in the analysis.

* indicates 2-sided nominal p-value<0.05.

Source: CLCZ696D2301 Study Report Figure 11-7

The LWYY analysis of CEC confirmed primary events (total HHF and CV death) indicate potential differential treatment effect by LVEF and sex.

In females, subgroup analyses indicated a stronger trend (27% reduction) in the RR of the composite endpoint of total HHF and CV death in favor of Entresto than in males (none to slightly worsening effect). This effect seems to be driven by a reduction in the RR of total HHF

(joint frailty analysis results of approximately 31%). In patients with LVEF ≤ 57%, subgroup analyses indicated a stronger trend (22% reduction) in the RR of the composite endpoint of total HHF and CV death in favor of Entresto than in patients with LVEF > 57% (none to slightly worsening effect). These findings suggest that Entresto has a greater treatment effect in females and in patients with LVEF at the lower end of the spectrum for HFpEF, i.e., LVEF ≤ 57% where there may be some overlap with patients with HFrEF.
Given this noticeable differential trend in treatment effect, we used descriptive statistics to further break down these subgroups into sub-subgroups to see if there was potential confounding between them (Table 17). The breakdown between sub-subgroups was fairly even with the biggest groups being males with LVEF below the median, and females with LVEF above the median. Females with LVEF below the median only made up 23% of the study population and had an event rate slightly lower, but close to their male counterparts. However, breaking down this event rate by treatment arms (Table 18) we see that lower LVEF females on valsartan had the highest event rate of all sub-subgroups and those on Entresto had the lowest.

Table 17. Breakdown of proportion of patients in subgroups by LVEF and Sex, PARAGON-HF

		LVEF ≤ 57	LVEF > 57	Total
Male	n (%)	1395 (29.09%)	922 (19.22%)	**2317 (48.31%)**
	events per 100 patient years	15.06 (597 / 3964)	14.47 (383 / 2647)	**14.82 (980 / 6612)**
Female	n (%)	1100 (22.94%)	1379 (28.75%)	**2479 (51.69%)**
	events per 100 patient years	14.08 (451 / 3204)	11.66 (472 / 4047)	**12.73 (923 / 7251)**
Total	n (%)	**2495 (52.02%)**	**2301 (47.98%)**	**4796**
	events per 100 patient years	**14.62 (1048 / 7168)**	**12.77 (855 / 6694)**	**13.73 (1903 / 13863)**

Source: Reviewer's analysis

Table 18. Subgroup results by Left Ventricular Ejection Fraction (LVEF) LVEF and Sex, PARAGON-HF

	N (events per 100 patient years)		
Subgroup	**Sacubitril/Valsartan**	**Valsartan**	**RR (95% CI)**
Male	1166 (15.06)	1151 (14.57)	1.03 (0.84, 1.25)
Female	1241 (10.78)	1238 (14.68)	0.73 (0.59, 0.90)
LVEF≤57	1239 (12.82)	1256 (16.40)	0.78 (0.64, 0.95)
LVEF>57	1168 (12.85)	1133 (12.69)	0.99 (0.80, 1.23)
Male, LVEF≤57	686 (15.03)	709 (15.09)	0.99 (0.77, 1.27)
Male, LVEF>57	480 (15.13)	442 (13.74)	1.11 (0.81, 1.54)
Female, LVEF≤57	553 (10.15)	547 (18.06)	0.57 (0.42, 0.76)
Female, LVEF>57	688 (11.28)	691 (12.04)	0.91 (0.69, 1.21)

LVEF: left ventricular ejection fraction
Source: Reviewer's analysis

Based on these general descriptive statistics, confounding does not seem to be an issue, and the sub-subgroup of females with LVEF below the median seem to be achieving the most benefit from the study treatment. Conversely, it is questionable as to whether males in any sub-subgroup

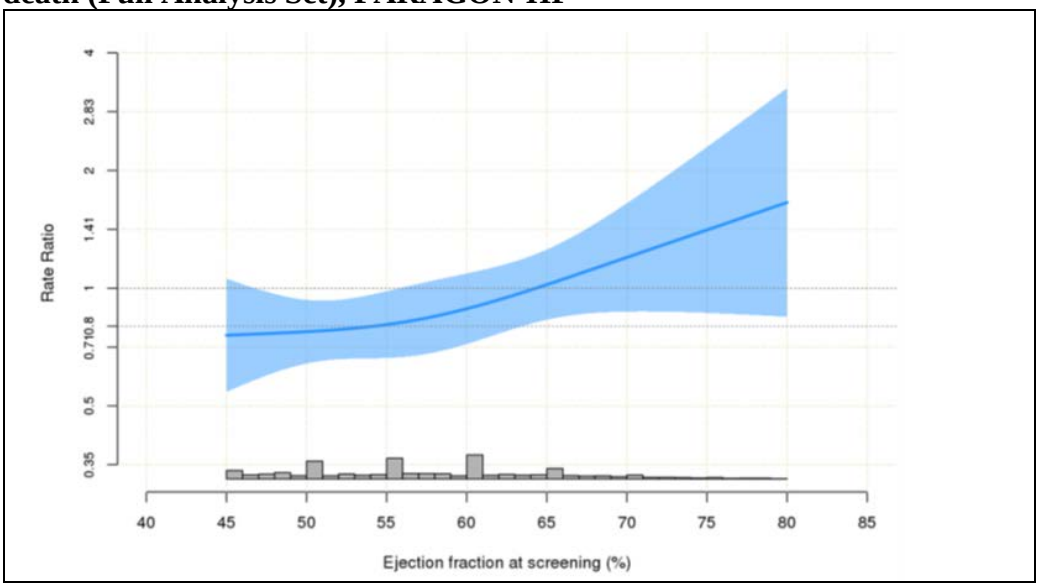
of this study population are gaining any benefit from treatment (Table 18). Further exploratory analyses could be done to see if males at a lower LVEF could derive some benefit. However, further explanation with clinically plausible reasons as to why females with lower LVEF seem to achieve the best outcomes and males within this study population may not derive benefit should be brought forth. Additional studies designed around these hypotheses would need to be run for reliable interpretation of these findings. Results shown in this section are merely hypothesis generating and should not be construed as robust evidence of a strong/non-existent treatment effect within a subgroup without further evidence outside of the PARAGON-HF study.

Treatment Effect by LVEF

Greater benefit of Entresto observed in patients with lower LVEF in HFpEF is likely a credible finding given biologic plausibility and known treatment effect of Entresto in an adjacent patient population i.e.; patients with HFrEF with LVEF < 40%.

Figure 9 displays the estimated treatment effect (RR) of Entresto versus valsartan against LVEF at screening as a continuous variable. The estimated RR and 95% confidence intervals are plotted for recurrent CEC-confirmed total HHF and CV death as a function of LVEF at screening. The RR is < 0.8 in patients with LVEF between 45 to 55% and between 0.8 and 1 in patients with LVEF between 55 and 65%.

Figure 9. Treatment Effect (rate ratio) against Ejection Fraction at Screening for Recurrent CEC-Confirmed Total Hospitalization for Heart Failure and Cardiovascular death (Full Analysis Set), PARAGON-HF



Source: NDA 207620/S-018 – Applicant Response to FDA Information Request dated May 27, 2020

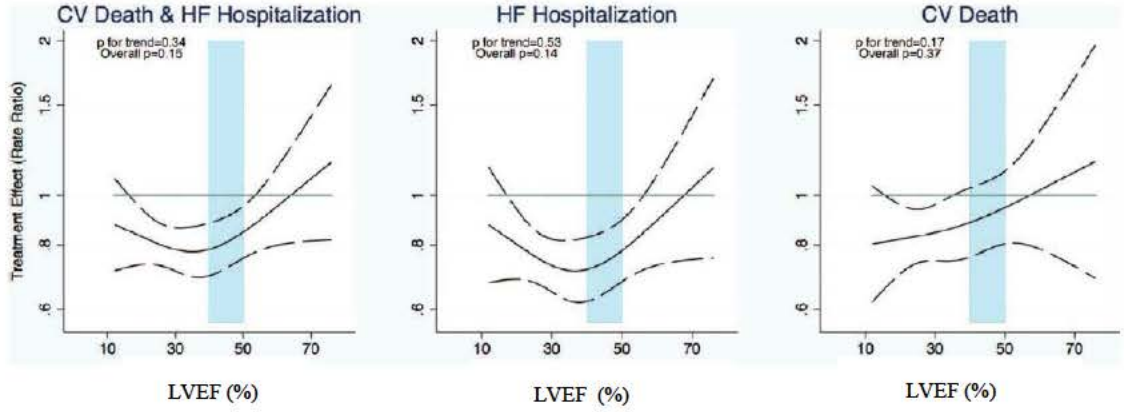
Relationship between treatment effect (HHF) and LVEF observed in CHARM program[42] for candesartan and TOPCAT[43] for spironolactone in patients with HF indicates that patients with

[42] Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. Eur J Heart Fail;20:1230-1239.
[43] Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. Eur Heart J;37:455-462.

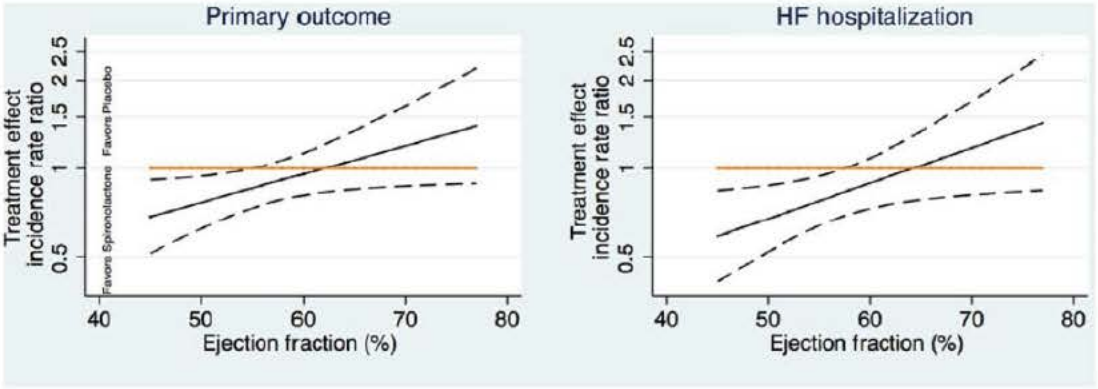
mildly reduced LVEF derive benefit with these therapies, similar to patients with moderate to severely reduced LVEF (Figure 10). These findings are consistent with findings from PARADIGM-HF and PARAGON-HF.

Figure 10. Treatment Effect by Left Ventricular Ejection Fraction in CHARM Program and TOPCAT

CHARM program[1]



TOPCAT[2]



[1] Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. Eur J Heart Fail;20:1230-1239.

[2] Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. Eur Heart J;37:455-462.

TOPCAT: treatment effect modification for LVEF as a linear continuous variable using Cox proportional hazards models and Poisson regression models of spironolactone by LVEF. The primary outcome of TOPCAT was a composite of adjudicated hospitalization for heart failure, cardiovascular death, or aborted cardiac arrest.

Abbreviations: CV, cardiovascular; HF, heart failure; CV

Sponsor Figures 8-1 and 8-2 from Novartis Briefing Information for December 15, 2020 CRDAC Meeting

TOPCAT randomized patients with HFpEF with LVEF ≥ 45% to spironolactone versus placebo. LVEF in TOPCAT ranged from 44 to 85% (mean 57.1%, median 56%, IQR [51, 61%]). Spironolactone did not reduce the primary outcome of CEC adjudicated HHF, CV death, or

aborted cardiac arrest, but was associated with reduced HHF.[44] A post-hoc analysis of TOPCAT that evaluated relationship between screening LVEF and treatment effect of spironolactone in 3444 patients demonstrated that LVEF modified the spironolactone treatment effect for the primary outcome (P = 0.046) and for HHF (P = 0.039). The estimated treatment effect of spironolactone was greater at the lower end of the LVEF spectrum with respect to the primary endpoint (LVEF < 50%: HR 0.72, 95% CI 0.50, 1.05; LVEF ≥60%: HR 0.97, 95% CI 0.76, 1.23) and HHF (LVEF < 50%: HR 0.76, 95% CI 0.46, 1.27; LVEF ≥60%: HR 0.98, 95% CI 0.74, 1.30). For the composite endpoint of CV death and HHF, the HR of 0.72 in patients with LVEF < 50% in TOPCAT is closer to the HR observed in other trials of mineralocorticoid receptor antagonists (MRAs) in HFrEF for example RALES[45] and EMPHASIS-HF[46]. Table 19 shows the treatment effect of MRAs in patients with HFrEF and HFpEF.

Table 19. Treatment Effect of Mineralocorticoid Receptor Antagonists (MRAs) in Heart Failure

HFrEF		HFpEF	
RALES[1] (LVEF < 35%) N = 1663 Treatment: Spironolactone	**EMPHASIS-HF[2] (LVEF < 35%) N = 2737 Treatment: Eplerenone**	**TOPCAT[3] (LVEF < 50%) N = 520 Treatment: Spironolactone**	**TOPCAT[3] (LVEF ≥ 60%) N = 1333 Treatment: Spironolactone**
CV death + hospitalization for cardiac causes RR (95% CI)	CV death + HHF HR (95% CI)	CV death + HHF HR (95% CI)	CV death + HHF HR (95% CI)
0.68 (0.59, 0.78)	0.63 (0.54, 0.74)	0.72 (0.50, 1.05)	0.97 (0.76, 1.23)

HFrEF: heart failure with reduced ejection fraction, HFpEF: heart failure with preserved ejection fraction, LVEF: left ventricular ejection fraction, CV: cardiovascular, HHF: hospitalization for heart failure, HR: hazard ratio, RR: relative risk, CI: confidence interval

Sources

[1]Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709–717.

[2]Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011;364:11–21.

[3]Solomon SD, Claggett B, Lewis EF, et al. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. *Eur Heart J*. 2016;37(5):455-462. doi:10.1093/eurheartj/ehv464.

Reviewer's Comments: *These observations suggest that patients with HF with mildly reduced LVEF (~ 40-55%) tend to derive benefit from therapies that are efficacious in patients with HFrEF with LVEF < 40%. This questions the prudence of combining patients with HF with LVEF 40 to 50% or even up to 55%, the now classified HFmrEF group, with patients with heart failure with LVEF > 50-55% as a single HFpEF population.*

[44] Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, Clausell N, Desai AS, Diaz R, Fleg JL, Gordeev I, Harty B, Heitner JF, Kenwood CT, Lewis EF, O'Meara E, Probstfield JL, Shaburishvili T, Shah SJ, Solomon SD, Sweitzer NK, Yang S, McKinlay SM; TOPCAT Investigators. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383–1392.

[45] Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709–717.

[46] Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B; EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med 2011;364:11–21.

Table 20 and Figure 11 present the distribution of patients in PARAGON-HF by treatment arm by LVEF in increments of 5%. There was only one patient with LVEF < 45% in the FAS in PARAGON-HF. In PARAGON-HF, 46% patients had a mildly reduced LVEF of 45 to 55%.

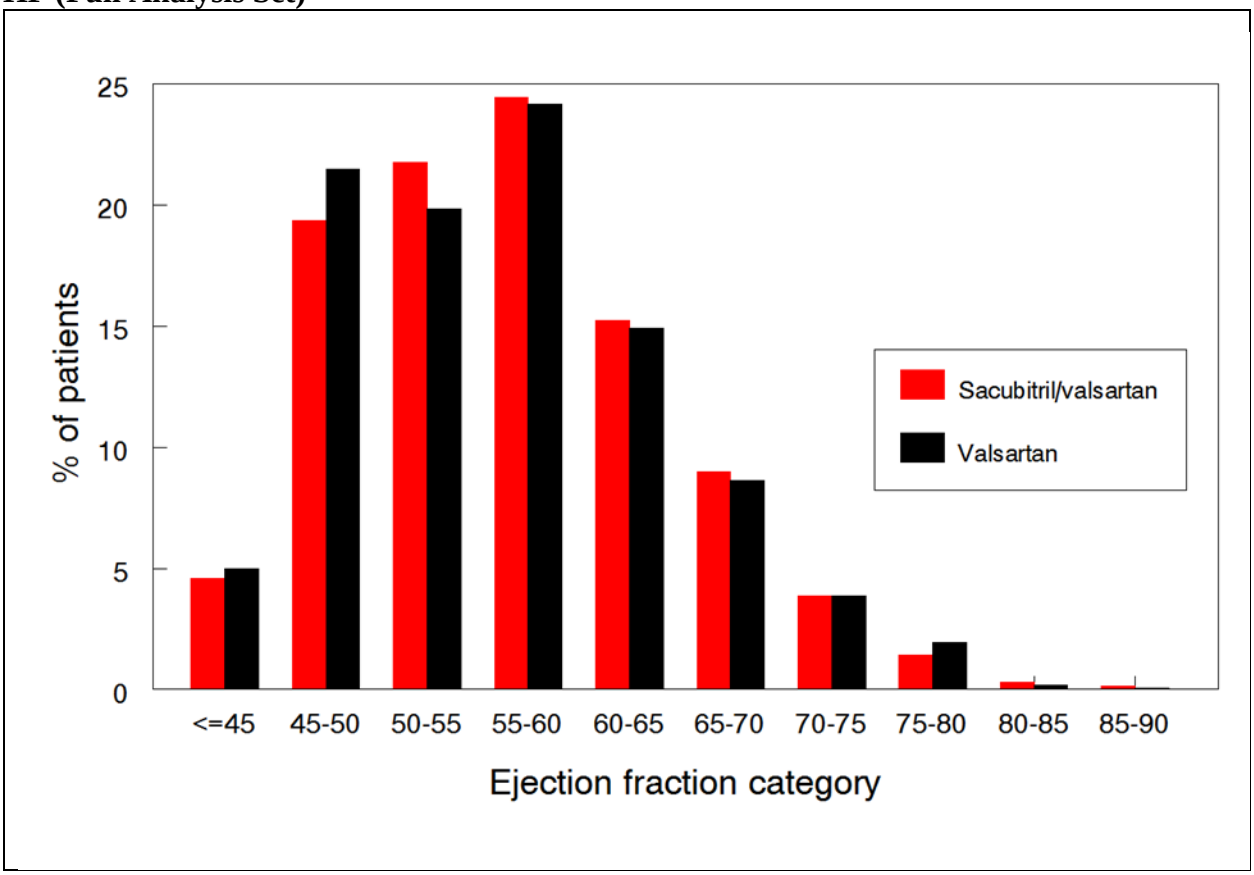
Table 20. Distribution of Patients by Treatment Arm by LVEF Categories, PARAGON-HF (Full Analysis Set)

LVEF Range	Sacubitril/valsartan 200 mg bid	Valsartan 160 mg bid	Total
LVEF≤45	110 4.57%	119 4.98%	229
>45, ≤50	466 19.36%	513 21.47%	979
>50, ≤55	524 21.77%	474 19.84%	998
>55, ≤60	588 24.43%	577 24.15%	1165
>60, ≤65	366 15.21%	356 14.9%	722
>65, ≤70	216 8.97%	206 8.62%	422
>70, ≤75	93 3.86%	92 3.85%	185
>75, ≤80	34 1.41%	46 1.93%	80
>80, ≤85	7 0.29%	4 0.17%	11
>85, ≤90	3 0.12%	2 0.08%	5
Total	2407	2389	4796

LVEF: Left ventricular ejection fraction

Source: Reviewer's analysis

Figure 11. Distribution of Patients by Treatment Arm by LVEF Categories, PARAGON-HF (Full Analysis Set)

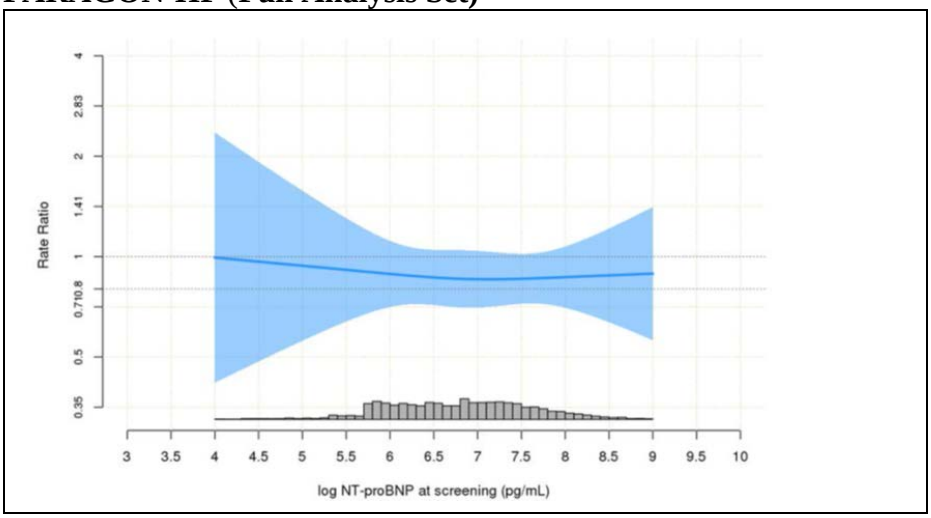


LVEF: Left ventricular ejection fraction
Source: Reviewer's analysis

The relationship between the level of NT-proBNP at screening and treatment response was also explored.

Figure 12 displays the estimated treatment effect (RR) of Entresto versus valsartan plotted against NT-proBNP at screening for recurrent CEC-confirmed total HHF and CV death. The RR is consistent across the range of NT-proBNP levels at screening.

Figure 12. Treatment Effect (rate ratio) against NT-proBNP at Screening for Recurrent CEC-Confirmed Total Hospitalization for Heart Failure and Cardiovascular death, PARAGON-HF (Full Analysis Set)



Source: NDA 207620/S-018 – Applicant Response to FDA Information Request dated May 27, 2020

These findings demonstrate that therapeutic benefit with Entresto tends to be more pronounced at the lower LVEF range, though there may be some effect in patients with higher LVEFs. The treatment effect did not vary with screening NT-proBNP levels in PARAGON-HF.

Treatment Effect by Sex

Table 21 displays the prevalence of some baseline co-morbidities / clinical characteristics that are associated with, or can worsen, HF, by sex in the randomized set. Males had a higher prevalence of atherosclerotic CV disease, atrial fibrillation/flutter and prior HHF; and females had a higher prevalence of hypertensive cardiomyopathy and depression. These differences do not help explain a potential difference in response to Entresto. Note that the point estimate for observed HR in CHARM-PRESERVED,[47] I-PRESERVE,[48] and PARADIGM-HF did not differ significantly by sex.

[47] Yusuf S, Pfeffer MA, Swedberg K, et al for the CHARM Investigators and Committees (2003) Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved trial. Lancet; 362:777-781.
[48] Massie BM, Carson PE, McMurray JJ, et al for the I-PRESERVE Investigators (2008) Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med; 359:2456-67.

Table 21. Baseline Prevalent Co-morbidities in Randomized Set (N=4822) by Sex, PARAGON-HF

Clinical Characteristic	Female N 2491	Male N 2331
Primary Heart Failure Etiology		
Ischemic	671 (27%)	1052 (45%)
Hypertensive	1651 (66%)	1156 (50%)
Diabetic	287 (12%)	236 (10%)
One heart failure hospitalization within 12 months prior to screening	852 (34 %)	894 (39%)
Baseline LVEF (%) Mean ± SD	59 ± 8	56 ± 8
Baseline LVEF (%) Median	60	55
LA volume index (ml/m^2) Mean ± SD overall	47 ± 17	46 ± 18
LA volume index (ml/m^2) Mean ± SD in patients with atrial fibrillation	52 ± 17	51 ± 20
LV septal wall thickness (cm) Mean ± SD	1.21 ± 0.22	1.27 ± 0.23
LV posterior wall thickness (cm) Mean ± SD	1.13 ± 0.21	1.20 ± 0.23
NT-proBNP (pg/ml) Mean ± SD overall	1245 ± 1397	1362 ± 1667
Angina Pectoris	664 (27%)	724 (31%)
Coronary Artery Bypass Graft	172 (7%)	398 (17%)
Percutaneous Coronary Intervention	369 (15%)	608 (26%)
Peripheral Vascular Disease	176 (7%)	238 (10%)
Prior Stroke	260 (10%)	258 (11%)
Dyslipidemia	1475 (59%)	1440 (62%)
Hypertension	2392 (96%)	2192 (94%)
Diabetes	1001 (40%)	1061 (46%)

Source: Reviewer's analysis of ADBS, ADCM data sets

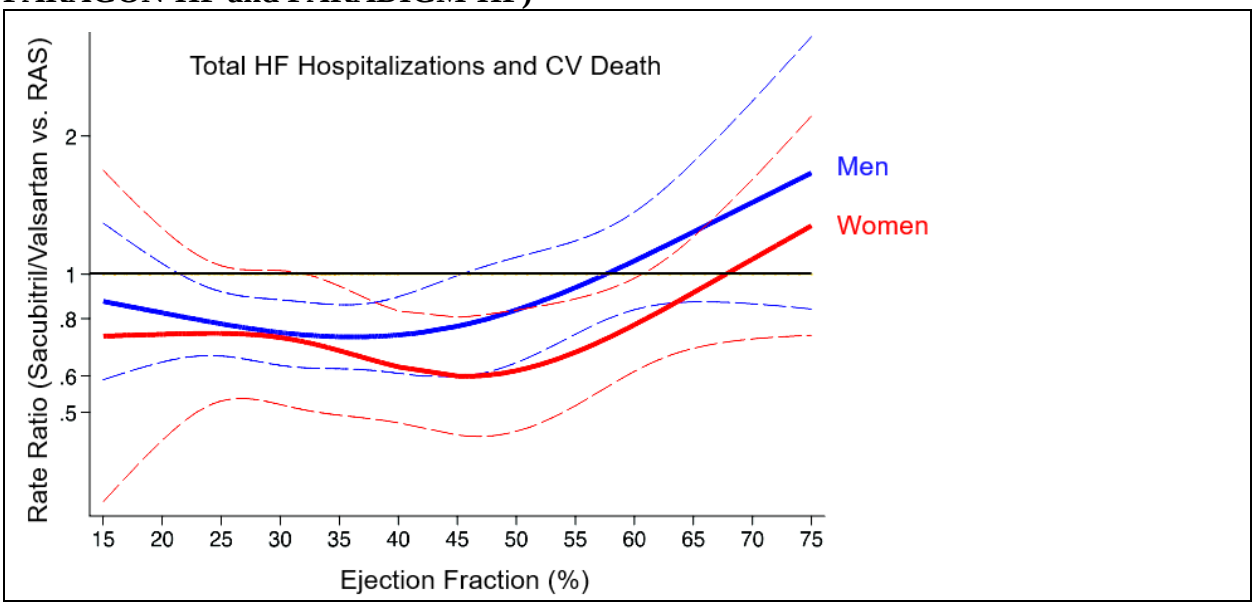
Treatment Effect by Sex and LVEF

The Applicant analyzed treatment effect on the recurrent composite endpoint of total HF hospitalizations and CV death versus LVEF as a continuous variable by sex using the pooled data from PARAGON-HF and PARADIGM-HF (Figure 13). This analysis indicates that while women seem to derive benefit with Entresto up to LVEF of 60-65%, men derive benefit up to a lower LVEF of 45-55%. A similar trend was observed with candesartan and MRA's in HF (Figure 14), but the curves of treatment effect by sex separate at a higher LVEF and with a smaller separation than observed with Entresto. Limitations of combined analysis of

PARADIGM-HF and PARAGON-HF include differences in trial design, trial size and the comparator used.

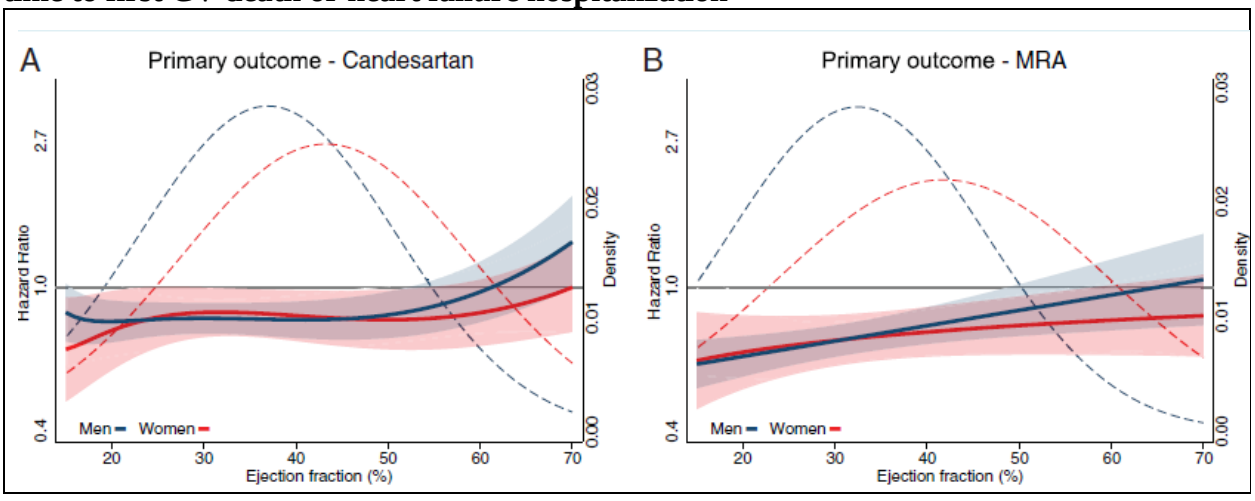
In PARAGON-HF, the median LVEF in males and females was 55 and 60%, respectively. Patients with LVEF below the respective median LVEF by sex appear to derive a greater benefit with Entresto compared to patients with LVEF higher than the median (Table 22).

Figure 13. Estimated treatment effect (rate ratio) against baseline LVEF and sex for CEC-confirmed total (first and recurrent) HF hospitalizations and CV death (pooled data from PARAGON-HF and PARADIGM-HF)



Source: Sponsor Figure 6-10 from Novartis Briefing Information for December 15, 2020 CRDAC Meeting

Figure 14. Treatment effect of candesartan and mineralocorticoid receptor antagonists on time to first CV death or heart failure hospitalization



Source: Sponsor Figure, Appendix 2 from Novartis Briefing Information for December 15, 2020 CRDAC Meeting

Interactions between left ventricular ejection fraction, sex and effect of neurohormonal modulators in heart failure. Eur J Heart Fail; 22(5):898-901.

Table 22. Treatment effect (rate ratio) by LVEF and sex for CEC-confirmed total (first and recurrent) HF hospitalizations and CV death, PARAGON-HF, FAS

	N (events per 100 patient years)		
Subgroup	**Entresto**	**Valsartan**	**RR (95% CI)**
Male, LVEF≤55*	621 (14.92)	627 (16.09)	0.93 (0.72, 1.21)
Male, LVEF>55	545 (15.23)	524 (12.77)	1.18 (0.87, 1.58)
Female, LVEF≤55	479 (10.48)	479 (19.04)	0.56 (0.41, 0.77)
Female, LVEF>55	762 (10.96)	759 (11.97)	0.89 (0.68, 1.17)
Male, LVEF≤60	887 (14.89)	890 (15.10)	0.97 (0.77, 1.21)
Male, LVEF>60	279 (15.64)	261 (12.86)	1.26 (0.83, 1.89)
Female, LVEF≤60**	801 (10.23)	793 (16.75)	0.61 (0.47, 0.80)
Female, LVEF>60	440 (11.80)	445 (11.15)	1.02 (0.72, 1.43)

*median LVEF in males, **median LVEF in females

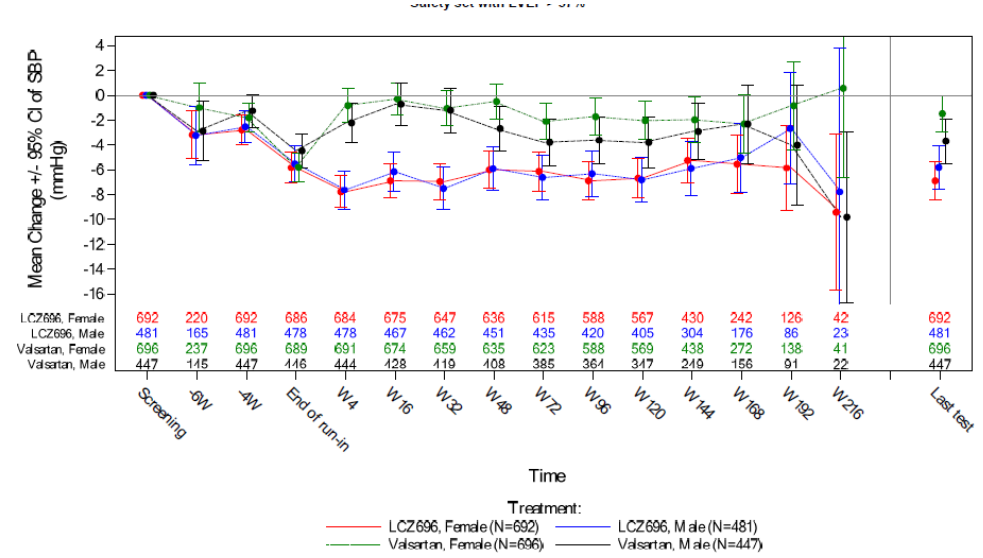
LVEF: left ventricular ejection fraction, FAS: full analysis set

Source: Reviewer analysis

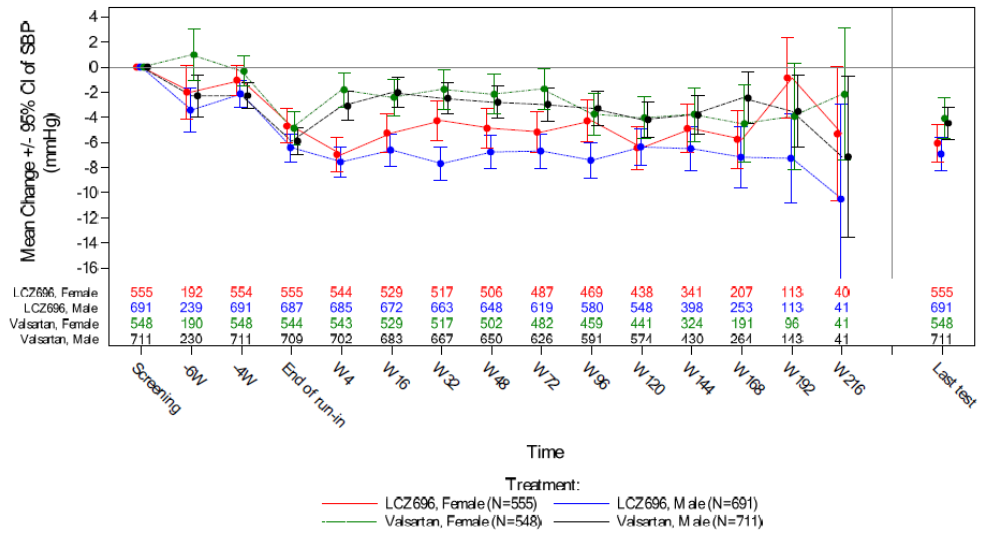
Figure 15 displays the change from baseline (CFB) in BP by treatment arm by sex by median LVEF. In patients with LVEF > 57%, BP CFB is generally similar in both men and women, but patients in Entresto arm experienced a greater BP reduction versus valsartan arm. In patients with LVEF ≤ 57%, BP CFB is generally similar by sex in valsartan arm, but men experienced slightly greater BP reduction than women in the Entresto arm.

Figure 15. Sitting systolic and diastolic arterial blood pressure during treatment run-in and randomized treatment by treatment arm by sex by LVEF, PARAGON-HF (Safety Set)

Sitting systolic blood pressure change from screening by treatment arm and sex, Safety set with LVEF > 57%



Sitting systolic blood pressure change from screening by treatment arm and sex, Safety set with LVEF ≤ 57%



Source: Source: Sponsor Figures 2-3.5, 2-3.7

***Reviewer's Comments**: These data suggest that both men and women respond to Entresto in terms of reduction in BP and HHF. One possible reason for the observed differential treatment effect for the primary composite endpoint by sex in PARAGON-HF may be related to a lower normal LVEF range in men. Given that PARAGON-HF was under powered for the observed treatment effect, no conclusions can be drawn for these subgroup findings.*

Some have hypothesized that, compared to men, women with HFpEF have a higher prevalence of the inflammatory-metabolic HFpEF phenotype.[49] The proposed clinical characteristics of inflammatory-metabolic HFpEF phenotype include impaired left ventricular distensibility, increase in diastolic stiffness and left ventricular pressures, and atrial remodeling. It is thought to be associated with various systemic inflammatory or metabolic diseases (Table 23).[19] The myocardial inflammatory process in these patients may be associated with mildly reduced LVEF, mostly > 40%. Such decline in LVEF, is different than in patients with LVEF where the etiology of LV dysfunction is mostly cardiomyocyte injury and stretch. The authors state that the diagnosis of inflammatory-metabolic HFpEF is not based on LVEF but is primarily determined by evidence of systemic and adipose tissue inflammation, microvascular endothelial dysfunction, and myocardial fibrosis. These patients have higher levels of inflammatory biomarkers such as C-Reactive Protein and lower levels of natriuretic peptides.

Table 23. Systemic Diseases Proposed to be Associated with Inflammatory-Metabolic HFpEF[19]

Inflammatory Disorders	Metabolic Disorders
• Rheumatoid arthritis • Systemic lupus erythematosus • Psoriasis • Systemic sclerosis • Inflammatory bowel disease • Chronic kidney disease • Late-onset asthma • Multiple sclerosis	• Obesity • Diabetes • Metabolic Syndrome • Non-alcoholic fatty liver disease • Hypothyroidism • Hypercortisolism (iatrogenic or endogenous) • Primary hyperaldosteronism

Reviewer's Comments: *The proposed characteristics of inflammatory-metabolic HFpEF significantly overlap with HFpEF due to any other etiology; i.e.; most patients with HFpEF have elevated left ventricular end diastolic pressure (LVEDP) leading to HFpEF symptoms, and varying degrees of diastolic dysfunction and left atrial enlargement as measured by transthoracic echocardiogram. The disparate etiologies for inflammatory-metabolic HFpEF beg the following questions 1) if management of HFpEF should be individualized according to the underlying etiopathogenesis, 2) is it an inflammatory disorder that will likely respond to anti-inflammatory drugs, 3) should clinical features such as epicardial fat pad thickness and inflammatory biomarkers be used as eligibility criteria to enroll a pathologically more homogenous group, 4) does the trial population in PARAGON-HF actually represent the inflammatory-metabolic HFpEF phenotype where high levels of neprilysin actually mediated sodium retention – the eligibility criteria for PARAGON-HF stated that if investigators thought that the HF symptoms were likely due to an alternative diagnoses such as obesity, specifically patients with BMI > 40 kg/m^2 should be excluded. Only 12 percent of total FAS had a history of obesity at screening; the mean BMI of patients enrolled in PARAGON-HF HF was 30 kg/m^2 with*

[49] Packer M, Lam CSP, Lund LH, Maurer MS, Borlaug BA. Characterization of the inflammatory-metabolic phenotype of heart failure with a preserved ejection fraction: a hypothesis to explain influence of sex on the evolution and potential treatment of the disease [published online ahead of print, 2020 May 22]. *Eur J Heart Fail*. 2020;10.1002/ejhf.1902. doi:10.1002/ejhf.1902

a SD of 5 in Entresto and 30 and SD of 6 in valsartan group. Available data within PARAGON-HF do not allow evaluation of response to Entresto based on this phenotypic characterization.

Table 24 displays the analysis of secondary endpoints by sex in the full analysis set in PARAGON-HF. Analysis of change in KCCQ and NYHA class at 8 months indicates that women did not experience greater symptom improvement compared to men. To the contrary, statistically men experienced better improvement in KCCQ than women with a least square mean difference of 2.10 in men and -0.0012 in women at Month 8. These changes in KCCQ and NYHA class are small and not considered clinically meaningful.

Table 24 Secondary Endpoint Analysis by Sex, PARAGON-HF (Full Analysis Set)

Table 11-24 Gender subgroup rate ratios (95% CIs) for secondary endpoints (Full Analysis Set)

Analysis	Effect Modification (95% CI)		Interaction p-value
	Male	Female	
KCCQ[1]	LSM = 2.0967 (0.7595, 3.4340)	LSM = -0.0012 (-1.3114, 1.3091)	0.0134*
NYHA[2]	OR = 1.4240 (1.0379, 1.9536)	OR = 1.4672 (1.0771, 1.9985)	0.8775
Composite renal endpoint[3]	HR = 0.5181 (0.2876, 0.9333)	HR = 0.4897 (0.2687, 0.8926)	0.8956
All-cause mortality[3]	HR = 0.9765 (0.7983, 1.1945)	HR = 0.9586 (0.7678, 1.1969)	0.9040

Source: CLCZ696D2301 Study Report Table 11-24

Secondary Efficacy Results

Since PARAGON-HF did not meet statistical significance for the primary endpoint, results of the following secondary efficacy endpoints are only considered exploratory.

1) **Change from baseline in KCCQ clinical summary score at Month 8**
   KCCQ clinical summary score (CSS) included HF symptoms and physical limitation domains. The mean change from baseline to Month 8 in the KCCQ CSS was -1.51 points in the Entresto group and -2.53 points in the valsartan group with a mean difference between the two groups of 1.03 points in favor of Entresto (95% CI: 0.0047, 2.0576; 2-sided p=0.0510). The mean difference of 1.03 is not considered clinically meaningful.

2) **Change in NYHA class from baseline to Month 8**
   Mean change in NYHA class was not reported. At Month 8 NYHA functional class improved in 14.98 and 12.55% of patients in the Entresto and valsartan groups, respectively. No change in NYHA class was reported in 76 and 78% patients in the Entresto and valsartan groups, respectively.

3) Time to first occurrence of the composite renal endpoint

The incidence of composite renal endpoint, defined as renal death, reaching end stage renal disease, or experiencing a ≥50% decline in eGFR relative to baseline, was 33/2407 (1.37%) and 64/2389 (2.68%) in Entresto and valsartan groups, respectively with a HR of 0.50, p 0.0014. This difference in renal composite endpoint was driven by ≥50% decline in eGFR component observed in 27/2407 (1.12%) and 60/2389 (2.51%) in Entresto and valsartan groups, respectively.

The rate of change in eGFR was -0.21 mL/min/1.73 m^2 per month in the valsartan group, while it was -0.16 mL/min/1.73m^2 per month in the sacubitril/valsartan group. The rate at which the eGFR declined was significantly slower by 0.04 mL/min/1.73m^2 per month (0.48 mL/min/1.73m^2 per year) in the sacubitril/valsartan group relative to the valsartan group during the randomized treatment .

4) Time to all-cause mortality

There was no difference in all-cause mortality; 342/2407 (14.21%) and 349/2389 (14.61%) all-cause mortality events were observed in Entresto and valsartan groups, respectively.

Entresto in Patients with Heart Failure with LVEF ≤ 40%

PARADIGM-HF trial that supported approval of Entresto to treat patients with symptomatic HFrEF, randomized 8,442 adult patients with symptomatic chronic HF with LVEF ≤ 40%. In PARADIGM-HF, Entresto reduced the time to composite endpoint of CV death or HHF with a hazard ratio of 0.80, 95% CI 0.73, 0.87, p < 0.0001. Table 25 displays the number of events and the number of patients with events in PARADIGM-HF trial. In the time to event analysis, there were 82 and 121 fewer CV death and HHF events, respectively in Entresto versus enalapril group. There were 135 and 121 fewer patients who experienced CV death and HHF, respectively in Entresto versus enalapril group.

Table 25. Treatment Effect for the Primary Composite Endpoint and its Components in Patients with Heart Failure with Reduced Ejection Fraction, PARADIGM-HF

	Entresto N = 4,187 n (%)	Enalapril N = 4,212 n (%)	Hazard Ratio (95% CI)	*p*-value
Primary composite endpoint of cardiovascular death or heart failure hospitalization	914 (21.8)	1,117 (26.5)	0.80 (0.73, 0.87)	< 0.0001
Cardiovascular death as first event	377 (9.0)	459 (10.9)		
Heart failure hospitalization as first event	537 (12.8)	658 (15.6)		
Number of patients with events: *				
Cardiovascular death**	558 (13.3)	693 (16.5)	0.80 (0.71, 0.89)	
Heart failure hospitalizations	537 (12.8)	658 (15.6)	0.79 (0.71, 0.89)	

*Analyses of the components of the primary composite endpoint were not prospectively planned to be adjusted for multiplicity
**Includes patients who had heart failure hospitalization prior to death

Source: Reviewer's compilation

Reviewer's Comments: *Data from PARADIGM-HF and PARAGON-HF suggest that while Entresto has greater efficacy in patients with moderate to severely reduced LVEF, there is some efficacy in patients with mildly reduced LVEF in the HFpEF spectrum. In PARAGON-HF, the number of patients with HHF events in various LVEF categories may have impacted the demonstrated heterogeneity of treatment effect by median LVEF.*

6. Evidence of Risk (Assessment of Safety)

6.1. Potential Risks or Safety Concerns Based on Drug Mechanism

Known adverse reactions for Entresto include angioedema, hypotension, hyperkalemia, renal failure, cough, and dizziness.

6.2. Potential Safety Concerns Identified Through Post market Experience

Hypersensitivity including rash, pruritus, and anaphylactic reaction have been reported as adverse reactions in post market experience. There is an on-going post market requirement (PMR) evaluating effects of Entresto comparing with valsartan on cognitive function.

6.3. FDA Approach to the Safety Review

There are no concerns regarding submission quality, conduct of the studies with respect to assessment of safety, or the Applicant's characterization of adverse events.

The safety review focused on the safety population in the randomized treatment period in PARAGON-HF. Results are presented for this population unless otherwise specified. Table 26 shows the review strategy for each adverse event of special interest (AESI). Adverse events

(AEs) were coded using MedDRA dictionary (version 22.0). In addition to replicating the sponsor's results, we also used FDA MedDRA query (FMQ, current version: "BIRRS_Final_FMQs_2020_01_29.xpt") for existing terms that most closely correspond to each AESI. Labs and vital signs related to AESIs were also reviewed to confirm findings in AEs. Analysis of lab results were based on data pooled from the central and the local labs. Baselines were defined as the last non-missing record on or before the first dose in the randomized treatment period. Analysis using data from only the central lab revealed similar results.

In addition, we reviewed AEs related to thrombotic disorders, which included a list of PTs compiled by the clinical reviewer. Data were pooled from the safety population from both PARADIGM-HF and PARAGON-HF. Broad and narrow SMQs were also performed on the pooled dataset.

Table 26. The Sponsor's and FDA's approach for adverse events of special interest

AEs of special interest	Dataset	Sponsor's approach	FDA's additional approach	Lab/vital signs reviewed
Angioedema	PARAGON-HF	NMQ[1] "Angioedema" and adjudicated events		
Hypotension	PARAGON-HF	NMQ "Hypotension"	FMQ[2] "Hypotension"	Blood pressure
Hyperkalemia	PARAGON-HF	NMQ "Hyperkalemia"		Serum potassium
Renal impairment	PARAGON-HF	SMQ "Acute renal failure"	FMQ "Acute kidney injury"	eGFR & Creatinine
Cognitive impairment	PARAGON-HF	SMQ "Dementia"	FMQ "Confusional state"	
Hypersensitivity	PARAGON-HF	SMQ "Hypersensitivity"	FMQ "Anaphylactic reaction"	
Thrombosis	PARAGON-HF & PARADIGM		Reviewer's complied list of PTs	

[1] NMQ: Novartis MedDRA Query
[2] FMQ: FDA MedDRA Query

6.4. Adequacy of the Clinical Safety Database

Table 27 shows the duration of treatment exposure (including temporary interrtuption) and study drug exposure (excluding temporary interruption) in the randomized treatment Period. There is no imbalance in exposure between the treatment groups.

Table 27. Duration of Exposure in Randomized Treatment Period, Safety Population, PARAGON-HF

	Treatment Exposure[1]		Study Drug Exposure[2]	
Parameter	Entresto N=2419	Valsartan N=2402	Entresto N=2419	Valsartan N=2402
Duration of treatment (unit: months)				
Mean (SD)	31.0 (12.3)	30.6 (12.7)	30.5 (12.4)	30.1 (12.7)
Median	32.8	32.7	32.4	32.2
(min, max)	(0.1, 56.4)	(0.1, 56.0)	(0.1, 56.2)	(0.1, 55.2)
Patients treated, by duration, n (%)				
Any duration (at least 1 dose)	2419 (100%)	2402 (100%)	2419 (100%)	2402 (100%)
< 2 weeks	19 (0.8%)	13 (0.5%)	19 (0.8%)	14 (0.6%)
2 to < 8 weeks	43 (1.8%)	56 (2.3%)	48 (2.0%)	56 (2.3%)
8 weeks to < 3 months	28 (1.2%)	22 (0.9%)	28 (1.2%)	26 (1.1%)
3 months to < 1 year	187 (7.7%)	222 (9.2%)	193 (8.0%)	228 (9.5%)
1 year to < 2 year	249 (10.3%)	246 (10.2%)	259 (10.7%)	256 (10.7%)
2 year to < 3 year	1020 (42.2%)	990 (41.2%)	1032 (42.7%)	1001 (41.7%)
3 year to < 4 year	762 (31.5%)	736 (30.6%)	741 (30.6%)	717 (29.9%)
4 year to < 5 year	111 (4.6%)	117 (4.9%)	99 (4.1%)	104 (4.3%)

Source: Reviewer's analysis on adexods, cross reference sponsor's table 12-1 in Clinical Study Report (CSR).
[1] With temporary interruption.
[2] Without temporary interruption.
Abbreviations: N, total number of subjects in group; SD, standard deviation.

6.5. Safety Findings and Safety Concerns Based on Review of the Clinical Safety Database

6.5.1. Overall Adverse Event Summary

Table 28 shows a summary of overall adverse events. There is no imbalance in overall deaths, adverse events (AEs), serious adverse events (SAEs), adverse events leading to discontinuation of the study or dose adjustment/interruption. These findings are consistent with the known Entresto safety profile.

Table 29 shows the MedDRA preferred terms of AEs with the mean risk difference (Entresto minus valsartan) higher than 1%. Hypotension has the highest mean risk difference of 6.4%. It is an expected risk due to the vasodilatory action of Entresto. No other AEs have mean risk difference higher than 2%.

Table 30 shows a summary of overall adverse events for subjects with LVEF ≤ 57% and LVEF > 57%. There is no imbalance between the two treatment arms in overall deaths, AEs, SAEs, AEs leading to discontinuation of the study or dose adjustment/interruption within each LVEF subgroup. Subgroup LVEF ≤ 57% has slightly more deaths than LVEF > 57%.

Table 28. Overview of Adverse Events, Safety Population, PARAGON-HF, Randomized Treatment Period

Risk Category	Entresto N = 2419		Valsartan N = 2402		Entresto vs Valsartan Risk difference[2] (95% CI)	
	n	%[1]	n	%		
Any AE	2301	95.1	2294	95.5	-0.4	(-1.6, 0.8)
Severe AE	947	39.2	957	39.8	-0.7	(-3.5, 2.1)
Death	347	14.3	357	14.9	-0.5	(-2.5, 1.5)
SAE	1424	58.9	1416	59.0	-0.1	(-2.9, 2.7)
SAE with fatal outcome	345	14.3	357	14.9	-0.6	(-2.6, 1.4)
Discontinue due to AE	493	20.4	520	21.7	-1.3	(-3.6, 1.0)
Dose adjustment/interruption	856	35.4	846	35.2	0.2	(-2.5, 2.9)
Suspected drug related AE	768	31.8	725	30.2	1.6	(-1.0, 4.2)

Source: Reviewer's analysis on adae, cross reference Sponsor's Table 12-9 in CSR.
[1]The percentage of subjects in each risk category (n/N*100).
[2] The risk difference (n/N*100) between Entresto and Valsartan (Entresto – Valsartan).
Abbreviations: AE, adverse event; SAE, serious adverse event; CI, confidence interval; N, total number of subjects in each group; n, number of subjects with at least one event.

Table 29. Adverse Events Shown by MedDRA Preferred Terms, in Descending Order of Risk Difference (≥ 1%), Safety Population, PARAGON-HF, Randomized Treatment Period

Preferred Term[1]	Entresto N = 2419		Valsartan N = 2402		Total N = 4821		Entresto vs Valsartan Risk difference[3] (95% CI)	
	n	%[2]	n	%	n	%		
Hypotension	562	23.2	408	16.9	970	20.1	6.4	(4.1, 8.6)
Cough	191	7.9	149	6.2	340	7.1	1.7	(0.3, 3.2)
Dizziness	241	10.0	200	8.3	441	9.2	1.7	(0.1, 3.3)
Nasopharyngitis	207	8.6	178	7.4	385	8.0	1.2	(-0.3, 2.7)
Fall	135	5.6	110	4.6	245	5.1	1.0	(-0.2, 2.3)

Source: Reviewer's analysis on adae, cross reference Sponsor's Table 12-8 in CSR.
[1] Coded as MedDRA preferred terms (v22.0)
[2] The percentage of subjects in each risk category (n/N*100).
[3] The risk difference (n/N*100) between Entresto and Valsartan (Entresto – Valsartan).
Abbreviations: CI, confidence interval; N, number of subjects in each group; n, number of subjects with at least one event.

Table 30. Overview of Adverse Events for LVEF ≤ 57% and LVEF > 57%, Safety Population, PARAGON-HF, Randomized Treatment Period

Risk Category	LVEF ≤ 57%						LVEF > 57					
	Entresto (N = 1246)		Valsartan (N = 1259)		Risk Difference %		Entresto (N = 1173)		Valsartan (N = 1143)		Risk Difference[2] %	
	n	%[1]	n	%	(95% CI)		n	%	n	%	(95% CI)	
Any AE	1181	94.8	1191	94.6	0.2	(-1.6 , 1.9)	1120	95.5	1103	96.5	-1.0	(-2.6, 0.6)
Death	202	16.2	201	16.0	0.2	(-2.6 , 3.1)	145	12.4	156	13.6	-1.3	(-4.0, 1.5)
SAE	724	58.1	730	58.0	0.1	(-3.7 , 4.0)	700	59.7	686	60.0	-0.3	(-4.3, 3.7)
Severe AE	484	38.8	493	39.2	-0.3	(-4.1 , 3.5)	463	39.5	464	40.6	-1.1	(-5.1, 2.9)
Discontinue due to AE	260	20.9	275	21.8	-1.0	(-4.2 , 2.2)	233	19.9	245	21.4	-1.6	(-4.9, 1.7)
Dose interrupted/adjusted	432	34.7	414	32.9	1.8	(-1.9 , 5.5)	424	36.1	432	37.8	-1.6	(-5.6, 2.3)

Source: Reviewer's analysis on adae.
[1]The percentage of subjects in each risk category (n/N*100).
[2] The risk difference (n/N*100) between Entresto and Valsartan (Entresto – Valsartan).
Abbreviations: AE, adverse event; SAE, serious adverse event; CI, confidence interval; N, total number of subjects in each group; n, number of subjects with at least one event

6.5.2. Deaths

Table 31 shows the Clinical Endpoint Committee (CEC) adjudicated primary cause of deaths in the safety population. The number of subjects who died (including deaths that were not adjudicated) is similar in Entresto and valsartan. The major cause of death is cardiovascular (CV) death. The most common CV death is "sudden death". The most common non-cardiovascular cause of death is "malignancy". The mean risk difference between Entresto and valsartan in any death risk category in Table 31 is less than 1%. There is no imbalance between the two treatment groups in death.

Cardiovascular death is part of the primary endpoint. For more details please see the Assessment of Efficacy section.

Table 31. CEC Confirmed Primary Causes of Deaths (Total Incident Rate Higher than 1%) in Safety Population, PARAGON-HF, Randomized Treatment Period

	Entresto N = 2419		Valsartan N = 2402		Total N = 4821		Entresto vs Valsartan Risk difference[2] (95% CI)
Risk Category	**n**	**%[1]**	**N**	**%**	**n**	**%**	
Number of patients with CEC adjudicated cause of death	342	14.1	349	14.5	692	14.3	-0.4 (-2.4, 1.6)
Cardiovascular death[3]	204	8.4	212	8.8	416	8.6	-0.4 (-2.0, 1.2)
Sudden Death - Witnessed Or Last Seen Alive Less Than 24 Hr	66	2.7	75	3.1	141	2.9	-0.4 (-1.3, 0.5)
Heart Failure	60	2.5	58	2.4	118	2.5	0.1 (-0.8, 0.9)
Presumed Cardiovascular Death	35	1.5	34	1.4	69	1.4	0.1 (-0.6, 0.7)
Non-Cardiovascular death[3]	100	4.1	120	5.0	221	4.6	-0.9 (-2.0, 0.3)
Malignancy	40	1.7	42	1.8	83	1.7	-0.1 (-0.8, 0.6)
Infection	26	1.1	28	1.2	54	1.1	-0.1 (-0.7, 0.5)
Unknown death	38	1.6	17	0.7	55	1.1	0.9 (0.3, 1.5)
Death not adjudicated (after cutoff)	5	0.2	8	0.3	13	0.3	-0.1 (-0.4, 0.2)

Source: Reviewer's analysis on adzd, cross reference sponsor's table 12-10 in CSR.
[1]The percentage of subjects in each risk category (n/N*100).
[2] The risk difference (n/N*100) between Entresto and Valsartan (Entresto – Valsartan).
[3] CEC adjudicated cause of death. Only causes with total incident rate larger than 1% are shown.
Abbreviations: CEC, clinical endpoint committee; N, number of subjects in group; n, number of deaths; CI: confidence interval.

6.5.3. Serious Adverse Events

SAEs occurred in 58.9% and 59.0% of the safety population in the Entresto and the valsartan group. The most common SAE is cardiac failure, which occurred in a slightly lower percentage of patients in the Entresto (14.0%) than the valsartan (15.8%) group. Table 32 shows the PTs of SAEs in descending order of the risk difference (Entresto minus valsartan). No SAE has a notable higher mean risk (≥ 1%) in Entresto than valsartan. Atrial fibrillation has the highest risk difference of 0.7%.

Table 32. Serious Adverse Events, in Descending Order of Mean Risk Difference (Entresto vs Valsartan, Cutoff 0.3%), Safety Population, PARAGON-HF

	Entresto N = 2419		Valsartan N = 2402		Total N = 4821		Entresto vs Valsartan Risk difference[3] (95% CI)
Preferred Term[1]	n	%[2]	n	%	n	%	
Atrial fibrillation	162	6.7	145	6.0	307	6.4	0.7 (-0.7, 2.0)
Hypoglycemia	20	0.8	6	0.3	26	0.5	0.6 (0.2, 1.0)
Peripheral arterial occlusive disease	18	0.7	7	0.3	25	0.5	0.5 (0.1, 0.9)
Death	34	1.4	23	1.0	57	1.2	0.5 (-0.2, 1.1)
Atrial flutter	31	1.3	23	1.0	54	1.1	0.3 (-0.3, 0.9)
Transient ischemic attack	34	1.4	26	1.1	60	1.2	0.3 (-0.3, 1.0)
Cardiac failure acute	85	3.5	77	3.2	162	3.4	0.3 (-0.7, 1.3)

Source: Reviewer's analysis on adae, cross reference the sponsor's table 12-11 in CSR.
[1] Coded as MedDRA preferred terms (v22.0)
[2] The percentage of subjects in each risk category (n/N*100).
[3] The risk difference (n/N*100) between Entresto and Valsartan (Entresto – Valsartan).
Abbreviations: CI, confidence interval; N, number of subjects in each group; n, number of subjects with adverse event; PT, preferred term.

6.5.4. Discontinuations Due to Adverse Events

AEs led to permanent discontinuation of the study occurred in 20.4% and 21.7% of the safety population in the Entresto and the valsartan group. The most common AE led to discontinuation is hypotension, which occurred in a similar number of subjects in Entresto (2.1%) and Valsartan (2.0%). Table 33 shows the PTs of AEs led to discontinuation in descending order of the risk difference (Entresto minus valsartan). No AE has a notable higher risk (≥ 1%) in Entresto than valsartan. Death has the highest risk difference of 0.4%.

Table 33. Adverse Events Leading to Discontinuation, in Descending Order of Mean Risk Difference (Entresto vs Valsartan, Cutoff 0.1%), Safety Population, PARAGON-HF

	Entresto N = 2419		Valsartan N = 2402		Total N = 4821		Entresto vs Valsartan Risk difference[3] (95% CI)
Preferred Term[1]	n	%[2]	n	%	n	%	
Death	14	0.6	4	0.2	18	0.4	0.4 (0.1, 0.8)
Sepsis	9	0.4	3	0.1	12	0.3	0.3 (-0.0, 0.5)
Dizziness	6	0.3	1	0.0	7	0.2	0.2 (-0.0, 0.4)
Anemia	5	0.2	1	0.0	6	0.1	0.2 (-0.0, 0.4)
Pneumonia	15	0.6	12	0.5	27	0.6	0.1 (-0.3, 0.5)
Hypotension	51	2.1	48	2.0	99	2.1	0.1 (-0.7, 0.9)

Source: Reviewer's analysis on adae, cross reference Sponsor's Table 12-12 in Clinical Study Report
[1] Coded as MedDRA preferred terms (v22.0)
[2] The percentage of subjects in each risk category (n/N*100)
[3] The risk difference (n/N*100) between Entresto and Valsartan; negative values indicating the results favor Entresto
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in group; n, number of subjects with adverse event; PT, preferred term.

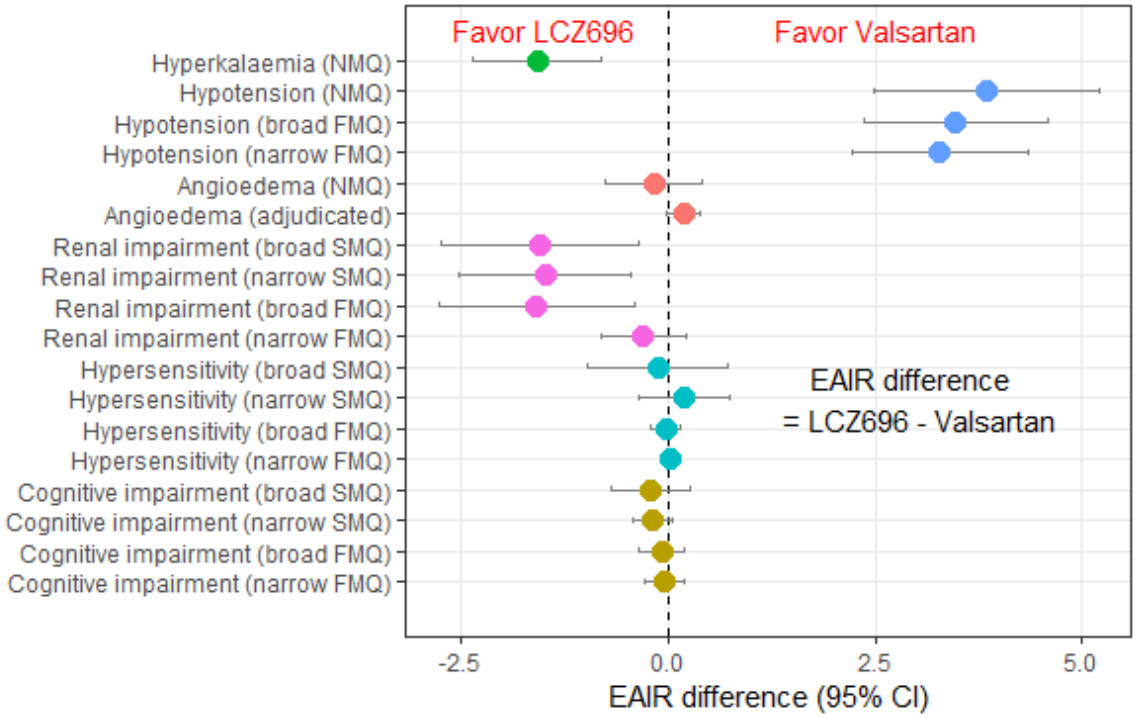
6.5.5. Adverse Events of Special Interest (AESI)

The findings of AESIs are consistent with the known Entresto profile. Figure 16 shows the mean difference of the exposure adjusted incident rate (EAIR) between the Entresto and the valsartan group from different queries on AESI. Each color represents one AESI. The negative value indicates that Entresto has a lower risk. Different queries revealed consistent results. Entresto has a lower risk in hyperkalemia and renal impairment and a higher risk in hypotension. The risk difference is small in angioedema, hypersensitivity, and cognitive impairment between Entresto and valsartan.

For each AESI, we showed the results of broad FMQ, if available. If no FMQ is available or FMQ showed little information, replication of the sponsor's query was presented. Results from different queries are similar.

There is no notable imbalance in thrombotic disorder-related AEs between the Entresto and the active control group, pooled from PARADIGM-HF and PARAGON-HF.

Figure 16. Difference in Exposure Adjusted Incident Rate (EAIR) and 95% Confidence Interval (CI) of AEs of Interest, Safety Population, PARAGON-HF, Randomized Treatment Period



6.5.5.1. Angioedema

Similar number of angioedema-related AEs (NMQ "angioedema") were reported in Entresto and valsartan, shown in Table 34. The number of subjects had SAEs (0.6% vs 0.6%), discontinued the study due to AEs (0.4% vs 0.2%), or had dose adjustment/interruptions (0.3% vs 0.2%) are low in both treatment arms. All reported angioedema-related adverse events required adjudication by the Angioedema Adjudication Committee (AAC) except for the lower extremities peripheral edema, which contributes to most of the reported angioedema-related events (208 events in 168 subjects in Entresto and 235 events in 189 subjects in valsartan). The confirmed angioedema-related AEs are low in both arms with a higher number in Entresto (Table 34). Among the confirmed cases, one subject from the Entresto group is African American. Time-to-event analysis shows no notable separation in the time course of the cumulative incident rate between the two treatment groups.

Table 34. Reported (NMQ) and Adjudicated Angioedema-Related Adverse Events, Safety Population, PARAGON-HF, Randomized Treatment Period

	Entresto			Valsartan		
	Even	Subjects	%	Events	Subjects	%
Reported (NMQ)	242	193	8.0	253	202	8.4
Adjudicated	37	33	1.4	20	20	0.8
Confirmed	15	14	0.6	4	4	0.2
I. No treatment administered or antihistamines only	6	5	0.2	2	2	0.1
II. Treated with catecholamines or steroids	5	5	0.2	1	1	0.0
IIIA. Hospitalized, no mechanical airway protection, without airway compromise	4	4	0.2	1	1	0.0

Source: Reviewer's analysis on adae, cross reference Sponsor's Table 12-18 in CSR.
Abbreviations: NMQ, Novartis MedDRA query; AE, adverse event; CI, confidence interval; N, number of subjects in group; n, number of subjects with adverse event

6.5.5.2. Hypotension

More subjects had hypotension-related adverse events (broad FMQ) in the Entresto group than the valsartan group but the number of subjects had SAEs are balanced, as shown in Table 35. More subjects had dose adjustment in Entresto (15.9%) than valsartan (10.6%), but there is no imbalance in subjects who discontinued the study due to AEs (2.2% vs 2.3%).

Subjects with LVEF > 57% had more hypotension-related AEs (29.4% for Entresto and 21.8% for valsartan) than subjects with LVEF ≤ 57% (23.3% for Entresto and 17.3% for valsartan). The risk difference between the two treatment arms is similar between the two LVEF subgroups. The

Entresto group has a consistently higher cumulative incident rate than the valsartan group, and the difference is stable during the study after about 180 days (Figure 17).

Figure 18 shows that systolic blood pressure (SBP) decreased/increased from baseline in the Entresto/valsartan group. There is a clear separation in the two time-course curves. Similar trends were also observed in the diastolic blood pressure with a smaller difference between the two treatment arms. Decreased mean blood pressure confirmed that hypotension is more prevalent in the Entresto group.

Table 35. Most Common (AE incident rate ≥ 1% in Either Treatment Group) Hypotension-Related AEs (Broad FMQ), Safety Population, PARAGON-HF, Randomized Treatment Period

	AE				SAE						
	Entresto N = 2419		Valsartan N = 2402		Entresto N = 2419		Valsartan N = 2402		Entresto vs Valsartan Risk Difference[3] (95% CI)		
Preferred Term[1]	n	%[2]	n	%	n	%	N	%			
Total	635	26.3	467	19.4	75	3.1	76	3.2	6.8	(4.5,	9.2)
Hypotension	562	23.2	408	17.0	52	2.2	47	2.0	6.2	(4.0,	8.5)
Dehydration	56	2.3	56	2.3	18	0.7	26	1.1	-0.0	(-0.9,	0.8)
Orthostatic Hypotension	34	1.4	31	1.3	5	0.2	9	0.4	0.1	(-0.5,	0.8)

Source: Reviewer's analysis on adae, cross reference Sponsor's Table 12-16 in CSR
[1] Coded as MedDRA preferred terms (v22.0)
[2] The percentage of subjects in each risk category (n/N*100).
[3] The risk difference (n/N*100) between Entresto and Valsartan (Entresto – Valsartan).
Abbreviations: FMQ, FDA MedDRA query; AE, adverse event; CI, confidence interval; N, number of subjects in group; n, number of subjects with adverse event

Figure 17 Kaplan Meier Plot for Hypotension-Related AEs (Broad FMQ), Safety Population, PARAGON-HF, Randomized Treatment Period

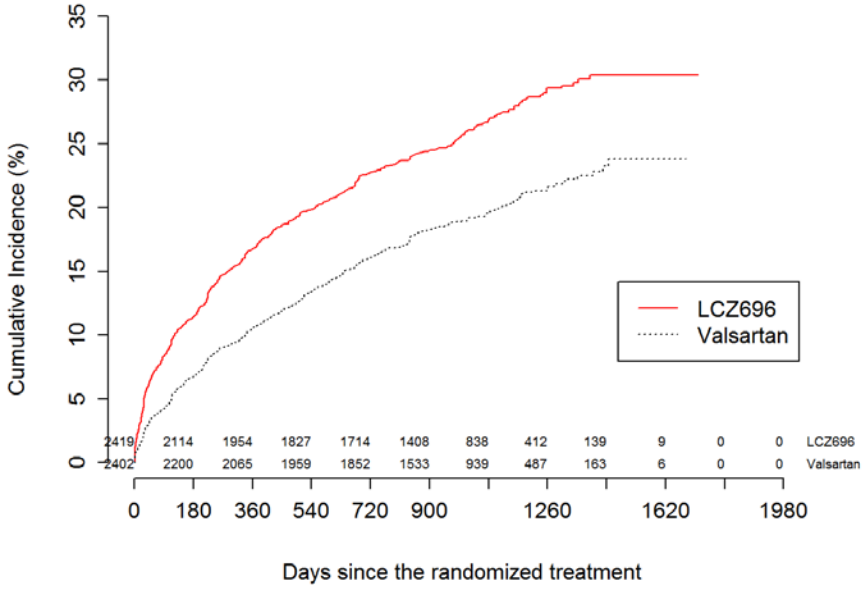
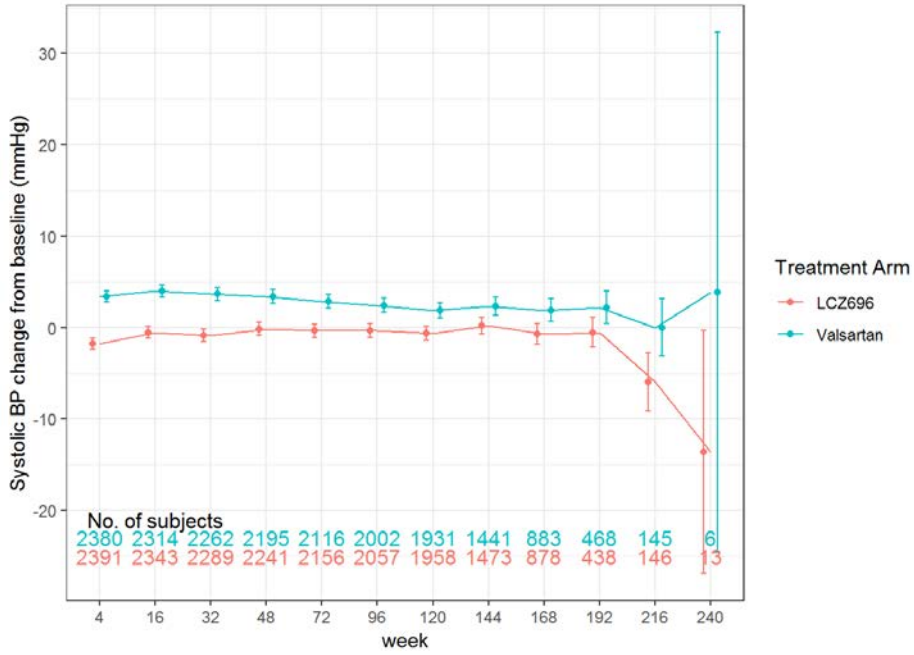


Figure 18 Time Course of Change from Baseline of Systolic Blood Pressure (SBP), Safety Population, PARAGON-HF, Randomized Treatment Period



Error bars are 95% Cis

Source: Reviewer's analysis

6.5.5.3. Hyperkalemia

Fewer subjects had hyperkalemia-related AEs (NMQ "hyperkalemia") and SAEs in the Entresto arm than the valsartan arm, as shown in Table 36. Fewer subjects had dose adjustment in Entresto (3.6%) than valsartan (5.3%), but the number of subjects who discontinued the study due to AEs is low in both groups (1.1% vs 1.5%). The most common PT is "hyperkalemia".

Figure 19 shows a higher cumulative incident rate of hyperkalemia-related AEs in valsartan than Entresto, and the two curves gradually separate throughout the study.

Table 37 shows that slightly more subjects had increased potassium levels from baseline in the valsartan group than the Entresto group. This confirms the finding that the valsartan group has a higher risk in hyperkalemia.

Table 36. Most Common (AE incident rate ≥ 1% in Either Treatment Group) Hyperkalemia-Related AEs (NMQ), Safety Population, PARAGON-HF, Randomized Treatment Period

	AE				SAE				Entresto vs Valsartan		
	Entresto N = 2419		Valsartan N = 2402		Entresto N = 2419		Valsartan N = 2402		Risk Difference[3]		
Preferred Term[1]	n	%[2]	n	%	n	%	n	%	(95% CI)		
Total	272	11.2	363	15.1	19	0.8	42	1.8	-3.9	(-5.8,	-2.0)
Hyperkalemia	252	10.4	328	13.7	19	0.8	42	1.8	-3.2	(-5.1,	-1.4)
Blood Potassium Increased	32	1.3	43	1.8	0	0.0	0	0.0	-0.5	(-1.2,	0.2)

Source: Reviewer's analysis on adae, cross reference Sponsor's Table 14.3.1-1.20 in CSR.
[1] Coded as MedDRA preferred terms (v22.0)
[2] The percentage of subjects in each risk category (n/N*100).
[3] The risk difference (n/N*100) between Entresto and Valsartan (Entresto – Valsartan).
Abbreviations: NMQ, Novartis MedDRA query; AE, adverse event; CI, confidence interval; N, number of subjects in group; n, number of subjects with adverse event

Figure 19 Kaplan Meier Plot for Hyperkalemia-Related AEs (NMQ), Safety Population, PARAGON-HF, Randomized Treatment Period

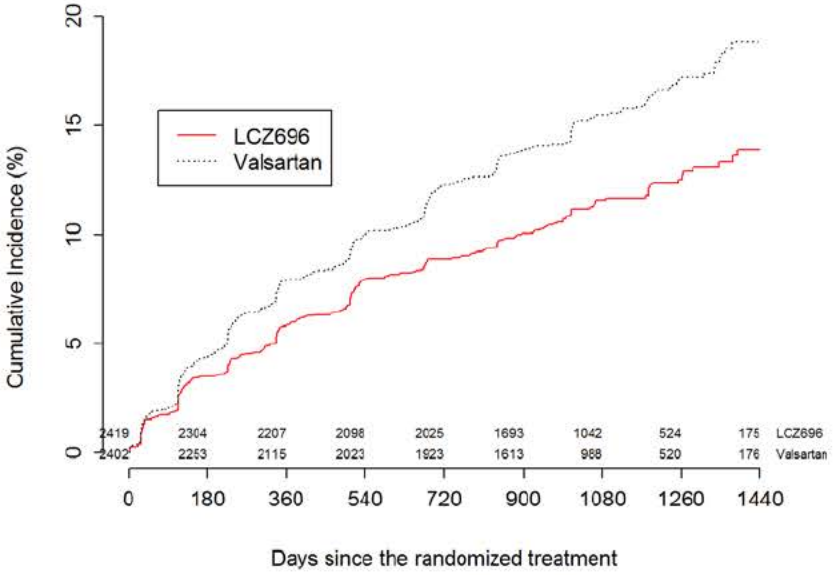


Table 37. The number of patients with serum potassium ≥ 5.5 mmol/L, > 6 mmol/L, and > 6.5 mmol/L at baseline and any postbaseline visit by treatment groups.

	Entresto (N = 2419)					Valsartan (N = 2401)				
	Baseline		Post Baseline		Total	Baseline		Post Baseline		Total
	n	%	n	%	n	n	%	n	%	n
Serum Potassium ≥ 5.5 mmol/L	37	1.54	426	17.76	2398	42	1.76	466	19.57	2381
Serum Potassium > 6.0 mmol/L	2	0.08	75	3.13	2398	2	0.08	101	4.24	2381
Serum Potassium > 6.5 mmol/L	0	0.00	24	1.00	2398	0	0.00	33	1.39	2381

6.5.5.4. Renal impairment

Fewer subjects reported AEs, SAEs (Table 38) or had dose adjustment/interruptions (7.2% vs 10.7%) related to renal impairment (broad FMQ "acute kidney injury") in Entresto than valsartan. A similar number of subjects discontinued from the study (3.0% vs 3.8%) in the two treatment groups. The most common PT is "renal impairment". For all the common PTs, risk is higher in the valsartan group (Table 38).

Figure 20 shows that the cumulative incident rate increased steadily through the study and the valsartan group had a higher cumulative incident rate than the Entresto group.

Average eGFR continuously declined for both treatment groups during the study with a larger mean decrease from baseline to week 144 in valsartan (10.3%) than Entresto (7.7%). Of the safety population, 15.5% vs 20.1% in Entresto and valsartan had more than 40% of eGFR declining from baseline at any postbaseline visit.

Average serum creatinine continuously increased in both treatment arms with a larger increase from baseline to week 144 in valsartan (15.6%) than Entresto (11.3%). Of the safety population,

20.2% vs 26.0% in Entresto and valsartan had serum creatine level increased by more than 0.5 mg/dL from baseline at any postbaseline visit.

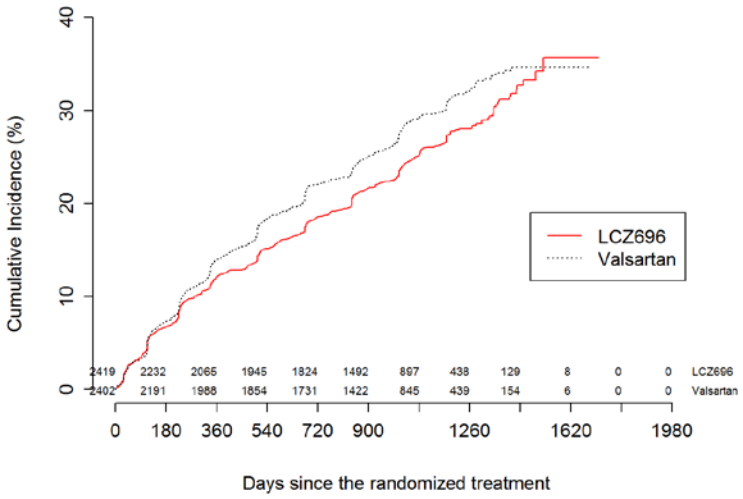
Findings in both AEs and lab results confirmed a higher risk in renal impairment in the valsartan group.

Table 38. Most Common (AE incident rate ≥ 1% in Either Treatment Group) Renal-Impairment-Related AEs (Broad FMQ "Acute Kidney Injury"), Safety Population, PARAGON-HF, Randomized Treatment Period

	AE				SAE				Entresto vs Valsartan	
	Entresto N = 2419		Valsartan N = 2402		Entresto N = 2419		Valsartan N = 2402		Risk Difference[3]	
Preferred Term[1]	n	%[2]	n	%	n	%	n	%	(95% CI)	
Total	605	25.0	679	28.3	140	5.8	178	7.4	-3.3	(-5.8, -0.8)
Renal Impairment	301	12.4	356	14.8	24	1.0	48	2.0	-2.4	(-4.3, -0.4)
Acute Kidney Injury	136	5.6	159	6.6	90	3.7	110	4.6	-1.0	(-2.4, 0.4)
Renal Failure	110	4.6	132	5.5	31	1.3	29	1.2	-1.0	(-2.2, 0.3)
Glomerular Filtration Rate Decreased	85	3.5	96	4.0	0	0.0	3	0.1	-0.5	(-1.6, 0.6)
Blood Creatinine Increased	64	2.7	68	2.8	1	0.0	4	0.2	-0.2	(-1.1, 0.7)

Source: Reviewer's analysis on adae, cross reference Sponsor's Table 12-17 in CSR
[1] Coded as MedDRA preferred terms (v22.0)
[2] The percentage of subjects in each risk category (n/N*100).
[3] The risk difference (n/N*100) between Entresto and Valsartan (Entresto – Valsartan).
Abbreviations: FMQ, FDA MedDRA query; AE, adverse event; CI, confidence interval; N, number of subjects in group; n, number of subjects with adverse event

Figure 20 Kaplan Meier Plot for Renal-Impairment-Related AEs (Broad FMQ), Safety Population, PARAGON-HF, Randomized Treatment Period



6.5.5.5. Cognitive impairment

The number of subjects reported AEs, SAEs (Table 39), discontinued the study (0.12% vs 0.17%), or had dose adjustment/interruptions (0.08% vs 0.21%) due to AEs that are related to cognitive impairment (broad FMQ “confusional state”) is low in both Entresto and valsartan groups. The most common PT is “delirium”. There is no notable difference between the two treatment groups in any common PT (Table 39).

Search for PTs of broad SMQ “dementia” detected a larger number of events but the risk difference between Entresto and valsartan is low (5.25% vs 5.83%). The most common PT is “dementia” (0.79% vs 0.87%)

The time-to-event analysis of the cognitive impairment-related adverse events (broad FMQ) in the randomized treatment period shows little difference in the time-course of the cumulative incident rate between the two treatment groups.

Table 39. Most Common (AE incident rate ≥ 0.5% in Either Treatment Group) Cognitive-Impairment-Related AEs (Broad FMQ "Confusional State"), Safety Population, PARAGON-HF, Randomized Treatment Period

Preferred Term[1]	AE				SAE				Entresto vs Valsartan Risk Difference[3] (95% CI)		
	Entresto N = 2419		Valsartan N = 2402		Entresto N = 2419		Valsartan N = 2402				
	n	%[2]	n	%	n	%	n	%			
Total	47	1.9	52	2.2	18	0.7	24	1.0	-0.2	(-1.0,	0.6)
Delirium	18	0.7	19	0.8	7	0.3	11	0.5	-0.1	(-0.5,	0.5)
Confusional State	16	0.7	19	0.8	6	0.3	7	0.3	-0.1	(-0.6,	0.4)

Source: Reviewer's analysis on adae, cross reference Sponsor's Table 14.3.1-1.20 in CSR
[1] Coded as MedDRA preferred terms (v22.0)
[2] The percentage of subjects in each risk category (n/N*100).
[3] The risk difference (n/N*100) between Entresto and Valsartan (Entresto – Valsartan).
Abbreviations: FMQ, FDA MedDRA query; AE, adverse event; CI, confidence interval; N, number of subjects in group; n, number of subjects with adverse event

6.5.5.6. Hypersensitivity

The number of subjects reported hypersensitivity-related AEs and SAEs (broad SMQ "hypersensitivity") is similar in Entresto and valsartan (Table 40). There is no notable difference in the number of subjects who discontinued the study (0.95% vs 0.87%) or had dose adjustment (0.99% vs 0.96%). The most common PT is "pruritus". There is no notable difference between the two treatment groups in any common PT (Table 40).

Search for PTs of broad FMQ "anaphylactic reaction" detected hypersensitivity-related events in less than 1% of subjects in each arm.

The time-to-event analysis of the hypersensitivity-related adverse events (broad SMQ) in the randomized treatment period shows little difference in the time-course of the cumulative incident rate between the two treatment groups.

Table 40. Most Common (AE incident rate ≥ 1% in Either Treatment Group) Hypersensitivity-Related AEs (Broad SMQ), Safety Population, PARAGON-HF, Randomized Treatment Period

Preferred Term[1]	AE				SAE				Entresto vs Valsartan Risk Difference[3] (95% CI)		
	Entresto N = 2419		Valsartan N = 2402		Entresto N = 2419		Valsartan N = 2402				
	n	%[2]	n	%	n	%	n	%			
Total	380	15.7	385	16.0	80	3.3	82	3.4	-0.3	(-2.4,	1.7)
Pruritus	46	1.9	51	2.1	0	0.0	0	0.0	-0.2	(-1.0,	0.6)
Asthma	40	1.7	45	1.9	9	0.4	10	0.4	-0.2	(-1.0,	0.5)
Respiratory Failure	39	1.6	45	1.9	29	1.2	32	1.3	-0.3	(-1.0,	0.5)
Rash	36	1.5	36	1.5	1	0.0	0	0.0	-0.0	(-0.7,	0.7)
Eczema	27	1.1	17	0.7	2	0.1	0	0.0	0.4	(-0.1,	0.9)
Acute Respiratory Failure	25	1.0	27	1.1	20	0.8	24	1.0	-0.1	(-0.7,	0.5)
Conjunctivitis	18	0.7	29	1.2	0	0.0	0	0.00	-0.5	(-1.0,	0.1)

Source: Reviewer's analysis on adae, cross reference Sponsor's Table 14.3.1-1.20 in CSR.
[1] Coded as MedDRA preferred terms (v22.0)
[2] The percentage of subjects in each risk category (n/N*100).
[3] The risk difference (n/N*100) between Entresto and Valsartan (Entresto – Valsartan).
Abbreviations: SMQ, standard MedDRA query; AE, adverse event; CI, confidence interval; N, number of subjects in group; n, number of subjects with adverse event

6.5.5.7. Thrombosis

In the data pooled from PARADIGM-HF and PARAGON-HF, the percentage of subjects having thrombotic disorder-related AEs is similar in the Entresto group and the active control group (enalapril from PARADIGM-HF and valsartan from PARAGON-HF), shown in Table 41. No individual PT has a risk difference higher than 0.3% (Entresto minus active control). Most of the thrombotic disorder-related AEs (14.9%) are SAEs (10.9%), but only a few discontinued (1.4%). There is also no imbalance in SAEs or AEs leading to discontinuation.

There are more thrombotic AEs in PARAGON-HF than PARADIGM-HF (Table 41), which is expected since PARAGON-HF in general have more AEs than PARADIGM-HF.

Table 41. Most Common (AE incident rate ≥ 1% in the Total Number of Subjects) Thrombotic Disorder-Related AEs (Reviewer's Compiled PTs), Safety Population, Pooled from PARADIGM-HF and PARAGON-HF, Randomized Treatment Period

	PARADIGM				PARAGON				Pooled					
	Entresto N = 4203		Enalapril N = 4229		Entresto N = 2419		Valsartan N = 2402		Entresto N = 6622		Active control N = 6631		Diff[2]	Total[3]
PT	n	%[1]	n	%	n	%	n	%	n	%	n	%	%	%
Total	527	12.5	540	12.8	469	19.4	440	18.3	996	15.0	980	14.8	0.3	14.9
Angina pectoris	172	4.1	170	4.0	123	5.1	123	5.1	295	4.5	293	4.4	0.0	4.4
Acute myocardial infarction	69	1.6	70	1.7	61	2.5	55	2.3	130	2.0	125	1.9	0.1	1.9
Cerebrovascular accident	72	1.7	77	1.8	40	1.7	43	1.8	112	1.7	120	1.8	-0.1	1.8
Angina unstable	60	1.4	57	1.3	59	2.4	45	1.9	119	1.8	102	1.5	0.3	1.7
Coronary artery disease	41	1.0	45	1.1	34	1.4	35	1.5	75	1.1	80	1.2	-0.1	1.2
Ischemic stroke	41	1.0	37	0.9	32	1.3	29	1.2	73	1.1	66	1.0	0.1	1.0
Transient ischemic attack	22	0.5	33	0.8	47	1.9	36	1.5	69	1.0	69	1.0	0.0	1.0

Source: Reviewer's analysis on adae, data pooled from PARADIGM and PARAGON-HF.
[1] The percentage of subjects in each risk category (n/N*100).
[2] The risk difference (n/N*100) between Entresto and active control, pooled from PARADIGM and PARAGON-HF.
[3] The total risk (n/N*100) from both Entresto and active control, pooled from PARADIGM and PARAGON-HF
Abbreviations: AE, adverse event; N, number of subjects in group; n, number of subjects with adverse event

6.5.6. SMQ

Seven broad SMQs on AEs have risk difference higher than 1% between the Entresto and the active control group, pooled from PARADIGM-HF and PARAGON-HF (Table 42). Among these SMQs, PARADIGM-HF and PARAGON-HF show consistent risk differences between their two treatment arms, except for "anaphylactic reaction". No narrow SMQ has a risk difference higher than 1%. No broad or narrow SMQs on SAEs have risk difference higher than 1%.

Table 42. Most Common Broad SMQs (AE incident rate ≥ 1% in the Total Number of Subjects), Safety Population, Pooled from PARADIGM-HF and PARAGON-HF, Randomized Treatment Period

	PARADIGM				PARAGON				Pooled					
	Entresto N = 4203		Enalapril N = 4229		Entresto N = 2419		Valsartan N = 2402		Entresto N = 6622		Active control N = 6631		Diff[2]	Total[3]
SMQ	n	%[1]	n	%	n	%	N	%	n	%	n	%	%	%
Hypokalemia	946	22.5	711	16.8	738	30.5	592	24.6	1684	25.4	1303	19.7	5.8	22.5
Dehydration	886	21.1	677	16.0	756	31.3	614	25.6	1642	24.8	1291	19.5	5.3	22.1
Neuroleptic malignant syndrome	965	23.0	852	20.1	894	37.0	826	34.4	1859	28.1	1678	25.3	2.8	26.7
Hearing and vestibular disorders	355	8.4	294	7.0	358	14.8	293	12.2	713	10.8	587	8.9	1.9	9.8
Vestibular disorders	335	8.0	279	6.6	329	13.6	272	11.3	664	10.0	551	8.3	1.7	9.2
Anaphylactic reaction	1263	30.0	1303	30.8	1007	41.6	882	36.7	2270	34.3	2185	33.0	1.3	33.6
Anticholinergic syndrome	472	11.2	446	10.5	461	19.1	413	17.2	933	14.1	859	13.0	1.1	13.5

Source: Reviewer's analysis on adae, data pooled from PARADIGM and PARAGON-HF.
[1] The percentage of subjects in each risk category (n/N*100).
[2] The risk difference (n/N*100) between Entresto and active control, pooled from PARADIGM and PARAGON-HF.
[3] The total risk (n/N*100) from both Entresto and active control, pooled from PARADIGM and PARAGON-HF
Abbreviations: SMQ, standard MedDRA query; AE, adverse event; N, number of subjects in group; n, number of subjects with adverse event

7. Therapeutic Individualization

7.1. Pediatric Labeling/Plans for Pediatric Drug Development

Agreed Initial Pediatric Study Plan (iPSP)Agreement was issued for the development program of Entresto for the indication of "heart failure in patients with chronic heart failure (NYHA Class II-IV) and preserved ejection fraction" under IND 104628 on April 4, 2018. Under the agreed iPSP agreement, FDA agreed to the Sponsor's proposal of a PREA Full Waiver for pediatric studies in subjects aged 0 to <18 years for Entresto for the treatment of heart failure with preserved ejection fraction because the causes of heart failure in children and adults are different.

8. Human Subjects Protections/Clinical Site and Other GCP Inspections/Financial Disclosure

PARAGON-HF was conducted in compliance with Good Clinical Practice (GCP). The Clinical Study Report describes that the Applicant has a GCP audit program comprised of audits of investigator sites, vendors, and Novartis systems which were performed by auditors (i.e., either internal Novartis Auditors or external contracted Auditors), independent from those involved in conducting, monitoring, or performing quality control of the clinical study. Per Applicant, audits were conducted to assess GCP compliance with global and local regulatory requirements,

protocols and internal standard operating procedures (SOPs), and were performed according to written SOPs. The clinical audit process used a knowledge/risk based approach.

9. Advisory Committee Summary

The Cardiovascular and Renal Drugs Advisory Committee (CRDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research met on December 15, 2020. The committee discussed supplemental new drug application (sNDA) 207620-S18, for the angiotensin receptor-neprilysin inhibitor, ENTRESTO (sacubitril and valsartan) tablets, submitted by Novartis Pharmaceuticals Corp., for the proposed indication of heart failure with preserved ejection fraction (HFpEF).

Issues presented before the CRDAC for discussion and vote, and related committee discussion is summarized below:

1) DISCUSSION: Please comment on the various pre-specified and post-hoc analyses. Which ones contribute to the strength of evidence supporting an indication? Which ones do not?

   Committee Discussion: Committee members voiced concerns over potential competing risk between cardiovascular death and heart failure hospitalization. Members found the pre-specified secondary endpoints and non-pre-specified analyses compelling and consistent. Some members commented that the post-hoc analyses, including investigator-reported readjudication, had little impact on how they interpreted relative risk in the PARAGON-HF trial. Members also supported a graded adjudication process. In general, members thought that the post-hoc analyses supported the idea of a "continuum" of heart failure, rather than distinct classifications of HFpEF and HFrEF. It was also noted that the PARAGON-HF trial population lacked racial diversity.

2) VOTE: Does PARAGON-HF, perhaps supported by previous studies, provide sufficient evidence to support ANY indication?

   Vote Result: Yes: 12 No: 1 Abstain: 0

   Committee Discussion: The majority of committee members agreed that PARAGON-HF provides sufficient evidence to support an indication. Those who voted in favor of an indication voted based on the totality of evidence and unmet need for treatments for HFpEF. These members generally agreed that while PARAGON-HF failed to achieve statistical significance for the primary endpoint, the data were compelling and showed potential benefit outweighing risk. The member who voted "No" expressed concern that no trial, including PARAGON-HF, demonstrated efficacy of any drug in the HFpEF population. There was additional discussion on balancing risk versus benefit over unmet need.

3) DISCUSSION: If an indication for ENTRESTO were not granted on the basis of available information, what would be necessary to augment the support for approval?

   Committee Discussion: If another study were needed, there were various thoughts on how to characterize the population of interest based on ejection fraction. Several members encouraged future efforts to recruit racial minorities, women, and those with multiple comorbidities. Additional suggestions included: broadening the composite endpoint and using a different biomarker rather than left ventricular ejection fraction.

4) DISCUSSION: If ENTRESTO warranted an indication, how would you describe the patients in whom such benefit applies?

Committee Discussion: Members had various proposals to describe an indication for ENTRESTO that was warranted by trial results. Such proposals included: prevention of heart failure hospitalizations in patients with an ejection fraction "less than the lower limit of normal," or a "mildly reduced ejection fraction." Several members favored using an ejection fraction range of 45-55%. Other members debated inclusion of ejection fraction up to 57%. These members believed that an ejection fraction of up to 57% would capture the higher threshold in women. One member raised concerns over imprecision in echocardiography. There was also substantial deliberation on use of the term "mildly reduced" ejection fraction causing subjectivity among treating physicians.

III. Appendices

10. Trial Design: Additional Information and Assessment

10.1. Trial # CLCZ696D2301 (PARAGON-HF)

Table 43 displays the Schedule of Assessments. Table 44 describes the clinical source documents utilized for endpoint event adjudication.

Table 43. Schedule of Assessments, PARAGON-HF

Epoch		Screen	Treatment Run-in			Randomized Treatment																
Visit	DS/S	1	101†	102	103	199/201†	202	203	204	205	206°	207	208°	209	210°	211	212°	213	214° 216° 218° 220°	215 217 219 221*	UNS	299††† EOS
Day		-70/-49	-56/-35	-42/-28	-28/-14	1	28	112	224	336	420	504	588	672	756	840	924	1008	1092 1260 1428 1596	1176 1344 1512 1680		
Week(w)		-10/-7	-8/-5	-6/-4	-4/-2	0	4	16	32	48	60	72	84	96	108	120	132	144	156 180 204 228	168 192 216 240		
Obtain informed consent	S	x																				
Inclusion/Exclusion criteria	DS	x																				
Safety monitoring criteria	DS			(x)[1][5]	x	x[6]																
Relevant Medical History/Current Medical Conditions /Demography	DS	x																				
Medical History Possibly Contributing to Liver Dysfunction	DS	x																				
HF and Diabetes History/Smoking History/Alcohol History	DS	x																				

Epoch		Screen	Treatment Run-in			Randomized Treatment																
Visit	**DS/SS**	**1**	**101†**	**102**	**103**	**199/201†**	**202**	**203**	**204**	**205**	**206°**	**207**	**208°**	**209**	**210°**	**211**	**212°**	**213**	**214° 216° 218° 220°**	**215 217 219 221***	**UNS**	**299††† EOS**
Day		**-70/-49**	**-56/-35**	**-42/-28**	**-28/-14**	**1**	**28**	**112**	**224**	**336**	**420**	**504**	**588**	**672**	**756**	**840**	**924**	**1008**	**1092 1260 1428 1596**	**1176 1344 1512 1680**		
Week(w)		**-10/-7**	**-8/-5**	**-6/-4**	**-4/-2**	**0**	**4**	**16**	**32**	**48**	**60**	**72**	**84**	**96**	**108**	**120**	**132**	**144**	**156 180 204 228**	**168 192 216 240**		
Concomitant Medications	DS	x	x	x	x	x§	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Visit Contact Information	DS		x	x	x	x§	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
NYHA Classification (HF Signs/Symptoms)	DS	x		x	x	x§	x	x	x	x		x		x		x		x		x	x	x
Physical Exam[1]	S	x		x	x	x	x	x	x	x		x		x		x		x		x	x	x
Vital signs (BP and pulse)	DS	x	x	x	x	x§	x	x	x	x		x		x		x		x		x	x	x
Height	DS	x																				
Weight	DS	x				x§	x	x	x	x		x		x		x		x		x	x	x
Waist/hip circumference	DS					x§																x
ECG[2]	DS	x				x				x				x				x		X[2]	(x)	x

Epoch		Screen	Treatment Run-in			Randomized Treatment																
Visit	**DS/SS**	**1**	**101†**	**102**	**103**	**199/201†**	**202**	**203**	**204**	**205**	**206°**	**207**	**208°**	**209**	**210°**	**211**	**212°**	**213**	**214° 216° 218° 220°**	**215 217 219 221***	**UNS**	**299††† EOS**
Day		**-70/-49**	**-56/-35**	**-42/-28**	**-28/-14**	**1**	**28**	**112**	**224**	**336**	**420**	**504**	**588**	**672**	**756**	**840**	**924**	**1008**	**1092 1260 1428 1596**	**1176 1344 1512 1680**		
Week(w)		**-10/-7**	**-8/-5**	**-6/-4**	**-4/-2**	**0**	**4**	**16**	**32**	**48**	**60**	**72**	**84**	**96**	**108**	**120**	**132**	**144**	**156 180 204 228**	**168 192 216 240**		
Echocardiography[3]	DS	x																				
QOL Questionnaire (KCCQ)[4]	DS		x			x		x	x	x				x				x		X		x
Patient Global Assessment[4]	DS					x		x	x	x				x				x		X		x
EuroQol (EQ-5D)[4]	DS					x		x	x	x				x				x		X		x
Mini-Mental State Examination (MMSE)[16]	DS					x				x				x				x		X		x
Complete Laboratory Evaluations[5]	DS	x			x	x§		x		x				x				x		x[13]		x
Abbreviated Laboratory Evaluations[6]	DS			(x)			x		x			x				x				x[13]	(x)	
Local Laboratory[15] Evaluation				(x)	(x)	(x§)															(x)	
Urinalysis	DS	x				x		x		x				x				x			(x)	x

Epoch		Screen	Treatment Run-in			Randomized Treatment																
Visit	DS/S	1	101†	102	103	199/201††	202	203	204	205	206°	207	208°	209	210°	211	212°	213	214° 216° 218° 220°	215 217 219 221*	UNS	299††† EOS
Day		-70/-49	-56/-35	-42/-28	-28/-14	1	28	112	224	336	420	504	588	672	756	840	924	1008	1092 1260 1428 1596	1176 1344 1512 1680		
Week(w)		-10/-7	-8/-5	-6/-4	-4/-2	0	4	16	32	48	60	72	84	96	108	120	132	144	156 180 204 228	168 192 216 240		
FSH[7]	DS	x																				
Plasma NT-proBNP[8]	DS	x	x		x	x		x		x												
Biomarkers/Biobanking[9]	DS		x		x	x		x		x												
1st morning void (urine)[9]	DS		x		x	x		x		x												
Pharmacogenomics[14]	DS				x			x		x												
Pharmacogenetics[10]	DS				x																	
Pharmacokinetic Sampling[11]	DS					x		x		x												
Serum/Urine Pregnancy Test[12]	DS	x	x	x	x	x§	x	x	x	x		x		x		x		x		x	(x)	x
AEs/SAEs	DS		x	x	x	x§	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x

Epoch		Screen	Treatment Run-in			Randomized Treatment																
Visit	DS/S	1	101†	102	103	199/201††	202	203	204	205	206°	207	208°	209	210°	211	212°	213	214° 216° 218° 220°	215 217 219 221*	UNS	299††† EOS
Day		-70/-49	-56/-35	-42/-28	-28/-14	1	28	112	224	336	420	504	588	672	756	840	924	1008	1092 1260 1428 1596	1176 1344 1512 1680		
Week(w)		-10/-7	-8/-5	-6/-4	-4/-2	0	4	16	32	48	60	72	84	96	108	120	132	144	156 180 204 228	168 192 216 240		
Drug Accountability	DS			x	x	x§	x	x	x	x		x		x		x		x		x	(x)	x
Contact IVRS/IWRS	S	x	x	x	x	x§	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dispense Study Medication	S		x	x	x	x	x	x	x	x		x		x		x		x		x	(x)	
Screening Disposition	DS	x																				
Endpoint Information	DS		x	x	x	x§	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Run-in Disposition	DS					x§																
Treatment Disposition	DS																					x

UNS = Unscheduled visit
EOS = End of Study
DS = assessment to be recorded in clinical database
S = assessment to be recorded on source document
(x) = optional assessment

† = Visit performed only for patients that entered the treatment run-in epoch due to having been on an ACEI or ARB medication at doses lower than the total daily dose or per the investigator's discretion based on the patient's clinical status.

†† = Visit 199/201 completed for all patients who entered the treatment run-in epoch. For patients that were randomized, Visit 199/201 was to be combined into one clinic visit. For patients who discontinued during the treatment run-in epoch, only procedures with "§" were performed and no Visit 201 was conducted.

††† = Visit 299 (end of randomized treatment visit) completed for all patients that entered the randomized treatment epoch

° Indicates study visits to be conducted as a telephone contact visit, except for patients enrolled in Japan where these visits were conducted as clinic visits with procedures similar to Visit 202 with the exception that study medication dispensing, drug accountability and serum/urine pregnancy tests were not required.

§ At Visit 199/201, only procedures marked with "§" were performed for patients who discontinued during the run-in epoch.

[1] Complete physical examination required at Visit 1 and 201 and annually thereafter (Visit 205, 209, 213, 217, 221) up until Visit 299 (EOS). Short physical exam required at all interim visits.

[2] ECG performed at Visits 1, 201, and annually thereafter.

[3] Qualifying LVEF measurements/documentation of structural heart disease was based on locally obtained echocardiograms (echo) performed ≤ 6 months prior to Visit 1. If an echo performed ≤ 6 months prior to Visit 1 was not available, an echo was to be performed during the screening epoch.

[4] Patient Global Assessment was not evaluated at Visit 201; patients were asked to remember how he/she felt at Visit 201, throughout the study the patient was asked to rate how he/she felt compared to at the randomization visit (Visit 201). KCCQ value was assessed at the beginning of run-in, i.e. Visit 101 or 102 (whichever occurred first), If the study extended beyond Visit 221, KCCQ, Patient Global Assessment, and EuroQOL would be conducted annually.

[5] Complete laboratory evaluations were collected and sent to the central lab at all specified visits for all patients. If the study was extended beyond Visit 221 a complete laboratory evaluation was performed annually. Complete blood chemistry laboratory was evaluated at Visit 103.

[6] Abbreviated laboratory includes: blood urea nitrogen (BUN), creatinine, potassium and eGFR. If the study extended beyond Visit 221 an abbreviated laboratory evaluation was performed at all interval visits except annual visits.

[7] Not required for males or pre-menopausal women.

[8] Visits 1, 101/102 (whichever was first), 103, 199/201, 203 and 205 (central lab) for all patients. Only the Visit 1 NT-proBNP results were reported to the investigator and the sponsor.

[9] For patients participating in the biomarker substudy. If patient had biomarker sampled at Visit 101, biomarker sample at Visit 102 was not needed.

[10] If the pharmacogenetics substudy sample was not obtained at Visit 103, it could be obtained at any time during the study.

[11] Patients participating in the PK substudy were also to participate in the biomarker substudy; however patients could participate in the biomarker substudy without having to participate in the PK substudy.

Table 44. Table of required source documents needed for event adjudication, PARAGON-HF

Endpoint	Source Documents
Death	Discharge summary or physician narrative, cerebral imaging reports in case of fatal stroke, autopsy report (if performed), cardiac biomarkers and ECG in setting of fatal myocardial infarction
Non-fatal stroke and transient ischemic attack	Discharge Summary, cerebral imaging reports (if performed), neurology consult notes (if available)
End-stage renal disease	Discharge summary, dialysis sheets, clinical note documenting need for dialysis or renal transplant, central lab reports of baseline and two follow-up creatinine values at least 1 month apart
Urgent heart failure visit	Emergency room / clinic notes, medication logs, any documentation of presenting signs and symptoms of heart failure, cardiac markers (if applicable), BNP / NT-proBNP (if available), chest x-ray (if done)
Hospitalization for heart failure	Discharge summary, admitting history and physical documenting presenting signs and symptoms of heart failure, medication logs/clinic notes, cardiac markers (if applicable), chest x-ray (if done)
Non-fatal myocardial infarction and hospitalization for myocardial ischemia	Discharge summary, cardiac biomarkers (if abnormal), electrocardiograms
New onset atrial fibrillation/flutter	Discharge summary or physician narrative, progress/clinic notes, any ECG with evidence of sustained atrial fibrillation/flutter
New onset diabetes mellitus	Central lab reports of baseline and two follow-up glucose values, physician narrative documenting abnormal glucose levels, clinic note documenting treatment initiation for diabetes mellitus

Data Monitoring Committee:

An independent Data Monitoring Committee (DMC) regularly reviewed accumulating study data and the results of pre-specified interim analyses. The committee membership and responsibilities were defined by a written charter and included cardiology, nephrology, and statistical expertise. The Applicant submitted minutes for meetings of the DMC. An external independent statistician and programmer performed analyses and generated reports for the DMC according to a pre-specified analysis plan.

Reviewer's comment: *Review of the meeting minutes did not raise any additional concerns regarding trial conduct.*

10.2. Trial # CLCZ696B2214 (PARAMOUNT)

Title: A 36-Week, randomized, double-blind, multi-center, parallel group, active controlled study to evaluate the efficacy, safety and tolerability of Entresto compared to valsartan in patients with chronic heart failure and preserved left-ventricular ejection fraction.
Study : November 3, 2009 (first subject first visit) to December 22, 2011 (last subject last visit)
Phase: 2
Objectives and Endpoints:
Primary: To demonstrate that Entresto is superior to valsartan in reducing NT-proBNP after 12 weeks of treatment, measured as mean change from baseline to Week 12 in log transformed NT-proBNP.

Secondary: To evaluate efficacy of Entresto compared to valsartan on

1. NT-proBNP, quality of life, NYHA class, renal dysfunction, and echocardiography, measured as combined truncated-achieved-significance-level (CTASL score) based on three domains of six variables: NT-proBNP, quality of life (including the clinical composite score in the Kansas City Cardiomyopathy Questionnaire and the clinical composite assessment), and echocardiography parameters of e', E/e', and left atrial size at both the Week 12 and Week 36
2. Reduction in NT-proBNP from baseline at Week 36 measured as log-transformed NT-proBNP
3. Brain natriuretic peptide (BNP), mid region pro-atrial natriuretic peptide (MR-pro-ANP) and cyclic guanine monophosphate (cGMP)
4. Echocardiographic parameters of diastolic function
5. Improvement in signs and symptoms of heart failure, changes in quality of life assessments and changes in clinical composite assessment
6. Major adverse cardiovascular events
7. Renal function as measured by estimated Glomerular Filtration Rate (eGFR), serum creatinine, and proteinuria change (UACR)
8. Vascular arterial stiffness
9. Mean sitting blood pressure and pulse pressure changes
10. Safety and tolerability of Entresto compared to valsartan

Exploratory: To explore the impact of Entresto as compared to valsartan on

1. Predefined biomarkers (e.g., inflammatory, renal, collagen, metabolism and vascular biomarkers)
2. Days alive out of the hospital

Safety: Data on all adverse events (AEs), serious adverse events (SAEs), pregnancies, laboratory assessments, electrocardiograms (ECGs) and physical examination findings were collected. Angioedema and angioedema-like adverse events were adjudicated by an Angioedema Adjudication Committee (AAC).

Study Design: Study CLCZ696B2214 was a 36 week, randomized, double-blind, active-controlled trial that evaluated the efficacy, safety and tolerability of Entresto compared to valsartan in patients with HFpEF (LVEF ≥ 45%). The study comprised of 1-2 week single-blind, placebo run-in ; 12 week core double-blind ; and a 24 week extension double-blind . Study activities during each are described below:

1. Run-in : 1-2 week single-blind, placebo run-in to complete screening and eligibility assessments.
2. Core Double-Blind : 12 week where patients were randomized to Entresto 200 mg bid versus valsartan 160 mg bid. During the initial 2-4 weeks of this , the study medications were titrated to their final doses. ACEi or ARBs were required to be discontinued 24-hours prior to the randomization visit. Randomization was stratified by prior use of ACEi or ARB.
3. Extension Double-Blind : 24 week that followed the initial 12 week core double-blind .

Study Population: The study was planned to randomize approximately 290 patients (145 patients per treatment arm) with the following key eligibility criteria:

- Inclusion Criteria: Male or female outpatients ≥40 years of age with stable chronic HF, NYHA class II-IV, a left ventricular ejection fraction (LVEF) ≥45%, and a baseline NT-proBNP > 400 pg/mL, on diuretic therapy prior to Visit 1, stable doses of ACEi/ARB and/or beta blocker if prescribed and systolic blood pressure (SBP) < 140 mm Hg or SBP ≥ 160 mm Hg on three or antihypertensive medications. Patients with atrial fibrillation as documented on electrocardiogram (ECG) at Visit 1 were limited to 25% of the overall study population.

- Exclusion Criteria: Patients with a prior LVEF < 45% at any time or who required treatment with both an ACEI and an ARB; isolated right heart failure due to pulmonary disease; dyspnea and/or edema from non-cardiac causes, such as lung disease, anemia or severe obesity; hemodynamically significant mitral and/or aortic valve disease or significant obstructive lesions of the left ventricular outflow tract, including aortic stenosis, hypertrophic obstructive cardiomyopathy; secondary forms of cardiomyopathy such as restrictive cardiomyopathy or infiltrative cardiomyopathy (e.g., amyloid disease); patients with a history of any organ transplant or who were on a transplant list (life expectancy < 6 months at time of entry into the study); SBP ≤ 100 mm Hg; coronary artery disease likely to require coronary artery bypass graft

(CABG) or percutaneous coronary intervention (PCI) during the course of the study; a history of myocardial infarction, unstable angina, coronary bypass surgery or any PCI, stroke or transient ischemic attack (TIA) during the 3 months prior to Visit 1.

Study Treatment: Entresto Arm: Target dose 200 mg of Entresto twice daily
Active Control Arm: Target dose 160 mg of valsartan twice daily

Statistical Approach: The primary efficacy null hypothesis was H0: $\mu1 = \mu2$ vs. Ha: $\mu1 \neq \mu2$, where $\mu1$ and $\mu2$ were mean changes from baseline to Week 12 in log-transformed NT-proBNP for the treatment groups of Entresto and valsartan, respectively. The analysis of covariance (ANCOVA) model was used, with treatment (two levels according to the treatments), randomization stratification (prior use of ACEi/ARB), and region as the fixed factors and the baseline in log-transformed NT-proBNP as a covariate. Statistical testing was performed at the two-sided significance level of 0.05 and estimated geometric means for the ratios, estimated effect sizes, and their 95% confidence intervals were provided based on the ANCOVA model. The last-observation-carry-forward (LOCF) technique was used to impute missing efficacy values at Week 12 and Week 36. The result was referred to as the Week 12 and Week 36 endpoints, respectively. The following two LOCF approaches were also used:

- LOCF (Full): Carry forward earlier last post-baseline measurement if the value at Week 12 or Week 36 is missing.
- LOCF (Week 8): Carry forward last post-baseline measurements collected at Week 8 or later if Week 12 or Week 36 is missing.

A sensitivity analysis was conducted using the LOCF (Week 8) for all post-randomization values using the above ANCOVA model.
Secondary efficacy variables were analyzed using the ANCOVA approach for continuous variables and logistic regression model for variables with a binary endpoint.

10.3. Trial # CLCZ696D2302 (PARALLAX-HF)

Title: A 24-week, randomized, double-blind, multi-center, parallel group, active controlled study to evaluate the effect of Entresto on NT-proBNP, exercise capacity, symptoms and safety compared to individualized medical management of comorbidities in patients with heart failure and preserved ejection fraction.
Study : August 22, 2017 (first subject first visit) to October 28, 2019 (last subject last visit)
Phase: 3
Objectives and Endpoints:
Primary:

1. To demonstrate that Entresto is superior to individualized medical therapy for comorbidities in reducing N-terminal pro-brain natriuretic peptide (NT-proBNP) from baseline after 12 weeks of treatment. The endpoint was change from baseline in NT-proBNP (in log scale) at Week 12.

2. To demonstrate that Entresto is superior to individualized medical therapy (IMT) for comorbidities in improving exercise capacity as assessed by the six-minute

walk test (6MWT) at Week 24 in a subset of patients. The endpoint was change from baseline in six-minute walk distance (6MWD) at Week 24.

Secondary:

11. To compare Entresto to IMT on mean change of Kansas City Cardiomyopathy Questionnaire (KCCQ) clinical summary score (CSS) at Week 24 measured as change form baseline in KCCQ CSS at Week 24.
12. To compare Entresto to IMT on proportion of patients with ≥ 5-points change in KCCQ CSS at Week 24 (separate analyses for ≥ 5-points improvement and ≥ 5-points deterioration).
13. To compare Entresto to IMT in improving NYHA functional class at Week 24 measured as change from baseline in NYHA functional class at Week 24.
14. To compare Entresto to IMT in improving symptoms as assessed by The Short Form (36) Health Survey (SF-36) physical component summary (PCS) score at Week 24 measured as change from baseline in SF-36 PCS score at Week 24.
15. Safety was evaluated by collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, laboratory data, physical examination findings, and electrocardiogram. Angioedema or angioedema-like events were reported and Angioedema Adjudication Committee (AAC) assessed all angioedema reports. Liver safety monitoring was performed, and liver events were categorized as: liver events of special interest (which consist of liver function test elevations) and medically significant liver events (which were considered as SAEs and which consist of marked elevations of liver function tests and / or pre-specified AEs).

Study Design: Study CLCZ696D2302 was a 24 week, randomized, double-blind, active controlled trial that evaluated the effect of Entresto versus individualized medical therapy on NT proBNP, exercise capacity, symptoms and quality of life (QoL) in patients with heart failure and preserved left ventricular ejection (HFpEF) fraction (LVEF > 40%). Eligible patients were stratified into three strata based on treatment that they were receiving at the time of screening i.e.; angiotensin converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB) or no prior renin angiotensin system inhibitors (RASi). Patients in each stratum were then randomized in a 1:1 ratio to Entresto or comparator (i.e.; enalapril for patients in ACEi strata, valsartan for patients in the ARB strata and placebo for patients in the No RASi strata). The study comprised of screening (2 weeks) and randomized treatment (24 weeks) s. Study drug up titration was performed during the first 1 to 4 weeks of the randomized treatment .

Study Population: The study was planned to randomize 2500 patients with the following key eligibility criteria:

- Inclusion Criteria: Patients ≥ 45 years of age, male or female, LVEF > 40% and evidence of structural heart disease (left atrial enlargement and/or left ventricular hypertrophy), current symptoms of HF (NYHA class II-IV), use of diuretics within the prior 30 days, NT-proBNP > 220 pg/mL for patients with no atrial fibrillation (AF) or > 600 pg/mL for patients with AF, and KCCQ CSS < 75, on appropriate medical therapy for comorbidities as assessed by the investigator.

- Exclusion Criteria: Any prior LVEF ≤ 40%; acute coronary syndrome (including myocardial infarction [MI]), cardiac surgery, other major cardiovascular (CV) surgery, or urgent percutaneous coronary intervention (PCI) within the 3 months prior to Visit 1 or an elective PCI within 30 days prior to Visit 1; current (within 30 days from Visit 1) acute decompensated HF requiring augmented therapy with diuretics, vasodilators and/or inotropic drugs; known history of angioedema; walk distance limited by non-cardiac comorbid conditions; probable alternative diagnoses that in the opinion of the investigator could account for the patient's HF symptoms (i.e. dyspnea, fatigue) such as significant pulmonary disease (including primary pulmonary HTN), anemia or obesity; systolic blood pressure (SBP) ≥ 180 mmHg at Visit 1; SBP > 150 mmHg and < 180 mmHg at Visit 1 unless the patient is receiving 3 or more antihypertensive drugs; SBP < 110 mmHg or symptomatic hypotension at Visit 1; HbA1c > 7.5% not treated for diabetes; history of any dilated cardiomyopathy, including peripartum cardiomyopathy, chemotherapy induced cardiomyopathy, or viral myocarditis; right sided HF in the absence of left-sided structural heart disease; known pericardial constriction, genetic hypertrophic cardiomyopathy, or infiltrative cardiomyopathy; clinically significant congenital heart disease; hemodynamically significant valvular heart disease; stroke, transient ischemic attack, carotid surgery or carotid angioplasty within the 3 months prior to Visit 1; coronary or carotid artery disease or valvular heart disease likely to require surgical or percutaneous intervention during the trial; life-threatening or uncontrolled arrhythmia, including symptomatic or sustained ventricular tachycardia and atrial fibrillation or flutter with a resting ventricular rate > 110 beats per minute (bpm); cardiac resynchronization therapy (CRT) device; SGOT (AST) or SGPT (ALT) values exceeding 3 × the upper limit of normal (ULN), bilirubin > 1.5 mg/dl at Visit 1; eGFR < 30 mL/min/1.73m2 as calculated by the Modification in Diet in Renal Disease (MDRD) formula at Visit 1.

Study Treatment: Entresto arm: Target dose 200 mg of Entresto twice daily;
Comparator arm: Target dose 10 mg of enalapril daily or 160 mg of valsartan twice daily or matching placebo

Statistical Approach:
The sample size of 2500 patients provided a power of 92% to > 99% to detect a relative reduction of 11 to 25% in change from baseline to Week 12 in NT-proBNP. No interim analysis was planned.

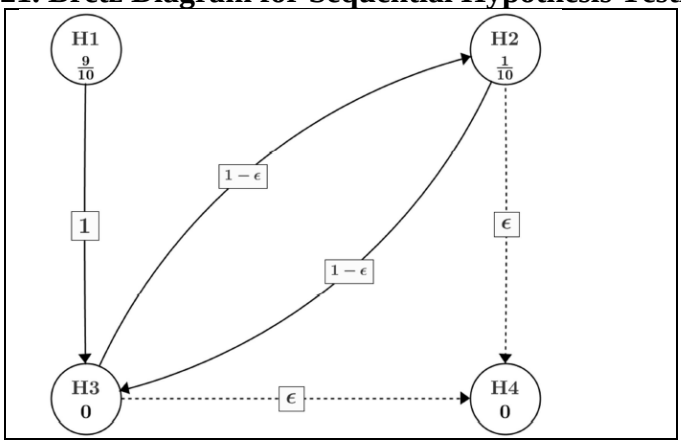
The following null hypotheses were included in the testing strategy:

1. H1: Entresto is no better than IMT in change from baseline in log(NT-proBNP) at Week 12 in the overall study population
2. H2: Entresto is no better than IMT in change from baseline in 6MWD at Week 24 in patients with baseline 6MWD (B6MWD) ranging from 100 m to 450 m.
3. H3: Entresto is no better than IMT in change from baseline in KCCQ CSS at Week 24 in the overall study population (secondary null hypothesis).

4. H4: Entresto is no better than IMT in NYHA change from baseline at Week 24 in the overall study population (secondary null hypothesis).

In order to control the family-wise type-I error rate at the one-sided 0.025 significance level, a sequentially rejective multiple testing procedure was employed, whereby H1 and H2 were tested first at initially assigned level of one-sided $(9/10) \times \alpha = 0.0225$ and one-sided $(1/10) \times \alpha = 0.0025$, respectively. The statistical model used to test H1, H2, and H3 was mixed model for repeated measures; H4 was proportional cumulative odds model; and change in 6MWD, KCCQ CSS, NYHA, and SF-36 PCS was longitudinal binary logistic regression model. Figure 21 displays the sequential hypothesis testing procedure in Study CLCZ696D2302.

Figure 21. Bretz Diagram for Sequential Hypothesis Testing Procedure in Study D2303



Source: Figure 9-1 of Clinical Study Report Study No. CLCZ696D2302

Changes in planned analysis: The planned subgroup analyses model assumed that the treatment-by-subgroup interaction terms (between subgroup differences in treatment effects) are identical across all visits. However, the Applicant states that based on the study data this assumption may be violated. Therefore, the Applicant changed the analysis approach, and subgroup-by-visit and subgroup-by-treatment-by-visit interaction terms were added to the original subgroup analyses model (Section 9.7.5.4 and Section 9.7.6.4) for primary and secondary endpoints (except the NYHA class change).

Reviewer's Comment: *Including a three-way interaction term for subgroup-by-treatment-by-visit is the correct model when you know that your treatment effect will change over time. However, such an analysis should have be pre-specified before examining the data. While the correct model was used, it should have been what was pre-specified unless strong evidence existed that the treatment effect over time remained constant. Any results run from analyses that were specified after looking at the data must be interpreted with caution.*

Protocol Amendments: Two protocol amendments for Study CLCZ696D2302 are listed below:

1) Version 01, January 24, 2017: No patients were randomized at the time of this amendment. The eGFR exclusion criteria was corrected from < 15 mL/min/1.73m^2 (typographical error) to < 30 mL/min/1.73m^2.

2) Version 02, September 12, 2018: Approximately 1095 patients had been randomized at the time of this amendment. The amendment included the following changes:
    i. The LVEF inclusion criteria was changed from ≥ 45% to > 40% so that the Entresto development program included a full LVEF spectrum

ii. The sample size was increased from 2,200 to 2,500 patients to include 300 patients with LVEF > 40%

iii. 6MWD was changed from secondary endpoint to a primary endpoint in a subset of patients with baseline 6MWD ranging from 100 meters to 450 meters. The stated rationale for this change was an increasing importance to generate exercise capacity data in HFpEF population.

iv. Multiple testing strategy for the primary and secondary endpoints was added to control the family-wise Type-1 error rate.

Reviewer's Comment: *Protocol Amendment in Version 02 that broadened the LVEF criteria to include patients with LVEF > 40% instead of 45% dilutes the study population with a group of patients with reduced LVEF in whom efficacy of Entresto has already been demonstrated. This amendment was included after half of the study population had been randomized.*

11. Efficacy Assessment Additional Information and Assessment

11.1. Trial # CLCZ696D2301 (PARAGON-HF)

The original protocol for PARAGON-HF is dated June 3, 2013. There were 4 amendments to the PARAGON-HF study protocol dated June 10, 2014; May 6, 2015; December 4, 2015; and December 9, 2015. On February 18, 2016 a protocol addendum was added to Protocol V03 and V04. Relevant changes in these protocol amendments are listed below:

Amended Protocol Version 01 dated June 10, 2014 was updated with:

1. Results of the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial.
2. Decision of the Data Monitoring Committee (DMC) to stop PARADIGM-HF study ahead of schedule because compared to enalapril, patients treated with sacubitril/valsartan were less likely to die from CV causes or be admitted to the hospital with worsening HF.

Amended Protocol Version 02 dated May 06, 2015 was changed as follows:

1. Secondary objective of comparing sacubitril/valsartan to valsartan on changes in the clinical summary score for HF symptoms and physical limitations (as assessed by Kansas City Cardiomyopathy Questionnaire [KCCQ]) at 8 months was added as number 1 secondary objective.
2. The endpoint of time to first occurrence of a composite renal endpoint, defined as: renal death, or reaching end stage renal disease (ESRD), or ≥ 50% decline in estimated

glomerular filtration rate (eGFR) relative to baseline was changed from exploratory to secondary objective number 3.

3. The alpha relocation in sequentially rejective multiple test procedure for the secondary hypotheses was updated.
4. Secondary objective of comparing sacubitril/valsartan to valsartan in reducing the rate of the composite endpoint of CV death, total non-fatal HF hospitalizations, total nonfatal strokes, and total non-fatal myocardial infarctions (MIs) was changed to an exploratory objective.
5. Secondary objective of comparing sacubitril/valsartan to valsartan in delaying the time to new onset atrial fibrillation (NOAF) in patients with no history of AF and without AF on ECG at baseline was changed to an exploratory objective.
6. Objective to compare effect of sacubitril/valsartan to valsartan on changes in cognitive function assessed by Mini-Mental State Examination [MMSE]) at 2 years was added.
7. Subgroup by baseline eGFR (<60 vs ≥60 mL/min/1.73 m2) was added to the planned subgroup analyses.
8. Cardiac monitoring sub study to measure atrial fibrillation burden in approximately 600 patients was removed.
9. Age inclusion criteria was changed from ≥ 55 to ≥ 50 years to include younger patients.
10. Patients who had HHF within 9 months prior to Visit 1 also needed to have NT-proBNP >200 pg/ml for patients not in atrial fibrillation/flutter (AF) or >600 pg/ml for patients in AF on Visit 1 ECG to be eligible.
11. Exclusion criteria of any prior echocardiogram measurement of LVEF <45% was changed to <40%.
12. Exclusion criteria for systolic blood pressure was changed from < 105 to < 100 mm Hg at Visit 103 (end of treatment run-in) or Visit 199/201 (randomization visit).
13. Exclusion criteria of eGFR <25 mL/min/1.73m2 at Visit 103 (end of treatment run-in) or Visit 199/201 was added.
14. Assessment of endpoints - total non-fatal myocardial infarctions, non-fatal strokes, KCCQ overall summary score and subdomain scores, new onset atrial fibrillation, mini-mental state examination score was added.
15. The efficacy interim analysis plan was changed from 50% to when two-thirds of target number of adjudicated primary events are obtained (approximately 1148 instead of 860 events).
16. Plan to conduct a futility analysis during interim efficacy analysis if superiority boundary was unlikely to be crossed was removed.

Amended Protocol Version 03 dated December 4, 2015:

There were 1508 patients randomized into the trial at the time of this amendment.

- Sample size was increased from 4300 to 4600 to increase statistical power from 81 to 85% to detect a 25% reduction in recurrent HHF. The sample size re-estimation was based on an analysis of recurrent heart failure hospitalization in the PARADIGM-HF, which showed that sacubitril/valsartan resulted in approximately a 25% reduction in recurrent heart failure hospitalizations relative to enalapril. The target number of primary events was also increased to 1847, which corresponded to conducting the interim efficacy analysis when ~1231 primary composite events have been confirmed

by adjudication. A 25% reduction in recurrent heart failure hospitalizations was expected to correspond to an overall 19% reduction in the primary endpoint (CV deaths and total recurrent heart failure hospitalization).

- The target number of primary events was increased to 1847.
- Statistical stopping rules for superiority of sacubitril/valsartan over valsartan were modified from one-sided p-value of <0.0001 for the primary endpoint to one sided p-value of <0.001 for both the primary endpoint and CV death at the interim efficacy analysis.
- Source documentation verification to ensure adherence to the study eligibility criteria as needed was incorporated.

Amended Protocol Version 04 dated December 9, 2015 was updated with additional study visits for Japan and India, and LVEF assessment in India had to be performed using 2D volumetric methods.

GCP Deviations:

Site 3305 was prematurely closed due to significant GCP deviations which affected the integrity of the data. As a result, the 26 randomized patients at this site were excluded from the efficacy analyses but were included in the safety analyses. Protocol deviations were assigned to these patients.

Treatment Unblinding:

A total of 5 patients were unblinded during the study leading to treatment discontinuation.

Protocol Deviations:

In the randomized set, 34.6% of patients had at least one protocol deviation during the study. The percentage of patients with protocol deviation(s) was balanced between the two treatment groups. The most common protocol deviation was "overall drug compliance < 80%" at one or more medication compliance assessment visit and was similar between Entresto (16.4%) and valsartan (16.6%) groups. There were 119 (4.9%) and 139 (5.8%) patients in Entresto and valsartan groups, respectively who used an open-label ACEI, ARB, or renin inhibitor concomitantly while taking study medication at some point in the study. A total of 12 (0.50%) and 14 (0.58%) patients in Entresto and valsartan groups, respectively were excluded from the full analysis set due to protocol deviations for GCP reasons.

Additional Baseline Characteristics

Table 45 shows baseline demographic characteristics of patients with LVEF ≤ 40%, ≤ 57% and > 57% in PARADIGM-HF and PARAGON-HF.

Table 45. Baseline demographic characteristics of patients with LVEF ≤ 40%, 45- 57%, and > 57% in PARADIGM-HF and PARAGON-HF

		LVEF ≤ 40% PARADIGM-HF		LVEF 45-57% PARAGON-HF		LVEF > 57% PARAGON-HF	
Characteristic	Category	Entresto N=4209	Enalapril N=4233	Entresto N=1239	Valsartan N=1256	Entresto N=1168	Valsartan N=1133
Age 65 years	Below 65	2122 (50.4%)	2177 (51.4%)	248 (20.0%)	251 (20.0%)	164 (14.0%)	162 (14.3%)
	At least 65	2087 (49.6%)	2056 (48.6%)	991 (80.0%)	1005 (80.0%)	1004 (86.0%)	971 (85.7%)

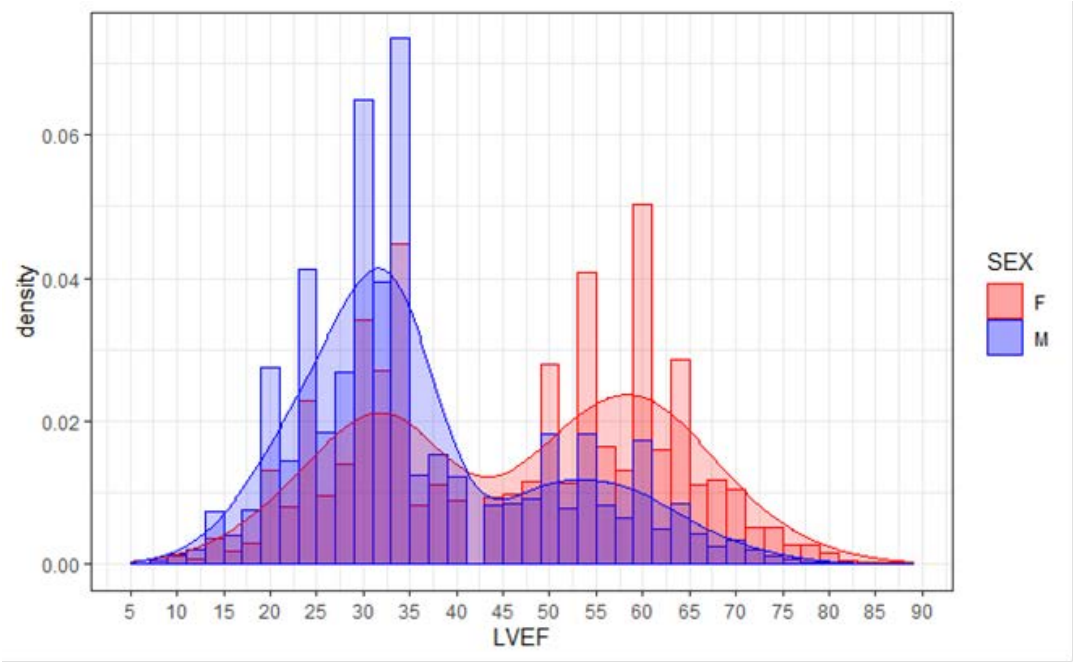
		LVEF ≤ 40% PARADIGM-HF		LVEF 45-57% PARAGON-HF		LVEF > 57% PARAGON-HF	
Sex	Male	3321 (78.9%)	3274 (77.3%)	686 (55.4%)	709 (56.4%)	480 (41.1%)	442 (39.0%)
	Female	888 (21.1%)	959 (22.7%)	553 (44.6%)	547 (43.6%)	688 (58.9%)	691 (61.0%)
Race	White	2780 (66.1%)	2799 (66.1%)	1039 (83.9%)	1043 (83.0%)	924 (79.1%)	901 (79.5%)
	Black	213 (5.1%)	215 (5.1%)	21 (1.7%)	23 (1.8%)	31 (2.7%)	27 (2.4%)
	Asian	760 (18.1%)	750 (17.7%)	137 (11.1%)	143 (11.4%)	160 (13.7%)	167 (14.7%)
	Am. Indian Or Alaska Native	84 (2 %)	88 (2.1%)	14 (1.1%)	14 (1.1%)	14 (1.2%)	9 (0.8%)
	Pacific Islander	0 (0 %)	1 (0.02%)	0 (0.0%)	1 (0.1%)	39 (3.3%)	29 (2.6%)
	Other	372 (8.8%)	380 (9 %)	28 (2.3%)	32 (2.5%)		
Diabetes	No	2747 (65.3%)	2768 (65.4%)	679 (54.8%)	706 (56.2%)	679 (58.1%)	663 (58.5%)
	Yes	1462 (34.7%)	1465 (34.6%)	560 (45.2%)	550 (43.8%)	489 (41.9%)	470 (41.5%)
Hypertension	No	1229 (29.2%)	1243 (29.4%)	69 (5.6%)	69 (5.5%)	34 (2.9%)	40 (3.5%)
	Yes	2990 (70.8%)	2990 (70.6%)	1170 (94.4%)	1187 (94.5%)	1134 (97.1%)	1093 (96.5%)
NYHA Class	Missing			42 (3.4%)	42 (3.3%)	48 (4.1%)	45 (4.0%)
	1	183 (4.4%)	213 (5%)	35 (2.8%)	29 (2.3%)	35 (3.0%)	35 (3.1%)
	2	3007 (71.4%)	2930 (69.2%)	908 (73.3%)	917 (73.0%)	884 (75.7%)	859 (75.8%)
	3	979 (23.3%)	1056 (24%)	248 (20.0%)	262 (20.9%)	199 (17.0%)	191 (16.9%)
	4	33 (0.8%)	27 (0.6%)	6 (0.5%)	6 (0.5%)	2 (0.2%)	3 (0.3%)
Age (years)	N	4209	4233	1239	1256	1168	1133
	Mean (SD)	63.8 (11.5)	63.8 (11.3)	71.9 (8.4)	72.0 (8.7)	73.6 (8.2)	73.7 (8.2)
	Median (Min, Max)	64 (18, 93)	64 (21, 96)	73.0 (50.0, 94.0)	73.0 (50.0, 96.0)	74.0 (50.0, 98.0)	74.0 (51.0, 93.0)
LVEF (%)	N	4209	4232	1239	1256	1168	1133
	Mean (SD)	29.6 (6.1)	29.4 (6.2)	51.4 (3.7)	51.3 (3.8)	64.1 (5.2)	64.3 (5.4)
	Median (Min, Max)	30 (5, 39.8)	30 (5, 39.9)	51.0 (30.0, 57.0)	50.0 (45.0, 57.0)	63.0 (58.0, 89.0)	63.0 (57.2, 89.0)
BMI (kg/m^2)	N	4203	4229	1239	1255	1167	1133
	Mean (SD)	28.1 (5.5)	28.2 (5.5)	30.1 (4.9)	30.3 (5.1)	30.2 (4.9)	30.2 (5.1)

		LVEF ≤ 40% PARADIGM-HF		LVEF 45-57% PARAGON-HF		LVEF > 57% PARAGON-HF	
SBP (mm Hg)	Median (Min, Max)	27.5	27.5	29.7 (17.2, 45.5)	29.9 (16.2, 46.2)	29.8 (15.7, 44.4)	29.9 (15.0, 46.7)
	N	4209	4233	1239	1255	1168	1133
	Mean (SD)	121.5 (15.2)	121.2 (15.4)	130.3 (15.1)	130.6 (14.8)	130.7 (16.0)	130.6 (15.9)
	Median (Min, Max)	120.0	120.0	130.0 (100.0, 200.0)	130.0 (100.0, 185.0)	130.0 (100.0, 190.0)	130.0 (92.0, 185.0)
NT proBNP (pg/ml)	N	4204	4224	881	867	809	773
	Mean (SD)	2916 (4040)	2924 (3985)	943.5 (1069.9)	981.7 (1357.6)	871.9 (1690.5)	843.4 (1369.3)
	Median (Min, Max)	1639 (46, 64524)	1612 (10, 84208)	616.0 (25.0, 9230.0)	628.0 (12.5, 22727)	503.0 (30.0, 29804)	503.0 (36.0, 27799)

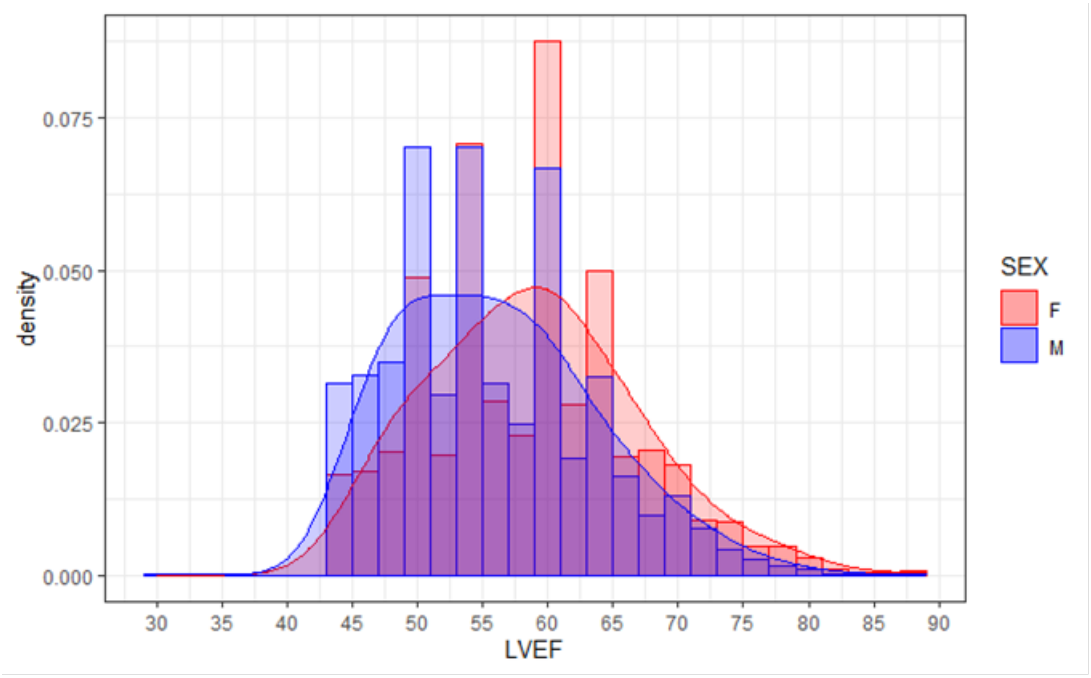
Figure 22 displays the distribution of patients by left ventricular ejection fraction by sex in PARAGON-HF and PARADIGM-HF (unadjusted). Note that there were nominal number of patients in the LVEF range of 40-45% because of the inclusion criteria for each trial. PARAGON-HF enrolled almost half the number of patients enrolled in PARADIGM-HF. PARADIGM-HF and PARAGON-HF population had greater proportion of men and women, respectively. The unadjusted LVEF range for women is slightly higher than men in these trials.

Figure 22. Distribution of Patients by Left Ventricular Ejection Fraction by Sex (unadjusted) in PARAGON-HF and PARADIGM-HF (Safety set)

PARADIGM-HF and PARAGON-HF



PARAGON-HF



F: Female, M: Male, LVEF: Left ventricular ejection fraction

Source: Reviewer's analysis

Other Supportive Pre-Specified Efficacy Analyses Results in PARAGON-HF

1) In a time to event analysis conducted to support the primary efficacy results, the incidence of HHF was 405/2407 (17%) versus 433/2389 (18%), and i-th HHF to (i+1)th HHF was 285/405 (70%) versus 364/433 (84%) in Entresto versus valsartan arm, favoring Entresto.
2) Analysis of adjudicated expanded primary composite endpoint of total HHF, urgent HF visits and CV death demonstrated a RR of 0.86; 95% CI: 0.75, 0.99 favoring Entresto. There were 40 and 55 adjudicated urgent heart failure events in Entresto and valsartan arms, respectively.
3) A sensitivity analysis of investigator-reported primary composite endpoint of total HHF and CV death demonstrated a RR of 0.84; 95% CI: 0.74, 0.97. Investigator-reported events added 226 and 290 HHF events but decreased CV death by 56 and 58 events in Entresto and valsartan arms, respectively. Hence, net 170 and 232 events were added to the adjudicated primary composite endpoint in Entresto and valsartan arms, respectively.
4) Analysis of investigator-reported expanded primary composite endpoint of total HHF, urgent HF visits and CV death demonstrated a RR of 0.83; 95% CI: 0.73, 0.95 favoring Entresto. There were 136 and 173 investigator-reported urgent heart failure events in Entresto and valsartan arms, respectively.
5) Analysis of the adjudicated primary composite endpoint in the Per-Protocol set and On-Treatment set yielded RR similar to the FAS.

Other Efficacy Analyses

1) A post-hoc win ratio analysis of time to CV death, HHF (CV death tested before HHF), combination of change in NYHA class and change in KCCQ, and time to composite renal endpoint with a prespecified hierarchal sequence demonstrated a win ratio (WR) of 1.087. Respective number of contributions of CV death, HHF, combination of change in NYHA class + KCCQ CSS, and composite renal endpoint to wins and losses was 17 and 18%; 31 and 31%; 51 and 51%; 1 and 0%. These results suggest a neutral effect of Entresto on the primary composite endpoint of CV death and HHF.
2) An analysis of recurrent events for composite endpoint of CV death, total HHF, total strokes, and total myocardial infarctions (MI) in FAS demonstrated a RR of 0.89 (0.79 - 1.02). There was a slightly higher incidence of MI in Entresto group with exposure-adjusted rate per 100 patient years of 2.01 and 1.87 in Entresto and valsartan groups, respectively.
3) Time to new onset atrial fibrillation: There was no difference in time to new onset atrial fibrillation in Entresto versus valsartan groups (HR=1.04; 95% CI: 0.82, 1.33).
4) Health related quality of life- EQ-5D VAS: A repeated measures analysis of change from baseline in EQ-5D VAS to compare changes in the health related quality of life between treatment groups showed no difference between the treatment groups up to Year 3.

5) Number of days alive out of the hospital: Analyses based on ANCOVA model with treatment and region as fixed-effect factors were conducted evaluating days alive out of the hospital and days alive out of hospitalization for heart failure. During the randomized , patients in Entresto group had approximately 7 more days alive out of the hospital adjusted for the duration of exposure compared to valsartan group.
6) Intensive Care Unit (ICU) Days: During randomized treatment , the number of days in ICU per patient per year adjusted for treatment and region was 0.50 (0.40, 0.63) and 0.58 (0.46, 0.72) in Entresto and valsartan groups, respectively.
7) 30-Day Rehospitalization Rate for Heart Failure: There was no significant difference in the rate of 30-day re-hospitalization for HF. 88.15 and 87.53% patients had no 30-day re-hospitalization, and 11.85 and 12.47% had at least one 30-day re-hospitalization in Entresto and valsartan groups, respectively.
8) All-cause Hospitalizations: The rate of total hospitalizations per patient per year adjusted for treatment and region was 0.47 (0.45, 0.50) and 0.49 (0.46, 0.52) in Entresto and valsartan groups, respectively. The number of re-hospitalizations per patient per year adjusted for treatment and region was 0.52 (0.48, 0.56) and 0.55 (0.51, 0.60) in Entresto and valsartan groups, respectively.
9) Biomarkers: The ratio of NT-proBNP to baseline levels was approximately 19% and 17% lower in the Entresto versus valsartan group at Week 16 and Week 48 post randomization, respectively (Table 46).

Table 46. Repeated measures analysis of NT-proBNP by Treatment Arm, PARAGON-HF (Full Analysis Set (1))

	LCZ696 N=1400		Valsartan N=1374		LCZ696 vs. Valsartan	
Visit	n	LSM of ratio: E/B Geometric Mean (95% CI)	n	LSM of ratio: E/B Geometric Mean (95% CI)	LSM of ratio: LCZ696/ Valsartan	(95% CI)
Visit 203 (Week 16)	1345	0.7644 (0.7362, 0.7937)	1315	0.9450 (0.9097, 0.9816)	0.8089	(0.7668, 0.8534)
Visit 205 (Week 48)	1273	0.8062 (0.7724, 0.8415)	1229	0.9666 (0.9254, 1.0095)	0.8341	(0.7847, 0.8866)

(1) Includes patients in the Full analysis set who had NT-proBNP samples available for analysis at either V101 or V102. Baseline is Visit 101 or 102, whichever occurs first. The change from baseline in logarithmic scale is analyzed using a repeated measure ANCOVA model with treatment, region, visit, treatment-by-visit interaction as fixed-effect factors, log transformed baseline value as a covariate, and a common unstructured covariance matrix among visits for each treatment group. The analysis is using all available data up to Visit 205 (week 48) based on likelihood method with an assumption of missing at random (MAR) for missing data. Ratio: E/B=Endpoint/Baseline; CI=Confidence interval; Geometric mean= back-transformed from the LS mean based on the ANCOVA model. The same transformation is applied to the 95% CI.

Source: CLCZ696D2301 Study Report Table 11-19

Table 47, Table 48, and Table 49 show the days alive and out of hospital, incidence of hospitalization (regardless of etiology), and emergency room visits for heart failure, respectively. These data indicate that compared to valsartan, Entresto was associated with approximately 7

and 6.5 more days alive out of the hospital (for any etiology) and days alive out of heart failure hospitalization, respectively. Given the high prevalence of HF, this reduction in duration of hospitalization may have a significant public health impact.

Table 47. Number of days alive out of the hospital by treatment arm, PARAGON-HF (Full Analysis Set)

Parameter	Entresto N=2407	Valsartan N=2389	Entresto - Valsartan
	LSM (SE)	LSM (SE)	LSM of difference (95% CI)
DAOOH during first 12 months in the randomized treatment	356 (0.80)	354 (0.81)	1.78 (-0.45, 4.01)
DAOOH during randomized treatment adjusting for follow-up time	1046 (4.68)	1039 (4.70)	7.14 (-5.86, 20.15)
Days alive out of heart failure hospitalization during first 12 months in the randomized treatment	359 (0.76)	357 (0.76)	1.99 (-0.12, 4.10)
Days alive out of heart failure hospitalization during randomized treatment adjusting for follow-up time	1056 (4.63)	1049 (4.65)	6.49 (-6.36, 19.38)

LSM: Least Square Mean; DAOOH: days alive out of hospital; SE: Standard Error of Mean; CI: Confidence Interval

Source: Reviewer's Compilation

Table 48. Incidence of hospitalizations by treatment arm, PARAGON-HF (Full Analysis Set)

Parameter	Entresto N=2407	Valsartan N=2389	Rate Ratio (Confidence Interval)
All-cause hospitalizations n (%)	1335 (55.5 %)	1323 (55.4%)	0.96 (0.88, 1.04)
All-cause hospitalizations per patient mean, SD, range	1.38, 1.97, 0 - 17	1.45, 2.23, 0-27	0.96 (0.88, 1.04)
Total CV hospitalizations (exposure adjusted rate per 100 patients years)	23	24	0.95 (0.85, 1.05)
30-day HF re-hospitalization rate % following in-study, CEC-confirmed HHF	12	13	0.84 (0.52, 1.35)

SD: standard deviation, CV: cardiovascular, HF: hear failure, CEC: clinical endpoints committee, HHF: hospitalization for heart failure

Source: Reviewer's Compilation

Table 49. Emergency room visits for heart failure by treatment arm, PARAGON-HF (Full Analysis Set)

Parameter	Entresto N=2407	Valsartan N=2389	Rate Ratio (Confidence Interval)
Patients with at least one ER visit for HF n (%)	64 (2.66)	82 (3.43)	
Number of ER visits for HF per patient mean (SD, range)	0.03 (0.25, 0-9)	0.05 (0.32, 0-7)	0.644 (0.45, 0.93)

ER: emergency room, HF: heart failure

Source: Reviewer's Compilation

Reviewer's Comments: *The additional efficacy analyses suggest a trend in favor of Entresto for HHF and days alive and out of the hospital, without any benefit in health related quality of life measures or 30-day rehospitalization rate.*

Table 50 summarizes the change in NT-proBNP by treatment arm by median LVEF in PARAGON-HF, PARALLAX and PARAMOUNT trials. These data demonstrate that Entresto is consistently associated with a greater reduction of NT-proBNP compared to ACEi/ARB/placebo regardless of LVEF, and that patients with LVEF greater than the median of 57% may derive some benefit with Entresto. An adequately powered trial could be considered to explore a potential clinical benefit with Entresto in this population.

Note that in PARAGON-HF, NT-proBNP was not measured beyond Week 48.

Table 50. Change in NT-proBNP by Treatment arm by median LVEF in PARAMOUNT, PARALLAX and PARAGON-HF

			Entresto		Comparator			Entresto vs. Comparator
Trial	LVEF	Visit	n/N	LSM of E/B Geometric Mean (95% CI)		n/N	LSM of E/B Geometric Mean (95% CI)	LSM of E/B Geometric Mean (95% CI)
B2214	≤ 56%	Week 12	62/148	0.73 (0.61, 0.87)	Valsartan	62/146	1.04 (0.88, 1.25)	0.70 (0.54, 0.90)
D2302	≤ 55%	Week 12	576/1203	0.79 (0.76, 0.83)	ARB/ACEI/No RASi	639/ 1216	0.97 (0.93, 1.01)	0.82 (0.77, 0.87)
D2301	≤ 57%	Week 16	699/1400	0.76 (0.72,0.80)	Valsartan	695/1374	0.96 (0.91, 1.01)	0.79 (0.74, 0.85)
D2301	≤ 57%	Week 48	660/1400	0.80 (0.75, 0.84)	Valsartan	656/1374	0.98 (0.93, 1.03)	0.81 (0.75, 0.88)
B2214	> 56%	Week 12	61/148	0.75 (0.63, 0.90)	Valsartan	61/146	0.90 (0.75, 1.07)	0.84 (0.65, 1.08)
D2302	>55%	Week 12	627/ 1203	0.85 (0.81, 0.89)	ARB/ACEI/No RASi	577/1216	1.00 (0.95, 1.05)	0.85 (0.80, 0.91)
D2301	>57%	Week 16	646/1400	0.77 (0.73, 0.82)	Valsartan	620/1374	0.93 (0.88, 0.98)	0.83 (0.77, 0.90)
D2301	>57%	Week 48	613/ 1400	0.82 (0.77, 0.86)	Valsartan	573/1374	0.95 (0.90, 1.01)	0.86 (0.80, 0.93)

NT-proBNP: N-terminal pro-brain natriuretic peptide, LVEF: left ventricular ejection fraction

Trial B2214 – PARAMOUNT, Trial D2302 – PARALLAX, Trial D2301 – PARAGON-HF

B2214: The MMRM model includes randomization stratification (prior use of ACEi/ARB), region, treatment, subgroup, visit, treatment-by-visit interaction and treatment–by-subgroup interaction as fixed-effect factors; baseline log-transformed NT-proBNP (BLNTBNP) as covariate; and models the within-patient covariance using an unstructured covariance matrix (a common matrix for the two treatment groups). The analysis includes data observed up to Week 12. Ratio: E/B=Endpoint/Baseline; CI=Confidence interval. Geometric mean=exponentially back-transformed from the LS mean based on the ANCOVA model. The same transformation is applied to the 95% CI.

D2302: The MMRM model includes stratum (ACEi, ARB, No RASi), region, treatment (Entresto, IMT), visit, treatment-by-visit interaction, sub-group, sub-group-by-visit interaction, treatment–by-sub-group interaction and treatment–by-sub-groupby- visit interaction as fixed-effect factors; baseline log-transformed NT-proBNP (BLNTBNP), stratum-by-BLNTBNP and visit-by-BLNTBNP interactions as covariates; and models the within-patient covariance using an unstructured covariance matrix (a common matrix for the two treatment groups). The analysis includes data observed up to Week 12. Test values below lower/above upper limit of quantification are imputed by 0.5xLLOQ/1.5xULOQ.

D2301: The MMRM model includes randomization stratification (prior use of ACEi/ARB), region, treatment, subgroup, visit, treatment-by-visit interaction and treatment–by-subgroup interaction as fixed-effect factors; baseline log-transformed NT-proBNP (BLNTBNP) as covariate; and models the within-patient covariance using an unstructured covariance matrix (a common matrix for the two treatment groups). The analysis includes data observed up to Week 12. Ratio: E/B=Endpoint/Baseline; CI=Confidence interval. Geometric mean=exponentially back-transformed from the LS mean based on the ANCOVA model. The same transformation is applied to the 95% CI.

n = number of patients with non-missing change at that visit

N = total number of patients in that treatment arm

Source: Reviewer's compilation of sponsor data provided in tables 1-18.1, 1-18.5, 1-1.3 under response to FDA Request for Information dated October 5, 2020

Table 51 displays subgroup analyses by LVEF for all-cause mortality, KCCQ-CSS, adjudicated first hospitalization for heart failure, adjudicated first primary composite endpoint, and adjudicated cardiovascular death in PARAGON-HF.

Table 51. Subgroup anlaysis by LVEF for all-cause mortality, KCCQ-CSS, adjudicated first hospitalization for heart failure, and adjudicated first primary composite endpoint, PARAGON-HF (Full Analysis Set)

Subgroup anlaysis by LVEF, PARAGON-HF

Table 14.2-2.10 (Page 6 of 11)
Subgroup analysis of all-cause mortality using Cox's proportional hazards model
Full analysis set

Subgroup variable	Category	LCZ696 n/N (%)	Valsartan n/N (%)	LCZ696 n/T EAIR (95% CI)	Valsartan n/T EAIR (95% CI)	Hazard ratio (LCZ696 vs Valsartan) (95% CI) (1)	p-value (1)
LVEF	<= median (57%)	201/1239 (16.22)	198/1256 (15.76)	201/35.65 5.638 (4.885, 6.473)	198/36.03 5.496 (4.757, 6.317)	1.0248 (0.8421, 1.2471)	0.4155
	> median (57%)	141/1168 (12.07)	151/1133 (13.33)	141/34.00 4.147 (3.491, 4.891)	151/32.94 4.584 (3.882, 5.376)	0.9039 (0.7184, 1.1372)	

Table 14.2-2.2 (Page 3 of 6)
Between-treatment analyses for changes from baseline to Month 8 for KCCQ clinical summary score (CSS) by pre-specified subgroups
Full analysis set (1)

Subgroup	Category	LCZ696 N=2387 n/N	LCZ696 N=2387 LSM of CFB (SE)	Valsartan N=2369 n/N	Valsartan N=2369 LSM of CFB (SE)	LCZ696 - Valsartan LSM of difference	LCZ696 - Valsartan (95% CI)	Treatment by subgp. int. p-value (2)
	No	1278/1350	-1.0778 (0.4542)	1284/1360	-2.2483 (0.4533)	1.1704	(-0.0868, 2.4277)	
LVEF	<= median (57%)	1164/1231	-1.5026 (0.4719)	1175/1246	-2.6516 (0.4702)	1.1490	(-0.1544, 2.4523)	0.7609
	> median (57%)	1086/1156	-1.5067 (0.4839)	1051/1123	-2.3973 (0.4898)	0.8906	(-0.4572, 2.2383)	

Table 14.2-1.9.2 (Page 6 of 11)
Cox's proportional hazards model for CEC confirmed first hospitalization for heart failure by subgroups
Full analysis set

Subgroup variable	Category	LCZ696 n/N (%)	Valsartan n/N (%)	LCZ696 n/T EAIR (95% CI)	Valsartan n/T EAIR (95% CI)	Hazard ratio (LCZ696 vs Valsartan) (95% CI) (1)	p-value (1)
LVEF	<= median (57%)	205/1239 (16.55)	241/1256 (19.19)	205/32.73 6.264 (5.436, 7.183)	241/32.47 7.422 (6.515, 8.421)	0.8337 (0.6918, 1.0046)	0.2081
	> median (57%)	200/1168 (17.12)	192/1133 (16.95)	200/31.12 6.427 (5.567, 7.382)	192/30.06 6.387 (5.516, 7.357)	0.9929 (0.8144, 1.2104)	

Subgroup anlaysis by LVEF, PARAGON-HF

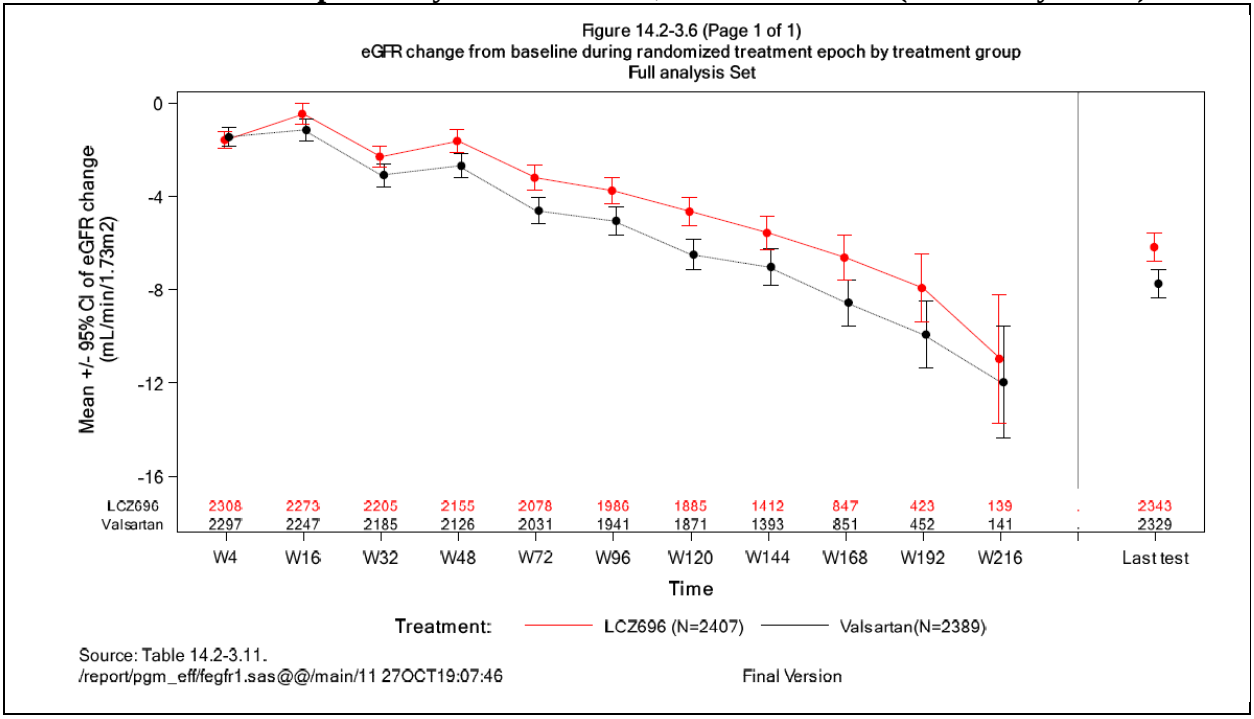
Table 14.2-1.9.1 (Page 6 of 11)
Cox's proportional hazards model for CEC confirmed first primary composite endpoint (cardiovascular death or hospitalization for heart failure) by subgroups
Full analysis set

Subgroup variable	Category	LCZ696 n/N (%)	Valsartan n/N (%)	LCZ696 n/T EAIR (95% CI)	Valsartan n/T EAIR (95% CI)	Hazard ratio (LCZ696 vs Valsartan) (95% CI) (1)	p-value (1)
LVEF	<= median (57%)	285/1239 (23.00)	317/1256 (25.24)	285/32.73 8.709 (7.727, 9.781)	317/32.47 9.763 (8.718, 10.899)	0.8850 (0.7540, 1.0388)	0.5037
	> median (57%)	241/1168 (20.63)	240/1133 (21.18)	241/31.12 7.745 (6.798, 8.787)	240/30.06 7.984 (7.006, 9.061)	0.9606 (0.8033, 1.1487)	

Source: Sponsor material, Clinical Study Report D2301

Figure 23 displays the trend of eGFR change from baseline during the randomized treatment period by treatment arm in PARAGON-HF. Patients in Entresto arm appear to experience a slower rate of decline in renal function compared to valsartan arm. Clinical significance of these findings is unclear. Given that PARAGON-HF failed on its primary endpoint, the secondary renal composite endpoint findings are considered exploratory only.

Figure 23. Estimated glomerular filteration rate (eGFR) change from baseline during randomized treatment period by treatment arm, PARAGON-HF (Full Analysis Set)



Source: Sponsor material

Blood Pressure in PARAGON-HF

Throughout the randomized treatment , patients in the Entresto arm experienced lower systolic and diastolic blood pressure (BP) compared to the valsartan arm. The mean BP at screening and baseline was approximately 137/77 and 131/74 in both Entresto and valsartan arms. The baseline BP was at the end of the Entresto run-in . The mean BP at last test was approximately 130/74 and 133/75 in Entresto and valsartan arms, respectively. The systolic BP changed by - 0.81 and + 2 from baseline to last test in Entresto and valsartan arms, respectively. The diastolic BP changed by - 0.26 and + 0.34 from baseline to last test in Entresto and valsartan arms, respectively. A recurrent events analysis of the treatment effect on the primary composite endpoint adjusted for systolic blood pressure (SBP) over time suggests that the treatment effect size was unaffected by SBP [unadjusted RR = 0.87 (95% CI: 0.75, 1.01; 1-sided p = 0.029) vs. SBP adjusted RR = 0.87 (95% CI: 0.74, 1.00; 1-sided p = 0.027)].

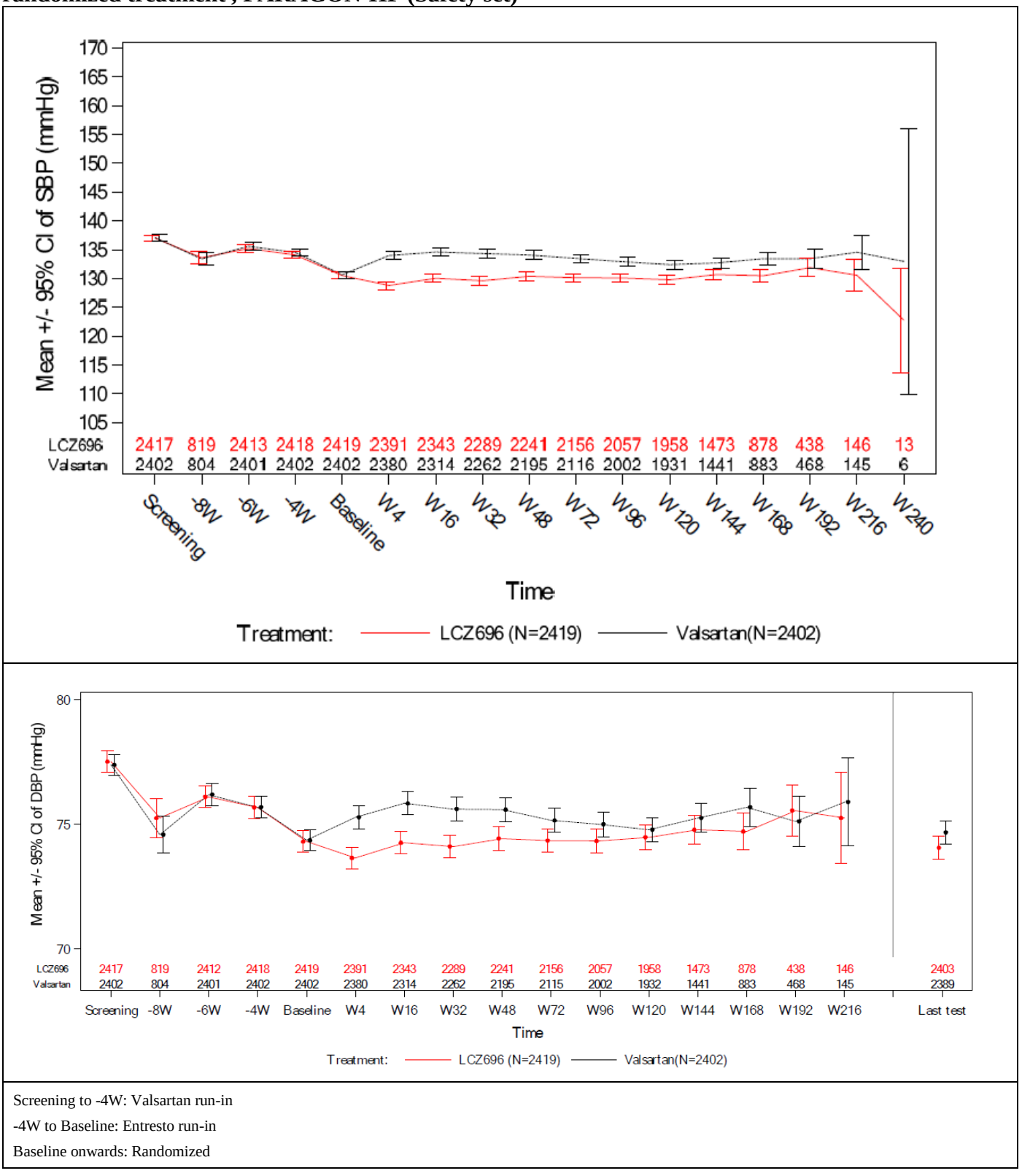
Figure 24 displays the change in systolic and diastolic BP from baseline by treatment arm in PARAGON-HF.

Reviewer's Comments: *Hypertension treatment guidelines[50,51] recommend treating BP to a target of <130/80 mm Hg but >120/70 mm Hg to reduce the incidence of HHF. The mean BP at last test was approximately 130/74 and 133/75 in Entresto and valsartan arms, respectively. The protocol stated that patients had to be on an optimal medical regimen of diuretics and background medications to treat co-morbidities such as hypertension (HTN), diabetes mellitus (DM), atrial fibrillation (AF) and coronary artery disease (CAD). The BP data in PARAGON-HF suggest that patients in LCZ96 versus valsartan arm achieved better BP control, closer to the goal SBP of < 130.*

[50] Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, Ramirez A, Schlaich M, Stergiou GS, Tomaszewski M, Wainford RD, Williams B, Schutte AE. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Hypertension. 2020 Jun;75(6):1334-1357. doi: 10.1161/HYPERTENSIONAHA.120.15026. Epub 2020 May 6.

[51] 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2018;71:e127-e248.

Figure 24. Sitting systolic and diastolic arterial blood pressure during treatment run-in and randomized treatment , PARAGON-HF (Safety set)



Screening to -4W: Valsartan run-in

-4W to Baseline: Entresto run-in

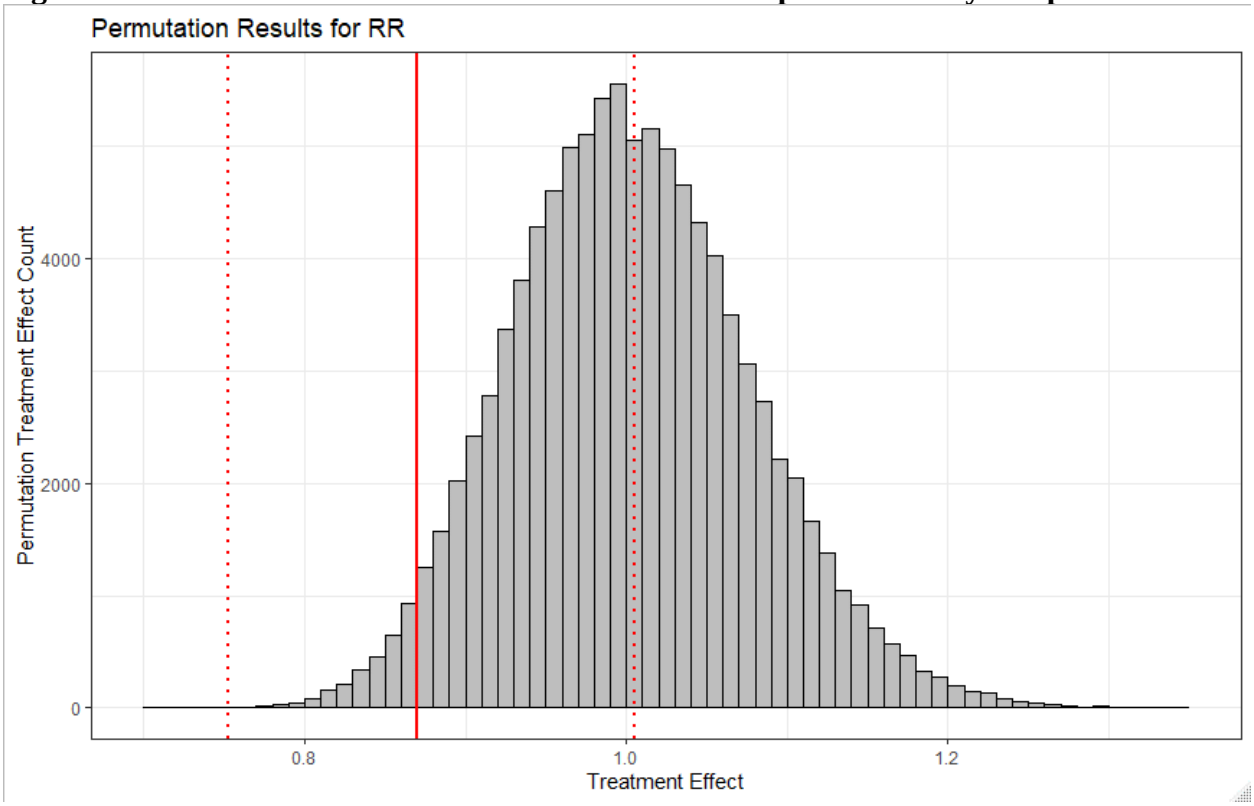
Baseline onwards: Randomized

Source: Clinical Study Report CLCZ696D2301 Sponsor Figures 12-9 and 14.3-3.2

Recurrent Event Methodology Assessment

There are some complex underlying assumptions when using recurrent event methods. We used a non-parametric permutation test in order to determine if these assumptions were impactful in the results. We used 100,000 resampled permutations to build a null distribution. These results for the RR based on resampling are shown in Figure 25. The point estimate and 95% CIs for the study results are shown in red in these figures. The 1-sided p-value from the permutation distribution for the number of permutations that were more extreme than the study was 0.02916, which is similar to the recurrent events model results 1-sided p-value of 0.029. This is still greater than the pre-specified 1-sided alpha level of 0.024 and gives a strong indication that the recurrent events methodology is performing as it should.

Figure 25. Permutation Results Distribution for the Composite Primary Endpoint



11.2. Trial # CLCZ696B2214 (PARAMOUNT)

Study Results: A total of 308 patients were randomized with 7 patients (3 in Entresto and 4 in valsartan arm) being excluded for major GCP violations resulting in 303 patients in the randomized set (Entresto N =149, valsartan N=152). Patient disposition was similar between the two treatment arms. Approximately 87% patients completed the 12 Week randomized . The Full analysis set (FAS) consisted of all randomized patients who had baseline and at least one post-baseline efficacy measurement during the double-blind . There were 294 patients in the FAS (Entresto N =148, valsartan N=146).

The mean duration of treatment exposure was 219 and 216 days in Entresto versus valsartan arms, respectively. Target dose, defined as taking the intended dose (Entresto 200 mg bid or Valsartan 160 mg bid) for at least 80% of the time, was achieved in 121 (81%) patients in the Entresto arm and in 119 (78%) in the valsartan arm.

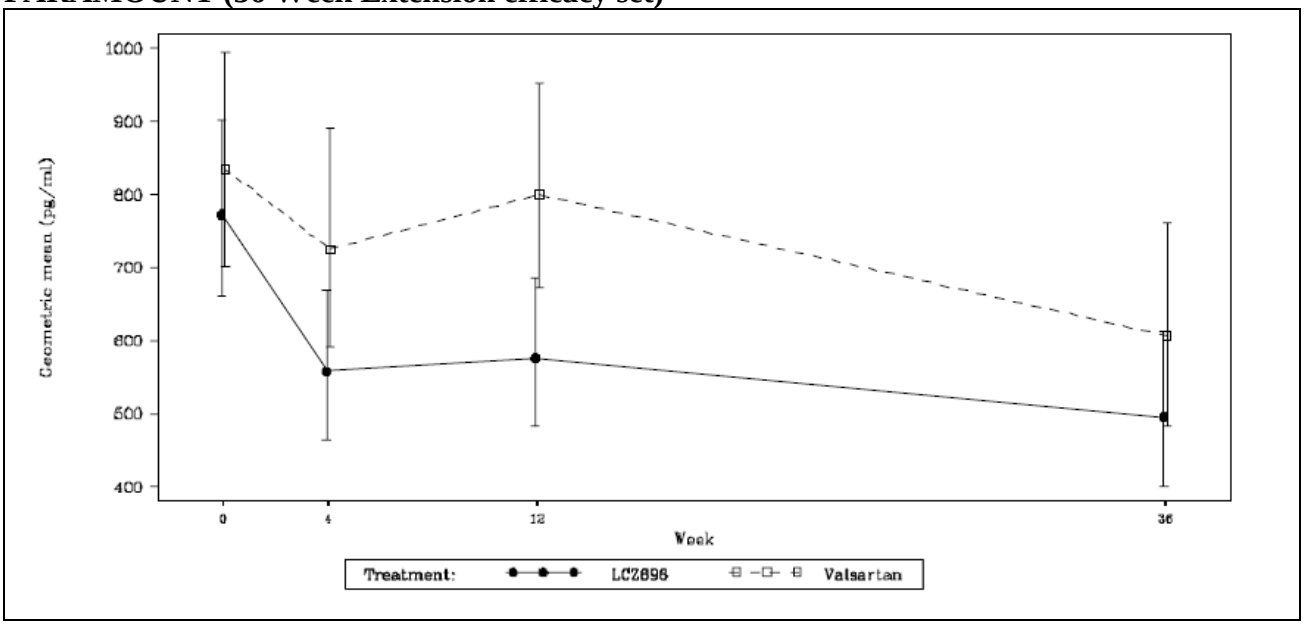
The baseline demographic and clinical characteristics were balanced between the two arms. The study population comprised of 57% females, mean age 71 years, mean systolic blood pressure 135 mm Hg, mean BMI 30 kg/m^2, mean LVEF 58% (12% and 79% patients had an LVEF < 50% and > 50%, respectively), 79% patients were in NYHA Class II, mean NT-proBNP was 1228 pg/mL and mean eGFR was 65 $mL/min/1.73m^2$. Prior history of heart failure hospitalization was present in 40 and 45% of patients in Entresto versus valsartan arm. 94% of all patients in the FAS had been treated with ACEI/ARB prior to randomization, 79% were treated with beta-blocker, 21% were treated with aldosterone antagonist, 94% had hypertension, 62% had non-ischemic HF, 42% had history of atrial fibrillation and 37% had history of type 2 diabetes mellitus (T2DM). The mean duration of treatment exposure was 252 days and was balanced between the two treatment arms.

Primary Efficacy Results: The change from baseline to Week 12 in NT-proBNP (in log scale) was 0.83 (0.68, 1.01) in Entresto (N 134) arm and 1.08 (0.89, 1.32) in valsartan arm (N 132) with Entresto versus valsartan ratio of 0.77 (0.64, 0.92) with p-value 0.005 (full analysis set).

Subgroup analysis demonstrated that females experienced a greater reduction in NT-proBNP with Entresto compared to males (26 versus 21%), as did patients age ≥ 65 years, and patients with diabetes, baseline NT-proBNP ≤ median, LVEF < 50%, no atrial fibrillation, SBP > 140, NYHA class II, prior use of ACEI/ARB, prior use of beta blocker and no prior HF hospitalization.

Secondary Efficacy Results: There was a statistically insignificant reduction in NT-proBNP at Week 36 in Entresto versus valsartan arm with an adjusted geometric mean ratio (AGMR) of 0.85, 95% CI: 0.65, 1.09; p-value 0.20. The number of patients evaluated at Week 36 were 115 in Entresto and 116 in valsartan arm. Figure 26 displays the geometric mean of NT-proBNP by visit and treatment group in PARAMOUNT.

Figure 26. Geometric mean of NT-proBNP by Week and treatment group, PARAMOUNT (36 Week Extension efficacy set)



Source: Sponsor Figure 11-1, Clinical Study Report CLCZ696B2214

Reviewer's Comment: *There was a statistically significant greater reduction in NT-proBNP with Entresto versus placebo by 23% in patients with heart failure with LVEF ≥ 45% after 12 weeks of treatment. This difference reduced to 15% at Week 36 which may suggest an attenuation of effect of Entresto on NT-proBNP and/or reflect a decrease in sample size at Week 36.*

Other Secondary Efficacy Endpoint Results: Given that the secondary efficacy endpoint of change in NT-proBNP at Week 36 was statistically insignificant, results of subsequent secondary efficacy endpoints are only exploratory. The secondary endpoint of change in echocardiographic parameters at Week 36 demonstrated a decrease in left atrial size measured by left atrial dimension and left atrial volume index with Entresto compared to valsartan. The reduction in left atrial volume index from baseline in Entresto versus valsartan arm was 3.14 mL/m^2. There was no difference in echocardiographic measures of diastolic function, left ventricular ejection fraction or left ventricular mass between the two treatment arms. The NYHA Class or KCCQ scores did not improve with Entresto compared to valsartan.

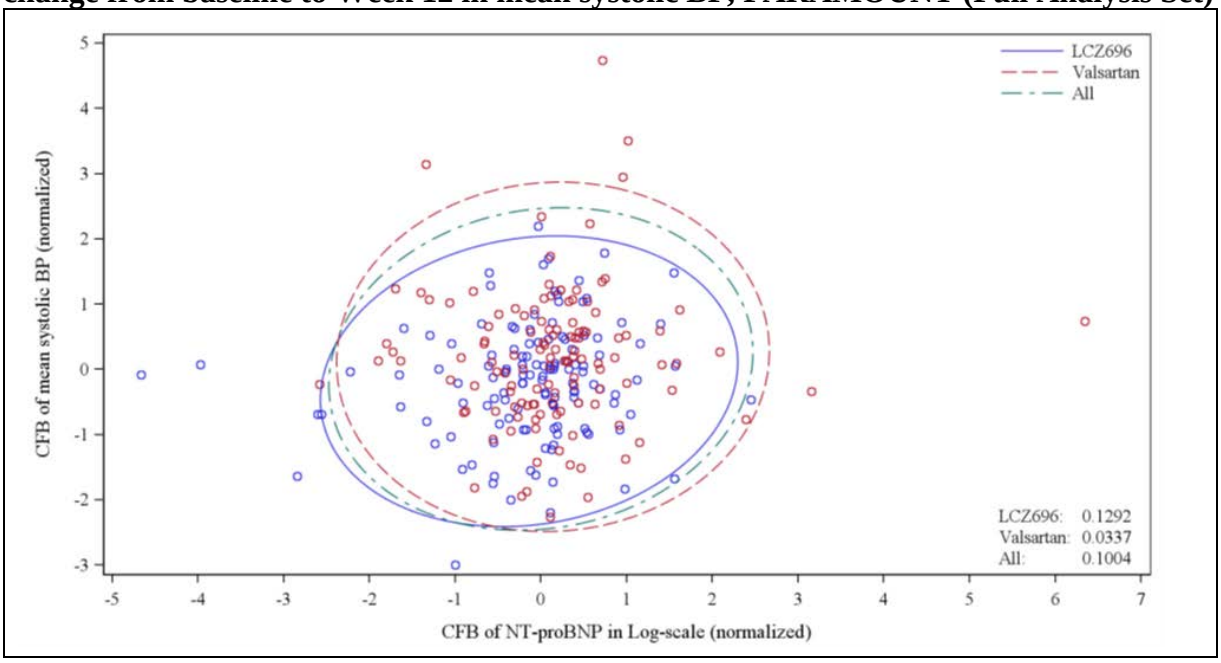
Blood Pressure Change: At Week 12, mean blood pressure reduction from baseline was 7.2/4.5 and 1.4/2.6 in Entresto and valsartan treatment arm, respectively. The baseline BP was 136/78 and 134/77 in Entresto and valsartan arms, respectively. Additional data on blood pressure change in PARAMOUNT trial is presented in the appendices.

Reviewer's Comment:

Blood pressure change in valsartan arm – *In PARAMOUNT, the mean blood pressure reduction at Week 12 in patients with heart failure with LVEF ≥ 45% (mean baseline blood pressure of 135/76 mm Hg) with valsartan 160 mg bid was 1.4/2.6. Whereas in Val-HeFT[52] trial, the mean systolic blood pressure reduction at 4 months in patients with heart failure with LVEF < 40% (mean baseline blood pressure 123/76) with valsartan 160 mg bid was 5.2 mm Hg. Per Diovan (valsartan) label, valsartan doses of 80, 160 and 320 mg produced dose-related decreases in systolic and diastolic blood pressure compared to placebo of approximately 6-9/3-5 mm Hg with 80-160 mg and 9/6 mm Hg with 320 mg dose in patients with hypertension over 4 to 12 weeks. Note that in controlled trials, the antihypertensive effect of once daily valsartan 80 mg was similar to once daily enalapril 20 mg or once daily lisinopril 10 mg. Data from PARAMOUNT demonstrates that patients with heart failure with LVEF ≥ 45% did not experience as much blood pressure lowering with valsartan as observed in patients with hypertension or heart failure with LVEF < 40%. The interpretation of BP change attributable to valsartan in PARAMOUNT may be limited by the use of concomitant antihypertensive agents.*

Figure 27 displays the correlation between change from baseline in NT-proBNP and mean systolic BP in the FAS.

Figure 27. Correlation between change from baseline to Week 12 in NT-proBNP and change from baseline to Week 12 in mean systolic BP, PARAMOUNT (Full Analysis Set)



Source: Clinical Study Report CLCZ696B2214, Sponsor figure 11-4

[52] Cohn JN, Tognoni G, for the Valsartan Heart Failure Trial Investigators. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 2001;345:1667—75.

Reviewer's Comments: *The BP change data in PARAMOUNT suggest that patients with heart failure with LVEF ≥ 45% experienced greater BP reduction with Entresto than with valsartan. There is no clear relationship between change in NT-proBNP versus change in BP.*

Table 52 summarizes the mean and geometric mean of NT-proBNP and BNP by Week and treatment group in PARAMOUNT. Table 53 displays the change in blood pressure from baseline to Week 36 in extension efficacy set. Figure 28 displays mean blood pressure by visit and treatment arm in extension efficacy set. These data demonstrate that Entresto versus valsartan lead to a greater reduction in NT-proBNP and BP.

Table 52. Mean and Geometric Mean of NT-proBNP and BNP by Week and treatment group, PARAMOUNT

	Entresto (N 148) FAS		Valsartan (N 146) FAS		Entresto-Valsartan	Entresto (N 127) Extension Efficacy Set		Valsartan (N 125) Extension Efficacy Set		Entresto-Valsartan
	NT-proBNP pg/ml		NT-proBNP pg/ml			BNP pg/ml		BNP pg/ml		
	n	Mean (SD)	n	Mean (SD)	Difference of Mean	n	Mean (SD)	n	Mean (SD)	Difference of Mean
Week -2 or -1	134	1531 (2542)	129	1468 (1697)	63					
Baseline Week 0	137	1225 (1552)	133	1232 (1051)	-7	119	208 (241)	113	225 (176)	-17
Week 4	122	950 (1276)	124	1109 (861)	-159	109	224 (239)	104	172 (127)	52
Week 12	125	930 (1213)	123	1187 (1117)	-257	112	251 (313)	109	205 (164)	46
Week 36	115	938 (2064)	116	1120 (1475)	-182	98	235 (220)	100	213 (270)	22
		Geometric Mean (pg/ml)		Geometric Mean (pg/ml)			Geometric Mean (pg/ml)		Geometric Mean (pg/ml)	
Week -2 or -1	134	988	129	978	-		-		-	-
Baseline (Week 0)	137	794	133	870	-	119	150	113	166	-
Week 4	122	573	124	751	-	109	165	104	127	-
Week 12	125	584	123	802	-	112	169	109	154	-
Week 36	115	496	116	607	-	98	150	100	213	-

Geometric mean is the geometric mean of the Value to Base ratio, FAS: Full analysis set, NT-proBNP: N-terminal pro-brain natriuretic peptide, BNP: brain natriuretic peptide, pg/ml: picogram/milliliter, SD: standard deviation

Source: Reviewer's compilation from Clinical Study Report CLCZ696B2214

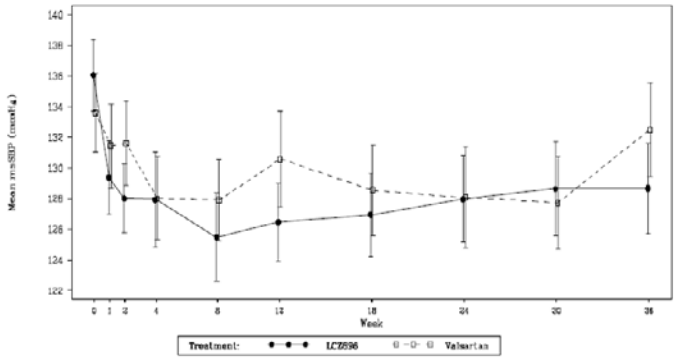
Table 53. Between-treatment analysis for change from baseline to Week 36 endpoint in mean sitting systolic/diastolic blood pressure and mean pulse pressure (Extension efficacy set), PARAMOUNT

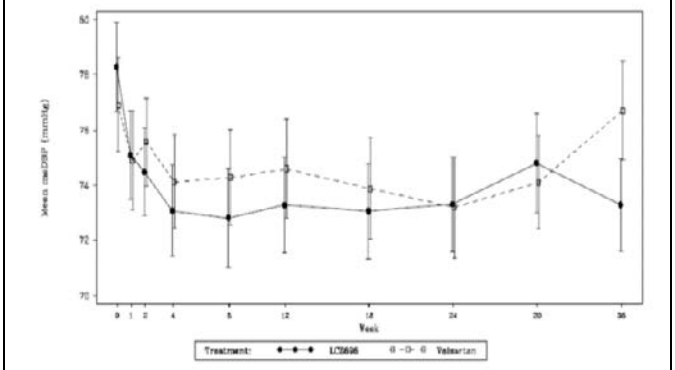
	LCZ696 N=127		Valsartan N=125		LCZ696 vs. Valsartan	
	N	LSM of CFB (SE)	n	LSM of CFB (SE)	LSM of difference (95% CI)	P-value
Mean sitting systolic blood pressure (mmHg)	127	-7.47 (1.909)	125	-2.18 (1.936)	-5.30 (-8.93, -1.66)	0.0045*
Mean sitting diastolic blood pressure (mmHg)	127	-5.28 (1.188)	125	-1.39 (1.204)	-3.89 (-6.15, -1.63)	0.0008*
Mean pulse pressure (mmHg)	127	-2.24 (1.482)	125	-1.17 (1.497)	-1.07 (-3.89, 1.74)	0.4542

P-values and treatment comparisons were evaluated using an ANCOVA model with treatment, randomization stratification (prior use of ACEi/ARB), and region as the fixed factors and baseline as a covariate.
Change from baseline (CFB) = Endpoint — Baseline; LSM = Least squares mean; CI = Confidence interval; SE = Standard error.
Week 36 endpoint = Week 36 value or the last post-randomization value collected on or after Week 8.
* Indicates statistical significance at 0.05 level.

Source: Clinical Study Report CLCZ696B2214, Sponsor table 11-14

Figure 28. Average of mean sitting systolic and diastolic blood pressure, by visit and treatment group (Extension efficacy set), PARAMOUNT





msSBP: mean sitting systolic blood pressure, msDBP: mean sitting diastolic blood pressure

Source: Clinical Study Report CLCZ696B2214, Sponsor figures 11-2 and 11-3

11.3. Trial # CLCZ696D2302 (PARALLAX-HF)

Study Results: Study CLCZ696D2302 randomized 2572 patients with 1286 patients each in Entresto and comparator arm. The full analysis set (FAS) comprised of 2566 patients. Baseline demographic and clinical characteristics of patients in Entresto and comparator arms were similar. The study population comprised of 76% Caucasian, 51% female patients, 68% with NYHA class II symptoms from European region with a mean age 73 years, body mass index (BMI) 31 kg/m^2, LVEF 57%, NT-proBNP 1139 pg/mL, KCCQ CSS 53, and systolic blood pressure (SBP) 133 mm Hg. 75% (1926/2566) of the patients had an LVEF ≤ 60% and 25% (640/2566) had an LVEF of > 60%. The use of concomitant cardiovascular medications was similar across both groups.

Reviewer's Comment: *The baseline characteristics of the study population were balanced between the two treatment arms. Only 25% of the patients population had an LVEF > 60%.*

A total of 2564 patients received the study medication, 1280 patients received Entresto and 1284 patients received comparator treatment - 533 received enalapril, 588 received valsartan and 163 received placebo. 86 and 88% of the patients in Entresto and comparator arms, respectively completed the study treatment. The mean duration of study drug exposure was approximately 23 weeks in both groups. In the ACEI stratum, the overall mean daily dose per patient was 292 mg/day of Entresto and 16 mg/day of enalapril. In the ARB stratum, the overall mean daily dose per patient was 296 mg/day of Entresto and 250 mg/day of valsartan.

Primary Efficacy Results

H1 (NT-proBNP): There was a statistically significant reduction in NT-proBNP at Week 12 in Entresto arm versus comparator arm with an adjusted geometric mean ratio (AGMR) of 0.84, 95% CI: 0.80, 0.88; p <0.0001.

H2 (6MWD): The adjusted mean difference for change from baseline to Week 24 in 6MWD was – 2.5, 95% CI: -8.5, 3.5; p 0.42 indicating no improvement in exercise capacity as measured by 6MWT in HFpEF patients with baseline 6MWD between 100 to 450 meters with Entresto versus the comparator. The adjusted mean Change from Baseline to Week 24 in 6MWD in Entresto and comparator arms was 10 (5, 14) and 12 (9, 16) meters, respectively.

Secondary Efficacy Results

Given that H2 did not meet statistical significance, all other comparisons/results are outside the type 1 error control and are considered exploratory. Table 54 lists the relevant results of Study CLCZ696D2302.

The Applicant conducted several sensitivity and subgroup analyses for the efficacy endpoints in study D2301. The results of these analyses were generally consistent with the primary and secondary efficacy results with some exceptions (described below).

Subgroup analysis for the efficacy endpoint of 6MWD demonstrated a significant treatment interaction by sex (interaction p 0.002) and region (interaction p 0.03). The adjusted mean difference in 6MWD at Week 24 was 6.6 m (-1.8, 15) in favor of Entresto in women compared to -12.1 (-21, -3.5 m) not favoring Entresto in men. Table 55 displays the results of Change from baseline in 6MWD at Week 24 by sex. The adjusted mean treatment difference (95% CI) for the regions of North America, Europe, Asia/Pacific & other and Latin America were 2.8 (-23, 29), 1.7 (-5, 9), -8.9 (-34, 17), -25.2 (-41, -9), respectively.

Subgroup analysis for the efficacy endpoint of improvement from baseline in NYHA class at Week 24 demonstrated a significant treatment interaction by prior medication strata (interaction p 0.04), baseline NYHA class (interaction p 0.04), by LVEF (interaction p 0.008) and by prior HHF (interaction p 0.03). The number of patients who experienced worsened NYHA class at Week 24 in patients with LVEF ≤ 60% were 42/913 (4.6%) and 34/930 (3.7%) in Entresto versus comparator arm with an adjusted odds ratio of 1.7 (0.75, 3.8). The number of patients who experienced worsened NYHA class at Week 24 in patients with LVEF > 60% were 9/315 (2.9%) and 19/299 (6.4%) in Entresto versus comparator arm with an adjusted odds ratio of 0.18 (0.04, 0.75).

These subgroup analyses findings should be interpreted with caution because the main efficacy endpoint analyses of H2 (6MWD) demonstrated no treatment effect with Entresto.

Table 54. Efficacy Results, PARALLAX-HF

Primary Efficacy Results					
	Entresto	**Comparator** (ACEI/ARB/Placebo)	**Comparison** Entresto versus Comparator	**2-sided P-Value**	**Statistical Model**
NT-proBNP change from Baseline at Week 12 (FAS)	AGM 0.82 (0.80, 0.85) n 1203	AGM 0.98 (0.95, 1) n 1216	AGMR 0.84 (0.80, 0.88)	<.0001	MMRM
6MWD change from baseline at Week 24 (FAS subset of patients with baseline 6MWD from 100 to 450 m)	AMCFB 9.70 (5.43, 14) n 1082	AMCFB 12.2 (7.9, 16.5) n 1075	AMD -2.50 (-8.5, 3.5)	0.42	MMRM
Efficacy Analyses Outside Type 1 Error Control					
6MWD – thirty meter improvement - at Week 24 (FAS subset of patients with baseline 6MWD from 100 m to 450 m)	389/1082 (36%)	380/1075 (35%)	Adjusted Odds Ratio 1.02 (0.72, 1.5)		Responder Analysis
KCCQ CSS – change from baseline at Week 24 (FAS)	AMCFB 12.3 (11.3, 13.4) n 1207	AMCFB 11.8 (10.8, 12.8) N 1210	AMD 0.52 (-0.92, 2)		MMRM
KCCQ CSS – five-point improvement at Week 24 (FAS)	820/1207 (68%)	795/1210 (66%)	Adjusted Odds Ratio 1.1 (0.83, 1.5)		Responder Analysis
NYHA class – change from baseline at Week 24 (FAS)	Observed n 1228 Improved 290 (24%) Unchanged 887 (72%) Worsened 51 (4%)	Observed n 1229 Improved 295 (24%) Unchanged 881 (72%) Worsened 53 (4%)	Adjusted Odds Ratio 0.98 (0.8, 1.2)		Proportional Cumulative Odds
SF-36 PCS – change from baseline at Week 24 (FAS)	AMCFB 2.5 (2.1, 3) n 1185	AMCFB 2.7 (2.2, 3.2) n 1191	AMD -0.16 (-0.81, 0.50)		MMRM
NT-proBNP Change from Baseline at Week 24 (FAS)	AGM 0.86 (0.83, 0.90) n 1190	AGM 0.98 (0.95, 1.02) n 1191	AGMR 0.88 (0.83, 0.93)		MMRM
Mean monthly reduction in eGFR from baseline	Adjusted Mean Change Per Month -0.25 (-0.35, -0.14)	Adjusted Mean Change Per Month -0.43 (-0.53, -0.32)	AMD 0.18 (0.03, 0.33)		MMRM

NT-proBNP: N-terminal pro-brain natriuretic peptide, FAS: Full analysis set, AGM: adjusted geometric mean, AGMR: adjusted geometric mean ratio, 6MWD: six-minute walk distance, AMCFB: adjusted mean change from baseline, AMD: adjusted mean difference, MMRM: mixed model for repeated measures, KCCQ CSS: Kansas City Cardiomyopathy Questionnaire clinical summary score, NYHA: New York Heart Association, SF-36 The Short Form (36) Health Survey, PCS: physical component summary, eGFR: estimated glomerular filtration rate measured in mL/min/1.73m^2.

Source: Reviewer's compilation from Clinical Study Report CLCZ696D2302

Table 55. 6MWD - Change from baseline up to Week 24 - Mixed Model for Repeated Measures (MMRM) with treatment-by-sub-group-by-visit interaction (pre-specified sub-group variables) - post-death 6MWD set to zero Full Analysis Set: baseline 6MWD from 100 meters to 450 meters, PARALLAX-HF

Sub-Group Variable: Sex
Treatment-by-Sub-Group-by-Visit Interaction P-Value: 0.0167 *

		LCZ696		IMT		Comparison (LCZ696 versus IMT)	
			Adjusted Mean CFB		Adjusted Mean CFB	Adjusted Mean Difference (LCZ696 - IMT)	
Visit	Sub-Group	n	Estimate (95% CI)	n	Estimate (95% CI)	Estimate (95% CI)	Interaction P-Value
WEEK 16							0.2020
	Female	549	6.5593 (1.0940, 12.0246)	553	1.9910 (-3.4631, 7.4450)	4.5684 (-3.0990, 12.2357)	
	Male	524	7.7340 (2.1501, 13.3180)	532	10.3056 (4.7157, 15.8956)	-2.5716 (-10.4202, 5.2770)	
WEEK 24							0.0024 *
	Female	555	12.2635 (6.2915, 18.2354)	548	5.6773 (-0.3150, 11.6696)	6.5862 (-1.8211, 14.9934)	
	Male	527	6.9490 (0.8369, 13.0611)	527	19.0192 (12.8755, 25.1628)	-12.0701 (-20.6835, -3.4567)	

-6MWD = Six-minute walking distance (meter), CFB = change from baseline. An adjusted mean difference > 0 favors Entresto.
- Interaction p-value is for the subgroup-variable-by-treatment interaction at each visit. * = nominal p-value < 0.05.
- The MMRM model includes stratum (ACEi, ARB, No RASi), region, treatment (Entresto, IMT), visit, treatment-by-visit interaction, sub-group, sub-group-by-visit interaction, treatment–by-sub-group interaction and treatment–by-sub-group by- visit interaction as fixed-effect factors; baseline 6MWD (B6MWD), baseline systolic blood pressure (BSBP), stratum by- B6MWD, stratum-by-BSBP, and visit-by-B6MWD interactions as covariates; and models the within-patient covariance using an unstructured covariance matrix (a common matrix for the two treatment groups).

Source: Sponsor Table 14.2-2.1.8.post.01; page 1447 of Clinical Study Report CLCZ696D2302

Reviewer's Comment: *The clinical significance of treatment by sex interaction for change in 6MWD at Week 24 is unclear. There was no such interaction noted for the primary efficacy analysis of change from baseline in NT-proBNP or for NYHA class change from baseline. In comparison, subgroup analysis in PARAMOUNT demonstrated that females experienced a greater reduction in NT-proBNP with Entresto compared to males (26 versus 21%). These findings may be hypothesis generating that women with HFpEF derive more benefit with Entresto versus comparator arm or may be a chance finding. These findings may be confounded by the LVEF distribution by sex.*

Safety Findings in CLCZ696D2302: The incidence of permanent study drug discontinuation was 14 and 12% respectively in Entresto and comparator group, respectively. The most common reason for permanent study treatment discontinuation in the randomized set was experiencing an AE, 9 and 7% in Entresto and comparator groups, respectively. Table 56 summarizes the important adverse events in Study CLCZ696D2302. Hypotension, hyperkalemia, hypersensitivity [broad standard MedDRA query (SMQ)], and renal impairment (broad and narrow SMQ) were reported more frequently in the Entresto arm versus the comparator arm with an exposure adjusted incidence ratio (EAIR) of 48.5 (incidence: 19% vs 10%), 31.7 (incidence: 13% vs 12%), 12.9 (incidence: 6% vs 4%), and 94 (incidence: 35% vs 30%) and 38.8 (incidence: 16% vs 12%) per 100 patient-years, respectively. Angioedema-like events, hypersensitivity (narrow SMQ), anaphylaxis, hepatotoxicity, malignancy, and cognitive impairment (broad and narrow SMQ) were reported at comparable frequencies in both study arms.

Table 56. Adverse events by Treatment Arm in Safety Analysis Set, PARALLAX-HF

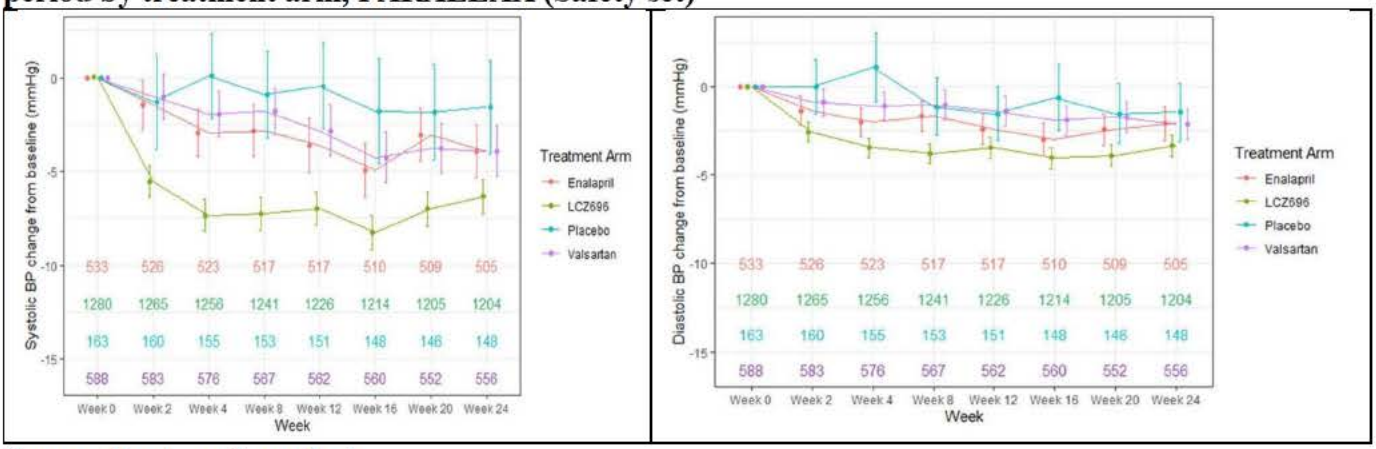
Adverse Event (AE)	Entresto N = 1280 n (%)	Comparator Arm N = 1284 n (%)	Total N = 2564 n (%)
Deaths	23 (1.8)	17 (1.3)	40 (1.6)
AEs leading to study treatment discontinuation	121 (10)	93 (7)	214 (8)
At least one treatment emergent AE	1087 (85)	1030 (80)	2117 (83)
At least one treatment emergent AE, severe	108 (8)	110 (9)	218 (9)
Serious AEs	186 (15)	191 (15)	377 (15)
Hypotension	180 (14)	70 (6)	250 (10)
Urine albumin/creatinine ratio increased	157 (12)	97 (8)	254 (10)
Hyperkalemia	149 (12)	140 (11)	289 (11)
Renal impairment	149 (12)	110 (9)	259 (10)
Hematuria	145 (11)	105 (8)	250 (10)
Glomerular filtration rate decreased	137 (11)	150 (12)	287 (12)
Proteinuria	121 (9)	84 (7)	205 (8)
Renal failure	52 (4)	38 (3)	90 (4)
Cardiac failure	39 (3)	61 (5)	100 (4)

Source: Reviewer's compilation from Clinical Study Report CLCZ696D2302

Reviewer's Comment: *The incidence of death is slightly higher in Entresto versus comparator arm. Given that this was a short-term study that was not powered to evaluate mortality, the minimal difference in mortality between the two arms does not necessarily reflect an increased risk of death with Entresto. There was a higher incidence of AEs overall, in some system organ classes and AEs leading to treatment discontinuation in the Entresto arm, partly because 13% of the patients in the comparator arm received placebo, and there was a higher rate of treatment discontinuation during Entresto titration run-in phase.*

In PARALLAX-HF, blood pressure reduction was most pronounced in the Entresto arm followed by enalapril and valsartan arms (Figure 29).

Figure 29. Systolic and diastolic blood pressure change from baseline during randomized period by treatment arm, PARALLAX (Safety set)



Source: Reviewer's analysis

12. Data Integrity-Related Consults (OSI, Other Inspections)

No inspections were performed.

13. Post marketing Requirements and Commitments

No post marketing requirement (PMR) or commitment is recommended for this sNDA. A post marketing study to better characterize the risk of serious angioedema in the black population treated with Entresto in the United States was recommended in 2015 during NDA review. The Applicant is conducting Study (b) (4) to estimate the incidence of serious angioedema among black HF patients initiating Entresto (b) (4) Another trial to meet a previous PMR to evaluate the impact of Entresto on cognitive function is ongoing.

14. Future Direction

There is a signal for potential renal benefit with Entresto in patients with chronic heart failure in PARAGON-HF which can be explored further.

15. Financial Disclosure

Table 57. Covered Clinical Studies: PARAGON-HF

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 4800		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 14		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

16. Review Team Acknowledgements

Table 58. Reviewers of Interdisciplinary Assessment

Role	Name(s)
Regulatory Project Manager	Alexis Childers
Nonclinical Reviewer	James Willard
Nonclinical Team Leader	Jean Wu
Office of Clinical Pharmacology Reviewer(s)	Snehal Samant
Office of Clinical Pharmacology Team Leader(s)	Manoj Khurana
Clinical Reviewer	Charu Gandotra, Yanyan Ji
Clinical Team Leader	Fortunato Senatore
Statistical Reviewer	Jennifer Clark
Statistical Team Leader	Jialu Zhang
Cross-Disciplinary Team Leader	Fortunato Senatore
Division Director	Norman Stockbridge

Table 59. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Kris Raman
OPDP	Zarna Patel
OSE/DMEPA	Max Straka

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ALEXIS T CHILDERS
02/12/2021 01:27:47 PM

JENNIFER J CLARK
02/12/2021 02:18:42 PM

JIALU ZHANG
02/12/2021 02:29:54 PM

MARK D ROTHMANN
02/12/2021 03:02:53 PM
I concur

YANYAN JI
02/12/2021 03:24:41 PM

CHARU GANDOTRA
02/12/2021 04:31:28 PM

FORTUNATO F SENATORE
02/13/2021 05:16:08 PM

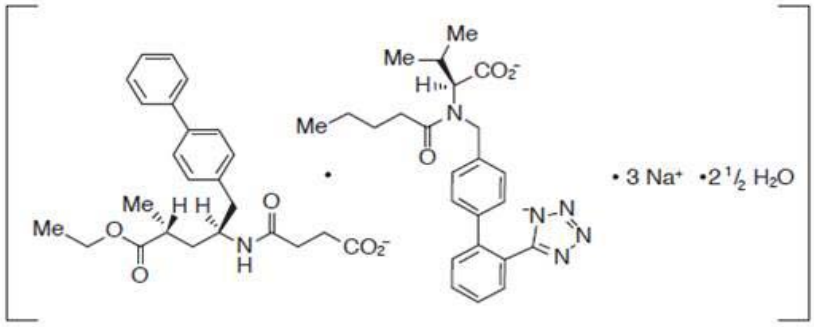
NORMAN L STOCKBRIDGE
02/14/2021 06:32:04 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207620Orig1s018

PRODUCT QUALITY REVIEW(S)

CMC REVIEW	1. ORGANIZATION: OLDP	2. NDA Number: 207-620
3. Name and Address of Applicant (City & State): Novartis Pharmaceutical Corporation One Heath Plaza East Hanover, NJ 07936		**4. Supplement(s):** **Number(s)** **Date(s)** S-018 4/20/2019
5. Drug Name: ENTRESTO™	**6. Nonproprietary Name:** Sacubitril/Valsartan	**7. Amendments - Dates**
8. Supplement Provides For: updated the registration of Entresto to reduce mortality and morbidity in **HFrEF** (heart failure with reduced ejection fraction) and to describe the treatment benefit to reduce morbidity in **HFpEF** (heart failure and preserved ejection fraction)in the heart failure.		
9. Pharmacological Category Heart failure	**10. How Dispensed** Rx	**11. Related NDAs/DMFs:**
12. Dosage Form(s): Tablets	**13. Potency:** 24/26 mg, 49/51 mg and 97/103 mg	
14. Chemical Name and Structure: The complex is chemically described as Octadecasodiumhexakis- (4-{[(1S,3R)-1-([1,1´-biphenyl]-4-ylmethyl)-4-ethoxy-3-methyl-4-oxobutyl]amino}-4-oxobutanoate)hexakis(N-pentanoyl-N-{[2´-(1H-tetrazol-1-id-5-yl)[1,1´-biphenyl]-4-yl]methyl}-L-valinate)—water (1/15).  Molecular Formula: $C_{48}H_{55}N_6O_8Na_3 \cdot H_2O$ Molecular Mass: 957.99		**15. Records/Reports:** **Current** **Yes X No** **Reviewed** **Yes No X**

16. Comments: This is an Efficacy supplement submitted to update the registration of Entresto to reduce mortality and morbidity in HFrEF and to describe the treatment benefit to reduce morbidity in HFpEF in the following proposed indication:

ENTRESTO is indicated for the treatment of chronic heart failure:

- to reduce cardiovascular death and hospitalization for heart failure in patients with chronic heart failure and reduced ejection fraction
- to reduce worsening heart failure (total HF hospitalizations and urgent heart failure visits) in patients with chronic heart failure and preserved ejection fraction.

There are no CMC related changes in the PI except for the revised storage condition per USP in the How Supplied/Storage and Handling section, which is acceptable.

Request for categorical exclusion is acceptable.		
17. Conclusions and Recommendations: This supplement is **approved** from CMC perspective.		
18. Reviewer:		
Name: Kris Raman, Ph.D. Sr. Review Chemist	**Signature:**	**Date Completed:** 6/1/2020, revised 6/19/2020

CMC REVIEW NOTES

Entresto (sacubitril/valsartan), also known as LCZ696, is a first-in-class angiotensin receptor neprilysin inhibitor. The purpose of this submission is to update the registration of Entresto to reduce mortality and morbidity in HFrEF and to describe the treatment benefit to reduce morbidity in HFpEF in the following proposed indication:

ENTRESTO is indicated for the treatment of chronic heart failure:

- to reduce cardiovascular death and hospitalization for heart failure in patients with chronic heart failure and reduced ejection fraction
- to reduce worsening heart failure (total HF hospitalizations and urgent heart failure visits) in patients with chronic heart failure and preserved ejection fraction.

Categorical Exclusion for Environmental Assessment:

As set forth in 21 CFR Part 25.31(b), action on a New Drug Application (NDA) is categorically excluded from the requirement to prepare an Environmental Assessment or an Environmental Impact Statement if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be less than 1 part per billion (ppb). "Increased use", as defined in 21 CFR Part 25.5(a), will occur if the drug is "administered at higher dosage levels, for longer duration or for different indications than were previously in effect, or if the drug is a new molecular entity."

Novartis Pharmaceuticals Corporation has filed a supplemental New Drug Application (sNDA) for Entresto (sacubitril/valsartan). This sNDA provides for the treatment of heart failure with preserved ejection fraction.

Novartis Pharmaceuticals Corporation certifies that this submission for Entresto qualifies for a categorical exclusion in accordance with 21 CFR Part 25.31(b) as the concentration of each of the two active moieties, sacubitril and valsartan, will be less than 1 ppb.

Further, Novartis Pharmaceuticals Corporation states that, to the best of its knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment and would thus require the preparation of at least an Environmental Assessment.

Comment: Request for categorical exclusion is acceptable.

LABELING:

2 Dosage and Administration

No changes are proposed

11 Description

No changes are proposed

16 How Supplied

Current:

Store at [redacted] *with excursions between 15°C and 30°C (59°F and 86°F) permitted [see USP Controlled Room Temperature]. Protect from moisture.* [redacted]

Addition of storage starting temperature (Fahrenheit) is proposed per USP:

Proposed:

Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Protect from moisture.

Comment: Revised storage condition is acceptable per USP.

Conclusion:

There are no CMC related changes in the PI except for the revised storage condition per USP in the How Supplied/Storage and Handling section.

Request for categorical exclusion is acceptable.

The supplement is **approved** from CMC perspective.

Krishna Raman

Digitally signed by Krishna Raman
Date: 7/30/2020 09:54:57AM
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Ramesh Raghavachari

Digitally signed by Ramesh Raghavachari
Date: 7/30/2020 04:02:29PM
GUID: 502d0913000029f375128b0de8c50020

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207620Orig1s018

OTHER REVIEW(S)

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Regulatory Project Manager Overview

sNDA: 207620 S018
Drug: Entresto (sacubitril/valsartan) Tablets
Class: a combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin receptor inhibitor

Applicant: Novartis Pharmaceutical Corp.

Proposed Indication in original supplemental submission: to reduce worsening heart failure (total heart failure hospitalizations and urgent heart failure visits) in patients with chronic heart failure and preserved ejection fraction

Amended Proposed Indication in original submission: to reduce worsening heart failure (total heart failure hospitalizations and urgent heart failure visits) in patients with chronic heart failure and preserved ejection fraction with left ventricular ejection fraction (LVEF) below normal

Final indication: to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal.
LVEF is a variable measure, so use clinical judgment in deciding whom to treat

Date of submission: April 20, 2020
PDUFA date: February 20, 2021
Action date: February 16, 2021

❖ **REVIEW TEAM**

- Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN), Division of Cardiology and Nephrology
  - Cross Discipline Team Leader (CDTL)
    - Fortunato (Fred) Senatore
  - Medical Reviewer
    - Charu Gandotra
    - Yanyan (Claire) Ji
- Office of Regulatory Operations, Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
  - Regulatory Health Project Manager
    - Alexis Childers
- Office of Clinical Pharmacology

- Snehal Samant (clinpharm)
- Office of Biostatistics, Division of Biometrics I
  - Jennifer Clark
- Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis
  - Max Straka
- Office of Pharmaceutical Quality
  - Kris Raman

BACKGROUND

Entresto is a combination of sacubitril and valsartan approved in 2015 to reduce the risk of cardiovascular (CV) death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction (HFrEF). Pediatric studies were waived under PREA because of the small number of patients, but the Agency issued a Written Request (WR) in 2017, and a supplement was submitted April 1, 2019. The supplement was approved On October 1, 2020 providing for a new indication for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. ENTRESTO reduces NT-proBNP and is expected to improve cardiovascular outcomes.

Entresto was also being studied in patients with preserved ejection fraction (HFpEF). The pivotal trial known as PARAGON-HF was a double-blind randomized clinical trial comparing Entresto 200 mg BID to Valsartan 160 mg BID. Eligible patients had symptomatic HFpEF (NYHA class II-IV) with LVEF $\geq$ 45% requiring diuretics. Other entry criteria were left ventricular hypertrophy (LVH) or left atrial enlargement (LAE), and elevated N-terminal-proB-type natriuretic peptide (NT-proBNP). The primary efficacy endpoint was a composite of total (first and recurrent) hospitalizations for heart failure and cardiovascular death. Secondary endpoints were NYHA class, KCCQ, renal composite outcome and all-cause mortality. The trial fell short of meeting statistical significance, but the Division suggested that the data might support a new claim. This supplement was submitted proposing a new indication to include HFpEF patients.

Primary reviewers completed their assessments according to the 21st century review timelines although a combined review was completed by statistics and clinical. The CDTL and Signatory also provided their concurrence in the document. All people singed the single document in DARRTS.

User Fee

No user fee required.

Pediatric Review Committee (PeRC) (January 5, 2021)

An agreed iPSP was issued under IND 104628 in April 2018 for a full waiver in HFpEF. This product was discussed at PeRC, without Division attendance, and PeRC agreed with the waiver. Subsequently it was decided that the data in the supplement provided for an extension of the existing indication instead of a new indication. It was therefore decided that PREA was not triggered and documentation of the pediatric page in DARRTS was removed.

Advisory Committee (AC)
The Cardiovascular and Renal Drugs Advisory Committee (CRDAC) met on December 15, 2020 to discuss this supplement. Four discussion items were presented to the Committee and one voting question. For the voting question, the Committee voted 12 to 1 that the PARAGON-HF, perhaps supported by previous studies, provides sufficient evidence to support ANY indication. The integrated review from clinical provides a detailed commentary of the discussion items and voting discussion. A transcript will also be publicly available in the future.

Trade name
No trade name was submitted as this is a supplement.

Facilities Inspection
There were no facility inspections as no new CMC information was submitted.

Division of Scientific Investigations
No clinical sites were inspected. The Division did not feel an inspection was needed since the drug is approved and the study results appeared straight forward.

❖ **REVIEWS**
Below are the conclusions reached by the Farxiga team members, organized by role or discipline.

Divisional Concurrence, Cross-Discipline Team Leader (CDTL) Review, and Medical/ Biostatistics Review (dated February 14, 2021)
A joint collaborative review was written by clinical and statistics. Dr.'s Gandotra (clinical) and Clark (statistics) focused on efficacy data, and Dr. Ji (clinical) focused on safety. Dr. Senatore, CDTL, provided the Executive Summary within the review. Dr. Stockbridge, signatory, signed the review in concurrence.

The review team recommended approval of the application as an expansion of its prior claim and not as a "first-ever claim in a fundamentally different form of heart failure" (HFpEF). The review provided rationale for reviewing the failed trial, as well as discussed in depth the review process for drawing the conclusions that were made. This discussion includes outcomes from the AC meeting.

Below are a few points from the review indicating why the findings of efficacy in the PARAGON -HF trial provide additional supportive evidence of treatment effect with Entresto.

- Although PARAGON-HF narrowly missed statistically significance for the primary composite endpoint, additional prespecified exploratory and post-hoc analyses support a treatment effect of Entresto versus valsartan.
- The patient population enrolled in PARAGON-HF was heterogenous i.e.; it included patients with mildly reduced /abnormal and normal LVEF. Subgroup analyses demonstrated a heterogeneity of treatment effect by sex and LVEF suggesting that females and patients with LVEF $\leq$ 57%, derive a greater benefit with Entresto compared to males and patients with LVEF > 57%.
- Analysis of treatment effect by LVEF as a continuous variable indicate that patients with mildly reduced LVEF or mild left ventricular systolic dysfunction resemble patients with moderate to severely reduced LVEF in terms of therapeutic response to these therapies

The review indicated that "the benefit-risk in the subgroup of subjects with a reduced LVEF in PARAGON-HF reflects comparability with that from PARADIGM-HF. The review also states "the safety findings in PARAGON-HF were consistent with the well-known safety profile of Entresto. Similar to the findings in PARADIGM-HF, Entresto was associated with a higher risk for angioedema and hypotension, compared to active comparator, valsartan. Current labeling is considered sufficient to manage these risks.

See review for full details.

CMC Review (dated June 30, 2020)
Dr. Raman provided a brief review stating that no new information was submitted, and the only CMC change in the PI was the revised storage condition per USP in the How Supplied/Storage and Handling section, which is acceptable. The review stated that an Environmental Assessment was submitted and the request for Categorical Exclusion is acceptable.

Division of Medication Error Prevention and Analysis DMEPA (dated September 18, 2020)
Dr. Straka's review stated that they performed a risk assessment of the proposed Prescribing Information and Patient Information, and determined they are acceptable from a medication error perspective.

CONSULTS

Office of Medical Policy Initiatives, Division of Medical Policy Programs (dated February 3, 2021)
Dr. Mills did a combined review with Dr. Patel evaluating the Patient Package Insert (PPI). See full review for comments regarding the PPI. They concluded that the document is acceptable pending proposed corrections.

Office of Prescription Drug Promotions, Division of Professional Drug Promotion (dated February 2, 2021)
Dr. Patel provided comments on the draft prescribing information during internal label meetings. No additional comments were included in her review.

Labeling
Labeling discussions occurred with the applicant. The final agreed upon labeling will be attached to the approval letter. Attached to this review is the label showing all changes in track changes.

CONCLUSION: The review team recommended approval of the supplement providing for an expanded indication: "to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal.
LVEF is a variable measure, so use clinical judgment in deciding whom to treat". Dr. Stockbridge signed the approval letter on February 16, 2021.

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ALEXIS T CHILDERS
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	February 3, 2021
To:	Alexis T. Childers, RAC, CQIA Senior Regulatory Project Manager **Division of Cardiology and Nephrology (DCN)**
Through	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Zarna Patel, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	ENTRESTO (sacubitril/valsartan)
Dosage Form and Route:	tablets
Application Type/Number:	NDA 207620
Supplement Number:	S-018
Applicant:	Novartis Pharmaceuticals Corporation

1 INTRODUCTION

On April 20, 2020, Novartis Pharmaceuticals Corporation submitted for the Agency's review a Prior Approval Supplement (PAS)- Efficacy to their approved New Drug Application (NDA) 207620/S-018 for ENTRESTO (sacubitril/valsartan) tablets. With this supplement, the Applicant proposes a new indication to allow the use of ENTRESTO in adult patients with chronic heart failure and preserved ejection fraction (HFpEF).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Cardiology and Nephrology (DCN) on May 6, 2020, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ENTRESTO (sacubitril/valsartan) tablets.

2 MATERIAL REVIEWED

- Draft ENTRESTO (sacubitril/valsartan) tablets PPI received on April 20, 2020 and September 22, 2020, and received by DMPP on January 28, 2021.
- Draft ENTRESTO (sacubitril/valsartan) tablets Prescribing Information (PI) received on April 20, 2020, revised by the Review Division throughout the review cycle, and received by DMPP on January 28, 2021.
- Approved ENTRESTO (sacubitril/valsartan) tablets labeling dated October 1, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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BARBARA A FULLER
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

Memorandum

****PRE-DECISIONAL AGENCY MEMO****

Date: February 2, 2021

To: Alexis T. Childers, RAC, CQIA
Senior Regulatory Health Project Manager
Division of Cardiology and Nephrology (DCN)

Michael Monteleone, Associate Director for Labeling, DCN

From: Zarna Patel, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, PharmD, Team Leader, OPDP

Subject: OPDP Labeling Comments for ENTRESTO® (sacubitril and valsartan) tablets, for oral use

NDA: 207620/Supplement 018

In response to DCN's consult request dated May 5, 2020, OPDP has reviewed the proposed product labeling (PI) and the patient package insert (PPI) for ENTRESTO® (sacubitril and valsartan) tablets, for oral use. This efficacy supplement (S018) provides for the revision of the heart failure indication for adults based on the PARAGON-HF trial.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DCN (Alexis Childers) on January 28, 2021 and have no additional comments at this time (comments were previously provided during internal labeling discussions on SharePoint).

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Zarna Patel at 301.796.3822 or zarna.patel@fda.hhs.gov.

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ZARNA PATEL
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 18, 2020
Requesting Office or Division:	Division of Cardiology and Nephrology (DCN)
Application Type and Number:	NDA 207620/S-018
Product Name and Strength:	Entresto (sacubitril/valsartan) tablets, 24 mg/26 mg, 49 mg/51 mg, 97 mg/103 mg
Applicant/Sponsor Name:	Novartis Pharmaceuticals Corporation
OSE RCM #:	2020-848
DMEPA Safety Evaluator:	Maximilian Straka, PharmD, FISMP
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Novartis Pharmaceuticals Corporation submitted supplemental NDA 207620/S-018 for Entresto (sacubitril/valsartan) to revise the indication in adult patients with chronic heart failure and preserved ejection fraction based on the pivotal study CLCZ696D2301 (PARAGON_HF). We reviewed the proposed Prescribing Information (PI) and Patient Information for Entresto (Appendix A) for areas of vulnerability that may lead to medication errors.

2 CONCLUSION

Novartis proposed changes to the Prescribing Information including revision to the Highlights of Prescribing Information, Section 1: Indications and Usage, Section 5: Warnings and Precautions, Section 6: Adverse Reactions, Section 8: Use in Specific Populations, Section 12: Clinical Pharmacology, Section 14: Clinical studies and Section 16: How Supplied/ Storage and Handling. We note that in Section 16: Storage and Handling, the temperature range was updated to include the starting Fahrenheit temperature, i.e. 68 F.

The Applicant has also added the statement (b) (4) to the Patient Information along with other minor edits.

We performed a risk assessment of the proposed Prescribing Information and Patient Information to determine if it is acceptable from a medication error perspective. We defer to the review team for analysis of the proposed changes to various sections of the PI. The proposed PI and Patient Information is acceptable from a medication error perspective. We have no further recommendations at this time.

APPENDIX A. LABEL AND LABELING RECEIVED ON April 20, 2020
Prescribing Information (image not shown), available from:
\\CDSESUB1\evsprod\nda207620\0120\m1\us\proposed-clean.pdf

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